Asian Journal of Surgery (2019) 42, 244–250

Available online at www.sciencedirect.com

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journal homepage: www.e-asianjournalsurgery.com

ORIGINAL ARTICLE

Study design and recruitment for a prospective controlled study of diabesity: Taiwan Diabesity Study

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Received 13 November 2017; received in revised form 27 January 2018; accepted 21 February 2018
Available online 6 April 2018

KEYWORDS
Type 2 diabetes mellitus;
Obesity;
Diabesity;
Metabolic surgery;
Bariatric surgery;
Recruitment

Summary *Background:* Strong evidence has shown that metabolic surgery is more effective than medical treatment in the treatment of type 2 diabetic patients. However, no study demonstrated a survival benefit and reduction of diabetes-related end-organ damage. Here, we describe the study design of a large prospective cohort study, the Taiwan Diabesity Study (TDS) which would compare the long-term survival rate and end-organ damage between overweight/obese type 2 diabetic patients receiving metabolic surgery and medical treatment.
Methods: Eligibility criteria include type 2 diabetic patients with duration > 6 months, body mass index (BMI) over 25 kg/m^2 and age between 20 and 67 years. Exclusion criteria are serum creatinine over 2.0 mg/dL, C-peptide below 1.0 ng/ml, recent history of cancer, and major diabetic complications. Eligible participants were recruited from six medical centers in Taiwan. The survival rate and diabetes-related end organ damage will be compared between the metabolic surgery group and medical group after follow-up for 10 years.

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https://doi.org/10.1016/j.asjsur.2018.02.007

Results: In 3 years, 1016 participants were identified from 38,751 patients. The average BMI of patients was 30.6 (±2.6) kg/m^2 and the average hemoglobin A1c was 8.2% (±1.5%) with 18% of them receiving insulin treatment. Among them, 126 patients received metabolic surgery and 890 patients received conventional medical treatment. The metabolic surgery group are younger, have a higher proportion of females, higher BMI and blood lipids as compared to the medical group.
Conclusion: The TDS recruited 1016 overweight/obese type 2 diabetic patients including 126 patients receiving metabolic surgery and 890 patients receiving medical treatment.

1. Introduction

Type 2 diabetes mellitus (T2DM), fueled by an obesity epidemic, has emerged as a major health problem worldwide.[1] Unfortunately, conventional medical management fails to provide adequate glycemic control in T2DM patients.[2] Metabolic surgery is now proposed for treating overweight/obese T2DM patients, also called patients with "diabesity".[3,4] Metabolic surgery comes from bariatric surgery, which has been shown to be an effective treatment for severe obesity and results in marked improvement of T2DM control.[5,6] Metabolic surgery focused on T2DM treatment in mild/moderate obese or overweight patients (BMI $<$ 35 kg/m^2).[7] Many studies have reported glycemic or metabolic improvements after metabolic surgery with long-term follow-up.[8–10] Several randomized trials aimed at treating obese T2DM patients have been conducted and universally showed metabolic surgery is more effective than medical treatment in glycemic control.[11–15] However, none of these studies demonstrated a survival benefit and end-organ damage such as blindness, chronic kidney disease, dialysis, and major adverse cardiovascular events because of the small case number and short in follow-up.[11–19] A long follow-up period is probably needed to demonstrate the benefits of metabolic surgery on survival and end-organ damage. Several randomized trial of bariatric surgery for severely obese patients (BMI $>$ 35 kg/m^2) suggested that bariatric surgery may reduce the complications of T2DM, such as myocardial infarction, stroke, renal failure, blindness, and mortality.[6,20–22] However, it is very difficult to perform a large scale randomized trial for metabolic surgery because of the huge cost and difficulty in recruitment.[23,24] Here we describe the study design, recruitment, and current progress of this first large multicenter prospective cohort study, the Taiwan Diabesity Study (TDS) which aims to compare the survival and end-organ damage of overweight/obese T2DM patients receiving metabolic surgery and conventional medical treatment.

2. Methods

2.1. Study design

The Taiwan Diabesity Study (TDS) is a prospective controlled observational cohort of obese patients with T2DM (diabesity). The study is conducted at six sites in Taiwan: Min-Sheng General Hospital, National Taiwan University Hospital, Jen-Ai Hospital, Chia-Yi Christian Hospital, China Medical University Hospital, Chang Gung Memorial Hospital. All sites provide metabolic surgery service and all have Diabetes Center of Excellence accreditation from the Taiwan Diabetes Association. The Criteria for sites included the ability to recruit and retain participants and strengths in diabetes management. Annual follow-up visits continuing for 10 years will be performed at the diabetes center of each site. The primary end point is the mortality rate and major end-organ damage (myocardial infarction, stroke, renal failure, amputation and blindness). The secondary end point is the glycemic control (HbA1c level), organ function (glomerular filtration rate, proteinuria, neuropathy and visual acuity), and medical costs.

Inclusion criteria were as follows:

1. Age 20-67 years, with Taiwan Citizen identification number
2. Type 2 diabetes has been treated in a diabetes center for six months
3. Body mass index (BMI) $\geqq$ 25 kg/m^2

Exclusion criteria were as follows:

1. Cancer in past five years
2. Previous bariatric surgery
3. Body mass index (BMI) $>$ 60 kg/m^2
4. Significant T2DM complications including blindness, amputation, chronic kidney disease, dialysis, major adverse cardiovascular events, and stroke
5. Patients with diabetic retinopathy with visual acuity $<$0.1.
6. Patients with kidney disease (serum creatinine $>$ 2 mg/dL)
7. Patient who refuses

2.2. Patient recruitment

All sites had institutional review board (IRB) approval for the study. Informed consent was obtained from all participants included in the study. The TDS is registered in the National Institutes of Health of the United States as NCT02166372. All information about the choice of medical and surgical treatment was equally provided to each

patient. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Since the data regarding the survival rate and diabetes-related end-organ damage in overweight/obese type 2 diabetic patients is lacking, it is difficult to estimate the accurate sample size required. Sample size was determined empirically based on prior related studies.[11,15,25] In three previous randomized clinical trials comparing the outcome of obese patients receiving medical control and bariatric surgery, the sample size for medical and surgical arm is 60 vs. 60[11], 39 vs. 96[15] and 20 vs. 40.[25] In our study, the sample size for each arm is 890 vs. 128, which outnumber the size of all previous trials.

2.3. Data collection and analysis

Data were collected at baseline with annual medical visit for 10 years. Collected data included height, weight, blood pressure, pulse rate, medical and surgical history, medication, alcohol, betel nut chewing and smoking. Each patient received standardized ophthalmic examinations including visual acuity and fundus examination and peripheral neurological examination including inspection, fork vibration test, and 10 g monofilament tests. Laboratory measurements collected included serum HbA1c, fasting lipid profile, complete blood count, fasting C-peptide, creatinine levels, dipstick urine protein test and urine microalbumin to creatinine ratio.

The primary outcome is mortality and end-organ damage, including myocardial infarction, stroke, renal failure and blindness. We established the longitudinal medical history of each patient by linking several computerized administrative, claims datasets and National Death Registry through the civil identification number unique to each beneficiary and date of birth.

Taiwan National Health Insurance Research Database (NHIRD) includes complete outpatient visits, hospital admissions, pharmacy prescriptions, disease, and vital status for 99% of the 23 million population of Taiwan.[26] We could establish the longitudinal medical history of each beneficiary because the Taiwan government has a computer file for all deaths of citizens, which is coded from each death certificate. Through linking the specific Taiwan citizen identification number of each participant with this computerized file, we could obtain overall mortality with 100% follow-up.[27] The data of major organ damage and medical costs can be traced from the NHIRD of Taiwan. The reimbursement claim records of the National Health Insurance consisted hospital admission, outpatient visit, laboratory tests, and pharmacy prescription. The medical costs will be derived from these claims data.[27,28] The patients will be divided into two groups. For those who received metabolic surgery including sleeve gastrectomy and gastric bypass surgery will be identified and classified as the surgery group. Those who did not receive metabolic surgery will be classified as the conventional medical treatment group.

All statistical analysis are performed using SPSS version 19.0.0 (SPSS Inc., Chicago, IL., USA). For comparison of baseline characteristics, categorical variables are compared with Chi-square tests and continuous variable are compared using t test of independent samples. Continuous variables are expressed mean $\pm$ standard deviation.

3. Results

3.1. Participant characteristics

Recruitment of TDS started at March 2014 and ended at February 2017 when 1016 patients were recruited. The screening flow is depicted in Fig. 1. Of the 38,751 T2DM patients screened, 37,220 subjects excluded due to age, BMI, significant diabetic complications, and DM duration. Of the remaining 1531 (4.0%) candidates that pass first screening, 231 patients have inadequate beta-cell function (fasting C peptide $<$ 1 ng/ml), 133 patients show a change of BMI $<$ 25 kg/m^2, 47 patients have recent history of cancers, 14 patients have diabetic retinopaty with visual acuity $<$0.1, 3 patients have serum creatinine$>$ 2.0 mg/dL, and 93 patients refuse to join this study. After excluding of these 515 patients, a total of 1016 (2.6%) eligible patients were recruited. Among them, 126 patients received metabolic surgery.

The distribution of patients recruited from the six sites is: 500 patients from Min-Sheng General Hospital, 108 from National Taiwan University Hospital, 46 from Jen-Ai Hospital, 155 from Chia-Yi Christian Hospital, 70 from China Medical University Hospital, and 46 from Chang Gung Memorial Hospital.

The patient characteristics at baseline are summarized in Table 1. Participants had average diabetes duration of 6.2 $\pm$ 5.0 years at enrollment. Mean BMI was 30.6 $\pm$ 4.6 kg/m^2 and 548 patients (54%) had a BMI of less than 30 kg/m^2 Mean age was 49.5 $\pm$ 10.0 years with mean HbA1c level of 8.2 $\pm$ 1.5%. All patients were on oral anti-glycemic medication and 18% of patients required insulin treatment at baseline. Additionally, 561 patients (51%) received lipid-lowering treatment and 40% were on antihypertensive medications. At recruitment, 176 patients (17%) had diabetic peripheral neuropathy; 119 patients (11.7%) have foot deformities, 72 (7.1%) patients have charcot arthropathy, 17 patients (1.7%) have positive 128-Hz fork vibration test, 10 patients (9.8%) have positive 10-g monofilament test, and 2 patients (0.2%) have foot ulcer. Among 942 patients who completed ophthalmic examination, 102 patients (10.8%) had retinopathy with 80 (7.9%) having non-proliferative diabetic retinopathy and 22 patients (2.8%) having proliferative diabetic retinopathy.

3.2. Comparison of surgical group and medical group

The comparison of patient characteristics between the metabolic surgical group and the conventional medical treatment group are summarized in Table 2. Patients in the metabolic surgery group are significantly younger (age: 43.5 $\pm$ 10.6 vs. 50.3 $\pm$ 9.7 year, $p < 0.001$), have a higher proportion of females (58.6% vs. 37.9%, $p < 0.001$), have higher BMI (35.8 $\pm$ 6.1 vs. 29.8 $\pm$ 3.8 kg/m^2, $p < 0.001$) and waist circumference (110.5 $\pm$ 13.8 vs. 98.9 $\pm$ 9.2 cm,

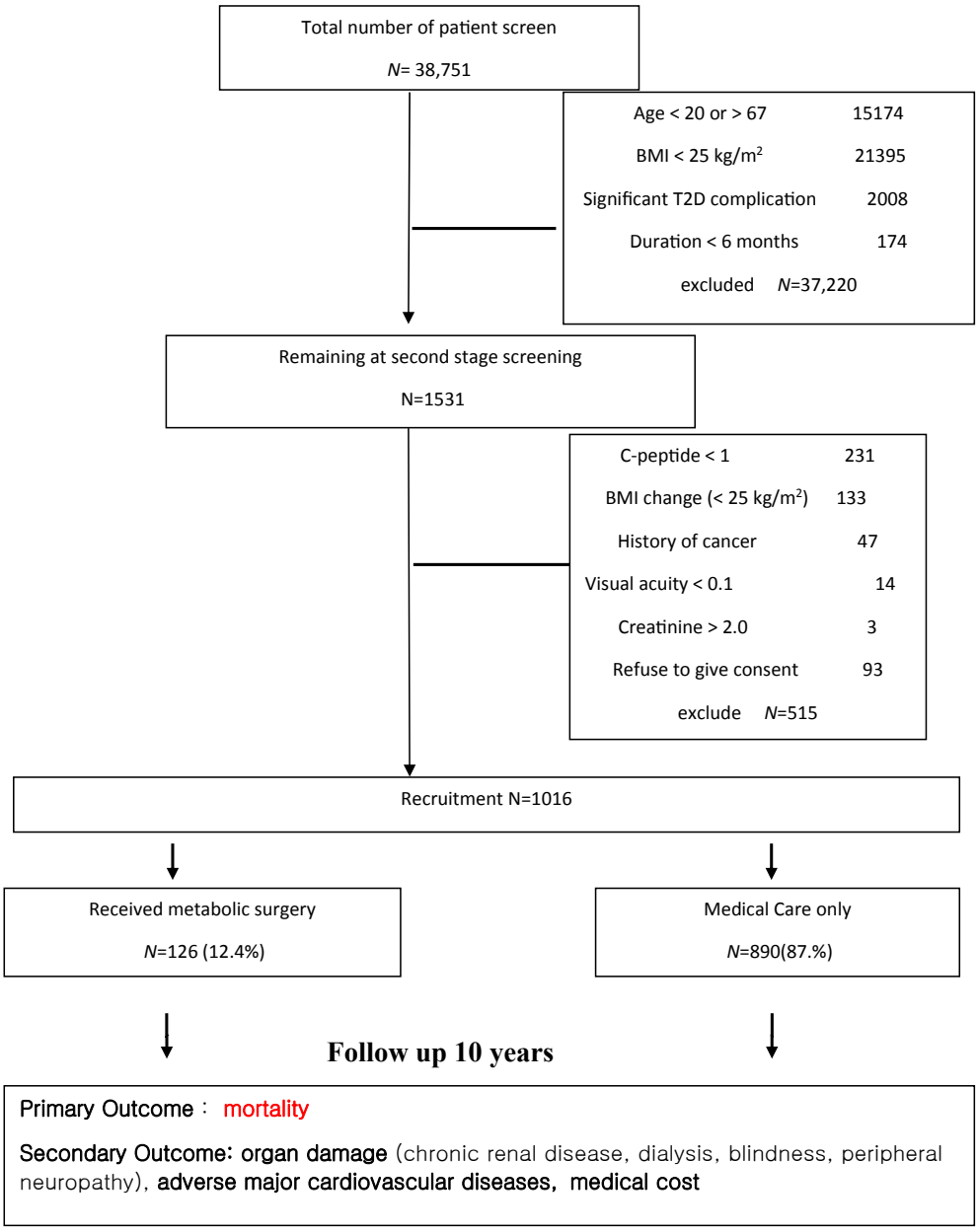

Figure 1 Flow diagram of the study.

$p < 0.001$), have shorter duration of diabetes (4.8 ± 4.5 vs. 6.5 ± 5.0 years, $p < 0.001$), higher hemoglobin A1c (8.5% ± 1.6 vs. 8.1% ± 1.5%, $p = 0.018$), higher low-density lipoprotein (LDL) cholesterol (107.8 ± 31.3 vs. 98.7 ± 27.5 mg/dL, $p = 0.002$) and higher triglyceride (246 ± 242.4 vs. 176.3 ± 130.4 mg/dL, $p = 0.002$) than the medical group. Patient distribution in different age and BMI category is shown in Table 3. The mean follow-up time is 16.8 (range: 3–36) months and 18.0 (range: 4–36) months for the surgical and the medical groups respectively.

4. Discussion

Here we described the design and recruitment of the first large, multicenter, prospective controlled trial specifically to investigate the mortality and morbidity rates among overweight/obese T2DM (diabesity) patients who received metabolic surgery as compared with conventional treatment. Although not a randomized trial, the recruitment process took three years to complete and was more challenging than expected. A total of 38,751 T2DM patients were screened but only 1531 (4%) eligible patients could be selected for further screen. The major hurdles for recruitment were the desired age and BMI. T2DM is usually a disease of old age. In Taiwan, more than half of the T2DM patients aged 60 or above, which excluded about half of the patients screened. Since metabolic surgery aims at better glycemic control to prevent long-term diabetic complication, it may not be worth initiating in elderly T2DM patients and limits the application of metabolic surgery. In addition, a recent study showed that metabolic surgery may have a more important role in young-onset T2DM patients than in

Table 1 Baseline Data of 1016 participants.

Variables	Mean (SD)	Range	Abnormal N (%)	Abnormal reference
Age (year)	49.5 (10.0)	20–67		
Sex (M/F)	606/412			
BMI (kg/m^2)	30.6 (4.6)	25–60		
HbA1C (%)	8.2 (1.5)	5.1–13.9	978 (96.1%)	>6.0%
			750 (73.7%)	>7.0%
Fasting Glucose (mg/dl)	160.1 (53.5)	68–380	720 (70.8%)	>126
			566 (55.6%)	>140
LDL-C (mg/dl)	99.7 (28.2)	37–228	137 (13.6%)	>130
HDL-C (mg/dl)	42.6 (18.8)	20–551	436 (43.6%)	<40
Total cholesterol (mg/dl)	170.2 (36.1)	97–405	177 (17.7%)	>200
Triglycerides (mg/dl)	184.3 (150.0)	12–1997	462 (46.2%)	>150
Creatinine (mg/dl)	0.9 (0.3)	0.32–1.9	45 (4.4%)	>1.3
microalbumin/creatinine ratio (mg/g)	156.1 (789.8)	0.3–19892.1	375 (37.5%)	>25
Hemoglobin (g/dl)	M 15.0 (1.2)	M 10.1–18.0	29 (2.9%)	<13
	F 13.1 (1.3)	F 7.5–17.4	39 (3.8%)	<11.5
C-peptide (ng/dl)	2.9 (1.6)	0.8–15.4	71 (7.0%)	>5.2

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; M: male; F: female.

Table 2 Comparison of Medical group and Surgical group.

Number	Medical group n = 890	Surgical group n = 126	P
Variable	Mean (SD)	Mean (SD)	
Age (year)	50.3 (9.7)	43.6 (10.6)	<0.001*
Gender (male/female)	553/337	53/75	<0.001*
BMI (kg/m^2)	29.8 (3.8)	35.8 (6.1)	<0.001*
Waist circumference (cm)	98.9 (9.2)	110.5 (13.8)	<0.001*
Duration (year)	6.5 (5.0)	4.8 (4.5)	<0.001*
SBP (mmHg)	131.8 (14.6)	134.2 (13.1)	0.082
DBP (mmHg)	81.9 (10.5)	81.7 (9.4)	0.889
HbA1c (%)	8.1 (1.5)	8.5 (1.6)	0.018*
Fasting glucose (mg/dL)	158.4 (50.6)	170.4 (68.3)	0.063
LDL-C (mg/dL)	98.7 (27.5)	107.8 (31.3)	0.002*
HDL-C (mg/dL)	42.8 (19.6)	41.4 (9.3)	0.441
Triglyceride (mg/dL)	176.3 (130.4)	246 (242.4)	0.002*
Creatinine (mg/dL)	0.834 (0.26)	0.84 (0.24)	0.908
Urine albumin creatinine ratio (mg/g)	134.5 (497.4)	215.4 (928.2)	0.139
eGFR (1.73 ml/min/1.73 m^2)	100.6 (30.7)	95.4 (20.5)	0.066
Use of insulin	157 (17.6%)	20 (15.6%)	0.574

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.
* $p < 0.05$.

an adult-onset group.[29] Therefore, additional recruitment of younger patients in the medical arm and elderly patients for metabolic surgery will be conducted.

BMI is the second major hurdle for metabolic surgery. Recently, the Diabetes Surgery Summit II (DSS-II) and International Diabetes Federation (IDF) joint consensus for metabolic surgery was lowered to BMI of 27.5 kg/m^2 for Asians.[2–4] However, a BMI cutoff point of 25 kg/m^2 for obesity was proposed for Asians by the World Health Organization (WHO) because Asian people tend to have visceral adiposity with a high prevalence of diabetes and hypertension at a very modest increase in BMI.[30] The median BMI of patients with T2DM in Asian is approximately 24 kg/m^2 which is different from median BMI of 30 kg/m^2 in the Western population.[31] Previous studies showed that the risk of T2DM increase to 2.2 fold in men and 8.1 fold in women for those with BMI> 25 kg/m^2 in comparison to those with BMI <23 kg/m^2.[32,33] Studies clearly demonstrate significant improvement in fasting glucose and HbA1c and a decrease in the need for anti-diabetic agents with only about 5% weight loss in overweight and obese T2DM patients.[34,35]

The DSS-II/IDF joint consensus also pointed out the number of patients with BMI <35 kg/m^2 studied in RCTs is modest, and there are even fewer patients with BMI <30 kg/m^2,[3] which is a knowledge gap. Therefore, here we thought to explore whether a lower BMI> 25 kg/m^2, which

Table 3 Patient distribution in different age and BMI categories.

Number	Medical group n = 890	Surgical group n = 126	P
Variable	Number (%)	Number (%)	
Age (year)			<0.001*
20–29	35 (4.0%)	13 (10.3%)	
30–39	112 (12.6%)	38 (30.2%)	
40–49	211 (23.8%)	30 (23.8%)	
50–59	385 (43.3%)	38 (28.6%)	
60–67	147 (16.5%)	9 (7.1%)	
BMI (kg/m^2)			<0.001*
25–27.4	282 (31.6%)	6 (4.8%)	
27.5–29.9	250 (28.0%)	16 (12.7%)	
30.0–32.4	176 (19.7%)	15 (11.9%)	
32.5–39.9	162 (18.2%)	61 (46.8%)	
>40	22 (2.5%)	30 (23.8%)	

BMI: body mass index.
* $p < 0.05$.

is also the indication for metabolic surgery in China,[36] could still result in better outcome than conventional medical control. However, this indication can only cover ~38% of all T2DM patients.[31]

In this study, less than 5% of the all screened T2DM patients were candidates for metabolic surgery and only 11.4% of these candidates received surgery, much lower than the previous estimation.[37] However, in one population-based randomized trial comparing bariatric surgery and medical treatment of T2DM recruited only 2.4% of the screened patients.[24] In another randomized trial comparing metabolic surgery with medical treatment for T2DM, only 4.5% of the total screened candidates could be recruited over a period of 4 years, which corresponds with our results.[12] Female patients with younger age and more severe disease stage are more likely to receive surgical treatment of their disease, which is similar to the findings of another population-based randomized trial.[24] The reasons patients do not want metabolic surgery included the fear of the surgical invasiveness, lack of confidence in its efficacy, and concern about its cost. Although all the patients had medical coverage in the Taiwan national health program, a metabolic surgery required about 5000 U.S. dollars in co-payment in Taiwan. How to increase the acceptance of and access to metabolic surgery remains a challenge.

The strengths of design of this study include its large sample size, multiple recruitment sites, concrete end points, the robust follow-up data by linking to the national registry system, and the long follow-up duration of 10 years. In the landmark Swedish obese subjects by Sjostrom L, et al the cumulative mortality rate between the bariatric surgery arm and medical arm started to separate after 6–8 years of follow-up.[6] Therefore, a long follow-up is probably required for this present study to demonstrate the effect of metabolic surgery on mortality and end organ damage. The weaknesses of this study include the non-randomized design, significantly different baseline characteristics, and difficulties in standardization among multiple centers including surgical technique, care standards, and ophthalmological/neurological examinations. However, it is currently almost impossible to perform a large scale randomized trial involving surgical treatment after considering the ethic issue, cost and difficulty in recruitment. The significantly different patient's characters between surgical arm and medical arm can be overcome by selecting a matched group from the medical arm for comparison, multiple regression model adjusted for baseline covariates, or adjustment for propensity score in the future. Furthermore, add-on recruitment of younger patients in the medical arm and elder patients for metabolic surgery will be required to increase the power and validity of this study.

5. Conclusion

Over a 3-year period, the TDS successfully recruited 1016 overweight/obese T2DM patients for long-term study of diabesity. Less than 4% of the screened T2DM patients were eligible for the study. Among the recruited candidate, 12.4% received metabolic surgery after recruitment while the other received conventional medical treatment.

Conflict of interest statement

All authors have no financial or non-financial interests that may be relevant to the submitted work.

Acknowledgments

The authors would like to acknowledge the contributions of the following individuals in the conduct of this study: The TDS Study Team: Yi Shan Huang, Shu Chun Chen, Chung Keong, Ming-Sheng General Hospital; Tzu-Ying Yen, Jen-Ai Hospital; Meng-Lun Hsieh, National Taiwan University Hospital; Hsiang-Hsun Chuang, Chia-Yi Christian Hospital. This study was supported by the Taiwan Society of Metabolic and Bariatric Surgery and no author received financial support.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.02.007.

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