Joint impact of modifiable lifestyle behaviors on glycemic control and insulin resistance in patients with type 2 diabetes: the Fukuoka Diabetes Registry

Toshiaki Ohkuma^{1,2} · Masanori Iwase^{1,3} · Hiroki Fujii^{1,4} · Hitoshi Ide¹ · Shinako Kaizu¹ · Tamaki Jodai¹ · Yohei Kikuchi¹ · Yasuhiro Idewaki³ · Akiko Sumi¹ · Udai Nakamura¹ · Takanari Kitazono¹

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Abstract

Aims Little is known about the combined effects of unhealthy lifestyle behaviors on glycemia. The objective of this study was to examine the association between combined modifiable lifestyle and glycemic control, as well as markers of insulin resistance and secretion.

Patients and methods In total, 4,870 patients with type 2 diabetes were sorted by lifestyle scores. Scores were determined by summing the number of unhealthy lifestyle factors that showed a significant association with hemoglobin A_{1c} (HbA_{1c}) (current smoking, decreased dietary fiber intake, eating quickly, inadequate sleep duration, and obesity). The associations between lifestyle score and hemoglobin A_{1c} (HbA_{1c}), homeostasis model assessment of insulin resistance (HOMA2-IR), and β -cell function (HOMA2-%B) were cross-sectionally analyzed.

Results HbA_{1c} increased progressively with increases in lifestyle score (p for trend <0.001). Mean HbA_{1c} was 0.48% (95% confidence intervals 0.34–0.63) higher in patients with scores of four to five than in those with zero scores. HOMA2-IR and high-sensitivity C-reactive protein

also revealed a similar tendency, but adiponectin showed an inverse association. However, these graded tendencies were not observed for HOMA2-%B. Additionally, lower HOMA2-%B levels enhanced the effects of lifestyle score on glycemia. Increases in HbA_{1c} per point in the lifestyle score in patients with the lowest and highest quartiles of HOMA2-%B were 0.25% (0.18–0.32) and 0.10% (0.06–0.15), respectively (p for interaction <0.001).

Conclusions Accumulation of unhealthy lifestyle factors was dose-dependently associated with poor glycemic control, which may be modified by insulin secretory capacity.

Keywords Diabetes mellitus · Epidemiology · Insulin resistance · Lifestyle modification

Abbreviations

BDHQ	Brief-type Self-administered Diet History Questionnaire
BMI	Body mass index
CI	Confidence interval
HS-CRP	High-sensitivity C-reactive protein
HbA _{1c}	Hemoglobin A _{1c}
HOMA2-%B	Homeostasis model assessment of β -cell function
HOMA2-IR	Homeostasis model assessment of insulin resistance
MET·h/w	Metabolic equivalent hours per week
VIF	Variance inflation factor

Introduction

Increases in the prevalence of type 2 diabetes mellitus (T2DM) are associated with lifestyle changes [1], suggesting that lifestyle modifications may prevent the

✉ Masanori Iwase
iwase@intmed2.med.kyushu-u.ac.jp

¹ Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan

² Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan

³ Diabetes Center, Hakujyujii Hospital, Ishimaru 3-2-1, Nishi-ku, Fukuoka 819-8511, Japan

⁴ Division of General Internal Medicine, School of Oral Health Science, Kyushu Dental University, Manazuru 2-6-1, Kokurakita-ku, Kitakyushu 803-8580, Japan

development of this disease. Lifestyle modifications are also regarded as critical for glycemic control of patients with T2DM [2]. Although lifestyle modifications in clinical settings address multiple aspects of lifestyle, most previous reports have targeted either diet or exercise [3]. We previously reported an inverse association between glycemic control and individual unhealthy lifestyle factors, including eating quickly [4], too short or too long sleep duration [5], decreased dietary fiber consumption [6], physical inactivity [7], and tobacco smoking [8] in ~5,000 Japanese patients with T2DM. However, relatively little is known about the effects of combinations of modifiable lifestyle factors on glycemic level in patients with T2DM [3]. Moreover, to our knowledge, no epidemiologic study to date has examined the joint effects of lifestyle behaviors on insulin resistance and secretion, two major pathogenetic factors of diabetes, in patients with this disease.

The global epidemic of T2DM has created increases in healthcare costs associated with chronic complications, which may necessitate a study of the joint impact of lifestyle factors on glycemic control of patients with diabetes. Therefore, this study examined the association of a combination of lifestyle factors with glycemic control and the markers of insulin resistance and secretion in patients with T2DM.

Patients and methods

Study participants

The Fukuoka Diabetes Registry is a multicenter prospective cohort study investigating the effect of modern treatments on the prognosis of diabetic patients who regularly attend teaching hospitals or diabetes clinics certified by the Japan Diabetes Society in Fukuoka Prefecture, Japan (UMIN Clinical Trial Registry 000002627) [4]. A total of 5131 patients with diabetes aged ≥ 20 years were registered between April 2008 and October 2010. Patients were excluded from the registry if they:

- (1) Had drug-induced diabetes or were taking steroid preparation
- (2) Were under renal replacement therapy
- (3) Had serious diseases other than diabetes, such as decompensated liver cirrhosis or advanced malignancies
- (4) Were unable to attend hospitals regularly

After excluding 261 patients with type 1 DM (T1DM), the remaining 4870 were included in this cross-sectional analysis. The Kyushu University Institutional Review Board approved the study. Written informed consent was obtained from all participants.

Clinical evaluation

At baseline survey, participants, who completed a self-reported questionnaire; provided information on diet, smoking habits, physical activity level, sleep duration, alcohol intake, and depressive symptoms. Lifestyle factors were dichotomized. Participants were classified as current smokers or nonsmokers based on current smoking status. Dietary habits were evaluated by the Brief-type Self-administered Diet History Questionnaire (BDHQ) (Gender Medical Research Inc., Tokyo, Japan) regarding consumption frequency of 58 items. The validity to rank the energy-adjusted intake of dietary fiber was examined in adult Japanese [9]. The correlation coefficient for intake of dietary fiber between BDHQ and the semiweighed dietary records for 16 days was 0.70 in men ($n = 92$) and 0.66 in women ($n = 92$). Participants were categorized as consuming less dietary fiber intake if consumption was < 7.37 g/1000 kcal, the median consumption by all participants.

As part of this questionnaire, the speed of eating was assessed using the question: "How fast is your speed of eating?" Answers were "very slow", "relatively slow", "medium", "relatively fast", and "very fast". The validity and reproducibility of this question have been described [10, 11]. Participants who answered eating relatively fast and very fast were categorized as fast eaters, with all other patients categorized as slow eaters. Leisure time-physical activity was assessed by a self-administered questionnaire. Metabolic equivalent hours per week (MET·h/w) was calculated as described [12]. Patients above and below the value of 6.6 METs·h/w were categorized as being physically active and inactive, respectively, based on results of a systematic review and meta-analysis of the association between physical activity and health outcomes [13]. Inadequate sleep duration was defined as < 5.5 or ≥ 8.5 h of sleep per day [5]. Obesity was defined as body mass index (BMI) ≥ 25 kg/m² [14]. We developed lifestyle score by assigning one point to each unfavorable lifestyle factor showing a significant association with hemoglobin A_{1c} (HbA_{1c}) levels after multivariate adjustment. Alcohol intake was not included in unhealthy lifestyle factors, because a systematic review and meta-analysis of interventional studies demonstrated that moderate alcohol consumption decreased HbA_{1c} levels [15]. Thus, clinical practice has permitted, but not recommended, alcohol consumption, as it increases the risk of hypoglycaemia [2]. In addition, we previously reported that there was no significant association between alcohol consumption and glycemic control in patients with T2DM [16]. Depressive symptoms were evaluated using the Center for Epidemiologic Studies Depression Scale [17]. Patients with ≥ 16 of

60 points were defined as having depressive symptoms. Patients were categorized as being treated with hypoglycemic agents orally, insulin, or no treatment.

Laboratory measurements

Blood collection was by venipuncture. HbA_{1c} levels were determined by high-performance liquid chromatography (HPLC; Tosoh Corp., Tokyo, Japan), plasma glucose by the glucose-oxidase method, and serum C-peptide by chemiluminescent immunoassays (Kyowa Medex, Tokyo, Japan). Determination of serum adiponectin (Mitsubishi Chemical Medience, Tokyo, Japan) and high-sensitivity C-reactive protein (HS-CRP) (Siemens Healthcare Diagnostics, Tokyo, Japan) were by latex immunonephelometry in 4869 and 4326 patients, respectively. Estimations of insulin resistance and β -cell function were based on fasting glucose and C-peptide concentrations using the HOMA calculator [18]. Estimations were expressed as homeostasis model assessment of insulin resistance (HOMA2-IR) and homeostasis model assessment of β -cell function (HOMA2-%B) in 3816 patients after excluding those who had already eaten breakfast ($n = 468$), those without measures of C-peptide ($n = 5$), and those with unacceptable plasma glucose (<3 or >25 mmol/l) or C-peptide (<0.2 or >3.5 nmol/l) concentrations ($n = 581$).

Statistical analysis

The associations between lifestyle factors and HbA_{1c} were examined using multiple linear regression model. A one-way analysis of variance (ANOVA) or chi square test was used to test differences in mean values or proportions of participants' characteristics, as appropriate. Age- and sex-adjusted mean HbA_{1c}, HS-CRP, adiponectin concentrations, and mean HOMA2-%B and HOMA2-IR scores were calculated and compared by analysis of covariance (ANCOVA). HS-CRP, adiponectin, HOMA2-%B, and HOMA2-IR were log-transformed prior to statistical analyses because they displayed a skewed distribution; these factors were subsequently back-transformed and presented with their 95% confidence intervals (CIs). The multivariate-adjusted partial regression coefficients and their 95% CIs were determined and examined for linear trends using multiple linear regression model. In multivariate-adjusted analysis, lifestyle factors, age, sex, diabetes duration, total energy intake, current drinking habits, depressive symptoms, treatment orally with hypoglycemic agents, and insulin use as the independent variables were included. Multicollinearity was checked by calculating variance inflation factor (VIF) in each analysis. There was no independent variable showing $VIF > 10$, which indicated no collinearity. To clarify the existence of interaction

between unhealthy lifestyle and insulin secretion capacity, participants were classified according to lifestyle score and HOMA2-%B quartiles, and we estimated the age- and sex-adjusted means of HbA_{1c} in each category. Interaction between lifestyle score and HOMA2-%B on HbA_{1c} was assessed by adding an interaction term to the statistical model. All statistical analyses were conducted using the SAS software package version 9.3 (SAS Institute Inc., Cary, NC, USA). Values of $p < 0.05$ were statistically significant in all analyses.

Results

First, the association between each lifestyle factor and HbA_{1c} was evaluated. The adjusted partial regression coefficients of HbA_{1c} as the dependent variable by the presence or absence of individual lifestyle factors are shown in Table 1. After adjustments for age and sex, all individual unhealthy lifestyle factors were significantly associated with higher HbA_{1c} levels. The mean increases in HbA_{1c} were 0.15% (95% CI 0.07–0.23) for current smoking habits, 0.13% (0.07–0.19) for physically inactive, 0.08% (0.03–0.14) for fast eating habits, 0.16% (0.10–0.22) for decreased dietary fiber intake, 0.12% (0.05–0.19) for inadequate sleep duration, and 0.34% (0.28–0.41) for obesity. These associations were substantially unchanged even after multivariate adjustment for age, sex, duration of diabetes, total energy intake, current drinking habits, depressive symptoms, use of hypoglycemic agents orally, insulin use, and all the lifestyle factors examined. However, statistical significance was no longer observed in patients who were physically inactive. On the basis of these findings, we defined the lifestyle score as the sum of unhealthy lifestyle: current smoking, lower dietary fiber intake, fast eating, inadequate sleep duration, and obesity. Because small numbers of participants had five ($n = 31$) points, patients with four to five points were combined into one category (range 0–4).

The characteristics of the study participants, categorized by lifestyle scores, are shown in Table 2. Mean age, duration of diabetes, amount of leisure-time physical activity, total dietary fiber intake, and sleep duration decreased as lifestyle scores increased. In contrast, total energy intake, BMI, the proportion of men, current smokers, fast eaters, patients with inadequate sleep duration, obese individuals, current drinkers, depressive symptoms, rates of oral treatment with hypoglycemic agents increased as lifestyle scores increased.

Figure 1 shows the age- and sex-adjusted means of HbA_{1c} according to lifestyle score. Levels increased progressively with increased lifestyle score (p for trend

Table 1 Adjusted partial regression coefficients (95% CIs) of HbA_{1c} with respect to the presence or absence of lifestyle factors

Independent variables	N of corresponding patients/N of all patients	β (95% CI) of HbA _{1c} as dependent variable	
		Age- and sex-adjusted	Multivariate-adjusted
Current smoking	902/4870	0.15 (0.07, 0.23)	0.14 (0.06, 0.21)
Physically inactive	2373/4870	0.13 (0.07, 0.19)	0.03 (−0.02, 0.09)
Eating quickly	2317/4870	0.08 (0.03, 0.14)	0.07 (0.01, 0.12)
Decreased dietary fiber intake	2435/4870	0.16 (0.10, 0.22)	0.11 (0.05, 0.16)
Excess or deficiency of sleep	1159/4870	0.12 (0.05, 0.19)	0.08 (0.02, 0.14)
Obesity	1504/4870	0.34 (0.28, 0.41)	0.27 (0.21, 0.33)

Numbers in parentheses represent the 95% CI

Multivariate adjustment included adjustments for age, sex, duration of diabetes, total energy intake, current drinking habits, depressive symptoms, hypoglycemic agent use orally, insulin use, and all other lifestyle factors listed in this table

β partial regression coefficients, CI, confidence interval

Table 2 Clinical characteristics of the study participants according to the lifestyle score

	Lifestyle score					P value
	0	1	2	3	4–5	
N	728	1476	1480	894	292	
Age (years)	68.9 ± 8.6	67.3 ± 9.1	65.3 ± 10.0	62.5 ± 10.5	58.1 ± 11.7	<0.001
Men (%)	42	52	60	67	75	<0.001
Duration of diabetes (years)	16.7 ± 11.2	16.4 ± 10.5	15.6 ± 10.3	15.0 ± 10.1	12.0 ± 9.1	<0.001
Current smoker (%)	0	7	19	36	66	<0.001
Leisure-time physical activity (METs-h/w)	14.2 ± 15.3	13.4 ± 15.9	10.9 ± 14.3	9.9 ± 14.6	6.4 ± 10.3	<0.001
Eating quickly (%)	0	33	58	79	92	<0.001
Total energy intake (kcal/day)	1664 ± 434	1670 ± 475	1679 ± 492	1718 ± 540	1796 ± 583	<0.001
Total dietary fiber intake (g/1000 kcal)	9.5 ± 1.7	8.3 ± 2.1	7.1 ± 2.0	6.3 ± 1.8	5.8 ± 1.3	<0.001
Sleep duration (h)	7.0 ± 0.8	7.0 ± 1.2	6.9 ± 1.4	6.7 ± 1.7	6.3 ± 2.0	<0.001
Sleep excess or deficiency (%)	0	14	26	43	66	<0.001
BMI (kg/m ²)	21.4 ± 2.2	22.6 ± 2.9	24.2 ± 3.8	25.7 ± 3.9	27.6 ± 3.6	<0.001
Obesity (%)	0	13	35	60	90	<0.001
Current drinker (%)	30	34	43	46	49	<0.001
Depressive symptoms (%)	5	8	9	12	13	<0.001
Hypoglycemic agent orally (%)	60	62	65	68	65	0.003
Insulin use (%)	27	28	28	29	27	0.93

Values are expressed as mean ± standard deviation or percentage

METs-h/w metabolic equivalent hours per week, BMI body mass index

<0.001), with mean levels of $7.22 \pm 0.04\%$ [standard error (SE)], 7.28 ± 0.03 , 7.52 ± 0.03 , 7.66 ± 0.03 , and $7.70 \pm 0.06\%$ for patients with 0, 1, 2, 3, 4–5 points, respectively. Mean HbA_{1c} level was 0.48% (95% CI 0.34–0.63) higher in participants with 4–5 than in those with 0 points. Multivariate adjustment by age, sex, duration of diabetes, total energy intake, current drinking habits, physically inactive, depressive symptoms, oral use of hypoglycemic agents, and insulin use did not materially alter this relationship (Table 3).

Additional analyses were conducted to evaluate the association of lifestyle score with HOMA2-IR and HOMA2-%B, HS-CRP, and adiponectin as the dependent variables. HOMA2-IR and HS-CRP increased and adiponectin decreased significantly in parallel with increases in lifestyle score (Fig. 2a, c, d, p for trend <0.001), even after multivariate adjustment for confounding factors (Table 2). However, this graded tendency was not observed between lifestyle score and HOMA2-%B (Fig. 2b, p for trend = 0.30).

Fig. 1 Age- and sex-adjusted mean hemoglobin A_{1c} (HbA_{1c}) level according to lifestyle score. Bars represent standard errors. * $p < 0.001$ vs. lifestyle score of 0 point

Effects of an increase in lifestyle score on HbA_{1c}, HOMA2-IR, and HOMA2-%B levels as the dependent variables were subsequently evaluated in patients subgrouped by treatment (Fig. 3). The magnitude of the

increasing HbA_{1c} due to unhealthy lifestyle tended to be greater with changes in treatment. Age- and sex-adjusted increase in HbA_{1c} per one point increase in lifestyle score was 0.08% (95% CI 0.03–0.12) for patients without hypoglycemic agents, 0.11% (0.07–0.14) for those on hypoglycemic agent oral therapy without insulin, and 0.24% (0.18–0.30) for those on insulin therapy (p for interaction <0.001). Log-transformed HOMA2-IR increased significantly with an increase in lifestyle score, regardless of treatment type (p for interaction = 0.58). On the other hand, log-transformed HOMA2-%B increased with lifestyle score in patients without hypoglycemic agents and those on hypoglycemic agent oral therapy without insulin, but did not increase in those on insulin therapy (p for interaction = 0.02).

Finally, the modification effects of insulin secretion capacity on the association between lifestyle score and glycemic level (HbA_{1c} as the dependent variable) were examined. The age- and sex-adjusted mean values of HbA_{1c} according to categories classified by lifestyle score and HOMA2-%B quartiles are depicted in Fig. 4. Although HbA_{1c} levels increased linearly with an increase in lifestyle score irrespective of HOMA2-%B quartiles (p for trend <0.001 for all), the magnitude of increase in HbA_{1c} tended

Table 3 Multivariate-adjusted partial regression coefficients of hemoglobin A_{1c} (HbA_{1c}), HOMA2-IR, HOMA2-%B, HS-CRP, and adiponectin concentration according to lifestyle score

	Lifestyle score					<i>P</i> for trend
	0	1	2	3	4–5	
HbA _{1c}						
Model 1 (%)	0 (referent)	0.04 (−0.05 to 0.12)	0.26 (0.17 to 0.35)	0.37 (0.27 to 0.47)	0.45 (0.31 to 0.58)	<0.001
HOMA2-IR						
Model 1 + log HOMA2-%B	0 (referent)	0.06 (0.02 to 0.10)	0.16 (0.12 to 0.20)	0.25 (0.20 to 0.28)	0.32 (0.26 to 0.38)	<0.001
HOMA2-%B						
Model 1 + log HOMA2-IR	0 (referent)	−0.008 (−0.05 to 0.04)	−0.02 (−0.07 to 0.02)	−0.04 (−0.09 to 0.01)	0.006 (−0.07 to 0.08)	0.30
HS-CRP (mg/l)						
Model 1	0 (referent)	0.16 (0.04 to 0.28)	0.39 (0.26 to 0.51)	0.66 (0.52 to 0.80)	0.73 (0.54 to 0.92)	<0.001
Adiponectin (μg/ml)						
Model 1	0 (referent)	−0.02 (−0.07 to 0.03)	−0.07 (−0.12 to −0.02)	−0.13 (−0.19 to −0.08)	−0.22 (−0.29 to −0.14)	<0.001

β was calculated after log-transformation of HOMA2-IR, HOMA2-%B, HS-CRP, and adiponectin

The numbers in parentheses represent the 95% confidence intervals

Model 1: adjusted for age, sex, duration of diabetes, total energy intake, current drinking habits, physical inactivity, depressive symptoms, hypoglycemic agent orally, and insulin use

β partial regression coefficients, HS-CRP high-sensitivity C-reactive protein, HOMA2-IR homeostasis model assessment of insulin resistance; HOMA2-%B, homeostasis model assessment of β -cell function

Fig. 2 Age- and sex-adjusted mean HOMA2-IR (a), HOMA2-%B (b), HS-CRP (c), and adiponectin (d) concentration according to the lifestyle score. *HS-CRP* high sensitivity C-reactive protein, *HOMA2-IR* homeostasis model assessment of insulin resistance, *HOMA2-%B* homeostasis model assessment of β -cell function. HOMA2-IR, HOMA2-%B, HS-CRP, and adiponectin levels are presented as geometric means. Bars represent 95% confidence intervals. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. lifestyle score of 0 point

Fig. 3 Effects of one point increment in lifestyle score on hemoglobin A_{1c} (HbA_{1c}), HOMA2-IR, and HOMA2-%B levels in patients subgrouped by treatment of diabetes. HbA_{1c}, HOMA2-IR, and HOMA2-%B values were adjusted for age and sex. *HOMA2-IR*

homeostasis model assessment of insulin resistance, *HOMA2-%B* homeostasis model assessment of β -cell function, *OHA* oral hypoglycemic agents. Bars represent the 95% confidence intervals

Fig. 4 Age- and sex-adjusted mean values of hemoglobin A_{1c} (HbA_{1c}) according to lifestyle score and HOMA2-%B quartiles. Sample size ranged from 49 to 312 (mean 239). HOMA2-%B homeostasis model assessment of β -cell function

to be greater in patients with lower than with higher HOMA2-%B levels (p for interaction <0.001). The effect of each one-point increment in lifestyle score on HbA_{1c} level was 0.25% (95% CI 0.18–0.32), 0.19% (0.14–0.24), 0.13% (0.09–0.17), and 0.10% (0.06–0.15) in patients with lowest first, second, third, and fourth quartile HOMA2-%B levels, respectively.

Discussion

This study showed that an increase in unhealthy lifestyle factors compounded the problem of increased HbA_{1c} levels in Japanese patients with T2DM. Further, the marker of insulin resistance showed a similar tendency, which may explain its underlying pathological mechanism. These relationships were unchanged even after adjusting for confounding factors. Furthermore, we observed significant interactions between lifestyle score and markers of insulin secretion on glycemic levels. Patients with lower versus higher insulin secretion capacity showed a more pronounced association between lifestyle score and glycemic control. These findings indicate that individual insulin secretion capacity can modify the adverse effect of unhealthy lifestyle on glycemia. To the best of our knowledge, this is the first large-scale study that indicates a graded relationship between lifestyle factors and glycemic control and insulin resistance, as well as the interaction with insulin secretion, in patients with T2DM.

Studies show that lifestyle interventions are effective in preventing [19, 20] and treating [3] T2DM but do not yet

fully explain the contributions of individual and combined lifestyle factors. A 10-year prospective study of 4883 elderly participants [21] reported that individual lifestyle factors, such as higher level of physical activity, better dietary habits, nonsmoking, nonuse of alcohol, and non-obese BMI and waist circumference, were independently associated with lower rates of diabetes, with risk reductions of 26, 31, 23, 34, 45, and 46%, respectively. Further, assessments of combinations showed a dose–response relationship with incident diabetes. Each additional healthy lifestyle factor was associated with a 35% lower risk of diabetes (hazard ratio 0.65; 95% CI 0.59–0.71). In contrast, a recent meta-analysis showed that lifestyle interventions effectively reduce HbA_{1c} concentrations in patients with T2DM [3]; the effects of combined lifestyle factors on glycemic control remain to be elucidated.

Results of our study show a graded positive association between the number of unhealthy lifestyle factors and HbA_{1c} (p for trend <0.001), thus extending the findings regarding the incidence of T2DM [21] to treatment for it. The magnitude of difference in HbA_{1c} levels between the highest and lowest lifestyle score categories was 0.48%, which may be equivalent to the hypoglycemic effects of medication for diabetes in clinical practice.

Several mechanisms may explain the association between lifestyle factors and glycemic control. Besides the association between obesity and insulin resistance [22], there are other reports of individual lifestyle behaviors on the association with insulin resistance. These include cigarette smoking [8, 23], decreased dietary fiber intake [6, 24], fast eating habits [25], and too short or long habitual sleep duration [26, 27]. Taken together, combinations of unhealthy lifestyle factors may alter glycemic control mainly by enhancing insulin resistance, as shown by our finding of a linear association between lifestyle score and HOMA2-IR. However, a similar effect on HOMA2-%B score was not observed. These findings suggest that insulin resistance is the main mechanism underlying poor glycemic control. In addition, the combinations of unhealthy lifestyle factors were associated positively with HS-CRP, systemic microinflammation, and inversely with adiponectin, adipokine with insulin-sensitizing, anti-inflammatory, and vasoprotective effects. Collectively, these factors may mediate deterioration of insulin resistance.

Additionally, an increase in HbA_{1c} with increasing lifestyle score tended to be enhanced with changes in treatment; the greatest increase in HbA_{1c} was observed in patients using insulin therapy (Fig. 3). Meanwhile, a significant increase in HOMA2-%B was not shown in these patients. Taken together, we speculate that the reason for the difference in change in HbA_{1c} by unhealthy lifestyle is due to the difference in insulin secretion ability. Findings

in Fig. 4 may support this hypothesis, which indicates that unhealthy lifestyle shows a more pronounced impact with the decreasing levels of HOMA2-%B. This finding suggests the impairment of compensatory insulin secretion in response to insulin resistance. Although additional studies are needed, lifestyle interventions may be more effective if patients with impaired insulin secretion are selected rather than all patients. The growing economic burden of diabetes suggests that these findings may have both clinical and public healthcare effects.

This study has several strengths, including the large number and uniform ethnicity of the study participants. Increased rates of diabetes in the Asian population, characterized by impaired insulin secretion [28], may extend the generalizability of our findings. A further strength was the simple nature of using the lifestyle score. The evaluation of the five assessed factors required less time completing and assessing questionnaires or measurements, and the relative simplicity of these assessments is suitable in clinical settings. In addition, the costeffectiveness of lifestyle modification relative to pharmacotherapy may strengthen the importance of these results.

Our study also has several limitations. First, we evaluated lifestyle factors, such as eating rate, dietary fiber intake, sleep duration, physical activity, and smoking, by self-reported questionnaires. Thus, we cannot exclude the possibility of misclassification. However, some measurements were validated by objective measures [10, 29–32]; for example, a self-reported eating rate was validated with friend-reported eating rate as a standard by showing high levels of agreement between self- and friend-reported eating rate (percentage of exact and adjunct agreement was 46 and 47%, respectively) [10]. In addition, recalled duration of eating meals decreased significantly with changes in self-reported eating rate from slow to rapid [32]. A positive association between self-reported and measured eating rate in the laboratory was also indicated; slow eaters ate 53.0 ± 23.6 (SD) kcal/min, medium eaters ate 63.8 ± 24.7 kcal/min, and fast eaters ate 83.0 ± 43.6 kcal/min, [31]. Second, because the effects of each lifestyle factor on glycemia were different (Table 3), we calculated lifestyle score weighted by each multivariate-adjusted partial regression coefficient for HbA_{1c} as the dependent variable, and then conducted the analyses. The adjusted results did not change significantly (data not shown). Therefore, we used the equally weighted lifestyle score for simplicity and ease of interpretation, as done in previous studies [21, 33–36]. In addition, correlations between lifestyle factors may be possible. However, there was no evidence of collinearity between lifestyles factors included in lifestyle score in association with HbA_{1c}. Third, we did not investigate which combination pattern of the particularly unhealthy behaviors was more harmful on

glycemic control; this issue requires further studies for clarification. Fourth, the magnitude of insulin resistance and insulin secretion capacity were evaluated by indirect parameters derived from HOMA; however, it revealed significant correlations with clamp-measured indices ($r = -0.725$, $p < 0.0001$ [37] and $r = -0.820$, $p < 0.0001$ [38]) in patients with diabetes. Using the HOMA model in patients receiving insulin secretagogues or insulin may be applicable [39], although a cautious interpretation is needed. Its simplicity may be more appropriately used in large epidemiological studies [39]. The exclusion of patients without HOMA2-IR and HOMA2-%B ($n = 1,054$) did not change the main results regarding HbA_{1c} levels. Fifth, lifestyle factors vary across ethnicity, culture, and living environments; generalizability of findings to other populations may be limited. Sixth, the cross-sectional study design does not allow inference to any cause–effect relationships. Finally, there may be residual confounding factors, such as patient compliance, socioeconomic factors, and mental health status other than depressive symptoms, in addition to those in this study.

In conclusion, results of this study demonstrated that an increase in unfavorable lifestyle behaviors is associated with poor glycemic control in patients with T2DM. An examination of the combination of lifestyle factors, compared with analyses of individual factors, showed an enhanced magnitude of difference. There were also indications of similar gradual tendencies for insulin resistance, systemic low-grade inflammation, and adiponectin concentration. In addition, markers of endogenous insulin secretion affected the association between lifestyle factors and glycemic control. These findings show the importance of the reinforcement of multifaceted lifestyle modifications in managing T2DM.

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Author contributions TO, HF and MI were responsible for the study concept and design. TO and MI performed the analyses and TJ, HF, HI, SK, YK, YI, AS, UN, and TK helped interpret the data and contributed to the discussion. TO and MI drafted the manuscript. All authors participated in critically revising the manuscript and approved the final version. MI is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

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