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Prevalence of diabetic peripheral neuropathy and relation to glycemic control therapies at baseline in the BARI 2D cohort

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Abstract

We evaluated the associations between glycemic therapies and prevalence of diabetic peripheral neuropathy (DPN) at baseline among participants in the Bypass-Angioplasty-Revascularization-Investigation-2-Diabetes (BARI 2D) trial on medical and revascularization therapies for coronary artery disease (CAD) and on insulin-sensitizing versus insulin-providing treatments for diabetes. 2368 patients with type 2 diabetes and CAD were evaluated. DPN was defined as clinical examination score >2 using the Michigan Neuropathy Screening Instrument (MNSI). DPN odds ratios across different groups of glycemic therapy were evaluated by multiple logistic regression, adjusted for multiple covariates including age, sex, HbA1c, diabetes duration. 51% BARI 2D subjects with valid baseline characteristics and MNSI scores had DPN. After adjusting for all variables, use of insulin was significantly associated with DPN (OR1.57, 1.15, 2.13). Patients on sulfonylurea or combination of sulfonylurea/metformin/TZD had marginally higher rates of DPN than the metformin/TZD group. This cross-sectional study in a cohort of patients with type 2 diabetes and CAD showed association of insulin use with higher DPN prevalence, independent of disease duration, glycemic control and other characteristics. The causality between a glycemic control strategy and DPN cannot be evaluated in this cross-sectional study, but continued assessment of DPN and randomized therapies in BARI 2D trial may provide further explanations on the development of DPN.

Keywords

diabetic peripheral neuropathy; type 2 diabetes; coronary artery disease; Michigan Neuropathy Screening Instrument; glycemic control therapy

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Introduction

In the United States, more than 23 million people 20 years of age and older have diabetes (www.diabetes.org; www.cdc.gov) and the incidence is increasing by 5% per year. Diabetic peripheral neuropathy (DPN) is the most common chronic complication of diabetes and is the leading cause of diabetes-related hospital admissions and nontraumatic amputations (Pirart, 1977; Boulton et al., 2005). DPN leads to major physical disability, poor quality of life (Vileikyte et al., 2005), high mortality (Boulton et al., 2005), and estimated total annual costs of \$22 billion (www.diabetes.org, www.cdc.gov). Despite its high morbidity (Boulton et al., 2005), results from most randomized clinical trials assessing the efficacy of various therapeutic agents have been disappointing, most likely due to the complexity of mechanisms involved in its pathogenesis (Pop-Busui et al., 2006). Therefore to date no effective treatment exists for DPN, other than control of hyperglycemia (Diabetes Control and Complications Trial Research Group, 1995; Ohkubo et al., 1995).

The initial screening and diagnosis of DPN in clinical practice depend on assessment of subjective complaints. A variety of validated scales and composite scores semi-quantitatively assess sensation, strength and reflexes and are frequently used as the primary outcome measure in clinical trials (Dyck et al., 1997; Dyck, 2003). The Michigan Neuropathy Screening Instrument (MNSI) is a validated clinical screening instrument for the assessment of DPN designed to balance the contribution of motor and sensory findings (Feldman et al., 1994) and has been widely used in clinical trials and longitudinal cohort studies including the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intensive Control study (DCCT/EDIC) (Brown et al., 2004; Martin et al., 2006). The examination score of the MNSI was established to achieve high specificity (95%) and sensitivity (80%), with a positive predictive value of 97% and a negative predictive value of 74% (Feldman et al., 1994).

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial is a National Institutes of Health-sponsored randomized clinical trial that evaluates treatment efficacy for patients with type 2 diabetes mellitus (T2DM) and angiographically documented, stable coronary artery disease (CAD) (Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group, 2008). One of the unique hypotheses of the BARI 2D trial is that insulin-providing agents will differ from insulin-sensitizing agents in their effects on cardiovascular outcomes (Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group, 2008). DPN as assessed by the MNSI at baseline and annual examinations thereafter is one of the secondary outcomes followed in the BARI 2D cohort.

Intensive glycemetic control can reduce the incidence of neuropathy in both type 1 and type 2 diabetic subjects (Diabetes Control and Complications Trial Research Group, 1995; Ohkubo et al., 1995), but different anti-diabetic agents may have other effects besides lowering glucose. For instance, animal studies reported beneficial effects of the insulin sensitizers thiazolidinediones and metformin on markers of experimental DPN via prevention of increased oxidative stress, inflammation and signaling in the protein kinase C pathway (Yamagishi et al., 2008) and prevention of neuronal apoptosis (El-Mir et al., 2008). However, whether different anti-diabetic therapies could play a role in DPN prevalence in T2DM or whether insulin sensitizers may be protective is unknown. The association of diabetic therapies and the prevalence of DPN have been reported in population studies (Franklin et al., 1994; Savage et al., 1997; el-Shazly et al., 1998), but those findings from over ten years ago would not reflect the use of newer drugs such as metformin and/or thiazolidinediones for glycemetic control. Therefore, in this large, ethnically diverse cohort of patients with type 2 diabetes in the BARI 2D trial, we examined the association of prior diabetes therapy and the prevalence of DPN at baseline.

Materials and Methods

The BARI2D trial design and patient population have been described elsewhere (Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group, 2008). Briefly, a total of 2368 patients, with T2DM and angiographically documented CAD, were recruited from 49 international clinical sites and randomized to early revascularization and aggressive medical therapy versus aggressive medical therapy alone and to insulin-sensitizing versus insulin-providing treatments for diabetes. All participants signed an informed consent and study was approved by Institutional Review Boards at all participating institutions.

Glycemia treatments

Upon enrollment, the current diabetes management regimen was recorded (within 6 months) and laboratory data were obtained on all participants (Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group, 2008). The glycemic control medication for the present analysis was categorized into five mutually exclusive classes: 1) no diabetes medication; 2) insulin sensitizers (IS) only, which included metformin and/or thiazolidinediones (Met/TZD); 3) insulin providers (IP) only without insulin, which included sulfonylurea and/or meglitinide and/or phenylalanine derivative (SU for all); 4) combination of IS and IP without insulin (Met/TZD+SU); and 5) insulin alone or in combination with any other diabetes medication(s) (Insulin). The neutral agents, alpha glucosidase inhibitors, were not categorized separately from IS or IP drugs since only 26 patients took these drugs at baseline, and they were equally distributed among the five groups.

Neuropathy screening

The MNSI consists of a brief symptom questionnaire of 15 “yes or no” questions on foot sensation and a clinical examination (Feldman et al., 1994). The clinical examination portion of the MNSI, the most objective portion, is a simple 8-point score evaluating ankle reflexes, light touch and vibration sensation in the great toe and foot appearance. One point per side is assigned for abnormalities of foot appearance (deformities, dry skin, calluses, infection and ulcers) and 1 point per side (in 0.5 point increments) for abnormalities of ankle reflexes, light touch or vibration at the great toe. BARI 2D nurse-coordinators were trained in a central session and certified to perform the MNSI in all BARI 2D subjects at the enrollment visit. DPN was defined operationally as a score greater than 2.0 on the MNSI examination, thresholds defined by prior validation studies (Feldman et al., 1994; Brown et al., 2004; Martin et al., 2006). A score >2 requires at least one abnormality in reflexes, vibration or light touch.

Statistical methods

The primary outcome was the presence of DPN as defined by a MNSI clinical score >2. Relevant baseline characteristics of demographics, lifestyle, clinical history, and laboratory measures were evaluated for the association with DPN, using Chi-square tests and Student's t-tests to test the significance at an alpha level of 0.05. Logistic regression models were built to evaluate the association of DPN with glycemic control therapies. To test our hypothesis, patients on Met/TZD only were selected as the reference group. A model was built to estimate the unadjusted odds ratios of DPN by glycemic control medication, without any other covariates in the model. The following covariates were then added to the model: demographic characteristics (sex, age, race/ethnicity), current cigarette use and alcohol consumption as categorical variables and hemoglobin A 1C (HbA1c), diabetes duration, body mass index (BMI), systolic blood pressure, high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc) and triglycerides as continuous variables. Although age and duration of DM are statistically correlated, they are not

collinear and independently contribute to the model. Significance was evaluated at a 0.05 level for all odds ratio estimates. SAS v.9.1.3 software (Cary, NC) was used for all data processing and statistical analysis.

Results

Among the 2368 patients enrolled in the BARI 2D trial, 2314 patients had valid baseline MNSI clinical scores, specified glycemic control strategies, and at least 80% baseline information available. This group formed the basis of the present analysis.

The demographic and clinical characteristics show a cohort with an average age of 62.4 ± 8.9 years, with predominance of males (71%) and of non-Hispanic whites (66%) (Table 1). 43% of these subjects reported more than 10 years diabetes duration (mean: 10.4 ± 8.7 years) and 61% had an HbA1c above target (i.e., $\geq 7\%$) at baseline (HbA1c mean \pm SD: 7.7 ± 1.6).

At baseline the MNSI clinical score ranged from 0 to 8. 1173 out of 2314 subjects (51%) had a MNSI clinical score >2 consistent with DPN (Fig. 1). In this cohort, the higher prevalence of DPN was significantly associated with older age, male sex, black non-Hispanic ethnicity, longer diabetes duration, HbA1c $\geq 7\%$, history of hypertension and albuminuria ($p < 0.05$) (Table 1). On the other hand, none of the lipid variables, current cigarette use or ethanol intake was significantly associated with the prevalence of DPN (Table 1). Of note, 79% of the subjects were on treatment for dyslipidemia. The mean diabetes duration and HbA1c correlated with each other in the different glycemic control therapy groups with the shortest duration and lowest mean HbA1c values in subjects without a diabetes drug and the longest duration and highest HbA1c values in the subjects treated with insulin (Table 2).

In unadjusted analysis, subjects treated only with Met/TZD had the lowest DPN prevalence compared to the other groups and were therefore used as the comparator group for further analysis. Subjects treated with insulin had the highest DPN prevalence at baseline (Table 2, $p < 0.001$). After adjusting for all the selected covariates including HbA1c and DM duration, the use of insulin was associated with a significant increase in the rate of DPN, compared with Met/TZD group (Fig. 2). Subjects in the SU or on the SU-Met/TZD groups had insignificantly higher rate of DPN than the Met/TZD group (Fig. 2).

To further investigate the association of insulin use and the prevalence of DPN, we analyzed the rate of DPN in all insulin users compared to all non-insulin users at the time of randomization. In a logistic regression model that simultaneously adjusted for all the covariates mentioned in the methods, the odds ratios of DPN remained over 30% higher in subjects taking insulin compared to subjects not taking insulin (OR=1.34, 95% CI 1.08, 1.67).

Given the importance of DM duration to the risk of neuropathy, we analyzed the prevalence of DPN in a subgroup of the cohort who reported a diabetes duration ≥ 10 years. Based on this subgroup analysis, insulin use was associated with about a two-fold higher prevalence of DPN compared to the Met/TZD group (OR 1.91 95% CI 1.0, 3.6). In this subgroup insulin users had also higher prevalence of DPN as compared with all noninsulin users (OR 1.32 95% CI 0.99, 1.76).

Discussion

In this ethnically diverse and large cohort of patients with T2DM and angiographically confirmed CAD, we observed a high prevalence of DPN (51%) using a validated, easy to

use clinical instrument. In addition, after controlling for age, sex, race/ethnicity, diabetes duration, HbA1c and all other described variables, insulin use at baseline was the glycemic control strategy that was independently associated with a significantly higher prevalence of DPN. On the other hand, a lower prevalence of DPN was seen in the Met/TZD group as compared with all other diabetes medication groups, although it did not reach statistical significance.

In general, the development of diabetic complications is related to the degree of metabolic control that is determined by multiple factors. Until recently, hyperglycemia, the common clinical expression of both types of diabetes, has been regarded as the major culprit initiating the cascade of metabolic and molecular abnormalities resulting in degenerative phenomena and progressive neurological deficits. This concept alone, however, does not account for the results from trials designed to achieve optimal glycemic control but only show a partial reduction in the development of complications in general, and on neuropathy in particular (Diabetes Control and Complications Trial Research Group, 1995; 1998; Azad et al., 1999). These data therefore suggest that factors other than hyperglycemia are involved in the pathophysiology of DPN and that such factors may account for the differences in the prevalence and progression of DPN.

At study entry in BARI 2D, the use of insulin was significantly associated with higher rates of DPN in a cross-sectional analysis even after adjusting for many identified confounders such as HbA1c and duration of diabetes. Some prior and smaller observational studies reported similar associations. For instance, a cross sectional population study of 890 T2DM subjects from the Denver metropolitan area reported that the use of insulin was significantly associated with the presence of all microangiopathic complications, but especially with DPN, as compared with oral hypoglycemic agents. The association continued to remain quite strong after adjusting for multiple variables including diabetes duration, HbA1c and sex (Savage et al., 1997). In the San Luis Valley Diabetes Study of 277 T2DM subjects, insulin use was a strong independent factor associated with DPN (Franklin et al., 1994). In a European case-control cohort of 1300 subjects with diabetes, treatment with insulin was significantly associated with the presence of lower limb complications, in spite of similar prevalence of other complications or comorbidities (el-Shazly et al., 1998). The current study extends these prior observations on diabetes and DPN to a much larger and well-characterized population of over 2000 T2DM patients recruited through the BARI 2D trial. The population is also well-represented by black non-Hispanics (17%) and Hispanics (13%).

As for the other epidemiologic studies, the cross-sectional results presented here cannot address causality between insulin use and DPN. The reasons why a certain glycemic control therapy was prescribed are not known. The presence of DPN may have prompted the initiation of insulin therapy to forestall worsening DPN and other microvascular complications. If insulin therapy was added after the failure of diet and various oral hypoglycemic agents singly or in combination, then the insulin use cohort could have had several periods of poor glycemic control before the therapy was intensified. Also, the association of insulin use and DPN must be taken in the context that moderately severe CAD was a selection criterion for the BARI 2D cohort. The development of DPN may be affected by the presence of atherosclerosis and possible peripheral artery disease.

Besides methodological issues related to the cross-sectional study design, insulin use could be associated with DPN by nerve damage from exogenous insulin. Some have previously postulated that exogenous insulin therapy in T2DM might be associated with DPN through an exacerbation of obesity, fluid retention, hypertension and hyperlipidemia (Savage et al., 1997). However, several randomized clinical trials in T1DM have shown that intensive insulin therapy can prevent or delay the development of DPN compared to conventional

insulin therapy (Diabetes Control and Complications Trial Research Group, 1995; Ohkubo et al., 1995). Additionally, experimental evidence suggests that, beyond improving glycemic control, insulin may have complex protective vascular actions (*Pop-Busui and Stevens, 2005*).

Another possible explanation for the association of insulin use with the prevalence of DPN in this cohort could be that insulin use indicates beta cell failure in a group of patients. If insulin therapy was initiated because of beta cell failure, then it may be a biologic marker of a later stage of the natural history of diabetes and more accurately reflect the severity of diabetes than the HbA1c levels or the reported duration of diabetes in patients for whom the true onset of diabetes is not clear. In addition, several mechanisms such as glucotoxicity *per se* and its downstream increase in oxidative stress and free fatty acids have been shown to negatively impact beta-cell function and to induce peripheral nerve damage and thus could have contributed to the association we found with insulin use and DPN (*Pop-Busui et al., 2006*). The decrease in C-peptide secretion that accompanies beta-cell failure may also directly contribute to neuropathy since evidence from animal models suggests that C-peptide can reverse DPN (*Stevens et al., 2004*). However, this still needs to be confirmed in humans.

Another interesting observation is the trend towards DPN protection observed in the Met/TZD group, which raises the question whether different pharmacologic and molecular effects of various antihyperglycemic treatments may also play a role. A large prospective clinical trial has suggested that the beneficial effect of metformin on the incidence of diabetes complications was not entirely related to its glycemic effects (UK Prospective Diabetes Study (UKPDS) Group, 1998a). For instance, metformin has pleiotropic effects with direct vascular implications, such as improvements in lipid profiles (*Wu et al., 1990*), prevention of oxidative stress-induced endothelial cell death (*Detaille et al., 2005*) and direct neuroprotective effects via inhibition of oxidative stress-related apoptotic cell death in primary neurons (*El-Mir et al., 2008*). On the other hand, sulfonylureas promote increases in circulating insulin levels by closing beta-cell ATP-dependent potassium channels (K^+ -ATP) and K^+ -ATP channels are widely expressed on neurons. Data from animal studies have shown that blockage of the K^+ -ATP channels with SU may selectively potentiate neuronal mitochondrial dysfunction and neurotoxicity by potentiating mitochondrial inhibitors (*Kou et al., 2006*) and glutamate-induced generation of superoxide (*Yamauchi et al., 2003*), although similar human data are not yet reported. In the United Kingdom Prospective Diabetes Study (UKPDS), intensive blood-glucose control by SU did not decrease the risk of DPN, whereas it substantially decreases the risk of retinopathy and nephropathy (UK Prospective Diabetes Study (UKPDS) Group, 1998b).

TZDs may provide additional beneficial vascular effects beyond glycemic improvement, such as reduction of inflammation (*Sjoholm and Nystrom, 2005*), oxidative stress (*Chen et al., 2004*) and improvement in endothelial dysfunction (*Sjoholm and Nystrom, 2005*), all important mechanisms involved in the pathogenesis of DPN. In addition, preclinical evidence indicates that TZDs may exert direct neuroprotective effects after cerebral ischemia and motor neuron loss, myelin and microglial activation after spinal cord injury by inhibition of NF-kappaB and JNK activation and oxidative stress-mediated neuronal damage (*Xing et al., 2007*; *Rosa et al., 2008*; *Yu et al., 2008*).

In summary, the findings of this cross-sectional, baseline study in a cohort of patients with T2DM and confirmed CAD suggest that insulin use was associated with a higher prevalence of DPN and that the use of Met/TZD had a trend towards protection, independent of disease duration, glycemic control and other characteristics. A better understanding of the role of diabetes medications and other factors in the development of DPN is likely at the conclusion of the BARI 2D trial because the analysis will include standardized annual DPN exams on a

well-characterized population who received aggressive medical therapy and insulin-sensitizing or insulin-providing agents in a controlled and randomized fashion for the five years of the trial.

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Abbreviations

DPN	diabetic peripheral neuropathy
MNSI	Michigan Neuropathy Screening Instrument
BARI 2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
T2DM	type 2 diabetes mellitus
CAD	coronary artery disease
HbA1c	hemoglobin A 1C
BMI	body mass index
HDLc	high density lipoprotein
LDLc	low density lipoprotein
Met	metformin
TZD	thiazolidinediones
SU	sulphonylurea

DM	diabetes mellitus
BP	blood pressure
OR	odds ratio

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following pilocarpine-induced status epilepticus. *Brain Res.* 2008; 1200:146–158. [PubMed: 18289512]

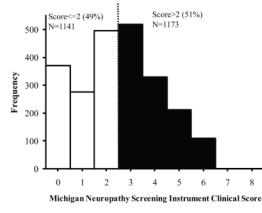


Figure 1. Distribution of MNSI clinical score in the BARI 2D cohort at baseline. Scores with 0.5 increments were rounded up to the next integer.

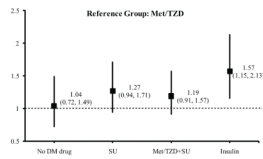


Figure 2. Odds ratios for DPN by glycemic control therapy. Reference group: Met/TZD. The full model was adjusted for sex, age, race/ethnicity, duration of diabetes diagnosis, BMI, HbA1c, HDL, LDL, triglycerides, systolic blood pressure, currently cigarette use, and alcohol consumption.

Table 1

Association of the presence of neuropathy and baseline characteristics.

HbA1c=hemoglobin A 1C, BMI=body mass index; HDLc=high density lipoprotein, LDLc=low density lipoprotein

Characteristic	Category	N	Neuropathy %	p-value
Age	< 50 years	195	35.4%	<0.001
	50-59 years	725	47.4%	
	60-69 years	892	52.6%	
	≥ 70 years	502	58.0%	
Sex	Women	682	46.2%	0.005
	Men	1632	52.6%	
Race/Ethnicity	White non Hispanic	1518	50.9%	0.026
	Black non Hispanic	392	55.4%	
	Hispanic	293	47.4%	
	Others	111	40.5%	
HbA1c	< 7%	906	47.7%	0.021
	≥ 7%	1403	52.6%	
Diabetes Duration	< 5 years	767	43.0%	<0.001
	5-9 years	541	51.9%	
	10-14 years	401	57.1%	
	≥ 15 years	595	55.5%	
BMI	< 30 kg/m ²	1014	49.2%	0.208
	≥ 30 kg/m ²	1300	51.8%	
History of Hypertension	No	401	42.6%	<.001
	Yes	1885	52.1%	
Blood Pressure (mmHg) *	≤ 130/80	1097	50.1%	0.569
	> 130/80	1210	51.3%	
Urine Albumin/Creatinine Ratio	≤ 30	1450	48.1%	<0.001
	> 30	697	57.2%	
HDL (mg/dl) *	> 40 men/ > 50 women	558	47.8%	0.112
	≤ 40 men/ ≤ 50 women	1750	51.7%	
LDL (mg/dl) *	< 100	1346	51.3%	0.498
	≥ 100	928	49.9%	
Triglycerides (mg/dl) *	< 150	1165	50.3%	0.704
	≥ 150	1147	51.1%	
Current Cigarette Use	No	2028	51.1%	0.287
	Yes	285	47.7%	
Alcohol Consumption	Not regular	1696	51.9%	0.101
	Regular	376	46.0%	
	Binge	242	49.2%	

* 79% of patients were taking at least one kind of lipid lowering agent at baseline. 96% of patients took at least one kind of antihypertensive agent at baseline. Lipid lowering agents include statins, fibrates, niacin, bile acid sequestrants, omega-3 fatty acid, and cholesterol absorption inhibitor. Antihypertensive agents include beta blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and diuretics.

Table 2

Clinical characteristics and unadjusted odds ratio of DPN by glyemic control group. Met=metformin; TZD=thiazolidinediones; SU=sulphonylurea; DM=diabetes mellitus.

Characteristics	Glycemic Control Medication					P value
	Met/TZD ¹	No DM drug	Sulphonylurea	Met/TZD + SU	Insulin ²	
Number of patients	366	199	388	716	645	-
Mean Age (years)	61.2	62.6	63.7	62.4	62.2	0.004
Mean Duration of DM (years)	5.3	3.7	8.2	10.9	16.3	<0.001
Mean HbA1c (%):	7.1	6.7	7.4	7.7	8.3	<0.001
% having neuropathy	41.5%	43.2%	51.8%	49.9%	58.4%	<0.001
Unadjusted odds ratio (95% CI)	Reference Group	1.07 (0.76, 1.52)	1.51 [†] (1.14, 2.02)	1.40 [†] (1.09, 1.81)	1.98 [†] (1.53, 2.57)	-

¹ Among the 366 patients in the Metformin/TZD category at baseline, 274 (75%) took only metformin; 39 (11%) took only a TZD; and 53 (14%) took the combination of metformin and TZD.

² Patients in the insulin category could be on insulin alone or with any other diabetes medication.

[†] Significant at α level = 0.05.