Original Article

Management trajectories in the type 2 diabetes Integrated Delivery System project in Taiwan: accounting for behavioral therapy, nutrition education and therapeutics

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Background and aim: Glycated hemoglobin (HbA1c) assessment is basic to diabetes management. Little is done to describe the whole spectrum of the trajectory, its related temporal patterns of metabolic indices, and comorbidities. **Methods and Results:** This was a longitudinal study. In the Diabetes Management through Integrated Delivery System project in Taiwan, enrollees had diabetes, but no major comorbidities. They were randomized into intensive or conventional education (health, diet and exercise) groups. HbA1c was classified by a group-based trajectory model on the basis of repeated six-monthly measurements. We analyzed data from 1091 subjects who had at least two measurements on HbA1c. HbA1c exhibited three distinct ranges of low (42-53 mmol/mol), intermediate (64-75 mmol/mol) and high (97 mmol/mol), all of which persisted for 4.5 years regardless of receiving intensive education or not. Temporal changes and a time-group interaction were found for triglycerides, total cholesterol, HDL-C and LDL-C. The high trajectory was associated with the major co-morbidities of retinopathy, nephropathy, neuropathy, stroke, hypoglycemia, and ketoacidosis. Patients in the intensive education group (62.4%), which were equally distributed in the three trajectories, had significantly lower HbA1cs (-0.14%= -1.5 mmol/mol, p=0.026). The intermediate trajectory patients with intensive education had HbA1cs higher than the low trajectory patients with conventional education (β=0.189, p=0.033). Though not significant, a similar pattern was found for DM education in the high group (β=0.223, p=0.154). **Conclusions:** Novel strategies beyond current education and pharmacotherapeutic regimens are needed to lower HbA1c at least 11 mmol/mol for the high HbA1c group to minimize comorbidities.

Key Words: glycemic control, diabetes complications, metabolic memory, trajectory, DMIDS

INTRODUCTION

Diabetes severity is appreciable in Taiwan, among the five leading causes of death since 1983[1] with increasing prevalence and high mortality.[2] The glycated hemoglobin (HbA1c) has been found to be 65±18 mmol/mol in Taiwanese with diabetes, over half having an HbA1c>57 mmol/mol.[3] In 230 diabetes centers in Asia, the HbA1c was 70±22 mmol/mol (N=18211) and 55% of patients had an HbA1c>44 mmol/mol, which indicates poor gly-

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cemic control across this region.[4]

Intensive glycemic control has been studied extensively. Type 2 diabetes patients treated with multiple insulin injections have less retinopathy and nephropathy than those with conventional insulin injections for 6 years[5]; while intensive treatment is associated with higher all-cause mortality.[6] Hypoglycemia has been considered a reason for the higher mortality at the lower glycemic end.[7] Yet, intensive blood glucose control results in no reduction in major macrovascular events, although it does in microvascular events, manifested mainly as nephropathy.[8] Nevertheless, long-term benefits of intensive control on diabetes have been observed.[9,10]

To minimize complications of diabetes, multifactorial intervention has been used.[11,12] In a randomized trial, with intensive treatment more tied to goals, the onsets of nephropathy and retinopathy were delayed during 3 years follow-up.[12] After that, both patients received standard treatment, and those treated intensively remained at a lower risk of cardiovascular events and mortality for another 5 years.[11] However, a Cochrane systematic review and meta-analysis found no improvement in all-cause mortality with intensive therapy or conclusive evidence for macrovascular or microvascular end-points, while severe hypoglycemic episodes were increased by 30%.[13]

Most studies of glycemic control use baseline data to predict outcomes. Few have described the trajectories of the chosen glycemic indicator. In this study, we first identified the HbA1c trajectories in diabetes patients managed by Taiwanese community-based clinics. Then, we assessed the temporal changes in related metabolic indices in regard to the defined trajectory clusters of HbA1c. Finally, we evaluate whether intensive education overcomes trajectory clusters.

MATERIAL AND METHODS

Participants

Subjects were enrolled in the Diabetes Management through the Integrated Delivery System (DMIDS) project (NCT00288678 ClinicalTrial.gov) which was granted ethics approval by the Institutional Review Board of National Health Research Institutes. Informed consent was obtained to link health insurance claim data from the Bureau of National Health Insurance (BNHI) to the study. Only those subjects who provided consent forms were included in the study.

The project aimed to investigate the effectiveness of randomized educational interventions and case management for type 2 diabetes in community-based clinics.[14] Teaching hospitals in northern, central and southern Taiwan were chosen as the study centers. They recruited 36 local clinics between August 2003 and December 2005. The intervention lasted until December 2008. All patients treated in the collaborating clinics were eligible except (i) age < 30 or > 70 years; (ii) type 1 diabetes; (iii) women with gestational diabetes; and (iv) those with major complications of diabetes. Participants were randomized into conventional or intensive education groups. The conventional group continued their routine care, whereas the intensive education group received instruction on self-monitoring glucose, medication, exercises, diet control, foot care, and complication management from a qualified health manager who had a diabetes shared-care license. However, some clinics already practiced intensive education. We asked the participants if they received intensive education.

Study variables

Baseline demographic characteristics included family history of diabetes, smoking, betel nut chewing, alcohol drinking, and disease history. At baseline and every 6 months, a medical history, behavioral and nutritional assessments, a physical check-up and blood samples were obtained.

Weight and height were measured at each visit. Body mass index (BMI) was calculated (kg/m^2). Waist circumference (WC) was measured at the midpoint between the lowest rib and the iliac crest. Blood pressure (BP) was the mean of three repeats measured with a mercury sphygmomanometer after participants sat for at least 10 min.

Fasting venous blood was collected. All blood and urine specimens in 2-8 °C containers were express transported to a central laboratory. HbA1c was assayed by HPLC (Variant II; Bio-Rad Laboratories, Hercules, CA, USA). Fasting blood glucose, triglycerides (TG), total cholesterol, and high-density lipoprotein cholesterol (HDL-C) were analyzed by an automatic analyzer. The average intra-assay and inter-assay coefficients of variation for all analytes were all <5%. The urine albumin to creatinine ratio (ACR) was calculated.[14] Glomerular filtration rate (GFR), was calculated as $186.3 \times (\text{creatinine}^{-1.54}) \times (\text{age}^{-0.203}) \times 1.227 \times (\text{men: } 1; \text{ women: } 0.742)$.[15]

The BNHI data were linked to DMIDS. We extracted information on medication which included medication 1 year prior to study entry and at the last observation point. The BNHI allows 3-month prescriptions for chronic diseases, which determined the medication analysis intervals.

Complications and their corresponding ICD-9-CM codes were as follows: for acute complications: (a) hypoglycemia (251.1 or 251.2); and (b) ketoacidosis (250.1); for chronic complications: (a) peripheral circulatory disorders (2507), gangrene (7854, 0400, 4402), amputation (885, 886, 887, 895, 896, 897), or surgery (841); (b) retinopathy (361, 362, 2505) or blindness (369); (c) nephropathy (580, 581, 582, 583, 590, 2504) or kidney failure (584, 585, 586, 588); (d) neuropathy (250.6); (e) ischemic heart disease (410, 411, 412, 413, 414); and (f) stroke (430-438).

Statistical methods

We used the group-based trajectory model, which combines the methods for finite mixture models and cluster analysis with longitudinal data, to identify the patterns of HbA1c. The model classifies individuals into clusters with similar trajectories according to the longitudinal data of individuals, assuming that individual differences in trajectories can be summarized by a finite set of different polynomial functions for age or time by an SAS macro (http://www.andrew.cmu.edu/user/bjones/index.htm).[16] The Bayesian information criterion (BIC) was used to select the optimal model.[17]

Then we examined the temporal patterns of other indices for diabetes management, including BMI, WC, blood lipids, ACR, GFR, and BP, based on the classified HbA1c

trajectory groups. The baseline characteristics among groups were compared using ANOVA or chi-square tests. The temporal patterns among groups were compared using multivariable analysis (GENMOD) to account for the nature of repeated measurements. The effect of intensive education was compared accounting for possible confounders as well as clusters of trajectories. The changes in medication between various time points were compared using Cochran's Q test. We also compared the diabetic complications among groups using a proportional-hazards model controlling for age and BMI. All analyses were carried out using SAS version 9.

RESULTS

There were 1223 subjects recruited. We excluded those with missing data. One site in eastern Taiwan dropped out of the study several months after study initiation; its patients were excluded. Individuals with at least two repeated measurements of HbA1c were included. This left 1091 eligible participants for analysis. The average follow-up time was 4.5 years. Their baseline characteristics are shown in Table 1. The participants were 55.9±8.7 years old with a mean duration of follow-up of 5.1±5.6 years. More than half (56.5%) had a family history of diabetes. Around 27.8% reported smoking, 9.0% chewing betel nuts, and 36.2% drinking alcohol. Regarding comorbidities, 30.4%, 29.3% and 16.0% had retinopathy, nephropathy, and neuropathy, respectively. Also at entry, 67.4% had hypertension, 71.6% dyslipidemia, 26.1% heart diseases, and 10.0% stroke, but very few had experienced hypoglycemia or ketoacidosis.

Nutrient intakes for a sub-set of participants are shown in Table 2. ANOVA for repeated measure was used to examine the change over time as well as treatment effects. The results indicated that, with intensive dietary education, energy intakes were reduced, but at the expense of reduced nutritional quality as judged by changes in protein (-5.1 g/1000 kcals) and vitamin C (-2.5 mg/1000 kcals) nutrient densities.

The group-based trajectory model clearly separated patients into three groups (Figure 1); 47.2% of them had HbA1c around 42-53 mmol/mol (low), 38.3% with HbA1c around 64-75 mmol/mol (intermediate), and the rest with HbA1c around 97 mmol/mol (high) in the follow-up period (BIC=-10738.9 for number of observations and -10728.5 for number of subjects; the real BIC fell in between). There were no differences in gender or education profiles among the three HbA1c groups. The group with the highest HbA1c was younger; had a longer duration of diabetes; less physically active; a higher proportion with family history of diabetes; more neuropathy; higher TG, cholesterol, LDL, ACR and GFR; and a lower BMI than their counterparts at baseline (Table 1).

The temporal changes of other management indices are plotted in Figure 2. A multivariate model assuming first-order autoregressive error was used to test the time trends, group differences and time-group interactions of each variable. Those statistically significant are identified. Both low and intermediate groups had significantly lower WC and higher ACR than the high group. Significant time differences were observed in TG, cholesterol, LDL, GFR, and SBP. Time–group interactions appeared in WC, TG, cholesterol, LDL, and ACR, meaning that the changes in different groups differed over time.

In the high group, more were on insulin, biguanides, sulfonylureas, thiazolidinediones, or α-glucosidase inhibitors, but this was not the case for statins (Table 3). A similar pattern was found at the last time point. The use of each medication in the entire study population increased over time, except for biguanides and statins. Over 80% participants were prescribed two medications. Proportions of patients using two or three medications increased by the last time point. About 65% of the high group were prescribed three or more medications.

The incidences of complications among the three HbA1c groups are plotted in Figure 3. Significant differences existed among the groups for the development of retinopathy, nephropathy, neuropathy, stroke and ketoacidosis. Most of these complications showed lower incidences in the intermediate trajectory group and high incidences in the high trajectory group compared with the low group after controlling for age and BMI.

Patients with a lower education or a longer duration of diabetes were more likely to be in the higher HbA1c group controlling for other factors (Table 4). Conversely, older age and a higher BMI were correlated with a lower HbA1c. Patients in the intensive education group (62.4%), which were equally distributed in the three trajectories, had significantly lower HbA1cs (-0.14%=-1.54 mmol/mol, p=0.026). Even so, the intermediate trajectory patients with intensive education still had HbA1cs higher than the low trajectory patients with conventional education (β=0.189, p=0.033). Though not significant, a similar pattern was found for DM education in the high group (β=0.223, p=0.154).

DISCUSSION

We demonstrated persistence of HbA1c status in diabetes care in local clinics engaged in a project to enhance diabetes management in Taiwan. Those who started with lower HbA1cs stayed low, and those who started with higher values stayed high for 4.5 years. The pattern persisted even to the end of 2012 (9 years) (Appendix 1). This phenomenon possibly may be regarded as a form of "metabolic memory".[18]

Long-term effects of lowering HbA1c have been reported previously.[10,19,20] However, little information has been available about HbA1c trajectory, interventions and outcomes. Lind and colleagues estimated the correlation coefficients from the same individuals for different time intervals and found the correlation coefficients differed little for up to 4 years. Later, they used the same method to identify the time effect of HbA1c and found that values from 2-3 or even 5 years prior made a greater contribution to the prediction of contemporary progression of retinopathy than did the current values.[21] This persistence supports our findings. The trajectory analysis makes the simultaneous analysis of classification and trajectory possible. We believe ours is the first attempt to describe time trends in HbA1c and to find them to be relatively persistent.

Dietary intake advice was the major part of DM education. Whether this was intensive or usual education is known for all participants. However, detailed food rec-

Table 1. Comparison of characteristics of the three HbA1c group participants in the DMIDS study at entry

Variable	All (n, %)	Low (n, %)	Intermediate (n, %)	High (n, %)	χ^2
	1091 (100)	515 (47.2)	418 (38.3)	158 (14.5)	
Categorical variables					
Gender					
Women	569 (52.1)	277 (53.8)	207 (49.5)	85 (53.8)	1.882
Men	522 (47.9)	238 (46.2)	211 (50.5)	73 (46.2)	
Education					
Illiterate	76 (6.9)	37 (7.2)	31 (7.4)	8 (5.1)	12.025
Literate & elementary	538 (49.3)	238 (46.2)	206 (49.3)	94 (59.5)	
Middle school	329 (30.2)	158 (30.7)	127 (30.4)	44 (27.9)	
College and above	148 (13.6)	82 (15.9)	54 (12.9)	12 (7.6)	
Family history of diabetes (Yes)	616 (56.5)	274 (53.2)	234 (56.0)	108 (68.4)	17.883**
Leisure time activities (Yes)	542 (65.9)	279 (69.9)	203 (64.4)	60 (55.1)	8.882*
Current smoker (Yes)	303 (27.8)	122 (23.7)	136 (32.5)	45 (28.5)	9.065*
Betel nut chewing (Yes)	98 (9.0)	40 (7.8)	42 (10.1)	16 (10.1)	1.790
Alcohol drinking (Yes)	393 (36.2)	167 (32.4)	170 (40.7)	56 (35.4)	6.811*
Disease history†					
Retinopathy (Yes)	332 (30.4)	147 (28.5)	127 (30.8)	58 (36.7)	
Nephropathy (Yes)	320 (29.3)	155 (30.1)	125 (29.9)	40 (25.3)	3.808
Neuropathy (Yes)	174 (16.0)	55 (10.7)	77 (18.4)	42 (26.6)	1.44
Heart disease (Yes)	286 (26.1)	128 (24.9)	112 (26.8)	46 (29.1)	25.9***
Stroke (Yes)	109 (10.0)	55 (10.7)	45 (10.8)	9 (5.7)	1.252
Hypoglycemia (Yes)	2 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	3.791
Ketoacidosis (Yes)	58 (5.3)	21 (4.1)	24 (5.7)	13 (8.2)	0.365
Hypertension (Yes)	735 (67.4)	370 (71.8)	261 (62.4)	104 (65.8)	4.381
Dyslipidemia (Yes)	781 (71.6)	365 (70.9)	303 (72.5)	113 (71.5)	9.484**
DM education (Yes)	678 (62.4)	353 (68.5)	246 (58.9)	79 (50.0)	0.296
Continuous variables (mean±SD)					F
Age (years)	55.9±8.7	56.4±8.9	56.0±8.3	54.1±8.7	4.27*
Duration of diabetes (years)	10.0±5.7	8.5±5.0	10.7±5.6	12.5±6.8	37.5***
Waist (cm)	88.1±10.4	88.7±10.4	87.8±9.6	86.7±12.2	2.67
BMI (kg/m^2)	26.0±3.6	26.2±3.5	25.9±3.6	25.3±3.5	3.97*
Triglycerides (mg)	179±169	155±114	196±196	210±220	10.1***
Cholesterol (mg)	193.9±41.9	185.9±37.1	197.8±43.3	210.2±47.1	24.0***
HDL (mg)	48.1±12.4	47.7±12.1	48.2±13.0	49.4±11.5	1.17
LDL (mg)	124.6±35.3	120.0±33.8	125.8±35.1	136.5±37.4	14.1***
ACR	10.0± 7.1	8.7±6.6	11.2±7.5	11.8±7.4	10.9***
GFR	127.1±54.7	121.2±39.6	130.3±72.2	137.9±38.8	6.85**
SBP (mmHg)	130.0±15.8	129.9±16.2	130.6±16.1	128.8±14.1	0.74
DBP (mmHg)	80.7±9.6	80.5±9.6	81.0±9.8	80.4±8.9	0.33

†All diseases were extracted from the NHI database. *$0.01 \le p < 0.05$; **$0.001 \le p < 0.01$; ***$p < 0.001$.

BMI: body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ACR: albumin to creatinine ratio; GFR: Glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table 2. Comparisons on nutrient intakes between intensive and conventional DM educations

Nutrients	Baseline Year 2003						Year 2005						F
	Total		Intensive		Conventional		Total		Intensive		Conventional		
	n	%	n	%	n	%	n	%	n	%	n	%	
	95	100.0	61	64.2	34	35.8	95	100.0	61	64.2	34	35.8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Energy (Kcal)	2205.3	506.3	2247.2	550.9	2130.1	411.6	1994.6	786.0	1924.1	775.5	2121.0	800.5	4.22*
Protein (g)	83.9	22.5	86.1	23.7	79.9	19.9	66.5	25.9	63.8	22.8	71.4	30.5	5.12*
Fat (g)	78.8	23.5	80.6	24.5	75.6	21.4	65.4	29.8	64.2	28.3	67.5	32.5	1.52
Carbohydrate (g)	283.9	69.8	288.5	69.0	275.5	71.5	265.3	88.5	256.1	89.1	281.6	86.3	3.34
Fiber (g)	4.7	2.6	4.9	2.9	4.4	2.0	5.3	3.9	5.2	3.0	5.4	5.2	0.63
Dietary fiber (g)	15.2	7.1	15.7	7.2	14.4	7.0	16.9	10.3	17.3	9.5	16.1	11.7	0.00
Phosphorous (mg)	1037.1	315.0	1072.2	309.2	974.1	320.0	965.1	453.3	962.9	476.5	969.2	415.2	1.08
Iron (mg)	11.5	8.5	12.1	9.4	10.4	6.6	11.4	10.7	11.3	11.4	11.5	9.5	0.43
Vitamin A (mg)	2185.6	3505.6	2049.7	3466.1	2429.6	3614.8	1076.3	2440.7	1198.6	2988.4	856.8	808.7	0.60
Vitamin B1 (mg)	1.8	3.5	1.6	2.2	2.3	5.1	1.3	3.8	1.4	4.3	1.2	2.9	0.89
Vitamin B2 (mg)	1.2	0.6	1.2	0.7	1.0	0.5	1.1	0.7	1.1	0.7	1.1	0.7	0.77
Vitamin B6 (mg)	1.6	0.7	1.6	0.8	1.5	0.7	1.4	1.0	1.4	1.0	1.6	1.0	1.33
Vitamin B12 (mg)	5.1	4.8	4.4	2.7	6.5	7.0	5.5	9.3	3.8	4.7	8.4	14.0	1.24
Vitamin C (mg)	163.0	121.6	171.1	131.0	148.5	102.7	163.5	163.9	141.7	96.1	202.6	239.3	4.50*
Vitamin E (mg)	8.2	4.0	8.8	4.1	7.2	3.6	6.0	3.0	6.1	3.0	5.9	3.1	2.54
Niacin (mg)	19.1	9.6	19.4	9.7	18.7	9.6	18.1	11.9	18.2	12.0	18.0	11.9	0.04
Cholesterol (mg)	290.6	199.4	312.2	216.3	251.8	160.4	240.3	213.3	225.5	198.6	266.8	238.3	3.63
Calcium (mg)	417.3	278.9	433.4	243.9	388.3	334.7	395.3	262.7	392.9	240.7	399.5	301.9	0.47
Sodium (mg)	1817.5	2505.4	2028.2	3033.5	1439.4	959.2	1394.8	978.6	1444.2	1030.6	1306.2	885.5	0.78
Potassium (mg)	2207.4	714.3	2304.7	784.4	2033.0	534.7	2118.5	956.2	2123.6	886.8	2109.5	1,083.6	1.34
Magnesium (mg)	242.2	85.2	245.9	82.5	235.6	90.8	258.8	178.7	258.5	188.1	259.4	163.2	0.08
Zinc (mg)	9.5	2.8	9.8	3.2	9.0	2.1	8.3	3.6	8.1	3.5	8.8	3.7	3.70

F value was generated for comparing change over time in two treatments, i.e. treatment differences in (time2-time1). It was a mixed model.$^{*}0.01 \leq p < 0.05$; $^{**}0.001 \leq p < 0.01$; $^{***}p < 0.001$.

Table 3. Proportions of uses and changes of medications for diabetes or lipids in the three HbA1c trajectory groups.

Medication	All (n, %)	Low (n, %)	Median (n, %)	High (n, %)	χ^2
Medication type					
1 year before study entry					
Insulin	58 (5.3)	16 (3.1)	25 (6.0)	17 (10.8)	14.7***
Biguanides	896 (82.1)	395 (76.7)	357 (85.4)	144 (91.1)	22.1***
Sulfonylurea	990 (90.7)	438 (85.1)	396 (94.7)	156 (98.8)	39.8***
Thiazolidinedione	126 (11.6)	33 (6.4)	64 (15.3)	29 (18.4)	26.3***
α-Glucosidase Inhibitors	66 (6.1)	23 (4.5)	26 (6.2)	17 (7.8)	8.46**
Statin	409 (37.5)	201 (39.0)	163 (39.0)	45 (28.5)	6.40*
Between 3 month before and 4.5 years after study entry					
Insulin	129 (11.8)***	24 (4.7)	55 (13.1)***	50 (31.7)***	85.6***
Biguanide	923 (84.6)	406 (78.8)	375 (89.9)	142 (89.9)	24.9***
Sulfonylurea	933 (85.5)***	421 (81.8)	369 (88.3)***	143 (90.5)**	11.7**
Thiazolidinedione	224 (20.5)***	65 (12.6)***	117 (28.0)***	42 (26.6)	37.5***
α-Glucosidase inhibitor	169 (15.5)***	55 (10.7)***	76 (18.2)***	38 (24.1)**	20.3**
Statin	417 (38.2)	202 (39.2)	154 (36.8)	61 (38.6)*	6.40*
Number of medications†					
1 year before study entry					
Any one	1076 (98.6)	503 (97.7)	415 (99.3)	158 (100)	7.00*
Any two	906 (83.0)	390 (75.7)	367 (87.8)	149 (94.3)	40.5***
3 or more	441 (40.2)	180 (35.0)	191 (45.7)	70 (44.3)	12.2**
Between 3 months before and 4.5 years after study entry					
Any one	1074 (98.4)	503 (97.7)	415 (99.3)	158 (100.)	8.58*
Any two	943 (86.4)	409 (79.4)	385 (92.1)	149 (94.3)	41.4***
3 or more	541 (49.6)	200 (38.8)	239 (57.2)	102 (64.6)	47.6***

*$0.01 \leq p < 0.05$; **$0.001 \leq p < 0.01$; ***$p < 0.001$ for comparing differences among groups using overall chi-squared test.

†Sum of the listed medications. *$0.01 \leq p < 0.05$; **$0.001 \leq p < 0.01$; ***$p < 0.001$ for comparing changes in using a certain drug over time using Cochran's Q test.

Table 4. Factors associated with HbA1c in the three groups, accounting for temporal effects

Variable	Coefficients	*p*
Age (years)	-0.008	0.013*
Women vs m	0.043	0.477
Education		
Illiterate vs. college and above	0.140	0.239
Literate & elementary vs. college +	0.169	0.011*
Middle school vs. college +	0.140	0.030*
Family history of diabetes (Yes)	0.003	0.947
Current smoker (Yes)	-0.003	0.962
Betel nut chewing (Yes)	-0.008	0.931
Alcohol drinking (Yes)	-0.026	0.642
Duration of DM	0.020	<0.0001***
Intensive DM education (Yes)	-0.146	0.021*
BMI (kg/m^2)	-0.017	0.0109**
Groups		
Intermediate vs. low	1.612	<0.0001***
High vs. low	3.627	<0.0001***
Interaction (conventional and low group as reference)		
Intensive DM education & median	0.197	0.028*
Intensive DM education & high	0.226	0.147
Increased number of medication from baseline		
1	0.063	0.181
2 or more	-0.087	0.409

*$0.01 \le p < 0.05$; **$0.001 \le p < 0.01$; ***$p < 0.001$

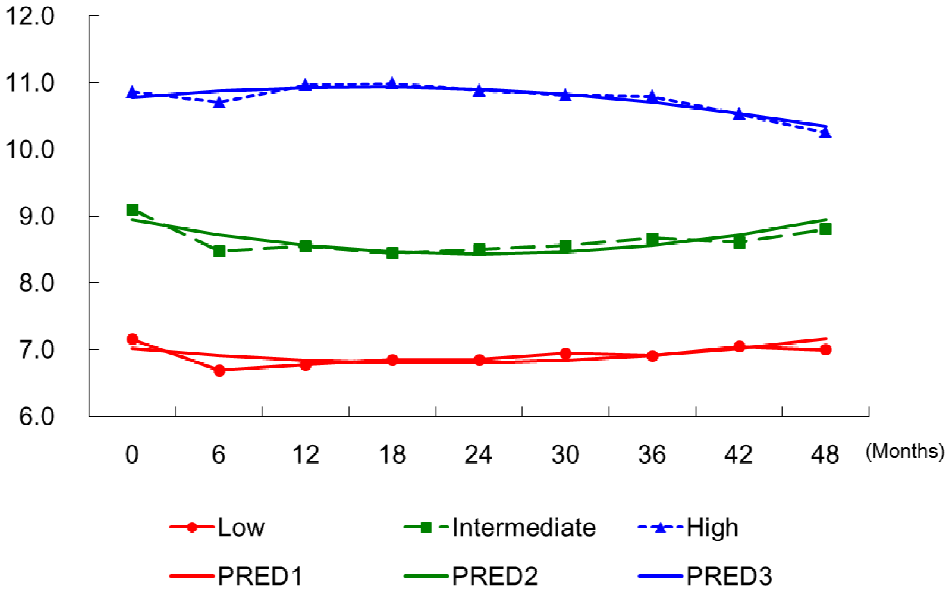


Figure 1. Trajectories of HbA1c. The solid line is the average observed value, whereas the dashed line is the average estimated value after grouping

ords were not routinely kept and those available were expressed in nutrient terms for the DMIDS project. Insofar as these data allow, we can say that with the 'best dietary education' total energy, protein and vitamin C intakes were reduced, so that there was no identifiable improvement in dietary quality (Table 2). Thus, it is conceivable that an achieved reduction in energy intake has been misinterpreted as success when it has compromised dietary quality, now known to be important not just in regard to glycaemic control, but also the likelihood of complications. Therefore, the current approach to dietary management may itself be a contributor to the inability to change the trajectories of glycaemic control and of complication rates.[22]

Progression of indicators

Body composition

Often, weight loss is welcomed in management of type 2 diabetes, but here it occurred with poor glycaemic control reflected in persistently elevated HbA1c levels. It would be expected that the phenomena usually seen with hyperglycaemia, namely osmotic diuresis and muscle breakdown with excessive gluconeogenesis from amino acids, leading to sarcopenia, would explain the weight and BMI findings here. Nevertheless, WC decreased as well, which, if it represents a reduction in abdominal obesity, is

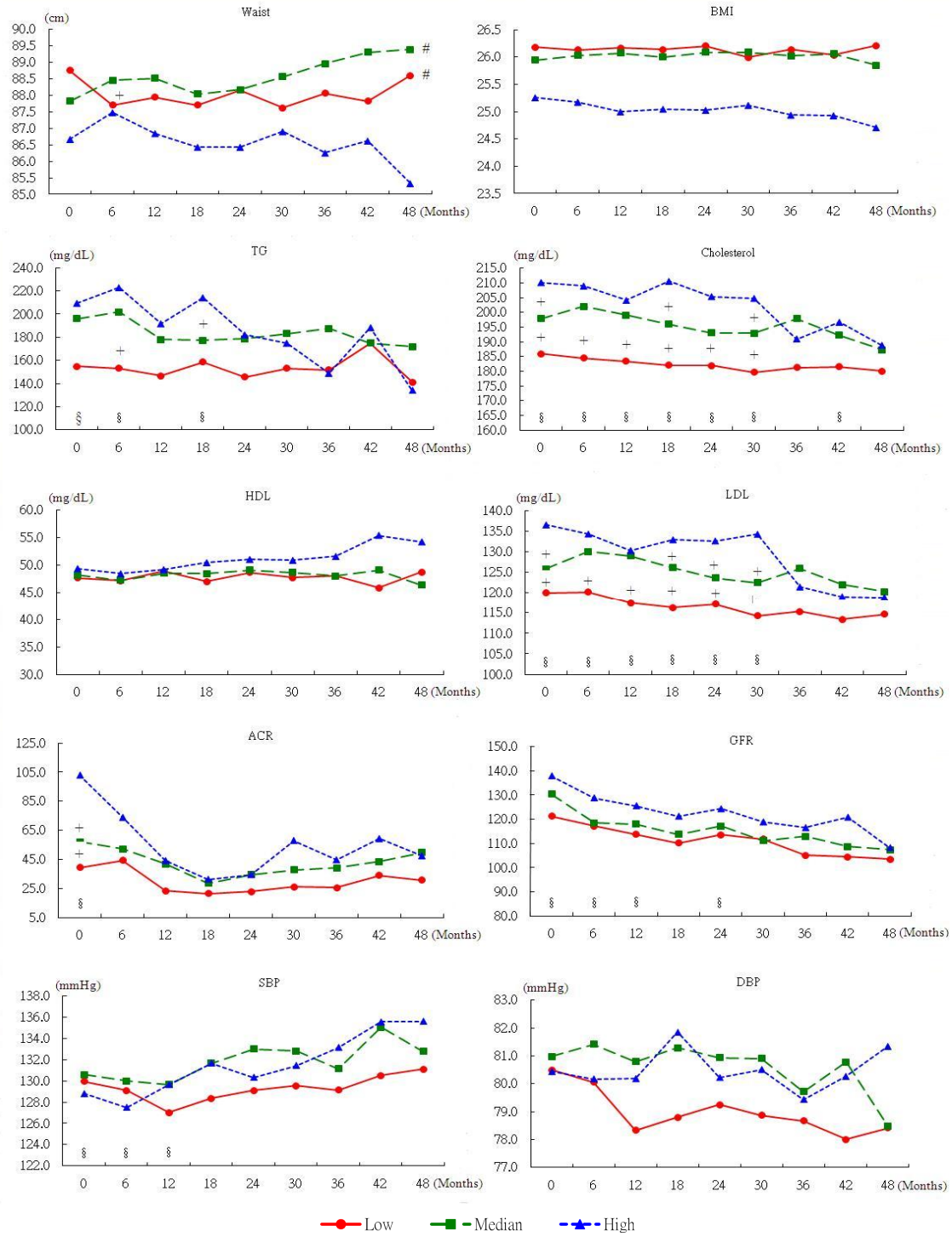


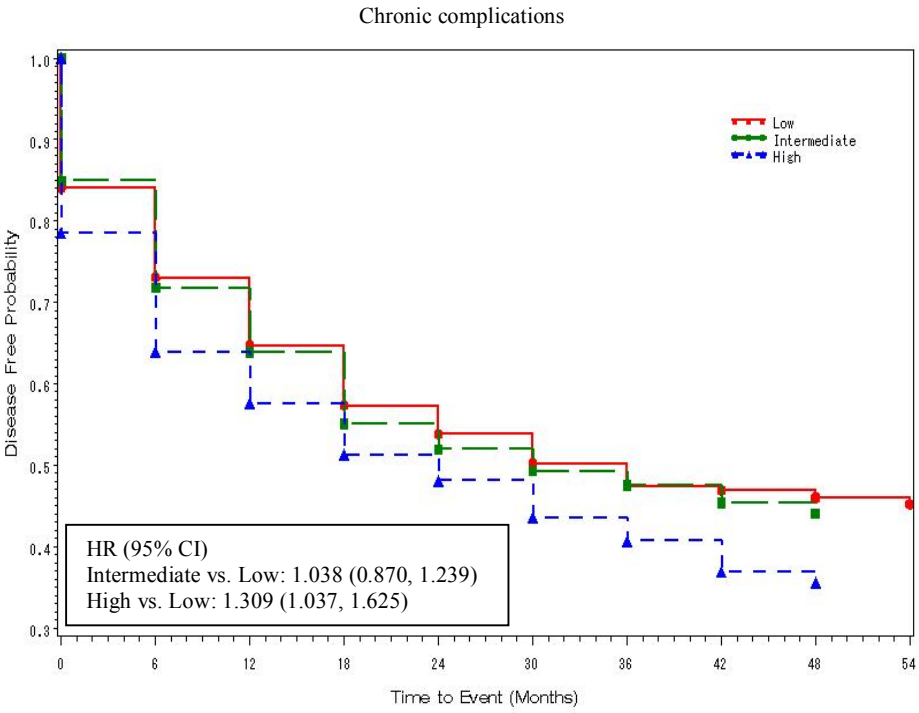
Figure 2. Temporal changes of the diabetes related indices based on the three groups. # indicates group difference. The high group is the reference group.§ indicates time difference. The 48 month value is the reference value.† indicates group × time interaction. The high group and the 49 month value is the reference.

likely to be a favorable contributor to the weight change alongside unfavorable body compositional changes.

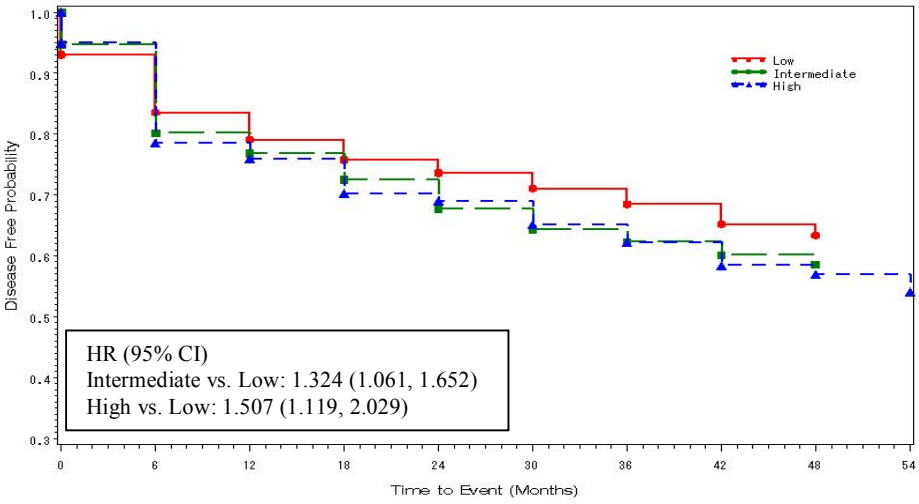
A weight trajectory study in diabetes concluded that weight loss, possibly some fat loss, at the time of diagnosis was an important predictor of future glycaemic control.[23] We looked at this from a different angle. Our study took a longer-term perspective of weight loss in type 2 diabetes with worse HbA1c, which, if recognized early, might alert to opportunities to maintain a healthier body composition.

Lipoproteins

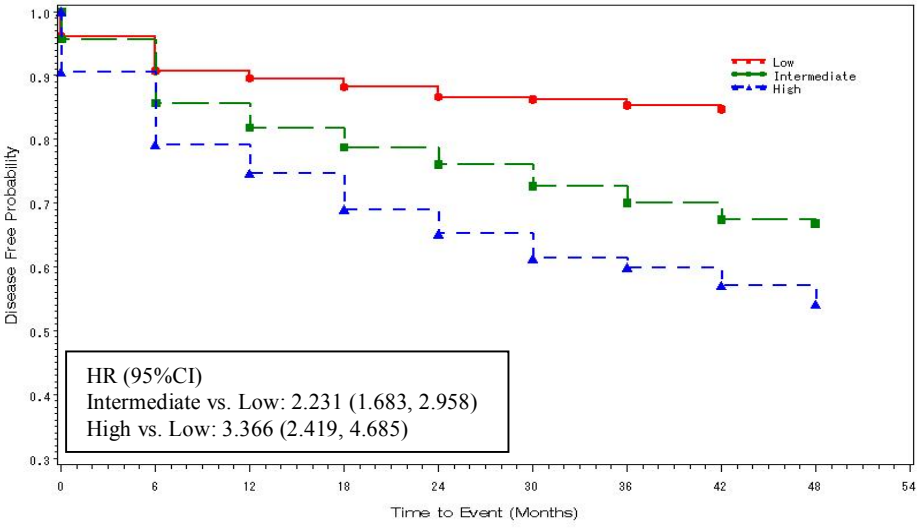
In the Taiwanese general population, higher TG are associated with relatively higher HDL-C than in Caucasians. Lipoprotein susceptibility to a high glycemic trajectory may be different in this population, and the quality of the higher HDL-C may be more reflective of a chronic inflammatory state than of more effective reverse cholesterol transport from atherosclerosis-vulnerable arteries. "Bad" HDL-C is found in various inflammatory disease states.[24] The rise in HDL-C may not represent less cardiovascular risk in this situation. The steady-state LDL-C



(a) Retinopathy

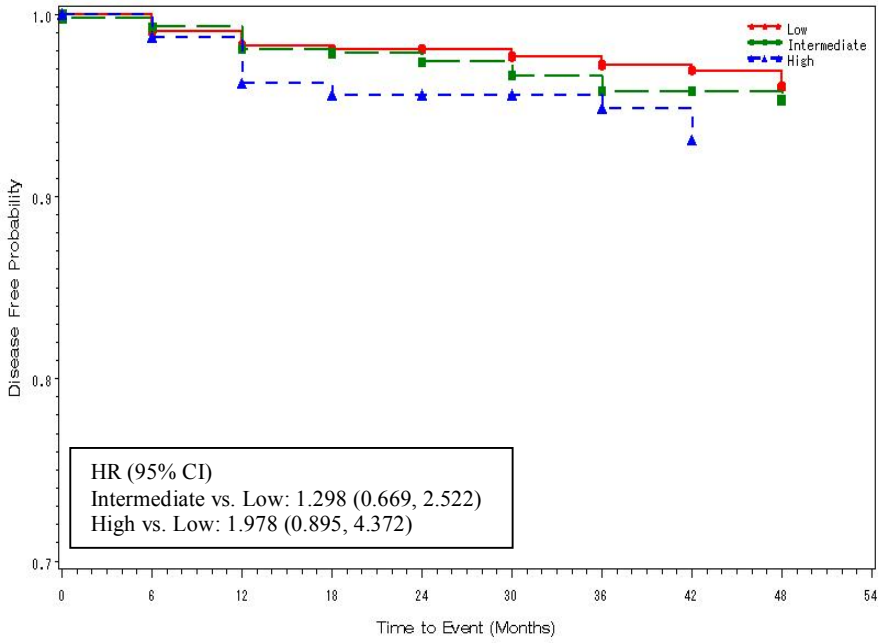


(b) Nephropathy

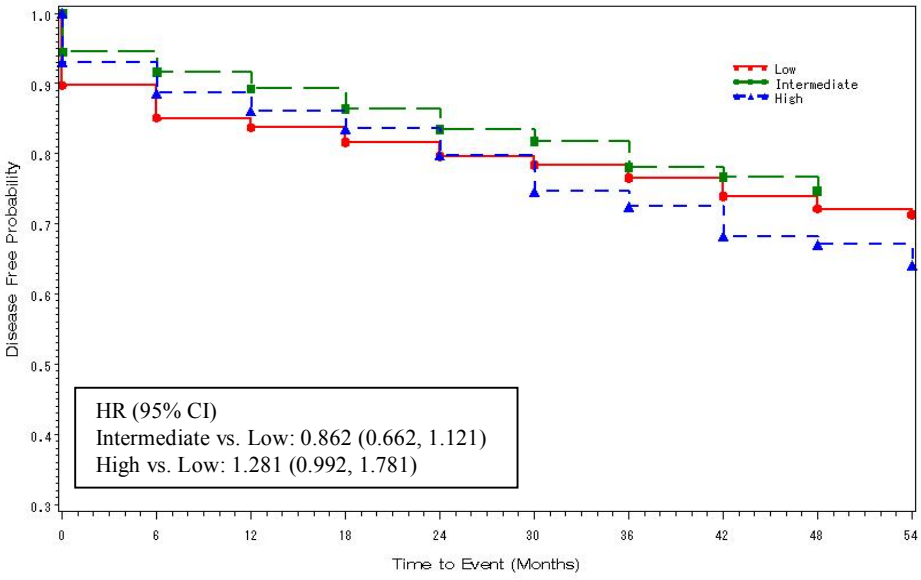


(c) Neuropathy

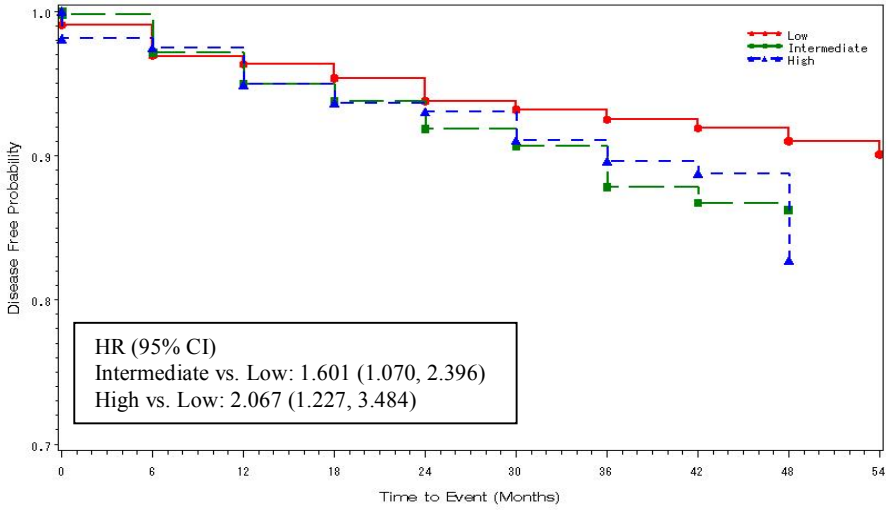
Figure 3. Comparisons of incidence of comorbidities among the three groups. All hazard ratios (HR) were adjusted for age and BMI.



(d) Gangrene

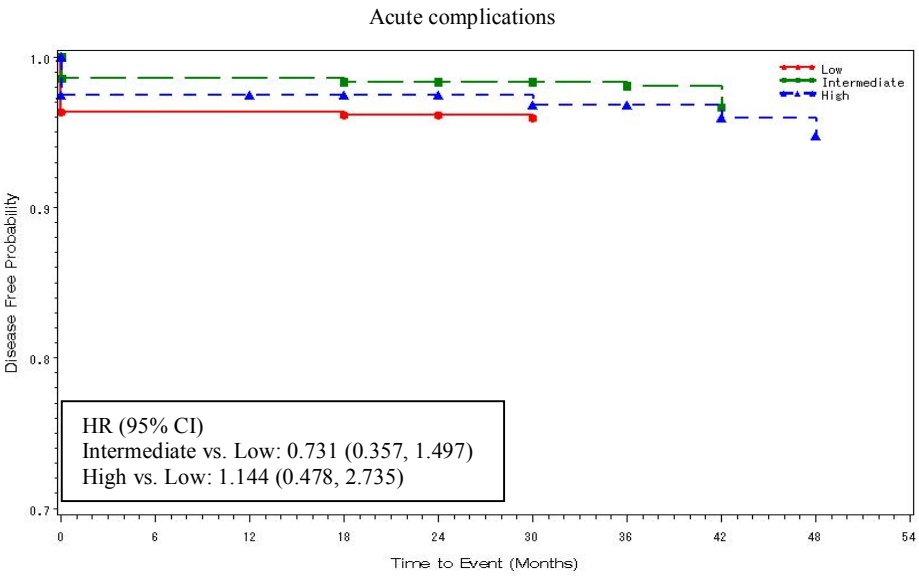


(e) Ischemic heart diseases

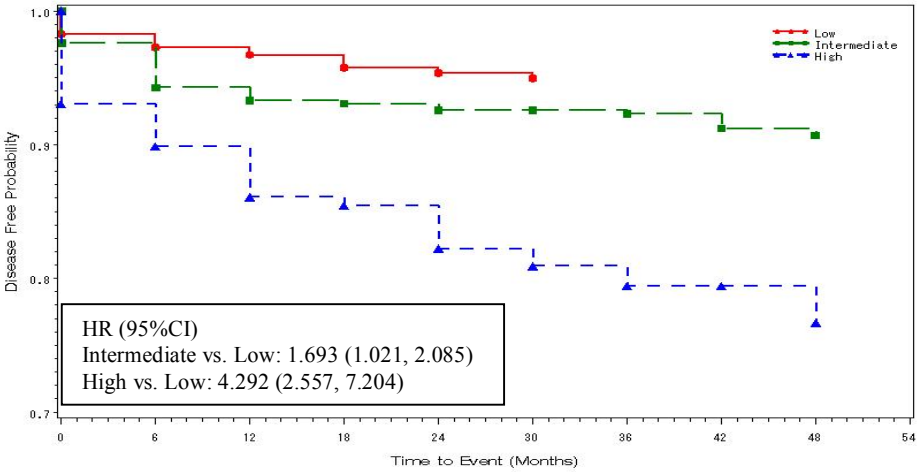


(f) Stroke

Figure 3. Comparisons of incidence of comorbidities among the three groups. All hazard ratios (HR) were adjusted for age and BMI. (cont.)



(g) Hypoglycemia



(h) Ketoacidosis

Figure 3. Comparisons of incidence of comorbidities among the three groups. All hazard ratios (HR) were adjusted for age and BMI. (cont.)

in this study may represent a form of resistance or adaptation to persistent glycemic trajectories in each stratum.

Blood pressure

The trajectories of SBP and DSP were dissociated, with that for SBP projecting upwards for all glycemic trajectories and that for DBP remaining unchanged. The responses among our study subjects may not be generalizable to other populations because of differences in the prevalence of these two forms of hypertension. Studies have observed that elevated diastolic BP being more common than elevated systolic BP in Chinese Taiwanese compared to their prevalence in Caucasians.[25,26] This dissociation may signal general difficulty in patient adherence to low sodium: potassium ratio diets in Taiwan, which would accentuate this problem with time.[27]

Persistent glycemic trajectories

The term "metabolic memory" has been used to describe the situation in which glycemic control at the early stage of the disease could persist for a long time.[28] Much focus has been placed on the negative effects of non-intensive treatment at early stages.[29] In turn, a diversity of "memories" may allow or disallow one complication compared with another, as appears to be the case in our various glycemic trajectories. In our study, glycemic trajectory predicted the development of nephropathy. Whatever the underlying glycemic disorder, early intensive glycemic control at its high end is warranted.[6-8]

Use of pharmaceuticals

There was greater use of both insulin and oral antihyperglycemic medications of all types used in Taiwan in the high trajectory patients (Table 2). Where there was use of only one or two medications, this did not change much over time, whereas the use of three medications increased slightly in the intermediate and high groups. It seems that physicians were satisfied with keeping patients at a stable HbA1c level, instead of lowering it. Some have identified a reluctance of physicians to increase medication usage in diabetes management, which they have termed "physician inertia".[30]

We found that total cholesterol decreased and HDL-C increased with time in the high trajectory group. This raises the possibility that there is a lipoprotein-metabolic phenomenon operating in this group. We have considered that weight loss might have accounted for the fall in total cholesterol, but LDL did not differ among the groups or change with time. This leaves us with reciprocal changes between VLDL-TG and HDL-C (Figure 2). These are favorable changes by current convention (although the literature now refers to "bad" HDL). Perhaps it is because the use of all oral anti-hyperglycemic agents and insulin have increased with time and been lipid-favorable. Alternatively, sustained high glycemic status may induce compensatory and CVD risk---favorable changes in lipoprotein status.

Factors associated with HbA1c level

The differences in education level implied people with higher education took better care of themselves. In addition, those who received intensive education had lower HbA1c levels. The magnitude of the trajectory group difference in HbA1c was around 2%; but education intervention could only account for <0.2% HbA1c, which would not move patients from the high to a lower group. It is clear that prevalent and multiple drug therapy with oral anti-hyperglycemic agents or insulin does little for those with the high HbA1c trajectory over a period of 4.5 years. Thus, while the potential value of avoidance of the high glycemic trajectory, through early and effective management, is evident, present measures are not able to realize this goal. Changing diet has been difficult, even it has been the major lifestyle intervention on DM. Even though most of DM patients claimed they practice diet control, [31] their actual dietary intakes might not meet the standard. Creative and easily implemented ways in diet control are needed.

Limitations

Patients recruited were not necessarily newly diagnosed; however, they did not have major diabetes complications at entry. Nevertheless, newly diagnosed subjects often present with conditions other than diabetes and where there has been a delay in diagnosis so that they may not be very different from our study population. This is especially so since patients treated in local or community clinics are considered less severe and more stable than those in regional hospitals or medical centers. However, within about 4.5 years, we observed the emergence of diabetes complications and more so in patients in the high HbA1c group. A longer period of follow-up might have changed the picture of HbA1c persistence and its relevance, most likely towards greater severity of outcomes.

The dietary records were only available in 95 patients. Among the study sites, only one site recorded the nutrient intakes. Nevertheless, the results were published for this site.[22] The information of food intakes was converted to nutrients. It would be more informative if food information was available.

Our observation of stratified HbA1c persistence seems to represent inadequately developed clinical diabetes programs in Taiwan for the high end of HbA1c, despite the intention that the DMIDS project represents best practice as we know it. But inadequate HbA1c trajectory control by current clinical standards is unlikely to explain persistence within a given stratum widely divergent from the other strata. Aside from the characteristics of clinical programs or poorly understood metabolic biology as limiting for optimal glycaemic control, our findings may also represent entrenched personal behaviors in a societal sector.[31] As for what biological explanations there might be for the stratification or its consequences it may represent a form of metabolic memory. It may also have a partial genetic, familial or epigenetic basis.[32]

Conclusions

Assignment to a high HbA1c group at an early stage can identify patients with diabetes whose health indicators progressively deteriorated over a period of 4.5 years, with the corollary that those in the intermediate and low HbA1c groups have persistent relative advantages. However, novel strategies beyond current education and pharmacotherapeutic regimens are needed to lower HbA1c by at least 11 mmol/mol (2%) in absolute terms for the high HbA1c group to minimize comorbidities.

ACKNOWLEDGEMENTS

Appreciations should go to the field workers who work diligently in recruiting patients. We greatly appreciate the participants without them the study would not be possible.

AUTHOR DISCLOSURES

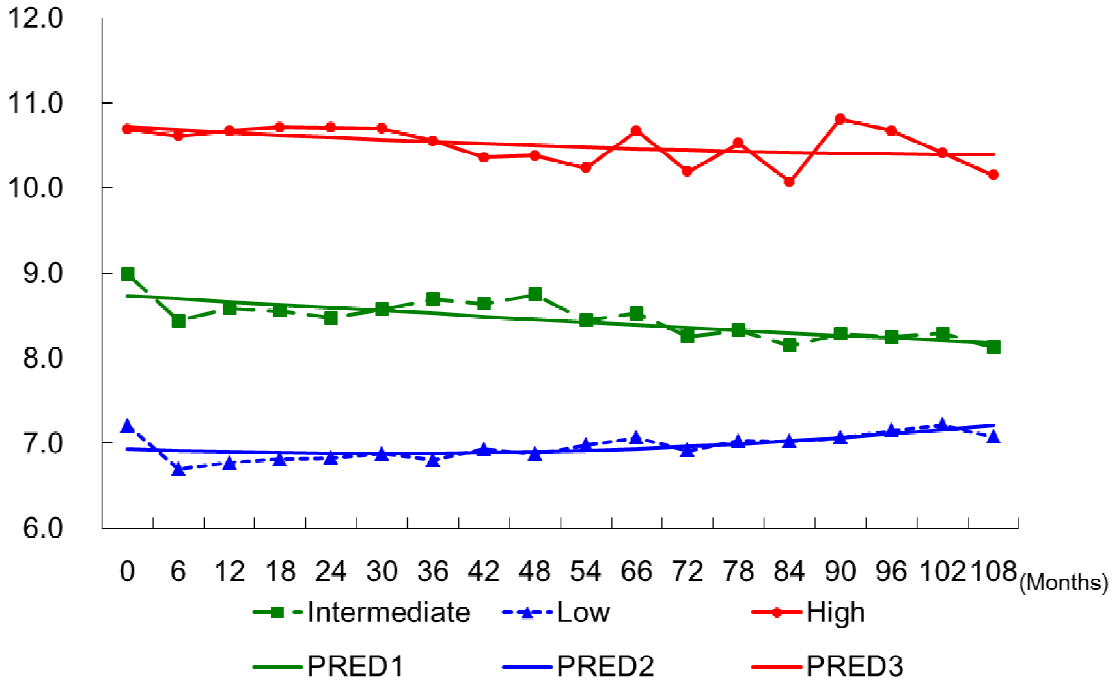
There is no conflict of interest with any author. The corresponding author, Chih-Cheng Hsu, has full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. National Health Research Institutes provided funding for the whole study, including design and conduct; data management, analysis, and interpretation of the data; and preparation, review of the manuscript.

REFERENCES

1. Health and Vital Statistics: (2) Vital Statistics, Taiwan area, ROC. In: Health. Do, editor. Taipei: Department of Health, The Executive Yuan, Republic of China; 2009.
2. Chang HY, Hsu CC, Pan WH, Liu WL, Cheng JYC, Tseng CH, Bai CH, Yeh WT, Hurng BS. Gender differences in trends in diabetes prevalence from 1993 to 2008 in Taiwan. Diabetes Res Clin Pract. 2010;90:358-64. doi: 10.1016/j.diabres.2010.09.032.
3. Chuang LM, Tsai ST, Huang BY, Tai TY. The current state of diabetes management in Taiwan. Diabetes Res Clin Pract. 2001;54(Suppl 1):S55-65. doi: 10.1016/S0168-8227(01)00310-2.
4. Chuang LM, Tsai ST, Huang BY, Tai TY. The status of diabetes control in Asia--a cross-sectional survey of 24 317 patients with diabetes mellitus in 1998. Diabet Med. 2002;19:978-85. doi:10.1046/j.1464-5491.2002.00833.x.
5. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract.1995;28:103-17. doi:10.1016/0168-8227(95)01064-K.
6. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr, Bigger JT, Buse JB et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545-59. doi: 10.1056/NEJMoa0802743.

7. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, Zagar T, Poole CD. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet. 2010;375:481-9. doi: 10.1016/S0140-6736(09)61969-3.
8. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560-72. doi:10.1056/NEJMoa0802987.
9. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999;281:2005-12.doi: 10.1001/jama.281.21.2005.
10. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-89. doi: 10.1056/NEJMoa0806470.
11. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358:580-91. doi: 10.1056/NEJMoa0706245.
12. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet. 1999;353:617-22. doi: 10.1016/S0140-6736(98)07368-1.
13. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, Wetterslev J. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ. 2011;343:d6898. doi: 10.1136/bmj.d6898.
14. Hsu CC, Hwang SJ, Tai TY, Chen T, Huang MC, Shin SJ et al. Cigarette smoking and proteinuria in Taiwanese men with Type 2 diabetes mellitus. Diabet Med. 2010;27:295-302. doi: 10.1111/j.1464-5491.2010.02947.x.
15. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med. 1999;130:461-70.
16. Jones BL, Nagin DS. Advances in group-based trajectory modeling and a SAS procedure for estimating them. Sociol Res Methods. 2007;35:542-71.
17. Nagin DS. Group-Based Modeling of Development. Cambridge, Massachusetts, USA: Harvard University Press; 2005.
18. Wright AD. Metabolic memory in type 1 diabetes. Br J Diab Vasc Dis. 2009;9:254-7. doi: 10.1177/ 1474651409351645.
19. Gore MO, McGuire DK. The 10-year post-trial follow-up of the United Kingdom Prospective Diabetes Study (UKPDS): cardiovascular observations in context. Diab Vasc Dis Res. 2009;6:53-5. doi: 10.3132/dvdr.2009.012.
20. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643-53.doi: 10.1056/NEJMoa052187
21. Lind M, Oden A, Fahlen M, Eliasson B. The shape of the metabolic memory of HbA1c: re-analysing the DCCT with respect to time-dependent effects. Diabetologia. 2010;53:1093-8. doi: 10.1007/s00125-010-1706-z.
22. Huang MC, Hsu CC, Wang HS, Shin SJ. Prospective randomized controlled trial to evaluate effectiveness of registered dietitian-led diabetes management on glycemic and diet control in a primary care setting in Taiwan. Diabetes Care. 2010;33:233-9. doi: 10.2337/dc09-1092.
23. Feldstein AC, Nichols GA, Smith DH, Stevens VJ, Bachman K, Rosales AG, Perrin N. Weight change in diabetes and glycemic and blood pressure control. Diabetes Care. 2008;31:1960-5. doi: 10.2337/dc08-0426.
24. Scanu AM, Edelstein C. HDL: bridging past and present with a look at the future. Faseb J. 2008;22:4044-54. doi: 10.1096/fj.08-117150.
25. Saad MF, Lillioja S, Nyomba BL, Castillo C, Ferraro R, De Gregorio M et al. Racial differences in the relation between blood pressure and insulin resistance. N Engl J Med. 1991;324:733-9.
26. Wahlqvist ML, Chang HY, Chen CC, Hsu CC, Chang WC, Wang WS, Hsiung CA. Is impaired energy regulation the core of the metabolic syndrome in various ethnic groups of the USA and Taiwan? BMC Endocr Disord. 2010;10:11. doi: 10.1186/1472-6823-10-11.
27. Chang HY, Hu YW, Yue CS, Wen YW, Yeh WT, Hsu LS, Tsai SY, Pan WH. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. Am J Clin Nutr. 2006;83:1289-96. doi: 10.1097/00005650-199711000-00004.
28. Drzewoski J, Kasznicki J, Trojanowski Z. The role of "metabolic memory" in the natural history of diabetes mellitus. Pol Arch Med Wewn. 2009;119:493-500.
29. Engerman RL, Kern TS. Retinopathy and tissue hexose in drug-treated animals. Arch Ophthalmol. 1998;116:543-4.
30. Grant R, Adams AS, Trinacty CM, Zhang F, Kleinman K, Soumerai SB, Meigs JB, Ross-Degnan D. Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. Diabetes Care. 2007;30:807-12. doi: 10.2337/dc06-2170.
31. Li CL, Lin NY, Wang HH, Hsu CC, Hurng BS, Chang HY. A population study on changes in diabetes self-care behaviors in Taiwan between 2001 and 2005. Prev Med. 2010;50:308-9. doi: 10.1016/j.ypmed.2010.03.005.
32. Tonna S, El-Osta A, Cooper ME, Tikellis C. Metabolic memory and diabetic nephropathy: potential role for epigenetic mechanisms. Nat Rev Nephrol. 2010;6:332-41. doi: 10.1038/nrneph.2010.55.

Appendix



Nine year trajectories of HbA1c. The solid line is the average observed value, whereas the dashed line is the average estimated value after grouping.

Original Article

Management trajectories in the type 2 diabetes Integrated Delivery System project in Taiwan: accounting for behavioral therapy, nutrition education and therapeutics

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「台灣糖尿病社區聯合照護網絡暨長期追蹤計畫」中管理指標的發展軌跡：控制行為、營養教育與藥物治療後的結果

背景: 監測糖化血色素（HbA1c）是糖尿病管理的重要指標。但過去未曾有人描述整個糖化血色素在第 2 型糖尿病進展過程中的改變趨勢，以及相關代謝指標及共病症的時間變化。**方法與結果:** 這是一個長期追蹤研究。「台灣糖尿病社區聯合照護網絡暨長期追蹤計畫」收集沒有重大共病症的糖尿病患者，然後將他們隨機分派到實驗組或對照組。對照組的病人除了按照原有之方式予以照護之外，每年並分發若干衛教教材及施以兩次完整之糖尿病追蹤檢查，而實驗組的病人則由健康管理師依據健保署之給付規定提供額外的諮詢及綜理共同照護服務。研究首先將每六個月測得的 HbA1c 值依據其長期變化軌跡分做三組，有 1091 位受試者在研究期間至少有兩次 HbA1c 的測量值，其明顯可分出三組：低（42-53 mmol/mol）、中（64-75 mmol/mol）及高（97 mmol/mol），這種現象不論在實驗組或對照組持續 4.5 年，三酸甘油脂（TG）、總膽固醇(total cholesterol）、高密度膽固醇（HDL-C）以及低密度膽固醇（LDL-C）都隨時間改變，並且其時間與分組有交互作用。高軌跡組（血糖長期控制不佳者)有較高的機率罹患眼底病變、腎病變、神經病變、中風、低血糖、及酮酸中毒。分在衛教組的病人（62%）平均分配在三個軌跡中，他們 4.5 年的 HbA1c 顯著低於對照組（-0.14%= -1.5 mmol/mol，p=0.026）。而中（β=0.189，p=0.033）、高（β=0.223，p=0.154）軌跡組的 HbA1c 都高於低軌跡組。**結論:** 要有不同於目前衛教及醫療方式，至少將 HbA1c 降 11 mmol/mol，臨床上有較多之機會降低第 2 型糖尿病患者共病症的發生。

關鍵詞：血糖控制、糖尿病併發症、代謝記憶、發展軌跡、DMIDS