Improvement in Neuropathy Outcomes With Normalizing HbA_{1c} in Patients With Type 2 Diabetes

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Diabetes Care 2019;42:110–118 | https://doi.org/10.2337/dc18-1560

OBJECTIVE

To investigate the impact of normalizing HbA_{1c} by extensive HbA_{1c} control (EHC) on neuropathy outcome measures (NOMs), nephropathy, and retinopathy in type 2 diabetes.

RESEARCH DESIGN AND METHODS

Detailed clinical and neurological examinations were performed in two cohorts of 38 patients with uncontrolled type 2 diabetes (HbA_{1c} 9.6% [81.4 mmol/mol]) at baseline and after glycemic control (GC) with or without EHC by diet restriction and hypoglycemic agents over 4 years along with 48 control subjects with normal glucose tolerance (NGT) and 34 subjects with impaired glucose tolerance (IGT) only at baseline. EHC patients, control subjects, and subjects with IGT underwent oral glucose tolerance tests. Glycemic variability (GV) was evaluated by SD and coefficient of variation of monthly measured HbA_{1c} levels and casual plasma glucose.

RESULTS

In the EHC cohort, HbA_{1c} levels over 4.3 years and the last 2 years improved to 6.1% (43.2 mmol/mol) and 5.8% (39.9 mmol/mol) with 7.3 kg body wt reduction, and 50% and 28.9% of patients returned to IGT and NGT, respectively, at end point. Baseline neurophysiological and corneal nerve fiber (CNF) measures were impaired in patients. Normalized HbA_{1c} with EHC improved neurophysiological and CNF measures to be similar for those for IGT, while GC without EHC (mean HbA_{1c} level 7.0% [53.5 mmol/mol]) improved only vibration perception. The mean normalized HbA_{1c} levels by EHC determined NOM improvements. The high GV and baseline HbA_{1c} levels compromised NOMs. Albumin excretion rate significantly decreased, while retinopathy severity and frequency insignificantly worsened on EHC.

CONCLUSIONS

Normalizing HbA_{1c} in type 2 diabetes of short duration improves microvascular complications including neuropathy and nephropathy more effectively than standard GC but not retinopathy.

Intensive glycemic control (GC) has shown an equivocal efficacy regarding diabetic peripheral neuropathy (DPN) in type 2 diabetes (1), mainly due to nonoptimized HbA_{1c} levels. Randomized trials (2,3) have not been able to establish the optimum GC level for improving neuropathy outcomes in type 2 diabetes. In type 1

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Received 20 July 2018 and accepted 12 October 2018

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-1560/-/DC1.

diabetes, near-normoglycemia for 24 years prevented nerve function declines (4). The simultaneous pancreas-kidney transplantation (SPK) can normalize HbA_{1c} levels without severe hypoglycemia and was shown to improve corneal nerve fiber (CNF) measures (5). However, the long-standing normalization of HbA_{1c} levels by insulin-providing agents (IPAs) in poorly controlled type 2 diabetes seems infeasible owing to potential severe hypoglycemia (3). Therefore, the benefit of normalizing HbA_{1c} levels without hypoglycemia to neuropathy outcome measures (NOMs) in type 2 diabetes has never been investigated.

Besides mean GC levels, glycemic variability (GV) (6) and metabolic memory influence DPN and other diabetic microangiopathies (7,8). Impaired glucose tolerance (IGT) may cause neuropathy and alter CNF morphology as an indicator of small-fiber neuropathy (9).

Here, we aim to investigate the impact of normalized HbA_{1c} levels without hypoglycemia on neurophysiological functions and CNF measures along with retinopathy and nephropathy in patients with poorly controlled type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

Among 671 patients who newly visited the Ishibashi Clinic between May 2011 and July 2013 after the diagnosis of hyperglycemia, we extracted 38 patients with type 2 diabetes fulfilling the following criteria (extensive HbA_{1c} control [EHC] cohort): *1*) baseline HbA_{1c} level >7.5% (58.5 mmol/mol) (mean level 9.6% [81.4 mmol/mol]), *2*) follow-up period >3 years, and *3*) annual mean HbA_{1c} levels <6.0% (42.1 mmol/mol) for the last 2 years before the final visit. Patients visited Ishibashi Clinic after repeated diagnosis of hyperglycemia. Thirty-eight patients with type 2 diabetes matched for age, sex, baseline HbA_{1c} levels, and height to patients with EHC were followed without EHC and served as a control for EHC patients. Forty-eight healthy control subjects with normal glucose tolerance (NGT) and 34 subjects with IGT were enrolled and studied only at baseline.

The patients with diabetes with or without EHC were followed for 3–5 years (4.3 and 4.1 years on average, respectively) until September 2017. Patients who were treated by insulin-sensitizing agent (ISA) or IPA were given biguanides or pioglitazone or given sulfonylureas or insulin, respectively (10). The exclusion criteria were as follows: any other clinically evident causes of neuropathy apart from diabetes, vitamin B deficiency, nonproliferative severe or proliferative diabetic retinopathy as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) (11), corneal diseases, history of refractive surgery, and use of contact lenses. All subjects provided written informed consent as per the Declaration of Helsinki, and the study protocol was approved by the ethics committee of Ishibashi Clinic.

Clinical and Laboratory Data

Patients with diabetes with EHC at end point, control subjects, and subjects with IGT at baseline underwent a 75-g oral glucose tolerance test (OGTT). The BMI, blood pressure, casual postprandial plasma glucose (CPPG), and HbA_{1c} levels were measured monthly during the terms of study. In patients with type 2 diabetes, SD and coefficient of variation (CV) of CPPG and HbA_{1c} levels over the follow-up period were calculated for estimating GV. The serum lipid levels and urinary creatinine and albumin levels were assessed every 3 months. An albumin-to-creatinine ratio (ACR) >30 mg/g creatinine twice a year was labeled as nephropathy (12).

At baseline and end point, bilateral retinal fundus images (45°) were captured and graded according to the ETDRS scale as no apparent retinopathy, 0; mild nonproliferative diabetic retinopathy, 1; and moderate nonproliferative diabetic retinopathy, 2 (11).

Assessment of Neuropathy

All patients with diabetes at baseline and end point, control subjects, and subjects with IGT at baseline underwent detailed neurophysiological examinations. Neurological deficits were assessed using the modified neuropathy disability score (NDS) (13), which evaluates vibration perception, pinprick, temperature perception, and ankle reflexes. The classification for evaluation of neuropathy was based on the recommendations of the Toronto Consensus on Diabetic Neuropathies (14), which considers a confirmed DPN as a combination of the presence of abnormal nerve conduction velocity (NCV) and a symptom, or a sign. As a result, patients with NDS >2 and sensory NCV (SCV) of sural nerve <42 m/s were labeled with neuropathy based on the Toronto consensus. The cutoff level of sural nerve SCV was determined according to the mean ± 2 SD (49.99 ± 8.02 m/s) of sural nerve SCV in healthy control subjects (n = 38), matched for age, sex, and height to patients with diabetes with EHC, recruited from 98 healthy control subjects at Ishibashi Clinic.

Electrophysiology and NCV studies have been measured with an electromyography instrument (Neuropak S1; Nihon Kohden, Tokyo, Japan). The motor NCV (MCV) (median nerve) and SCV (ulnar and sural nerves) and their action potential amplitudes were determined. Skin temperature was maintained above 32°C.

The vibration perception threshold (VPT) was measured at the left medial malleolus using a biothesiometer (Bio-Medical Instrument Company, Newbury, OH). Warm (WPT) and cold (CPT) perception thresholds at the dorsum of the foot were determined using a thermal stimulator (Intercross-200; Intercross Co., Tokyo, Japan). CAN was assessed by the CV of R-R intervals (CV_{R-R}) calculated from the R-R intervals of 200 electrocardiogram samples.

Corneal Confocal Microscopy

All patients with diabetes at baseline and end point, control subjects, and subjects with IGT once at baseline were examined using a Heidelberg Retina Tomograph (HRT III) in vivo corneal confocal microscope with the Rostock Corneal Module (Heidelberg Engineering, Heidelberg, Germany) (15). Based on an established protocol (16), six high-quality images per subject from Bowman's layer were captured and analyzed to quantify the following CNF morphological parameters: *1*) CNF density (CNFD): total number of major nerve fibers/mm^2 corneal tissue, *2*) CNF length (CNFL): total length of all nerve fibers (mm/mm^2), *3*) corneal nerve branch density (CNBD): number of branches emanating from all major nerve trunks/mm^2, *4*) beading frequency (per 0.1 mm), and *5*) bead size (μm^2) (17). Except for bead size, all measurements were performed using ImageJ (Texelcraft, Tokyo, Japan). The examiners and the team members who analyzed the images and study results

were all blinded and masked to the study groups.

Statistical Analysis

All statistical analyzes were performed using SPSS, version 19 (SPSS, Chicago, IL), and P value <0.05 was considered statistically significant.

A priori analysis of sample power (α = 0.05; β = 0.80) using G*Power 3.1 (http://gpower.software.informer.com/3.1/) revealed that 53 subjects per each group were required. We could not recruit enough subjects. Then a post hoc analysis of sample power was conducted with use of a one-sided ANOVA (significance of 0.05) and the Kruskal-Wallis test for CNF and neurophysiological measures. The subject's statistical power ranged from 0.89 to 0.99. Therefore, 158 subjects in total sample size gave us adequate statistical power.

All values are presented as mean ± SEM. All data sets were tested for normality using the Shapiro-Wilk test. The differences between baseline and end point in two patient cohorts were assessed using the paired t test and Wilcoxon signed rank test for normally and nonnormally distributed continuous variables, respectively, and χ^2 test and McNemar test for normally and nonnormally distributed categorical variables, respectively. Values at baseline in patients with or without EHC and control subjects or between NGT and IGT subgroups categorized by end point 75-g OGTT in patients with EHC were compared by t test and Mann-Whitney test for normally and nonnormally distributed continuous variables and χ^2 test for categorical variables. The comparison of normally distributed variables between end point in two patient cohorts, control subjects and subjects with IGT, was performed using one-way ANOVA for continuous variables and the χ^2 test for categorical variables followed by Bonferroni correction. For nonnormally distributed variables, the Kruskal-Wallis test was applied followed by the Mann-Whitney U test and Bonferroni correction for continuous variables and the χ^2 test for categorical variables. Correlations between the changes in NOMs by GC and mean clinical factors over follow-up period, GV parameters, or baseline HbA_{1c} levels in patients with EHC were assessed using Spearman rank correlation coefficient or multiple regression analysis.

The sensitivity and specificity of CNF and neurophysiological measures in differentiating between control subjects, subjects with IGT, and patients with EHC were assessed at baseline and end point using receiver operating characteristic analysis.

RESULTS

Demographic Data

The sex, age, height, and baseline HbA_{1c} levels were matched between two cohorts with diabetes with or without EHC. During follow-up period, BMI in patients with EHC decreased (mean ± SEM body weight reduction 7.3 ± 1.2 kg) but not in patients without EHC. Systolic (SBP) and diastolic (DBP) blood pressure at end point in two patient cohorts significantly decreased after GC. In patients with EHC, HbA_{1c} levels for the last 2 years of the follow-up period and at end point were <6.0% (42.1 mmol/mol). The mean HbA_{1c} levels during the whole follow-up period in patients without EHC were higher than those in patients with EHC. HbA_{1c} levels in control subjects were lower than those at end point in two patient cohorts and in subjects with IGT. In patients with EHC, SD and CV of CPPG and HbA_{1c} levels over the last 2 years from end point were significantly lower than those over the whole follow-up period. Plasma glucose levels before and after 75-g OGTT (30, 60, and 120 min) at end point in patients with EHC were 102 ± 2.2, 203 ± 7.2, 183 ± 5.0, and 152 ± 7.0 mg/dL, respectively. At end point, 120-min plasma glucose in EHC and IGT subjects was significantly higher than that in control subjects (Table 1). Of patients on EHC, 50.0% and 28.9% returned to IGT and NGT, respectively. Serum triglyceride levels in patients with EHC decreased after GC. The end point estimated glomerular filtration rate (eGFR) in two patient cohorts decreased to a level similar to that in control subjects and subjects with IGT, and ACR significantly decreased. At baseline, 86.8% and 68.4% of patients with diabetes with or without EHC, respectively, were not treated. Over the last 2 years from end point, IPAs were not prescribed for any patients with EHC (Table 1).

The smoking and alcohol consumption in the two cohorts with diabetes were similar between baseline and end point and also similar between baseline and end point in patients, control subjects, and subjects with IGT.

Comparison of CNF and Neurophysiological Measures Between Baseline and End Point in Patients With Type 2 Diabetes With or Without EHC, Control Subjects, and Subjects With IGT

All baseline CNF measures in both cohorts with diabetes were similar but altered compared with control subjects. The normalized HbA_{1c} levels for 2 years in patients with EHC improved all CNF measures but not CNFD (P = 0.225), with no improvement in those without EHC. CNFD and CNFL at end point in patients with EHC were less than those in IGT, while other CNF measures were similar to those in subjects with IGT. All CNF parameters but CNFD in subjects with IGT were significantly less than those in control subjects (Fig. 1*A*–*F* and Table 2).

The normalized HbA_{1c} levels in patients with EHC significantly decreased NDS, though NDS was still higher than in control subjects and subjects with IGT. NDS in subjects with IGT was significantly higher than that in control subjects. All baseline neurophysiological measures in two cohorts with diabetes were similar. The normalized HbA_{1c} levels for 2 years with EHC improved results of all neurophysiological tests to be similar to those in subjects with IGT except for the median nerve amplitude; in patients without EHC, GC improved only VPT. Most neurophysiological tests in subjects with IGT were inferior to those in control subjects (Table 2). The prevalence of retinopathy and ETDRS retinopathy scale at end point increased insignificantly with (P = 0.183 and 0.180, respectively) or without (P = 0.974 and 0.317, respectively) EHC. EHC significantly decreased the prevalence of neuropathy and nephropathy, while GC without EHC decreased only nephropathy (Table 2).

Comparison of Interval Changes During Follow-up Period in CNF and Neurophysiological Measures Between NGT and IGT Subgroups of Type 2 Diabetes With EHC

The improvements in NDS (mean ± SEM −1.36 ± 0.20 vs. −0.68 ± 0.21),

Table 1—Anthropometric and clinical characteristics at baseline, mean levels, and at end point in patients with type 2 diabetes treated with or without EHC, control subjects, and IGT subjects at baseline

	Patients with type 2 diabetes								
	With EHC				Without EHC				
		Mean levels							
	Baseline	Whole follow-up period	Last 2 years from end point	End point	Baseline	End point	Mean	Control subjects: baseline	Subjects with IGT: baseline
Number (M/F)	38 (25/13)	38 (25/13)	38 (25/13)	38 (25/13)	38 (25/13)	38 (25/13)	38 (25/13)	48 (27/21)	34 (16/18)
Age (years)	49.3 ± 1.6	51.0 ± 1.6	52.2 ± 1.6	53.3 ± 1.6	49.8 ± 1.2	53.9 ± 1.2	51.8 ± 1.2	50.6 ± 1.8	51.8 ± 2.4
BMI (kg/m^2)	28.8 ± 0.8	25.9 ± 0.7	25.8 ± 0.7	26.2 ± 0.7*†‡	26.8 ± 0.8§	26.7 ± 0.9	26.1 ± 0.9	22.5 ± 0.5	22.9 ± 0.8
Follow-up period (years)				4.3 ± 0.4		4.1 ± 0.2			
Duration of diabetes (years)	4.1 ± 0.7			8.2 ± 0.8	6.0 ± 0.9	10.1 ± 1.0			
SBP (mmHg)	152 ± 3.4	136 ± 1.3	134 ± 1.6	135 ± 1.8*	149 ± 3.8	137 ± 1.2‖	139 ± 1.4	132 ± 2.4	135 ± 2.9
DBP (mmHg)	91.4 ± 1.6	79.9 ± 0.7	78.2 ± 0.9	77.9 ± 1.2*	88.7 ± 1.7	80.8 ± 1.3*	83.5 ± 1.3¶	79.6 ± 1.3	83.0 ± 1.4
No. treated with ARB (%)	5.3			47.3*#**	23.7§	57.9*		12.5	11.8
CPPG (mg/dL)	217 ± 14.2	120 ± 3.0	112 ± 3.1	116 ± 4.8*	240 ± 14.9	154 ± 8.2*††	151 ± 4.2††		
SD (mg/dL)		30.8 ± 2.4	18.1 ± 1.4‡‡				39.4 ± 2.3¶		
CV (%)		25.4 ± 1.8	15.8 ± 1.0‡‡				26.3 ± 1.6		
HbA$_{1c}$ (%)	9.6 ± 0.30	6.1 ± 0.05	5.8 ± 0.04	5.9 ± 0.05*†	9.6 ± 0.31	7.0 ± 0.07*††	7.0 ± 0.04††	5.7 ± 0.04**	6.0 ± 0.05
SD (%)		0.74 ± 0.07	0.14 ± 0.01‡‡				0.64 ± 0.06		
CV (%)		12.1 ± 1.1	2.4 ± 0.1‡‡				9.20 ± 0.93§		
HbA$_{1c}$ (mmol/mol)	81.6 ± 3.4	43.2 ± 0.53	40.2 ± 0.45	41.4 ± 0.50*†	82.0 ± 3.4	52.6 ± 0.74*††	53.0 ± 0.48††	39.3 ± 0.47**	41.8 ± 0.54
75-g OGTT									
FPG (mg/dL)				102 ± 2.2				96.1 ± 1.1	96.9 ± 1.3
PG at 120 min (mg/dL)				152 ± 7.0#				107 ± 3.0	165 ± 3.4#
LDL cholesterol (mmol/L)	3.66 ± 0.15	3.14 ± 0.10	3.14 ± 0.11	3.32 ± 0.13	3.86 ± 0.17	3.38 ± 0.16‖	3.44 ± 0.12	3.13 ± 0.10	3.39 ± 0.14
No. treated with statins (%)	2.6			5.3	13.2	10.5		18.8	14.7
HDL cholesterol (mmol/L)	1.36 ± 0.06	1.44 ± 0.05	1.48 ± 0.06	1.47 ± 0.06	1.41 ± 0.06	1.45 ± 0.07	1.46 ± 0.07	1.75 ± 0.08	1.70 ± 0.09
Triglycerides (mmol/L)	2.31 ± 0.31	1.48 ± 0.11	1.40 ± 0.10	1.56 ± 0.12*#	2.53 ± 0.28	2.14 ± 0.31	1.95 ± 0.13¶	0.97 ± 0.09‡	1.47 ± 0.18
eGFR (mL/min)	88.7 ± 3.2	78.7 ± 2.6	76.6 ± 2.8	74.8 ± 2.7*	89.2 ± 4.3	76.7 ± 3.2*	79.1 ± 2.9	79.6 ± 2.0	75.8 ± 2.3
ACR (mg/g Cr)	82.9 ± 28.0	37.2 ± 12.4	21.1 ± 6.6	25.8 ± 8.1*	82.3 ± 28.5	31.7 ± 9.0§§	38.6 ± 11.1	8.0 ± 1.5	14.6 ± 5.0
Hypoglycemic treatment									
None/IPA/ISA/DPP4-I/diet alone (no.)	33/2/2/3/0		0/0/29/8/5	0/0/27/6/5	26/10/8/8/0	0/2/29/26/0			

Data are means ± SEM unless otherwise indicated. Data for patients with type 2 diabetes with or without EHC are from baseline and end point, as well as (for patients with EHC) over the whole follow-up period or for the last 2 years before end point. Data for control subjects with NGT are from baseline, as are data for subjects classified as IGT by 75-g OGTT at baseline. Cr, creatinine; DPP4-I, dipeptidyl peptidase 4 inhibitor; F, female; FPG, fasting plasma glucose; M, male; PG, plasma glucose. *$P < 0.001$ compared with baseline; †$P < 0.01$ compared with control subjects; ‡$P < 0.05$ compared with IGT subjects; §$P < 0.05$ compared with patients with EHC; ‖$P < 0.01$ compared with baseline; ¶$P < 0.01$ compared with patients with EHC; #$P < 0.001$ compared with control subjects; **$P < 0.001$ compared with IGT subjects; ††$P < 0.001$ compared with patients with EHC; ‡‡$P < 0.001$ compared with whole follow-up period; §§$P < 0.05$ compared with baseline.

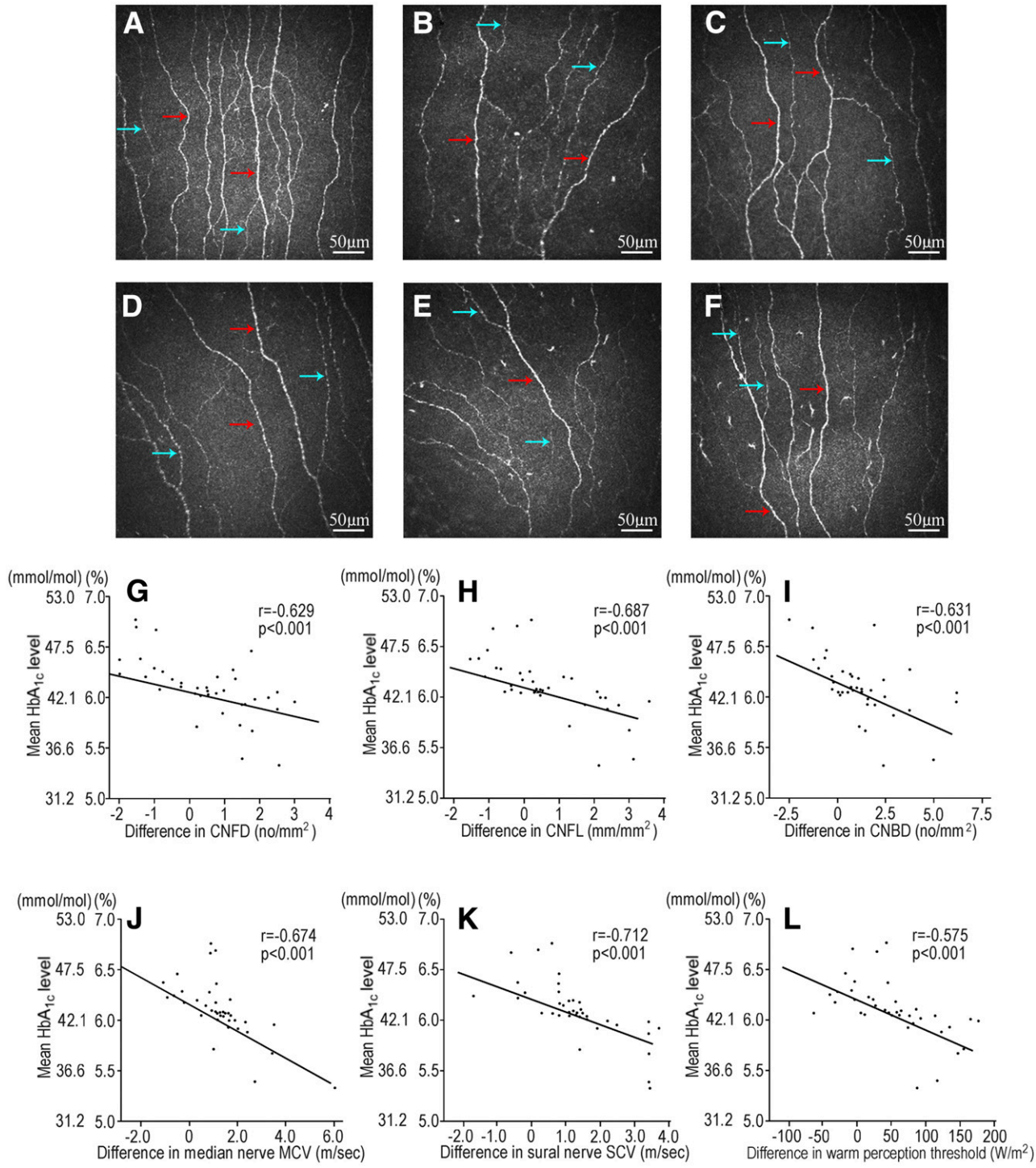

Figure 1—Representative confocal microscopic images of the corneal subbasal nerve plexus in a control subject (*A*) and a subject with IGT (*B*), at baseline (*C*) and end point (*D*) in a patient with type 2 diabetes without EHC, and at baseline (*E*) and end point (*F*) in a patient with EHC. Red arrows, main nerve fibers; blue arrows, branches. Linear regression between mean HbA_{1c} levels and changes during follow-up period in CNFD (*G*), CNFL (*H*), CNBD (*I*), median nerve MCV (*J*), sural nerve SCV (*K*), or WPT (*L*) in patients with type 2 diabetes with EHC. The difference = value at end point − value at baseline. no, number; sec, second.

median nerve MCV (1.84 ± 0.26 vs. 0.89 ± 0.25), and VPT (−0.81 ± 0.06 vs. −0.26 ± 0.16) in the NGT subgroup of type 2 diabetes with EHC were significantly ($P < 0.05$) greater than those in the IGT subgroup. CNFD, CNFL, CNBD, and all other neurophysiological tests in the NGT subgroup improved more than those in the IGT subgroup, but the differences were insignificant (P = 0.118–0.787).

Associations Between Changes in NOMs and Mean Clinical Factors, GV, and Baseline HbA_{1c} in Type 2 Diabetes, With HbA_{1c} Levels Normalized by EHC

The mean HbA_{1c} levels during the whole follow-up period were closely related

Table 2—CNF measures, neurophysiological tests, and microvascular complications at baseline and end point in patients with type 2 diabetes with or without EHC and at baseline in control subjects and subjects with IGT

	Patients with type 2 diabetes				Control subjects: baseline	IGT subjects: baseline
	With EHC		Without EHC			
	Baseline	End point	Baseline	End point		
CNF						
CNF density (no./mm^2)	19.1 ± 0.43*	19.4 ± 0.40*	19.0 ± 0.96*	18.6 ± 0.96	28.7 ± 0.59	25.7 ± 0.77†
CNF length (mm/mm^2)	10.3 ± 0.20*‡	10.9 ± 0.23§	9.4 ± 0.44*	9.4 ± 0.40	14.3 ± 0.24†	12.5 ± 0.33*‡
CNBD (no./mm^2)	8.38 ± 0.35*†	9.54 ± 0.36	8.85 ± 0.64*	9.25 ± 0.57	12.2 ± 0.42†	10.1 ± 0.71‖
Beading frequency (no./0.1 mm)	19.9 ± 0.31*‡	21.0 ± 0.29§	19.3 ± 0.40*	19.8 ± 0.25	22.4 ± 0.21†	21.5 ± 0.35‖
Bead size (μm^2)	10.3 ± 0.11*†	9.05 ± 0.14¶	10.4 ± 0.13*	9.9 ± 0.13	8.31 ± 0.08†	9.48 ± 0.10*
Neurophysiological tests						
NDS	3.9 ± 0.24*†	3.1 ± 0.22#	3.6 ± 0.39*	3.3 ± 0.33	0.4 ± 0.07†	1.0 ± 0.12‖
MCV of median nerve (m/s)	52.9 ± 0.69*†**	54.4 ± 0.67	52.2 ± 0.88*	53.2 ± 0.93	57.0 ± 0.56	55.5 ± 0.56
Amplitude of median nerve (mV)	5.29 ± 0.32*†#	6.00 ± 0.38	5.79 ± 0.30*	6.22 ± 0.44	9.48 ± 0.32†	8.10 ± 0.38‡††
SCV of ulnar nerve (m/s)	60.7 ± 0.46†‖	61.3 ± 0.42	59.6 ± 0.65‖	59.9 ± 0.70	63.3 ± 0.52	60.5 ± 0.70‖
Amplitude of ulnar nerve (μV)	15.6 ± 1.07*†**	17.7 ± 1.13*	16.6 ± 1.18*	17.3 ± 1.13	30.7 ± 1.70	20.7 ± 1.51*
SCV of sural nerve (m/s)	46.6 ± 0.54*†	47.9 ± 0.55	46.5 ± 0.96*	46.4 ± 0.94	50.5 ± 0.46‡	46.2 ± 0.59*
Amplitude of sural nerve (μV)	9.67 ± 0.53*†	10.8 ± 0.61*	9.61 ± 0.52*	9.38 ± 0.54	17.5 ± 0.69	10.6 ± 0.59*
VPT (microns/120 c/s)	2.94 ± 0.21†††	2.48 ± 0.19	3.42 ± 0.24‡‡	3.15 ± 0.27	2.27 ± 0.17	2.64 ± 0.32
$CV_{R\text{-}R}$ (%)	3.20 ± 0.17†‖	3.48 ± 0.19	3.24 ± 0.20††	3.42 ± 0.24	4.10 ± 0.23	3.45 ± 0.18
WPT (W/m^2)	−618 ± 27.6*†	−535 ± 39.9††	−568 ± 18.8††	−567 ± 19.5	−486 ± 11.4	−545 ± 18.4††
CPT (W/m^2)	528 ± 22.6†‖	481 ± 23.0§§	525 ± 17.2	536 ± 15.9	443 ± 10.5	531 ± 17.8*
Microvascular complications						
Prevalence of retinopathy (%)	7.9	13.2	21.1	23.7		
ETDRS retinopathy scale	0.13 ± 0.08	0.21 ± 0.09	0.34 ± 0.11	0.39 ± 0.12		
Prevalence of nephropathy (%)	34.2‡‡	18.4	31.6§§	13.2		
Prevalence of neuropathy (%)	13.2‡	2.6	18.4	10.5		

Data are means ± SEM. Data are for patients with type 2 diabetes with or without EHC at baseline and end point, control subjects with NGT, and subjects with IGT classified by 75-g OGTT at baseline. *$P < 0.001$ compared with control subjects; †$P < 0.001$ compared with end point in patients with EHC; ‡$P < 0.01$ compared with end point in patients with EHC; §$P < 0.01$ compared with patients without EHC; ‖$P < 0.01$ compared with control subjects; ¶$P < 0.001$ compared with patients without EHC; #$P < 0.001$ compared with IGT subjects; **$P < 0.05$ compared with IGT subjects; ††$P < 0.05$ compared with control subjects; ‡‡$P < 0.05$ compared with end point in patients with EHC; §§$P < 0.05$ compared with end point in patients without EHC. c, cycle.

with the improvement in CNFD, CNFL, CNBD, median nerve MCV, sural nerve SCV, and WPT (Fig. 1*G–L*).

The multiple regression analysis indicates that the changes in all CNF and neurophysiological measures by EHC were closely associated with the mean HbA_{1c} level over the whole follow-up period. Higher SD and CV of HbA_{1c} levels and CPPG were negatively associated with some CNF and neurophysiological measures. The high baseline HbA_{1c} levels deteriorated many NOMs (Table 3). High DBP, LDL cholesterol, and triglycerides levels negatively influenced interval changes in median nerve MCV, ulnar and sural nerve SCV, sural nerve amplitude, CPT (standard β −0.277 to −0.411 and 0.322–0.336, $P = 0.005$–0.049), CNFD, CNFL, and beading frequency (standard β −0.329 to 0.588; $P = 0.022$–0.008).

Ability to Differentiate on the Basis of CNF and Neurophysiological Measures at Baseline and End Point Among Control Subjects, Subjects With IGT, and Patients With Type 2 Diabetes With Normalized HbA_{1c} Levels

At baseline and end point, with use of CNFD and CNFL, our ability to differentiate between control subjects, subjects with IGT, and patients with type 2 diabetes with EHC was excellent. The neurophysiological tests clearly differentiated control subjects from patients with type 2 diabetes. However, between subjects with IGT and control subjects or patients, the sensitivity and specificity of CNFD and CNFL were not always good (Supplementary Table 1).

CONCLUSIONS

The intensive GC in type 2 diabetes is associated with a reduction in microvascular complications (mostly albuminuria). The strict GC may play a role in preventing and ameliorating DPN. However, in the Kumamoto Study (18), the tight GC (HbA_{1c} 7.1% [54.1 mmol/mol]) prevented NCV but not CAN decline in type 2 diabetes. In the UK Prospective Diabetes Study (UKPDS) (2), the intensive and conventional GC (HbA_{1c} 7.0% vs. 7.9% [53.0 vs. 62.8 mmol/mol]) had a similar effect on DPN and CAN. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (3), the intensive treatment (HbA_{1c} 6.3% [45.4 mmol/mol]) prevented loss of ankle jerk and light-touch sensation but increased total and CVD-related mortality and severe hypoglycemia. These randomized trials could not establish the optimum GC level for preventing the neurophysiological deterioration in type 2 diabetes.

When patients with recent-onset type 1 diabetes were followed under near-normoglycemia for 24 years, the

Table 3—Correlations between changes in NOMs by GC with EHC and mean levels of HbA_{1c} and CPPG, their variability, and baseline HbA_{1c} levels in patients with type 2 diabetes with EHC

	Parameters of HbA_{1c} levels								Parameters of CPPG					
	Mean		SD		CV		At baseline		Mean		SD		CV	
Interval changes in NOMs	Standard β	*P*	Standard β	*P*	Standard β	*P*	Standard β	*P*	Standard β	*P*	Standard β	*P*	Standard β	*P*
CNF														
Density	−0.519	**0.002**	−0.210	0.190	−0.162	0.314	−0.474	**0.021**	−0.113	0.485	−0.274	0.074	−0.261	0.097
Length	−0.664	**<0.001**	−0.430	**0.021**	−0.415	**0.015**	−0.518	**0.019**	−0.399	**0.023**	−0.454	**0.007**	−0.392	**0.025**
Branch density	−0.577	**0.003**	−0.249	0.192	−0.191	0.320	−0.493	**0.020**	−0.034	0.861	−0.357	**0.048**	−0.392	**0.033**
Beading frequency	−0.396	**0.017**	−0.183	0.261	−0.151	0.355	−0.328	0.146	0.100	0.545	−0.305	**0.049**	−0.319	**0.044**
Bead size	0.471	**0.007**	0.368	**0.030**	0.513	**0.001**	0.605	**0.003**	0.295	0.087	0.502	**0.001**	0.515	**0.001**
Nerve functions														
MCV of median nerve	−0.481	**0.002**	−0.215	0.157	−0.153	0.319	−0.487	**0.002**	−0.118	0.444	−0.111	0.459	−0.059	0.702
Amplitude of median nerve	−0.534	**0.006**	−0.098	0.615	−0.046	0.814	−0.308	0.163	−0.002	0.994	−0.069	0.717	−0.082	0.674
SCV of ulnar nerve	−0.626	**<0.001**	−0.396	**0.012**	−0.626	**<0.001**	−0.709	**0.001**	−0.362	**0.019**	−0.378	**0.012**	−0.340	**0.029**
Amplitude of ulnar nerve	−0.460	**0.016**	−0.138	0.466	−0.090	0.635	−0.409	0.067	0.033	0.862	−0.067	0.718	−0.068	0.717
SCV of sural nerve	−0.474	**0.001**	−0.382	**0.004**	−0.330	**0.016**	−0.733	**<0.001**	−0.151	0.289	−0.196	0.139	−0.179	0.189
Amplitude of sural nerve	−0.526	**0.006**	−0.230	0.244	−0.181	0.342	−0.586	**0.005**	−0.212	0.265	−0.197	0.287	−0.161	0.398
VPT	0.502	**0.004**	0.291	0.085	0.238	0.161	0.593	**0.004**	−0.227	0.194	0.202	0.225	0.118	0.493
$CV_{R\text{-}R}$	−0.498	**0.005**	−0.282	0.104	−0.240	0.169	−0.465	**0.029**	−0.116	0.506	−0.127	0.461	−0.101	0.565
WPT	−0.520	**0.004**	−0.425	**0.013**	−0.379	**0.028**	−0.767	**<0.001**	−0.371	**0.019**	−0.351	**0.025**	−0.266	0.103
CPT	0.467	**0.004**	0.407	**0.009**	0.361	**0.021**	0.749	**<0.001**	0.142	0.384	0.254	0.100	0.245	0.121

Statistically significant correlations appear in boldface type.

nerve function declines were completely prevented (4). Therefore, the near-normoglycemia is prerequisite for preventing the neurophysiological deterioration. We recently showed that all neurophysiological and some CNF measures are improved by subnormal HbA_{1c} levels (HbA_{1c} 6.5% [47.5 mmol/mol]) over 4 years in patients with poorly controlled type 2 diabetes, while some nerve functions in patients with conventional treatment (mean HbA_{1c} 7.2% [55.6 mmol/mol]) deteriorated (19). Therefore, standard diabetes care (HbA_{1c} ≥7.0% [53.0 mmol/mol]) is not beneficial for DPN. In the current study, the treatment without EHC improved only VPT. Because of potential severe hypoglycemia (3), the impact of long-term normalized HbA_{1c} levels on improving neuropathy outcomes in type 2 diabetes had never been reported.

Tight GC needs to be maintained for >3–5 years to yield benefit (20). The current study followed patients with poorly controlled type 2 diabetes for >4 years on average, and mean HbA_{1c} levels in patients with EHC over the whole follow-up period and last 2 years were 6.1% (43.2 mmol/mol) and 5.8% (39.9 mmol/mol), respectively. For the last 2 years from end point IPAs were not prescribed, and no hypoglycemic episodes were reported. All neurophysiological tests and most CNF parameters were improved significantly by normalizing HbA_{1c} levels for 2 years. The results showed that the mean HbA_{1c} levels over the whole follow-up period played a key role in improving NOMs. The high baseline HbA_{1c} levels compromised most NOMs as a negative metabolic memory (21,22).

GV may confer additional risk for DPN independent of HbA_{1c} levels (23,24). In the cross-sectional study in type 2 diabetes, GV estimated by continuous glucose monitoring (CGM) had a close relationship with DPN development (25). We assessed the GV using SD and CV of monthly measured CPPG and HbA_{1c} levels over 4.3 years. The large GV compromised some NOMs. SD and CV of CPPG compromised most CNF parameters, suggesting that daily glucose fluctuation is harmful on small nerve fibers (SNFs). GV parameters obtained by CGM had been used in a cross-sectional study associating GV with DPN (26). For long-term follow-up study, repeated CGM is required to estimate mean GV, but it is impractical.

Normal HbA_{1c} levels do not necessarily mean normoglycemia. IGT may play an important role in inducing neuropathy (9,27) and influences NOMs more profoundly than impaired fasting glucose (28). Therefore, determining glucose tolerance category (GTC) by OGTT in patients with normal HbA_{1c} levels after EHC is required for assessing the influence of remaining glucose intolerance on NOMs. However, OGTT had never been included in clinical studies assessing the benefit of EHC for DPN. In the current study, patients with poorly controlled type 2 diabetes returned to IGT after EHC, while 28.9% of patients returned to NGT. The interval changes in NOMs by EHC were compared between NGT and IGT subgroups. The improvements by EHC in NDS, median nerve MCV, and VPT in the NGT subgroup were significantly greater than in the IGT subgroup. Although insignificant, most other NOMs in the NGT subgroup improved more than those in the IGT subgroup, suggesting that remaining IGT after normalizing HbA_{1c} levels may compromise NOMs. The reversal of diabetes plays a role in improving diabetes complications. The improvement of NOMs in this study was significant, but the changes were small. This might be due to remaining IGT after normalized HbA_{1c} levels, negative influence of GV, and metabolic memory of hyperglycemia—or perhaps longer follow-up period is required.

As the SNFs are most likely to respond to interventions for DPN (29), the morphological and functional SNF measures are essential for evaluation of the benefit of normalized HbA_{1c} levels on NOMs. CNF visualized by corneal confocal microscopy (CCM), predominantly SNF (30), can quantify SNF pathology in DPN (31,32). Subjects having SNF neuropathy show a significant reduction of intraepidermal nerve fiber density and CNF measures (9). In subjects with IGT, CCM reveals dynamic CNF changes related to changing GTC; CNFD and CNFL increase in IGT subjects returning to NGT, while CNFL in subjects developing type 2 diabetes reduces (33). In type 1 diabetes in the context of a normal HbA_{1c} level (5.9% [41.0 mmol/mol]), CNFD, CNFL, and CNBD were improved in 12 months after SPK (5). However, this study did not determine the GTC after SPK.

In the current study, EHC improved all CNF measures apart from CNFD, with no improvement in those without EHC, indicating that the normalized HbA_{1c} levels are more beneficial than standard care. In subjects with IGT, most CNF measures were altered compared with NGT subjects.

Normalizing HbA_{1c} levels for 2 years improved most neurophysiological dysfunctions to levels similar to those of subjects with IGT, while standard care improved only VPT, indicating the superiority of normalized HbA_{1c} level by EHC compared with standard care for ameliorating neurophysiological dysfunctions. IGT impaired NDS and most neurophysiological functions compared with results in control subjects with NGT.

Because functions of SNFs as well as large nerve fibers were impaired in subjects with IGT compared with NGT control subjects, there was no preferential impairment of SNF functions in IGT. However, we performed a single OGTT at end point in patients with EHC and at baseline in control subjects and in subjects with IGT. There are issues concerning the reproducibility and reliability of a single OGTT in establishing GTCs (34). It is noteworthy that the reproducibility of IGT is lower than for other GTCs (35) which highlights a major limitation of all studies including ours relating GTCs to impaired NOMs (35). Furthermore, we did not follow up control subjects or subjects with IGT. Therefore, we could not compare the time-dependent changes in NOMs among patients with diabetes, control subjects, and subjects with IGT, which might function to mislead us in our attempt to draw conclusions of this study.

Although chronic hyperglycemia clearly plays a causative role in development of DPN in type 2 diabetes, metabolic syndrome components are likely to cause neuropathy (36). Obesity and glucose intolerance have a definite role in neuropathy, whereas hypertension and dyslipidemia have equivocal results. In this study, BMI, SBP, DBP, and triglycerides decreased after GC. The improvements in BMI, DBP, and dyslipidemia during follow-up were significantly associated with the improvement of some CNF and neurophysiological parameters. Therefore, besides the strict GC and smaller GV, the metabolic syndrome components should be controlled for ameliorating DPN even in the context of a normal HbA_{1c} level. Smoking and alcohol consumption, which may influence DPN (36), had no impact on NOMs in patients with diabetes in this study. The normalized HbA_{1c} levels for 2 years decreased nephropathy, while retinopathy increased insignificantly. The initial extreme hyperglycemia and substantial HbA_{1c} reduction might develop the retinopathy (37). Although angiotensin receptor blockers (ARBs) may protect against DPN, ARBs did not improve any NOMs (standard β = 0.011 to -0.347; P = 0.918–0.062).

Assessment of the performance and validity of CCM in longitudinal studies in type 2 diabetes is not an area of study that has investigated. The current study is the only study that has measured the main DPN risk factors, including CPPG, HbA_{1c} levels, blood pressure, and BMI, monthly, and the lipid profile, eGFR, and ACR (every 3 months). Therefore, the mean clinical factors influencing NOMs are representative; the benefits of normalized HbA_{1c} levels and improvement in other risk factors to NOMs were reliably evaluated. We estimated the morphological and functional SNF measures. CNFs at baseline in patients and in subjects with IGT were already altered. The normalized HbA_{1c} levels for 2 years improved all neurophysiological tests of SNFs and most CNF measures.

Our study had many limitations. Firstly, we assessed only baseline and end point NOMs. Ideally, these examinations should be performed annually for assessing trends in neuropathy changes. Secondly, we used SD and CV of CPPG and HbA_{1c} levels as GV parameters; however, GV can be assessed by several methods, and there is little consensus regarding the optimal method. Thirdly, patients with EHC at end point, control subjects, and subjects with IGT at baseline underwent a single OGTT. Therefore, the reproducibility of the OGTT was poor. Repeated OGTTs are desirable for association of GTCs with neuropathy progress. Fourthly, the prospective follow-up study of a large number of patients over a longer follow-up period is mandatory to reinforce the present results and establish the relationship between the development of neuropathy and IGT. Finally, the patients with type 2 diabetes in the current study had a relatively short diabetes duration. Because the duration of diabetes is one of the major risk factors for DPN and other complications, and

severe DPN may be less amenable to intervention, we could not extend the present results to patients with longer duration or advanced neuropathy.

In conclusion, patients with poorly controlled type 2 diabetes returned to IGT by normalizing HbA_{1c} level for 2 years without hypoglycemia. All neurophysiological tests and most CNF measures improved to IGT levels. However, standard care without EHC improved only VPT despite the same hypoglycemic strategies. This is due to a big difference in body weight reduction during follow-up. The high GV, negative metabolic memory, and metabolic syndrome components are harmful to most NOMs even in the context of normal HbA_{1c} levels. Along with normal HbA_{1c} levels by EHC without hypoglycemia, small GV and control of metabolic syndrome components are indicated for preventing and ameliorating DPN. The normalized HbA_{1c} levels are more effective than standard care for preventing the development of neuropathy but not retinopathy.

Funding. This study received no financial support.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. F.I. designed the study, researched data, and wrote the entire manuscript. M.Tan. performed CCM examinations and neurophysiological tests. A.K. and H.U. gathered the clinical and laboratory data and statistically analyzed all data. M.Tav. advised on the statistical analysis, interpreted the results, and reviewed and revised the whole manuscript. F.I. and M.Tav. are the guarantors of this work, and, as such, had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and interpretation.

References

1. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. Curr Diab Rep 2014;14:528
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in Lancet 1999;354:602]. Lancet 1998;352:837–853
3. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD Trial Group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–430
4. Ziegler D, Behler M, Schroers-Teuber M, Roden M. Near-normoglycaemia and development of neuropathy: a 24-year prospective study from diagnosis of type 1 diabetes. BMJ Open 2015;5:e006559
5. Tavakoli M, Mitu-Pretorian M, Petropoulos IN, et al. Corneal confocal microscopy detects early nerve regeneration in diabetic neuropathy after simultaneous pancreas and kidney transplantation. Diabetes 2013;62:254–260
6. Jin HY, Lee KA, Park TS. The impact of glycemic variability on diabetic peripheral neuropathy. Endocrine 2016;53:643–648
7. Pop-Busui R, Herman WH, Feldman EL, et al.; DCCT/EDIC Research Group. DCCT and EDIC studies in type 1 diabetes: lessons for diabetic neuropathy regarding metabolic memory and natural history. Curr Diab Rep 2010;10:276–282
8. Chalmers J, Cooper ME. UKPDS and the legacy effect. N Engl J Med 2008;359:1618–1620
9. Asghar O, Petropoulos IN, Alam U, et al. Corneal confocal microscopy detects neuropathy in subjects with impaired glucose tolerance. Diabetes Care 2014;37:2643–2646
10. Pop-Busui R, Lu J, Brooks MM, et al.; BARI 2D Study Group. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) cohort. Diabetes Care 2013;36:3208–3215
11. Wilkinson CP, Ferris FL III, Klein RE, et al.; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677–1682
12. Molitch ME, DeFronzo RA, Franz MJ, et al.; American Diabetes Association. Nephropathy in diabetes. Diabetes Care 2004;27(Suppl. 1):S79–S83
13. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993;36:150–154
14. Tesfaye S, Boulton AJ, Dyck PJ, et al.; Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010;33:2285–2293
15. Ishibashi F, Okino M, Ishibashi M, et al. Corneal nerve fiber pathology in Japanese type 1 diabetic patients and its correlation with antecedent glycemic control and blood pressure. J Diabetes Investig 2012;3:191–198
16. Tavakoli M, Malik RA. Corneal confocal microscopy: a novel non-invasive technique to quantify small fibre pathology in peripheral neuropathies. J Vis Exp 2011
17. Ishibashi F, Kojima R, Taniguchi M, Kosaka A, Uetake H, Tavakoli M. The expanded bead size of corneal C-nerve fibers visualized by corneal confocal microscopy is associated with slow conduction velocity of the peripheral nerves in patients with type 2 diabetes mellitus. J Diabetes Res 2016;2016:3653459
18. Ohkubo Y, Kishikawa H, Araki E, et al. 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;28:103–117
19. Ishibashi F, Tavakoli M. Impact of normoglycemia in reducing microvascular complications in patients with type 2 diabetes: a follow-up study. Front Endocrinol (Lausanne) 2018;9:52
20. Giorgino F, Home PD, Tuomilehto J. Glucose control and vascular outcomes in type 2 diabetes: is the picture clear? Diabetes Care 2016;39(Suppl. 2):S187–S195
21. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
22. Intine RV, Olsen AS, Sarras MP Jr. A zebrafish model of diabetes mellitus and metabolic memory. J Vis Exp 2013;72:e50232
23. Gorst C, Kwok CS, Aslam S, et al. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. Diabetes Care 2015;38:2354–2369
24. Yang CP, Li CI, Liu CS, et al. Variability of fasting plasma glucose increased risks of diabetic polyneuropathy in T2DM. Neurology 2017;88:944–951
25. Xu F, Zhao LH, Su JB, et al. The relationship between glycemic variability and diabetic peripheral neuropathy in type 2 diabetes with well-controlled HbA1c. Diabetol Metab Syndr 2014;6:139
26. DeVries JH. Glucose variability: where it is important and how to measure it. Diabetes 2013;62:1405–1408
27. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care 2006;29:1294–1299
28. Dimova R, Tankova T, Guergueltcheva V, et al. Risk factors for autonomic and somatic nerve dysfunction in different stages of glucose tolerance. J Diabetes Complications 2017;31:537–543
29. Malik RA, Veves A, Tesfaye S, et al.; Toronto Consensus Panel on Diabetic Neuropathy. Small fibre neuropathy: role in the diagnosis of diabetic sensorimotor polyneuropathy. Diabetes Metab Res Rev 2011;27:678–684
30. Müller LJ, Marfurt CF, Kruse F, Tervo TMT. Corneal nerves: structure, contents and function. Exp Eye Res 2003;76:521–542
31. Quattrini C, Tavakoli M, Jeziorska M, et al. Surrogate markers of small fiber damage in human diabetic neuropathy. Diabetes 2007;56:2148–2154
32. Chen X, Graham J, Dabbah MA, et al. Small nerve fiber quantification in the diagnosis of diabetic sensorimotor polyneuropathy: comparing corneal confocal microscopy with intraepidermal nerve fiber density. Diabetes Care 2015;38:1138–1144
33. Azmi S, Ferdousi M, Petropoulos IN, et al. Corneal confocal microscopy identifies small-fiber neuropathy in subjects with impaired glucose tolerance who develop type 2 diabetes. Diabetes Care 2015;38:1502–1508
34. Rajabally YA. Neuropathy and impaired glucose tolerance: an updated review of the evidence. Acta Neurol Scand 2011;124:1–8
35. Balion CM, Raina PS, Gerstein HC, et al. Reproducibility of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) classification: a systematic review. Clin Chem Lab Med 2007;45:1180–1185
36. Grisold A, Callaghan BC, Feldman EL. Mediators of diabetic neuropathy: is hyperglycemia the only culprit? Curr Opin Endocrinol Diabetes Obes 2017;24:103–111
37. Shurter A, Genter P, Ouyang D, Ipp E. Euglycemic progression: worsening of diabetic retinopathy in poorly controlled type 2 diabetes in minorities. Diabetes Res Clin Pract 2013;100:362–367