Impaired Glycemia and Diabetic Polyneuropathy

The OC IG Survey

PETER J. DYCK, MD[1]
VICKI M. CLARK, CRA[1]
CAROL J. OVERLAND, CRA[1]
JENNY L. DAVIES, BA[1]
JOHN M. PACH, MD[2]
P. JAMES B. DYCK, MD[1]
CHRISTOPHER J. KLEIN, MD[1]
ROBERT A. RIZZA, MD[3]
L. JOSEPH MELTON III, MD[3,4]
RICKEY E. CARTER, PHD[5]
RONALD KLEIN, MD[6]
WILLIAM J. LITCHY, MD[1]

OBJECTIVE—To test whether diabetic polyneuropathies (DPNs), retinopathy, or nephropathy is more prevalent in subjects with impaired glycemia (IG) (abnormality of impaired fasting glucose [IFG], impaired glucose tolerance [IGT], or impaired HbA_{1c} [IA1C]) than in healthy subjects (non-IG).

RESEARCH DESIGN AND METHODS—Matched IG and non-IG volunteers were randomly identified from population-based diagnostic and laboratory registries, restudied, and reclassified as non-IG (n = 150), IG (n = 174), or new diabetes (n = 218).

RESULTS—Frequency (%) of DPN in non-IG, IG, and new diabetes was 3 (2.0%), 3 (1.7%), and 17 (7.8%) narrowly defined (no other cause for polyneuropathy) and 19 (12.7%), 22 (12.6%), and 38 (17.4%) broadly defined. Mean and frequency distribution of composite scores of nerve conduction and quantitative sensation tests were not significantly different between IG and non-IG but were worse in new diabetes. Frequency of retinopathy and nephropathy was significantly increased only in new diabetes. In secondary analysis, small but significant increases in retinopathy and nephropathy were found in IGT, IFG, and IGT combined groups.

CONCLUSIONS—In population studies of Olmsted County, Minnesota, inhabitants, prevalence of typical DPN, retinopathy, and nephropathy was significantly increased only in subjects with new diabetes—not in subjects with IG as defined by American Diabetes Association (ADA) criteria of abnormality of IFG, IGT, or IA1C. For atypical DPN, such an increase was not observed even in subjects with new diabetes. In medical practice, explanations other than IG should be sought for patients with atypical DPN (chronic idiopathic axonal polyneuropathy) who have IG.

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The prevalence of impaired glycemia (IG) and type 2 diabetes mellitus (T2DM) is increasing to epidemic frequencies (1–4). This increase is associated with high morbidity and mortality due mainly to atherosclerotic complications, but diabetic polyneuropathy (DPN), retinopathy, and nephropathy may also be increasing. Since IG typically evolves into T2DM, it is inferred that IG itself causes microvessel complications (5–18), but the evidence for this is contradictory. Weight loss and vigorous exercise reportedly resulted in increased numbers of epidermal nerve fibers, interpreted as indicating nerve fiber regeneration (19) but an alternative explanation, increased packing density from decreased surface area due to weight loss, might also explain it.

The neuropathies associated with diabetes have been classified into generalized and focal and multifocal varieties, and the former into typical and atypical varieties (20). Typical DPN (or diabetic sensorimotor polyneuropathy [DSPN]) is a distal sensorimotor polyneuropathy thought to be due to vascular and metabolic derangements secondary to chronic hyperglycemia and sensitively diagnosed by nerve conduction abnormality (20). Atypical DPNs (also called chronic idiopathic axonal polyneuropathy [CIAP]) are intercurrent, small fiber, painful, and autonomic neuropathies. Whether or not IG itself causes DPN (and of which kind), retinopathy, or nephropathy has been studied, but the results have been questioned because of methodologic concerns and discordant results (5,8,16,18,21–24). To amplify these concerns, in established T2DM, chronic hyperglycemia is a strong risk covariate for DSPN with models of exponents of A1C (%), duration of diabetes (years), and type of diabetes or age of onset of diabetes correlating with and predicting the severity of DSPN (25–27). However, such quantitative studies have not been extended to IG (22). Confirmation that chronic hyperglycemia and secondary metabolic derangements (26) are important risk factors for DSPN came from randomized clinical trials comparing rigorous to conventional management of hyperglycemia (28,29).

The question addressed here is, does IG alone cause DPN? This question has become more complicated since it is now recognized that generalized DPN needs to be classified into at least two varieties—typical (typ) and atypical (atyp) DPN (20), and IG may be ascertained by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), impaired HbA_{1c} (IA1C), or combinations. However for both varieties, previous studies of the question provided contradictory results. Considering typ DPN in a study of Japanese American men, nerve conduction abnormality was found in 46.2% with diabetes (type 2), 2.9% with IGT, and 5.1% with non-IGT (5). Also, no increase in retinopathy or nephropathy was found with IGT. By

From the [1]Department of Neurology, Mayo Clinic, Rochester, Minnesota; the [2]Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota; the [3]Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, Minnesota; the [4]Division of Epidemiology, Mayo Clinic, Rochester, Minnesota; the [5]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; and the [6]Department of Ophthalmology and Visual Sciences, University of Wisconsin–Madison, Madison, Wisconsin.
Corresponding author: Peter J. Dyck, dyck.peter@mayo.edu.
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contrast in the San Luis Valley Study using only clinical evaluation by nurses (albeit trained for this purpose), an intermediate prevalence of DPN between that of non-IG and diabetes was found (6,7). de Neeling et al. (8) studied nerve conduction abnormality and other neurophysiologic tests in patients without and with IGT, new-onset diabetes, and prevalent diabetes and found "large fiber nerve dysfunction" within the range of IGT to diabetes ($P < 0.05$). However in a study by Isak et al. (23) using objective nerve conduction measurements, no increase attributable to IG was found.

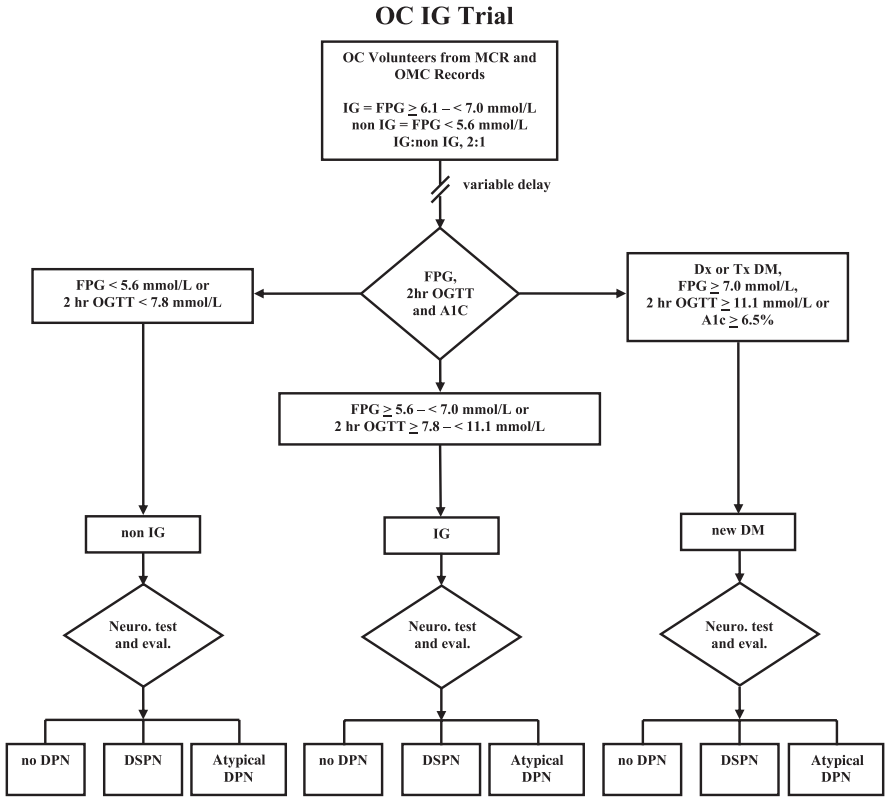
As concerns intercurrent painful and autonomic small-fiber polyneuropathies (atyp DPNs), the reported conclusions also differ (9–15,17,19,21,30). Studies mainly of symptomatic patients seen in tertiary referral centers (9–15,17,19) found higher frequencies of IG than in historic control subjects. In prospective studies, a low frequency of painful neuropathies was found in people with IGT (31,32), whereas in another prospective trial of idiopathic axonal polyneuropathies versus control subjects, hyperlipidemia rather than hyperglycemia was thought to be the likely cause of CIAP (21). Studies of sweating and epidermal nerve fiber densities in patients with IGT have provided only suggestive evidence of abnormality in IG (16,18).

Knowing that the health care community is advocating healthier diets, a more active physical lifestyle, and avoidance of obesity, is it even appropriate to address the question studied here of whether impaired glycemia causes polyneuropathy, retinopathy, and nephropathy? We think the question should be addressed for the following reasons: *1*) scientific reasons because some previous studies have had methodologic problems, which have provided contradictory results; *2*) if IG does not cause atyp DPN (CIAP), it is important that other causes be considered; *3*) answering the question definitively is important information relating to minimal diagnostic criteria for diabetes itself; and *4*) it might have therapeutic implication, e.g., whether or not IG itself should be treated.

RESEARCH DESIGN AND METHODS

—The essential features of the Olmsted County, Minnesota, USA, Impaired Glycemia (OC IG) Survey were identification of persons with IG and non-IG in local population-based medical and laboratory registries, obtaining consent by letter, assessing their glycemia status (non-IG, IG, and new diabetes) at study (Fig. 1) and then evaluating their microvessel complications (typ and atyp DPN, retinopathy, and nephropathy) by masked and objective examination criteria (Supplementary Fig. A). The survey was made possible by the unique nature of the medical practice in this community, which facilitates population-based epidemiologic surveys and therapeutic trials of prospectively defined groups of patient cohorts using masked, objective, and quantitative assessment of complications previously described (33).

The OC IG Survey (NS36797) was initiated on 1 April 2004 (22). Following approval by the respective institutional review boards, the medical and laboratory data of the Mayo Clinic and the Olmsted Medical Center were used to identify the Olmsted County residents with IG (i.e., fasting plasma glucose [FPG] values ≥6.1 to <7.0 mmol/L from blood taken between 5:00 and 9:30 A.M.) between the years 2000 and 2005. The slightly higher, lower limit of abnormality of FPG was deliberately set to avoid inclusion of borderline IG patients. A matched (by age and sex) list of local residents without IG (FPG <5.6 mmol/L) for the same time period was also prepared. Specifically, nerve, eye, or kidney complications, as recorded in an index of medical diagnoses (33), were not used as exclusion criteria. Institutional review board–approved letters inviting IG and non-IG people to participate in the restudy of their IG status, as well as complications of typ and atyp polyneuropathy, retinopathy, and nephropathy, were sent. At restudy, which was sometimes delayed for months or even a year or two, the IG status was reassessed and clinical microvessel complications and tests were assessed independently of each other.



Abbreviations: OC = Olmsted Country, MCR = Mayo Clinic Rochester, OMC = Olmsted Medical Center, IG = impaired glucose, DM = diabetes mellitus, non IG = non-impaired glucose, FPG = fasting plasma glucose, OGTT = oral glucose tolerance test, DPN = diabetic polyneuropathy, DSPN = diabetic sensorimotor polyneuropathy

Figure 1—*Shown is the algorithm used to identify IG and non-IG patients from Mayo Clinic Rochester (MCR) and Olmsted Medical Center (OMC) disease and laboratory registries. At study (usually delayed by months), volunteers were classified by their IG status and microvessel complications (e.g., no DPN, DSPN, or atyp DPN) in non-IG, IG, and new diabetes (DM) groups. Eval., evaluation; Dx, diagnosis; Neuro, neuropathy; Tx, treated as DM.*

At restudy, patients were defined as having IG when their FPG was ≥5.6 mmol/L, their 2-h 75-g oral glucose tolerance test (OGTT) plasma glucose values were ≥7.8 mmol/L, and they did not have new diabetes as judged by one or more of the following: FPG value ≥7 mmol/L, a 2-h OGTT plasma glucose value ≥11.1 mmol/L, or an A1C value ≥6.5% (Fig. 1). An A1C value was not used as a lower limit for IG (because the lower limit [6.0%] was later changed to 5.7%). Also, if patients revealed at restudy that they had previously been diagnosed or treated as having diabetes, they were included in the new diabetes group.

Power for a comparative study of 300 IG and 300 non-IG patients was determined to be 84% ($\alpha = 0.05$ one-sided) for detecting a relative risk for DPN (typ and atyp varieties combined) of 5.0 (frequencies of DPN were assumed to be 1% and 5% for non-IG and IG, respectively) (22). The distribution of non-IG and IG patients and the total sample size, however, had to be modified because of budgetary considerations and a greater than expected number of people whose status had changed from IG to new diabetes. Data were analyzed according to the IG status at the time of study evaluation using standard measures of association and tests for proportions.

To recognize a subtle functional neurophysiologic change of nerves in IG, we compared composite scores of nerve conduction (NC) (Σ 2 NC nds, Σ 4 NC nds, Σ 5 NC nds, and Σ 6 NC nds) spanning normal and abnormal values among the three study groups. Assessed were summated normal deviate scores (from percentiles corrected for age, sex, and physical characteristics [34], with all abnormalities expressed in the lower tail of the normal distribution, obtained from the study of a healthy subject cohort).

The minimal criterion for DSPN was NC abnormality (Σ 2 NC nds ≤2.5th percentile, i.e., Stage 1a) with increased severity staged by additional neuropathic signs and symptoms (Supplementary Fig. A) (20,35). All neurologic assessments were performed (by P.J.D.) by entering neurologic signs in the Neuropathy Impairment Score and symptoms in the Neuropathy Symptoms and Change into paper and electronic form (Clinical Neuropathy Assessment) (35). A distinction of typ from atyp DPN was made using the criteria recently described (20). Patients classified as typ or atyp DPN were further classified by narrow and broad criteria. The latter patients were those in whom another diagnosis other than diabetes was considered, e.g., lumbosacral disk disease, spinal stenosis, a family history suggestive of inherited neuropathy, and others.

Retinopathy was staged as R0 (no retinopathy), R1 (mild preproliferative), R2 (severe preproliferative), and R3 (proliferative) from 7 stereoscopic photographs of each eye and as read in the Department of Ophthalmology and Visual Sciences, University of Wisconsin–Madison (R.K.). Nephropathy was judged as being present if the 24-h urinary albumin excretion was ≥30 mg.

RESULTS

Recruitment and disease characteristics of the survey subjects

Of 558 volunteers recruited to be studied, 542 (150 non-IG, 174 IG, and 218 new diabetes) completed the studies. In the IG group, 31 of 174 (17.8%) chose not to have the 2-h 75-g OGTT. The diagnosis of IG was based on abnormality of only IFG (60/174, 34.5%); IFG and A1C (58/174, 33.3%); IFG, IGT, and A1C (28/174, 16.1%); IGT and A1C (10/174, 5.7%); IFG and IGT (9/174, 5.2%); and IGT only (9/174, 5.2%). Small differences in age, sex, and physical features among study groups (Supplementary Table A) should not have influenced the results since neurophysiologic end points (e.g., attributes of NC) were corrected for applicable variables affecting the frequency and severity of DPNs (34,36). Significant differences among studied groups were observed for pulse, blood pressure, and some lipid and lipoprotein classes (Supplementary Table A).

Prevalence of typ or atyp DPN was not increased in IG, but DSPN (typ DPN) was significantly increased in new diabetes

The primary outcome measure, the prevalence of DPN (typ or atyp or combined), was not significantly different between IG and non-IG, whether defined narrowly or broadly (Fig. 2). By contrast, the frequency of typ DPN only was significantly increased in new diabetes.

In secondary analysis using IFG only, IGT only, or IFG and IGT combined as the criterion for IG, no significant increase in typ, atyp, or typ and atyp DPN was found whether narrowly or broadly defined. Significant increases were found for typ DPN in new diabetes.

Confirmation of a functional NC abnormality in new diabetes but not in IG

None of the four composite NC scores assessed showed a significant difference in mean values between IG and non-IG (Fig. 3). The 25th, 50th, 75th percentiles and range values were essentially overlapping between IG and non-IG. By comparison, a definite and significant downward shift toward abnormality was shown for new diabetes. As a further test of the validity of these composite NC scores, we compared them with those of an earlier healthy subjects' cohort (the Rochester Diabetic Neuropathy Study of Healthy Subjects [RDNS-HS]) and to a previously studied prevalence diabetes cohort (the Rochester Diabetic Neuropathy Study [RDNS]) (Fig. 3). The composite scores of the non-IG and IG groups did not differ significantly from the scores in the previously studied RDNS-HS (34). In RDNS (25,27), the scores were significantly worse than in the presently studied non-IG, IG, and new diabetes groups (Fig. 3).

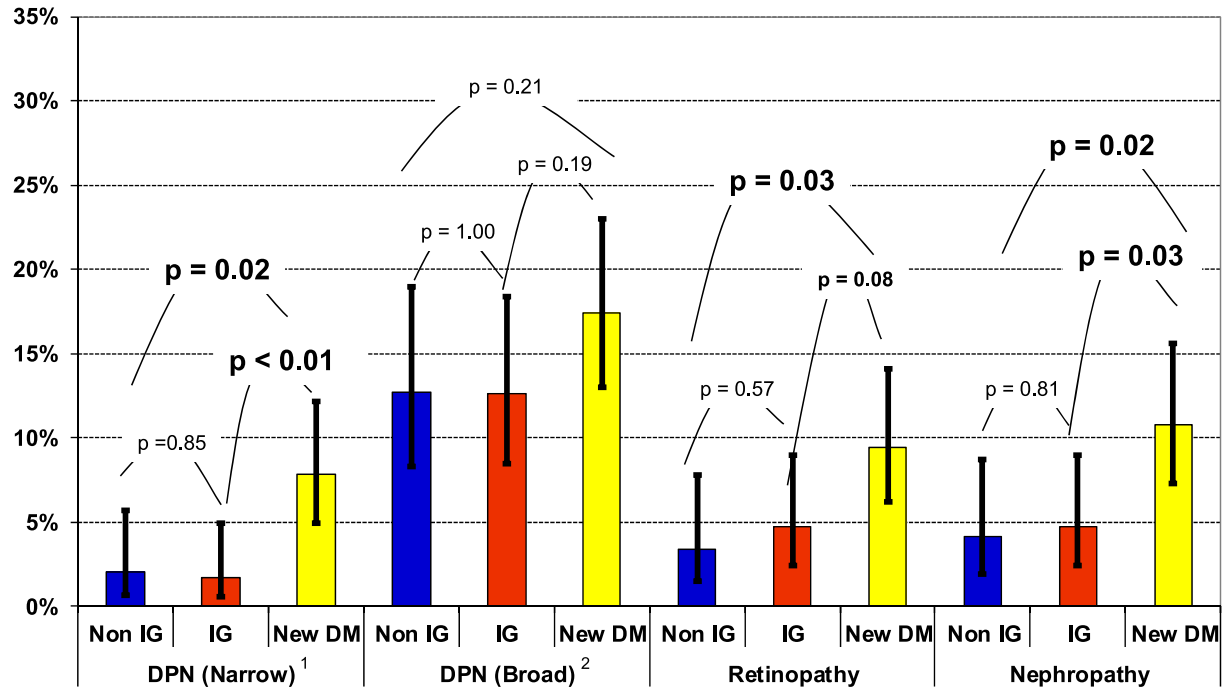
Additional confirmation of a functional abnormality in new diabetes but not in IG: quantitative sensation test results

Quantitative sensation test (QST) results were confirmatory of the clinical and NC observations reported above (i.e., increased prevalence of typ DPN and composite NC abnormality only in new diabetes). No significant difference in quantitative sensation scores was found between the non-IG and IG groups, but scores were significantly worse in the new diabetes group than in the other two tested groups (Table 1).

In contrast to the QST results, a decrease in heart rate response to deep breathing (HR_{db}) was found in IG as compared with non-IG, but a further significant decrease was not found in new diabetes. In secondary analysis, a similar result was found when IFG only was used as the indication of IG. When IGT was the indicator of IG, no significant decrease of HR_{db} was observed.

Retinopathy and nephropathy increased in new diabetes but not in IG

The frequency of diabetic retinopathy was 3.4, 4.7, and 9.4%, respectively, for non-IG, IG, and new diabetes (Fig. 2). The difference was not significant between the non-IG and IG groups ($P = 0.57$) but was significantly increased for new



Odds Ratio (95% Confidence Interval)				
IG vs. non IG	0.9 (0.2, 4.3)	1.0 (0.5, 1.9)	1.4 (0.5, 4.4)	1.1 (0.4, 3.4)
New DM vs. non IG	4.1 (1.2, 14.4)	1.5 (0.8, 2.6)	2.9 (1.1, 8.0)	2.8 (1.1, 7.0)
New DM vs. IG	4.8 (1.4, 16.7)	1.5 (0.8, 2.6)	2.1 (0.9, 4.9)	2.4 (1.1, 5.6)

Figure 2—*Data are the prevalence and 95% CIs by IG classification and disease end point.* P *values are for unadjusted pairwise comparisons using Pearson* χ^2 *tests.* [1]*Typical DPN was significantly more frequent in new diabetes (DM) (6.0%) than in IG (0.6%,* P *<0.01) and more frequent than in non-IG (2.0%), although this latter difference was almost significant* (P = *0.07). Atypical DPN was more frequent in DM (1.8%) than in non-IG (0.0%) or IG (1.%), but these differences were not significant.* [2]*Typical DPN was more frequent in DM (8.3%) than in non-IG (5.3%) or IG (4.6%), but these differences were not significant. Atypical DPN was more frequent in DM (9.2%) than in non-IG (7.3%) or IG (8.1%), but these differences were not significant.*

diabetes versus non-IG (P = 0.03) and borderline significant for IG versus new diabetes (P = 0.08).

In secondary analysis and using IFG only as the IG criterion, retinopathy was found in 5.2, 4.3, and 10.2%—significantly increased in new diabetes versus IG. Using IGT only, retinopathy was found in 3.4, 9.9, and 12.1%—significantly increased in IG versus non-IG and new diabetes versus non-IG. Using combined IFG and IGT abnormality, retinopathy was found in 4.4, 8.7, and 10.9%—significantly increased only in new diabetes versus non-IG.

In primary analysis, nephropathy was recorded in 4.1, 4.7, and 10.7% of patients with non-IG, IG, and new diabetes (Fig. 2). The difference was significant for non-IG versus new diabetes (P = 0.02), as well as for IG versus new diabetes (P = 0.03).

In secondary analysis of nephropathy, nephropathy occurred in 3.5, 7.2, and 10.9% in non-IG, IG, and new diabetes—being significantly more frequent only in new diabetes. Using IGT, only nephropathy was found in 3.8, 10.0, and 9.3%—significant for IG versus non-IG (P = 0.03), diabetes versus non-IG (P = 0.03), but not significant for new diabetes versus IG (P = 0.87). When both IFG and IGT were used, frequency was 3.6, 13.3, and 9.4%—significant increase of IG versus non-IG ($P < 0.01$), diabetes versus non-IG (P = 0.02), but not significantly different for new diabetes versus IG.

CONCLUSIONS—Our prospective, population-based survey using masked and quantitative assessment for the prevalence of polyneuropathy, retinopathy, and nephropathy did not find an increased prevalence of any of them in IG, defined as any abnormality of IFG, IGT, or IA1C (the latter used only to recognize new diabetes). Using the criterion of IGT for the diagnosis of IG, 31% had new diabetes by IFG or IA1C criteria. In a secondary analysis when IG was defined by IFG only, IGT only, or IFG and IGT combined criteria, no significant increase in typ, atyp, or combined typ and atyp DPN was observed whether narrowly or broadly defined; however, small but significant increases of retinopathy and nephropathy were observed. Since other risk covariates than chronic hyperglycemia (e.g., microalbuminuria or hypertension) might be implicated in early retinopathy or nephropathy, it is unclear whether this low level of increase can be attributed to impaired glycemia (37).

To relate our results to those of earlier studies, we make a distinction between

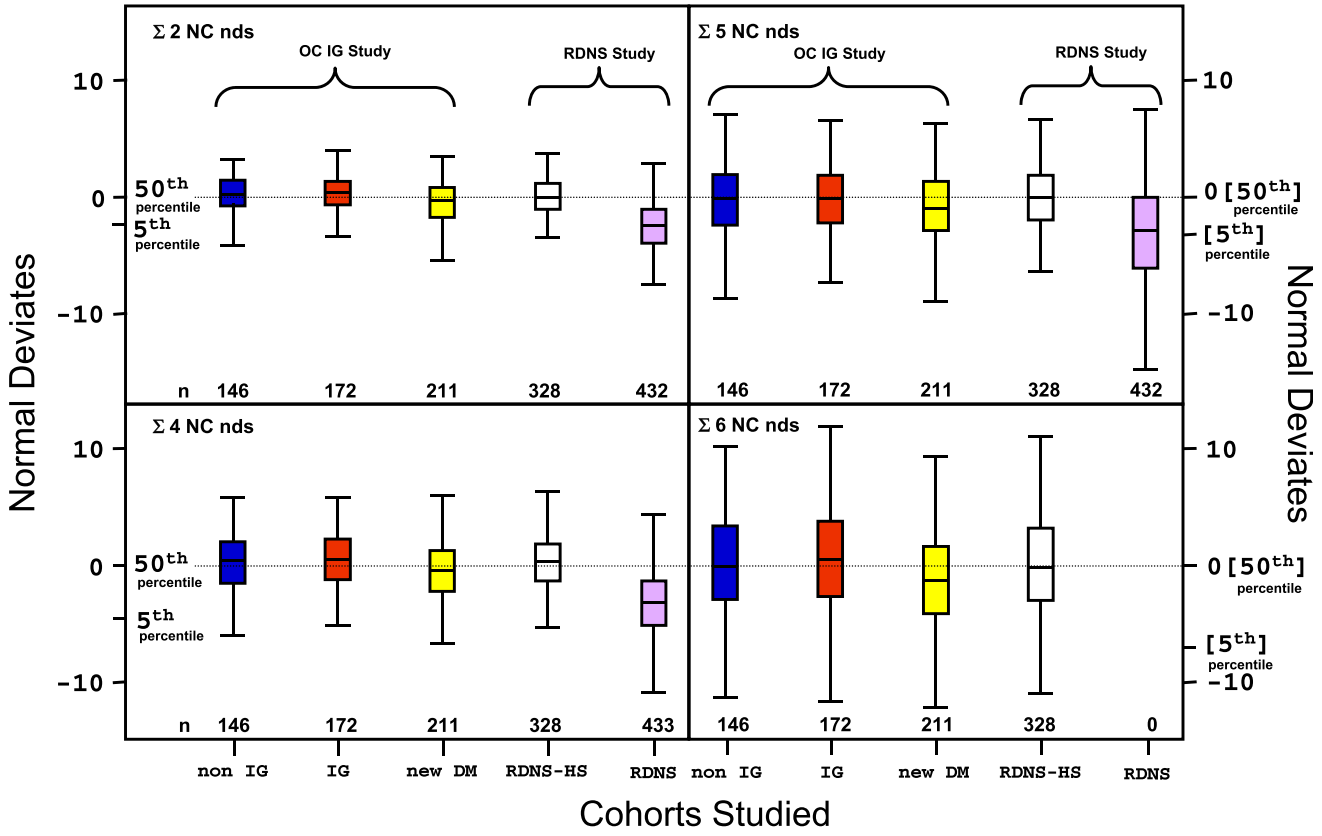


Figure 3—*Cohorts studied are described in text* (n = *number of patients studied*). *Σ 2 NC nds is the sum of peroneal MNCV and sural SNAP nds; Σ 5 NC nds is the sum of peroneal CMAP, MNCV, and MNDL, tibial MNDL, and sural SNAP nds; Σ 4 NC nds is the sum of peroneal, tibial, and ulnar CMAP and sural SNAP nds; Σ 6 NC nds is the sum of peroneal, tibial, and ulnar MNCV and f-wave latency nds (all percentiles expressed in the lower tail of the distribution). Two-sample* t *tests: Σ 2 NC nds – 1 vs. 3 0.002, 1 vs. 5 <0.001, 2 vs. 3 <0.001, 2 vs. 5 <0.001, 3 vs. 4 <0.001, 3 vs. 5 <0.001, 4 vs. 5 <0.001; Σ 5 NC nds – 1 vs. 3 0.033, 1 vs. 5 <0.001, 2 vs. 3 0.044, 2 vs. 5 <0.001, 3 vs. 4 0.002, 3 vs. 5 <0.001, 4 vs. 5 <0.001; Σ 4 NC nds – 1 vs. 3 0.008, 1 vs. 5 <0.001, 2 vs. 3 <0.001, 2 vs. 5 <0.001, 3 vs. 4 0.002, 3 vs. 5 <0.001, 4 vs. 5 <0.001; Σ 6 NC nds – 1 vs. 3 0.006, 2 vs. 3 <0.001, 3 vs. 4 0.002. Among 1, 2, and 4, there were no significant differences for any composite score. CMAP, compound muscle action potential; MNCV, motor nerve conduction velocity; MNDL, motor nerve distal latency; SNAP, sensory nerve action potential.*

typ and atyp DPN as agreed to at a recent consensus meeting (20). Typ DPN was defined as a length-dependent DPN, usually developing on a background of chronic hyperglycemia and secondary metabolic derangement (polyol shunting, accumulation of advanced glycation end products, oxidative stress, altered lipid metabolism, or other). Typical early manifestations of typ DPN are abnormalities of NC and associated with it or developing later signs and symptoms of a distal sensorimotor polyneuropathy. The occurrence of typ DPN is associated with diabetic retinopathy and nephropathy. Both large and small sensory fibers and motor and autonomic fibers may be affected. By contrast, atyp DPN (CIAP) is

Table 1—*QST and HR_{db} test results* in the OC IG Trial*

	non-IG			IG			new DM			*P*†			
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	All groups	non-IG vs. IG	non-IG vs. new DM	IG vs. new DM
VDT nd	143	0.58	1.10	169	0.34	1.07	206	0.62	1.07	**0.036**	0.056	0.731	**0.013**
CDT nd	142	0.44	1.15	168	0.41	1.10	205	0.70	1.25	**0.037**	0.808	0.055	**0.021**
HP:5 nd	145	0.19	1.40	170	0.39	1.55	204	0.59	1.80	0.073	0.223	**0.020**	0.258
HP:0.5 nd	145	−0.25	1.57	170	0.04	1.53	204	0.21	1.80	**0.037**	0.101	**0.013**	0.314
HP:5–0.5 nd	145	0.48	1.34	170	0.41	1.27	204	0.56	1.38	0.576	0.646	0.602	0.295
Σ 3 QST nds	145	1.23	2.37	170	1.16	2.47	206	1.89	2.91	**0.013**	0.824	0.019	**0.009**
HR_{db} nd	137	−0.04	1.13	154	−0.46	1.08	196	−0.46	1.25	**0.002**	**0.001**	**0.002**	0.975

*Abnormality for VDT, CDT, HP, and Σ 3 QST is expressed in the upper tail of the normal distribution. Abnormality for HR_{db} is expressed in the lower tail. DM, diabetes; CDT, cooling detection threshold; HP, heat as pain; VDT, vibratory detection threshold. †One-way ANOVA for all groups and two sample *t* tests for two group comparisons. Values in boldface indicate statistical significance.

manifested by intercurrent development of pain and autonomic symptoms and more selective involvement of small sensory and autonomic nerve fibers. NC abnormality is not a necessary feature.

To ensure that clinical evaluations of complications were standard, detailed, and comprehensive, we used the Neuropathy Symptoms and Change Score, a broad survey of muscle weakness and sensory and autonomic symptoms. To guard against biased exclusion of patients with atyp DPN, we included all patients with the symptoms and findings (into the broad category of CIAP) even when we thought they might have another cause than IG or diabetes for their neuropathy. To avoid overdiagnosis of typ DPN, we used a composite score of NC abnormality as a minimal criterion.

Considering typ DPN, our data do not support the hypothesis that IG causes it. While the power of our study is insufficient to rule out a small increase, a substantial increase appears unlikely for the following reasons: *1*) we were able to demonstrate an unequivocal increase of this polyneuropathy in a new diabetes cohort that was not much larger than the IG cohort; *2*) average values of composite NC scores spanning normal and abnormal values showed no significant abnormality in IG, whereas they were significantly shifted in new diabetes; *3*) similar results to those recorded in reason 2 were found for quantitative sensation test values; and *4*) occurrence of the complications of retinopathy and nephropathy known to be correlated with typ DPN also were not significantly increased in IG but were unequivocally increased in new diabetes. The small but significant increase of retinopathy and nephropathy found only in secondary analysis may relate to a greater degree of chronic hyperglycemia with use of the IGT, and IGT and IFG combined criteria than we used—or any abnormality of the three criteria.

Our lack of finding an increased prevalence of typ DPN in IG agrees with the results of Fujimoto et al. (5) and Isak et al. (23), who used NC as a primary indication of polyneuropathy, but not with that of Franklin et al. (6) based on clinical examination by trained nurses. Use of clinical neurologic examination only may overestimate the frequency, especially signs of DSPN (38), emphasizing the need for use of objective minimal criteria for the diagnosis. As we have recently shown, composite scores of NC, such as Σ 2 NC nds or Σ 5 NC nds, perform very well because they define the neurophysiologic test exactly by avoiding type 1 error, and they are representative, sensitive, and specific for the diagnosis and therefore are useful for epidemiologic survey and conduct of controlled trials (38).

Our finding that atyp DPN was not significantly increased in IG fits the conclusions of Hughes et al. (21) and is not markedly different from that of Ziegler et al. (31,32) who found only low frequencies of such neuropathies in IGT patients but whose results differ strikingly from that of several earlier studies using historic control subjects (9–15,17,19). Our studies focusing mostly on symptomatic painful and autonomic polyneuropathies did not address the related question of whether counts of epidermal nerve fibers were decreased in IG. However, the tests we used (QSTs and HR_{db}, presumably less sensitive or specific) did not detect abnormality in IG or new diabetes. Our findings are in keeping with the findings of Hughes et al. (21) using a concurrent control group. Thus, the inferences that IG is a common or the usual underlying cause of symptomatic atyp DPN (or CIAP) are not supported by our data nor that of Hughes et al. or Ziegler et al. The likely explanation for the difference in the results of the studies of Hughes et al. (21), Ziegler et al. (31,32), and our present study—finding no or only small increases of atyp DPN as compared with other studies reviewed in the beginning of this article—is difficult to reconcile but can be attributable, at least in part, to selection bias in the earlier studies (selectively recruiting patients with IG to study), to inappropriate use of historic control subjects, or to use of only clinical criteria used for diagnosis. In this study, we may have more rigorously defined IG using any one of three criteria, i.e., IFG, IGT, or IA1C. To avoid the first two pitfalls, we recruited patients from a population-based disease and laboratory database (39), selected patients by their non-IG or IG status to avoid referral bias, and made judgments about the presence of atyp DPN by masked evaluation using both narrow and broad criteria.

A priori power was not obtained in the study because of a decrease in the overall sample size and the realization of a third patient classification (new diabetes), which further limited the sample size for each classification group. Nonetheless, adequate power and precision (CI width) remained for between classification comparisons and the description of the prevalence of DPN. The realized sample sizes in each classification (i.e., 150, 174, and 218 for non-IG, IG, and new diabetes, respectively) helped maintain precision by providing large sample sizes where higher prevalence of DPN could be anticipated (note, precision decreases as prevalence approaches 0.5). For a range of hypothesized prevalences, say 1–10%, sample sizes ranging from 150 to 218 would be expected to have precision of approximately plus or minus 4 percentage points as measured by the width of a 95% score CI.

What are the implications of our studies? By showing that IG alone does not cause diabetic microvessel complications, our results support present ADA criteria for the diagnosis of diabetes, based on the idea that the lowest level of chronic hyperglycemia that induces microvessel complications should be the minimal criteria for the diagnosis of diabetes. Also, our results have important implications for the diagnosis and management of polyneuropathy in IG or diabetes. Our studies may also have implications for the degree of hyperglycemia control that is desirable for management of diabetes. Our observations might be taken as a further argument not to overdo rigorous control of hyperglycemia in IG (40).

Our findings, however, should not allay concerns about IG as a risk covariate for macro- and microvessel complications since IG usually leads to T2DM, which is known to cause such complications. Finally, our study sheds doubt on the common assumption that IG is the proximate and usual cause of chronic idiopathic painful and autonomic polyneuropathy (atyp DPN or CIAP) since IG does not appear to be an adequate explanation of their cause.

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P.J.D. contributed to the overall design and execution of the OC IG Trial and the drafting the manuscript, and is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. V.M.C., C.J.O., and J.M.P. coordinated patient recruitment, study execution, and evaluation of data. P.J.B.D., C.J.K., and W.J.L. designed and executed the clinical and electrophysiologic measurements.

J.L.D., L.J.M., and R.E.C. contributed to the statistical design and analysis. R.A.R. contributed to the study design and the drafting of the paper. R.K. contributed to the assessment and supervision of retinal evaluation.

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