Original Article

Diabetes remission after a lifestyle-medicine intervention on type 2 diabetes in lean and obese Chinese subjects: a prospective study

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Background: Whether diabetes remission still happened among non-obese type 2 diabetes (T2DM) patients with a body mass index (BMI) <25 kg/m^2 following lifestyle-medicine interventions was quite necessary to be reported because many diabetes happened with normal or low BMI in China.

Methods: The criteria for subject inclusion: <20 years after T2DM diagnosis, ≥6 months treatment with oral anti-diabetic drugs, without serious complications, and no history of insulin use. They were divided into two groups: the obesity group (BMI ≥25 kg/m^2) and the lean group (BMI <25 kg/m^2). All subjects received the following lifestyle-medicine interventions: stopping oral anti-diabetic therapy, initiating a low-carbohydrate (contributing by 35–40% to calorie intake) diet for the first month (gradual transition to a normal diet for the next 5 months), participating in resistance and aerobic exercise, and receiving strengthen management. Diabetes remission was defined as glycosylated hemoglobin (A1C) level <6.5% (<48 mmol/mol) after 6 months of not taking any anti-diabetic medications during the lifestyle-medicine intervention. Finally, 125 individuals completed the lifestyle-medicine intervention in the prospective study. The efficacy and safety of lifestyle-medicine intervention were assessed and compared between lean and obese Chinese subjects with T2DM.

Results: We found that 64.52% of the T2DM subjects in the obese group and 60.64% of T2DM subjects in the lean group achieved diabetes remission [i.e., an A1C level <6.5% (48 mmol/mol)] without any anti-diabetic medications after the 6-month lifestyle-medicine intervention. Our multiple linear regression analysis showed that decreases in the fasting plasma glucose (FPG) level had the most powerful effect on decreases in the A1C level after the intervention (R^2=0.3072).

Conclusions: Lifestyle-medicine interventions may have increased effectiveness in controlling mild T2DM as compared with the oral antidiabetic-based treatment; unexpectedly, there seems no further improvement in lean relative to obese patients. Three in five subjects could achieve diabetes remission though the lifestyle-medicine intervention regardless of whether their BMI was below or above 25 kg/m^2.

Keywords: Lifestyle-medicine intervention; remission; type 2 diabetes mellitus (T2DM)

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Introduction

Type 2 diabetes mellitus (T2DM) was long regarded as an irreversible chronic disease based on traditional means of treatment. However, extensive research has since shown that T2DM is a reversible condition, especially in recent years (1,2). It is thought that lifestyle-medicine interventions could reverse T2DM (3). For example, it has been reported that an intensive lifestyle intervention approach (i.e., a decrease in diet and calorie intake and an increase in the physical exercise level) leads to the T2DM remission (4). More rigorous and precise research involving calorie control and carbohydrate ratio control have been conducted to examine diabetes remission; for example, recent studies have reported that glycemic control or T2DM remission/reversal can be achieved with low-calorie diets (5-7) or low-carbohydrate diets (8). However, in most studies on diabetes remission/reversal, the cohorts have comprised obese diabetic patients with a body mass index (BMI) ≥25 kg/m^2, and the main factor affecting the remission/reversal of diabetes was weight loss after intensive interventions. To date, no research has examined the remission/reversal of T2DM in non-obese patients with a BMI <25 kg/m^2. However, such research is very important for Asian diabetic patients, as obesity is not as prevalent in this population as it is in Asians in Western countries (9,10). A recent evidence from a nationally representative cross-sectional study showed that 57.67% of all diabetic patients (over 45 years old) with BMI ≥24 kg/m^2 (overweight or obese), which means still nearly half of the total diabetic patients with normal or low BMI (<24 kg/m^2) (11), and it also reported that one in five Asian Americans with diabetes are in low normal BMI (18.5 to ≤23 kg/m^2) (12). Thus whether lifestyle-medicine interventions which bring many benefits to obese T2DM patients will also be suitable for non-obese T2DM patients and even bring diabetes remission is worth to be investigated for guiding clinic treatment or management of non-obese T2DM.

It was well known that weight loss was the main factor associated with remission for overweight/obese T2DM patients after intensive lifestyle interventions, however, weight loss might be not suitable for non-obese diabetes patients to achieve diabetes remission. Thus, more directly or indirectly related effects contribute to diabetes remission need to be investigated. Actually, a previous study found that the blood glucose levels of T2DM patients could be improved even without weight loss (13). Diabetes prevention among Asian people has primarily been attributed to factors, such as changes in dietary composition and increased physical exercise, but not baseline or BMI (14,15). These findings led us to speculate that a more comprehensive intervention, which did not only focus on weight loss and BMI, might lead to diabetes remission. Indeed, directly or indirectly, many related factors contribute to diabetes remission/reversal, including glycemic control, insulin sensitivity, insulin resistance, the visceral fat index (VFI), body fat percentage, and muscle mass.

This study examined diabetes remission in non-obese T2DM patients after the implementation of a lifestyle-medicine intervention that combined an individualized diet plan and an individualized activity program, and the underlying attributing factors. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-369/rc).

Methods

Research design

We adopted a prospective study design. The patients were asked to maintain their diet and exercise habits until the start of the study. Assessments of insulin sensitivity, insulin resistance, β cell function, anthropocentric and body composition, and metabolism were carried out at the baseline immediately before the intervention commenced (at day-1), and again after 6 months of the lifestyle-medicine intervention. The patients were divided into the following 2 subgroups according to their baseline BMI: (I) the obese group, which comprised patients with a BMI ≥25 kg/m^2; (II) the lean group, which comprised patients with a BMI <25 kg/m^2. All the patients received the lifestyle-medicine intervention.

After the baseline measurements had been recorded, the T2DM patients started the lifestyle-medicine intervention,

which consisted of the withdrawal of anti-diabetic drugs and alcohol, a low-carbohydrate diet (35–40% carbohydrate, 20–30% protein, and 30–45% fat; 1,800 kcal/day for the lean group, and 700–900 kcal/day for the obese group; a limit of 6 g of salt per day; proper vitamins, minerals, and trace elements; 10–14 g/1,000 kcal dietary fiber for the 1st month), and resistance and aerobic exercise, followed by a stepped normal construction diet (50–55% carbohydrate, 15–20% protein, and 20–30% fat; 30–35 kcal/kg/day; a limit of 6 g of salt per day; proper vitamins, minerals, and trace elements; 10–14 g/1,000 kcal dietary fiber for the last 5 months), and resistance and aerobic exercise, and received strength management to achieve the target goal of glycemic control [i.e., a fasting plasma glucose (FPG) level <7.0 mmol/L and 2-hour postprandial blood glucose (2hPG) level <10.0 mmol/L].

The patients were also provided with suggestions of vegetable recipes, high-quality protein foods and nuts to enhance their compliance and vary their daily food intake. They were also encouraged to drink at least 2 L of water or other energy-free beverages each day and asked to engage in 30–45 minutes of home or supervised onsite exercise that combined aerobic and resistance training for a total of 5–6 days per week as recommended by the current Chinese Diabetes Association guidelines. Our exercise instructor gradually increased the exercise intensity over the following 3 stages: (I) in the primary foundation establishment period, the exercise intensity was low to medium, with a duration of 30–45 minutes; (II) in the stable stage of the intermediate stage, the exercise intensity was medium and low, with a duration of 25–35 minutes; (III) in the breakthrough stage, the exercise intensity was medium or high with a duration of 30 minutes.

Ongoing support and encouragement was provided by strengthened management, which comprised frequent consultations, including a 30-minute weekly face-to-face interview, 3×10-minute daily consultations via WeChat or regular telephone calls with a multi-center team that comprised a general practitioner, a health manager, a dietitian, and an exercise instructor. The patients were also provided classes for practicing and discussing diabetes management, and encouraged to adopt a strictly controlled diet and engage in sufficient aerobic and resistance exercise to improve the regulation of their blood glucose levels by a local diabetologist who supervised the treatment targets.

At the end of the 1st month of the intervention, the participants could return to their normal eating habits but were provided with information about portion size and healthy eating according to the "Food Guide Pagoda for Chinese Residents" (16).

Participants

The research was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Guangzhou Red Cross Hospital (No. 2020-168-01) and informed consent was taken from all the participants. The study subjects were patients at the Da'an Yifukang Specialist Outpatient Department, Guangdong Shengke Life and Health Technology Limited Company, Guangzhou, China.

Participants were included in the study if they met the following inclusion criteria: (I) had been diagnosed with T2DM according to the 1999 World Health Organization's criteria; (II) had been treated with anti-diabetic drugs for over 6 months. Participants were excluded from the study if they met any of the following exclusion criteria: (I) had been treated with insulin or steroids; (II) had acute complications of DM (e.g., diabetic ketoacidosis, diabetic hyperosmolar coma, or severe hypoglycemia); (III) had severe cardiopulmonary renal insufficiency; (IV) had a swallowing activity obstacle; (V) had an acute or chronic disease, including an acute or chronic infectious disease, autoimmune disease, or chronic tumor; (VI) had been applying hydrocortisone for a long time; (VII) had developed ≥3 kinds of complications; and/or (VIII) had taken more than 3 kinds of hypoglycemic drugs.

All the participants acknowledged and completed the diabetes questionnaire. The participants attended follow-up visits 6 months after the baseline study visit. Among the 1,077 participants in the original cohort, 200 were treated with insulin or steroids, 219 were treated without any anti-diabetic drugs or with anti-diabetic drugs for >6 months, 360 with other chronic diseases, and 46 for whom no body composition analysis data were available were excluded at the baseline. An additional 127 participants were excluded because they did not complete the follow-up examinations. Thus, according to our inclusion criteria and exclusion criteria, the data of a total of 125 participants at the baseline were included in the analysis.

Anthropometric methods

The same height meter and weight scale was used to measure the height and weight of all the patients, which were recorded by a single observer (Kunyuan Luo). The

BMI was calculated based on each patient's height and weight using the following formula: BMI = weight/height^2 (kg/m^2).

Body composition analysis

The VFI, body fat percentage, and muscle mass of each patient were measured following overnight fasting using a multi-frequency body composition detector (Tanita MC-780MA, TANITA, Japan); the patients were advised to avoid engaging in strenuous movements before the test.

Laboratory inspection

All the blood samples were sent to a company to determine the FPG level, and the 2hPG level was detected using an automatic biochemical analyzer (Hitachi 7600-020). Glycosylated hemoglobin (A1C) was tested using a Sysmex blood analyzer (XE-5000). Fasting serum insulin (FINS) was measured using the chemiluminescence method (Roche Elecsys 2010 electrochemiluminescence automatic immunoassay analyzer).

Calculations

The Homeostasis Model Evaluation of Insulin Sensitivity (HOMA-IS) used the following formula: 22.5/[FINS (μIU/mL) × FPG (mmol/L) (17)]. The Homeostasis Model Evaluation of Insulin Resistance (HOMA-IR) used the following formula: [FINS (μIU/mL) × FPG (mmol/L)]/22.5 (17). The Homeostasis Model Evaluation of β Cell Function (HOMA-β) used the following formula: 20 × FINS (μIU/mL)/[FPG (mmol/L) – 3.5] (17).

Statistical methods

The statistical analyses were performed using R version 3.6.1 in combination with RStudio (Version 1.2.5001, RStudio Inc., Boston, USA). The data are presented as the mean ± standard error. The Kolmogorov-Smirnov test was used to verify the normality of the data, and the Student's *t*-test was used to compare the diabetes groups and within-group differences. Changes in the sequential data within the experiments were examined using a repeated measure two-way analysis of variance with post-hoc Bonferroni testing as appropriate. Mixed models for repeated measurements were used to estimate the contribution of the variables in the model. The goodness of fit of the multiple linear regression models and the contribution rate of each factor were estimated using Pearson's chi-squared test, and the Pearson correlation coefficient was calculated. A P value <0.05 (two-sided) was considered statistically significant.

Results

Changes in weight and body composition

All the 125 recruited diabetic patients (male 70 and female 55, aged 30–79 years, A1C level 4.9–12.6% (30–114 mmol/mol), FPG level <13.0 mmol/L, duration of diabetes <20 years, stable BMI 17–37 kg/m^2), including 31 patients in the obese group (BMI 27.35 ± 2.58 kg/m^2; female: 39, male: 55; age: 56.93±10.26 years), and 94 patients in the lean group (BMI 21.99±1.86 kg/m^2; female: 16, male: 15; age: 59.29±8.81 years) completed the lifestyle-medicine intervention. As *Table 1* shows, after the 6-month lifestyle-medicine intervention, the body weight of patients in the lean sample had not changed significantly (59.12±7.82 *vs.* 56.35±7.24 kg; P>0.05), but it was significantly reduced compared to the baseline in the obese group (–7.46±3.41; P<0.001) and the entire cohort (–3.93±3.64; P<0.01). A reduction in the BMI after the intervention was observed in all patients (–1.47±1.37; P<0.001); that is, in both the obese (–2.81±1.25; P<0.01) and lean (–1.03±1.10; P<0.01) groups. The VFI and body fat percentage of all the patients were decreased after the intervention (–1.53±1.38 for the VFI; P<0.001; –2.72±3.27 for body fat percentage; P<0.01), and in both the obese group (–2.61±1.20 for the VFI; P<0.01; –4.00±3.03 for body fat percentage; P<0.05) and the lean group (–1.17±1.25 for the VFI; P<0.001; –2.37±3.17 for body fat percentage; P<0.01). The reductions in body weight, the BMI, the VFI, and the body fat percentage after the 6-month lifestyle-medicine intervention in the lean group were significantly less than those in the obese group. No significant change in muscle mass was observed in the obese group, the lean group, or the entire cohort (P>0.05).

Reductions in A1C levels and changes in FPG, 2hPG, FINS, HOMA-IS, HOMA-IR, and HOMA-β

After the 6-month lifestyle-medicine intervention, the A1C level decreased by –0.58%±1.03% (–6±11 mmol/mol) in all the diagnosed T2DM patients, who had a mean baseline A1C level of 6.88%±1.23% (51±13 mmol/mol), which resulted in a mean A1C level <6.5% (48 mmol/mol) [6.30%±0.64% (45±7 mmol/mol)] at the end of the trial.

Table 1 Summary of weight and body composition parameters of a 6-month lifestyle medicine intervention in the obese, lean, and whole groups of T2DM patients

Characteristics	Obese group (n=31)			Lean group (n=77)			Whole group (n=125)		
	Baseline	3rd month	Changes	Baseline	3rd month	Changes	Baseline	3rd month	Changes
Sex	F=16, M=15			F=39, M=55			M=70, F=55		
Age (years)	59.29±8.81			56.93±10.26			57.51±9.93		
Weight (kg)	72.89±9.92	65.43±8.45	–7.46±3.41***†	59.12±7.82	56.35±7.24	–2.77±2.90	62.53±10.27	58.60±8.49	–3.932±3.64**
BMI (kg/m^2)	27.35±2.58	24.54±1.90	–2.81±1.25**†	21.99±1.86	20.96±1.52	–1.03±1.10***	23.32±3.10	21.85±2.24	–1.47±1.37***
VFI	12.48± 3.25	9.87±3.43	–2.61±1.20**†	8.15± 3.29	6.98±2.91	–1.17±1.25*	9.22±3.77	7.70±3.29	–1.53±1.38***
Percentage body fat (%)	31.50±8.12	25.51±7.27	–4.00±3.03*†	22.57±6.34	20.21±6.46	–2.37±3.17**	24.77±7.80	22.05±7.36	–2.72±3.27**
Muscle mass (kg)	46.23±9.92	45.13±8.73	–1.1±2.95	43.05±7.14	42.69±7.76	–0.36±3.86	43.70±8.02	43.49±7.67	–0.212±3.19

*, P<0.05; **, P<0.01; ***, P<0.001. †, P<0.001, compared to lean group. T2DM, type 2 diabetes; F, female; M, male; BMI, body mass index; VFI, visceral fat index.

Thus, the mean A1C level decreased significantly to <6.5% in both the obese group [from 6.95%±1.16% to 6.26%±0.71%; P<0.01 (from 53±13 to 45±8 mmol/mol)] and the lean group [from 6.85%±1.25% to 6.31%±0.62%; P<0.001 (from 51±14 to 45±7 mmol/mol)]. The mean FPG level and mean 2hPG level were significantly reduced by –0.80±1.65 and –3.16±4.45 mmol/L in the entire cohort, –1.23 ±1.76 and –3.73±3.99 mmol/L in the obese group, –0.66±1.59 and –2.98±4.59 mmol/L in the lean group (P<0.001 or P<0.01). However, the differences in the reduction of the A1C, FPG, and 2hPG levels induced by the intervention were not statistically different between the obese and lean groups (P>0.05).

After the lifestyle-medicine intervention, the high secretion of FINS decreased to –2.04±4.23 (P<0.001) in the entire cohort, –3.70±5.62 (P<0.05) in the obese group, and –1.50±3.54 (P<0.05) in the lean group; the decrease in FINS in the obese group was statistically greater than that in the lean group (P<0.05). Patients' insulin sensitivity (HOMA-IS) increased significantly after the intervention in the entire cohort, and in both the lean and obese groups but did not differ statistically between the lean and obese groups (P>0.05). Conversely, insulin resistance (HOMA-IR) was statistically decreased after the intervention in the entire cohort and in both the lean and obese groups. The insulin resistance of the diabetes patients in the obese group was significantly improved compared to that of patients in the lean group (–1.62±2.21 *vs.* –0.67±1.36; P<0.05). However, no significant change in β cell function (HOMA-β) was found in the entire cohort, or in the lean and obese groups (P>0.05; see *Table 2*).

Remission in T2DM patients

Diabetes remission was defined as an A1C level <6.5% (48 mmol/mol) after the 6-month withdrawal of anti-diabetic medications from the baseline in our study. Before the lifestyle-medicine intervention, 32.26% of the 31 patients in the obese group and 46.81% of the 94 patients in the lean group had an A1C level <6.5% (48 mmol/mol) and were taking various kinds of anti-diabetic drugs. The proportion increased to 64.52% and 60.64%, respectively, and patients with an A1C level <6.5% (48 mmol/mol) after the withdrawal of anti-diabetic drugs for 6 months after the lifestyle-medicine intervention achieved T2DM remission. In the entire cohort, 43.20% of patients had an A1C level <6.5% (48 mmol/mol) after taking various kinds of anti-diabetic drugs; however, after the lifestyle-medicine intervention, 61.60% of the patients had an A1C level <6.5% (48 mmol/mol) after the withdrawal anti-diabetic drugs for 6 months, and these patients achieved T2DM remission (see *Table 3*).

An A1C level <7% (53 mmol/mol) is generally set as a control goal for T2DM in China. In this study, 54.84% of the 31 patients in the obese group, 70.21% of the 94 patients in the lean group, and 66.40% of 125 patients in the entire group had an A1C level <7% (53 mmol/mol) after taking various kinds of anti-diabetic drugs, and these proportions increased to 83.87% for the obese group, 85.11% for the lean group, and 84.80% for the

Table 2 Summary of metabolic and laboratory parameters of a 6-month lifestyle medicine intervention in the obese, lean, and whole groups of T2DM patients

Characteristics	Obese group (n=31)			Lean group (n=77)			Whole group (n=125)		
	Baseline	3rd month	Changes	Baseline	3rd month	Changes	Baseline	3rd month	Changes
A1C (%) [mmol/mol]	6.95±1.16 [52.21±12.68]	6.26± 0.71 [45.44±6.78]	–0.70±0.86 [–7.62±9.39]**	6.85±1.25 [51.38±13.70]	6.31± 0.62 [44.90±7.76]	–0.54±1.08 [–5.94±11.79]***	6.88±1.23 [51.66±13.42]	6.30±0.64 [45.30±7.01]	–0.58±1.03 [–6.35±11.23]***
FPG (mmol/L)	7.59±1.95	6.36±1.03	–1.23±1.76**	7.20±1.81	6.55±1.01	–0.66±1.59**	7.30±1.84	6.50±1.01	–0.80±1.65***
2hPG (mmol/L)	13.71±4.03	9.87±3.22	–3.73±3.99***	13.86±4.57	10.88±3.47	–2.98±4.59***	13.79±4.32	10.63±3.43	–3.16±4.45***
FINS (μIU/mL)	10.63±7.01	6.93±4.40	–3.70±5.62*†	7.00±4.49	5.50±3.75	–1.50±3.54*	7.90±5.43	5.86±3.95	–2.04±4.23***
HOMA-IS	0.44±0.35	24.87±15.38	24.43±15.53***	0.67±0.50	19.32±13.22	18.66±13.39***	0.61±0.47	20.70±13.93	20.09±14.11***
HOMA-IR	3.60±2.66	1.98±1.37	–1.62±2.21**†	2.27±1.76	1.60±1.13	–0.67±1.36**	2.60±2.09	1.69±1.20	–0.91±1.66***
HOMA-β	1.03±1.85	0.53±0.34	–0.50±1.83	0.44± 0.28	0.40±0.29	–0.04±0.27	0.59±0.97	0.44±0.31	–0.15±0.95
ALT (IU/L)	24.27±8.67	23.84±4.54	–0.43±8.71	–0.43±8.71	23.40±7.54	24.50±6.58	23.62±7.80	23.84±6.13	0.22±7.12
AST (IU/L)	26.57±14.00	21.84±7.22	–4.74±14.92	–4.74±14.92	24.37±14.74	24.71±11.00	24.92±14.54	24.00±10.24	–0.92±14.61
TG (mmol/L)	2.07±1.05	1.14±0.57	–0.93±1.02***	–0.93±1.02***	1.54±1.25	1.01±0.60	1.68±1.22	1.04±0.59	–0.64±1.03**
TC (mmol/L)	4.97±0.70	4.73±0.99	–0.24±1.02	–0.24±1.02	5.15±1.06	5.06±0.97	5.04±0.98	5.05±0.99	0.0092±1.07
HDL-c (mmol/L)	1.23±0.24	1.35±0.24	0.13±0.22*	0.13±0.22*	1.52±0.28	1.36±0.31	1.32±0.27	1.48±0.30	0.154±0.24***
LDL-c (mmol/L)	2.76±0.56	2.32±0.71	–0.44±0.67**	–0.44±0.67**	2.69±0.76	2.47±0.70	2.70±0.72	2.43±0.70	–0.27±0.72**
BUN (mmol/L)	5.65±1.21	6.66±1.47	1.01±1.26**	1.01±1.26**	5.72±1.33	7.01±1.56	5.71±1.30	6.92±1.54	1.22±1.37***
SCr (μmol/L)	74.29±22.29	71.64±18.22	–2.65±16.35	–2.65±16.35	74.81±21.77	75.71±20.72	75.36±21.82	74.02±20.10	1.34±18.70
UA (μmol/L)	404.29±89.08	367.23± 70.94	–37.06±80.49*‡	–37.06±80.49*‡	371.91±89.54	343.57± 71.18	379.94±90.16	349±71.57	–30.50±66.89**

Data are presented as mean ± standard deviation. *, P<0.05; **, P<0.01; ***, P<0.001, compared to baseline; †, P<0.05, compared to lean group; ‡, P<0.001, compared to lean group. T2DM, type 2 diabetes; A1C, glycated hemoglobin; FPG, fasting plasma glucose; 2hPG, 2-hour postprandial blood glucose; FINS, fasting serum insulin; HOMA-IS, insulin sensitivity; HOMA-IR, insulin resistance; HOMA-β, β Cell Function; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglyceride; TC, total cholesterol; HDL-c, high-density lipoprotein–cholesterol; LDL-c, low-density lipoprotein-cholesterol; BUN, blood urea nitrogen; SCr, serum creatinine; UA, uric acid.

Table 3 Remission at A1C <6.5% in participants with T2DM response to 6-month of lifestyle medicine intervention in the obese, lean, and whole groups

Baseline	Obese group (n=31)			Lean group (n=77)			Whole group (n=125)		
	6th month			6th month			6th month		
	A1C <6.5% [48 mmol/mol]	A1C ≥6.5% [48 mmol/mol]	Sum	A1C <6.5% [48 mmol/mol]	A1C ≥6.5% [48 mmol/mol]	Sum	A1C <6.5% [48 mmol/mol]	A1C ≥6.5% [48 mmol/mol]	Sum
A1C <6.5% [48 mmol/mol]	8	2	10 (32.26%)	40	4	44 (46.81%)	48	6	54 (43.20%)
A1C ≥6.5% [48 mmol/mol]	12	9	21	17	33	50	29	42	71
Sum	20 (64.52%)	11	31	57 (60.64%)	37	94	77 (61.60%)	48	125

A1C, glycated hemoglobin; T2DM, type 2 diabetes.

Table 4 Remission at A1C <7% in participants with T2DM response to 6-month of lifestyle medicine intervention in the obese, lean, and whole groups

Baseline	Obese group (n=31), 6th month			Lean group (n=77), 6th month			Whole group (n=125), 6th month		
	A1C <7% [53 mmol/mol]	A1C ≥7% [53 mmol/mol]	Sum	A1C <7% [53 mmol/mol]	A1C ≥7% [53 mmol/mol]	Sum	A1C <7% [53 mmol/mol]	A1C ≥7% [53 mmol/mol]	Sum
A1C <7% [53 mmol/mol]	17	0	17 (54.84%)	60	6	66 (70.21%)	60	6	66 (70.21%)
A1C ≥7% [53 mmol/mol]	9	5	14	20	8	28	20	8	28
Sum	26 (83.87%)	5	31	80 (85.11%)	14	94	80 (85.11%)	14	94

A1C, glycated hemoglobin; T2DM, type 2 diabetes.

Table 5 Multiple linear regression analysis using the change of A1C as a dependent variable and the change of FPG and VFI induced by lifestyle medicine intervention as predictors

Variable	Estimate	SE	P value
Intercept	$-1.369e^{-1}$*	0.066	1
Change_FPG	1.423*	0.240	0.0000
Change_Ratio FPG	$-9.141e^{-1}$*	0.240	0.0000
Change_Ratio VFI	$2.033e^{-1}$*	0.067	0.0046

*, for one-standard deviation decrease. Dependent variable: change of A1C after lifestyle medicine intervention compared to baseline. The baseline of FPG, ratio FPG and ratio VFI did not enter the model at P>0.05 level. A1C, glycated hemoglobin; FPG, fasting plasma glucose; VFI, visceral fat index.

entire cohort after the withdrawal of the anti-diabetic medicines and the implementation of the lifestyle-medicine intervention (see *Table 4*).

The lifestyle-medicine intervention induced the alleviation of the FPG level and the VFI in the reduction of A1C

To investigate the effects of the baseline and intervention-induced change for all the parameters in the reduction of A1C level, a multiple linear regression analysis was performed using A1C change as the dependent variable, and the baseline and changes induced by the lifestyle-medicine intervention of all our parameters as predictors (see *Tables 1*,*2*). The result of the analysis suggested that one standard deviation (1-SD) decreases in the FPG level, the FPG ratio, and the VFI ratio were significantly associated with a reduction in A1C level (P=0.0000 *vs.* P=0.0000 *vs.* P=0.0046; see *Table 5*), and that the FPG change had a more powerful effect on the A1C change than the FPG change ratio, and the VFI change ratio (partial R^2=0.3072 *vs.* partial R^2=0.0880 *vs.* partial R^2=0.0724; see *Table 6*).

Table 6 Association of the change of FPG, Ratio FPG and Ratio VFI with the change of A1C

Variable entered	Partial R^2	Model R^2	F value	P value
Change_FPG	0.3072	0.4676	69.83140	0.0000
Change_Ratio FPG	0.0880		20.00770	0.0000
Change_Ratio VFI	0.0724		16.45403	0.0000

FPG, fasting plasma glucose; VFI, visceral fat index; A1C, glycated hemoglobin.

Safety and adverse events

No severe adverse events were observed in the study (see *Table 2*). No significant changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), and serum creatinine (SCr) were observed in the entire cohort, or the lean and obese groups (P>0.05). The levels of triglycerides (TGs), low-density lipoprotein-cholesterol (LDL-c), and uric acid (UA) were significantly reduced compared to the baseline values in the entire cohort and both the lean and obese groups (P<0.05), but only the UA reduction in the lean group was statistically lower than that in the obese group (P<0.001). The levels of high-density lipoprotein-cholesterol (HDL-c) and blood urea nitrogen (BUN) were significantly increased compared to the baseline values in the entire cohort and in both the lean and obese groups (P<0.05), but the differences between the lean and obese groups were not statistically significant.

Discussion

The effects of diet and physical exercise in preventing or delaying T2DM are well known (18,19). A controlled diet and sufficient exercise, which lead to weight loss, can also lead to T2DM remission in overweight/obese patients; for example, an intensive lifestyle (diet-and-exercise) intervention led to the partial remission of T2DM in overweight adults (20). However, varying diabetes remission rates after intensive weight management were reported in a Diabetes Remission Clinical Trial (DiRECT) (21). Previous studies have stated that diabetes remission principally depends on the degree of weight loss (21,22). However, another DiRECT showed that most T2DM patients experience weight regain within 2 years of their diet-induced weight loss (23,24). Thus, extreme diet-induced weight loss in most diabetes remission studies appears not to be maintained. Additionally, weight loss may not be appropriate for lean T2DM patients (with a BMI <25 kg/m^2); however, research on diabetes remission among such patients had not previously been conducted. In this study, we found that the likelihood of diabetes remission for mild T2DM patients was similar regardless of whether the patients were lean or obese. We also investigated the association between various parameters and T2DM remission after a 6-month lifestyle-medicine intervention, and found that after the lifestyle-medicine intervention, a reduced FPG level and VFI were strongly associated with decreases in A1C levels. These findings suggest that remission is achievable for both lean or obese T2DM patients and is not dependent on weight loss.

All of the patients recruited in this study had been taking various kinds of anti-diabetic drugs for >6 months before the intervention to control their blood glucose levels. The patients stopped taking anti-diabetic drugs and instead participated in our lifestyle-medicine intervention. Compared to the baseline, the patients achieved much better benefits in terms of weight, BMI, VFI, body fat percentage, FPG level, 2hPG level, HOMA-IS, and HOMA-IR in the entire cohort and in both the obese and lean groups (see *Tables 1,2*). This might be because a more reasonable and healthier personalized diet and efficient exercise were used in our lifestyle-medicine intervention than before the intervention.

In most intensive lifestyle interventions, uniform low caloric or uniform low-carbohydrate diets are applied. However, these kinds of interventions have great limitations and disadvantages when used in the clinic, as different patients with different weights or different physical activity levels require different calorie in takes and there are individual differences among different patients. In our study, a relatively low-carbohydrate diet but different calorie diets were accepted for the 1st month to control the blood glucose levels, as all the patients stopped taking anti-diabetic drugs during the intervention. Optimized diets according to the "Food Guide Pagoda for Chinese Residents" and caloric of diets according to patients' weight were adopted for the last 5 months. Additionally, in our lifestyle-medicine intervention, the individual efficient exercise for each

patient was guided by an exercise instructor.

Compared to the baseline values in the entire cohort, and both the obese and lean groups, our patients had a significantly reduced BMI, VFI, body fat percentage, FPG level, 2hPG level, A1C level, FINS, and HOMA-IR, and enhanced HOMA-IS after the 6-month intervention. The reductions in patients' body weight, BMI, VFI, body fat percentage, FINS, and HOMA-IR after the 6-month lifestyle-medicine intervention in the lean group were significantly less than those in the obese group (see *Tables 1*,*2*). However, this might be because the baseline of those parameters in the lean group were lower than those in the obese group. There were no significant differences in the baseline A1C levels and the A1C level changes between the obese and lean groups. However, only 46.81% of the patients who had been taking different kinds of anti-diabetic drugs before entry to the trial had an A1C level <6.5% (48 mmol/mol), but 60.64% of the patients achieved an A1C level <6.5% (48 mmol/mol) after the withdrawal of the anti-diabetic drugs for 6 months after the lifestyle-medicine intervention in the lean group, and 32.26% of the patients who had been taking different kinds of anti-diabetic drugs before entry to the trial had an A1C level <6.5% (48 mmol/mol), but 64.52% of the patients achieved an A1C level <6.5% after the withdrawal of the anti-diabetic drugs for 6 months and the lifestyle-medicine intervention in the obese group. Thus, the lifestyle-medicine intervention produced better results than the anti-diabetic drugs for the patients, who achieved at least a partial T2DM remission at 6 months regardless of whether they were obese or lean.

Under the Chinese Diabetes Association guidelines, an A1C level <7% (53 mmol/mol) is generally set as the control goal for T2DM. If an A1C level <7% (53 mmol/mol) is taken as a measure, after our lifestyle-medicine intervention, 84.41% of patients in the lean group and 85.54% of patients in the obese group achieved diabetes remission. The rates of diabetes remission due to our lifestyle-medicine intervention were much higher than rates reported in a DiRECT trial (21) and a recent randomized clinical trial (25). In another study, a much higher rate of diabetes remission of up to 80% was reported following weight loss and exercise, but the recruited patients in that study had all been recently diagnosed (<1 year) (5), while the patients in the present study had had diabetes for up to 22 years.

We then investigated the main contributing factors regulating A1C level. Our multiple linear regression analysis results revealed that the reduction in FPG level, the FPG ratio and the VFI ratio after our lifestyle-medicine intervention contributed mostly to the reduction of the A1C level. The present findings support, and add to previous research, that has demonstrated associations between FPG and A1C levels (26). The VFI ratio was the 3rd contributing effect for diabetes remission in our patients. This might be because normal BMI Chinese populations still exist in severe accumulation of visceral fat (27). Our regression analysis results also suggested that diabetes remission was related to but not dependent on BMI or weight loss. These findings were quite similar to and provide further support for another study's finding that diabetes prevention is achievable with even only small changes in BMI (14).

Our lifestyle-medicine intervention also had health benefits for the liver and kidneys, as indicated by improvements in a number of parameters including TG, LDL-c, HDL-c, and UA. Other benefits, which were not measured but frequently referred to orally by both lean or obese T2DM patients, included improvements in depression, quality of life, physical function, and mobility.

Most previous studies on diabetes remission have only examined diabetes remission in overweight/obese patients with a BMI ≥25 kg/m^2. This study demonstrated that 60.64–64.52% of obese or lean T2DM patients achieved diabetes remission within 6 months of commencing our lifestyle-medicine intervention. Our excellent results may have originated from the partial diabetes remission in a subset of patients with T2DM, especially those with lower A1C levels, who have only mild diabetes symptoms, and who do not yet require insulin therapy. However, lifestyle-medicine interventions could undoubtedly be used instead of anti-diabetic medicines to achieve the target goal of plasma glucose control (i.e., a FPG level <7.0 mmol/L and 2hPG level <10.0 mmol/L), and even achieve diabetes remission for some lean and obese T2DM patients in China. The limitation of this study is that there were no data about the duration time of remission, which needs to be examined in the future.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-369/coif). KL, XZ, CF, DY, SL and CF are from Guangdong Shengke Life and Health Technology Limited Company. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The research was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by board of Guangzhou Red Cross Hospital Ethics Committee (No. 2020-168-01) and informed consent was taken from all the patients.

References

1. Taylor R, Valabhji J, Aveyard P, et al. Prevention and reversal of Type 2 diabetes: highlights from a symposium at the 2019 Diabetes UK Annual Professional Conference. Diabet Med 2019;36:359-65.
2. Hallberg SJ, Gershuni VM, Hazbun TL, et al. Reversing Type 2 Diabetes: A Narrative Review of the Evidence. Nutrients 2019;11:766.
3. Lemieux I. Reversing Type 2 Diabetes: The Time for Lifestyle Medicine Has Come! Nutrients 2020;12:1974.
4. Look AHEAD Research Group; Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145-54.
5. Ades PA, Savage PD, Marney AM, et al. Remission of recently diagnosed type 2 diabetes mellitus with weight loss and exercise. J Cardiopulm Rehabil Prev 2015;35:193-7.
6. Mottalib A, Sakr M, Shehabeldin M, et al. Diabetes Remission after Nonsurgical Intensive Lifestyle Intervention in Obese Patients with Type 2 Diabetes. J Diabetes Res 2015;2015:468704.
7. Bhatt AA, Choudhari PK, Mahajan RR, et al. Effect of a Low-Calorie Diet on Restoration of Normoglycemia in Obese subjects with Type 2 Diabetes. Indian J Endocrinol Metab 2017;21:776-80.
8. Kelly T, Unwin D, Finucane F. Low-Carbohydrate Diets in the Management of Obesity and Type 2 Diabetes: A Review from Clinicians Using the Approach in Practice. Int J Environ Res Public Health 2020;17:2557.
9. Qian X, Wang H, Yang G, et al. Pioglitazone Improved Insulin Sensitivity and First Phase Insulin Secretion Among Obese and Lean People with Diabetes: A Multicenter Clamp Study. Diabetes Ther 2018;9:815-26.
10. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci 2013;1281:64-91.
11. Wang Y, Liang X, Zhou Z, et al. Prevalence and Numbers of Diabetes Patients with Elevated BMI in China: Evidence from a Nationally Representative Cross-Sectional Study. Int J Environ Res Public Health 2022;19:2989.
12. Kobayashi KM, Chan KT, Fuller-Thomson E. Diabetes among asian americans with BMI less than or equal to 23. Diabetes Metab Syndr 2018;12:169-73.
13. Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev 2006;(3):CD002968.
14. Gong Q, Zhang P, Wang J, et al. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. Lancet Diabetes Endocrinol 2019;7:452-61.
15. Nanditha A, Snehalatha C, Ram J, et al. Impact of lifestyle intervention in primary prevention of Type 2 diabetes did

not differ by baseline age and BMI among Asian-Indian people with impaired glucose tolerance. Diabet Med 2016;33:1700-4.
16. Wang SS, Lay S, Yu HN, et al. Dietary Guidelines for Chinese Residents (2016): comments and comparisons. J Zhejiang Univ Sci B 2016;17:649-56.
17. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
18. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537-44.
19. Hemmingsen B, Gimenez-Perez G, Mauricio D, et al. Diet, physical activity or both for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk of developing type 2 diabetes mellitus. Cochrane Database Syst Rev 2017;12:CD003054.
20. Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489-96.
21. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391:541-51.
22. Gómez Huelgas R. Weight and type 2 diabetes: new recommendations. Med Clin (Barc) 2016;147 Suppl 1:17-21.
23. Thom G, McIntosh A, Messow CM, et al. Weight loss-induced increase in fasting ghrelin concentration is a predictor of weight regain: Evidence from the Diabetes Remission Clinical Trial (DiRECT). Diabetes Obes Metab 2020. [Epub ahead of print].
24. Brosnahan N, Leslie W, McCombie L, et al. Brief formula low-energy-diet for relapse management during weight loss maintenance in the Diabetes Remission Clinical Trial (DiRECT). J Hum Nutr Diet 2021;34:472-9.
25. Ried-Larsen M, Johansen MY, MacDonald CS, et al. Type 2 diabetes remission 1 year after an intensive lifestyle intervention: A secondary analysis of a randomized clinical trial. Diabetes Obes Metab 2019;21:2257-66.
26. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003;26:881-5.
27. Jia WP, Lu JX, Xiang KS, et al. Prediction of abdominal visceral obesity from body mass index, waist circumference and waist-hip ratio in Chinese adults: receiver operating characteristic curves analysis. Biomed Environ Sci 2003;16:206-11.

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