Original Research Article

Effect of blood glucose levels on sensory nerve conduction parameters in prediabetics: A cross sectional study

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Abstract

Background: "Prediabetic" is an intermediate state of increased blood sugar levels and is defined by American Diabetic Association as fasting blood sugar (FBS) levels in the range of 100 to 125 mg/dL. It is increasingly viewed with early forms of diabetic neuropathy in 25-62% of cases. Multiple studies showed hyperglycaemia to change the myelin's phospholipid, fatty acids and cholesterol content and thus modifying its fluidity, ultimately affecting the functional capacities of the nerve. This study was taken to investigate the sensory nerve conduction velocity (NCV) and latency in prediabetic healthy male adults and to study its relationship with levels of FBS in them. **Materials & Methods**: 60 clinically healthy prediabetic males of age 30-50 years were included in this observational study. For comparison 30 clinically age matched healthy normoglycaemic (FBS<100 mg/dl) male adults were taken as control. Demographic, anthropometric and sural latency and NCV were compared using't' test. Relations of FBS with different variables were investigated using Pearson's correlation test. A p value <0 .05 was taken as significant. **Results**: Bilateral sural nerve latency (right 3.52±1.88 ms and left 3.83±1.98ms) was significantly increased in the prediabetics compared to normoglycaemics (right 2.41±1.24 ms and left 2.48±0.79ms). NCV of sural nerves of both sides (right 50.38±18.89 m/sec and left 46.13±17.93m/sec) were significantly decreased in prediabetics as compared to normoglycaemics (right: 62.60±13.44m/sec; left: 53.95±11.93m/sec). Latency of right and left sural nerves was significantly and positively correlated with FBS levels in prediabetes (r= 0.61; p<0.01 and r= 0.33; p<0.01 respectively). Right sural nerve conduction velocity was significantly and negatively correlated with FBS levels in prediabetes (r= -0.514; p<0.01). **Conclusion**: Prediabetics seems to have a lower peripheral sensory NCV as compared to normoglycaemic male adults of 30-50 years of age.

Keywords: Prediabetes, NCV, sensory neuropathy.

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Introduction

Diabetes mellitus still remains one of the commonest non-communicable diseases causing high mortality all over the world[1]. In diabetics long standing high blood glucose levels have been associated with nonvascular damage to the myelin sheath of peripheral nerve[2], hence peripheral neuropathy remains the commonest complication of diabetes which may involve sensory and motor nerves[3] as it has been observed that almost half of the diabetic patients develop distal symmetric polyneuropathy[4]. Peripheral neuropathy is a major reason of morbidity and lower quality of life because of sensory loss, pain, gait disturbance, fall-related injury foot ulceration and amputation in the diabetics[5].

Usually prediabetes leads to the development of type 2 Diabetes Mellitus(T2DM)[6] and is defined as fasting blood sugar (FBS) concentration ≥ 100 mg/dl but below traditional thresholds for diagnosis of diabetes, i.e. FBS ≤125 mg/dl[7]. It has been observed that about 5–10% of people with prediabetes within a year develop overt diabetes[8] and 11–25% of prediabetics already have peripheral neuropathies[9].

Subclinical diabetic sensorimotor polyneuropathy (DSPN) means that neither the signs nor symptoms of neuropathy have appeared but changes in nerve conduction studies (NCS) are present. The changes in NCS suggest that the nerve damage has already started which is reflected upon by the conduction impairment of the nerves[10].

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There are suggestions, that subclinical cases of DSPN must be evaluated by NCS because DSPN abnormalities are most often detected by NCS in subclinical conditions[11]. Once symptoms appear; there are few effective therapeutic strategies. Hence, timely detection of damage to the nerve fibers and early management become extremely important[10].

Application of the elements of NCS and evaluation of values specific for prediabetes could improve its applicability as a sensitive index for early diagnosis of peripheral neuropathy in prediabetic adult males. With an aim to evaluate incipient peripheral neuropathy in hyperglycaemic state the present study was taken up to analyse the onset of peripheral neuropathy and its relation to levels of fasting blood sugar in pre-diabetic adult males.

Materials and method

Study Design

An observational analytical study

Study setting

Study was conducted in the Physiology department of Himalayan Institute of Medical Sciences, Swami Ram Nagar, Dehradun, over a period of 12 months.

Study population

90 male subjects, aged between 30 -50 years were recruited from a group of representative population of attendants either visiting the medicine outpatient department, or residents or employees of Swami Rama Himalayan University, Dehradun after prior approval from

institutional ethical committee for the research protocol and taking written informed consent from every participant of the study.

Inclusion criteria for prediabetics
i) Age-30-50 years
ii) Clinically healthy adult males with
iii) Fasting Plasma Glucose (100 mg/dl-125 mg/dl)

Inclusion criteria for controls
i) Age-30-50 years
ii) Clinically healthy adult males with
iii)Fasting Plasma Glucose (<100 mg/dl)

Exclusion criteria (same for both groups)
Individuals with history of daily alcohol intake, tobacco chewing, daily smoking, and systemic diseases like hypertension, thyroid disorders, etc and those on medications like steroids, anti-psychotic drugs, were excluded from the study. Not included in the study were also individuals who were fasting (religious or cultural cause) or who had consumed food in the morning. The sample size was calculated using standard deviation of sensory nerve conduction velocity among prediabetes [3.62 mm/sec][12] and normal control considering 80% study power and an alpha error of 0.05. The sample size calculated for cases was 60. As per the above ratio of 2:1 (case versus control), 30 controls were recruited for comparison. Thus 60 prediabetics and 30 normoglycaemics were selected for the study.

Study tools
FBS of the volunteers who reported in the morning in the department without having breakfast and overnight fasting were checked using glucometer (GlucOne BG 03 Auto by DrMorepan)[13] and noted. Based on the working definition, clinically healthy adult male subjects of 30 -50 years were considered prediabetic if their FBS level was ≥100 mg/dl and ≤125 mg/dl and normoglycaemic if their FBS was <100mg/dl and subsequently these volunteers were enrolled for NCS. Before conduction of NCS, anthropometric and demographic parameters along with a self-administered questionnaire were noted. Body mass index (BMI) was also calculated by Bio-Impedance body composition analyzer (Karada Scan).
The study of peripheral nerve conduction in the sensory nerves was performed following standard technique using the clarity vision EMG Octopus machine and 1 cm disc electrodes in the Physiology department. With the volunteer lying comfortably at 25-28°C room temperatures, electrodes attached to the body of the subject and leads attached to the monitor, supramaximal stimulus was given at the predefined area for effective nerve stimulation and recording NCS. Sweep speed was set at 2ms/division for sensory NCS. Antidromic stimulation was applied proximally to the active recording electrode. The latency to both the initial deflection (onset latency) and negative peak (peak latency) as well as nerve conduction velocity were recorded in accordance with the guidelines outlined by the American Association of Electrodiagnostic Medicine[14].

Ethical considerations
Approval from institutional ethical committee with number (SRHU/HIMS/ETHICS/2018/54) for the research protocol and written informed consent from every participant of the study was taken before initiation of the study.

Data Analysis
To evaluate the change in parameters, data obtained was subjected to statistical analysis using the software SPSS (Statistical Package for the Social Sciences), version 20.0 for Windows. Anthropometric and demographic parameters as well as latencies and nerve conduction velocities in sensory (sural) peripheral nerves between prediabetes male adults and normoglycaemic healthy controls were expressed as mean ± standard deviation assessed by unpaired 't' test. The relationship of fasting blood glucose levels with sensory nerve conduction studies (latency and NCVs) in prediabetes adults was observed by Pearson's correlation. Level of significance was set at $p<0.05$.

Results
As shown in the table below, there was no significant difference in the demographic and anthropometric parameters between the normoglycaemics and prediabetics.

Table 1: Demographic and anthropometric parameters among normoglycaemics and prediabetics (Mean±SD)

Sl. No.	Parameters	Normoglycaemic (n=30)	Prediabetic (n=60)	p value
1	Age (years)	41.10±6.39	43.18±5.63	0.11
2	Height (cm)	169.13±4.81	170.81±4.67	0.12
3	Weight (kg)	72.13±8.20	75.20±6.11	0.07
4	BMI(kg/m²)	25.36±2.31	25.63±2.30	0.59

Values: Mean ± SD; "t" test. BMI: Body Mass Index; p< 0.05was considered statistically significant.
When we compared the latencies and nerve conduction velocities (NCV) of sensory (sural nerves) of both lower limbs in normoglycaemics and prediabetics (Table 2), we found latencies of bilateral sensory (sural) nerves to be significantly greater in prediabetics as compared to normoglycaemics. The NCV of bilateral sensory (sural) nerves were also observed to be significantly lower in the prediabetics as compared to the normoglycaemics.

Table 2: Nerve conduction tests among normoglycaemics and prediabetics (Mean±SD)

Parameters	Normo-glycaemic (n=30)	Prediabetic (n=60)	p value
Right Sural Nerve latency (ms)	2.41±1.24	3.52±1.88	0.00
Left Sural Nerve latency (ms)	2.48±0.79	3.83±1.98	0.00
Right Sural NCV (m/s)	62.60±13.44	50.38± 18.89	0.00
Left Sural NCV (m/s)	53.95±11.93	46.13±17.93	0.02

Data presented as Mean ± SD; "t" test; NCV: Nerve Conduction Velocity. p< 0.05was considered statistically significant.

Table 3: Correlation of fasting blood sugar (FBS) with demographic, anthropometric and nerve conduction latencies and in normoglycaemic adult males (n=30):

	FBS (mg/ dl)	Age (years)	BMI	Right Sural Nerve latency(ms)	Right Sural NCV (m/s)	Left Sural Nerve latency (ms)	Left Sural NCV (m/s)
FBS (mg/ dl)	1	.154 (.415)	.107 (.573)	.000 (.999)	-.002 (.993)	-.156 (.412)	.192 (.310)
Age (years)		1	.257	.519**	-.618**	.379*	-.231

			(.170)	(.003)	(.000)	(.039)	(.219)
BMI (kg/m²)			1	-.096 (.613)	-.119 (.530)	.089 (.640)	-.311 (.095)
Right Sural latency (ms)				1	-.737** (.000)	-.059 (.757)	.170 (.370)
Right Sural NCV (m/s)					1	.165 (.384)	.035 (.855)
Left Sural latency (ms)						1	-.740 ** (.000)
Left Sural NCV (m/s)							1

Values are in correlation coefficient r; (p value). p>0.05 was considered statistically non-significant;
p value < 0.05*, p<0.01: **, p<0.001: *** was considered statistically significant.

Table 3 shows there is no correlation of FBS with any other variable. No significant (positive/negative) co relation of FBS in normoglycaemics with demographic, anthropometric and nerve conduction latencies and velocities (in sensory nerves of both lower limbs).

Table 4: Correlation of fasting blood sugar (FBS) with demographic, anthropometric and nerve conduction latencies and velocities among the prediabetic males (N=60)

	FBS (mg/ dl)	Age (years)	BMI (kg/m²)	Right Sural Nerve latency (ms)	Right Sural NCV (m/s)	Left Sural Nerve Latency (ms)	Left Sural NCV (m/s)
FBS (mg/ dl)	1	.093 (.482)	-.137 (.297)	.611** (.000)	-.514** (.000)	.334** (.009)	-.215 (.099)
Age (years)		1	.014 (.918)	.401** (.002)	-.380** (.003)	.241 (.063)	-.216 (.098)
BMI (kg/m²)			1	.056 (.673)	.086 (.513)	-.002 (.990)	.068 (.604)
Right Sural Nerve latency (ms)				1	-.881** (.000)	.405** (.001)	.388** (.002)
Right Sural NCV (m/s)					1	-.487 ** (.000)	.513** (.000)
Left Sural Nerve latency (ms)						1	-.885 ** (.000)
Left Sural NCV (m/s)							1

Values are in correlation coefficient r; (p value). p>0.05 was considered statistically non-significant; p value < 0.05*, p<0.01: **, p<0.001:*** was considered statistically significant.

Table 4 shows significant positive correlation of FBS in prediabetes with right sural (p=.000; r = .611) and left sural (p=.009; r = .334) nerve latency. The table also shows significant negative co relation of FBS with right sural (p=.000; r = -.514) NCV. Age also showed a significantly positive correlation with right sural (p=.000; r = .401) nerve latency and significantly negative correlation with right sural (p=.003; r = -.380) NCV.

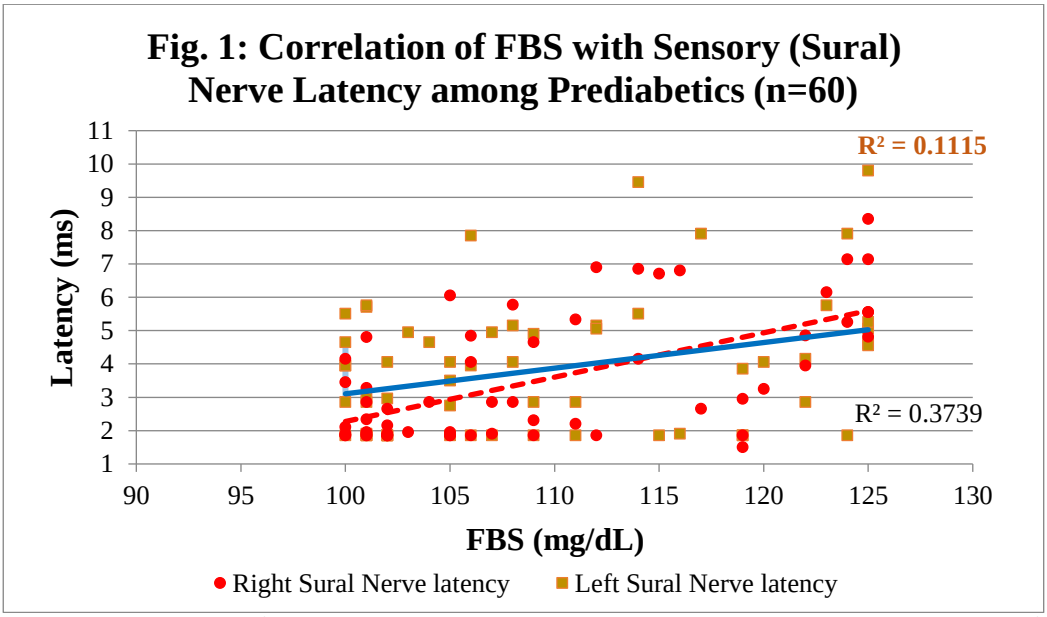

Fig.1 showed that variability prediction of nerve latency with increasing FBS was more in right sural (R^2=0.37) as compared to left sural nerve (R^2=0.11) among the prediabetics.

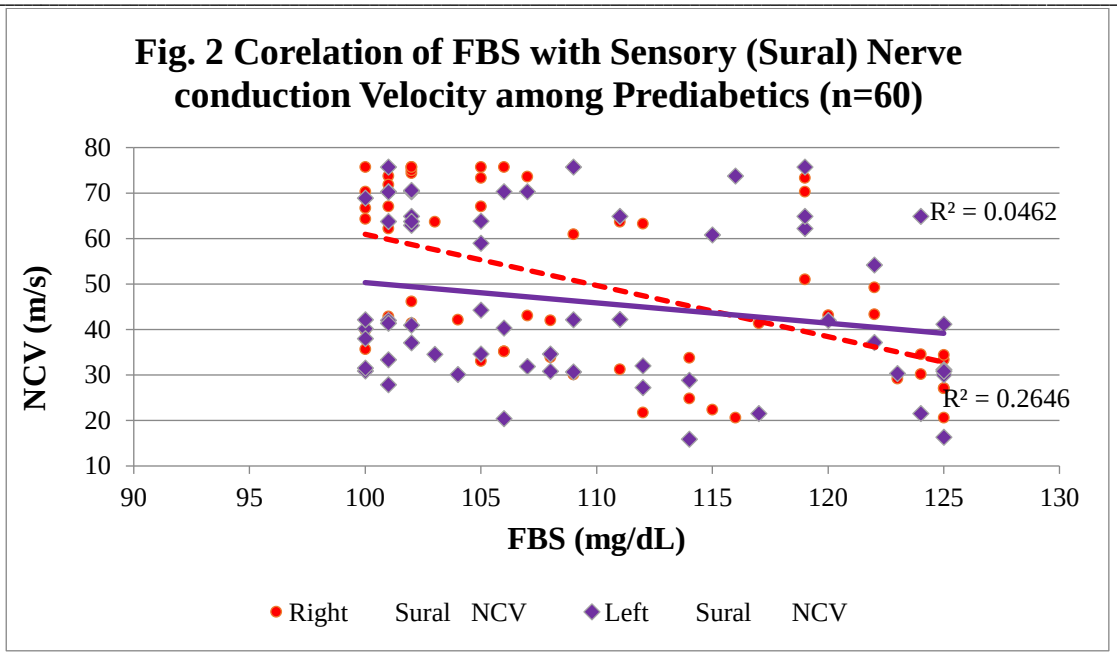

Fig. 2 showed that variability prediction of nerve conduction velocity with increasing FBS was more in right sural (R^2=0.26) as compared to left sural nerve (R^2=0.04) among the prediabetics

Discussion

Symptomatic diabetic sensory neuropathy is the commonest complication among diabetics with a high disability index[15]. Prediabetes is a high-risk state for development of diabetes with about 10% of prediabetics progressing to T2DM within a year[16].

Our study observed that the demographic and anthropometric parameters (age, height, weight, BMI, %) were not significantly different in prediabetics when compared with normoglycaemic healthy male adults suggesting no significant change in these variables occur due to hyperglycaemia in prediabetics. The findings of our study are contrary to the findings of Lee CC et al who in their study noted that age, height, and prediabetes to be independently associated with peripheral neuropathy[17].

Sural nerve measurements are reliable parameter to evaluate early diabetic polyneuropathy and have a value in the early diagnosis of diabetic polyneuropathy[18].

The principle of our study to study sensory polyneuropathy in prediabetics found support in the cohort study by Kannal et al. who in their study observed that 24.1% of subjects with prediabetes exhibited subclinical, asymptomatic peripheral neuropathy and it was demonstrated by the abnormalities of sural NCS[19].

When the sensory (sural) nerves were evaluated, we noticed a significant increase in the latency of sensory (sural) nerves on both the sides in the prediabetics as compared to the normoglycaemics. Significant decrease in the NCV of sensory (sural) nerves in both the lower limbs was also observed in the prediabetics when compared to normoglycaemics (Table 2).

Our research results matched with study results of Sachan et al. who observed increase in latency and decrease in the sural nerve conduction velocity in prediabetics They concluded that it is the demyelination of the nerves which increases the latency in them and which is more in diabetics than prediabetics due to higher levels of blood sugar in the former[20].

Devi MS et al., in their study observed, that the sural NCV was significantly decreased in both the diabetics (p value < 0.001) and prediabetics (p value of 0.047) when compared with the normal healthy controls. They proposed that neuropathy begins very early in diabetes and this can be detected at a much earlier, even before the development of diabetes i.e. in the prediabetic stage, which, by itself is a transitional phase towards the development of diabetes. The severity of neuronal dysfunction maybe related to the duration and level of hyperglycaemia in the individual[21]. Their findings are in line with our observations where we too hypothesized that neuropathy starts in the prediabetic stage.

In one of the nerve conduction studies done by Kocer et al. on prediabetics and age matched healthy controls; they mentioned that there was abnormality of sural NCS in the form of increased latencies and decreased NCVs in prediabetics. Moreover, the study also noticed that it was the right side of the prediabetics where the impairment of the nerve function was more. Their findings are in line with the concept that it is the small nerve fibers are damaged early in the course of glucose dysmetabolism[22]. This is what we have also noticed in the present study, as none of the prediabetics or healthy controls had any symptoms or signs of neuropathy. Abnormalities in sensory nerve excitability were detected in asymptomatic prediabetes.

We found abnormality in the sensory nerve conduction studies of prediabetics. Similar correlations between nerve excitability parameters were also discovered by Dimova R et al. in their study, wherein they found higher prevalence of sensory nerve dysfunction in prediabetics[23].

Sumner CJ et al in addition to others have recommended routine use of NCS as there is a great prevalence of unawareness of distal sensorimotor polyneuropathy in prediabetes because the neuropathy in them appears to be milder than that encountered in diabetes[24]. Herein lies our concept of utilizing this vital tool for early diagnosis of milder form of peripheral neuropathy in prediabetics which may often be missed or remain underdiagnosed. Sumner CJ et al., concluded that a dose-response type relationship is present between the severity of glucose dysmetabolism and the severity of neuropathy.

Our findings of abnormal nerve conduction studies in peripheral sensory is supported by the documented findings of the study of Zeng J et al. who ought to find the role of inflammation on sensory nerves in prediabetics observed, a high prevalence of neuropathy & greater degree of abnormality in the nerve conduction test (NCT) in the prediabetics as compared to healthy controls but less than the diabetic group. The study concluded that the proinflammatory phase starts long before the conversion of prediabetes phase to diabetes. The higher neuropathy frequency in patients with prediabetes indicates conceivable causative impact[25].

Some other researches like Tiftikcioglu IB et al., have reported alternate findings which may be attributed to disparity in the population studied as they did not find any difference in the NCS of prediabetics and healthy controls. Tiftikcioglu IB et al., in their cross-sectional study did not find any significant difference in the NCS of prediabetics and healthy controls[26].

The recent research findings of Lin Y et al., like our study also indicate that nerve damage in the form of polyneuropathy begins in the prediabetic stage[27].

The peripheral neuropathy evaluated by changes in NCS of nerves in the form of increased latency and decreased NCV was found in prediabetics in our study. Also, the increased FBS ≥100 mg/dL was associated with the impairment of nerve function of sensory peripheral nerves in prediabetics suggesting that in prediabetics, glucose dysmetabolism in the form of hyperglycaemia increases the oxidative stress of the nerves which causes their demyelination and eventual impairment of their functions.

With the significant association of the latency and NCV with prediabetes as observed in our study, it can be said with confidence that the damage to the nerves start early in the hyperglycaemia of ≥100 mg/dL and that NCS during prediabetic stage may be helpful in taking measures to decrease the development of diabetic neuropathy.

Conclusion

The present study was undertaken to evaluate peripheral neuropathy in prediabetics using NCS, as NCS are useful in identifying the development of incipient peripheral neuropathy in the early stages of hyperglycaemia. We conclude from our findings that demographic and anthropometric parameters (age, height, weight, BMI) did not play any significant role in the development of peripheral neuropathy in prediabetics and the impairment of physiology of peripheral nerves in the form of abnormality in conduction of impulses i.e. peripheral neuropathy in prediabetics as evident from the increased latency in both and decreased NCV in right sensory nerves is mainly due to increased blood sugar levels in them as compared to healthy normoglycaemic controls.

Limitations

Duration of prediabetes could not be ascertained because prediabetes is an incidental finding.

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