Original Article

The relation between HbA1c variability and diabetic autonomic neuropathy among type-2 diabetic patients

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Abstract:

Background: Diabetic autonomic neuropathy (DAN) is the most neglected major and widespread microvascular complication of type-2 diabetes mellitus, involving multiple body organs. DAN is a subtype of diabetic peripheral neuropathy. ***Objective:*** To investigate the relationship between the variability of HbA1c and diabetic autonomic neuropathy in type-2 diabetes patients. ***Materials and methods:*** This study recruited a total of 150 type-2 diabetic patients to screen for diabetic autonomic neuropathy and estimated quarterly levels of HbA1c were performed within the year before enrollment. With a non-invasive procedure, DAN was validated by careful history taking, anthropometric assessment, clinical manifestations and neurological assessment. ***Results:*** Out of 150 type-2 diabetic patients, recruited randomly, where 81 were female and 69 were male. Among all patients 29 (19.33%) had been screened positive for DAN which showed higher HbA1c than non-DAN patients. Different autonomic neuropathic dysfunction among total diabetic patients were also studies and found that the highest prevalence of sexual dysfunction among all autonomic dysfunction prevalence which is 16.66% whereas the lowest prevalence was postural hypotension that is 6.66%. The second higher prevalence is urinary incontinence (10.66%). Abnormal sweating (9.33%) and nocturnal diarrheas (7.33%) are in third and fourth position respectively. No significant ($p>0.05$) differences were found in the case of BMI, sex, systolic, and diastolic blood pressure between DAN and non-DAN. Data shows a major ($p<0.05$) risk factor for DAN has also been the prolonged period of diabetes and older age. ***Conclusion:*** The study indicates that the increased level of HbA1c in type-2 diabetic patients is closely correlated with DAN and may be considered a potent predictor of DAN in the recruited patients.

Keywords: Diabetic autonomic neuropathy, diabetic peripheral neuropathy, HbA1c, diabetes mellitus, type-2 diabetes.

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The most severe and overlooked complication of diabetic peripheral neuropathy that induces parasympathetic and/or sympathetic nerve damage in people with diabetes, excluding other causes of neuropathy, is diabetic autonomic neuropathy[1].

diabetes. Its prevalence depends on the form of diagnosis, patient cohort features, and the type of diabetes evaluated[2]. Consistent hyperglycemia and hypoglycemia cause oxidative stress in nerves, ultimately resulting in autonomic neuropathy[3].

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As a result of damage to the sensory, autonomic, and motor nerves, diabetic peripheral neuropathy develops and may have different effects and deficits. Somatic and autonomic neuropathy manifestations are the most common, and early diagnosis of these subtypes is recommended[4]. Globally, diabetes mellitus is a massive health problem[5]. The worldwide prevalence of diabetes was 9.3%, according to the International Diabetic Federation, which will be raised 10.9% in 2045 (between 20-79 years)[6]. This immense pressure is related to complications[7]. 4.2 million peoples have died from complications related to diabetes[6]. Chronic hyperglycemia as calculated by HbA1c is a known risk factor for diabetes-related microvascular disease and is used to evaluate and guide clinical care of people with diabetes[8-9]. Glycosylated hemoglobin (HbA1c) serves as a long-term diabetes regulation index and HbA1c is considered to be good glycemic control by 7.0% of patients[10]. The sympathetic, parasympathetic, and enteric nerves are affected in the autonomic disease. Myelinated and non-myelinated nerve damage has been reported[11]. They also reported that autonomic neuropathies have been found irreversible by several experts. The initial symptoms linked to diabetes neuropathy are traceable to John Rollo's writings, and in Pavy's papers, the sweating symptom was described[12]. In type-2 diabetes cases, subclinical autonomic dysfunction can develop within a year of diagnosis, but clinical signs of autonomic neuropathy occur long after diabetes starts. In symptomatic autonomic neuropathy, the symptoms and signs differ greatly as they affect every organ of the body. The symptoms and signs of DAN differ significantly and depend on the affected organ, such as postural hypotension (cardiac), nocturnal diarrhea (gastrointestinal), abnormal sweating (skin), urinary incontinence and sexual dysfunction (genitourinary system), etc.[13-14]. DAN is normally intermittent and can survive without deterioration for several years, but full remission is rare[15]. For patients with type-2 diabetes, aggressive blood glucose regulation is important, as it can avoid microvascular and macrovascular complications[16]. In type-2 diabetes, glycemic control can help to delay the progression of diabetic peripheral neuropathy[17]. To improve the manifestation, decrease sequence and improve personal satisfaction American diabetes association rule suggested early acknowledgment and treatment of DAN[18-19]. A survey in Bangladesh estimated that DPN prevalence was 19.7% in type-2 diabetic patients[20] and also 24% DPN (Sensory and motor) neuropathy in Bangladesh[21], but there is no DAN study in Bangladesh as far as our knowledge is concerned. The main objectives of this research were to consider the relationship amid the variability of HbA1c and diabetic autonomic neuropathy for the early assessment of the risk factors of DAN among diabetic patients and control of HbA1c and appropriate preventive measures.

Material and methods:

This study was performed in the outpatient department of the Rajshahi Diabetic Association General Hospital, Rajshahi, Bangladesh, from July 2017 to December 2020. A total of 150 patients with type-2 diabetes were randomly included with or without diabetic autonomic neuropathy and met the inclusion requirements (age>25, both male and female, patients meeting the WHO type-2 diabetes mellitus criteria) and exclusion criteria (other known cause of autonomic neuropathy, taking any drugs to cause autonomic neuropathy, other types of diabetics rather than DM-2). This study was done mainly depend upon the careful history taking, sign symptom and simple bedside non-invasive examinations and investigations. Data were collected from the outpatient department by a self-prescribed data collection sheet containing a questionnaire to assess the autonomic neuropathy symptoms from the patient's diabetic record book containing personal demographic data, investigation records, treatment, and other diseases, through careful personal interview of patients and their spouses, anthropometric measurement, investigation, examination with the written consent of all patients. The HbA1c level was determined once every 3 months using ionic exchange HPLC (IE-HPLC) in the D-10 hemoglobin analysis system (Bio-Rad). Postural hypotension was confirmed by measuring blood pressure in sitting and laying the patient. Nocturnal diarrhea, sexual dysfunction, urinary incontinence, abnormal sweating was depended upon the careful history taking examination and investigation records on which outdoor patient primary treatment is started. Diabetic peripheral neuropathy (DPN) was assessed by Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS). At least one autonomic symptom with DPN confirms the diagnosis of DAN.

All of the data are articulated as mean±SD (standard deviation) of the mean. Data have been analyzed with IBM SPSS software (version 20) and compared by Student t-test. P-value <0.05 was considered statistically significant.

Results:

The clinical parameters of all participants are summarized in Table 1. Out of 150 type-2 diabetic patients, recruited randomly, where 81 were female and 69 were male. Among all patients 29 (19.33%) had been screened positive for DAN. Out of 29 DAN patients, 17 patients were male and 12 patients were female. However, when compared to the without DAN patient, DAN patients presented significantly ($p<0.05$) higher age 55.00±5.57 years, higher diabetic duration 9.79±5.78, higher HbA1c 11.75±2.21 level than non-DAN patients where mean age was 50.42±8.96 years, mean duration of diabetes 5.94±3.72 and mean HbA1c 9.72±1.89 has been shown. In our study, no significant ($p>0.05$) deferent was found in the case of BMI, sex, systolic, and diastolic blood pressure between DAN and non-DAN. Data shows the prevalence of this investigation of diabetic autonomic neuropathy is 19.33% (Table 1).

Table 1: Statement on autonomic neuropathy of type-2 diabetes (n = 150)

Parameters	Age	Body mass index	Blood pressure (systolic)	Blood pressure (diastolic)	Duration of diabetes	HbA1c level	Total (male, female)
Diabetic autonomic neuropathy	55.00 ± 5.57	26.14 ± 3.91	128.42 ± 14.78	76.87 ± 8.12	9.79 ± 5.78	11.75 ± 2.21	29 (19.33%) (M-17, F-12)
Without diabetic autonomic neuropathy	50.42 ± 8.96	25.72 ± 2.83	123.74 ± 12.17	77.14 ± 13.61	5.94 ± 3.72	9.72 ± 1.89	121 (80.66%) (M-52, F-69)
p-value	0.000	0.134	0.104	0.756	0.000	0.000	-

HbA1c = Glycosylated hemoglobin, M = Male, F = Female.

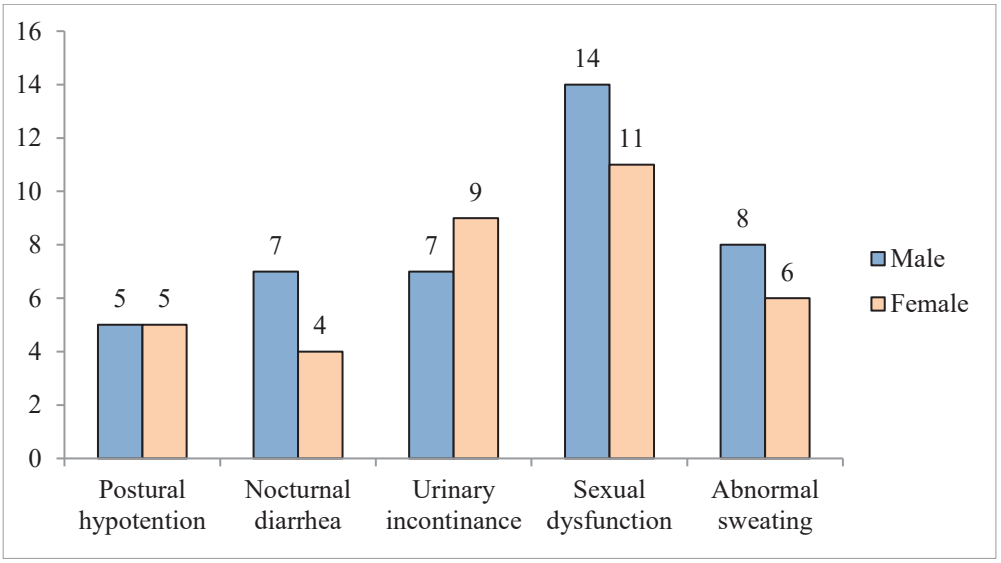

Figure 1. Frequency of impaired autonomic neuropathic signs in patients with DAN according to sex (among 17 males, and 12 females).

The most frequently observed symptoms were sexual dysfunction in the case of males while urinary incontinence was the most frequent one in females and the number was 14 and 9 respectively. The second most frequent symptom in males was abnormal sweating. The signs like postural hypotension, nocturnal diarrhea, and urinary incontinence were observed in 5, 7, 7 males in each case among the total number of male patients. On the other hand, the least frequent symptom with DAN was nocturnal diarrhea in the case of females (Figure 1).

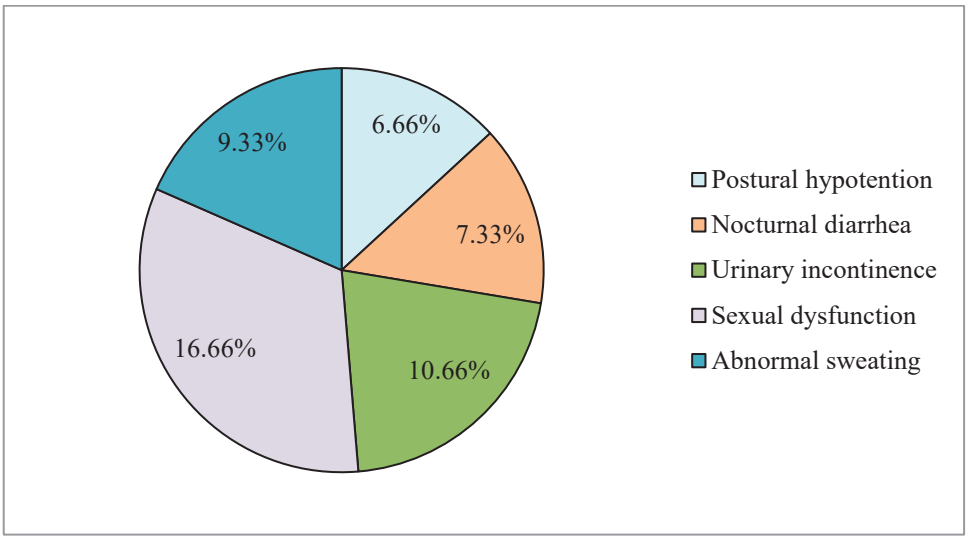

Figure 2. Prevalence distribution of different autonomic neuropathic dysfunction among total diabetic patients.

Figure 2 shows the highest prevalence of sexual dysfunction among all autonomic dysfunction prevalence which is 16.66% whereas the lowest prevalence was postural hypotension that is 6.66%. The second higher prevalence is urinary incontinence (10.66%). Abnormal sweating (9.33%) and nocturnal diarrheas (7.33%) are in third and fourth position respectively.

Discussion:

The present study explored the relationship of HbA1c with DAN in type-2 diabetic patients in the present study. The strength of the analysis is that an important and independent contributor to DAN was found to be the increased variability of HbA1c. In our study, the mean age of the DAN patients was 55.00±5.57 years, the mean duration of diabetes of DAN patients were 9.79±5.78 years and mean HbA1c level 11.75±2.21 significantly higher than mean age 50.42±8.96, mean duration 5.94±3.72 and mean HbA1c level 9.72±1.89 of non-DAN patients. These is important and indicating that increasing age, prolong duration of diabetes and higher HbA1c level raise the risk of DAN compare to non-DAN patients. According to this study it means that the mean age, mean duration of diabetes and mean HbA1c level of DAN participants is more than the mean age, mean duration of diabetes and mean level of HbA1c of DPN (diabetic sensory and motor neuropathy)[21]. That's means diabetic Sensory and motor neuropathy ultimately progress to autonomic neuropathy with increasing age, duration of diabetes and HbA1c level. According to Thekkur et al.[22], older age has an independent impact on autonomic neuropathy and diabetes duration also has a positive correlation with autonomic neuropathy screening. Valensi et al.[23] and Kempler et al.[24] also demonstrate that the continuation of the course of the disease phase and its occurrence increases in the progression and degree of DAN in direct proportion to the duration of the disease. Dimitropoulos et al.[1] reported DAN prevalence in type-2 diabetes range from 20% to 73%, which is consistent with the present study. Another community-based survey from a diabetic center in India recorded that DAN prevalence among diabetic patients is 10.6 %, as reported by Thekkur et al.[22], which is significantly lower than the current study that is 19.33%. This indicates DAN prevalence of outpatients is more than community-based diabetes patients. Ziegler et al.[25] reported the same statement. This difference may also due to our study were among only type-2 diabetic patients but Indian studies included all types. The prevalence of DAN dependent on the type of diabetes, cohort and diagnostic method[26]. Signs of diabetic autonomic neuropathy (DAN) are found in 3.5-6% of patients at the onset of the disease, and in 100% of patients with prolonged

duration of diabetes mellitus[27-28] and our result within the above range. The prevalence of postural hypotension in our sample is 6.66%, which is consistent with the 7.4% recorded in type-2 diabetes patients in a study. Gupta et al.[29] and Sharma et al.[30] recorded a 5.7% and 6% occurrence of postural hypotension respectively. In DAN patients, nocturnal diarrhea and fecal incontinence are common. Prevalence of diarrhea reported 20% (type-1 and type-2), bladder dysfunction 25% in type-2 diabetic patients[31-32] whereas our results 7.33% and 10.66% respectively. This variation may be due to our study included only nocturnal diarrhea and urinary incontinence compared to their various symptoms, various types of diabetes, study time frame and different population, etc. Sexual disorder encompasses erectile dysfunction (ED), retrograde ejaculation, and female sexual dysfunction, which is more prevalent in diabetes[33]. In our sample, the incidence of sexual dysfunction (SD) in males (9.33%) is marginally higher than in females (7.33%), similarly reported by Vapaeimanesh et al.[34] that women report SD at a rate slightly lower than men. There was no significant association between systolic and diastolic blood pressure and peripheral neuropathy[35], which is the same as our results. Assessment of HbA1c variability reflects the long-term glycemic variability and may promote oxidative stress[36]. Oxidative stress deprives the nerve cells of oxygen, impedes growth, and leads to cellular apoptosis or cell death; this contributes to the development of progressive neuropathy or DAN[37-38]. In this study, increasing levels of HbA1c above almost 9.0% were found to be significantly correlated with increased DAN prevalence. The results of this study were consistent with others[39], who suggested that peripheral neuropathy in increasing HbA1c groups had a higher prevalence. It has been shown that reducing HbA1c below or around 7% decreases microvascular and neuropathic risks by the American diabetes association and others[18]. The duration of diabetes and the degree of glycemic regulation depends on the magnitude of diabetic peripheral neuropathy[40]. Poor glycemic control is an important determinant of the progression of autonomic nerve dysfunction in type-2 DM[41]. So, the variability of HbA1c is an independent risk factor for DAN.

Conclusion:

Findings of this study suggest that increasing HbA1c level is significantly associated with increased prevalence of DAN and the risk increases markedly at HbA1c levels ≥9.72%. The prevalence and risk of DPN also increased with advanced age, longer duration of diabetes, etc. Careful assessment of the risk factors of DAN among diabetic patients and control of HbA1c and appropriate preventive measures are thus recommended.

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Conflict of interest: The authors declare that there is no competing interest.

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Ethics approval: This study was approved by ethical research committee of Institutional Animal, Medical Ethics, Biosafety and Biosecurity Committee (IAMEBBC) for Experimentations on Animal, Human, Microbs and Living Natural Sources at the Institute of Biological Sciences, University of Rajshahi, Bangladesh.

Author's contributions: MAH designed the study, performed the experimental work, collected data, interpreted data, performed the statistical analysis, and wrote the first draft of the manuscript. SMSI, MKS, IM supervised the work and contributed scientific advice and helped in study design. SMSI provided technical support, editing and approval of final draft. All authors reviewed and approved the final version of the manuscript.

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