ORIGINAL ARTICLE

Non-Achievement of Clinical Targets in Patients With Type 2 Diabetes Mellitus

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Summary

The study was conducted to determine whether the clinical targets for the control of diabetes recommended by American Diabetes Association can be met in the context of routine diabetes practice.

This cross-sectional study was undertaken on 211 type 2 diabetic patients at the Outpatients Diabetes Clinic, Hospital Universisti Sains Malaysia (HUSM) Kubang Kerian, Kelantan between the year 2001 – 2002. Patients' physical examination and their medical history as well as their family history were obtained by administering a structured questionnaire. Samples of patients' venous blood during fasting were taken and analysed for plasma glucose, glycated haemoglobin and lipid profile.

Analysis showed that many patients had comorbidities or complications. A large number of them had poor glycaemic control (73%). Systolic and diastolic blood pressures of 75% and 85% subjects were ≥ 130 and ≥ 80 mmHg, respectively. Body Mass Index (BMI) values of 66% of the patients were outside the clinical target (BMI ≥ 25 in male and ≥ 24 kg/m^2 in female). The lipid profile showed that 96% of the patients had at least one lipid value outside the clinical target level. In this study, 70% of the patients had total cholesterol ≥ 5.2 mmol/L, 87% had LDL cholesterol ≥ 2.6 mmol/L, 57% had HDL cholesterol less than the normal range, ≤ 1.15 mmol/L in men and ≤ 1.4 mmol/L in women, while 46% had triglycerides ≥ 1.71 mmol/L. Complications of diabetes were observed in 48% of the total number of patients. As for the patients' systolic blood pressure, age and duration of diabetes were found to have significant effects. Older subjects with a longer duration of diabetes were more hypertensive. Variables that had significant effects on BMI were age, duration of diabetes, glycaemic control and gender. Younger females and newly diagnosed subjects with better glycaemic control (A1C < 7%) were found to have higher BMI values.

The overall clinical targets were suboptimal. The prevalence of hyperlipidaemia and hypertension was high. It is imperative that better treatment strategies and methods be adopted to enhance diabetes control and reduce long-term complications of the disease.

Key Words: Type 2 Diabetes, Hypertension, Dyslipidaemia, Body Mass Index

Introduction

People with diabetes are vulnerable to a variety of complications over time. The most common complications of diabetes are vascular complications. These can be divided into microvascular and macrovascular complications. Cardiovascular disease is the leading cause of mortality in people with diabetes[1,2]

This article was accepted: 5 August 2003

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and is 2 – 4 times more common in people with diabetes than in those without diabetes[3].

Diabetic retinopathy is a major cause of blindness in diabetic patients. After 20 years of diabetes diagnosis all patients with type 1 and > 60% of patients with type 2 diabetes have some degree of retinopathy. Hyperglycaemia (poor glycaemic control), duration of diabetes, presence of nephropathy, hypertension and dyslipidaemia increase the risk of retinopathy[4-6]. Diabetic nephropathy is the single leading cause of end-stage renal disease (ESRD) and it is a major cause of mortality in diabetic patients. Diabetic nephropathy is present in 20 – 40% of diabetic patients[2, 7, 8]. Nearly 70% of people with diabetes experience some degree of nerve damage or neuropathy. Peripheral neuropathy is the most common form and will develop in up to 60% of type 2 diabetic patients over a 15 year period [9]. Ulcers of the legs and feet occur in most people with diabetes due to the combination of neuropathy and peripheral vascular disease[10]. Autonomic neuropathy involves the nerve supply to small blood vessels and sweat glands of the skin, the stomach, the bowels, the bladder, the heart, and the nervous system[11].

Duration of diabetes and hyperglycaemia are the most important risk factors of diabetic complications. Other risk factors for complications of diabetes are dyslipidaemia, hypertension, obesity, smoking, and lack of exercise. Prevalence of traditional risk factors (hypertension, dyslipidaemia, obesity) is higher in diabetic patients than non-diabetic people[12,13]. Hypertension is an independent risk factor for cardiovascular, cerebral, renal, and peripheral atherosclerotic vascular disease[2,14,15]. Hypertensive diabetic patients have two times higher risk of cardiovascular disease than non-diabetic hypertensive patients[16, 17]. Approximately 20 – 60% of patients with diabetes are hypertensive, depending on age, ethnicity, and obesity[16-18]. According to one of the UKPDS[19] studies 50% of newly diagnosed type 2 diabetic patients will be hypertensive and have an increased risk of cardiovascular mortality and morbidity.

In an attempt to reduce the complications of diabetes mellitus, various diabetes organizations have produced guidelines in the management of this condition. All these guidelines are similar in nearly all aspects and one of the most frequently quoted guideline is that of the American Diabetes Association[2].

The aim of this study is to determine whether the clinical targets for the control of diabetes as recommended by American Diabetes Association are met in a normal diabetes clinic.

Materials and Methods

Type 2 diabetic patients were selected for study from among patients attending the Outpatient Diabetes Clinic, Hospital Universiti Sains Malaysia (HUSM). The inclusion criteria were male and non-pregnant female type 2 diabetic patients aged 18 years or above. The exclusion criteria were type 1 diabetes, patients with cardiac, renal or liver failure or cancer or patients on steroid therapy. Patients fulfilling these criteria were invited to enroll for the study. The patients were asked to come to the clinic between 8 and 9 a.m. after overnight (12 hours) fast. After history taking and physical examination, 10ml venous blood was taken. 2.5ml blood was aliquoted into a tube containing potassium ethylene diamine tetrachloroacetic acid (EDTA) for determining glycated hemoglobin level. Another 2.5ml blood was aliquoted into a tube containing sodium oxalate for determining fasting plasma glucose. The remaining 5ml of blood was aliquoted into a plain tube for determining lipid profile (total, HDL cholesterol, and triglycerides). The sample was allowed to clot and then centrifuged for 3 minutes at 4000 rpm. Serum was separated and analyzed for lipid profile.

The height and body weight of each subject were measured using the SECA weighing balance with height attachment to the nearest decimal point with shoes and outer garments removed. Body weight status was estimated by the body mass index (BMI) computed in metric units as weight (kg)/height^2 (m^2). Blood pressure was measured on the right arm after 5 – 10 minutes rest in the sitting position using a standard mercury sphygmomanometer. At least two readings of blood pressure were taken from each patient and the latter reading was used for statistical analysis. In each measurement blood pressure was read to the nearest 10 mm Hg.

The concentration of plasma glucose was determined by automated enzymatic GOD-PAP method using commercial kits (RANDOX) on Hitachi 912 autoanalyzer. All samples were determined for glycated hemoglobin concentration using the DiaSTAT hemoglobin A1c programme on the Bio-Rad DiaSTAT analyzer. Standard procedures recommended by DiaSTAT hemoglobin A_{1c} programme for analyzing A1C were followed. Serum total cholesterol concentration

was determined by automated enzymatic CHOD-PAP method using commercial kits (Roche) on Hitachi 912 autoanalyzer. Serum HDL cholesterol was measured by precipitation method (HDL cholesterol precipitant, Roche). HDL cholesterol was quantitated by analyzing the supernatant obtained following precipitation of plasma aliquot with phosphotungstic acid and Mg^{2+} ions. The LDL cholesterol concentration was calculated for each sample according to the Friedewald formula [LDL cholesterol (mmol/L) = Total cholesterol – (Triglycerides/2.2 + HDL Cholesterol)]. Serum triglycerides concentration was determined by automated enzymatic GPO- PAP method using commercial kits (Roche) on Hitachi 912 autoanalyzer.

Statistical analysis

Statistical Package for Social Sciences (SPSS) statistical software (version 10.0, SPSS) was used for the analysis of biochemical and personal data in this study. The normality of each variable was tested by histogram and box plot and finally confirmed by Kolmogrov-Smirnov test. Association with baseline continuous variable was assessed with Pearson's correlation coefficients, and it was confirmed by linear regression. The association between a pair of binary variable was examined by Chi-square (χ^2) analysis. To analyze the difference between group means, Student t-test for two groups (two independent means) was used for variable with normal distribution. Mann Whitney test was used for variable with non normal distribution. One-way ANOVA test was used to analyze differences between groups (more than two means). For group comparisons Bonferroni's method was used. Level of significance (α) was set at 0.05 and P value < 0.05 was accepted as significant.

Results

Altogether 500 type 2 diabetic patients who were on treatment for diabetes and complications at the Outpatient Diabetes Clinic in HUSM Kubang Kerian between 2001 – 2002 fulfilled the criteria for the study of whom 211 patients agreed to participate in the study. The study group contained 101 (48%) males and 110 (52%) females. Among these subjects, 178 (84%) were Malays, 30 (14%) were Chinese and 3 (2%) were Indians. Out of 211 type 2 diabetic patients, 31 (15%) were current smokers and 180 (85%) were non-smokers. Only 62 (29%) had a positive family history of diabetes mellitus. Basic characteristics of type 2 diabetic patients are listed in Table I.

Out of 211 type 2 diabetic patients, 101 (48%) patients had complications of diabetes. Numbers and percentages of patients with microvascular (retinopathy, neuropathy and nephropathy) macrovascular (ischaemic heart diseases, cerebrovascular accident and peripheral vascular diseases) and microvascular + macrovascular complications of diabetes are listed in Table II. Eye complications, neuropathy, ischaemic heart diseases, foot ulcer, skin problems, and cerebrovascular accident were observed in 65 (31%), 43 (20%), 20 (10%), 14 (7%), 9 (4%), and 3 (2%) patients, respectively. Distribution of patients with one, two, three, or four complications are listed in Table III. The types of eye complications are shown in Figure 1.

Clinical targets for glycaemic control in type 2 diabetes

The specific targets for metabolic control in patients with type 2 diabetes include: A fasting (preprandial) plasma glucose level between 5 – 7.21 mmol/L (90 –130 mg/dl) and a glycated hemoglobin (A1C) level of < 7%[2]. Fasting Plasma Glucose (FPG) and Glycated Hemoglobin (A1C) levels outside of target level were observed in 127 (60%) and 153 (72%) of type 2 diabetic patients, respectively.

Clinical targets for lipids in type 2 diabetes

The ADA guidelines recommend an LDL cholesterol level of < 2.6 mmol/L (100 mg/dl), a triglyceride level of < 1.71 mmol/L (150 mg/dl), and an HDL cholesterol level of 1.15 mmol/L (45 mg/dl) in men and 1.4 mmol/L (55 mg/dl) in women as clinical targets[2]. For total cholesterol the clinical target was defined as < 5.2 mmol/L according to National Cholesterol Education Programme[20]. Out of 211 type 2 diabetic patients the lipid (total, HDL, LDL cholesterol and triglycerides) of 203 (96%) patients were outside of clinical target level. There were 148 (70%) patients with total cholesterol value outside of clinical target level. HDL cholesterol outside of clinical target level were observed in 121 (57%) patients (47 [22%] male and 74 [35%] female), respectively. There were 20 (10%) and 184 (87%) patients with LDL cholesterol value at clinical target and outside of clinical target level, respectively. LDL cholesterol was not calculated for 7 (3%) patients because of high TG level (TG > 4.5 mmol/L). Triglycerides at clinical target level was observed in 115 (54%) patients. There were 96 (46%) patients with triglycerides value outside of clinical target level.

Clinical targets for BMI in type 2 diabetes

Patients with type 2 diabetes should attempt to achieve a body mass index < 25 kg/m^2 in men and < 24 kg/m^2

in women[2]. BMI value above target level was observed in 140 (66%) of patients. The variables with significant effects on BMI were gender, age and duration of diabetes mellitus in univariate analysis (correlation, difference in mean, and/or in proportion). Chi-square (χ^2) test was performed to examine sex influences on the probability of having BMI values that were outside of recommended clinical target. The number of female subjects who had BMI values at clinical target and outside of clinical target were 30 (14%) and 80 (38%) and of male subjects were 41 (19%) and 60 (29%), respectively. Women had significantly greater probability of having BMI values outside of clinical target compared with men (P = 0.041, χ^2 test, sex comparison). Linear regression analysis showed significant negative correlation of BMI with age and duration of diabetes (degree of correlation = - 0.188 and - 0.163, and P = 0.006 and P = 0.018, respectively). Multiple logistic regression analyses were performed to evaluate further the association of baseline risk factors with BMI. The variables with significant effects on BMI were age (P = 0.008) and A1C (P = 0.006).

Clinical targets for blood pressure in type 2 diabetes

The blood pressure goal for patients with type 2 diabetes who are 18 years or older is < 130/80 mm Hg[16, 17]. Out of 211 patients, the blood pressure of 195 (92%) patients were outside of clinical target level (BP ≥ 130/80 mm Hg). Systolic blood pressure 159 (75%) patients were outside of clinical target level. Diastolic blood pressure outside of clinical target level was observed in 179 (85%) patients. The variables with significant effects on systolic blood pressure were age, and duration of the diabetes mellitus in univariate analysis (correlation, difference in mean, and/or in proportion). Linear regression analysis showed positively significant correlation of systolic blood pressure with the age of patients (degree of correlation = 0.319 and P < 0.005) but there was no correlation between diastolic blood pressure and the age of patients (degree of correlation = - 0.085 and P = 0.219). Figure 2 shows the systolic blood pressure at clinical target and outside clinical target level in the patients grouped according to duration of diabetes. Percentages of patients with systolic blood pressure outside of clinical target level were higher than patients with systolic blood pressure at clinical target level in all four groups. There was statistically significant association of having systolic blood pressure outside of clinical target level with the duration of diabetes (P = 0.001). Multiple logistic regression analyses were performed to evaluate further the association of baseline risk factors with systolic blood pressure. The variables with significant effects on systolic blood pressure were duration of the diabetes mellitus (P = 0.000) and age (P = 0.023).

Distribution of type 2 diabetic patients with one, two, three, four or all five (blood pressure ≥ 130/80 mm Hg, Body Mass Index ≥ 25 kg/m^2 for male and ≥ 24 kg/m^2 for female, hyperglycaemia, dyslipidaemia, and complication of diabetes) medical problems are listed in Table IV.

Table I: Basic characteristics, fasting plasma glucose, glycated hemoglobin and lipid profile of type 2 diabetic patients

Parameter	Mean ± SD	Median	Mode	Range	Min	Max	N
Age (years)	53.65 ± 9.53	54	52	58	19	77	211
Duration of diabetes (years)	9.27 ± 6.05	9	10	35	1	36	211
SBP (mm Hg)	138.34 ±18.50	140	130	100	90	190	211
DBP (mm Hg)	84.16 ± 9.64	80	80	50	60	110	211
BMI (kg/m^2)	26.55 ± 4.45	26.22	24.97	30.34	13.94	44.27	211
FPG (mmol/L)	9.25 ± 4.08	8.2	6.4	21.4	2.8	24.2	211
A1C (%)	8.53 ± 2.26	8.3	6.8	16.2	4.0	20.2	211
TC (mmol/L)	5.87 ± 1.22	5.75	6.7	9.05	2.79	11.84	211
HDLC (mmol/L)	1.26 ± 0.39	1.21	1.13	3.01	0.01	3.02	211
LDLC (mmol/L)	3.79 ± 1.09	3.68	2.72	7.58	1.37	8.95	204*
TG (mmol/L)	1.91 ± 1.20	1.62	0.69	7.93	0.50	8.43	211

FPG: Fasting plasma glucose, A1C: glycated hemoglobin, TC: total cholesterol, HDLC: high density lipoprotein cholesterol, LDLC: low density lipoprotein cholesterol, TG: triglycerides, Min: minimum, Max: maximum, SBP: systolic blood pressure, DBP: diastolic blood pressure, N: number of patients.

*LDL cholesterol was not calculated for 7 patients because of TG exceeded > 4.5 mmol/L

Table II: Distribution of patients with microvascular, macrovascular, and microvascular + macrovascular complications of diabetes

	Complications	No. of patients	Percentage
Complicated type 2 diabetic patients	Microvascular	73	34.6
	Macrovascular	17	8.1
	Microvascular and Macrovascular	11	5.2
	Sub total	101	47.9
Uncomplicated type 2 diabetic patients		110	52.1
Total		**211**	**100**

Table III: Distribution of type 2 diabetic patients with one, two, three, or four complications

No. of complications	Type of complications	No. of patients	Percentage
One complication	Eye complications	34	16.1
N = 65 (30.8 %)	Neuropathy	13	6.2
	IHD	11	5.2
	Foot ulcer	5	2.4
	Dermopathy	1	0.5
	CVA	1	0.5
Two complications	Eye complications + Neuropathy	12	5.7
N = 23 (10.9 %)	Eye complications + IHD	5	2.4
	Neuropathy + IHD	2	0.9
	Neuropathy + Foot ulcer	1	0.5
	Neuropathy + Dermopathy	1	0.5
	Neuropathy + CVA	1	0.5
	Eye complications + CVA	1	0.5
Three complications	Eye complications + Neuropathy + Foot ulcer	5	2.4
N = 9 (4.3 %)	Eye complications + Neuropathy + Dermopathy	3	1.4
	Eye complications + Neuropathy + IHD	1	0.5
Four complications	Eye complications + Neuropathy + Dermopathy + Foot ulcer	3	1.4
N = 4 (1.9 %)	Eye complications + Neuropathy + Dermopathy + IHD	1	0.5
Uncomplicated		110	52.1
Total		**211**	**100**

Table IV: Clinical summary of type 2 diabetic patients

Diagnosis and diabetic complication		No. of patients	Percentage
1 Criterion	Hypertension	1	(0.47 %)
N = 2 (0.95 %)	Dyslipidaemia	1	(0.47 %)
2 Criteria	Hypertension + Obesity	2	(0.95 %)
N =19 (9.00 %)	Hypertension + Dyslipidaemia	8	(3.79 %)
	Hypertension + Complication	1	(0.47 %)
	Dyslipidaemia + Obesity	5	(2.37 %)
	Hypertension + Hyperglycaemia	1	(0.47 %)
	Dyslipidaemia + Hyperglycaemia	2	(0.95 %)
3 Criteria	Hypertension + Obesity + Hyperglycaemia	1	(0.47 %)
N = 54 (25.59 %)	Hypertension + Dyslipidaemia + Hyperglycaemia	18	(8.53 %)
	Dyslipidaemia + Obesity + Hyperglycaemia	4	(1.90 %)
	Dyslipidaemia + Complication + Hyperglycaemia	3	(1.42 %)
	Hypertension + Dyslipidaemia + Obesity	18	(8.53 %)
	Hypertension + Obesity + Complication	2	(0.95 %)
	Hypertension + Dyslipidaemia + Complication	8	(3.79 %)
4 Criteria	Hypertension + Dyslipidaemia + Complication + Hyperglycaemia	28	(13.27 %)
N = 90 (42.65 %)	Hypertension + Dyslipidaemia + Obesity + Complication	12	(5.69 %)
	Hypertension + Dyslipidaemia + Obesity + Hyperglycaemia	49	(23.22 %)
	Dyslipidaemia + Obesity + Complication + Hyperglycaemia	1	(0.47 %)
5 Criteria	Hypertension + Dyslipidaemia + Obesity		
N = 46 (21.80%)	+ Complication + Hyperglycaemia	46	(21.80 %)
Total		**211**	**(100 %)**

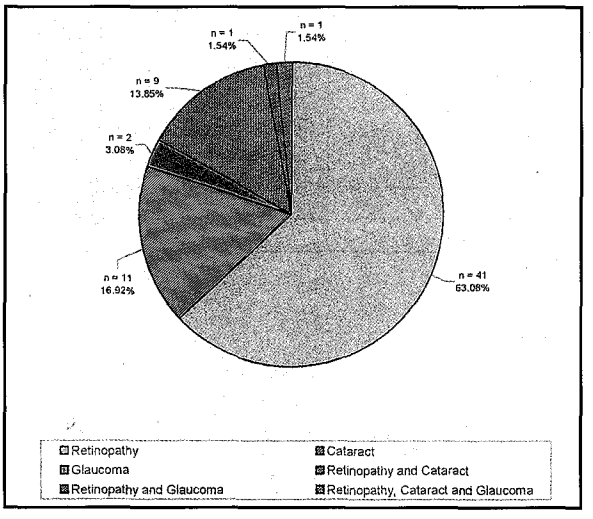

Fig. 1 : Type of eye complications in type 2 diabetic patients

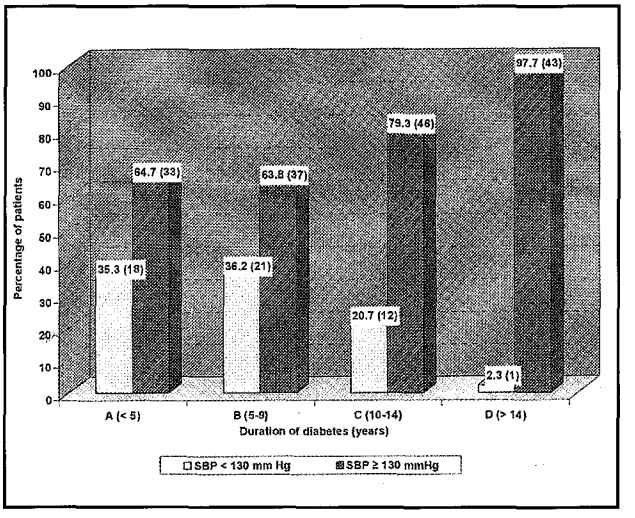

Fig. 2 : Frequency of patients having systolic blood pressure (SBP) at clinical target and outside of clinical target grouped according to the duration of diabetes

Discussion

In this study a large proportion of the patients had A1C levels outside the clinical target level. This finding is similar to previous report[21, 22]. In this study BMI values above target level were observed in 66% of type 2 diabetic patients. Similar results were found by Mohamad et al. (1997)[21]. A total of 45% of type 2 diabetic patients (male, 19% and female, 26%) had BMI values greater than upper recommended values of > 27 and 26 kg/m^2, respectively. Similar results were reported by Paterson *et al.* (1991)[24]. The variables with significant effects on BMI were age, duration of the diabetes mellitus, glycaemic control and gender. Younger and shorter duration of type 2 diabetic patients with good glycaemic control were found to have higher BMI values than older and longer duration of type 2 diabetic patients with poor glycaemic control. Female subjects were significantly more obese than male subjects[25]. In this study the prevalence of hypertension was high (93%). A similar finding was reported by Miller *et al.* (2000)[23]. Blood pressure of 18.5% of patients was more than 160/95 mm Hg, which is still higher than prevalence of hypertension in the non-diabetic population[25]. Hypertension in patients with diabetes depends on age, ethnicity, and obesity[16-18]. In this study the variables with significant effects on systolic blood pressure were age, and duration of the diabetes mellitus. Older type 2 diabetic patients with long duration of diabetes were more hypertensive. Blood pressure of < 130/80 mm Hg, the American Diabetes Association recommended clinical target for diabetic patients, was achieved by only 1% of patients in spite of the anti hypertensive drug therapy. The most common pattern of dyslipidaemia was the combination of both high total cholesterol and LDL cholesterol, which was found in 24% of patients. The second most prevalent dyslipidaemia was a combination of high total cholesterol, LDL cholesterol and triglycerides, which was observed in 19% of patients. Pattern of dyslipidaemia involving all four lipid values (total, HDL, LDL cholesterol and triglycerides) was observed in 14% of the patients. Subjects with diabetes should receive lipid-lowering therapy tailored to reach target level, rather than standard dosage, in order to reduce atherogenic risk[26]. Miller *et al.* (2000)[23] have shown that, in the context of routine specialist practice, achieving good control of glucose, blood pressure, and lipid levels outside of a study setting is possible, although, complex treatment regimens would be required. Poor control of diabetes in our study may be due to dietary habits in this region. The local diet contains high carbohydrates especially sugar, eggs, coconut and its products. Second contributory factor may be reduced daily physical activity, which was observed in most subjects. Most of them had no daily physical activity. The third contributory factor may be lack of knowledge of the disease and its medication. It was found that most patients did not know about their disease and the complication of their disease. They were also not taking their medication regularly. All these three factors have important roles in the control of hyperglycaemia, dyslipidaemia, hypertension and obesity.

The overall clinical targets were sub optimal. Control of glycaemia, serum lipids, blood pressure, and BMI were poor in a majority of the study subjects. The current study has shown that the American Diabetes Association guidelines for glycaemic control cannot always be achieved in specialist clinic practice, although this was claimed to be achieved in another study[23]. However, even in this study only 41% of their subjects had blood pressure ≤ 130/85 mmHg and 61% had A1C ≤ 7.0%. Similarly in another study in Malaysia by Mustaffa et al [27], only 27% of their subjects had A1C ≤ 7.5%; 41% had triglycerides < 1.7 mmol/L; 24% had total cholesterol < 5.2 mmol/L, 50% had HDL-cholesterol > 1.1 mmol/L, 48% had BMI ≤ 25 kg/m^2 and 63% had blood pressure ≤ 140/90 mmHg. As this study and other studies have shown, achieving clinical targets is difficult under the present clinic setting. There is a need to review the organization and running of the diabetes clinic to ensure more effective care and better treatment strategies.

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