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The metabolic drivers of neuropathy in India

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Abstract

Aims: To determine the association between the metabolic syndrome (MetS) and neuropathy in Chennai, India.

Methods: We recruited participants attending the M.V. Hospital for Diabetes. Neuropathy was defined using the Michigan Neuropathy Screening Instrument combined index and MetS was defined using the updated National Cholesterol Education Program criteria. Multivariable logistic regression models were used to assess the associations between individual metabolic components and neuropathy.

Results: Of the 652 participants (42% female and mean (SD) age of 45.5 (9.7)) included in the study, the prevalence of neuropathy was 9.8%. Neuropathy prevalence increased with worsening glycemic status ($p < 0.01$), but not as the number of MetS components increased ($p = 0.12$). Among normoglycemic participants, an increasing neuropathy trend was observed as the number of MetS components increased ($p = 0.04$). Multivariable logistic regression found that diabetes (OR:3.41, 1.28-9.11) was associated with neuropathy, but waist circumference was not (OR:1.002, 0.88-1.14).

Conclusions: Similar to previous studies, diabetes was the most important metabolic risk factor for neuropathy in a population from Chennai, India. In contrast to other population-based studies, waist circumference was not associated with neuropathy. Whether the distribution of obesity affects nerves differently in Indian populations requires future studies with more precise anthropometric measures.

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Keywords

Neuropathy; Diabetes mellitus; Obesity; Metabolic Syndrome

1. Introduction

Neuropathy is a prevalent condition (2-7% in the general population) that causes substantial pain and reduced quality of life¹⁻⁴. While diabetes is the most common cause, obesity has emerged as the second most important metabolic risk factor for neuropathy based on studies in the United States, China, Denmark, Netherlands, and Germany⁵⁻¹². The distribution of obesity is particularly important, with central obesity measures such as waist circumference having the most robust association with neuropathy⁷. However, it is unknown which metabolic risk factors are associated with neuropathy in Asian Indian populations.

Outside of obesity and diabetes, specific metabolic syndrome (MetS) components have not been consistently associated with neuropathy⁵⁻⁸. Most studies reveal associations between pre-diabetes and neuropathy; however, these findings are not universal. While specific MetS components outside of obesity and diabetes reveal inconsistent findings with neuropathy, the number of MetS components are consistently associated with neuropathy, particularly in those without diabetes^{5,6,8}. Although there is a high prevalence of MetS in Asian Indian populations, it is unknown whether specific individual MetS components or the number of MetS components are associated with neuropathy^{13,14}.

In this study, we aimed to quantify the associations between individual MetS components and neuropathy in a cohort of Asian Indian participants. Additionally, we sought to determine the prevalence of neuropathy, stratified by glycemic status and the number of MetS components, to establish whether Asian Indian populations had similar risk factors to other previously described populations.

2. Methods

2.1. Population and Recruitment

Participants were recruited based on a convenience sample of consecutive participants attending the M.V. Hospital for Diabetes in Royapuram, Chennai, India between 07/04/2016 and 08/26/2019. Participants were being seen for a possible new diagnosis of diabetes and therefore, we excluded those with a previous diagnosis of diabetes from the study. Inclusion criteria were age 18 to 65 and willingness to undergo glucose tolerance testing and a fasting lipid panel. Pregnant women and nursing mothers were excluded as were participants with foot ulcers. Demographic information including age, sex, family history, smoking status, alcohol use, occupation, education, income and socio-cultural practices, were collected at study entry.

2.2 Metabolic Syndrome Components

Participants underwent glucose tolerance testing and a fasting lipid panel. Patients also had waist circumference (measured at the umbilicus), HbA1c, blood pressure, height, weight,

and BMI measurements at the time of study entry. Diabetes and pre-diabetes were defined according to the Expert Committee on the diagnosis and classification of diabetes mellitus¹⁵. The updated National Cholesterol Education Program (NCEP) criteria were used to define the metabolic syndrome and its individual components¹⁶, with the exception of waist circumference, which we utilized the South Asian specific cutoffs¹⁷. Participants receiving medication for hypertension were considered to meet the individual MetS cutoff for high blood pressure. Participants receiving medication for dyslipidemia were considered to meet the individual MetS component for low HDL.

2.3 Peripheral Neuropathy

The primary outcome was the Michigan Neuropathy Screening Instrument (MNSI) combined index, which utilizes the MNSI questionnaire and MNSI examination components^{18,19}. The four secondary outcomes include the MNSI examination, MNSI questionnaire, monofilament and biothesiometer testing. Monofilament testing was performed with a Semmes Weinstein 5.07/10-g monofilament on the dorsum of the dominant great toe²⁰. Biothesiometer testing was performed using Vibrometer on the plantar surface of both great toes. We did not record a continuous measure of vibration threshold, but defined neuropathy based on participants with a vibration threshold above 25 volts.

2.4 Statistical Analysis

Descriptive statistics were used to characterize participant demographic information and metabolic phenotyping. Pearson's Chi-Square tests or Fisher's exact tests were used to compare categorical factors and t-tests were used to compare continuous factors for participants with and without neuropathy. We determined the prevalence of neuropathy (primary and secondary definitions) stratified by glycemic status and tested for a trend in neuropathy prevalence using a Cochran-Armitage test. Similarly, we determined the prevalence of neuropathy by number of MetS components, stratified by glycemic status, and tested for trend using a Cochran-Armitage test. We also assessed the association between the number of MetS components and neuropathy after adjusting for age, sex, and height using a multivariable logistic regression model. For the primary and secondary outcomes, multivariable logistic regression was used to model neuropathy as a function of the metabolic syndrome components (waist circumference, pre-diabetes, diabetes, HDL, triglycerides, systolic blood pressure), after adjusting for demographic factors (age, sex, height). All analyses were completed using R.v.3.4.2 or SAS.v.9.3.

This study was approved by the Professor M. Viswanathan Diabetes Research Centre Ethics Committee on 5/8/2014. All testing and measurements were performed in accordance with the World Medical Association Declaration of Helsinki²¹. Additionally, informed written consent was obtained from each study participant.

3. Results

Between 07/04/2016 and 08/26/2019, 1751 consecutive patients attending the M.V. Hospital for Diabetes in Royapuram, Chennai, India for a suspected new diagnosis of diabetes were assessed for eligibility. Of patients assessed for eligibility, 1099 were excluded from the

study (853 had a previous diagnosis of diabetes, 186 were not age 18 to 65, 47 were pregnant or nursing and 13 had a foot ulcer). There were 652 participants that provided informed written consent and met all inclusion criteria.

Based on our primary neuropathy outcome (MNSI Index > 3.29), 64 participants (9.8%) had neuropathy. Based on secondary outcomes, the prevalence of neuropathy was as follows: MSNI questionnaire (9.1%), monofilament (6.4%), MNSI examination (14.6%) and biothesiometer (5.8%). Patients with neuropathy were older ($p < 0.01$) and had higher diastolic blood pressure ($p = 0.03$) (Table 1). While diastolic blood pressure was higher in those with neuropathy compared to those without, there was no significant association between diastolic blood pressure and neuropathy in fully adjusted models (OR: 1.22, 95% CI: 0.91-1.65, unit=10mmHg). The only difference in socio-cultural practice was the use of sandals with a toe-grip, which was more common in neuropathy patients ($p = 0.04$). However, adjusting for glycemic status, the use of toe grip sandals was not associated with neuropathy (OR: 2.02, 0.95-4.29).

There was a significant univariate trend between glycemic status and neuropathy defined by MNSI index ($p < 0.01$), biothesiometer ($p < 0.01$) and monofilament ($p = 0.046$), but not MNSI examination ($p = 0.07$) or MNSI questionnaire ($p = 0.07$) (Cochrane-Armitage Test of Trend) (Figure 1).

The primary multivariable logistic regression revealed a significant adjusted association between diabetes (OR: 3.41, 1.28-9.11) and age (OR: 1.04, 1.01-1.08) with neuropathy (Table 2). The predicted probabilities for neuropathy (based on MNSI Index), stratified by glycemic status are displayed in Figure 2. Of the secondary neuropathy measures, only age was associated with neuropathy based on the MSNI examination (OR: 1.04, 1.02-1.07) and monofilament (OR: 1.04, 1.01-1.08).

The proportion of participants with neuropathy did not significantly increase as the number of non-glycemic metabolic syndrome components increased (0: 0.0%, 1: 8.1%, 2: 9.9%, 3: 9.5%, 4: 15.2%) ($p = 0.12$) (Figure 3). Furthermore, after adjusting for age, sex, height, and glycemic status, the number of metabolic syndrome components was not significantly associated with neuropathy (OR: 1.13, 0.84-1.53). However, specifically among normoglycemic participants, there was a significant increasing univariate trend of neuropathy prevalence, as the number of metabolic syndrome components increased (Cochrane-Armitage test of Trend, $p = 0.04$).

4. Discussion

In a cohort of participants from Royapuram, Chennai, India, we found that diabetes was the primary metabolic factor associated with neuropathy. In contrast to other populations, other individual MetS components, including waist circumference, were not associated with neuropathy. Although specific non-glycemic MetS components were not associated with neuropathy, among normoglycemic participants, there was a significant association between the number of MetS components and neuropathy.

Like previous studies, diabetes was the primary factor associated with neuropathy^{5–8,22–26}. In contrast to studies in non-Asian Indian populations^{5–12}, obesity was not associated with neuropathy. Specifically, we found that waist circumference measured at the umbilicus was not associated with neuropathy (OR: 1.00, 95% CI: 0.88–1.14). Importantly, our recent analysis of the association between 9 anthropometric measurements and neuropathy in a United States obese population, found that only the waist measurement at the top of the iliac crest was associated with neuropathy, but not the high waist or abdomen⁷. One possible explanation for our results is that we did not measure central obesity at the best anatomical landmark. Another possibility is that central obesity is less important in Asian India populations. Determining how the distribution of obesity is associated with neuropathy in Asian Indian populations warrants further study, and is the goal underlying the formation of a new participant cohort: the Chennai Complications Cohort. This new cohort will consist of participants that will undergo detailed clinical phenotyping including body fat distribution and assessment of neuropathy, nephropathy, cardiovascular autonomic neuropathy, retinopathy and cognition.

The prevalence of neuropathy increased in those with worsening glycemic status but not as the number of MetS components increased. However, among just normoglycemic patients, there was a significant univariate trend of increasing neuropathy prevalence as the number of MetS components increased. This result is in agreement with three previous studies in China and the United States, that the number of MetS components is particularly important for those with normoglycemia and less so for those with diabetes^{6,8,9}. Diabetes remains the most important risk factor for neuropathy, but in those without diabetes, other MetS components become important particularly when in combination.

The prevalence of neuropathy was higher amongst participants who wore sandals with a toe-grip. One previous study in India found that foot ulcers were common in diabetic patients who wore sandals with a toe-grip²⁷. Since a large proportion of this population uses sandals with toe-grips, future studies are needed to quantify the relationship between footwear and neuropathy.

Limitations of our study include the cross-sectional study design, and lack of information regarding nephropathy, retinopathy, family history of neuropathy and detailed anthropometric measurements such as waist-hip ratio. Additionally, our primary neuropathy measure, the MNSI index, has good, but not great, diagnostic characteristics for neuropathy, particularly mild sensory neuropathy, and likely performs better for large fiber compare to small fiber neuropathy²⁸. Furthermore, we did not evaluate pain in this population, therefore, we are unable to determine if there are difference in the risk factors for painful and non-painful neuropathy. Although this was a convenience sample, post-hoc power calculations revealed that we had 80% power to detect small associations (OR=1.35) between metabolic risk factors and neuropathy²⁹.

This study confirmed that diabetes is the most important metabolic risk factor for neuropathy in a population of participants from Royapuram, Chennai, India. However, in contrast to multiple other population-based studies, waist circumference was not associated with neuropathy. Further studies are needed to determine the importance of the obesity

distribution for neuropathy in Asian Indian populations using detailed anthropometric measurements and/or other measures of fat distribution.

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Highlights:

1. This was the first study to assess the associations between the metabolic syndrome and neuropathy in Asian Indian participants.
2. This study confirmed that diabetes is the most important metabolic risk factor for neuropathy in a population of participants from Royapuram, Chennai, India.
3. In contrast to multiple other population-based studies, waist circumference was not associated with neuropathy.
4. Among normoglycemic patients, there was a significant increasing prevalence of neuropathy as the number of metabolic syndrome components increased.

Figure 1. Neuropathy prevalence stratified by glycemic status

The prevalence of neuropathy as determined by primary (MNSI index) and secondary neuropathy outcomes (MNSI examination, questionnaire, monofilament, and biothesiometer) stratified by glycemic status (normoglycemia, pre-diabetes, diabetes).

Figure 2. Boxplot of predicted probabilities for neuropathy based on the primary multivariable logistic regression, stratified by glycemic status

Predicted probabilities for neuropathy (MNSI Index>3.29) based on the multivariable logistic regression model, stratified by glycemic status.

Figure 3. The prevalence of neuropathy with increasing metabolic syndrome components stratified by glycemic status.

Neuropathy was defined as those with a Michigan Neuropathy Screening Instrument (MNSI) Index score >3.29 . Glycemic status was determined by the glucose tolerance test according to the Expert Committee on the diagnosis and classification of diabetes mellitus. Metabolic syndrome components were defined using the updated NCEP criteria.

Table 1:

Patient demographics stratified by neuropathy status (defined MNSI index)

Variable	Full Cohort (n=652)	No Neuropathy (n=588)	Neuropathy (n=64)	P-Value
Age, mean (SD)	45.5 (9.7)	45.1 (9.7)	49.3 (9.2)	<0.01
Sex (Female), N (%)	274 (42.0%)	246 (41.8%)	28 (43.8%)	0.87
Height (cm), mean (SD)	161.8 (9.5)	161.8 (9.7)	161.4 (8.2)	0.67
Weight (kg), mean (SD)	75.6 (14.5)	75.5 (14.6)	76.8 (12.7)	0.42
BMI (kg/m ²), mean (SD)	28.8 (5.0)	28.8 (5.1)	29.3 (4.2)	0.30
Waist Circumference (cm), mean (SD)	97.2 (11.0)	97.2 (11.2)	97.7 (9.9)	0.67
SBP (mmHg), mean (SD)	123.7 (15.3)	123.5 (15.4)	125.4 (14.6)	0.33
DBP (mmHg), mean (SD)	78.6 (8.9)	78.4 (9.1)	80.6 (7.1)	0.03
Fasting Glucose (mg/dL), mean (SD)	127.0 (60.5)	124.7 (57.4)	147.9 (81.8)	0.03
1 Hour Glucose (mg/dL), mean (SD)	239.1 (103.8)	234.8 (101.2)	279.1 (118.6)	<0.01
2 Hour Glucose (mg/dL), mean (SD)	209.9 (120.9)	205.5 (119.8)	249.6 (125.0)	<0.01
HbA1C (%), mean (SD)	6.9 (2.0)	6.8 (1.9)	7.7 (2.2)	<0.01
Triglycerides (mg/dL), mean (SD)	147.8 (93.0)	147.0 (90.2)	154.8 (115.9)	0.61
HDL (mg/dL), mean (SD)	42.8 (9.1)	42.9 (9.1)	42.1 (9.2)	0.54
Glycemic Status, N (%)				
Normoglycemic	130 (19.9%)	124 (21.1%)	6 (9.4%)	<0.01
Pre-Diabetes	230 (35.3%)	214 (36.4%)	16 (25.0%)	
Diabetes	292 (44.8%)	250 (42.6%)	42 (65.6%)	
Family History of Diabetes, N (%)				
Mother	260 (39.9%)	232 (39.5%)	28 (43.8%)	0.60
Father	249 (38.2%)	231 (39.3%)	18 (28.1%)	0.11
Mother and Father	118 (18.1%)	105 (17.9%)	13 (20.3%)	0.75
Siblings	232 (35.6%)	210 (35.7%)	22 (34.4%)	0.89
Other Family	12 (1.8%)	11 (1.9%)	1 (1.6%)	1.00
Smoker (Current or Ex), N (%)	125 (19.2%)	110 (18.7%)	15 (23.4%)	0.46
Alcohol Use, N (%)	187 (28.9%)	170 (28.9%)	17 (26.7%)	0.80
Occupation, N (%)				
Unskilled Worker	26 (4.0%)	26 (4.4%)	0 (0.0%)	0.051
Skilled Worker	71 (10.9%)	70 (11.9%)	1 (1.6%)	

Variable	Full Cohort (n=652)	No Neuropathy (n=588)	Neuropathy (n=64)	P-Value
Clerical	12 (1.8%)	12 (2.0%)	0 (0.0%)	
Executive/Business	235 (36.0%)	208 (35.4%)	27 (42.2%)	
Retired	31 (4.8%)	26 (4.4%)	5 (7.8%)	
Housewife	220 (33.7%)	193 (32.8%)	27 (42.2%)	
Professional	56 (8.6%)	52 (8.8%)	4 (6.3%)	
Student	1 (0.2%)	1 (0.2%)	0 (0.0%)	
Education, N (%)				
Illiterate	91 (14.0%)	79 (13.4%)	12 (18.8%)	0.28
High School	238 (36.5%)	217 (36.9%)	21 (32.8%)	
Arts	219 (33.6%)	194 (33.0%)	25 (39.1%)	
Professional	102 (15.6%)	96 (16.3%)	6 (9.4%)	
Missing	2 (0.3%)	2 (0.3%)	0 (0.0%)	
Income, N (%)				
>25,000 RS	300 (46.0%)	272 (46.3%)	28 (43.8%)	0.11
10,000-25,000 RS	88 (13.5%)	84 (14.3%)	4 (6.3%)	
<10,000 RS	264 (40.5%)	232 (39.5%)	32 (50.0%)	
Sociocultural Practices, N (%)				
None of the below practices	50 (7.7%)	46 (7.8%)	4 (6.3%)	0.81
Prolonged Cross-Legged Sitting on Floors	309 (47.4%)	273 (46.4%)	36 (56.3%)	0.17
Barefoot Walking	65 (10.0%)	63 (10.7%)	2 (3.1%)	0.09
Toe Rings	202 (31.0%)	179 (30.4%)	23 (35.9%)	0.45
Barefoot Walking in Temple	475 (72.9%)	422 (71.8%)	53 (82.8%)	0.08
Barefoot Walking at Home	8 (1.2%)	8 (1.4%)	0 (0.0%)	1.00
Superstitious Beliefs (e.g. fire Walking)	7 (1.1%)	7 (1.2%)	0 (0.0%)	1.00
Use of Sandals with Toe Grip Strap	485 (74.4%)	430 (73.1%)	55 (85.9%)	0.04
Walking in Hot weather	16 (2.5%)	16 (2.7%)	0 (0.0%)	0.39
Michigan Neuropathy Screening Index, Mean (SD)				
MNSI Index	1.33 (1.25)	1.04 (0.95)	3.92 (0.41)	
MNSI Questionnaire	1.27 (1.46)	1.04 (1.27)	3.36 (1.43)	
MNSI Examination	1.12 (1.24)	0.94 (1.11)	2.78 (1.17)	

Table 2:

Logistic regression for neuropathy outcomes with Metabolic syndrome components, age, sex and height

Variable	MSNI Index	MNSI Questionnaire	MNSI Exam	Monofilament
Age	1.05 (1.02,1.08)*	0.99 (0.96,1.02)	1.04 (1.02,1.07)*	1.04 (1.01,1.08)*
Male (reference female)	1.18 (0.57,2.45)	0.65 (0.31,1.38)	0.83 (0.45,1.55)	1.00 (0.43,2.34)
Height unit=5 cm	1.00 (0.83,1.20)	0.91 (0.75,1.10)	0.97 (0.83,1.13)	0.98 (0.79,1.21)
Diabetes (reference normal)	2.91 (1.17,7.24)*	1.59 (0.74,3.45)	1.68 (0.85,3.33)	2.74 (0.90,8.29)
Pre-diabetes (reference normal)	1.34 (0.50,3.58)	0.71 (0.29,1.73)	1.00 (0.48,2.07)	1.69 (0.53,5.40)
SBP unit=10 mm Hg	1.00 (0.84,1.19)	1.17 (0.98,1.38)	1.03 (0.89,1.20)	0.90 (0.72,1.12)
Waist Circumference unit=5 cm	1.00 (0.88,1.14)	0.92 (0.81,1.06)	1.06 (0.95,1.18)	1.04 (0.89,1.20)
Triglycerides unit=50 mg/dL	1.03 (0.89,1.20)	0.97 (0.83,1.14)	0.90 (0.77,1.06)	1.00 (0.83,1.21)
HDL unit=10 mg/dL	0.86 (0.63,1.18)	1.02 (0.74,1.41)	0.93 (0.71,1.22)	1.04 (0.72,1.51)