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CO RELATION OF CARDIAC AUTONOMIC NEUROPATHY AND GLYCOSYLATED HAEMOGLOBIN IN TYPE 2 DIABETES PATIENTS

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ABSTRACT

Fifty patients of type 2 diabetes mellitus were studied to assess the correlation between cardiac autonomic dysfunction and glycosylated haemoglobin (HbA1c). Five simple bedside tests based on cardio-vascular reflexes (heart rate response to standing, heart rate response to valsalva manoeuvre, heart rate variation during deep breathing, blood pressure response to standing and blood pressure response to sustained hand grip) were carried out and glycosylated haemoglobin of each patient was measured.

Cardiac autonomic dysfunction was found in 56% diabetics and raised glycosylated haemoglobin was found in 76% patients. Incidence of parasympathetic autonomic neuropathy was 56 % in comparison to sympathetic neuropathy ,which was 20 %, suggesting that parasympathetic pathway may be more sensitive for detection of cardiac autonomic neuropathy. Highest incidence of cardiac autonomic neuropathy has been observed between age group of 51 to 60 and as the duration of diabetes increases the incidence of cardiac autonomic neuropathy also increases. Significant correlation of 73.9% has been observed between cardiac autonomic neuropathy and glycosylated haemoglobin.

INTRODUCTION

Diabetes Mellitus is a disease of complex aetiology characterised by disturbances of carbohydrate metabolism leading to variable degree of carbohydrate intolerance. Currently around 80 million people of India suffer from diabetes and globally around 463 million people having diabetes, which is 8.8 % of the population [1]. Diabetic autonomic neuropathy (DAN) is one of the microvascular complications of diabetes [2]. DAN causes autonomic dysfunction of many organs and cardiovascular autonomic dysfunction due to diabetes (CAN) is the most life-threatening condition [7].

Diabetic autonomic neuropathy is fairly common amongst Indian Type 2 diabetics and the incidences rises to an alarming proportion of 56 % in long standing diabetics. The development of symptomatic autonomic neuropathy in patients with diabetes is an ominous sign.

Both parasympathetic and sympathetic nervous system are involved in diabetic cardiac autonomic neuropathy. Parasympathetic nerve fibres are affected earlier than sympathetic nerve fibres. Integrity of cardiac autonomic function can be assessed with several simple bedside test found to occur with age and duration of diabetes. Indian studies on cardiac dysautonomia have reported a prevalence rate between 20-60%(26).

Present study was designed to evaluate the incidence and sensitivity of various tests for cardiac autonomic neuropathy in subjects with long standing diabetes and its co-relation with glycosylated haemoglobin level (HbA1C).

DISCUSSION

The prevalence of Type2 diabetes mellitus is increasing in India. Diabetic patients are susceptible to a series of complications that cause morbidity and premature mortality. Accumulated evidence suggests that hyperglycemia accelerates the development of diabetic complications.

CAN found to occur with age and duration of diabetes. Indian studies on cardiac dysautonomia have reported a prevalence rate between 20-60%(26)." Mohan et al reported cardiac dysautonomia in 35.7% among 336-type2 diabetic patients.(17) Microangiopathy is likely to be major contributor for high prevalence of cardiac autonomic neuropathy.

In our study an attempt was made to correlate the incidence of cardiac autonomic neuropathy with glycosylated haemoglobin. Out of 50 patients of type2 diabetes mellitus, 28 patients (56%) had cardiac autonomic neuropathy. 38 patients (76%) had raised glycosylated haemoglobin (>7%), out of which 21 patients (76%) also had cardiac autonomic neuropathy. When properly assayed the percent of glycosylated haemoglobin gives an objective assessment of metabolic control of diabetes for preceding 3 - months periods. We suggest that all the long standing type2 diabetes mellitus subjects with poor glycemic control for long periods, should be seriously assessed for cardio-vascular reflexes, so that poor prognosis may be warned well in advance.

Silent myocardial infarction and sudden cardio-respiratory arrest during anaesthesia or surgery makes for more awareness about diabetic cardiac autonomic neuropathy.

CAN is characterized by predominant damage to the vagus nerve innervating the heart with subsequent upper hand in sympathetic drive resulting in resting cardiac autonomic balance characterized by resting tachycardia [5]. However, sub-clinical CAN ensues largely from functional alteration of autonomic nerves and is considered a reversible disorder.

Reduced HRV is the earliest sign of subclinical CAN.HRV is reduced in type 2 diabetic patients with CAN compared to those without CAN Sympathetic nervous system via right and left cardiac nerves innervate atria and ventricles (including conducting system). Right cardiac nerve predominantly innervates SA node and it has more influence on heart rate (HR) and on the other hand left cardiac nerve predominantly controls myocardial contractility. Thus, the net effect of sympathetic stimulation is to increase HR, conduction velocity

and strength of myocardial contractility. Parasympathetic nervous system through right and left vagus nerves innervate predominantly atrial muscle and very sparsely ventricular myocardium. Right vagus nerve primarily innervates the SA node and left vagus nerve innervates mainly atrio-ventricular node (AV node). Thus, the net effect of parasympathetic stimulation is to decrease HR and slightly decrease strength of heart contractility. Dynamic interaction occurs between sympathetic and parasympathetic divisions. However, during rest, parasympathetic tone predominates over sympathetic tone. Therefore, resting HR is mainly controlled by the vagal nerve tone [18]. Hence, resting HR is a marker of vagal nerve function status [18].

DAN is quite common, yet remained mostly undiagnosed and micro-vascular complications of T2DM are affecting many organ systems (gastrointestinal, genitourinary, cardiovascular) of the body [7]. However, CAN is clinically the most important form of DAN as it is associated with life-threatening complications (arrhythmias, silent MI) and sudden death [5]. The underlying pathophysiology of DAN is still unclear; however, it has been attributed to chronic hyperglycemia induced oxidative stress and inflammation with subsequent neuronal injury and death [16, 17, 18, 19].

Hyperglycemia induced oxidative stress and inflammation

Oxidative stress and inflammation are interlinked, as one causes another and vice versa, and they occur even under normal physiological conditions. However, these two phenomena last for a brief period as they are suppressed by intrinsic negative feedback mechanisms; increased production of antioxidants and anti-inflammatory cytokines [19]. But, in certain chronic diseases like T2DM these altered states of internal environment sustain for a prolonged period as positive feedback mechanisms overrides the negative feedback mechanisms [19]. In addition, reduced parasympathetic nerve function due to autonomic dysfunction in T2DM leads to chains of inflammatory responses [20]. Thus, oxidative stress and inflammation are very prominent features in T2DM linked to both microvascular and macrovascular complications associated with T2DM [19]. Certain cells are particularly susceptible to hyperglycemic induced injury as their intracellular glucose concentration increases in a linear fashion with respect to the extracellular glucose level [18]. This is especially true for endothelial cells and neurons as the transport of glucose through their cell membranes is mediated by insulin-independent GLUTs [18].

Hyperglycemia induces overproduction of mitochondrial superoxide in endothelial cells of large and small blood vessels and neuronal axons [5]. This leads to intracellular accumulation of reactive oxygen species (ROS) with subsequent activation of five major metabolic pathways: polyol pathway flux, increased formation of advanced glycation end-products (AGEs), increased expression of the receptor for AGEs and its activating ligands, activation of protein kinase C (PKC) isoforms, and overactivity of the hexosamine pathway [5, 18]. Over activity of these five metabolic pathways leads to accumulation of toxic metabolic derivatives and pro-inflammatory substances, bringing about following consequences: vascular endothelial damage, vasoconstriction, neuronal hypoxia, neuronal cell necrosis, neuronal apoptosis and axonal degeneration (Figure 1) [5, 18, 20].

Impairment of autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes.

The T2DM patients with a higher age, longer duration of diabetes, poor and perhaps unstable glycaemic control, comorbid diabetic polyneuropathy, retinopathy and nephropathy, hypertension (on treatment), and other cardiovascular risk factors (in particular obesity and metabolic dyslipidaemia) are high risk of developing CAN [24].

Detecting CAN at subclinical stage is of paramount importance to provide early intervention on modifiable risk factors of CAN to prevent progression CAN to its severe or advanced form

Gely determined by changes of autonomic nervous system control (predominantly by the vagal tone) and the stretch of SA node [20]. On the contrary, long-term measurement of HRV obtained through 24-hour Holter ECG can be influenced by concomitant illness, use of medications, and lifestyle factors (exercise, stress, smoking, etc.) in addition to afore mentioned factors [20]. HRV is also varies due to other physiological factors . Short-term HRV (5 minutes) measurement is a reliable technique to detect autonomic dysfunction [9]. HRV describes the variations of both instantaneous heart rate and RR intervals which in turn reflect the cardiac autonomic nervous control [18]. HRV measurement obtained from 5 min-ECG recording represents marker for the measurement of resting autonomic tonic activity; the balance between sympathetic & parasympathetic nervous activity at any instant. Thus, alteration of HRV can detect the impairment of resting sympathetic and parasympathetic activity individually and shift of the normal sympathovagal balance.

MATERIALS AND METHODS

50 diagnosed patients of Type2 diabetes mellitus were selected from diabetic clinic. Glycosylated haemoglobin of all 50 patients was measured. Patients of hypertension, ischemic heart disease and autonomic neuropathy due to other etiology were excluded from the study. All the patients were subjected to the following tests

Tests reflecting parasympathetic involvement:

- Immediate Heart rate response to standing
- Heart rate response to Valsalva maneuver
- Heart rate response to deep breathing.

Tests reflecting sympathetic involvement:

- Orthostatic hypotension
- Blood pressure response to sustained hand grip.

Observation

Out of 50 patients of type2 diabetes mellitus, 28 patients (56%) had cardiac autonomic neuropathy. Parasympathetic dysfunction was seen in 28 patients (56%) while sympathetic dysfunction was seen in 10 patients (20%). (Table No.1) Out of 50 patients of Type2 diabetes meliitus, 38 patients (76%) had raised glycosylated haemoglobin. Cardiac autonomic neuropathy with raised glycosylated haemoglobin was present in 21 cases (76 %) (Table No.2)

Table 1. Autonomic Neuropathy In Type 2 Dm Patients

Sr No	Type of autonomic neuropathy	No of type 2 DM patients	No of type 2 DM patients having autonomic neuropathy	Percentage
1	Parasympathetic autonomic neuropathy	50	28	56
2	Sympathetic autonomic neuropathy	50	10	20

Table 2. Levels Of Glycosylated Haemoglobin In Type 2 Dm Patients

Glycosylated haemoglobin (HbA1C)	No. of patients	Percentage	No.of patients having cardiac autonomic neuropathy
0-6	12	24	7
7-10	33	66	16
11 or more	5	10	5

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