Original Article

Association of ABC (HbA1c, blood pressure and LDL-cholesterol) goal achievement with visit-to-visit ABC variability and postprandial dysmetabolism in type 2 diabetic patients

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Background and Objectives: Although roles of ABC (HbA1c, blood pressure [BP] and LDL-cholesterol) goal attainment on CVD risk outcomes have been well established, it is less studied whether ABC goal attainment associates with ABC variability, non-traditional risk factors. **Methods and Study Design:** : Intrapersonal mean levels and standard deviation (SD) of HbA1c, BP and LDL-cholesterol, fasting and post-breakfast plasma glucose (PG) and serum triglyceride (TG) during 12 months were calculated in 168 type 2 diabetes patients (aged 62.3 years, 53.6% men). Associations of ABC goal attainment with non-traditional glycemic, BP and lipid risk factors were analyzed. **Results:** Among 168 patients, 92 (54.8%), 91 (54.2%) and 111 (66.1%) patients achieved HbA1C, BP and cholesterol goal, respectively, and 47 (28.0 %), 45 (26.8 %), 63 (37.5 %) and 13 (7.7 %) achieved triple-goal, dual-goal, single-goal and no-goal, respectively. Achieving more ABC goals was associated with stepwise decreases in mean levels and SD of fasting and post-breakfast PG, and HbA1c. It was also associated with stepwise decreases in mean levels and SD of fasting and post-breakfast TG, and LDL-cholesterol. Further, achieving more ABC goals was associated with stepwise decreases in brachial pulse pressure and mean levels and SD of systolic BP. **Conclusions:** ABC goal achievement was associated with a broad range of non-traditional glycemic, BP and lipid risk factors in type 2 diabetic patients. Reaching more ABC treatment targets may be important for reductions in long-term ABC variability and postprandial dysmetabolism.

Key Words: visit-to-visit variability, HbA1c, blood pressure, LDL cholesterol, postprandial glycemia, postprandial triglyceridemia

INTRODUCTION

The objectives of diabetes management are to reduce symptoms of diabetes, to prevent development or progression of diabetic complications and disease conditions associated with diabetes, and to enable affected individuals to maintain their quality of life and life expectancy comparable to those seen in healthy individuals.[1] Intensive glycemic, blood pressure (BP), and LDL cholesterol (LDL-C) control have been shown to reduce cardiovascular outcomes and death.[2-4] The "ABCs of Diabetes" include reduction of HbA1c, BP, and LDL-C and are defined as HbA1c <7.0%, BP <130/80 mmHg, and LDL-C <120 mg/dL by Japan Diabetes Society (JDS).[1]

Studies including ours have demonstrated that not only mean levels of HbA1c and systolic BP but also visit-to-visit variability in HbA1c and systolic BP were associated with micro- and macrovascular complications in patients with type 2 diabetes.[5-10] In addition, visit-to-visit variability in LDL-C has been shown to be associated with subclinical atherosclerosis and development of chronic kid-

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ney disease in type 2 diabetes.[11,12] Further, visit-to-visit variability in LDL-C, non-HDL-C and fasting TG has been shown to be associated with cardiovascular events.[13-16]

In addition to long-term fluctuations in glycemia, BP and LDL-C, postprandial fluctuations in glycemia and triglyceridemia may have important impact of vascular complications.[17,18] Another risk factor for the development and progression of vascular diseases include brachial pulse pressure (PP),[19-21] a readily available hemodynamic parameter. In the present study, we examined whether ABC (HbA1c, blood pressure and LDL-cholesterol) goal attainment associated with non-traditional vascular risk factors in patients with type 2 diabetes.

METHODS

We cross-sectionally studied 168 patients with type 2 diabetes, whose details have been reported previously.[5] The setting for this observational study was an outpatient diabetes clinic in a private hospital in Japan. They had been regularly attending the clinic in 2004 and 2005. After enrollment at the first visit in 2005 they had monthly visits for 12 months. Patients with hepatitis B surface antigen or antibodies against hepatitis C virus were excluded. Those who had aspartate aminotransferase and alanine aminotransferase of 100 U/L or greater, serum creatinine ≥2.0 mg/dL were excluded as well. Study protocol was consistent with the Japanese Government's Ethical Guidelines Regarding Epidemiological Studies in accordance with the Declaration of Helsinki. Informed consents were obtained from all participants.

On each monthly visit in the morning, all participants had blood samplings and measurements of waist circumference, height, weight, and BP. Thus, 168 patients had 12 consecutive measurements during a given 12 months. Among 168 patients, 153 (91 %) had blood samplings on 2 occasions; at 2 h after breakfast taken at home and after an overnight fasting, as previously reported in detail.[5-8,22,23] In the remaining 15 patients, blood was withdrawn after an overnight fasting. Plasma glucose (PG), serum total cholesterol, triglycerides (TG) and HDL-C were measured by standard methods using an autoanalyzer. HbA1C values were determined by high performance liquid chromatography. LDL-C was calculated by Friedewald's formula using lipid levels obtained in blood samples taken after an overnight fasting. Non-HDL-C was calculated as total cholesterol minus HDL-C. PP was calculated as the difference between the systolic and diastolic BP readings.

Intrapersonal mean levels of BMI, waist circumference, systolic and diastolic BP, PP, HbA1c, total cholesterol, non-HDL-C and HDL-C were calculated based on 12 measurements in 168 patients. LDL-C were calculated based on 6 measurements in 153 patients and 12 measurements in the remaining 15 patients. Intrapersonal mean levels of fasting PG and TG (FPG and FTG, respectively), post-breakfast PG and TG (PPG and PTG, respectively) were calculated based on 6 measurements in 153 patients. Goal achievement (HbA1c <7%, BP <130/80 mmHg and LDL-C <120 mg/dL)[1] was evaluated using these means. Intrapersonal standard deviation (SD) of systolic BP, FPG, PPG, HbA1c, FTG, PTG and LDL-C were calculated as well.

Data were presented as mean ± SE unless otherwise stated. Associations of continuous variables and frequencies of conditions with the number of ABC goals attained and p trend were derived using Jonckheere-Terpstra test and Cochran-Armitage trend analysis, respectively. A two-tailed $p<0.05$ was considered statistically significant. All calculations were performed with SPSS system 15.0 (SPSS Inc., Chicago, IL).

RESULTS

As previously reported in detail[5-8,22,23] and shown in Table 1, 115 patients (68.5%) were on oral anti-diabetes drugs or insulin while the remaining 53 patients (31.5%) were treated with personal behaviour modification. Eighty-seven patients (51.5%) were on BP-lowering drugs and 63 (37.3%) on statin or ezetimibe while only 12 patients (7.1%) received fibrates. They had relatively good glycemic, lipid and BP control. The prevalence of meeting HbA1C, BP and cholesterol goal were 54.8% (n=92), 54.2% (n=91) and 66.1% (n=111), respectively.

Of 168 patients, 47 (28.0%) achieved triple-goal while 13 (7.7%) achieved no-goal (Table 2). Dual-goal and single-goal attainment was found in 45 (26.8%) and 63 patients (37.5%), respectively. Triple-goal compared with no-goal achievers had shorter diabetes duration and lower percentage of users of insulin and BP-lowering drugs. The proportion of men was highest in dual-goal achievers, followed by single- and then triple goal achievers and then lowest in no-goal achievers. However, four groups did not differ in age, anthropometric indices and the proportion of users of oral anti-diabetes drugs, statin or ezetimibe and fibrates and smokers.

Achieving more ABC targets decreased FPG, PPG and mean levels and visit-to-visit variability in HbA1c (Table 3) despite an increase in the proportion of insulin users (Table 2). In addition, despite no difference in BMI and waist circumference (Table 2), FTG, PTG, total cholesterol and LDL-C decreased, and HDL-C increased in a stepwise fashion as the number of ABC goals achieved increased (Table 3, Figure 1). Non-HDL-C, SD of FPG, FTG, and LDL-C decreased as well (Figure 2).

Mean levels and SD of systolic BP, diastolic BP and brachial PP decreased in a stepwise fashion as the number of ABC goal increased (Figure 3).

DISCUSSION

The present study is, to our knowledge, the first to investigate the association between ABC goal achievement and long-term variability in cardiovascular risk factors and has shown that even in type 2 diabetic patients with relatively good ABC control, achieving more ABC targets was associated with not only lower mean levels of, but also lower visit-to-visit variability in FPG and HbA1c. It also was associated with not only lower mean levels of, but also lower visit-to-visit variability in LDL-C and systolic BP. Further, achieving more ABC targets was associated with lower postprandial glucose and TG and brachial PP. These findings indicate that achieving more ABC goals is important to reduce a broad range of non-traditional cardiovascular risk factors even in type 2 dia-

Table 1. Anthropometric, clinical and biochemical features of 168 patients with type 2 diabetes

	Mean±SE or n, %
Male sex (n, %)	90, 53.6
Age (years)	62.3±0.8
BMI (kg/m^2)	24.2±0.3
Waist circumference (cm)	86.9±0.8
Duration of diabetes (years)	9.9±0.6
Users of oral anti-diabetes drugs (n, %)	85, 50.6
Insulin users (n, %)	30, 17.9
Users of BP-lowering drugs (n, %)	87, 51.5
Users of statin/ezetimibe (n, %)	63, 37.3
Users of fibrates (n, %)	12, 7.1
Smokers (n, %)	58, 34.3
FPG (mg/dL)	125±2
SD-FPG (mg/dL)	18±1
PPG (mg/dL)	154±4
SD-PPG (mg/dL)	35±2
HbA1c (%)	7.0±0.1
SD-HbA1c	0.48±0.04
Total C (mg/dL)	188±2
HDL C (mg/dL)	56±1
LDL C (mg/dL)	111±2
SD-LDLC (mg/dL)	16±1
non-HDLC (mg/dL)	131±2
FTG (mg/dL)	115±4
SD-FTG (mg/dL)	30±2
PTG (mg/dL)	145±5
SD-PTG (mg/dL)	38±2
Systolic BP (mmHg)	128±1
SD-Systolic BP (mmHg)	10.3±0.2
Diastolic BP (mmHg)	72±1
Pulse pressure (mmHg)	56.1±0.8

BP: blood pressure; FPG: fasting plasma glucose; PPG: post-breakfast plasma glucose; SD: standard deviation; C: cholesterol; FTG: fasting triglyceride; PPG: post-breakfast triglyceride; respectively. SD: standard deviation; PP: pulse pressure.

Table 2. Anthropometric and clinical features of 168 patients with type 2 diabetes according to ABC goal attainment[†]

	Triple-goal achievers	Dual-goal achievers	Single-goal achievers	No-goal achievers	*p* values
n	47	45	63	13	
Sex-male (n, %)	20, 42.6	30, 66.7	35, 55.6	5, 38.5	0.003
Age (years)	62±1	62.6±1.3	62.1±1.4	63.8±2.9	0.95
Body mass index (kg/m^2)	23.8±0.5	23.9±0.6	24.6±0.5	25.0±0.5	0.53
Waist circumference (cm)	85.9±1.4	85.0±1.2	88.7±1.5	88.4±1.5	0.22
Duration of diabetes (years)	7.4±0.7	12.2±1.2	9.6±0.9	12.1±2.3	<0.001
Diabetes therapy (n, %)					
Diet/exercise	19, 40.4	15, 33.3	18, 28.6	1, 7.7	0.26
Oral hypoglycemic agents	24, 51.1	22, 48.9	32, 50.8	7, 53.8	0.99
Insulin	4, 8.5	8, 17.8	13, 20.6	5, 38.5	<0.001
Users of BP-lowering drugs (n, %)	23, 48.9	19, 42.2	34, 54.0	11, 84.6	0.01
Users of statin/ezetimibe (n, %)	18, 38.3	15, 33.33	27, 42.9	3, 23.1	0.518
Users of fibrates (n, %)	4, 8.5	4, 8.9	4, 6.3	0, 0	0.70
Smokers (n, %)	12, 25.5	18, 40.0	24, 38.1	4, 30.8	0.29

ABC: HbA1c, blood pressure and LDL-cholesterol
[†]Data expressed as mean ± SE or n, %.

betic patients with relatively good ABC control.

The present results were similar to those reported in a large-scale survey in Japan[24] and USA.[25] The rates of achieving targets using JDS guidelines for HbA1c, BP, and lipids in large-scale study[24] (the present study) were 52.9% (54.8%), 46.8% (54.2%) and 65.5% (66.1%), respectively, which yielded 20.8% (28.0%) that met all three treatment targets and 11.8% (7.7 %) that achieved none of the targets. The percentage of triple-goal achievers assessed using JDS guidelines was 11% in 3070 employees with diabetes (94% of men) in manufacturing companies in Japan.[26] The percentage of triple-goal achievers was 61 % even in the structured versus usual care, the former of which included a predefined protocol and tight treatment targets delivered by diabetologist-led multidisciplinary, specialist diabetes teams.[27]

Some studies investigated determinants preventing achievement of ABC targets in type 2 diabetes. Liu et al[28]

Table 3. Glycemic and lipid control of 168 patients with type 2 diabetes according to ABC goal attainment†

	Triple-goal achievers	Dual-goal achievers	Single-goal achievers	No-goal achievers	*p* values
FPG (mg/dL)	112±2	125±3	132±3	141±5	<0.001
SD-FPG (mg/dL)	12±1	19±2	22±2	21±3	<0.001
PPG (mg/dL)	128±6	149±7	173±7	177±12	<0.001
SD-PPG (mg/dL)	23±2	34±3	44±3	40±4	<0.001
HbA1c (%)	6.4±0.1	7.0±0.1	7.4±0.1	7.6±0.1	<0.001
SD-HbA1c (%)	0.25±0.03	0.54±0.09	0.60±0.06	0.59±0.16	<0.001
Total C (mg/dL)	179±3	187±3	194±3	198±4	<0.001
HDLC (mg/dL)	59±2	59±3	52±2	48±3	0.002
LDLC (mg/dL)	100±2	107±3	119±3	128±5	<0.001
SD-LDLC (mg/dL)	14±1	15±1	17±1	19±3	0.02
non-HDLC (mg/dL)	120±2	126±3	140±3	150±6	<0.001
FTG (mg/dL)	105±7	109±7	123±7	128±13	0.02
SD-FTG (mg/dL)	25±3	27±2	35±3	34±6	0.01
PTG (mg/dL)	127±9	146±11	152±8	179±22	0.02

BP: blood pressure; FPG: fasting plasma glucose; PPG: post-breakfast plasma glucose; SD: standard deviation; C: cholesterol; FTG: fasting triglyceride; PPG: post-breakfast triglyceride; respectively. SD: standard deviation; PP: pulse pressure
†Data expressed as mean ± SE or n, %.

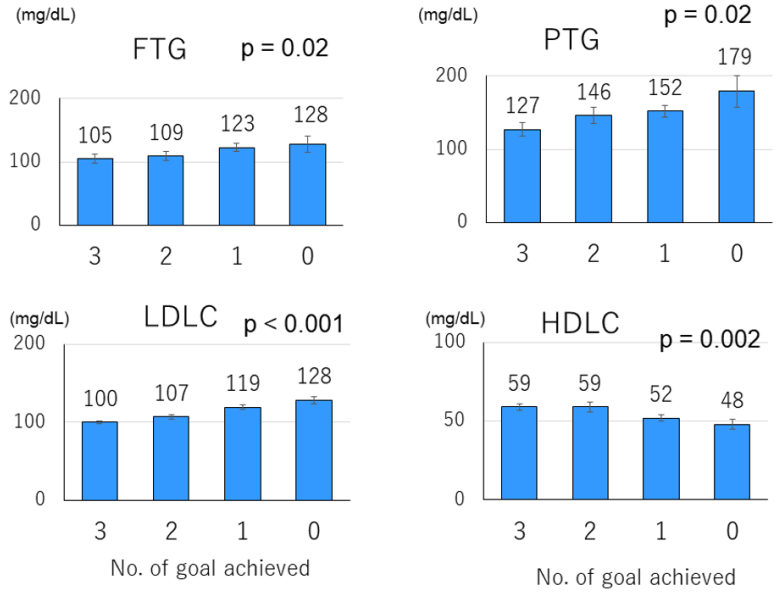

Figure 1. Annual means of fasting and postprandial serum triglycerides (FTG and PTG, respectively), LDL- and HDL-cholesterol (LDLC and HDLC, respectively) according to the number of goals achieved. Data are means ± SE.

studies 5961 type 2 diabetes patients with triple-goal achievers of 5% and found that smoking, higher BMI and insulin use were associated with no-goal achievement. Camara et al[29] have demonstrated that triple-goal achievement was associated with shorter diabetes duration, less familial diabetes history and lower waist/visceral fat in patients with triple-goal achievement of 9%. In the present study, shorter diabetes duration and less users of insulin and BP-lowering drugs were associated with triple-goal achievement.

Underlining mechanisms through which achieving less ABC goal was associated with higher ABC variability and postprandial dysmetabolism remained unclear. It is biologically plausible that achieving less ABC goal and higher visit-to-visit ABC variability both could be explained by non-adherence to respective medications among treated individuals. Although seasonal variation in ABC has been reported,[30-33] this is not the case in the present study because all variables including ABC were repeatedly measured throughout 12 months. It seems reasonable to assume that achieving less ABC goal is associated with greater degree of atherosclerosis and arterial stiffness, which contribute to higher pulse pressure found in the present study.

The strength of the current study is that mean and SD of ABC and other traditional and non-traditional risk factors were calculated from 6-12 measurements in 94 % of participants. Therefore, evaluation of ABC goal achievement was based on 6-12 measurements. Major limitations are that study participants were small in the number and from a single clinic in Japan. However, the characteristics of our study participants are similar to those reported in a previous large-scale study in Japan.[33] In addition, this cohort of participants consisted of Japanese only, which limits generalizability. Finally, statistical power was not calculated.

In conclusions, ABC goal achievement was associated with a broad range of non-traditional glycemic, BP and lipid risk factors in type 2 diabetic patients. Reaching more ABC treatment targets may be important for re-

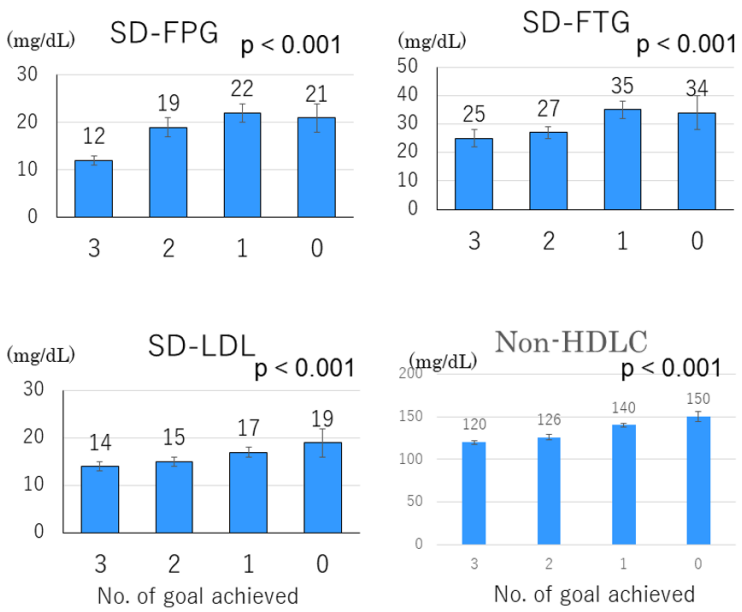

Figure 2. Visit-to-visit variability (expressed as standard deviation [SD]) in fasting plasma glucose (FPG), fasting serum triglycerides (FTG) and LDL-cholesterol (LDLC), and annual means of non-HDL-cholesterol (non-HDLC) according to the number of goals achieved. Data are means ± SE.

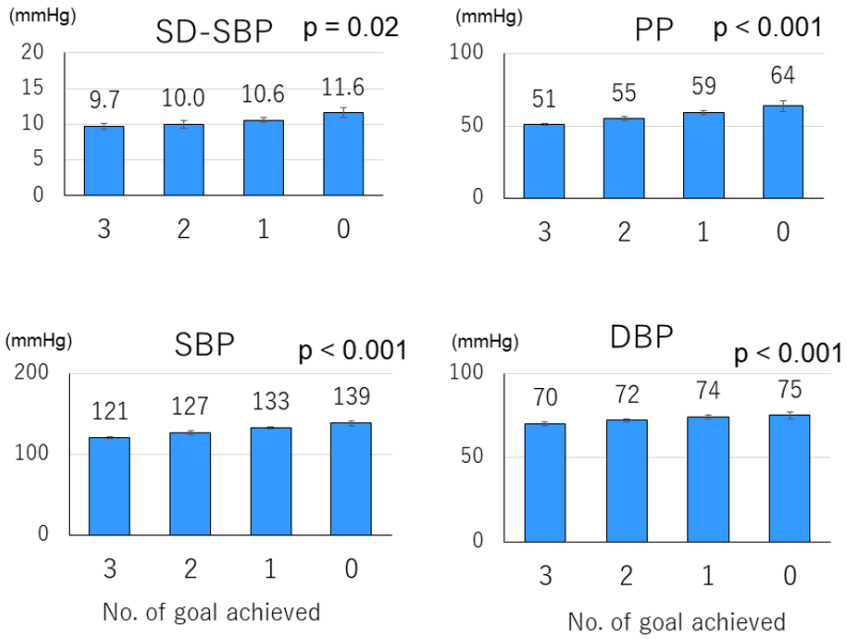

Figure 3. Annual means and visit-to-visit variability (expressed as standard deviation [SD]) in systolic blood pressure (SBP), annual means of pulse pressure (PP) and diastolic blood pressure (DBP) according to the number of goals achieved. Data are means ± SE.

ductions in, and stability of ABC levels in type 2 diabetes. Further studies are needed to confirm these associations in other ethnic groups with more patients.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest. No competing financial interests exist.

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