

## The Association of Dyslipidemia and Peripheral Diabetic Neuropathy: The Influence of Urea

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### Abstract

Peripheral neuropathy is a common complication of diabetes mellitus. In the EURODIAB study, total cholesterol and triglycerides were associated to peripheral diabetic neuropathy (PDN). The study's aim was to evaluate the influence of cholesterol, triglycerides and statin use on a clinical score of peripheral neuropathy in patients with diabetes mellitus.

Ninety patients at a university hospital in Manaus, Brazil were included in this study. They were evaluated using Michigan Neuropathy Screening Instrument (MNSI) and the clinical component of the Michigan Diabetic Neuropathy Score (MDNS). According to MDNS clinical component, 20 (22.2%) patients had PDN and compared to those patients who did not have PDN, they had more time of diabetes diagnosis ( $16.2 \pm 11.3$  vs.  $10.2 \pm 8.6$  years), more stroke (15 vs. 3%), more insulin use (75.0 vs. 48.6%) and also higher serum urea levels. When considering only the 65 (72.2%) patients with serum urea below 50 mg/dl, there was a positive correlation between total cholesterol and MDNS ( $r=0.2580$ ,  $p<0.05$ ) and between triglycerides and MDNS ( $r=0.2585$ ,  $p<0.05$ ). In patients who had serum urea below 50 mg/dl, total cholesterol and triglycerides correlated weakly but significantly to MDNS.

**Keywords:** Lipids; Urea; Diabetic peripheral neuropathy

### Introduction

Peripheral diabetic neuropathy (PDN) is a somatic and, or also, autonomic neuropathy exclusively attributed to diabetes mellitus (DM). Symmetric distally type is the most common and affects about 50% of patients with diabetes as reported by Cornblath [1] and Feldman [2].

PDN has a multifactorial pathogenesis with different biochemical mechanisms, such as increased oxidative stress, neuro-inflammation, reduced peripheral perfusion and subsequent inter-neuronal hypoxia. Al-Ani [3].

In Eurodiab Study, Elliot et al. [4] found that total cholesterol, HDL-C, LDL-C and triglycerides were associated with the PDN. Besides, triglycerides were shown as an independent risk factor for PDN.

Padilla et al. [5] observed that Schwann cells exposed to saturated fatty acid associated with palmitic acid at high glucose concentrations had a greater degree of apoptosis.

### Goals

To evaluate the influence of cholesterol, triglycerides and statin use in a clinical score of peripheral neuropathy in patients with diabetes mellitus.

### Methodology

The study included patients with DM with or without previous diagnosis of PDN, attended in Getulio Vargas University Hospital (HUGV), from Federal University of Amazonas (UFAM) in the city of Manaus, Brazil. Exclusion criteria were: bearers of other diseases or users of medications that cause symptoms of peripheral neuropathy; children under 18 years of age; pregnant women; and patients who could not participate in the study. Lipid profile was measured by commercial tests in laboratories routinely used in clinical practice. There was no interference of research or researchers on the required exams. Brazilian Society of Cardiology guidelines recommended lipid levels were considered for both the diagnosis and follow-up of patients.

“Michigan Neuropathy Screening Instrument” (MNSI) evaluates

pain, numbness, temperature sensitivity, asthenia and signs relevant to peripheral vascular disease. The questionnaire is then followed by a brief clinical examination involving: inspection of feet deformities, calluses, dry skin, infection or ulceration; evaluation of vibration sense in the back of the hallux and Achilles reflexes. PDN was diagnosed when the patient carrier had clinical score  $>2$  on MNSI Feldman et al. [2]. As Abbott et al. [6], only the clinical component of the “Michigan Diabetic Neuropathy Score” (MDNS) score was used to quantify the diabetic neuropathy in this study. The clinical MDNS component consists of the evaluation of vibration, painful and superficial tactile sensitivities measured with a 128 Hz tuning fork, a stick and the monofilament 10 g (Semmes-Weinstein), respectively. Subjects who scored 7 or more on this component of the MDNS were considered as having PDN Feldman et al. [2].

The study protocol was approved by the local ethics committee, and informed consent was obtained from all participants.

### Results

From August 2013 to June 2015, 90 patients with diabetes mellitus (DM) were evaluated. Of these, 95.6% had a diagnosis of type 2 DM, 66.7% were female, mean age was  $56.2 \pm 12.8$  years-old and mean time of diabetes diagnosis was  $11.5 \pm 9.5$  years. According to MDNS clinical component, 20 (22.2%) patients had PDN. These patients, compared to those patients who did not have PDN, had more time of diabetes diagnosis ( $16.2 \pm 11.3$  vs.  $10.2 \pm 8.6$  years), more stroke (15 vs. 3%), more

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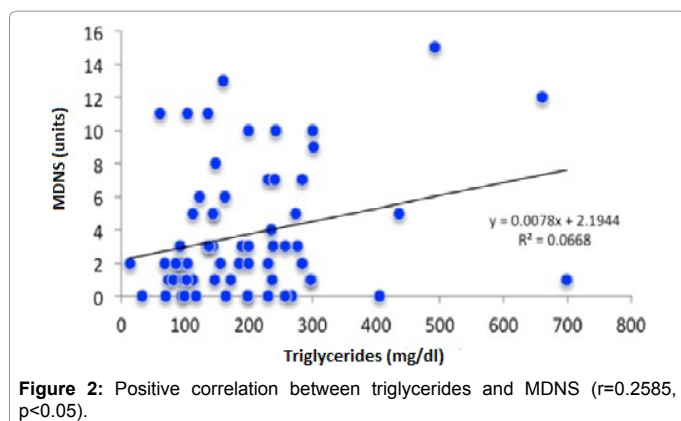
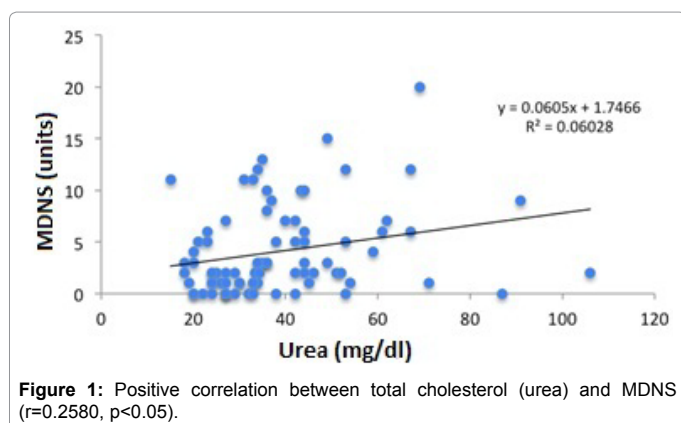
**Received:** June 06, 2016; **Accepted:** July 18, 2016; **Published:** July 22, 2016

**Citation:** Aguiar PCM, Coletta MVD, de Souza JJS (2016) The Association of Dyslipidemia and Peripheral Diabetic Neuropathy: The Influence of Urea. Diabetes Case Rep 1: 109. doi: [10.4172/2572-5629.1000109](https://doi.org/10.4172/2572-5629.1000109)

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Variants	No Neuropathy According MDNS N=70	Neuropathy According MDNS N=200	P
Gender (male/female)	25/45	5/15	NS
Age (years old)	55.8 ± 12.2	57.5 ± 14.8	NS
Time of diagnosis of Diabetes (years)	10.2 ± 8.6	16.2 ± 11.3	<0.05
Retinopathy (%)	17.1	30.0	NS
Nephropathy (%)	12.9	25.0	NS
Coronary artery disease (%)	11.4	10.0	NS
Stroke (%)	2.9	15.0	<0.05
Peripheral vascular disease (%)	7.1	5.0	NS
Diabetic Neuropathy ** (%)	5.7	15.0	NS
Statin (%)	54.3	65.0	NS
Fibrate (%)	4.3	0.0	NS
Sulphonyl urea (%)	32.9	25.0	NS
Metformin (%)	61.4	55.0	NS
Insulin (%)	48.6	75.0	<0.05
Corrected HbA1c (%)	6.9 ± 1.9	7.8 ± 2.2	NS
Urea (mg/dl)	33.2(24.3-44.0)	40.0(34.5-51.0)	<0.05
Creatinine (mg/dl)	0.9(0.7-1.3)	1.1(0.9-1.4)	NS
Total cholesterol (mg/dl)	193.4±53.5	203.1±58.2	NS
HDL-c (mg/dl)	46.6 ± 15.9	40.4 ± 11.8	NS
LDL-c (mg/dl)	97.5(69.0-137.3)	108.0(94.0-148.8)	NS
Triglycerides (mg/dl)	151.0(99.8-230.8)	235.5(127.8-299.3)	NS

Table 1: Clinical and laboratory characteristics of patients.



insulin use (75.0 vs. 48.6%). They presented also higher serum urea levels: patients without PDN had 30mg/dl (24,3-44,0), while those with PDN had 40,0 (34,5-51,0). The clinical and laboratory characteristics of patients can be seen in Table 1. There were no differences between patients with and without PDN in relation to age, retinopathy, nephropathy previous diagnosis, coronary heart disease, glycated

hemoglobin, serum creatinine or statin use. No association was found between PDN and cholesterol (r=0.1297, p=NS) or triglyceride levels (r=0.0315, p=NS). But, a positive correlation was found between serum urea levels and MDNS (r=0.2957, p<0,01). However, when considering only the 65 (72.2%) patients with serum urea below 50 mg/dl, there was a positive correlation between total cholesterol and MDNS (r=0.2580, p<0.05) and between triglycerides and MDNS (r=0.2585, p<0.05) how it can be seen in Figures 1 and 2 respectively.

### Conclusion

Patients with high urea showed abnormalities in peripheral diabetic neuropathy scores. This variable should therefore be considered in both the clinical evaluation of patients with diabetes mellitus and scientific research on diabetic neuropathy. There is a weak, but significant correlation between plasma levels of total cholesterol and triglycerides and diabetic peripheral neuropathy score, which can be detected after the exclusion of patients with high urea levels. Diabetic patients with high cholesterol and triglycerides levels should therefore be considered at higher risk for peripheral neuropathy.

### Acknowledgement

This research was funded by the National Counsel of Technological and Scientific Development - CNPq - and Fundação de Amparo à Pesquisa do Estado do Amazonas – FAPEAM - scholarships.

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