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Lipid Profile and Investment of Oxidants and Antioxidants in Hypertension and Ischemic Heart Disease of Tribal and Non-Tribal Patients

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Abstract

Introduction: Hypertension (HT) and Ischemic Heart Disease (IHD) are two pandemic cardiovascular health problems. The alarming feature of 1HD is that majority of burden is now shifting to developing and deprived economies. This includes India also. The present paper highlights the Lipid Profile, Oxidative Stress (OS) Nutrient Antioxidants and Endogenous Antioxidants Enzymes in Tribals, who represent deprived community, and non-tribals who represent developing community. *Methods:* This study included 353 subjects (Normal; tribals – 62, nontribals-52: HT-tribals-10 non-tribals-169: 1HD-tribals-4, non-trbal-41; HT+1HD-tribal-1 and non-tribal 14). All the subjects were investigated for lipid profile (Total Cholesterol, HDL-Cholesterol, LDL-Cholesterol, VLDL-Cholesterol, Triglyceride),Total Protein and Hb; antioxidant enzymes (SOD, GPx and Cat) and TBARS levels in blood and urine.Creatinine was also estimated in urine. *Results:* The total plasma cholesterol was almost touching the upper limit of normal in both tribals and non-tribals, was significantly higher iin IHD patients in both the communities. The LDL- cholesterol (LDLC+VLDLC) was one of the important risk factors. OS (plasma TBARS) was significantly raised in IHD patients. Urine TBARS levels did not provide any conclusive trend. Vitamin A and beta-carotene levels were almost normal in both control and patient groups but vitamin C and E level and were low in both control and patients groups. SOD and GPx were low in patients group but catalase did not provide any regular trend. *Conclusion:* Cumulatively data suggest: I- LDL-Cholesterol and triglyceride are risk factors, II -Lop-sided redox status in patients.

Keywords: Lipid Profile; Oxidative Stress; Nutrient Antioxidants; Antioxidant Enzymes; Hypertension; Ischemic Heart Disease; Tribals; Non-Tribals.

Introduction

Hypertension (HT) and Ischemic Heart Disease (IHD) are the two most common and devastating problems of cardiovascular diseases (CVD) and have attained pandemic proportions in both developed and developing populations. An extensive and elaborate data on HT among Indians have been reviewed by Anchala et al [1] for the period 1950 to 30th April 2013. They have collected data from different database and have concluded that 33%, urban and 25% rural Indians suffer from HT Fauci et al [2] have described the risk factors in IHD and have stated that with rapid urbanization, the incidence of IHD is attaining epidemic proportion; that the risk factors for IHD are increasing rapidly; and that most importantly majority of IHD burden is now shifting to lower income group and middle income countries. India, Nepal and many other Asian countries fall in this category. IHD is rapidly increasing due to economic and health transitions in these countries [3]. Gupta et al [4] have concluded from their study that IHD is around 3-4% in rural and 8-10% in urban India which indicates that there is two fold increase in rural and six fold increase in urban areas in adult population over 20 years of age between 1960 – 2000. Vasudevan and Prabhakaran [5] have reviewed IHD in Indians and implications of INTERHEART study. This study

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included 15152 cases of incident acute myocardial infarction (AMI) and 14820 controls from 52 countries [6], The risk factors stated therein are HT, diabetes mellitus, abdominal obesity, psychological stress, decreased consumption of fruits and vegetables, even moderate consumption of alcohol, low physical activity, dyslipidemia and smoking. Indeed, "Dyslipidemia" and "Oxidative Stress" (OS) are not mandatory risk factors in HT or IHD [7-15]. In recent years there is again a gathering support that raised OS endangers many diseases including HT and IHD [16-22]. Atherosclerosis is a powerful risk factor in majority of IHD cases and often in HT also. Both these factors are principal instigators of atherogenic process. Sata and Fukuda [23] have described atherosclerosis as chronic inflammatory disease promoted by dyslipidemia and OS; howfar, they behave as complice in HT and IHD is still a matter of debate. Maharjan et al [24-25]have examined dyslipidemia and OS in Nepali population and have observed significant dyslipidemia and raised OS in HT and IHD. However, they did not find any effect of smoking and alcohol. Another case controlled study on Nepali population revealed that smoking induced a very mild OS but not to the degree it can be labeled as risk factor [26]. Further, another study by Risal et al [27], also noticed a very mild degree of raised OS, and that vitamin C and Vitamin E were not risk factors in CVD. Similarly, observations in Indian population have also been variable [28].

Reactive oxygen species (ROS) are strong molecular scissors and or distorters and also regulators and motivators of physiological processes due to their redox supervising property[22,18]. On the contrary, antioxdants (AO) act as modifiers of ROS activity [28,26]. Under physiological conditions ROS have slightdge over antioxidants [17-18]. This balance of oxidants and antioxidants represent & redox status of cell and is called OS. Further optimal physiological status of nutrient antioxidants (Vit A, Vit C, Vit E and beta –carotene, is mandatory to cover antioxidant activity beside their other physiological activities but gathering evidence strongly suggests that their excess intake could be harmful. Obviously, the endogenous antioxidant enzymes (superoxide dismutase, glutathione peroxidase and catalase) are major players. Since they are inducible enzymes, they have flexibility to meet exigencies of requirement [18,28,29].

The raised OS representing redox imbalance could be due increased ROS production or weak antioxidant defense [17,18,28]. Chronic redox imbalance could be cause or consequence in many diseses [18,29]. [The process of oxidative phosporylation (ATP synthesis), utilization of O2 and production of ROS in mitochondria function in the range of about 380 mv-800mv]. Just a 30 mv change in redox state (energy balance i.e concentration of electrons in cells) causes 10 fold change in the ratio of oxidants and reductants and can lead to serious consequences [16].In conclusion an adequate support of antioxidants (both exogenous antioxidants and endogenous antioxidants) is necessary to balance the "Redox Box of Cellular Homeostasis" test pathophysiologies will propel to many disease including IHD and HT [16-18,28].

In the light of these reports we have examined lipid profile, OS, antioxidative enzymes and nutrient antioxidants in tribal and nontribal populations in Rajasthan. The strength of this study is that these two types of populations, who have distinct and vast differences in their living style, diet, alcohol intake and smoking (all tribals smoke and drink alcohol heavily as per availability) are adjacently based in Zawar area located in base of Arawali Hills of Rajasthan. To best of our knowledge similar type of study has not been carried out in Zawar or elsewhere in India.

Material and Methods

Patients and Controls

The present study included 353 subjects in total (patients and controls) in the age group of 30 – 75 years. (HT-tribal and non tribal 169, IHD – tribal 4 and non – tribal 41 and HT+IHD 15 (tribal – 1 and non tribal – 14). Neither of the patients were obese or diabetics nor suffered from any other disease relevant to HT and IHD. The control group consisted of 52 tribal and 62 non tribals (age, sex and socio-economically matched healthy subjects). HT patients were freshly dedected. IHD and IHD+HT cases were on prophylactic and preventive measures. All clinical details were carried out by a senior physician (SLP). All the tribals (controls as well as patients) were heavy smokers and consumers of home made hard liquor. Despite explicit instructions to stop smoking and drinking,all tribal patients continued smoking and drinking.

Collection of Blood Samples and Analyses

All subjects were advised for overnight fasting for collection of blood and urine samples. Fasting blood samples were collected in the morning between 8 AM to 9 AM from anticubital vein in EDTA or plain vials. The EDTA samples were immediately centrifuged. The RBC button and plasma were separated. The RBC button was suspended in 0.9% saline water and

washed thrice. Serum was separated from blood samples collected in plain vials. Fasting urine sample was collected in plain vial for determination of TBARS and creatinine.

Standard procedures were used for the analyses of lipid profile (Auto-Analyzer), nutrient antioxidants beta-carotene, vitamin A, VitaminC,Vitamin E, SOD GPx catalase and TBRS [33-37]Hb was measured by Drablin, method [38] and total protein was measured by the method of Strove and Makarova. Urinary creatinine was measured by Jaffes method.

Results

We have examined lipid profile, nutrient antioxidants, enzyme antioxidants, and OS plasma TBARS level in tribals and non-tribals. Simultaneously we have also determined urinary TBARS excretion, serum Hb and total proteins. The results are given in Tables 1-3. Table 4 gives a comparative lipid profile data of normal subjects and IHD patients from some countries, whereas table 5 provides data on HT cases. Total cholesterol was not significantly raised in either group of HT patients but was significantly raised in IHD patients. LDL-C levels (LDL-C+VLDL-C) levels were markedly raised in all patient groups and suggest an aggressive treatment because presently LDL-C is considered be most important as well as potent risk factor. The normal SOD levels in RBC of tribal and non tribal were 6.76±2.09 and 8.22 ±3.06 EU per ml RBC. It was significantly lower in HT and IHD patients of both tribals and non-tibals. GPx also showed similar pattern but catalase did not exhibit any regular pattern. Plasma OS (TBARS level) was raised in both HT and IHD. Again tribals and not tribals did not show any regular pattern. Interestingly the urinary TBARS excretion decreased in IHD patients. It was more marked in patients suffering from both diseases (HT and IHD). Vitamin A and beta carotene levels were with in normal limits in all the groups of both the communities. However vitamin E and Vitamin C were sigrificantly low both in normal and patient groups. The deficiency of these nutrient antioxidants was more marked in HT and IHD patients.

Table 1: Lipid profile,serum total proteins,haemoglobin levels in tribal and non tribal hypertensive and ischemic heart disease pateints along with controls

Parameters	Normal subject		Hypertension HD		1HD		HT+1HD
	Tribals n=62 mean±SD	Nontribals n=52 mean±SD	Tribals n=10 mean±SD	Nontribals n=169 mean±SD	Tribals n=4 mean±SD	Nontribals n=41 mean±SD	n=15 tribal nontribal 14 mean±SD
Total cholesterol	185	184	192	191	237	198	197
mg/dl	±27	±16.4	±28	±40	±24	±37	±39
HDL cholesterol	48.4	48.4	47.0	47.2	44.7	47.8	43.3
mg/dl	±16.4	±16.4	±10.0	±16.4	±6.4	±17.0	±13.7
LDLcholesterol	116	48.4	118	117	127.9	128.7	115.2
mg/dl	±32	±16.4	±28	±35	±58.9	±32.7	±37.7
VLDL cholesterol	20.3	48.4	26.5	29.1	29.3	29.5	29.1
mg/dl	±7.4	±16.4	±8.6	±9.9	±12.0	±15.4	±6.3
Triglyceridel	101	48.4	132	145	146.7	147.7	145.0
mg/dl	±37	±16.4	±43	±49	±59.8	±17.2	±32.1
Total protein	6.86	48.4	6.88	7.12	7.07	6.86	6.67
gm/dl	±0.62	±16.4	±0.74	±0.80	±0.63	±0.54	±0.69
Haemoglobin	12.37	48.4	12.1	12.16	12.62	12.35	12.92
gm/dl	±0.70	±16.4	±0.27	±1.16	±0.47	±0.97	±1.63

Table 2: Antioxident enzyme and oxidative stress (as TBARS) tribaland non-tribal hypertensive and ischemic heart disease patients along with control

Parameters	Normal		Hypertention		Ischemic Heart		HT+1HD
	Tribals n=62 Mean±SD	Nontribals n=52 Mean±SD	Tribals n=10 mean±SD	Nontribals n=169 mean±SD	Tribals n=4 mean±SD	Nontribals n=169 mean±SD	n=15 tribal nontribal mean±SD
SOD	6.76	8.22	4.11	4.56	4.20	5.12	4.68
(EU/ml RBC)	±2.09	±3.06	±1.29	±2.11	±0.64	±1.43	±1.82
SOD	3.30	3.70	2.01	2.64	2.23	2.44	2.72
(EU/ml plasma)	±1.67	±1.11	±0.90	±0.99	±1.10	±0.67	±1.14
Catalase (mol H_2O_2	155	166	143	139	213	141	141
Consumed/mg protrein	±31	±42	±48	±65	±137	±44	±54
GP_X	2.89	2.93	2.14	2.43	1.88	2.14	2.00
	±0.75	±0.77	±1.04	±0.28	±1.13	±0.83	±0.63
(TBARS)	3.55	3.18	4.31	5.07	5.43	5.23	4.96
Gmol/ml	±1.07	±0.95	±1.31	±1.40	±1.43	±1.13	±1.20
(TBARS)	10.96	9.09	8.56	9.16	8.27	7.66	5.55
Gmol/ml/mg creatirine	±2.74	±3.33	±4.51	±5.77	±3.42	±3.44	±1.89

Table 3: Plasma nutrient antioxidants levels in tribal and non-tribal hypertensive and ischemic heart disease patients

Parameters	Normal		Hypertension		1HD		HT+HD
	Tribal n=62 Mean±SD	Non-tribal n=52 Mean±SD	Tribals n=10 Mean±SD	Non tribals n=169 Mean±SD	Tribals n=41 Mean±SD	Non tribals n=41 Mean±SD	n=15 Trial nontribal 114 Mean±SD
Retinol (µg/dl)	21.53 ± 5.51	25.32 ± 5.61	20.43 ± 5.96	25.37 ± 8.52	18.9 ± 6.61	24.47 ± 12.02	28.9 ± 12.8
Beta-carotene (µg/dl)	106 ± 23	114 ± 19	87 ± 16	96 ± 32	93 ± 29	95 ± 32	95 ± 35
Alpha toeopherol (mg/dl)	0.69 ± 0.18	0.85 ± 0.23	0.57 ± 0.13	0.67 ± 0.30	0.68 ± 0.19	0.68 ± 0.19	0.47 ± 0.14
Ascorbic acid (mg/dl)	0.63 ± 0.23	0.90 ± 0.27	0.67 ± 0.1	0.68 ± 0.36	0.56 ± 0.28	0.56 ± 0.28	0.72 ± 0.3

Table 4: Comparetive values of lipid profile in 1 hd patiens as compared to normal subject

	TC	HDLC	LDLC	VLDLC	TG
Aparna et.al(2016) Tribals	231±24	44.7±6.4	127.9±58.9	29.3±12.0	146.7±59.8
nontribals	198±37	47.8±17.0	128.7±32.7	29.5±15.4	147.7±17.2
Madegourda and satish(2015)	187.2±37.7*	40.2±6.2*	116.1±37.0*	32.2±12.1*	159.8±1.5*
Misra et al (1980)	249.8.7±58.8 NS	57.9±13.1*	137±44.2*	56.9±2.33 NS	NM
Miller et al(1990)	175±20*	34±9*	119±22*	23±14*	123±62*
Dasguptaghosh (2015)	221.9±32.0*	43.0±10.6*	111.3±38.7 NS	------	190.7±77.8*
Haddad et al (2002)	231.4±57.9*	44.4±8.3*	118.9±45.9*	-------	164±93.8*
Maharjan et al (2008)	177±37*	40±7*	106±28*	30±10*	146±44*

*significant<p<0.05

Table 5: Lipid profile in hypertension cases in india, nepal and bangladesh

Present study	TC	HDLC	LDLC	ULDLC	TG
India(Rajasthan)tribal	192±28	47.0±10	118.0±28	26.5±8.6	132±43
Non tribal	191±40	47.2±12.6	117±35	29.1±9.9	145±49
India (Naz et al 2015)	196.89 ±28.05	46.26±6.37	119.02±28.12	31.19±7.66	159.55±38.33
Nepal (Maharjan)	185±38	44±7	107±31	34±18	162±90
Bangladesh (Chaudhary et al 2014)	238.3±34	41.2±3.2	151.3±78	----	178.3±63

Discussion

The present study saliently points out: (i) total cholesterol level in the normal subjects was on the higher side of upper limits of normal in both tribals (185 ± 27 mg%) and non-tribals (184 ± 22 mg%), (ii) it was only slightly higher in hypertensive patients (iii) significantly higher in tribal IHD patients as compared to non-tribal IHD patients (iv) IHD patients with hypertension had total cholesterol level comparable to patients with non -tribal IHD patients without HT (v) LDL cholesterol (>130 mg/dl) did not appear to be much prevalent risk factor, but considered alongwith VLDL -cholesterol, became a risk factor in majority of tribal controls and in all groups of hypertensive and IHD patients. (vi) hypercholesterolemia (>200 mg/dl) was present in 9.7% tribal and 5.8% non-tribal normal subjects (vii) non-tribal hypertensive subjects had more or less normal cholesterol values, whereas it was higher in tribal hypertensive (40%) and IHD patients (75%). (viii) it was also higher in non-tribal IHD patients (19.5%) and IHD plus hypertensives (33.3%). However, it may be pointed out that number of tribal subjects was small to derive conclusive answer in both control and patient groups(ix) there was smaller percentage of subjects with both normal lipid profile and raiced OS (x) OS was significantly though only mildly raised in patients and both hypertensive and IHD patients compared to controls,(xi) catalase did not provide a discernible pattern, but Gpx was significantly low(xii). SOD is exclusive enzyme to dismutate O_2 to H2O2 and that GPx instead of catalase plays quantitative important role in human [16] (xiii). plasma peroxide levels were high. (xiv) Surprisingly haemoglobin and serum protein levels were almost normal in all groups despite their poor nutrition. (xv)plasma SOD and urinary TBARS levels did not

provide any regular trend.

A critical appraisal of the literature vis-a-vis our data show a wide variation with regard to dyslypidemia as well as OS [4,13,15,24,25,34,41]. Concepts have changed for dyslipidemia from "Targedy to Disaster" where as vice versa for OS (i.e. participation of ROS and antioxidants). In a study from Nepal Mahrajan et al [24] observed much lower level of cholesterol in normal subjects (155 ± 38 mg/dl) and that level was significantly raised in HT. In another study Maharajan et al [25] observed no difference between smokers and non-smokers or between alcoholics and non-alcoholics. Their observations support our data in tribals as well as non-tribals. A recent study from this region observed dyslypidemia in hypertension[12]. They observed relatively lower level of cholesterol in normal subjects (152.90±11.71mg/dl) but comparable level of total cholesterol (196.89±28.05 mg/dl) in HT. Dasgupta Ghosh [11]examined 100 cases of IHD from rural area of Bengal and 50 age and sex matched controls. The striking feature of their study was alarming and low incidence of HDL cholesterol. There is consistent evidence that HDL-C is a strong independent inverse predictor risk of 1HD total cholesterol was relatively on higher side of normal limit (195.20±37.28 mg/dl) and was still on higher side in IHD patents (221.94± 12.03 mg %). They noted lower values of HDL but not LDL cholesterol; recommended early detection of lipid profile for preventive measures. The most extensive study, to best of our knowledge, is ICMR study by Joshi et al [41]. They examined four diverse populations from Tamil-Nadu, Maharashtra, Jharkhand and Chandigarh for lipid profile of 16007 subjects – representative of 213 million people. Interestingly hypercholesterolemia, high LDLC, low HDLC and high triglycerdemia were present in 13.9%, 11.8%, 72.3 and 29.5%, respectively. The striking feature of this study was alarmingly high incidence of low HDLC levels and hypertringlyceridema. The latter is also now a well recognized independent risk factor [9]. In our study hypercholesterolemia was present in 9.8% and 5.8% tribal and non tribal subjects, the respective figures for IHD were 75.0% and 19.5%, 14.5% in tribals and 13.5% non-tribals had both normal lipid profile and normal oxidative stress, reemphasizing that neither lipid profile nor OS are essential features.

OS is defined as a tilled balance in favour of oxidants in cells and tissues [42,45]. Initial euphoria and bias to implicate raised OS in diseases [29,42], has drastically been pruned and judiciously ablated [28,29]. The emerging view is that there is never excessive generation of oxidants, in human cells and tissues but persistent smoulding production of ROS can definitely abet chronic diseases such as cancer [29] neurological disorders diabetes and CVD [18-20, 23,35] thus role of raised OS is again progressively gaining support.

In our study we observed significantly raised OS (raised TBARS activity in plasma) in both tribal and non-tribal hypertensive patients. It was still higher in IHD patients. The patients with both HT and IHD did not show additional oxidative burden. As regard to antioxidant enzymes, SOD and GPx were significantly lower both in HT and IHD but catalase did not provide any regular pattern. As stated above recent studies have demonstrated that GPx plays dominant role to rein ROS activity in human tissues [16]Interestingly TBARS excretion was not affected in HT and IHD. Presently the data are sparse to explain this issue.

Our Data on Nutrient Antioxidants Convey

Useful information; the serum retinol and beta-carotene levels were largely normal in both the diseases but ascorbic acid and α-tocopherol levels were significantly and considerably low. These observations suggest that both tribals and non-tribals in Zawar area require vitamins C and E supplement. However, nutrient antioxidants cannot be supplemented indiscriminately because excess supplementation can cause undesirable affects including increased mortality [43,44]. The prevailing concept for nutrient antioxidant is that provided one is not deficient in them, additional supplement should not be given [17,28] although Rodrigo et al [46] observed beneficial effects of short term vitamin E (400 mg/d) and vitamin C (1 g/d) supplementation for 2 months in HT. Presently endogenous s antioxidants are supposed to play far more important role . Endogenous antioxidant enzymes are inducible enzymes and have good capacity to cope up with the situation [41,44].

In our study all tribal males were heavy smokers (bidi) and drinkers. Alcohol drinking is almost universal among them, majority of females were also smoking and drinking but were shy to admit them openly. All tribal patients continued smoking and drinking even during management regimen, despite explicit instructions not to do so. Surprisingly in spite of these excesses their OS (in terms of plasma TBARS levels) was significantly but only mildly raised. Further, many patients had OS in normal range. An exclusive case controlled study on smoking from Nepal did not find any significantly raised OS in smokers [26]. Raised OS was observed in smokers in some Indian populations but it is not a universal finding in all populations. However, smoking [19] and

alcohol consumption are long established risk factors in HT and IHD Processed bidi or cigarette smoke contains 3500-45000 chemicals; many of them are brazenly toxic molecules which trigger and/or aggravate CVD, cancer, diabetic complications, COPD and many other diseases, it shortens telomeres and each cigarette takes away 5-7 minutes of life; and that unfortunately 278 crore Indians are smoking (rural 21.6 crore and urban 5.9 crore) and about 25% deaths occur among middle aged men from smoking. About 4.2% death occurred in 2002 and about 10 millions death are predicted by twenties or early 2030 [47]. Strikingly 60 mg of nicotine on the tongue will kill a person with in few minutes [47]. In same book [47] Director General in her introductory remark admonished that tobacco should not be given space for advertisement or admiration [47] consequently there is a global anxiety and anguish to discourage smoking. Incidentally, tobacco smoke is also loaded with free radicals. One study reported frightening figure of free radicals in smoke [35]. However role of OS as a risk factor in CVD still remains a debatable and moot issue. Singh and his colleagues noted only a mildly raised OS in smokers in Indian population but no significant difference in Nepali population [49].

Alcohol is injurious to health and raises OS [50]. Furthermore, alcohol drinking has prodigious proclivity for smoking for the reasons unknown and in tandem increases the risk. A recent study done in 52 countries indicates that even moderate consumption of alcohol is harmful.

Our data collectively give inkling of credible redox imbalance. Redox represents energy changes due to a balance between oxidants (ROS and RNS) and antioxidants (enzymes and non-enzymes). They are now well known to be hallmarks of redox machinery driving and controlling energy dynamics which precisely supervise numerous cellular reactions through "redox switches" and "redox flashes" (process akin to phosphorylation of large spectrum of chemical species which also drive and regulate numerous reactions.

In summary our data broadly place the cases of IHD and HT in four categories in context to hyperlipidemia and raised OS viz. a) patients with no lipid abnormality and normal OS, b) abnormality in lipid profile but normal OS, c) patients with raised OS. Obviously corrective measurement will depend accordingly. Presently good medicines, especially statins, are available to manage lipid profile but no effective regimen is still available to manage raised OS. There is strong re-merging evidence in the recent years that chronic and excess production of ROS under adverse set of circumstances leads to several chronic disease including HT and IHD [2,17]. Dyslipidemia, besides hypercholesterolemia, high LDL-C should also be aggressively managed Nutrient and other dietary or synthetic antioxidant treatment can be tried to normalize OS but unfortunately clinical trials have largely been unsuccessful. There is still another unresolved issue; whether hyperlipidemia and OS have synergistic influence on disease processes of HT and IHD? If so, what possible link they may have? Chaddha et al [51] proposed that in developing and deprived economies air pollution is common and may act as risk factor. They hypothesized that polluted air has more oxidants (ROS) which possibly may increase O-LDL levels in body O-LDL is a recognized risk factor in atherosclerosis a condition well known to induce HT and IHD. However, this hypothesis is not applicable in developed countries where air pollution is negligible, although patients of all the four aforesaid categories exist there also further; researches are, needed to resolve these issues in etiopathogenesis of these diseases.

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