Cardiovascular autonomic dysfunction in type 2 diabetes mellitus and essential hypertension in a South Indian population

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Diabetes mellitus (DM) and hypertension (HTN) are risk factors for cardiovascular disease. There has been an alarming rise in their incidence especially in developing countries like India. The global prevalence of diabetes cases is 285 million, of which India harbors 50.8 million cases, whereas the prevalence of HTN globally is 972 million, and India accounts for 65.5 million cases. The coexistence of type 2 diabetes mellitus (T2DM) and essential HTN is common. Previous studies have demonstrated that both diabetes and HTN impair cardiovascular autonomic function.[1] However, the combined effects of diabetes and HTN on cardiovascular autonomic control have not been fully understood. We hypothesize that the association of these 2 diseases might have an additive or synergistic role in affecting the cardiovascular system and in hastening autonomic dysfunction. Thus, the objective of this study was to assess the presence of cardiovascular autonomic dysfunction in T2DM and HTN patients, and those affected with both diabetes and HTN.

A case-control study was conducted after approval from the Institutional Ethics Committee and obtaining written consent from all participants from February 2007 to June 2009 on 63 volunteers in the age group of 37-65 years at Osmania Medical College, Hyderabad, South-India. The inclusion criteria were normotension, HTN and T2DM, and the subjects were divided into 4 groups: non-diabetic normotensives (group I, control group), non-diabetic hypertensives (group II), diabetic normotensives (group III), and diabetic hypertensives (group IV). Plasma glucose levels were assessed by the glucose oxidase method and sphygmomanometer (Diamond, Pune, India) was used to measure left arm arterial blood pressure (BP). Lead II ECG was recorded using an automated ECG machine (Cardiart 408, BPL Ltd., Bengaluru, India) for calculating heart rate (HR). Fasting plasma glucose level of ≤110 mg/dL without the

previous diagnosis of DM were labeled non-diabetics, whereas levels >110 mg/dL or within normal range but with a previous history of diabetes and treatment were labeled diabetics. A systolic BP (SBP) of ≤140 mm Hg and diastolic BP (DBP) of ≤90 mm Hg without the previous diagnosis of HTN were labeled normotensives, whereas SBP >140 and/or DBP >90 mm Hg, or within normal range but with previous history of HTN or treatment were labeled hypertensives. The exclusion criteria were (a) type 1 diabetes and secondary causes of diabetes, (b) secondary causes of HTN, (c) gross nutritional deficiency, (d) exposure to alcohol, heavy metals, neurotoxic drugs, and drugs affecting the autonomic function, (e) established diseases like ischemic heart disease, stroke, nephropathy, and (f) symptoms related to autonomic neuropathy, such as, postural hypotension, localized sweating, urinary incontinence, urinary retention, constipation, and diarrhea.

Autonomic function tests included orthostatic change in HR, orthostatic change in BP, HR response to deep breathing, Valsalva maneuver, sustained handgrip test, and cold pressor test. Baseline HR and BP were recorded in a lying down position, after which the subject was made to stand (orthostatic change). A rapid increase in HR maximal at around the fifteenth beat after standing, with a subsequent relative bradycardia, minimal at around the thirtieth beat occurs through a vagally mediated response. The HR at the fifteenth and thirtieth beat is estimated, and a 30/15 ratio computed. A ratio of <1.00 is considered abnormal. In response to standing, there is an immediate fall in BP due to pooling of blood in the legs, which in the presence of normal baroreceptor-initiated, centrally mediated sympathetic reflex, is rapidly corrected by peripheral vasoconstriction and tachycardia. A fall in SBP of >30 mm Hg and DBP for >10 mm Hg is considered abnormal. Subjects were asked to breathe deeply at a rate of 6 breaths per minute with equal time for inspiration and expiration (5 seconds each). Autonomic insufficiency was considered present when the decrease in HR was <10 beats/minute. The Valsalva maneuver was performed by asking subjects to blow into a mercury manometer maintaining the pressure at around 40 mm Hg for 30 seconds. The reflex response to the Valsalva maneuver includes tachycardia and peripheral vasoconstriction during strain, followed by bradycardia after release. The Valsalva ratio is calculated by dividing the maximum HR during the maneuver with the minimum HR after the maneuver. If the ratio is <1.1, it is abnormal. Sustained handgrip test was performed by asking the subjects to compress the hand dynamometer (Jetter & Scheerer, Tuttlingen, Germany) with maximum effort using the dominant

Table 1 - Demographic and clinical data of the study participants, including normotensives, hypertensives, and diabetics.

Parameters	Non-diabetic subjects		Diabetic subjects	
	Normotensives (n=18)	Hypertensives (n=12)	Normotensives (n=15)	Hypertensives (n=18)
Age, in years	50±6	52±4	50±7	51±8
Male gender (%)	33	50	13	44
Duration of diabetes, in years	-	-	9±4	8±5
Duration of hypertension, in years	-	7±4	-	10±5
Smoking (%)	17	50	33	33
Alcohol consumption (%)	17	50	27	22
Baseline SBP, in mm Hg	126±7	148±14	130±10	154±16
Baseline DBP, in mm Hg	85±8	100±7	84±8	99±7
Baseline HR, in beats per minute	81±14	74±10	83±8	86±12
SBP on sudden standing, in mm Hg	123±9	133±25	138±17	148±17
DBP on sudden standing, in mm Hg	87±6	110±13	90±7	96±7
30/15 ratio (M ± S.E.)	1.04±0.01	1.01±0.01	1.00±0.02	1.04±0.02
HR during deep breathing, in beats per minute	74±21	71±7	76±7	83±10
Valsalva ratio (M ± S.E.)	1.18±0.02	1.18±0.04	1.22±0.03	1.16±0.03
SBP during sustained hand grip, in mm Hg	143±10	162±10	145±21	164±20
DBP during sustained hand grip, in mm Hg	98±4	112±10	96±11	103±10
SBP during cold pressor test, in mm Hg	145±12	161±10	148±19	167±15
DBP during cold pressor test, in mm Hg	105±7	115±5	101±10	109±13

SBP - systolic blood pressure, DBP - diastolic blood pressure, HR - heart rate,
Numbers represent mean ± standard deviation except those specified, (%) represents percentage of subjects,
and (M ± S.E.) represents mean ± standard error

hand to note the maximum isometric tension (Tmax) developed. Thereafter, the subjects were asked to compress the dynamometer maintaining 30% of Tmax for 5 minutes. The BP was recorded before the release of the grip. In autonomic disorder, the rise in SBP and DBP is <10 mm Hg. For cold pressor test, both the subject's hands were kept immersed up to the wrists in cold water (4^0C), and BP was recorded at the end of one minute. Failure of the BP to rise by 16-20 mm Hg systolic, and 12-15 mm Hg diastolic was taken as an indication of autonomic neuropathy.[2]

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 13.0 was used for statistical analysis. Differences in percentages were analyzed using one-sided Fisher exact test. A $p<0.05$ was considered significant.

Table 1 shows the demographic and clinical data of the participants. Changes in the cardiovascular parameters were calculated from the baseline and compared with the normal values. Cardiovascular autonomic neuropathy (CAN) was considered present when 3 or more tests out of 6 were abnormal. Group I did not have any recorded CAN, whereas 42% of subjects in group II, 80% in group III, and 88% in group IV had CAN (**Figure 1**). The prevalence is significantly high in non-diabetic hypertensives ($p=0.005$), diabetic normotensives ($p=0.000$), and diabetic hypertensives ($p=0.000$) compared to controls, namely, non-diabetic normotensives, whereas the prevalence is slightly higher in diabetic hypertensives compared with diabetic normotensives, which is statistically not significant ($p=0.40$).

Cardiovascular autonomic neuropathy occurs as a result of damage to autonomic nerve fibers that innervate the heart and blood vessels leading to abnormalities of
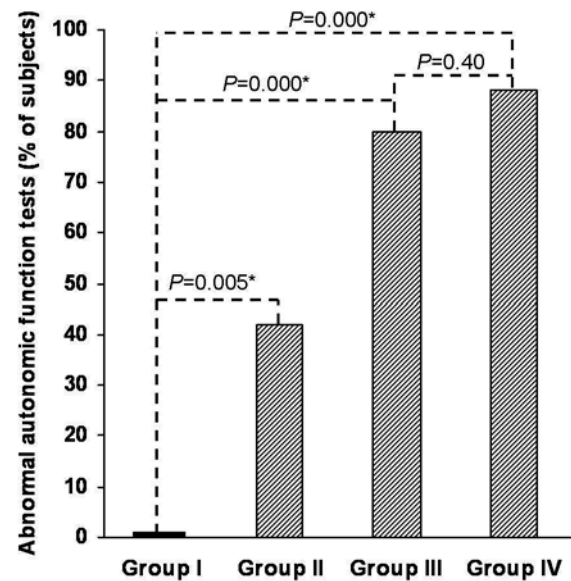
Figure 1 - Percentage of subjects with abnormal autonomic functions.

HR control and vascular dynamics. The CAN usually begins with impairment of the parasympathetic system, followed by damage to the sympathetic system; the process is patchy with increasing involvement of both systems.[3] The CAN in diabetic normotensives was 80% in this study against previous studies showing a prevalence between 1-90%.[3] The prevalence in India is reported between 54-60%.[4,5] Lefrandt et al[6] commented that autonomic dysfunction in diabetes does not solely depend on autonomic nervous system function, but also on the integrity of the cardiovascular autonomic reflex loops. Increased tunica intima or media thickness at the site of the baroreceptors, reduced vascular distensibility, endothelial dysfunction, and impaired cardiac contractility also contribute to cardiovascular autonomic dysfunction. Cardiovascular autonomic neuropathy in non-diabetic hypertensives is 42%, whereas it is 88% in diabetic hypertensives. The diabetic normotensives and diabetic hypertensives examined in our study were age-matched and had a similar duration of diabetes. Therefore, the cardiovascular autonomic dysfunction in this group may be due to the adverse effects of HTN. The CAN was reported as high as 80.9%,[7] with coexistence of T2DM and HTN, but in our study the occurrence was 88%. Takahashi et al[1] reported that HTN along with diabetes synergistically influenced cardiac autonomic control. Frontoni et al[8] concluded that insulin resistance precedes the onset of HTN and contributes to its pathogenesis, mainly through sympathetic activation. Taken together, it may be suggested that insulin resistance may serve as the mechanism for the clustering of HTN and T2DM in impairment of autonomic functions.

There are a few limitations in this study. First, the sample size in each group is small. Second, we considered worsening of cardiovascular autonomic function in diabetic hypertensives due to the effects of HTN. However, the converse is also applicable, namely, cardiovascular autonomic dysfunction may increase the risk of development of essential HTN.

In conclusion, diabetes and HTN are 2 important causative factors for CAN. The coexistence of T2DM and HTN may synergistically cause progression of CAN.

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