Original Research Article

Aggregated cardiovascular risk scores as a marker of neuropathy among patients with type 2 diabetes – A correlational analysis

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Abstract

Background: Diabetes is a metabolic disorder wherein the ensuing complications contribute to the morbidity and mortality to a major extent. According to the ticking-clock hypothesis, macrovascular complications like cardiovascular problems develop in the pre-diabetic stage in type 2 diabetes whereas microvascular complications are slower to develop. Recent studies suggest that besides hyperglycemia, many other vascular risk factors are also involved in the aetiology of neuropathy. **Aim:** This study aimed to predict the risk of developing neuropathy from the cardiovascular risk factors in patients with type 2 diabetes. **Materials and Methods:** This cross-sectional study was carried out at Dhanalakshmi Srinivasan Medical College Hospital, Perambalur. 102 biochemically proven type 2 diabetic patients, were included in the study by convenient sampling technique following specific inclusion and exclusion criteria. Data on demographics, duration of diabetes, nature of treatment and family history were collected; blood pressure was recorded in the dominant arm and the subjects were subjected to fasting and post-prandial blood sugars and lipid profile estimations. Neurological examination was performed to assess the risk of neuropathy using Michigan Neuropathy Screening Instrument (MNSI). Using the patients' examination and investigation reports, the cardiovascular risk scores were computed by Framingham Heart Risk Score. Correlation was sought between the MNSI symptom and sign scores and FHRS using Spearman Rank Correlation Test. **Results**: While the symptom scores of MNSI did not significantly correlate with the FHRS (r=0.04; p=0.64), the MNSI sign scores showed a significant positive correlation with the latter correlation (r =0.197; p=0.04), the correlation coefficient however was weak. **Conclusions**: As this study showed only very weak correlation between the aggregated cardiovascular risk scores, it is not conclusive to be used as a marker for assessing the risk of neuropathy at the earliest stage in diabetes, even when other risk factors namely, duration of diabetes, glycaemic status, BMI, hypertension and lipid profile were inconclusively associated.

Keywords: microvascular, neuropathy, type 2 diabetes mellitus

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Introduction

Diabetes is a metabolic disorder wherein the ensuing complications contribute to the morbidity and mortality to a major extent. Of these, the macrovascular complications like cardiovascular events occur earlier in the pre-diabetic stage, whereas microvascular complications like neuropathy, retinopathy and nephropathy occur little later.[1] References cite that duration of diabetes and glycaemic status are strongly associated with only microvascular complications whereas atherogenic risk factors like obesity, hypertension, and smoking may contribute to the risk of developing

macrovascular complications as much as the duration of diabetes itself.[1] The Diabetes Control Complications Trial (DCCT)[2]reported a significant reduction in neuropathy in the intensively treated group whereas the Veterans Affairs Diabetes Trial (VADT)[3] failed to present such a decrease in autonomic neuropathy in the intensive-therapy group. The 7 year EURODIAB study[4] has said that the development of peripheral neuropathy is also associated with potentially modifiable cardiovascular risk factors such as serum lipids, blood pressure (BP) and body mass index (BMI). Since the pathologic hallmark of both microvascular and macrovascular complications involves vasculature, few risk factors may be coexistent in both conditions as a continuum. This study was done to test the hypothesis that the risk of diabetic neuropathy can be assessed from the cardiovascular risk factors and to seek out the correlation between the risk factors of both microvascular and macrovascular complications.

Materials and Methods

This cross-sectional study was conducted in the Diabetic OPD of the Department of General Medicine in Dhanalakshmi Srinivasan Medical College Hospital, Perambalur, after getting an approval from the Institutional Ethics Committee. A total of 102 biochemically proven diabetic patients of both the genders were included in the study. Patients who were newly diagnosed and those under regular follow-up were chosen by convenient sampling technique after getting their written consent. Patients with history of diabetic foot ulcers, myocardial infarction, alcoholism, renal failure, symptoms of retinopathy and other diabetic emergencies were excluded from the study.

The general data on demographics, duration of diabetes, nature of treatment, lifestyle factors and family history were collected. Height (in cm), weight (in Kg), waist circumference (in cm) and hip circumference (in cm) were measured using standardized instruments and Body mass index (BMI) was calculated using Quetlet's formula. Blood pressure was recorded in the dominant arm after 10 minutes of rest by a standardized mercury sphygmomanometer.

Biochemical estimation of fasting and post-prandial blood sugars and lipid profile estimations including total cholesterol, HDL cholesterol and triglycerides were done in all the patients.

All the patients were subjected to neurological examination and were assessed for the risk of neuropathy using the Michigan Neuropathy Screening Instrument (MNSI).[5,6,7] The MNSI has two versions; a patient version wherein the investigator evaluates for symptoms of neuropathy in a one-to-one interview basis and a physician version wherein the investigator evaluates for the signs of neuropathy. Assessment of the signs of neuropathy included examination of the foot, evaluation of ankle jerk, vibration perception test (using 128 Hz tuning fork) and monofilament test (using 10 g filament). The MNSI score was determined using the MNSI manual. For this study, neuropathy was defined operationally as at least 7 positive responses on the MNSI questionnaire or a score greater than 2.0 on the MNSI examination.[5, 6, 7]

Using the patients' examination reports and biochemical values, the cardiovascular risk scores were computed by the Framingham heart Risk Score engine.[8] Framingham Heart risk score is calculated based on five parameters, viz, age, history of smoking, systolic blood pressure, total cholesterol level and HDL cholesterol level. Points were given for individual parameters and the total score is calculated as percentage of risk for 10 years as follows.

- For women - Under 9 points: <1%. 9-12 points: 1%. 13-14 points: 2%. 15 points: 3%. 16 points: 4%. 17 points: 5%. 18 points: 6%. 19 points: 8%. 20 points: 11%. 21=14%, 22=17%, 23=22%, 24=27%, >25= Over 30%

- For Men - 10-year risk in %: Points total: 0 point: <1%. 1-4 points: 1%. 5-6 points: 2%. 7 points: 3%. 8 points: 4%. 9 points: 5%. 10 points: 6%. 11 points: 8%. 12 points: 10%. 13 points: 12%. 14 points: 16%. 15 points: 20%. 16 points: 25%. 17 points or more: Over 30%

- Interpretation of the results:
  Low risk of CHD - 10%
  Intermediate risk of CHD - 10-20%
  High risk of CHD - 20% or more

Correlations were sought between the MNSI scores, fasting and postprandial blood sugar levels, BMI, Duration of diabetes, Waist-Hip ratio and FHR scores by Spearman Rank Correlation Test using SPSS 17.0. A probability value of < 0.05 with 95 % confidence limits was considered to be statistically significant.

Results

A total of 102 type 2 diabetic patients were included (49 male and 53 female patients). Table 1 shows the baseline characteristics of the study population. Table 2 shows the mean glucose concentration, lipid profile, FHRS and MNSI scores of the patients. The values are represented as Mean ± Standard Error

Table 1: Baseline characteristics of the study population (n=102)

No.	Variables	Values (Mean ± SEM)
1	Age (in years)	56.9 ± 1.1
2	BMI (Kg/m^2)	24.84 ± 0.48
3	WHR	0.94 ± 0.008
4	SBP in mm Hg	121.53 ± 1.63
5	DBP in mm Hg	77.37 ± 1.0.
6	Duration of diabetes in years	4.67 ± 0.47

Values expressed as Mean ± Standard Error of Mean (SEM); BMI = Body mass index; WHR = Waist-Hip ratio; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure

Table 2: Biochemical values, MNSI scores and FHR scores of Type 2 diabetic patients (n = 102)

No.	Parameter	Values (Mean ± SEM)
1	Fasting Blood Sugar (mg/dL)	221.01 ± 8.1
2	Postprandial Blood Sugar(mg/dL)	289.38 ± 9.6
3	Total cholesterol (mg/dL)	164.72 ± 4.4
4	HDL cholesterol (mg/dL)	37.31 ± 0.69
5	Triglycerides (mg/dL)	145.77 ± 6.2
6	FHRS	6.29 ± 0.65
7	MNSI symptom score	4.14 ± 0.27
8	MNSI sign score	2.18 ± 0.20

Values expressed as Mean ± Standard Error of Mean (SEM); FHRS=Framingham Heart Risk Score, MNSI= Michigan Neuropathy Screening Instrument; HDL=High Density Lipoprotein

On analyzing the correlations between variables by Spearman Rank correlation test, it was seen that FHRS showed a significant positive correlation with MNSI sign score (rho=0.197; p=0.04).Duration of diabetes showed a significant positive correlation with both MNSI symptom score (rho=0.2; p=0.04) and sign score (rho=0.19; p=0.04). Similarly, duration of reported diabetes among study population showed a positive correlation with blood sugar values and (rho= 0.25; p=0.01 for both fasting and post-prandial blood sugar) a negative correlation with HDL cholesterol (rho= -0.22; p= 0.02). Systolic and diastolic BP were found to have significant positive correlations with FHR score (rho=0.23; p=0.01 and rho=0.32; p=0.001, respectively). WHR and BMI neither correlated with FHRS nor MNSI score. FHRS was significantly much lower in female patients (p=0.0001). Though the above correlations are statistically significant, the correlation coefficients were weak and non-linear except for gender differences.

Discussion

This cross-sectional study was done on 102 type 2 diabetic patients comprising of both the genders. This study showed a positive correlation, though weak, between the FHRS and MNSI sign score. Similar results have been shown by Mayowa *et al.*[7] who proved that aggregate cardiovascular risk score was positively correlated with signs of diabetic neuropathy; in their study, however, the aggregate cardiovascular risk load had the strongest significant correlation with diabetic neuropathy. Another study by May *et al.* has demonstrated a significant correlation between diabetic neuropathy and the existence of one or more macrovascular complications showing that diabetic patients with peripheral neuropathy presented with significantly higher rates of cardiac events and peripheral vascular disease.[9] May *et al.* concluded that the risk of coronary heart disease estimation based on gender, age, systolic BP, total/HDL cholesterol, left ventricular hypertrophy, diabetes and smoking status using the Framingham algorithm was significantly correlated to the degree of Cardiac Autonomic Neuropathy (P=0.001).[9] There are observational results which prove that there are strong associations between prediabetes and early forms of nephropathy, chronic kidney disease, small fibre neuropathy, diabetic nephropathy and increased macrovascular disease which were predicted by Framingham heart risk scores.[10]

Duration of diabetes was positively correlated with MNSI symptom and sign scores in our study, although the correlation was weak. Similar results were obtained in the EURODIAB study.[4] However, unlike previous studies[7,11,12] the EURODIAB study[4] did not yield any correlation between glycaemic status, BMI, lipid levels, systolic and diastolic BP with neuropathic risk factors. We used fasting and postprandial blood sugar levels rather than HbA_1c as in other studies, hence the effect of chronic hyperglycemia could not be elicited in our study.

From the above findings, it is likely that a common pathology operates in the development of microvascular and macrovascular complications. Chawla *et al.,* in their review, have commented that injury to the peripheral nerves from hyperglycemia may be due to the mechanisms of hyperglycemia-induced polyol pathway, injury from Advanced Glycation End products (AGEs), and enhanced oxidative stress.[13] Since our study has not shown any correlation between hyperglycaemia and risk factors for neuropathy, there is a definite possibility that other mechanisms are operational in the pathogenesis of this complication.

Limitations of the study: The correlation found in the study is very weak and insufficient to show the relationship between aggregated cardiovascular risk score and risk of neuropathy. If the study is done in a larger sample of diabetic population, a better correlation may be observed. Another limitation of our study is that we did not employ any electrophysiological techniques to add to the evidence of the risk of neuropathy. However, the use of scoring systems and bedside evaluation methods has been validated and emphasized by this study. The individual perceptions about the symptoms may be the reason for the insignificant correlation of the MNSI symptom score with FHRS.

Conclusion

Since this study showed only very weak correlation between the aggregated cardiovascular risk scores it is not conclusive to be used as a marker for assessing the risk of neuropathy at the earliest stage in the prognosis of diabetes, even when the other risk factors namely, duration of diabetes, glycaemic status, BMI, hypertension and lipid profile were inconclusively associated. Further studies in a larger sample are warranted for confirmation that regular evaluation of the diabetic patient with simple routine tests and computation of Framingham Heart Risk Score could enable the clinician to determine the impending risk of neuropathy in his patients.

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Conflicts of interest: Nil

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