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Archives of Applied Science Research, 2009, 1 (2) 57-66
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-508X

Overt Diabetic Complications in Obese Type 2 Diabetes Mellitus Patients from North India

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Abstract

Heredity is a major determining factor in the development of diabetes and obesity. Obesity decreases the number of insulin receptors in the insulin target cells throughout the body; thus reducing the metabolic effect of insulin. Our objective was to evaluate the complications in Type 2 diabetic (T2DM) patients from North India. The study was conducted on 300 patients with a mean age of 48.61 ± 9.96 (range 22-77 years). Lipid profile was estimated by using *Ecoline* Kits. Clinical parameters were analyzed and recorded for association. Out of the 300 diabetic patients (171 males and 129 females); 241 (127 males and 114 females) manifested one or more diabetic complications such as retinopathy (Rt); nephropathy (Np) and neuropathy (Nu). Out of these 241; 109 were obese and 132 were non-obese. Obese diabetics when compared to non obese diabetic patients showed statistically significant increase in the levels of serum total cholesterol (TC) ($p = 0.030$); serum Low Density Lipoprotein (LDL)-cholesterol ($p = 0.049$); Very Low Density Lipoprotein (VLDL)-cholesterol ($p = 0.008$); serum creatinine ($p = 0.047$) and decreasing serum High Density Lipoprotein (HDL)-cholesterol ($p = 0.000$). Single complications *viz* Rt; Np and Nu were manifested by 62.39; 10.19 and 16.51% obese T2DM patients respectively while 1.83% had Rt+Np; 7.34% had Rt+Nu and 1.83% showed all the three complications. The difference between obese and non obese subjects was highly significant ($p=0.000$). Our study also indicated that the prevalence of complications was 2.7-3.7 times high in obese diabetics in the North Indian population and showed significant association with lipid profiles.

Key Words: Type 2 Diabetes Mellitus; Obesity; Diabetic Complications; Clinical Parameters

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Introduction

The incidence of T2DM has been increasing rapidly in the past 2 decades and is expected to increase further [1; 2]. The World Health Organization (WHO) has estimated that the number of adults with diabetes will be more than double from an estimated 143 million in 1997 to 300 million by 2025 [3]. Prevalence of diabetes varies to some degree with sex and ethnicity for example it occurs more frequently in people of ≥ 20 years of age. T2DM is accompanied notably by a high prevalence of associated disorders; such as hypertension; atherogenesis; metabolic syndrome; myocardial infarction (MI); Retinopathy (Rt); Nephropathy (Np); Neuropathy (Nu); vascular diseases (cardiac; cerebral and peripheral); and cardiovascular disease (CVD); which lead to significantly high morbidity and mortality [4-9]. The chronic complications of diabetes mellitus translate into a significant economic burden on individuals and community at large [10].

According to International Obesity Task Force (IOTF); Greece shows the highest prevalence of both overweight and obese women (74%) and second highest in case of men (72%) [11]. The interrelationship between obesity and insulin resistance; dyslipidemia and hypertension may contribute to cardiovascular risk; but the extent is not known [12; 13]. However; few studies reveal that insulin resistance is not a necessary component of obesity [14]. Insulin affects mammalian lipid metabolism by stimulating synthesis of fatty acid in liver; adipose tissue and intestine. Since insulin is also known to increase cholesterol synthesis; various lipid fractions and plasma insulin may help in the prognosis of T2D patients and prevent complications or secondary disorders [15]. Various measures of adiposity and fat distribution; such as % body fat and waist girth; can more precisely assess the associations between obesity and T2DM. Therefore; in the present study an attempt was made to examine the combined association of fitness and obesity on T2DM in men and women and risk of diabetic complications (Rt; Np; Nu); serum lipid profiles and insulin levels in obese and non-obese T2DM patients.

Materials and Methods

Patient Selection:- The study was approved by the institutional ethical committee of the CSMMU; Lucknow. Patients with T2DM were enrolled from the outpatients attending the Diabetes Clinic of CSMMU; Lucknow; India. Screening and management of patients was done as per American Diabetes Association guidelines (American Diabetes Association. 2004) [16]. This study was conducted on 300 T2DM patients (22-77 yrs) with normal glucose tolerance test (GTT). A known diabetic on dietary control with the blood sugar load at 8-10 hour fasting and 2 hour post prandial were recorded. Among 300 T2DM patients; 109 were categorized as obese (Basal Metabolic Index; BMI >25 Kg/m^2). Patients (n=241) with overt complications of diabetes like Rt; Np and Nu were included in the study while those with ischemic heart disease; angina; MI; electrocardiogram abnormalities; those with other concurrent sickness like chronic liver disease; hypothyroidism or those on drugs like diuretics and oral contraceptives (women) were excluded from the study.

BMI Estimation:- Weight was recorded to the nearest kilogram (kg) with the subject standing on the weighing machine without shoes and using minimum of clothing. The same weighing machine was used for all the patients and the machine was tested with a known set of weights for any error [17]. Height was recorded with the subject erect; bare footed ; feet together; back and

heels against the upright bar of height scale; head upright in Frankfort horizontal plane 'look straight ahead'. The height measuring equipment consisted of a vertical bar with a steel tape attached. Attached perpendicularly to the vertical bar was a horizontal bar which was brought down snugly on the examinee's head [18]. Body Mass index was calculated from the formula;

$$BMI = \text{Weight in Kilograms} / (\text{Height in meters})^2$$

Patients were grouped in three categories viz. Underweight (BMI < 18.5 Kg/m2); Normal (BMI 18.5-25 Kg/m2) and Overweight (BMI > 25 Kg/m2). A detailed clinical history was taken and physical examination performed.

Biochemical Assays:- After an informed consent; 5-ml blood sample was taken in EDTA and plain vials for DNA analysis and biochemical estimations respectively. Investigations performed included detailed plasma insulin level; blood sugar profile including fasting (F) and two hours post-prandial (PP) and complete lipid profile. Lipid profile included Total Cholesterol (TC) (mg/dl); Low Density Lipoprotein (LDL)-cholesterol (mg/dl); High Density Lipoprotein (HDL)-cholesterol (mg/dl); Very Low Density Lipoprotein (VLDL)-cholesterol (mg/dl) and Triglyceride (TG) (mg/dl) in blood samples after overnight fasting. The estimations were done with *Ecoline* kits (Merck) using UV-Vis double beam spectrophotometer (Shimadzu).

Statistical Analysis:- Statistical analysis was applied to all data using SPSS software (v15.0). Mean ± SD (Standard Deviation) of all clinical parameters and diabetic duration were calculated in each age group ($\leq$ 40 years; 41-59 years and $\geq$ 60 years) as well as in BMI groups (< 18.5 Kg/m^2; 18.5-25 Kg/m^2 and > 25 Kg/m^2). P-values were calculated by 2x2 contingency table using paired t-test. All p values were two sided and differences were considered statistically significant for $P<0.05$; all significant data suggest the strength of association with clinical parameters. The diabetic complications in obese and non obese subjects were compared by using Pearson's chi-square test.

Results

The study was conducted on 300 T2DM patients (171 males (57%) and 129 females (43%)). The mean age ± SD of patients was 48.61 ± 9.96 (range 22-77 years). Out of 171 males; 34 were under 40; 96 between 41-59 and 41 above 60 years of age while out of 129 females; 37 were under 40; 79 were between 41-59 and 13 were above 60 years of age (Table 1). Clinical characteristics (Mean ± SD) of T2DM patients in different age groups have been detailed in Table 1.

Age Group (years) → Clinical Parameters ↓	≤40 (n=71)				P value	41-59 (n=175)				P value	≥60 (n=54)				P value	Total	P value
	Male (n=34)	P value	Female (n=37)	P value		Male (n=96)	P value	Female (n=79)	P value		Male (n=41)	P value	Female (n=13)	P value		(N=300)	
Diabetic Duration	2.87 ± 5.60	0.986	2.12 ± 2.79	0.033*	0.871	4.60 ± 4.60	0.638	3.53 ± 4.35	0.905	0.162	6.67 ± 7.59	0.188	7.52 ± 9.192	0.276	0.163	4.04 ± 4.99	0.000*
Body Mass Index(Kg/m2)	21.20 ± 3.26	0.441	26.5 ± 4.87	0.218	0.210	23.16 ± 3.50	0.141	25 ± 5.14	0.251	0.146	22.88 ± 3.33	0.594	27.48 ± 4.143	0.336	0.752	23.95 ± 4.46	0.270
Waist Hip Ratio(WHR)	0.915 ± 0.065	0.143	0.87 ± 0.07	0.241	0.073	0.945 ± 0.11	0.032*	1.01 ± 0.98	0.999	0.267	0.947 ± 0.06	0.983	0.75 ± 0.321	0.614	0.995	0.95 ± 0.54	0.695
BP Systolic(mmHg)	129.3± 14.63	0.198	134 ± 16	0.841	0.676	135.2 ± 19.43	0.794	137 ± 17	0.239	0.969	130 ± 15.28	0.171	146.7 ± 21	0.253	0.163	134.53 ± 17.63	0.999
BP Diastolic(mmHg)	84.18 ± 11.36	0.872	87.2 ± 10.1	0.531	0.793	85.27 ± 10.54	0.983	86.1 ± 11	0.455	1.000	81.92 ± 9.40	0.023*	90.67 ± 8.165	0.527	0.057	85.41 ± 10.60	1.000
Fasting Plasma Glucose	181.9 ± 76.52	0.376	174 ± 59	0.483	0.704	164.2 ± 77.21	0.123	159 ± 60.8	0.725	0.058	157.75 ± 69.73	0.392	165.5 ± 75.02	0.336	0.261	165.40 ± 69.65	0.000*
Post Prandial Pllasma Glucose(mg/dl)	286 ± 108.5	0.282	278 ± 85.5	0.335	0.101	170.3 ± 83.73	0.253	168 ± 54.9	0.084	0.189	251.01 ± 102.71	0.267	277.3 ± 111.1	0.311	0.145	266.40 ± 97.04	0.000*
Fasting Plasma Insulin	27.24 ± 28.7	0.476	32.5 ± 24.9	0.013*	0.069	269.8 ± 107.7	0.297	254 ± 78.9	0.617	0.430	32.48 ± 31.63	0.110	14 ± 8.626	0.060	0.583	31.42 ± 29.69	0.000*
Serum Total Cholesterol (mg/dl)	229.5 ± 25.78	0.002*	226 ± 32.9	0.826	0.000*	225.6 ± 26.42	0.573	224 ± 25.3	0.003*	0.052	237.78 ± 32.37	0.153	213 ± 32.74	0.135	0.303	233.98 ± 26.13	0.749
Serum L.D.L Cholesterol (mg/dl)	162.6 ± 25.92	0.083	159 ± 32.5	0.820	0.151	161.4 ± 26.22	0.837	157 ± 25.3	0.013*	0.297	171.65 ± 31.98	0.259	144.3 ± 33.23	0.388	0.555	168.61 ± 26.13	0.012*
Serum V.L.D.L Cholesterol (mg/dl	22.59 ± 3.242	0.168	22.8 ± 3.86	0.591	0.847	21.78 ± 3.05	0.841	23.3 ± 3	1.000	1.000	21.77 ± 2.73	0.132	23.73 ± 1.573	0.334	0.818	23.34 ± 3.16	1.000
Serum H.D.L Cholesterol (mg/dl)	43.75 ± 4.475	0.856	43.4 ± 3.83	0.637	0.984	43.41 ± 3.649	0.271	43.9 ± 4.12	0.927	0.456	44.32 ± 4.93	0.429	45 ± 3.286	0.379	0.133	42.21 ± 4.19	0.007*
Serum Triglyceride (mg/dl)	112.9 ± 16.21	0.168	112 ± 15.3	0.733	0.796	109.4 ± 15.06	0.675	116 ± 13.7	1.000	0.989	108.86 ± 13.66	0.216	114.7 ± 12.04	0.041*	0.867	116.75 ± 15.31	1.000
S.creatinine	1.059 ± 0.108	0.781	1.06 ± 0.11	0.662	0.779	1.052 ± 0.10	0.096	1.03 ± 0.09	0.377	0.002*	1.07 ± 0.086	0.858	1.033 ± 0.103	0.601	0.947	1.05 ± 0.10	0.264

Clinical characteristics of T2DM patients (n=300) showed significant association with diabetic duration (p=0.000); F-glucose (p=0.000); PP-glucose (p=0.000); fasting plasma insulin (FI) (p=0.000); serum-LDL (p=0.012) and serum-HDL (p=0.007) while other parameters showed no association (Table 1).

Diabetic patients (≤40 years) (n=72) showed highly significant association with TC (p=0.002). Males under 40 years (n=34) showed significant association with TC (p=0.002) while females (n=37) with diabetic duration (p=0.033) as well as FI (p=0.013) (Table 1).

Diabetics (41-59 years) (n=175) showed significant association with serum creatinine (p=0.002); males in this age group (n=96) showed significant association with waist hip ratio (WHR) (p=0.032) while females (n=79) with TC (p=0.003) and LDL (p=0.013) (Table 1).

Diabetes over ≥ 60 years of age (n=54) did not show association with any of the parameters. However; in this category male (n=41) and female (n=13) patients showed significant association with diastolic blood pressure (DBP) (p=0.023) and TG (p=0.041) respectively (Table 1).

Obese diabetics (n=109) when compared to non obese diabetics (n=191); showed statistically significant increase in the levels of TC (p=0.030); LDL (p=0.049); VLDL (p=0.008); serum creatinine (p=0.047) and decrease in HDL (p=0.000) (Table 2). In addition; the systolic blood pressure (SBP) of underweight diabetic patients (BMI<18.5 Kg/m^2; n=29) showed a significant association (p=0.009) while diabetics with BMI= 18.5-25 Kg/m^2 showed association with age (p=0.001); WHR (p=0.000). Unlike the above categories; obese diabetics (BMI>25Kg/m^2) showed significant association with diabetic duration (p=0.031); WHR (p=0.000); DBP (p=0.004); TC (p=0.030); LDL (p=0.049); HDL (p=0.000); VLDL (p=0.008) and serum creatinine (p=0.047) (Table 2).

Out of 300 diabetic patients; 241 individuals (127 males + 114 females) were diagnosed with complications (Fig 1). Around 170 patients (70.5%) showed Rt; 24 Np (11.0%) and 35 Nu (14.2%). Multiple complications were observed in the remaining 12 patients (4.3%). The percentage of male and female diabetics with single and multiple complications is shown in Fig.1.

Figs. 2a & b shows the percentage of obese (n=109) and non obese (132) diabetics manifesting single and multiple diabetic complications. The Pearson's chi-square test showed highly significant increase in the diabetic complications in obese when compared to non obese T2DM patients (p=0.000). Multiple diabetic complications were found to be 2.7-3.7 times higher in obese compared to non obese diabetics (Fig 2).

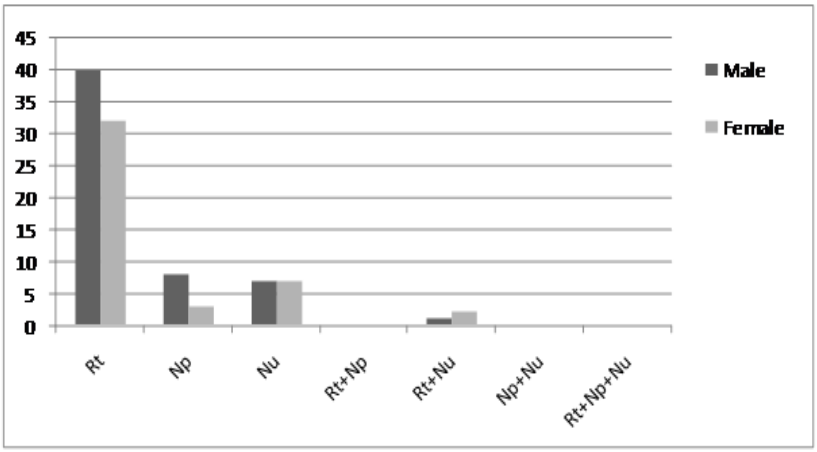

Fig 1

Fig 1 Percentage frequency of T2DM patients (n=241) with single and multiple diabetic complications

Table 2 Clinical characteristics and p values of underweight; normal and overweight diabetic patients (mean ± SD) * significant p-value <0.050

Variables	Underweight BMI (< 18.5 Kg/m^2) (N=29)	P value	Normal BMI (18.5-25 Kg/m^2) (N=162)	P value	Overweight BMI (> 25 Kg/m^2) (N=109)	P value
Age(yrs)	45.70 ± 11.55	0.362	49.16 ± 9.68	0.001*	48.61 ± 9.84	.803
Diabetic Status Duration	3.23 ± 3.86	0.596	4.39 ± 5.49	0.091	3.75 ± 4.47	0.031*
Waist Hip Ratio(WHR)	0.87 ± 0.073	0.047	0.97 ± 0.72	0.000*	0.93 ± 0.11	0.000*
BP Systolic(mmHg)	133.63 ± 20.23	0.009*	133.54 ± 17.79	0.712	136.23 ± 16.65	0.153
BP Diastolic(mmHg)	84.97 ± 14.64	0.174	84.65 ± 10.45	0.996	86.65 ± 9.44	0.004*
Fasting Plasma Glucose(mg/dl)	166.06 ± 77.16	0.357	162.40 ± 71.97	0.062	169.65 ± 64.22	0.068
Post Prandial GlucosePP)	251.57 ± 102.21	0.457	267.13 ± 103.24	0.429	269.39 ± 64.22	0.221
Plasma Insulin(F)	30.93 ± 25.22	0.118	27.99 ± 27.99	0.999	36.61 ± 32.60	0.544
Total-cholesterol (mg/dl)	227 ± 30.2	0.448	227 ± 26.6	1.000	248.81 ± 18.26	0.030*
LDL-cholesterol (mg/dl)	161 ± 29.5	0.449	161 ± 26.5	0.573	184.03 ± 17.85	0.049*
HDL-cholesterol (mg/dll)	44.1 ± 3.56	0.843	43.9 ± 4.15	0.460	39.63 ± 2.95	0.000*
VLDL-cholesterol (mg/dl)	21.9 ± 3.29	0.643	22.4 ± 3.09	0.062	25.15 ± 2.34	0.008*
Triglyceride (mg/dl)	110 ± 16.4	0.643	112 ± 14.6	0.819	125.78 ± 11.75	0.916
S.creatinine (µU/dl)	1.09 ± 0.08	0.578	1.05 ± 0.10	0.992	1.06 ± 0.09	0.047*

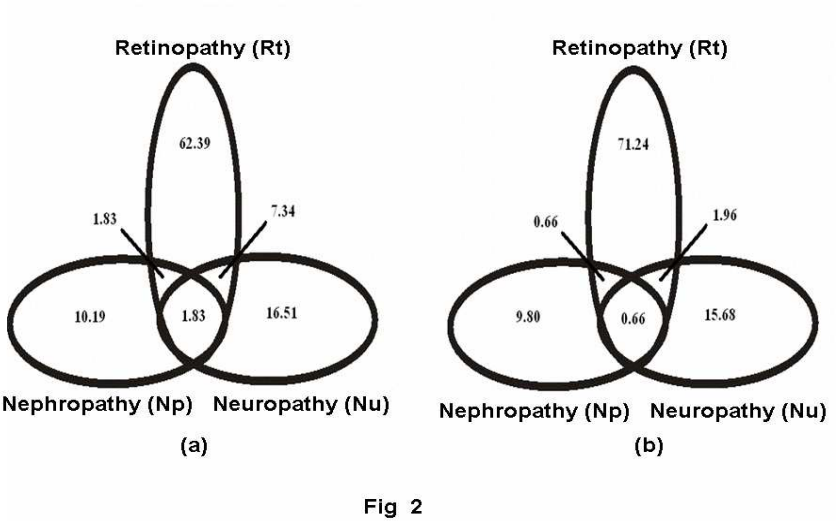

Fig 2

Fig 2 Percentage of (a) obese (n=109) and (b) non obese (n=132) T2DM patients with diabetic complications (p=0.000)

Discussion

Increasing modernization with sedentary life style and lack of physical activity is favoring increased incidence of obesity; diabetes and its complications [19]. In a report from U.S.A. [20] the importance of quantification of diabetic complications was emphasized. Lee et al [21] reported significant inverse dose-response relationships of fitness and positive associations of obesity measures on the risks of impaired fasting glucose (IFG) and T2DM. For instance; black Hispanics and Pima Indians are more susceptible for diabetic complications than white Americans [22]. Such differences among various races; necessitates the research in different populations in order to identify and take special care of the high risk groups. Early detection of persons at high risk of developing complications such as overweight leading to obesity is a prerequisite for the development of prevention strategies [23].

The present study is a comprehensive overview and recent insight into the diabetic complications in obese T2DM patients. It reveals that the North Indian population has an aggressive course of diabetic Rt; Np and Nu compared to other complications. Multiple complications were present in both males and females reported earlier by Mitka et al [20].

Accelerated coronary and peripheral vascular atherosclerosis is one of the most common and serious chronic complications of long term diabetes mellitus. Along with other risk factors such as hypertension; smoking; obesity etc.; increasing importance has been given to secondary hyperlipidaemias in the causation of accelerated atherosclerosis [24]. Prevalence of hyperlipidaemia; a metabolic abnormality frequently associated with diabetes mellitus is variable; depending on the type and severity of diabetes; glycaemic control; nutritional status; age and other factors. The most characteristic lipid abnormality in diabetics is hypertriglyceridaemia; with or without associated increase in plasma cholesterol [25; 26]. The central characteristic of dyslipidemia in patients with T2DM is an elevated TGL; particularly TGL-rich VLDL and decreased HDL. In T2DM patients; the concentration of LDL is usually not significantly different from that seen in non diabetic individuals. However; patients with T2DM

typically have a preponderance of smaller; denser; oxidized LDL (OxLDL) particles; which may increase atherogenicity [27] even if the absolute concentration of LDL is not elevated [28].

T2DM-Np is the leading cause of end stage renal disease (ESRD); 34-37% diabetic patients with T2DM-Np are at a high risk of fatal and non fatal cardiovascular and other complications [29-32]. Like Davies et al [33]; our study also showed that ~11.0% of obese and 9.8 % non obese T2DM patients showed Np. Not only stroke and myocardial infarction but retinopathy and peripheral vascular disease have also shown correlation with T2DM-Np [34-37]; almost 2 % obese subjects showed Rt + Np in our population as well. It has been proposed that in addition to genetic and racial predisposition; environmental and biochemical factors trigger the genetically prone individuals as well [38-40].

Cardio Arterial Disease (CAD) is a serious complication that affects a great majority (57.6%) of patients with T2DM-Np; especially in the older age group. Incidence of CAD is lower in western countries being 25% in patients of 45-59 yrs of age in a study from Finland and 9.1% in USA than 57.6% in Saudi population [40]. They concluded that T2DM-Rt was present in 47.8% and complete loss of vision in 1.6% [41]. In our study; retinopathy was the most frequent complication observed in T2DM patients (~70.5%).

Significant increase in the levels of TC and LDL along with no change in HDL levels was shown in obese diabetics when compared to obese controls [41]. However; our study showed significant increase in all lipid profile parameters such as TC; LDL; VLDL; serum creatinine and decrease in HDL in obese T2DM patients when compared to non-obese diabetics. Bijlani et al [42] found HDL to be significantly lower in obese diabetics as compared to normal weight diabetics. Many studies have strongly suggested an inverse correlation of HDL with the development of ischaemic heart disease [43; 44]. Sharma [45] and Jain [15] observed increase in the levels of serum total lipids (TL); TC; TGL and serum phospholipids (PPL) in diabetic subjects as compared to normal controls. Mean TGL was observed to be higher in obese diabetics in comparison to obese control subjects [46].

In 2007; a report from USA estimated the total direct cost spent on diabetes complications as 57 billion US dollars yearly. Heart attack cost $ 14150 per person followed by chronic kidney disease $ 9002 per person; foot problems $ 4687 per person; and eye damage $ 1;785 per person [20].

Conclusion

We conclude from our study that obese diabetics are at a higher risk (2.7-3.7 times) of having T2DM-Rt; T2DM-Nu and T2DM-Np than the non obese T2DM patients. Proper screening strategies for all above mentioned parameters will help to identify diabetics at risk of developing one or more complications such as cardiovascular and renal diseases. Apart from the three complications mentioned in this study there are several others such as angiogenesis; foot problem; myocardial and heart complications which should be studied further in future.

Acknowledgements

The authors are grateful to the support staff in the Department of Medicine; Chatrapati Sahuji Maharaj Medical University; Lucknow. Grant-in-Aid from the Department of Biotechnology; New-Delhi is duly acknowledged. Madhukar Saxena and Sunaina Gautam are thankful to University Grant Commission and Department of Biotechnology; New-Delhi respectively for their fellowships.

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