# Modeling Chronic Glycemic Exposure Variables as Correlates and Predictors of Microvascular Complications of Diabetes

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**OBJECTIVE** — The degree to which chronic glycemic exposure (CGE) (fasting plasma glucose [FPG], $HbA_{1c}$ [A1C], duration of diabetes, age at onset of diabetes, or combinations of these) is associated with or predicts the severity of microvessel complications is unsettled. Specifically, we test whether combinations of components correlate and predict complications better than individual components.

**RESEARCH DESIGN AND METHODS** — Correlations and predictions of CGE and complications were assessed in the Rochester Diabetic Neuropathy Study, a population-based, cross-sectional, and longitudinal epidemiologic survey of 504 patients with diabetes followed for up to 20 years.

**RESULTS** — In multivariate analysis, A1C and duration of diabetes (and to a lesser degree age at onset of diabetes but not FPG) were the main significant CGE risk covariates for complications. A derived glycemic exposure index ($GE_i$) correlated with and predicted complications better than did individual components. Composite or staged measures of polyneuropathy provided higher correlations and better predictions than did dichotomous measures of whether polyneuropathy was present or not. Generally, the mean $GE_i$ was significantly higher with increasing stages of severity of complications.

**CONCLUSIONS** — A combination of A1C, duration of diabetes, and age at onset of diabetes (a mathematical index, $GE_i$) correlates significantly with complications and predicts later complications better than single components of CGE. Serial measures of A1C improved the correlations and predictions. For polyneuropathy, continuous or staged measurements performed better than dichotomous judgments. Even with intensive assessment of CGE and complications over long times, only about one-third of the variability of the severity of complications is explained, emphasizing the role of other putative risk covariates.

*Diabetes Care* 29:2282–2288, 2006

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Received for publication 8 March 2006 and accepted in revised form 22 June 2006.

P.C.O.B. receives royalties from WR Medical Electronics.

**Abbreviations:** CGE, chronic glycemic exposure; DCCT, Diabetes Control and Complications Trial; DSPN, diabetic sensory polyneuropathy; FPG, fasting plasma glucose; $GE_i$, glycemic exposure index; NIS, Neuropathy Impairment Score; NSC, Neuropathy Symptoms and Change; QST, quantitative sensation test; RDNS, Rochester Diabetic Neuropathy Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0525



Chronic glycemic exposure (CGE) (the degree and duration of plasma hyperglycemia) is thought to be the important modifiable risk covariate for the complications of diabetes (1–3). This view comes from cohort studies (4–8) and from trials with clamping hyperglycemia at two levels of glycemic control (9–12). Although it has been debated whether a CGE threshold exists (13,14), such a threshold is assumed in estimating the lowest level of CGE that induces complications. This level of CGE may then be used to set minimal criteria for the diagnosis of diabetes itself (1,2,13). At issue, however, is how CGE should be estimated. Orchard et al. (13,15) evaluated the severity and duration of hyperglycemia and complications in young people with type 1 diabetes, but the CGE variable that was preset (the percentage of $HbA_{1c}$ [A1C] was more than or equal to the minimal criteria for diabetes times duration of diabetes in months) did not predict complications any better than its components.

Here, we study CGE and complications evaluated intensively and comprehensively in the Rochester Diabetic Neuropathy Study (RDNS). The following are specific questions addressed: Does a combination of significant CGE variables correlate and predict microvessel complications better than individual components? Are the correlations and predictors dependent on how frequently fasting plasma glucose (FPG) and A1C are measured? Is these a dependence on how severity of polyneuropathy is assessed? Is a continuous quantitative measurement of polyneuropathy better than a dichotomous judgment of whether polyneuropathy is present or not?

## RESEARCH DESIGN AND METHODS

— Included in the RDNS cohort are all consenting individuals in Rochester (later Olmsted County), Minnesota, with diabetes by the National Diabetes Data Group (and later by the American Diabetes Association) criteria as of 1 July 1986. This prospective cross-sectional and longitudinal study assesses the prevalence and incidence of complications and their risk covariates. The co-

**Table 1—*Median values of demographic and glycemic exposure variables in the RDNS cohort to the end of 2004***

| | *n* | Median (range) |
|---|---|---|
| First visit | | |
| Age (years) | 327 | 56.0 (13.0–86.0) |
| Mean FPG (mg/dl) | 326 | 158.0 (28.0–456.0) |
| Mean A1C (%)* | 325 | 7.9 (4.7–13.7) |
| Age at onset of diabetes (years) | 327 | 48.2 (3.5–82.4) |
| $GE_i$† | 325 | 4.7 (3.5–6.0) |
| Mean systolic blood pressure (mmHg) | 317 | 136.0 (88.0–204.0) |
| Mean diastolic blood pressure (mmHg) | 317 | 78.0 (50.0–110.0) |
| Averaged over time | | |
| Mean FPG (mg/dl) | 327 | 165.4 (95.3–313.3) |
| Mean A1C (%)* | 327 | 7.8 (5.2–12.4) |
| Mean systolic blood pressure (mmHg) | 327 | 132.4 (98.4–182.5) |
| Mean diastolic blood pressure (mmHg) | 327 | 76.1 (54.8–100.7) |
| First visit to last visit | | |
| Number of evaluations of FPG | 327 | 27.0 (2.0–70.0) |
| Number of evaluations of A1C | 327 | 27.0 (2.0–70.0) |
| Last visit | | |
| Duration of diabetes (years) | 327 | 18.0 (3.4–73.8) |
| Duration of follow-up (years) | 327 | 7.8 (1.4–20.0) |

*The mean A1C values were calculated with reference to DCCT standards. The corresponding mean A1C values using International Federation of Clinical Chemistry standards have a median of 6.3% and range of 2.9–12.6% at the first visit. The median (range) is 6.2% (3.3–12.2) for visits averaged over time. The mean difference between the first visit and visits averaged over time for A1C (percent) is 0.1692 ($P = 0.0054$) using DCCT standards. †$GE_i = -2.7912 + 3.7961 \times A1C^{1/4} + 0.7478 \times$ duration of diabetes$^{1/4} + -0.0725 \times$ age of onset of diabetes$^{1/4}$. Its derivation is provided in results. A1C is measured using DCCT standards.

hort of 504 subjects (327 subjects seen on two or more occasions) is mainly of northern European extraction. By the criteria of comorbidity, there were no significant differences between consenting and nonconsenting patients <70 years old (16). The RDNS Normal Subject Cohort of 430 subjects, of whom 330 did not have neurologic disease or disease predisposing to polyneuropathy, was described previously (17,18).

### Diabetes complication end points evaluated

All neuropathic end points assessed were described previously (19–21). Neurologic signs and symptoms were entered into the Clinical Neuropathy Assessment, allowing entry and interactive surveillance before entry into the database. Severity of neurologic signs was calculated using the Neuropathy Impairment Score (NIS); severity of symptoms was calculated by Neuropathy Symptoms and Change (NSC) (22,23). Neuropathic signs, symptoms, and test abnormalities were scored independently on each occasion without reference to previous or present other examination or test results. Nerve conduction results were expressed in measured units and as normal deviates (from percentiles) having corrected values for applicable variables (e.g., age, height, and weight) (18). Vibration, cooling, and heat pain (5, 0.5, and 5–0.5) thresholds were assessed on the left great toe or foot using CASE IV (WR Medical Electronics, Stillwater, MN) with thresholds expressed as just noticeable difference steps, measured units, percentiles, and normal deviates, with corrections being made for applicable variables (18). Assessment of patients by the Diabetes Control and Complications Trial (DCCT) criteria for polyneuropathy (two of three of decreased or absent ankle reflexes or vibration sensation of the great toes or symptoms of polyneuropathy not attributable to any other condition than diabetes) was based on information recorded in the Clinical Neuropathy Assessment. Complications of polyneuropathy, retinopathy, and nephropathy were staged into three categories of severity (none, mild or intermediate, and severe) as shown in Table 2 and Fig. 2. For polyneuropathy, five other measures of severity were also assessed (Table 2).

Severity of retinopathy was staged on the basis of masked grading of seven 30-degree color stereoscopic fundus photographs of each eye using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study severity scale at the University of Wisconsin Ocular Epidemiology Reading Center (R.K.). Nephropathy was staged as N0 = microalbuminuria <30 mg/24-h urine collection, N1 = microalbuminuria ≥30 to <300 mg/24-h urine collection, and ≥N2 = macroalbuminuria ≥300 mg/24-h urine collection (or a previous history of end-stage kidney disease).

### Measures of components of CGE

The duration of diabetes was ascertained by questioning of patients and review of their medical records. Type of diabetes was determined by the C-peptide response to glucagon stimulation (16,24). Assessed at first examination and at 3-month intervals (and beginning in 2003 at 6-month intervals) were FPG and A1C (as calculated from GHbA1) (using DCCT standards).

### Analysis

In testing for associations between putative risk covariates (e.g., FPG or A1C) and various complications, both baseline and averaged (calculating the mean value per year and then the mean of the annual values) values were considered independent variables; severity of complications (threshold or a continuous or staged level of abnormality at onset and at last evaluation) were the dependent variables. Associations between severity and risk covariates were evaluated univariately with Spearman rank correlations for quantitative risk factors and with rank-sum tests for dichotomous risk factors. Variables were then inspected for departures from a normal distribution, and appropriate transformations were made as needed for a multivariate assessment. Stepwise regression (stepping up) was used for the multivariate analysis, and the criterion for inclusion of a variable in the model was $P < 0.05$.

## RESULTS

### Demographic and disease characteristics

These are summarized in Tables 1 and 2. Of 504 subjects with diabetes entered into study, 327 had subsequent serial evaluations. By the criteria of CGE (duration of diabetes, FPG, and A1C) or staged severity of complications (retinopathy, polyneuropathy, or nephropathy), a significant difference was not found among patients who left the study after

**Table 2—*Prevalence of complications as a percentage of RDNS patients at first and last examinations to the end of 2004***

| | First visit | Last visit |
|---|---|---|
| Type of diabetes (% type 1) | 312 (26.6) | — |
| Sex (% male) | 327 (48.6) | — |
| DSPN* | | |
| Σ 5 NC nds (% ≥95th) | 327 (34.6) | 326 (51.8) |
| NIS (LL) (% ≥2 points) | 327 (32.7) | 327 (35.2) |
| Σ QST nds (% ≥95th) | 77 (27.3) | 239 (38.9) |
| NSC number or NSS number (% >1 point) | 327 (18.0) | 326 (23.0) |
| % ≥DCCT criteria | 327 (12.8) | 326 (14.1) |
| HP-DB (% ≤5th) | 317 (12.6) | 287 (13.9) |
| Retinopathy (% ≥stage 1) | 315 (53.7) | 296 (74.0) |
| Nephropathy (% ≥stage 1) | 82 (26.8) | 285 (37.5) |

*The different neuropathic end points used are explained under RESEARCH DESIGN AND METHODS and in ref. 28. The staging of retinopathy and nephropathy is given in RESEARCH DESIGN AND METHODS. HP-DB, heart pulse deep breathing; NSS, Neuropathy Symptoms Score.

one examination and patients who continued in the study (Table A available from the authors on written request). FPG and A1C had been measured frequently (median 27 times). Using A1C as a measure of CGE, our cohort did not have the degree of control recommended by the American Diabetes Association (A1C <7.0%); however, the mean of the A1C values averaged over time to the last examination was slightly and significantly better than at baseline. The prevalence of complications was highest for retinopathy, followed by polyneuropathy, and then by nephropathy (Table 2). The prevalence of polyneuropathy, however, depended critically on which end point criterion was used for diagnosis; the order from highest to lowest frequencies was the sum score of five attributes of nerve conduction (Σ 5 NC nds), NIS (lower limb [LL]), Σ quantitative sensation test (QST) nds, neuropathy symptoms (NSC or Neuropathy Symptoms Score), the DCCT criteria, and HP-DB (Table 2). For all measures of complications, the frequency was higher at the last examination. The comparable frequency of retinopathy increased from 54 to 74% and nephropathy increased from 27 to 38%.

### Modeling of components of CGE and complications

In univariate analysis, duration of diabetes (year)$^{1/4}$, and A1C (percent)$^{1/4}$ at baseline were positively and significantly associated with most measures of complications at baseline (correlations) (Table B available from the authors on written request). Age at onset was negatively and less frequently also significantly correlated with complications. By contrast, FPG was seldom correlated with complications. Duration of diabetes and A1C at baseline significantly predicted complications at the last examination. When A1C was averaged over time, the prediction of complications was strengthened. By contrast FPG, even when averaged over time, seldom predicted complications at the last examination (Table A available from the authors on written request).

### Derivation of a glycemic exposure equation

To develop a glycemic exposure regression equation, we included the statistically significant components of A1C, duration of diabetes, and age at onset of diabetes and plotted these values for type 1 or type 1 and 2 diabetic patients on Σ 5 NC nds to obtain a common regression equation. We chose the composite score Σ 5 NC nds as the best measure for this purpose because it is an objective and continuous measure without an obvious basement or ceiling effect and reflects differences within the range of normal values.

In linear regressions of the glycemic exposure equation (using combinations of A1C$^{1/4}$, duration of diabetes [years]$^{1/4}$, and age at onset [years]$^{1/4}$), by plotting the GE index ($GE_i$) of each patient on their Σ 5 NC nds (Fig. 1), values appear to be normally distributed around a common regression line. The three components of CGE were all included in the regression model, even though not all components were significant for all combinations of CGE and complications. The regression equation for type 1 diabetic patients at the last visit was $GE_i$ averaged over time = 4.70 + 0.043 × Σ 5 NC nds at the last visit. For all diabetic patients, the $GE_i$ averaged over time = 4.85 + 0.026 × Σ 5 NC nds at the last visit. Using the values for type 1 diabetic patients (because age of onset is more certain), we derived a general GE equation: $-2.79 + 3.8 \cdot A1C^{1/4} + 0.75 \times$ duration of diabetes $(years)^{1/4} + -0.07 \cdot$ onset of diabetes $(year)^{1/4}$. The correlation coefficient ($R^2$) was only slightly better when A1C was averaged many times.

### Multivariate analysis of components and the index of CGE and complications

To test whether the $GE_i$ correlates and predicts microvessel complications better than individual components, we performed multivariate analysis of significant CGE components and the index (calculated at baseline or as averaged over time) on complications at baseline and at last examination. With few exceptions, the $GE_i$ was the significant covariate for complications (Table 3). This was especially true when A1C was averaged over the duration of the study, and complications were assessed at the last evaluation. In only three cases was A1C$^{1/4}$ the sole significant multivariate variable predicting complications, whereas $GE_i$ was the sole covariate 18 times. FPG averaged over time was the significant covariate only once (for NIS [LL]) (Table 3). The table also provides information about the degree of the variability explained by the CGE variables. Considering all patients with diabetes and Σ 5 NC nds as complications, 28% of the variability is explained by the $GE_i$. The comparable figure for retinopathy is 31%. For type 1 diabetes, the percentages are higher, 42 and 43%, respectively. For nephropathy $GE_i$, was a significant factor for type 2 diabetes but explained only 8% of the variability of the data.

In Fig. 2, we provide the $GE_i$ (25th, 50th, and 75th percentiles and ranges) by staged severity of complications. With a few exceptions, the $GE_i$ was significantly greater with increasingly higher stages.

**CONCLUSIONS** — The RDNS data are suited for modeling CGE and complications because *1*) risk covariates and complications are prospectively and quantitatively studied for this purpose at regular and frequent intervals over many years and not at times of intercurrent illness, which if done, might have affected results; *2*) the cohort is representative of diabetic patients of northern European

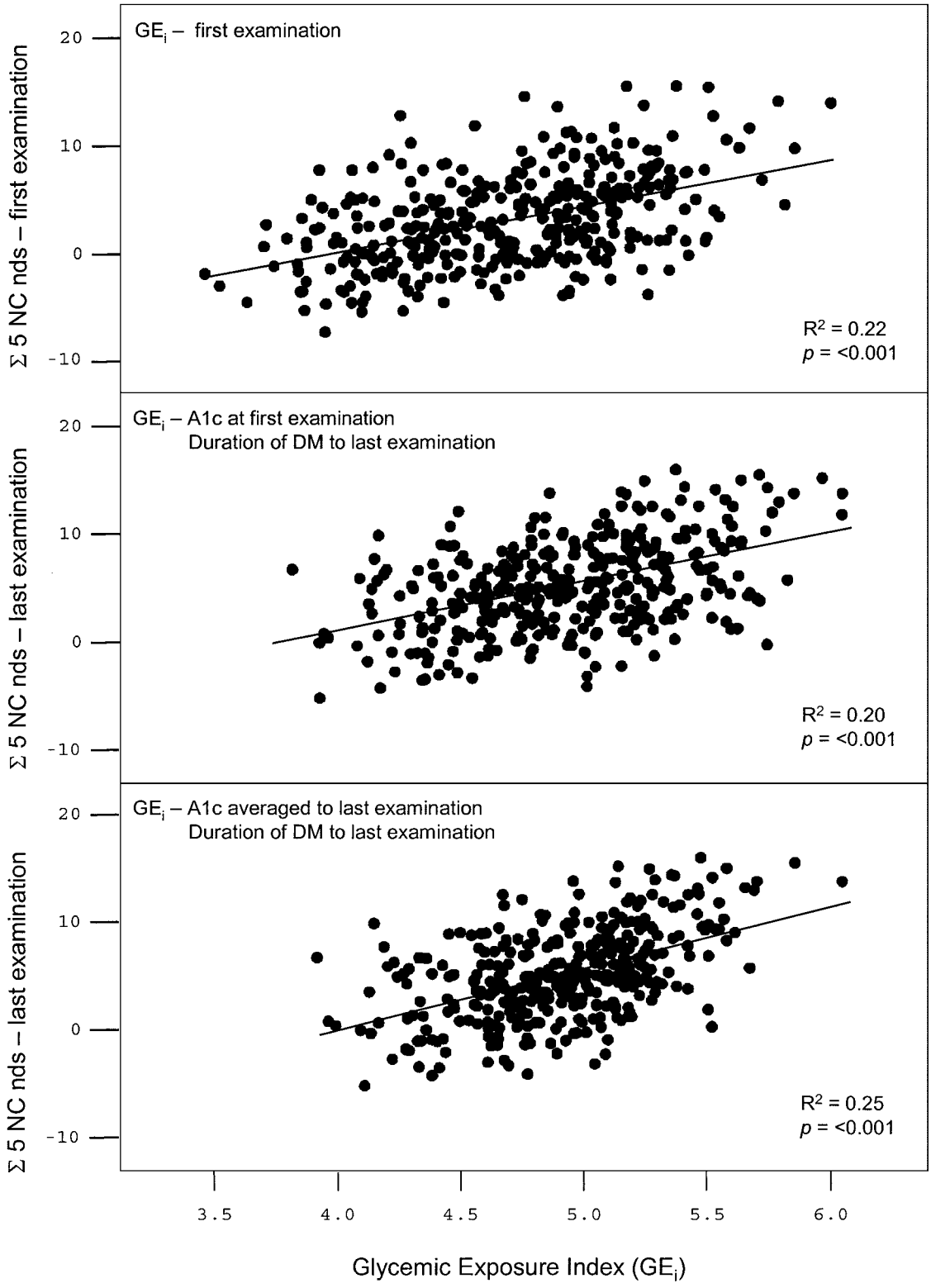


**Figure 1**—*Plotted values of the GE$_i$ of all patients in the RDNS cohort for Σ 5 NC nds score and their common regression lines. In the* top frame, *the GE$_i$ is calculated on the basis of the initial value of A1C and duration of diabetes (DM) at baseline. Diabetic sensorimotor polyneuropathy was measured by Σ 5 NC nds at the first examination (correlation of complications from GE$_i$ at baseline). In the* middle frame *for the GE$_i$, A1C is from measured values at baseline with the duration of diabetes at the last examination (prediction of complications from A1C at baseline). In the* bottom frame, *A1C is averaged over time to the last examination and the duration of diabetes is calculated to the last examination (prediction of complications from averaged A1C values over time). There is a surprising similarity in the plotted values and common regression lines. Note that prediction of Σ 5 NC nds at the last examination from assessment of multiple assessment of A1C over years (R$^2$ ~0.25) is only slightly better than that from a single measure of A1C at baseline (R$^2$ ~0.20). This finding suggests that despite a considerable effort on the part of community physicians to improve CGE, only a small improvement occurred (19,20).*

**Table 3—*Multivariate analysis using stepwise linear regressions of statistically significant CGE variables at baseline and averaged over time, and severity of microvessel complications at first and last evaluation in the RDNS cohort***

| | Partial $R^2$ | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CGE variable at first examination | | | | | | | CGE variable averaged over time (A1C) or at last visit (duration of diabetes, age at onset of diabetes): microvessel complication at last examination | | | |
| | Microvessel complication at first examination | | | Microvessel complication at last examination | | | | | | | |
| Microvessel complication and type of diabetes | $GE_i$ | Duration of diabetes | Age at onset of diabetes | $GE_i$ | A1C | Duration of diabetes | Age at onset of diabetes | $GE_i$ | A1C | Duration of diabetes | Age at onset of diabetes |
| Polyneuropathy | | | | | | | | | | | |
| Σ 5 NC nds | | | | | | | | | | | |
| All | **0.24** | | 0.03 | **0.25** | | | | **0.28** | | | |
| Type 1 | **0.34** | | | **0.25** | | | | **0.42** | | | |
| Type 2 | **0.14** | | | **0.13** | | | | **0.14** | | | |
| Stage severity | | | | | | | | | | | |
| All | **0.15** | | **0.03** | **0.12** | 0.02 | | | **0.13** | | | |
| Type 1 | **0.22** | | | | | **0.16** | | **0.28** | | | |
| Type 2 | **0.06** | | | 0.05 | | | 0.02 | 0.05 | | | |
| Neuropathy staged severity | | | | | | | | | | | |
| All | **0.06** | | | 0.01 | **0.05** | | 0.03 | | **0.06** | | 0.02 |
| Type 1 | 0.15 | | | | 0.08 | | | | 0.12 | | 0.03 |
| Type 2 | **0.09** | | | | **0.08** | | | **0.08** | | | |
| Retinopathy staged severity | | | | | | | | | | | |
| All | | **0.33** | **0.04** | **0.23** | 0.02 | | | **0.31** | 0.01 | | |
| Type 1 | | **0.48** | | | | **0.12** | | **0.43** | | 0.03 | |
| Type 2 | | **0.16** | | **0.13** | | | | **0.20** | | | |

All listed results have $P < 0.05$. Results in boldface indicate $P < 0.001$. *FPG or A1C was averaged over time as described in RESEARCH DESIGN AND METHODS. Duration of diabetes (years) was assessed at the first or last examination. Age of onset is given in years.

extraction and includes both type 1 and 2 diabetic patients of both sexes and all ages, allowing inferences to be applied broadly; and 3) bias was minimized by use of independent assessment of complications.

Considering both correlations and predictions of complications, a combination of the three significant components of CGE (expressed as $GE_i$) performed better than any one component alone. This result is different from that of Orchard et al. (13) but may be explained by differences in the choice of patients (in our studies all patients with diabetes and all degrees of severity) and differences in assessment of CGE and complications. In their study, CGE was predetermined as a variable emphasizing duration (in months) of A1C percent above a diagnostic level; in our studies, the actual contribution of the components was calculated from regression equations. The complication of polyneuropathy was also more comprehensively evaluated in our study in which the use of a continuous measure or staged severity of polyneuropathy provided greater power in assessing correlations and predictions.

The important insight that correlations and predictions depend not only on how well CGE is estimated but also on how complications are assessed needs emphasis. All complications in our studies were assessed using standard quantitative measures using reference values and staging. For diabetic sensory polyneuropathy (DSPN), severity was expressed as continuous measures of abnormality of nerve conduction (Σ 5 NC nds), summated neurological signs of the lower limbs (NIS [LL]), symptoms (NSC [LL]), and abnormality of QST (Σ QST). To avoid bias, all complications were independently assessed without reference to previous or concurrent other evaluations.

The use of continuous quantitative measures of DSPN provided stronger associations and predictions with CGE than did use of a dichotomous judgment of the presence or absence of polyneuropathy (e.g., the DCCT criterion). However, the Σ 5 NC nds performed only slightly better than did NIS (LL).

Considering any diabetic patients and all microvessel complications, we suggest that the $GE_i$ might be used to express the CGE of any patient. The $GE_i$ may be calculated from values that pertain at present. In this case, a single measure (or the mean of several measures) of A1C, duration of diabetes (at the present time), and age at onset of diabetes are used in the equation. The $GE_i$ can also be calculated for a future time (as a prediction) knowing age at onset of diabetes, duration of diabetes at a future time, and assuming that the A1C remains unchanged. The $GE_i$ can also be calculated, assuming better or worse A1C values.

What are the implications of the present studies for an understanding of microvessel complication and their management? First, glycemic exposure is an important correlate and predictor of microvessel complications. This fact is clinically relevant because A1C and weight are potentially modifiable. However, the fact that the A1C of our patients remained

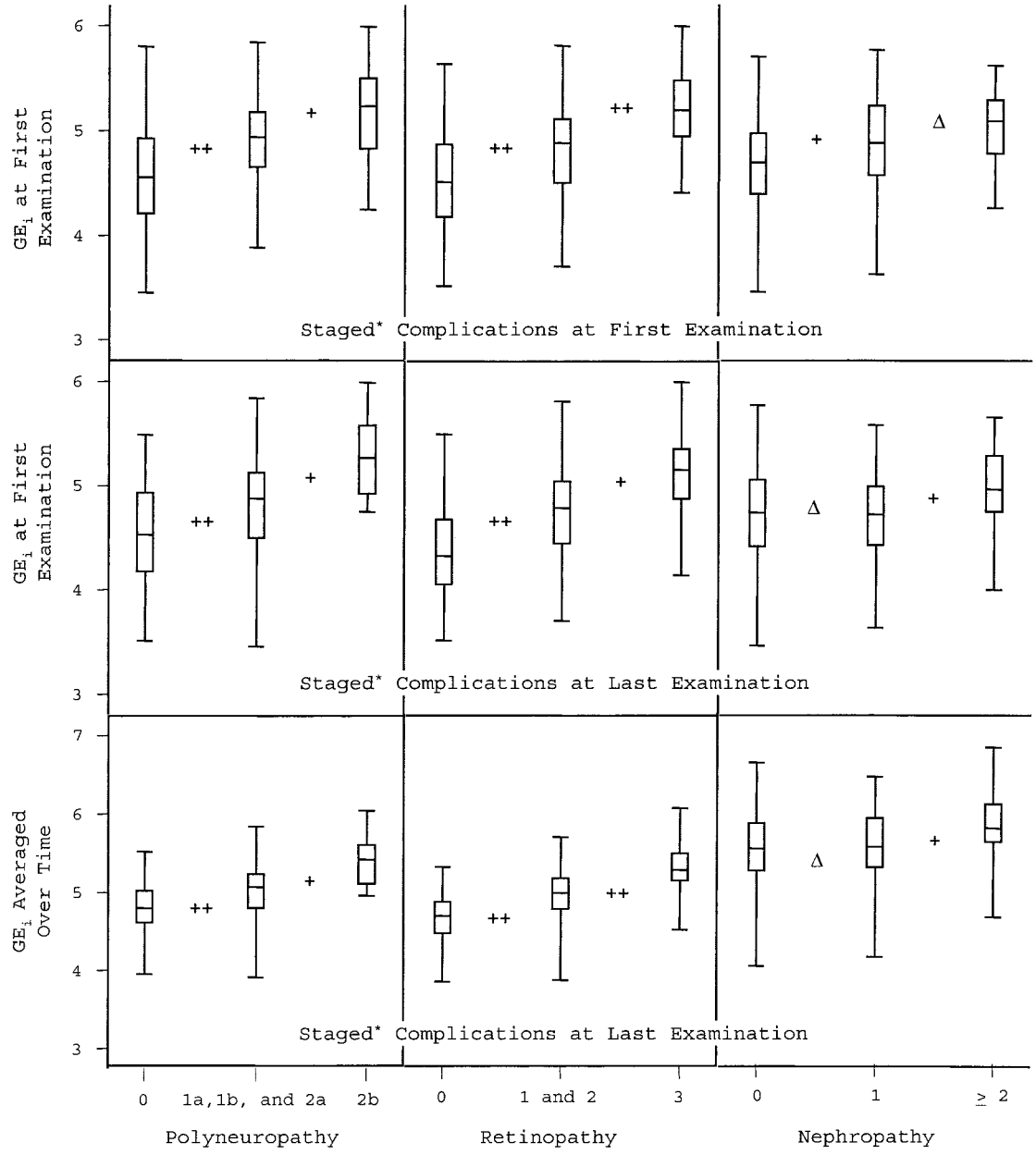


**Figure 2—***Staged severity of complications. DSPN: stage 0 = Σ 5 NC nds <95th percentile; stages 1a, 1b, and 2a = Σ 5 NC nds ≥95th percentile but <50% weakness of ankle dorsiflexors; and stage 2b = ankle dorsiflexors weakness ≥50%. Retinopathy: stage 0 = no retinopathy, stages 1 and 2 = nonproliferative retinopathy, and stage 3 = proliferative retinopathy or laser-treated proliferative retinopathy. Nephropathy: stage 0 = microalbuminuria <30 mg/24 h, stage 1 = microalbuminuria ≥30 to <300 mg/24 h, and stage >2 = macroalbuminuria ≥300 mg/24 h. For all complications, other causes for complications were excluded. For polyneuropathy, other neuropathies associated with diabetes are excluded (e.g., cranial neuropathies, focal and multifocal mononeuropathies, or radiculoplexus or entrapment neuropathies). For all correlations and predictions, the GE$_i$ is higher with increasingly severe stages of complication and, in most cases, these differences are significant. Box and whisker symbols represent 25th, 50th, and 75th percentile values and ranges. Differences between consecutive staged severities are shown by +0.001 < P ≤ 0.05; ++P ≤ 0.001; ΔP ≤ 0.05.*

relatively unchanged over the years, despite the emphasis of physicians on weight loss and improved glycemic control during the period of study, may be discouraging. The data obtained here also provides some information, albeit incomplete, about the equivalency of the degree of hyperglycemia and the duration of diabetes in development of complications. It would be of interest to know whether very high A1C levels for short times induce the same complications as mildly elevated A1C levels for long times. Our data suggest a rough equivalency, but further studies focused on this issue are needed. In studies done on cats, we found that severe hyperglycemia for short durations can cause severe nerve injury (25).

How well does the GE$_i$ correlate with and predict complications? As shown in Fig. 2, the GE$_i$ is usually significantly higher with increasing stages of severity of complications. The overlap of values makes clear that it does not correlate and

predict complications exactly. However, the correlative and predictive information is sufficient to be used to encourage patients to lower their A1C levels by loss of weight or treatment. Several reasons might be given for the fact that our correlations and predictions were not higher or better: inaccurate measurement of CGE and complications, nonlinear effects of CGE on complications, and the putative role of other mechanisms for complications (7). For example, it is likely that genetic mechanisms modulate the adverse effects of CGE by various metabolic pathways, and there is recent evidence suggesting such mechanisms for type 2 diabetes (26,27). Although we tried to exclude such cases, immune or mechanical events could also be implicated in complications (28).

**Acknowledgments**— This work was supported in part by a grant obtained from the National Institute of Neurological Disease and Stroke (NINDS 36797).

We gratefully acknowledge the help of Mary Lou Hunziker in preparation of the manuscript.

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