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Research Article

Metabolic and Cardiovascular Determinants of Type 2 Diabetic Patent Peripheral Neuropathy

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Keywords
• Peripheral neuropathy; Hba1c; Obesity ;CVD; Hypertension; UAE/24H; Hypertriglyceridemia

Abstract

Objective: To identify the main metabolic and cardiovascular determinants of peripheral neuropathy in type 2 diabetics.

Materials and methods: We collected 270 records of type 2 diabetic patients and compared 90 patients with peripheral neuropathy with 180 without neuropathy, and then we proceeded to a statistical analysis of the data by binary then multivariate logistic regression based on the $SPSS_{20}$ software.

Results: The average age of the cases is 65.5 ± 19.4 years with a sex ratio of 0.64. The majority are sedentary and obese. Tingling is the most frequent revealing symptom (86.5%) with the abolition of DTR (51.7%), Pain affected more than 83% of cases with an average score PN4 = 4.53 ± 1.61. More than 83% of PDN+ diabetics are hypertensive and ¾ suffer from proven cardiovascular disease. The risk factors for PDN are (univariate regression): android obesity [OR = 2.43], HbA1c > 7% [OR = 4.85], cardiovascular disease [OR=5.32], 24-hour micro albuminuria [OR=6.89], dysautonomic neuropathy [OR=9.72], hypertension [OR =3.49], a as well as triglyceride level > 1.50 g/L [OR =1.89]. The multivariate model retains: Glycemic imbalance, physical inactivity, and android obesity, presence of cardiovascular disease, EUA/24 hours and dysautonomic neuropathy.

Conclusion: Our study confirms the multifactorial etiology of diabetic peripheral neuropathy involving essentially the interaction of metabolic, cardiovascular among the other clinical and dietetic factors.

ABBREVIATIONS

BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease ; HbA1c, glycated hemoglobin; HBP, high blood pressure; DAN, dysautonomic neuropathy; DPN, diabetic peripheral neuropathy; DTR, deep tendon reflexes ; OR, odds ratio; UAE/24 hours, 24-hour urinary albumin excretion.

BACKGROUND

Diabetic peripheral neuropathy is the most common complication of diabetes. At least 50% of people with diabetes will develop it [1,2]; Its prevalence varies from 0 to 93% depending on the studies [3] and increases with the duration of diabetes evolution, 7% when the discovery of diabetes goes back less than 1 year, 50% after 20 years of diabetes evolution [4]. Regardless of glycemic control, about 50% of patients do not develop clinical neuropathy, even after 20 years of evolution. Furthermore, patients with good metabolic control may present with disabling neuropathy early after the diagnosis of diabetes. This suggests the existence of factors independent of the hyperglycemic state in the pathophysiology of neuropathy. These factors could be genetic, but also related to the environment, and in particular nutritional [5]. The main clinical features of DPN include symmetric, mainly sensory, deficits in the distal lower extremities and neuropathic pain [6,7]. In addition, DPN is a key risk factor for diabetic foot ulceration due to loss of protective superficial sensitivity [7-9]. Duration of diabetes and HbA1c level are major predictors of diabetic neuropathy [10]. These two predictors are commonly associated with other metabolic factors correlated with diabetic neuropathy, particularly in T2D, such as insulin resistance and high blood pressure (>130/85mmHg). Obesity is common in patients with neuropathy in population-based studies in several countries, including the United States, Denmark, China, and the Netherlands [10-15]. Independent of HbA1c levels, many components of the metabolic syndrome, such as hypertriglyceridemia, hypertension, abdominal obesity, and low high-density lipoprotein (HDL) levels, are consistently associated with diabetic neuropathy in patients with T2DM [11,12] and in some DT1 cohorts [16]. Other independent risk factors for the development of diabetic neuropathy include smoking, alcohol abuse, increased height, and advanced age [17].

Through this work, we will be able to achieve primary prevention of this complication or even secondary neurological complication by improving the management of these very high-risk patients.

MATERIALS AND METHODS

This is a retrospective sex-matched case-control study, carried out at the level of the Oran Hospital and University Establishment (EHUO) between December 2019 and December 2021, which aims to identify and measure the main risk factors for Type 2 diabetic peripheral neuropathy.

Study Location

The study was conducted in the city of Oran, an urban area located in the northwest region of Algeria; it is the second largest city in Algeria and one of the most important in Northern Africa. According to the 2022 National Census, approximately 1.52 million individuals lived in Oran.

Ethical Consideration

Ethical clearance was obtained from the Institutional Review Board of the University Hospital Institution of Oran (November 02, 2015, approval number ETAP-C.R.S 6) in accordance with the tenets of the Declaration of Helsinki (http://www.wma.net). The researcher explained the study to each person and gave them thorough information about the study and its purpose. In addition, we notified them of their right to terminate their participation in the study at any time without incurring any penalty. The concerned subjects having given a signed consent after having been duly informed. On occasion, the consent was orally given after explaining the aim of the biological assays. We collected more than 400 adult patients DT2 and retained 270 complete files.

Exclusion

Patients with psychiatric illness, amputees or undergoing treatment that can induce neurological pain and pregnant women. The information collected by direct questioning of patients on the one hand: Age, sex, origin and place of residence, profession, marital status, socioeconomic level and social coverage, height, weight, waist circumference, and BMI, Year of discovery, diabetes treatment, and family history of diabetes. Tobacco; Alcoholism and physical activity. On the other hand, the complete clinical examination: Measurement of blood pressure at rest in a supine or semi-seated position after 10 minutes of resting, using a sphygmomanometer or a validated electronic tensiometer. The figures to speak of a hypertension correspond to: SBP (Systolic blood pressure) > 130 mm Hg and/or a DBP (Diastoolic blood pressure) > 85 mm Hg. Eye's fundus examination using retinal photography was performed in all patients. Coronary artery disease was defined by the presence of angina pectoris, squeal of myocardial infarction, or ischemic changes on a standard resting electrocardiogram or on stress ultrasound or coronary angiography Blood samples were collected after 12 h of fasting from a vein in the antecubital fossa without venous occlusion. All collections were made between 8:00 and 9:00 a.m. Whole blood specimens were collected in different tubes to obtain plasma. The samples were separated in aliquots and frozen immediately at −80 ◦C until biochemical analyses could be performed. 2.6. Plasma Lipids and Glucose Plasma TC, HDL-C, TG, glucose and HbA1c were all measured by multiparametric automated procedure using Cobas 6000 analyzer with Roche Diagnostic's reactives. Plasma LDL-cholesterol (LDL-C) was estimated by the Friedewald equation. None of the participants had plasma TG > 4 g/L, which can affect the calculation of LDL-C by the Friedwald equation[18]. The criteria for the diagnostic of metabolic syndrome were those defined by the NCEP-ATPIII (National Cholesterol Education Program-Adult Treatment Panel III); A subject was considered to present an abdominal obesity with an abdominal perimeter 102 cm for men and 88 cm for women.

Glomerular filtration rate (GFR) was estimated using Equation MDRD: eDFG = 175 x (Scr x 0,0113)-1,154 x year-0,203 x 0,742 (if women) x 1,212 (if black) [Scr : µmol/l] [19]. Diabetic nephropathy or CKD (Chronic kidney disease) was considered if the GFR was <90 ml/min/1.73 m2 for men and <80 ml/min/1.73 m2 for women; Proteinuria was determined using a dipstick and manifest nephropathy was defined by the dosage of micro-albuminuria/24 hours (>30g/24hours or >20g/l).

The neurological investigations consisted of questionnaires on sensory, motor and autonomic symptoms; Peripheral neuropathy was defined by clinical symptoms (paresthesias) and/or abnormalities in sensation of touch, pinprick, pain and monofilament (Semmes Weinstein at 10g) abolition of DTR (deep tendon reflexes) at the ankle or patella and Vibration sensation was tested in the great toe, using a 128-Hz tuning fork (Rydel-Seiffer). Patent dysautonomia was defined by symptoms of gastroparesis or neurogenic bladder, diarrhea, symptomatic postural hypotension (fall in blood pressure after one minute of orthostatism of more than 20mmHg for SBP and/or 10mmHg for DBP), erectile dysfunction or sweating disorders without further explanation; Pain Neuropathy 4 survey (PN4) used to rate the degree of neuropathic pain.

STATISTICAL ANALYZES

Sociodemographic, clinical and biological parameters as well as complications were collected using a standardized questionnaire. Data were expressed as mean and percentages. The links between the characteristics of the patients will call upon statistical tests: The tests used are: the χ^2 test of independence or homogeneity, corrected by Yates, the exact test of Fisher, the Kruskall-Wallis test for two groups, with the determination of significance levels. Student's test for two independent samples and analysis of variance (ANOVA) were used for the comparison of continuous variables. For the bivariate analysis, the comparison of discontinuous variables between groups was carried out by non-parametric tests, the χ^2 test of conformity and homogeneity for the search for statistical associations between two qualitative variables; nonparametric Fisher's exact test for comparison of small groups. We used Pearson r correlation tests to estimate the relationship between two quantitative variables. A relationship is considered significant if the threshold was $p < 0.05$. Double contingency 2 × 2 cross tables were established for the calculation of Odds Ratio (OR) as an epidemiological association factor and the establishment of confidence intervals around the risk. Linear regression was used to search for a linear relationship between peripheral neuropathy and the other explanatory variables with multiple logistic regressions using maximum likelihood and 95% confidence intervals (CI). Statistical analyzes were performed using the following software: EpiData 3.0 and SPSS 20.

RESULTS

The general comparison of cases and controls finds a statistically significant difference for age, BMI and waist circumference; the cases were older with an average age of 65.5 ± 19.4 years ($p < 10^{-6}$). The sex ratio (M/F) in DPN cases is 0.63, while in controls it is 0.91, indicating a female predominance. Tingling is the most frequent revealing symptom (86.5%) with the following clinical signs: abolition of DTR (deep tendon

reflexes) (51.7%), abnormalities of the tuning fork test (48.3%), and non-sensitivity monofilament (27%). Pain affects more than 83% of cases with an average score PN4 = 4.53 ± 1.61. There is no significant difference for height (p = 0.49), the average height of men is 1.72 ± 0.07 m against an average height of 1.58 ± 0.06 m in women. The cases are more obese (p=0.002), with a waist circumference of 108 ±10.20 cm for men and 107.51 ± 12.83 cm for women, with a significant difference between cases and controls (p = 0.004). The group of cases with DPN is more sedentary than that of controls (p < 10-8). On the other hand, no significant difference is reported for lifestyle, level of education, smoking and family history of diabetes between the two groups. The duration of diabetes is longer in patients with DPN (13.83 ± 9.57 years vs. 7.36 ± 6.54 years in controls; $p<10^{-3}$). 83.33% of patients with peripheral neuropathy are hypertensive, and 76.67% have at least one cardiovascular complication, while 90% suffer from a microvascular complication (other than peripheral neuropathy) Patients with DPN have renal function lower than the controls ($p < 10^{-7}$) with a 24-hour microalbuminuria rate much higher than that found in the controls ($p < 10^{-8}$).

There is a significant difference between diabetics with DPN and controls concerning the glycemic profile: FPG and Hba1c (p < 0.0001), on the other hand this difference is not reported concerning the levels of total cholesterol, LDL and HDL. Nevertheless, there is a significant difference in the level of triglycerides (p=0.029). More than 75% of cases were taking a statin vs 45.55% of controls (p = 0.46). We note that 90% of cases are in glycemic imbalance: Hba1c > 7% (p < 0.0001), and this despite the fact that 71% of them benefit from insulin therapy (p < 10-6) (Table 1). The risk factors statistically linked to DPN according to the univariate analysis are: Age [OR = 2.94] (p<0.0001), duration of diabetes [OR = 2.68](p<0.001), physical inactivity [OR = 9.38](p<0.00000001), android obesity [OR =2.43](p<0.004), HbA1c > 7% [OR = 4.85](p<0.0001), cardiovascular disease [OR = 5.32](p<0.000..1), retinopathy [OR = 5.60](p<0.00..1), nephropathy [OR = 7.89](p<0.0000001), 24-hour micro albuminuria [OR = 6.89](p<0.00000001), autonomic neuropathy [OR = 9.72](p<0.0000001), HBP[OR =3.49] (p<0.001), a triglyceride level > 1.50g/L [OR =1.89] (p<0.029) as well as insulin therapy [OR=3.96](p <0.00001) (Table 2). There is no statistically significant relationship between gender, height and dyslipidemia in the occurrence of DPN in our population.

The multivariate model retains the following factors: Glycemic imbalance (HBA1c>7%) [OR = 2.8], physical inactivity [OR = 8.2], android obesity [OR = 3.6], macroangiopathy [OR = 2.4], 24-hour micro albuminuria [OR = 5.9] and dysautonomic neuropathy [OR = 8.5] (Figure 1).

DISCUSSION

The results of our study have identified a number of risk factors related to the occurrence of peripheral neuropathy. Hyperglycemia is undeniably a major risk factor for distal and symmetrical peripheral neuropathy (DSPN). It has been calculated that every 1% increase in HbA1c is associated with an

Table 1: Comparison of the general characteristics of the case-control sample.

Explanatory Factors		NPD + (n=90)	NPD – (n=180)	*p*
Age (years)		65,5 ± 19,4	58,02 ±10,5	$< 10^{-4}$
Sexe M/F		35/55	86/94	0,166
Height (m)		1,64±0,1	1,65±0,1	0,49
Normal		9	31	
BMI	Overweight	26	75	0,002
Obesity		55	73	
Weist sise(cm) M/F		108,00±10,20 107,51±12,83	100,59±13,42 100,71±10,49	0,004
Sedentary		32	10	$< 10^{-8}$
Familly history of T2D		71	140	0,934
Smoking		17	25	0,285
Duration of T2D (years)		13,81±9,57	7,36±6,54	$<10^{-3}$
High blood pressure		75	106	$< 10^{-3}$
Microalbuminuria (mg/24h)		105,66±188,7	19,98±25,50	$< 10^{-8}$
Clearance of creatinine (ml/min)		62,20±22,50	85,25±20,13	$< 10^{-7}$
Macroangiopathy		69	62	$< 10^{-8}$
Microangiopathy (except NDP)		86	113	$< 10^{-8}$
FPG (g/l)*		1,71±0,58	1,41±0,40	$< 10^{-4}$
HBA1c (%)		8,75±1,70	7,60±1,42	$< 10^{-4}$
HBA1c>7%		81	117	$< 10^{-4}$
Chol T (g/l)		1,68±0,50	1,60±0,37	0,15
LDL (g/l)		0,97±0,42	0,95±0,30	0,65
HDL (g/l) M/F		0,38±0,11	0,39±0,11	0,91
		0,46±0,15	0,44±0,12	0,52
TG (g/l)		1,47±0,70	1,23±0,56	0,029
Insuline		64	69	$< 10^{-6}$

*FPG : Fasting plasmatic glucose

Table 2: DPN Risk Factors after univariate regression.

Risk Factors	DPN+	DPN –	Brut OR	CI 95%	*P value*
Age ≥ 61 years	61	75	2,94	[1,66 –5,23]	$< 10^{-4}$
Obesity (Kg/m^2)	55	74	2,25	[1,29 –3,93]	0,002
waist size (cm)	74	118	2,43	[1,25 –4,78]	0,004
T2D Duration ≥ 8 ans	60	77	2,68	[1,52 – 4,73]	$< 10^{-3}$
Hba1c > 7%	81	117	4,85	[2,16 – 11,19]	$< 10^{-4}$
Insulin therapy	64	69	3,96	[2,21 – 7,14]	$< 10^{-6}$
Sedentarity	32	10	9,38	[4,08 – 22,03]	$< 10^{-8}$
BP > 130/85mmHg	75	106	3,49	[1,78 – 6,93]	$< 10^{-3}$
Triglyceridaemia > 1,5g/L	37	50	1,89	[1,02–3,19]	0,029
Albuminuria / 24h >30 mg	49	27	6,89	[3,66 – 13,04]	$< 10^{-8}$
Dysautonomic Neuropathy	71	50	9,72	[5,09 – 18,73]	$< 10^{-8}$
Heart failure	60	53	4,8	[2,78– 8,25]	$< 10^{-5}$
Coronaropathy	34	18	5,46	[2,72 – 11,07]	$< 10^{-7}$
Peripheral arteriopathy	26	12	5,69	[2,55 – 12,88]	$< 10^{-4}$
Cervical arteritis	22	10	5,50	[2,31 –13,32]	$< 10^{-5}$
Rétinopathy	62	51	5,60	[3,10 – 10,2]	$< 10^{-8}$
CKD*	80	87	7,89	[3,45 – 18,55]	$< 10^{-7}$

*CKD:Chronic Kidney Disease

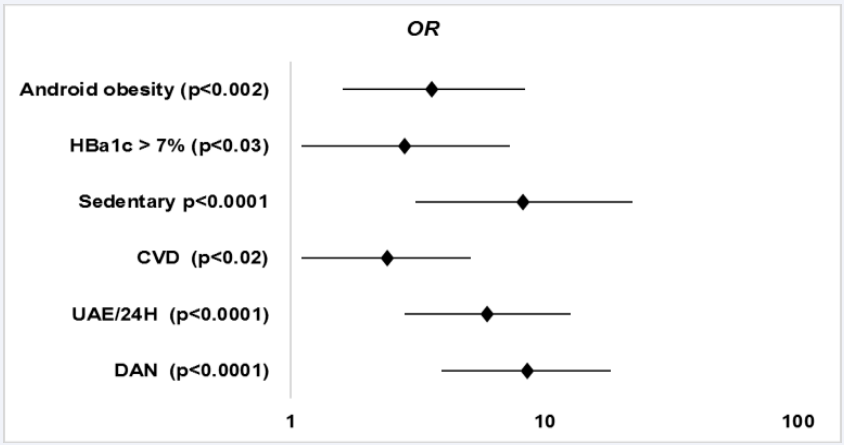

Figure 1 Forrest Plot of Independent DPN Risk Factors (Multivariate Analysis).

approximately 10-15% higher frequency of DSPN [6]. Therefore, the effectiveness of tight glycemic control in reducing the incidence and progression of DSPN has been the subject of several ambitious studies in both types of diabetes [20-27]. Weight and waist circumference are independent risk factors for both DSPN and painful DSPN in diabetic patients from the population-based MONICA cohort study/KORA surveys from southern Germany [28-30]. Low physical activity has been associated with the presence of DSPN in the southern German population [28,29] with an OR= 6.36 CI [2.94 –13.78] ($p < 0.001$) which confirms the results of our series where physical inactivity was identified as being a factor strongly correlated with the development of DPN. Bilateral and symmetrical neuropathy is frequently associated with cardiovascular disease [31-33], which makes cardiovascular involvement an independent factor in the development of neuropathy after 10 years of diabetes progression (OR = 2.32, 95% CI: 1.03–5.22) [34]. Compared to hyperglycemia which is a major risk factor in the development of diabetic polyneuropathy, evidence has emerged suggesting that vascular factors also appear to play a primary role in its pathogenesis and clinical phenotype. [35,36]. The results of the prospective EURODIAB study (Tesfaye et al. 2005) proved that systolic hypertension was an independent predictor of neuropathy after adjusting for age, duration of diabetes and metabolic control [35]. In the Tunisian series of Sebai et al. the presence of DPN was correlated with urinary albumin excretion > 30mg/24 hours ($r = 0.325$, $p = 0.005$). Zigler et al. demonstrated a significant association in diabetics with the rate of albumin excretion with an OR = 1.24 [1.09 –1.42] ($p = 0.001$) [28]. Overall, our results agree with those of the Algerian study by Ayad et al. conducted on a population

of diabetics from Oran, and which demonstrated a statistically strong relationship between DPN and CAN (Cardiac autonomic neuropathy)(p <0.0001), also they suggest the important role played by sympathetic hyperactivity in the development of microvascular complications via hemodynamic disorders that she leads [37]. The coexistence of DSPN and DAN increases crescendo with the duration of diabetes and poor metabolic control. Also, the concomitant presence of autonomic neuropathy is important for the prognosis, since it is a risk factor for mortality from cardiovascular disease [31]. Other factors described in the literature, such as height and smoking, show no statistical relationship with DPN according to our results (p = 0.49: NS; OR = 1.44 [0.69–3.00], p = 0.285: NS) respectively; Data from systematic meta-analyses are controversial if not contradictory: height is more likely a risk factor in T1Diabeties, while there is a rather protective effect of smoking in certain populations in the United States [6,38,39]. High total cholesterol [40] and hypertriglyceridemia [41] have been reported as independent risk factors for DSPN (after adjusting for HbA1c, age, and other potential confounders). In addition, there are several genes linked to diabetic neuropathy could explain some ethnic specificities ; Much more research is needed to better understand the role of genetics in the development of diabetic neuropathy, and several existing cohort studies are currently underway [40,41].

LIMIT OF THE STUDY

Retrospective analyzes of primary care databases are generally limited by the validity and completeness of the data. In particular, the exact daily doses of insulin prescribed, as well as the exact diagnosis of the onset of diabetes, but rather we used the data of the first diagnosis of diabetes recorded in the database. In conclusion, using real-world data, the prevalence of diabetic neuropathy affected at the time of diagnosis of type 2 diabetes was low in western Algeria. , it is not devoid of certain biases which can compromise the exact interpretation of the results; however, multivariate analysis makes it possible to control for these biases: Some factors no longer become significantly correlated with the development of DPN.

CONCLUSION

Diabetic neuropathy is common in patients in western Algeria, mainly in Oran. This complication is shown here to be associated with android obesity, lack of physical activity, poor glycemic control, cardiovascular disease, and other microvacular complications. The results underscore the need for intensified programs aimed at early detection and rapid implementation of health education. We were able to draw a profile of type 2 diabetic patients at high risk of developing DPN, which suggests the role of clinical recommendations for the management of diabetes in preventing the development of associated foot complications which should be further reduced in care primaries.

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