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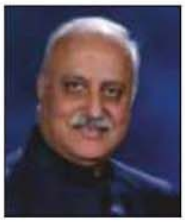
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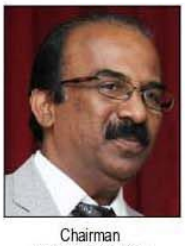
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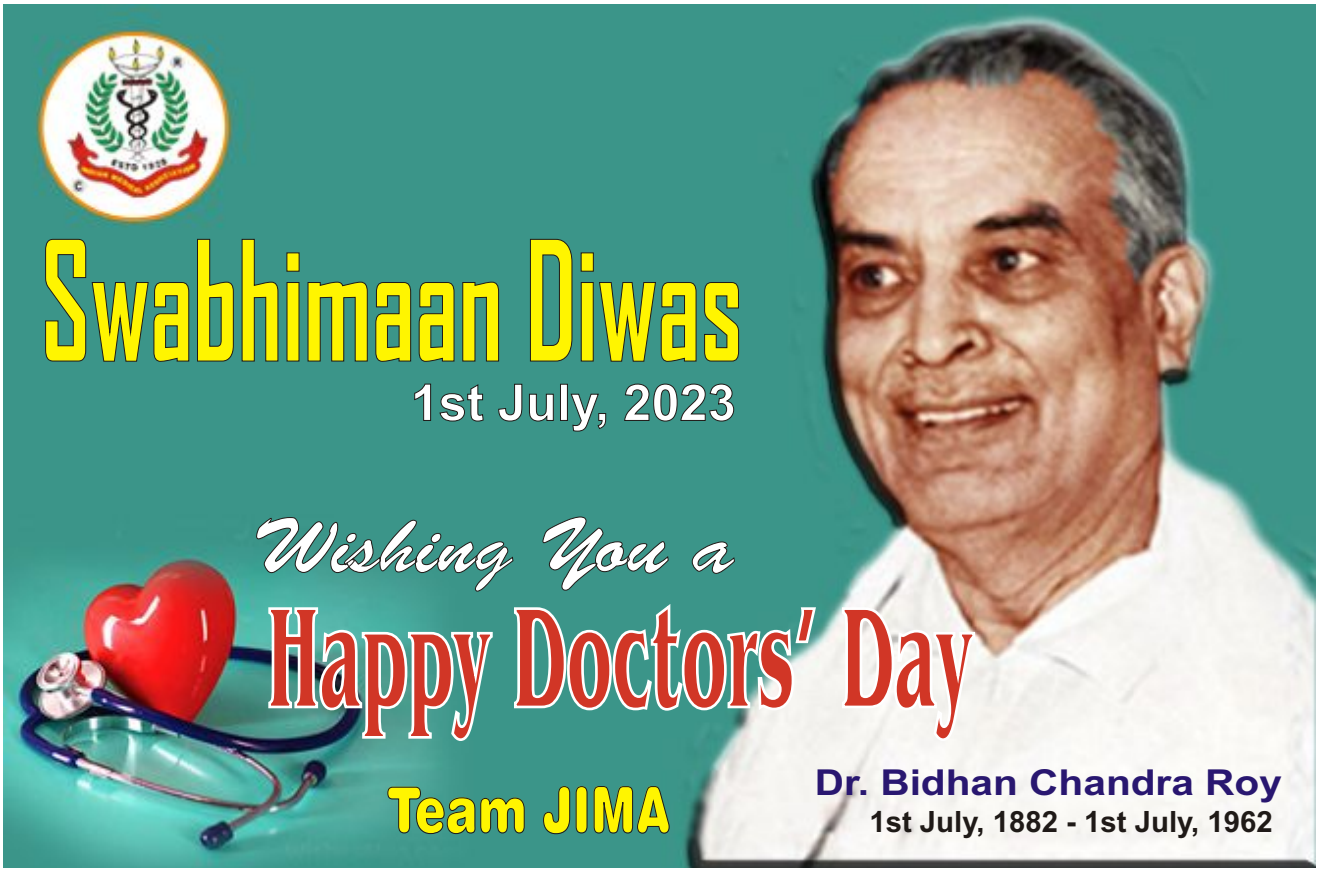

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Editorial

The Inheritence of Clarity

— Nandini Chatterjee
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The theme for this year's World No Tobacco Day was 'Grow food, not Tobacco'. The onslaught of wars, natural disasters and pandemics have led to a devastating food crisis and it is the need of the hour to device ways of increasing sustainable nutritious crop production to alleviate this problem. A global initiative to augment awareness about transition to alternative agricultural practices and marketing opportunities for tobacco farmers has been taken up.

How has tobacco affected human lives ?

Tobacco acts as a double edged sword harming the producers and the consumers both in the long run.

Growing tobacco contributes to deforestation, water scarcity , involves substantial use of pesticides and fertilizers, leading to soil degradation and depleted soil fertility. Harmful effects on health of the farmers have been documented adding to social and financial burdens.

Tobacco consumption has been designated as a health hazard for decades with identification of more than 43 carcinogens, such as nicotine, nitrosamines and alpha-emitting radionuclides such as polonium in its composition. Tobacco smoke contains carbon monoxide, thiocyanate, herbicide, fungicide and pesticide residues, tars, all of which lead to immunosuppression and potential carcinogenesis.

Smoking has been associated with over 85% deaths of all cancer deaths in men. It is estimated that 40-45% of all cancers and 90-95% of all lung cancers have an association with smoking. Chronic Pulmonary Obstructive Disease (COPD), cardiovascular diseases, strokes and peripheral vascular diseases all contribute to morbidity and mortality of the human race.

In regions where smokeless tobacco habits are endemic, like India, oral cancer can account for more than one-third of all cancers.

However, despite definite proof of its deleterious effects, tobacco production, marketing and consumption has been thriving down the ages.

How did it all begin ?

Tobacco is obtained from a plant from the night-shade family, indigenous to North and South America.

Use of tobacco has been traced back to the first century BC, when the Mayan population of Central America used tobacco leaves for smoking, in sacred and religious ceremonies. Migration of Mayan people led to the spread of tobacco use down south America.

Christopher Columbus arrived on the shores of America and apart from discovering the Red Indians, he also got familiarized with the use of tobacco leaves by the native tribes. Thereafter, Portuguese and Spanish sailors helped to spread different forms of tobacco around the world.

Tobacco cultivation in India was introduced by the Portuguese in 1605. Initially tobacco was grown in Gujarat and later spread to other areas of the country. In 1814, seven species of Nicotiana imported from America were cultivated in botanical gardens of Calcutta.

Tobacco has come a long way from this humble beginnings and now it is a booming billion dollar industry in countries like China, USA, the Former Soviet States, India and Brazil.

What is the way forward ?

The WHO and its global partners aims to diversify income options for tobacco farmers, building awareness for health hazards, preventing child labour,responsible water usage and provision of alternative healthier livelihoods .

The 2023 World No Tobacco Day campaign calls on policy-makers to develop suitable strategies for tobacco farmers to shift to growing food crops that would provide them and their families a secure and healthy life and livelihood.

Some of the ways out being contemplated are—

- Public awareness campaigns for community education.
- Healthcare services and screening programs for tobacco handlers.
- Strict regulations for tobacco farming practices.
- Support of research and innovation on alternative sustainable agriculture.

This is easier said than done as tobacco usage is not only addictive, it is rooted in our social and cultural domains coupled with ignorance about the potential harms.

However where there is a will, there is a way. What kind of a world we wish to leave for our children to live in ? The onus rests on our shoulders ....

Further Reading

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Original Article

Effect of Tocotrienol on Liver Enzymes, Fatty Liver and Liver Stiffness in People with Type 2 Diabetes and NAFLD : A Pilot Study Based on Biochemical and Transient Elastography Parameters

Arutselvi Devarajan[1], Lalith Kumar K Jayashankar[2], Prashanth Arun[3], Mitalee H Barman[4], Hemanga Barman[4], Satyavani Kumpatla[5], Vijay Viswanathan[6]

Background and Aims : Very few studies are available on the effect of Tocotrienol on Non-alcoholic Fatty Liver Disease (NAFLD) in people with diabetes in India. Hence our aim was to study the effect of tocotrienol on elevated liver enzymes, fatty liver and liver stiffness in people with Type 2 Diabetes.

Methods : A pilot randomized interventional study was conducted in a Tertiary Care Centre for Diabetes in Chennai during July, 2018 to March, 2020. A total of 34 individuals were recruited based on the inclusion criteria (age <65 years, elevated liver enzymes and an ultrasound finding of fatty liver) and randomized into two groups, group 1 (n=17) (control group) and group 2 (n=17) treated with Tocotrienol and followed up for 3 months. The data was analysed using SPSS version 28.

Results : There was no difference in any of the parameters among the groups at baseline except the levels of fasting glucose and globulin. The tocotrienol group showed significant reduction in the levels of SGOT (baseline *versus* follow up; 30.6±10.7 *versus* 25.1±10.1: p=0.035), SGPT, (46(21,104) *versus* 26.5(16,84): p=0.020), GGT, (35.5(16,103) *versus* 31.5(13,106): p=0.012), liver stiffness, 10.1(7.4,17.0) *versus* 9.1(5.5,17.6): p=0.046) and fatty liver (291.2±25.9 *versus* 272.6±20.4: p=0.023) after the intervention. The control group did not show improvement in any of the parameters post-intervention. The comparison of effect of intervention between the groups were found to be similar.

Conclusion : There was an improvement in fatty liver, liver stiffness and also the levels of SGOT, SGPT and GGT in group treated with Tocotrienol compared to control group.

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Key words **: Type 2 Diabetes, Tocotrienol, NAFLD, Intervention, India.**

The prevalence of Non-alcoholic Fatty Liver Disease (NAFLD) in Asia and the Pacific countries is markedly increasing over the last decades compared to the western countries[1-4]. The prevalence of NAFLD in India varies from 9-32% in the general population and 44 to 72% in people with diabetes[5]. Vitamin E is an essential nutrient as the human body cannot produce on its own. It is fat soluble in nature and has an anti-oxidative and anti- inflammatory properties against chronic diseases[6-8]. Tocopherols and Tocotrienols are the major derivatives of the Vitamin E family. Tocotrienols has the high potential of neuroprotective, anti-cancer properties and also reduces plasma cholesterol levels[9]. Suzuki, *et al* elucidated that Tocotrienol that contains unsaturated side chain would allow more efficient penetration into the brain and liver tissues compared to tocopherols that have saturated fatty layers[10]. A review that compiled the different functions and properties of tocotrienols in animal and human studies showed that there was an improvement in liver function in NAFLD among people without diabetes[8]. The literature on effect of administration of Tocotrienols for NAFLD among people with diabetes is limited. Hence, our aim

Editor's Comment :

- Tocotrienol reduced liver enzymes significantly in people with type 2 diabetes and NAFLD.
- A marked improvement was also noted in liver stiffness and fatty liver in the participants who were on tocotrienol for 3 months.
- The findings can be confirmed for any further effectiveness by conducting a longitudinal study with a larger sample.

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was to study the effect of tocotrienol on liver enzymes, fatty liver and liver stiffness in people with Type 2 Diabetes and NAFLD.

Materials and Methods

This was an open-labelled pilot study conducted in a Tertiary Care Centre for Diabetes in Chennai during July, 2018 to March, 2020. This randomized interventional trial was approved by the Institutional Ethics Committee(IEC/N-003/04/2018). A written informed consent was obtained from all the study participants. A total of 34 participants were recruited based on the inclusion criteria and randomized into two groups, group1 (n=17) (control group without Tocotrienol) and group 2 (n=17), treated with Tocotrienol (200mg twice daily) and both the groups were followed up after 3 months. The inclusion criteria were age <65 years, HbA1c≤8.5%, presence of elevated liver enzymes and an ultrasound finding of fatty liver. Viral markers were done to rule out the presence of viral hepatitis and those with Hepatitis B and C and those with habit of alcohol consumption were excluded from the study. The baseline treatment was not changed during the follow up period. No medicine known to influence the liver pathology was administered at baseline or during the follow up. The socio-demographic details, duration of diabetes, anthropometric details and blood pressure were collected at baseline. The bio-chemical parameters such as fasting and postprandial glucose, HbA1c, Serum albumin, protein, globulin, SGOT(AST), SGPT(ALT), ALP, GGT were collected at baseline and after intervention. BP and BMI were also recorded at follow-up visit. Glycated haemoglobin (HbA1c%) was estimated by immuno- turbidimetric method and liver enzymes by standard enzymatic procedures using fully automated biochemistry analysers. Fibrotouch (FT-100) (Wuxi Hiski Medical Technologies Co, Ltd, China) a non-invasive fibrosis diagnostic system that works on a Transient Elastography technology was used to measure Liver stiffness and also the degree of liver steatosis[11]. A sample of the report generated on Liver stiffness and Fatty liver from Fibrotouch is given as supplement 1. The compliance of medication was ensured by making telephonic calls or at their hospital visit during the study period.

During the study period, 1 participant each from the control and Tocotrienol group had dropped out due to personal reasons. At the end of the follow up, a total of 32 patients, 16 patients in each group were included for analysis. The paired t - test/Wilcoxon signed rank test was used respectively for intra-group comparison. The difference was calculated from baseline to follow up for all the study variables. Student 't' test or Mann Whitney 'U' test was performed appropriately to compare the difference between the groups at baseline and also the effect of intervention using the difference from follow up to baseline using SPSS version 28.

Results

Table 1 shows the baseline characteristics of the study groups. At baseline, the study groups were matched for their age, duration of diabetes, BMI, blood pressure, post prandial glucose levels, HbA1c levels of serum proteins, liver enzymes, measures of liver stiffness and fatty liver except for mean fasting glucose level (group 1 *versus* group 2;138±33.6 *versus* 164±33.3; p=0.043) and the median (min, max) globulin level (group 1 *versus* group 2; 2.8(2.4,3.4) *versus* 3.0(2.6,4.3); p=0.014. Around 94% of the study participants in group 1 were on Oral Hypoglycaemic Agents (OHA) compared to 81% in group 2 and the difference between the groups was not statistically significant.

There were also no changes found in parameters such as weight, BMI, blood pressure, blood glucose levels, HbA1c, total bilirubin, total protein, albumin and globulin levels in both the groups after intervention (Table 2). The tocotrienol group showed significant reduction in the levels of mean SGOT(IU/L) (baseline

Table 1 — *Basic clinical characteristics of the study groups*

Variables	Group I (n=16) (Control)	Group II (n=16) (Tocotrienol)	p value
Age (in years)*	53.4±8.9	54.3±8.1	0.824
Duration of diabetes (in years)*	4.3±2.1	4.6±2.3	0.630
BMI (Kg/m^2)	26.4(22.3,38.5)	27.9(25.4,37.3)	0.051
Systolic BP(mm/Hg)	130(110,140)	125(100,160)	0.461
Diastolic BP (mm/Hg)	80(70,90)	80(60,90)	0.381
Glucose levels(mg/dl)* :			
Fasting	138±33.6	164±33.3	0.043
Postprandial	222.5±77.1	254.4±66.6	0.230
HbA1c(%)*	7.3±1.4	8.0±0.9	0.163
T Bilirubin (mg/dl)	0.9(0.3,1.7)	0.5(0.4,1.5)	0.052
T Protein (gm/dl)*	7.6±0.40	7.9±0.6	0.136
Albumin (gms/dl)	4.9(4.1,5.3)	4.7(4.3,5.1)	0.255
Globulin (gms/dl)	2.8(2.4,3.4)	3.0(2.6,4.3)	0.014
SGOT (IU/L)*	32.3±11.2	30.6±10.7	0.667
SGPT (IU/L)	44(17,98)	46(21,104)	0.880
ALP (IU/L)	207(139,309)	174(79,378)	0.052
GGT (IU/L)	34(20,59)	35.5(16,103)	0.227
Liver Stiffness (kPa)	10.3(6.2,20)	10.1(7.4,17.0)	0.836
Fatty liver (db/m)*	285.1±39.2	291.2±25.9	0.602
Medication details			
OHA	15(93.7)	13(81.2)	0.285
OHA + Insulin	1(6.3)	3(18.8)	

Values are in median (min, max); * - Mean ±SD

Table 2 — *Intra group comparison of basic clinical profile and liver function before and after intervention*

Variables	Group I (n= 16) Control			Group II (n= 16) Tocotrienol		
	Baseline	Follow up	p value	Baseline	Follow up	p value
Weight (kgs)	73.7(57.2,109.1)	72.3(62.4,108.0)	0.470	79.7(60.5,98.1)	79.0(59.7,99.8)	0.311
BMI (Kg/m^2)	26.4(22.3,38.5)	27.1(21.6,39.0)	0.826	28.0(25.4,37.3)	28.5(24.6,39.3)	0.087
Systolic BP(mm/Hg)	130(110,140)	130(100,140)	0.291	125(100,160)	120(110,160)	1.000
Diastolic BP (mm/Hg)	80(70,90)	80(70,90)	0.178	80(60,90)	80(70,100)	0.957
Glucose levels (mg/dl)*						
Fasting	138.6 ±34.6	142.4±45.5	0.658	164±33.3	151.6±29.7	0.118
Postprandial	222.6±79.7	214.2±59.9	0.637	254.4±66.6	231.2±50.9	0.218
HbA1c(%)*	7.4±1.4	7.2±1.1	0.537	8.0±0.9	7.5±1.0	0.093
T Bilirubin (mg/dl)	0.9(0.3,1.7)	0.9(0.3,1.5)	0.730	0.5(0.4,1.5)	0.5(0.3,1.4)	0.314
T Protein (gm/dl)*	7.6±0.40	7.6±0.41	0.348	7.9±0.60	7.8±0.54	0.404
Albumin (gms/dl)	4.9(4.1,5.3)	4.8(3.8,5.2)	0.731	4.7(4.3,5.1)	4.7(4.2,5.1)	0.361
Globulin (gms/dl)	2.8(2.4,3.4)	2.8(2.3,3.3)	0.683	3.0(2.6,4.3)	3.2(2.1,3.7)	0.153

Values are in Median (min, max); * - Mean ± SD

versus follow up; 30.6±10.7 *versus* 25.1±10.1: p=0.035), median SGPT(IU/L), 46(21,104) *versus* 26.5(16,84): p=0.020), median GGT(IU/L), 35.5(16,103) *versus* 31.5(13,106): p=0.012), median liver stiffness (kPa), 10.1(7.4,17.0) *versus* 9.1(5.5,17.6): p=0.046) and mean fatty liver(dB/m) (291.2±25.9 *versus* 272.6±20.4: p=0.023) after the intervention. It was noted that the level of ALP (IU/L) was increased in both the groups after intervention, but the difference was non-significant. The control group did not show improvement in any of the parameters post-intervention (Fig 1 - Panel A & Panel B). None of the study participants reported any adverse events during the study period.

The difference in the levels of all study parameters from baseline to follow up visits were calculated and compared the effect of intervention between the groups. The difference between the groups was similar although there was a relative improvement found in many of the test parameters in the Tocotrienol group at follow up (data not shown).

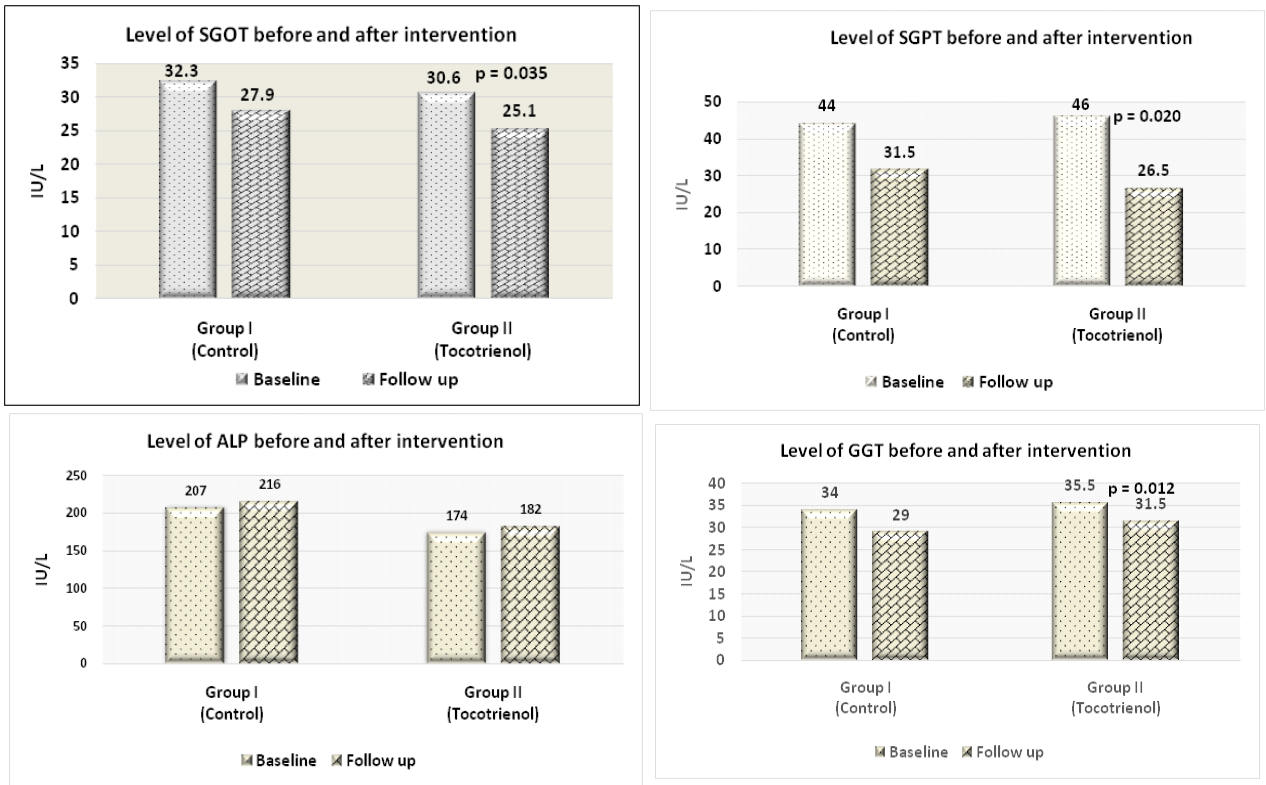

Fig 1 — Panel A: Levels of Liver enzymes before and after intervention

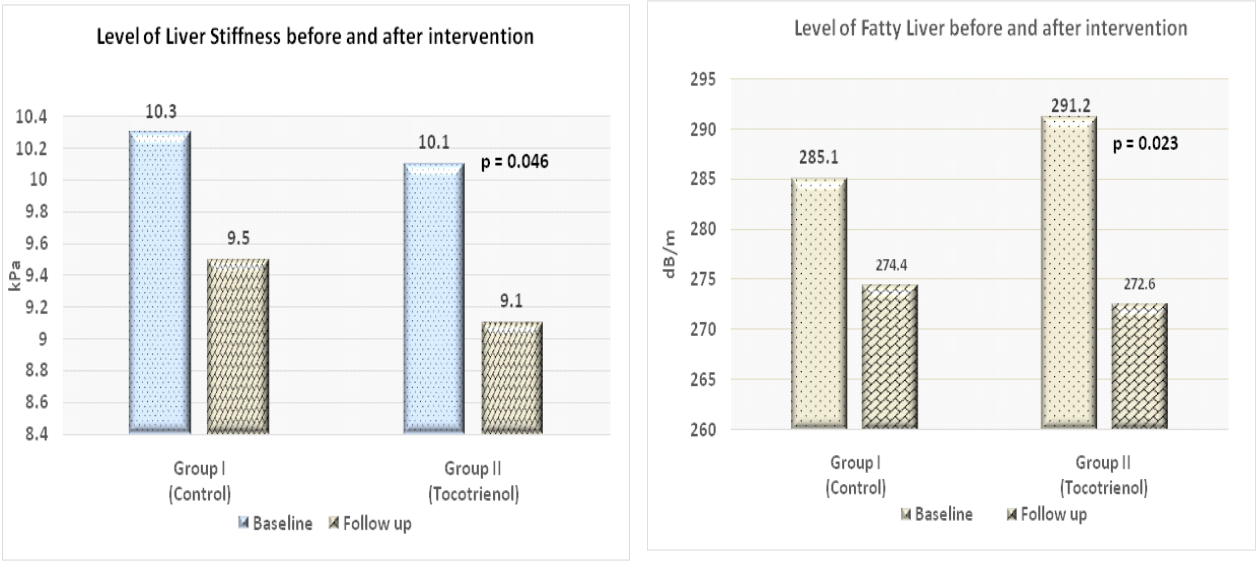

Fig 1 — Panel B: Measure of Liver Stiffness and Fatty Liver

Discussion

Our study findings highlighted that there was a significant reduction in liver enzymes and also measures of fatty liver and liver stiffness in patients who received tocotrienol for 3 months of follow up period. A randomized, double-blind, placebo-controlled study conducted in Pakistan showed significant reduction in the levels of SGOT, SGPT, GGT and ALP enzymes in the group that received d-tocotrienol compared to placebo[12] but ALP did not show any improvement in our study. A meta-analysis by Eder R, *et al* in 2019[13] reported that there was a significant decline in the SGPT level in people with NASH (n=61) who received 12 weeks' supplementation of Tocotrienol (200mg/twice daily).

In PIVENS trial[14], Vitamin E was found to be superior to placebo for the treatment of Non-alcoholic Steatohepatitis in adults without diabetes. There are very few studies conducted in assessing the effect of Vitamin E on NAFLD among people with diabetes. A three arm parallel-group, double-blind, randomized controlled study[15] was conducted among people who were having Type 2 Diabetes with NAFLD and followed them up for a period of 18 months. It showed reductions in SGOT and SGPT in both the intervention groups (that received a combination of pioglitazone(45mg/day) and Vitamin E 400IU b.i.d and only Vitamin E) compared to the placebo group. It also showed a significant improvement in steatosis in the intervention groups. But our findings revealed that there was no significant inter-group difference even though there was a fair reduction in Steatosis/fatty liver found in the tocotrienol group.

A multi-centric randomized double blinded placebo controlled study among children and adolescents having diabetes with NAFLD that observed the improvements occurred in ALT, histological features and resolution of NASH using 800 IU of Vitamin E in 58 patients, 1000mg of metformin in 57 patients and placebo in 58 patients. There was significant reduction in ALT in 24 weeks, 48 weeks in the Vitamin E group compared to placebo and metformin[16]. Madan, *et al*[17] compared lifestyle interventions, lifestyle interventions + UDCA and lifestyle interventions + UDCA + vitamin E in the management of NAFLD. They reported that the people who were in lifestyle interventions + UDCA + vitamin E group showed normal ALT levels and the difference was highly significant when compared to other two groups. Studies have shown both monotherapy of Vitamin E (tocopherol or tocotrienol) or combination of either or other agents improved the condition of NAFLD[18,19]. But the difference has been observed across the studies discussed in the method and design includes treatment allocation, randomization and duration of the study.

There are few limitations in the present study. First, it was pilot study with small sample size. Therefore, the findings have to be confirmed by further evaluating the effect of Tocotrienol in a larger sample. Second, the prolonged use of this may have beneficial or probable side effects which was not assessed in this study. Hence a longitudinal study will be planned to study the efficacy of Tocotrienol based on the current study.

Conclusion : In this pilot study, Tocotrienol was found to be effective in reducing liver enzymes and

showed improvement in fatty liver and liver stiffness. However, its' long term use needs to be evaluated for any further effectiveness.

Conflict of Interest : None

Sources of Funding : We did not receive any external funding for this study.

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Original Article

Etiological Heterogeneity of Pancytopenia without Organomegaly and Lymphadenopathy from A Tertiary Care Hematology Centre of Eastern India

Shuvra Neel Baul[1], Kusumita Mondal[2], Sandeep Saha[3], Biva Bhakat[4], Abhishek Sharma[5], Rajib De[6], Tuphan Kanti Dolai[7]

Most common cause of Pancytopenia without organomegaly and lymphadenopathy in pediatric age and adolescent group is Acute Leukemia. Hypoplastic Anemia is the most common cause in adult population. Elderly patients were least affected (6.66%) in this study.The sample size is small because of restricting ourselves to only Pancytopenia and no orgnomegaly, longer duration of follow up is not possible due to varied educational status of our patients and last but not the least, the COVID-19 pandemic was a huge deterrent for many patients to attend specialized health care facilities

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Key words **: Pancytopenia, Acute leukaemia, Hypoplastic anemia.**

Pancytopenia is an important clinico-hematological entity encountered in our day-to-day clinical practice. Pancytopenia is not a disease entity but a triad of findings in which all blood cell lineages ie, Leukocytes, Erythrocytes and Platelets are reduced in blood[1]. Presenting symptoms are usually attributable to anaemia, leucopenia or thrombocytopenia. Anaemia leads to fatigue, dyspnoea and cardiac symptoms. Thrombocytopenia leads to bruising, mucosal bleeding and neutropenia to sharply increased susceptibility to infection[2]. The common clinical manifestations of Pancytopenia are usually Fever (86.7%), Fatigue (76%), Dizziness (64%), Weight loss (45.3%), Anorexia (37.3%), Night sweats (28%), Pallor (100%), Bleeding (38.7%), Splenomegaly (48%), Hepatomegaly (21.3%) and Lymphadenopathy (14.7%)[3]. Etiological causes of Pancytopenia often vary by geographical region, age, and gender[4]. Nutritional megaloblastic anemia, caused by folate or Vitamin B12 deficiency, is one of the leading causes of Pancytopenia in developing countries[5]. The Bone Marrow picture may vary depending on the aetiology, from normocellular with non-specific changes to hypercellular being replaced completely by malignant cells. The marrow is generally hypocellular in cases of Pancytopenia caused by a primary production defect[6]. Cytopenia resulting from ineffective haematopoiesis, increased peripheral utilization or destruction of cells and Bone Marrow invasive processes are usually associated with a normocellular or hypercellular marrow[7]. It is recommended that Bone Marrow Aspiration (BMA) and Biopsy be done simultaneously in cases of Pancytopenia. Aspiration smears are superior for morphological details while Biopsy provides a more reliable index of cellularity and often reveals Bone Marrow Infiltration, Fibrosis and Granulomas[8]. Although Pancytopenia is a common clinical finding with extensive differential diagnosis, there is a paucity of data on patients without lymphadenopathy and organomegaly. This study has been undertaken to identify common causes of Pancytopenia in age based groups of such population.

Editor's Comment :

- It's not uncommon to encounter pancytopenia in clinical practices, the next step we do is an in detail clinical examination but when no organomgaly or lymphadenopathy is found, a clinician need to go deeper and in most cases.
- A bone marrow study needs to be performed and across different age groups acute leukaemia is most common and needs urgent attention.

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Materials and Methods

It is a descriptive cross-sectional study estimating the prevalence of the etiological causes of Pancytopenia without organomegaly and lymphadenopathy in four subgroups of patients stratified on the basis of age (pediatric ie, <12 years, adolescents and young ie, 13 -24 years, adults ie, 25-65 years and elderly ie, >65 years) over a period of one year from June, 2020-May, 2021. A total of 60 patients attending the OPD in NRS Medical College & Hospital from April 2021 to September 2021 presenting with Pancytopenia were analyzed. All patients were clinically examined in detail for palpable lymph nodes, hepatomegaly and splenomegaly. Peripheral blood samples were run on Sysmex XP 100 three part differential cell counter and pancytopenia was screened. Pancytopenia was defined as Hb <10gm/dl, WBC <4000/ml, Platelet Count<1, 00,000/ml. Peripheral Blood Smear (PBS) examination and morphological study of Bone Marrow Aspiration and Biopsy were done for all patients of Pancytopenia. The Peripheral Blood Smear (PBS) & Bone Marrow Aspirate (BMA) smears were stained by Leishman Giemsa (LG) stains and the Biopsy sections were stained with routine Hemotoxylin and Eosin (H&E). Iron status was assessed on the BMA smears with Perls stain where possible. Subsequently etiological causes of Pancytopenia were analyzed,peripheral smear were analyzed for Red Blood Cell (RBC) shape and size, any circulating immature White Blood Cells (WBC) and also exact platelet count. Reticulocyte count was also done with new methylene blue in all patients. Vitamin B12 & folic acid were done in all patients with Chemiluminescent Immunoassay Technology (CLIA) assay; the cut off blast percentage for diagnosis of acute leukaemia was taken as more than equal to 20%.Cytogenetics was sent for all patients and it was outsourced as this facility was unavailable in our lab. An Ultrasonography of abdomen was done to rule out hepato-splenomegaly.

Inclusion Criterion :

- Pancytopenic patients as defined
- Without any associated lymphadenopathy, splenomegaly & hepatomegaly

Exclusion Criterion :

- Less than 1 year of age
- Any associated lymphadenophathy
- Any associated splenomegaly & hepatomegaly
- Unwilling for bone marrow study
- Patients with chronic liver disease
- Pregnancy

Results

In Table 1,baseline parameters of the patients were mentioned, patients with Pancytopenia without organomegaly were divided into four age groups notably, pediatrics with age group less than equal to 12 years, adolescent and young adults, adults and elderly .Mean age in each group are 6,17,44 & 73 years respectively. There is male preponderance in each group. The Complete Blood Count (CBC) comprising of hemoglobin, total leucocyte count, platelet counts, absolute neutrophil counts and reticulocyte count depicts pancytopenia like blood picture at baseline.

Overall out of 60 patients 21 patients (35%) were diagnosed as acute leukemia, 28 patients (48 %) as hypoplastic anemia, 4(6%) as MDS, 1 (1.5%) as megaloblastic anemia and as lymphoma infiltrate each, lastly hemophagocytosis 5 (8%) (Fig 1).

Age and etiology of pancytopenias were further analyzed, it was noted that acute leukaemis are more

Table 1 — *Baseline parameters of patients (N=60)*

Pediatric (<12 years) n=16	Mean values	Range
Mean age	6 years	1-12 years
Sex(male:female)	11:5	-
Hemoglobin(Hb)	6.3 g/dl	4.3-8.1 g/dl
Total Leucocyte Count (TLC)	2300/cmm	1100-3200/cmm
Absolute Neutrophil Count (ANC)	800/cmm	400-1100/cmm
Total Platelet Count	53000/cmm	12000-80000/cmm
Reticulocyte Count	0.6%	0.4-1.1%
Adolescent & Young (13-24 years) n=11		
Mean age	17 years	13-24 years
Sex(male:female)	8:3	-
Hemoglobin(Hb)	7.6 g/dl	3.6-9.2 g/dl
Total Leucocyte Count (TLC)	1600/cmm	900-3400/cmm
Absolute Neutrophil Count (ANC)	400/cmm	300-700/cmm
Total Platelet Count	47000/cmm	10000-77000/cmm
Reticulocyte Count	0.6%	0.4-1.2%
Adults (25-65 years) n=29		
Mean age	44 years	25-65 years
Sex (male : female)	19:10	-
Hemoglobin (Hb)	6.2 g/dl	3.5-8.6 g/dl
Total Leucocyte Count (TLC)	2300/cmm	1000-3700/cmm
Absolute Neutrophil Count (ANC)	600/cmm	200-1200/cmm
Total platelet Count	52000/cmm	15000-84000/cmm
Reticulocyte Count	0.8%	0.6-1.4%
Elderly (>65 years) n=4		
Mean age	73 years	66-77 years
Sex (male : female)	3:1	-
Hemoglobin (Hb)	7.8 g/dl	4.4 -8.3 g/dl
Total Leucocyte Count (TLC)	1800/cmm	1100-2300/cmm
Absolute Neutrophil Count (ANC)	600/cmm	400-900/cmm
Total platelet Count	35000/cmm	8000-43000/cmm
Reticulocyte Count	0.6%	0.4-1.2%

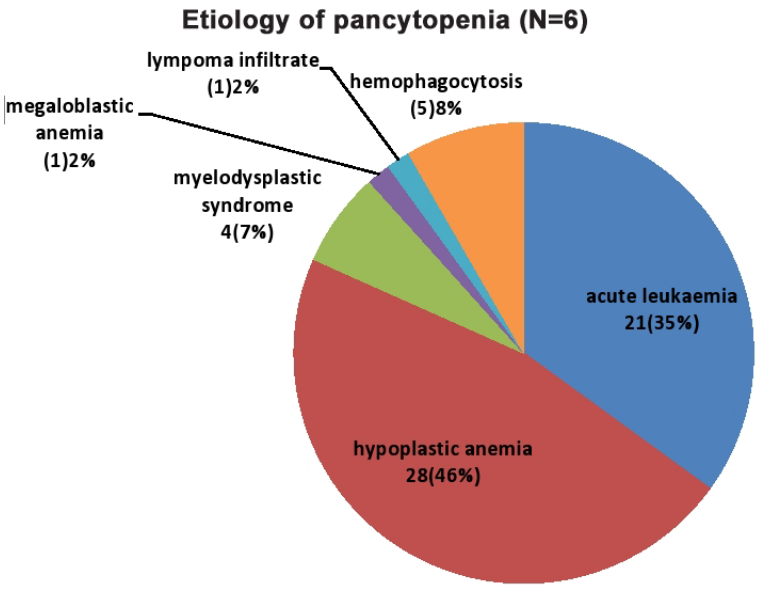

Fig 1 — Etiological distribution of 60 patients with Pancytopenia

common in the age group of paediatric and adolescents, compared to adults. Hypoplastic anemias were more common in the adults and other rarer etiologies as shown were more common in adults and elderly (Fig 2).

Discussion

In a study by Pizzo PA, *et al* from a different geographical region had shown that etiologies of Pancytopenia were quite varied, acute leukemia and Bone Marrow Failure Syndrome were well recognized causes where as infection and Megaloblastic anemia were not common in pediatric population[9]. Though the above study didn't excluded lymphadenopathy and organomegaly but their results were similar to ours.

A study from Eastern Mediterranean region conducted among adults by Nafil H, *et al* had shown that main causes of Pancytopenia were Megaloblastic Anemia (32.2%) and Acute Leukemia (23.7%) followed by Aplastic Anemia (15.2%)[10].

Another study from Karachi by Farooque R, *et al* also had shown that main cause of pancytopenia in adult was Megaloblastic Anemia (41.7%)[11]. But this study revealed main causes to be Hypoplastic Anemia followed by hypersplenism,so organomegaly was not excluded.

A study done among elderly population by Thyagaraj V, *et al* had shown that most common cause of Pancytopenia was Megaloblastic Anemia(60%) followed by aplastic anemia (7.5%) and Myelodysplastic syndrome (5%)[12]. Though a few elderly patients were included in the present study, the etiologies of Pancytopenia can be Hypoplastic Anemia and Myelodysplastic syndrome.

As etiology is concerned Megaloblastic anemia seems to be major contributing factor in different studies and it is curable. But in our study shows Hypoplastic anemia and acute Leukemia were the most common causes among younger age group and pediatric population. If Pancytopenia is associated with organomegaly such as lymphadenopathy and hepatospleomegaly as most studies across world has reported, but to report the causes of isolated Pancytopenia is unique in our study. This might be reason for our small sample size.

For any patients regardless of age Pancytopenia is a sinister finding in Complete Blood Count hence Bone Marrow studies are absolutely indicated along with other needful investigations such as immuopheotyping and cytogenetics.

It is also important to evaluate for Vitamin B12, folic acid

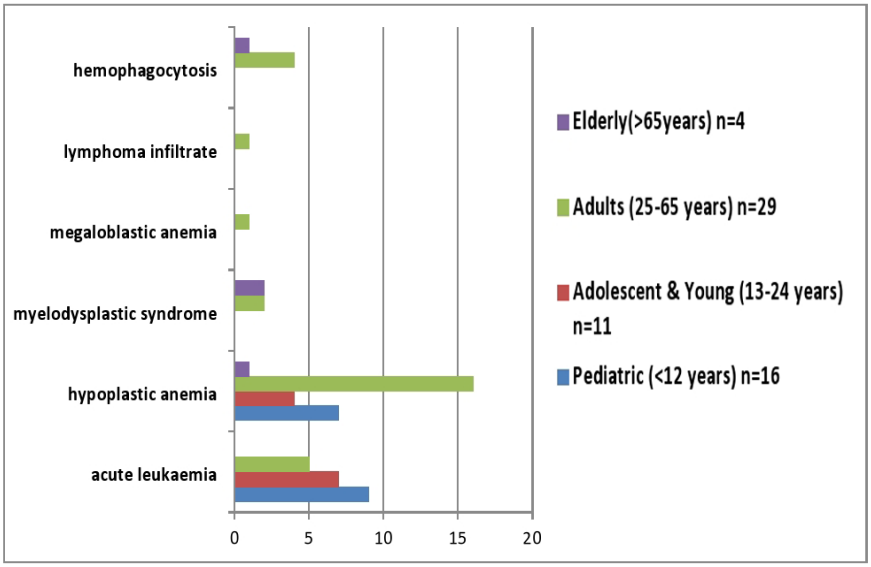

Fig 2 — Age wise etiological distribution of patients with Pancytopenia

deficiency as these are curable with replacement therapy. In our study however it was insignificant due to predominance of non- vegetarian population from Eastern India.

Such etiological knowledge is essential for clinicians in remote areas to intervene early and judicious management especially the hygiene for individual patients.

Limitations of the study :

The sample size is small because of restricting ourselves to only Pancytopenia and no orgnomegaly, longer duration of follow up is not possible due to varied educational status of our patients and last but not the least, the Covid-19 pandemic was a huge deterrent for many patients to attend specialized health care facilities.

Conclusion

Most common cause of pancytopenia without organomegaly and lymphadenopathy in pediatric age and adolescent group is acute leukemia. Hypoplastic anemia is the most common cause in adult population. Elderly patients were least affected (6.66%) in this study

Declaration of patient consent : Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship : Nil

Conflicts of interest : There are no conflicts of interest.

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Original Article

A Study of Knowledge, Attitude and Practice among the Mothers Regarding Management of Childhood Diarrhoea

Sweety Patel[1], Vaidehi V Mehta[2], Nisarg K Chaudhari[3], Ekta D Patel[4]

Background : Mothers are the primary health care providers so that mother's knowledge regarding causes of Diarrhoea, sign and symptoms, prevention and control are very essential for decreasing morbidity and mortality due to Diarrhoea.

Objective : To study knowledge, observe attitude and assess practice of mother regarding childhood diarrhoeal disease management.

Methods : A cross sectional observational study conducted in Department of Pediatrics at a Tertiary Care Hospital. Total 150 mothers of children affected with Diarrhea attending Pediatric Outpatient Department or admitted were included in study. All the mothers who were qualified under the inclusion criteria along with informed consent are subjected to Knowledge, Attitude and Practice (KAP) designed format for the record. Data was collected from mothers by standard questionnaire method.

Results : In our study, 44% mothers were having excellent knowledge, 52% of mothers have negative attitude towards management of Diarrhoea on home basis and using ORS and 42% of mothers practicing poorly. We found significant association of mother's education to their knowledge and practice and also between Socio-economic status and mother's attitude and practice.

Conclusion : There is need of proper and effective health education to mothers regarding diarrhoea, it's causes, prevention and management. Healthy practices adopted by mother can raise healthful living condition thereby lessens the morbidity and mortality of children.

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Key words **: Diarrhoea, Oral Rehydration Solution, Knowledge, Attitude, Practice.**

Diarrhoea remains the second leading cause of death for children under five worldwide[1]. In India, Control of Diarrhoeal Disease (CDD) was implemented from 1980 as a part of Sixth Five Year Plan (1980-85) with the primary thrust of improving the knowledge and practices of appropriate case management among caretakers and health care providers and primary objective of preventing deaths due to dehydration. This program was integrated within Child Survival and Safe Motherhood (CSSM) program[2]. Diarrhoea is due to infections caused by a wide range of organisms which include bacteria, viruses and protozoans. 58% of deaths due to Diarrhoea have been attributed to unsafe water supply and lack of sanitation and hygiene (inadequate wash)[3]. The key components of preventing childhood diarrhoea are improving access to safe drinking water, adequate sanitation and promoting good hygiene[4]. Diarrhoea-related mortality and morbidity can be decrease with implementation of clean water use, hand washing, exclusive breastfeeding, immunization and proper sanitary disposal of excreta. Secondary measures include early detection of dehydration due to Diarrhoea and prompt oral rehydration, increasing and continuing intake of energy-dense foods in addition to breastfeeding and Zinc therapy[5]. Timely and appropriate management at household and in health services remain an important intervention for reducing mortality and morbidity due to childhood Diarroea[6]. However, poor Socio-economic status, lack of caregiver's knowledge and inability to provide treatment when needed are barriers to preventing diarrheal deaths[7]. Its burden has reduced from 11% of childhood deaths to 9% from the year 2008 to 2015[8,9]. The mortality due to Diarrhoea in children under 5 years

Editor's Comment :

- Health education is the most important tool for effective management of childhood diarrhoea.
- It increases capability to recognize danger signs of diarrhoea in children and to encourage appropriate and early case seeking behaviours which can only be provided on the basis of an accurate understanding of prevailing knowledge, attitude and practices of mothers.

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has been reduced in last two decades. This reduction may be due to proper management of cases by following standard treatment guidelines recommended by WHO and using oral rehydration therapy as the cornerstone of management[10]. Effective health education can only be provided based on a thorough understanding of the community's general Knowledge, Attitudes and Practices (KAP). Therefore, obtaining relevant information on maternal KAP on Diarrhoea is essential for successful control activities. As mothers are the primary health care providers, their awareness of the causes, signs and symptoms, prevention and management of diarrhoea is of great importance, thereby reducing the morbidity and mortality of Diarrhoea. Considering the central role of mothers in managing Diarrhoea, the joint statement of the World Health Organization and UNICEF emphasized the need to understand the mother's knowledge, attitude and practice regarding Diarrhoea[11].

The purpose of this study is to evaluate and compare the level of awareness and observe the mother's attitude and practice regarding the causes of diarrhoea and its prevention and management.

Materials and Methods

A cross sectional observational study was conducted over a period of 2 year in Department of Paediatrics at a Tertiary Care Hospital, Ahmedabad. All Patients below 5 years of age from Outpatient and inpatient department with Acute Diarrhoea (<14 days) were included in this study and patients having chronic diarrhoea (>14 days), known case of malabsorption syndrome, Celiac disease and patients having dysentery were excluded from this study. 150 mothers of children affected with Diarrhoea who were qualified under inclusion criteria along with informed consent were subjected to KAP designed format for record. Data was collected from mothers in pre-designed proforma consisting of demographic data and standard questionnaire for knowledge, attitude and practice of mother about management of childhood Diarrhoea. Data were entered in Microsoft excel 2016 and analysis was carried out using SPSS version 21. Chi-square test with level of significance <0.05 was used for as statistical test to test various associations.

Discussion and Results

In present study, 68% of patients were below 24 months of age group followed by 20% patients which were in 25 to 59 months age group. In this study it was found that children less than 2 years of age are more prone to having Diarrhoea. Mean age is 26.89 months.

In a study by Walker, *et al*[12] Diarrhoea incidence rates were highest among children 6-11 month of age and lowest among children 24-59 month of age. Distribution according to age groups of mothers shows majority of the mothers 62.7% mothers were in age group of 21 to 30 years. In a study conducted by Workie, *et al*[13] 51.5% mothers were in the age group of 25 to 34 years. Another similar study conducted by Gollar, *et al*[14] 71% mothers were in age group of 21 to 30 years. It suggests 35.3% mothers were educated up to secondary level, 28% mothers were educated up to higher secondary level while 9.3% mothers were illiterate. In a study by Gollar, *et al*[14] 47% mothers were educated up to secondary level and 37% mothers were educated up to higher secondary level. Distribution according to area of residence showed amongst 150, 148 (98.7%) mothers were living in Urban area and only 2 (1.7%) mothers were living in Rural area. Socio-economic status of patients showed majority of the mothers (43.3%) were belongs to lower middle class followed by 22% to middle class and 18% to lower class. In the study conducted by Mukhtar, *et al*[15] 44.6% mothers were belonging to lower class. Lower Socio-economic status did influence knowledge, attitudes and practices, household with lower socio-economic status tends to rely more on local options, especially drug stores whereas higher Socio-economic status households preferred to visit private Physicians and even distant options more frequently. Amongst 150 children, overcrowding was present in 135 (90%) and absent in 15 (10%) children. Overcrowding makes sanitation difficult and makes children more susceptible to Diarrhoea. Distribution of patients according to immunization status shows majority of the children (82%) have completed their immunization for age and 18% children did not complete their immunization for age. Though the majority of patients are from Lower middle and lower Socio-economic status, immunization among the children is quite promising. It suggests strong results from impact of Anganwadi workers, ANM, ASHA workers and Government programs. According to feeding history of the patients 53.3% children practiced or practicing exclusive breastfeeding and 46.7% children did not practice exclusive breastfeeding. Moreover, history of bottle feeding was absent in 76.7% patients and present in 23.3% patients. A similar study conducted by Rokkappanavar KK, *et al*[16], showed that only 50.49% of mothers were exclusively breastfeeding at the time of the study. The rest were either unaware of exclusive breastfeeding or did not practice breastfeeding. Of the study subjects, 20.09% practiced/practicing bottle feeding at the time of the study.

Table 1(A) indicates majority of mothers know about causes of Diarrhoea.

When it comes to breastfeeding and ORS, most mothers are aware of its beneficial role. In a similar study, Rokkappanavar KK, *et al*[16] showed that most of the subjects (86.27%) were aware of ORS sachets. When asked about the appropriate time to administer ORS to their children, the majority (52.27%) of mothers gave the correct answer of administering ORS during an episode of Diarrhoea while 46.02% mother prefer to give ORS to child whenever child is sick. The majority of mothers (58.52%) had sufficient knowledge about the preparation and use of ORS solution. In our study, 44% mothers have excellent knowledge of childhood Diarrhoea and its management followed by 36% mothers who have poor knowledge about it. Mean knowledge score is 6.68 and SD is 4.05.

Table 1(B) shows association between knowledge and education and Socio-economic status of mothers, which is statistically significant. It can be observed that in all the knowledge components higher percentage of mothers with higher secondary and above educational level have correctly responded than those with lower educational level. Similarly, higher numbers of mothers from upper middle and above level of Socio-economic class have responded correctly than those from middle and lower socio-economic class.

Table 2(A) denotes attitude of mothers towards management and use of ORS in childhood Diarrhoea. Majority of mothers believe that Diarrhoea is not manageable at home with help of ORS. In our study, 48% of mothers have positive attitude about childhood Diarrhoea and its management with ORS while 52% mothers have negative attitude about it. Mean attitude score is 3.19 and SD is 2.58.

Table 2(B) suggest that education and Socio-economic status of mother is statistically significantly ($p<0.01$) associated with attitude of mother in majority of questions. So, it can be observed that in all the attitude components higher percentage of mothers have correctly responded whose education status is higher secondary and above level and from upper middle and above socio-economic class. In a similar study, Gollar, *et al*,[17] it was found that mothers who had serious attitude toward diarrheal illness were 71%. In mothers who were in the age group of <25 years, 42% mothers and 40% of mothers who had completed school education and 56% of mothers who belonged to higher socio-economic status had serious attitude regarding Diarrhoea.

Table 3(A) suggests practice of mothers about childhood Diarrhoea. Regarding practice we have observed that majority of mothers use ORS at home. Most of mothers increases food and fluid offering to their children and also higher percentage of mothers continue breastfeeding during Diarrhoea. In our study, we observed poor practice of management of childhood Diarrhoea in higher percentage ie, 42% of mothers followed by excellent practice in 36%. Mean practice score is 7.11 and SD is 4.03.

It is evident from Table 3(B) that there is statistically significant association of mother's educational and Socio-economic status with practice levels ($p<0.01$). It can be observed that 67.4% of mothers with education level higher secondary and above have excellent practice of management of childhood Diarrhoea as compared to mothers with secondary and below level education group among whom poor practice is in highest percentage ie, 44.4%. Similarly, it can be observed that higher percentage ie,76 % of mothers with Socio-economic status upper middle and above

Table 1(A) — *Knowledge of mothers regarding childhood diarrhoea (N=150)*

Knowledge of mothers regarding childhood diarrhoea	Response	
	No of mothers	% of mothers
What is diarrhoea		
Correctly described	122	81.3
Incorrectly described	28	38.7
Cause of diarrhoea		
Viral/bacterial infection	95	63.3
Teething	39	2
Eating spicy food	15	10
No idea	01	0.7
Knowledge about role of breast feeding in diarrhoea		
Correct response	81	54
Incorrect response	69	46
Knowledge about role of bottle feeding in diarrhoea		
Correct response	86	57.3
Incorrect response	64	42.7
Age at which child sufferfrom diarrhoea		
Less than 2 years	99	66
2 to 5 years	37	24.7
More than 5 years	14	9.3
Knowledge about use of ORS in diarrhoea		
Yes	133	88.7
No	17	11.3
How Oral Rehydration Solution is beneficial inchild?		
It replaces water lost in diarrhoea from child'sbody	113	75.3
It cures diarrhoeal disease	31	20.7
No idea	06	04
Are health care interventions required to treat diarrhoea?		
Yes	69	46
No	19	12.7
Not in all cases	62	41.3

Table 1(B) — *Association of Knowledge of mothers regarding childhood diarrhoea with their educational and socio-economic status (N=150)*

Knowledge of mothers regarding childhood diarrhoea Question/ Response	Education status: Secondary and below No of mothers	Secondary and below % of mothers	Higher secondary and above No of mothers	Higher secondary and above % of mothers	Test statistics	Socio-economic status: Middle level and below No of mothers	Middle level and below % of mothers	Upper middle and above No of mothers	Upper middle and above % of mothers	Test statistics
What is diarrhoea										
Correctly described	74	76.3%	48	90.6%	χ^2= 4.6 df=1	101	80.8%	21	84%	χ^2= 0.14 df=1
Incorrectly described	23	23.7%	05	9.4%	p=0.03	24	19.2%	04	16%	p=0.7
Cause of diarrhoea										
Correct	50	51.5%	45	84.9%	χ^2= 16.4 df= 1	72	56.7%	23	92%	χ^2= 10.6 df= 1
Incorrect	47	48.5%	08	15.1%	p<0.01	53	42.4%	02	8%	p<0.01
Knowledge about roleof breast feeding indiarrhoea										
Correct	30	30.9%	42	79.3%	χ^2=32.0 df= 1	49	39.2%	23	92%	χ^2= 23.2 df= 1
Incorrect	67	69.1%	11	20.8%	p<0.01	76	60.8%	02	8%	p<0.01
Knowledge about role of bottlefeeding in diarrhoea										
Correct	26	26.8%	39	73.6%	χ^2= 30.5 df= 1	46	36.8%	19	76%	χ^2= 13.03 df= 1
Incorrect	71	73.2%	14	26.4%	p<0.01	79	63.2%	06	24%	p<0.01
Age at which child suffer from diarrhoea										
Correct	37	38.1%	44	83%	χ^2= 27.8 df= 1	59	47.2%	22	88%	χ^2= 13.9 df= 1
Incorrect	60	61.9%	09	17%	p<0.01	66	52.8%	03	12%	p<0.01
Knowledge about use of ORS in diarrhoea										
Yes	43	44.3%	43	81.1%	χ^2= 18.9 df= 1	65	52%	21	84%	χ^2= 8.7 df= 1
No	54	55.7%	10	18.9%	p<0.01	60	48%	04	16%	p<0.01
How Oral Rehydration Solution is beneficial in child?										
Correct	54	55.7%	45	84.9%	χ^2= 13.0 df= 1	76	60.8%	23	92%	χ^2= 9.03 df= 1
Incorrect	43	44.3%	08	15.1%	p<0.01	49	39.2%	02	08%	p<0.01
Are health care interventions required to										
Correct	81	83.5%	52	98.1%	χ^2= 7.3 df= 1	108	84.6%	25	100%	Yate's χ^2= 2.6
Incorrect	16	16.5%	01	1.9%	p<0.01	17	13.6%	00	0%	df= 1 p<0.01
Mode of spread of diarrhoea										
Correct	66	68%	47	88.7%	χ^2= 7.8 df= 1	91	72.8%	22	88%	χ^2= 2.6 df= 1
Incorrect	31	32%	06	11.3%	p<0.01	34	27.2%	03	12%	p<0.01
What are danger signs associated with diarrhoea in children?										
Correct	23	23.7%	39	73.6%	χ^2= 35.1 df= 1	42	33.6%	20	80%	χ^2= 18.5 df= 1
Incorrect	74	76.3%	14	26.4%	p<0.01	83	66.4%	05	20%	p<0.01
How diarrhoea can be prevented?										
Correct	30	30.9%	45	84.9%	χ^2= 39.9 df= 1	50	40%	25	100%	χ^2= 30 df= 1
Incorrect	67	69.1%	08	15.1%	p<0.01	75	60%	00	0%	p<0.01

Table 2(A) — *Attitude of mothers towards childhood diarrhoea and its management (N=150)*

Attitude of mothers towards childhood diarrhoea and its management	Response: No of mothers	% of mothers
Diarrhoea is preventable disease and manageable at home		
Agree	67	44.7
Disagree	83	55.3
Oral rehydration solution is first line of treatment for diarrhoea in children		
Agree	72	48
Disagree	78	52
Mother/family member can prepareoral solution at home		
Agree	86	57.3
Disagree	64	42.7
Giving oral rehydration solution at home can treat diarrhoea		
Agree	69	46
Disagree	81	54
My child dislikes the taste of oral rehydration solution		
Agree	70	46.7
Disagree	80	53.3
Oral rehydration solution replaces the fluid lost in diarrhoea		
Agree	117	78
Disagree	33	22

have excellent practice of management of childhood Diarrhoea as compared to mothers with middle and below level Socio-economic status group among whom poor practice is in highest percentage ie, 39.2%.

Conclusion

Most of the mothers were aware of the causes and management of Diarrhoea with ORS and the beneficial role of breastfeeding in Diarrhoea. Our study found a strong association between educational status, Socio-economic status of mothers and knowledge, attitude and practices related to management of diarrheal disease (p<0.001). Lack of awareness can lead to improper use

Table 2(B) — *Association of attitude of mothers towards childhood diarrhoea with their educational and socio-economic status (N=150)*

Attitude of mothers towards childhood diarrhoea Question/ Response	Education status: Secondary and below — No of mothers	Education status: Secondary and below — % of mothers	Education status: Higher secondary and above — No of mothers	Education status: Higher secondary and above — % of mothers	Test statistics	Socio-economic status: Middle level and below — No of mothers	Socio-economic status: Middle level and below — % of mothers	Socio-economic status: Upper middle and above — No of mothers	Socio-economic status: Upper middle and above — % of mothers	Test statistics
Diarrhoea is preventable disease and manageable at home										
Agree	25	25.8%	42	79.2%	χ^2= 36.9 df=1	44	35.2%	23	92%	χ^2= 27.2 df=1
Disagree	72	74.2%	11	20.8%	p<0.01	81	64.8%	02	08%	p<0.01
Oral rehydration solution is first line of treatment for diarrhoea in children										
Agree	37	27.8%	45	84.9%	χ^2= 44.7 df= 1	47	37.6%	25	100%	χ^2= 32.5 df= 1
Disagree	70	72.2%	08	15.1%	p<0.01	78	62.4%	00	00%	p<0.01
Mother/family member can prepare oral solution at home										
Agree	39	40.2%	47	88.7%	χ^2= 32.9 df= 1	61	48.8%	25	100%	χ^2= 23.2 df= 1
Disagree	58	59.8%	06	11.3%	p<0.01	64	51.2%	00	00%	p<0.01
Giving oral rehydration solution at home can treat diarrhoea										
Agree	28	28.9%	41	77.4%	χ^2= 32.4 df= 1	46	36.8%	23	92%	χ^2= 25.5 df= 1
Disagree	69	71.1%	12	22.6%	p<0.01	79	63.2%	02	08%	p<0.01
My child dislikes the taste of oral rehydration solution										
Agree	26	26.8%	44	83%	χ^2= 43.5 df= 1	47	37.6%	23	92%	χ^2= 24.7 df= 1
Disagree	71	73.2%	09	17%	p<0.01	78	62.4%	02	08%	p<0.01
Oral rehydration solution replaces the fluid lost in diarrhoea										
Agree	67	69.1%	50	94.3%	χ^2= 12.7 df= 1	92	73.6%	25	100%	χ^2= 8.4 df= 1
Disagree	30	30.9%	03	5.7%	p<0.01	33	26.4%	00	00%	p<0.01

Table 3(A) — *Practice of mothers for management of childhood diarrhoea (N=150)*

Practice of mothers for management of childhood diarrhoea	Response: No of mothers	Response: % of mothers
Do you prepare ORS at home ?		
Yes	114	76
No	36	24
How ORS is prepared ?		
One sachet of ORS to be mixed with 500 ml of water	47	31.3
One sachet of ORS to be mixed with 1000 ml of water	89	59.3
One sachet of ORS to be mixed with 1500 ml of water	14	9.3
Others (Specify)_____		
Is water used for making ORS is boiled initially?		
Yes	107	71.3
No	43	28.7
How long prepare ORS isused?		
Up to 24 hours	93	62
Up to 48 hours	38	25.3
Up to 72 hours	09	6
Up to 96 hours	04	2.7
Don't know	06	4
How often do you give ORS to your child?		
After every stool	54	36
Once a day	20	13.3
Two to three times a week	22	14.7
Whenever child wants to drink	54	36
Do you taste ORS before giving it to child?		
Yes	31	20.7
No	119	79.3

Practice of mothers for management of childhood diarrhoea	Response: No of mothers	Response: % of mothers
Practice of breastfeeding to child during episode of diarrhoea		
Continue breastfeeding	81	54
Not giving breastfeeding	64	42.7
Don't know	05	3.3
What is practice of giving fluid for drinking when he/she is suffering from diarrhoea?		
Less than usual	31	20.7
Same as usual	25	16.7
More than usual	94	62.7
What is practice of giving food for drinking when he/she is suffering from diarrhoea?		
Less than usual	72	48
Same as usual	24	16
More than usual	54	36
Do you use homemade solution to your child for diarrhoea		
Yes	96	64
No	54	36
How do you prepare homemade solution?		
Correctly described	49	32.7
Incorrectly described	47	31.3
What do you do to your child in case of diarrhoea initially?		
Household remedies with ORS	87	58
Health care center consultation	63	42

Table 3(B) — *Association of mother's educational and socio-economic status with practice categories (N=150)*

Practice level	Education status				Socio-economic status			
	Secondary and below		Higher secondary and above		Middle level and below		Upper middle and above	
	No of mothers	% of mothers	No of mothers	% of mothers	No of mothers	% of mothers	No of mothers	% of mothers
Excellent	27	27.8%	36	67.4%	44	35.2%	19	76%
Good	27	27.8%	06	11.3%	32	25.6%	01	04%
Poor	43	44.4%	11	20.8%	49	39.2%	05	20%
χ^2= 22.6, df= 2, p<0.01					χ^2= 14.8, df= 2, p<0.01			

of health services available in the community. Therefore, health education should be used as a tool to promote knowledge and good practice. As Mothers are the primary health care providers, mother's knowledge regarding causes of diseases, sign and symptoms, prevention and control are very essential thereby decreasing morbidity & mortality due to diarrhoea.

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Original Article

Constraints of the Palliative Care Patients during Pandemic — A Cross-sectional Study

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Background : The challenge faced by Palliative care patients is vast even in the absence of a pandemic. COVID-19 is anticipated to surpass the capacity of the Healthcare system including Palliative care services.

Aim : To address the challenges faced by the palliative care patients during COVID-19 pandemic.

Setting and Design : This cross-sectional study was conducted in a Cancer institute.

Materials and Methods : This study was conducted among patients receiving Palliative care services in a Cancer Institute between September and October 2020 using semi-structure questionnaire.

Statistical Analysis Used : Independent and dependent variables were expressed as percentages. Analysis was done using IBM SPSS Version 20.0.

Results : The quantitative analysis revealed that 66% of the Palliative care patients were unable to access the health care facility, 41% had delay in diagnosis and 83% of them were unable to apply insurance schemes.

Conclusion : Accessibility of Healthcare facility, delay in diagnosis, and application of insurance schemes are the most common challenges faced by palliative care patients which led to the postponement of treatment, privatization of the health sector and increased hospital stay. Government should necessarily recognize the integration of Palliative care with various health schemes and digital Healthcare may support Palliative care to patients living in remote areas.

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Key words **: Constraints, Palliative care patients, COVID-19, Pandemic.**

Palliative care which is also known as supportive care is defined according to the World Health Organization (WHO) as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illnesses, through the prevention and relief of suffering by means of early identification, impeccable assessment and treatment of pain and other problems, Physical, Psychosocial and Spiritual"[1]. Since the proportion of elderly increases in India, the burden of non-communicable diseases increases leading to the drastic increase in need of Palliative Care Services.

A survey done at Villupuram district in Tamil Nadu stated that the prevalence of people in need of Palliative care is around 4.5/1000 population[2,3]. The highest proportion of adults in need of palliative care at the end of life is from low- and middle-income countries. As per the World Health Organization- Global Health estimates, around 54.6 million deaths occurred globally and among those deaths, 66% were due to Non-communicable diseases. The trend in India is as such similar.

Editor's Comment :

- Palliative care patients finding difficult to access centre facilities, diagnosis and application of insurance schemes.
- Digitalization of health care system by the government will improve the accessibility for the palliative care patients, increasing more centres.

The coverage of Palliative care services is very sparse in our country. According to the recent estimate, only <2% of people have access to any type of Palliative care[4,5]. The Role and Response of Palliative Care and Hospice Services in Epidemics and Pandemics: A Rapid Review to Inform Practice during the COVID-19 Pandemic mentioned that the hospice and palliative services have an essential role in the response to COVID-19 by responding rapidly and flexibly; ensuring protocols for symptom management are available and training non-specialists in their use; being involved in triage; considering shifting resources into the community; considering redeploying volunteers to provide psychosocial and bereavement care; facilitating trust and adopting measures to deal with

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stress; using technology to communicate with patients and carers; and adopting standardized data collection systems to inform operational changes and improve care[6].

A study done in 2020 stated many challenges to provide high-quality advance care planning during COVID-19. Professionals and Healthcare providers need to ensure advance care palnning is well-founded for individuals and genuinely tailored to their values and priorities and attuned to their ethnic, cultural, and religious context. Policymakers for health and social care need to consider carefully how high-quality ACP can be resourced and normalized as a part of standard Healthcare ahead of future pandemic waves[7].

A review article on "Identifying needs and improving palliative care of chronically ill patients: a community-oriented, population-based, public- health approach" concluded that the challenges are promoting early interventions that extend to all patients, in all settings, and to integrate Palliative care program with public health[8].

Hence, little is known about the challenges faced by Palliative care patients even in the absence of a pandemic. COVID-19 pandemic is anticipated to surpass the capacity of the healthcare system including Palliative care services. Therefore this study aimed to address the challenges and the solutions for the Palliative care services among patients during COVID-19.

Materials and Methods

After obtaining clearance from Institutional Human Ethical Committee we have conducted a mixed-methods study among patients (>18 years of age) receiving palliative care services in a Cancer Institute at Cuddalore for a duration of 2 months. The subjects were recruited based on the inclusion and exclusion criteria and informed written consent was obtained. The study was conducted using a pre-tested, semi-structured interview schedule. The sample size was calculated as 92 patients based on the prevalence.

Inclusion Criteria :

- Patients (>18 years of age) who are receiving Palliative care services in Cancer Institutes were included in the study.

Exclusion Criteria :

- Patients with cognitive impairment who are in the absence of care- givers.
- Moribund persons who were unable to answer.

Data Analysis :

The data was entered in EpiCollect[5] and analysis was done using IBM SPSS software Version 20.0. All the independent variables such as age, gender, monthly family income, morbidity profile, place of diagnosis, and treatment were expressed in frequency and percentage. The dependent variables such as constraints related to diagnosis and treatment, insurance schemes were also expressed in frequency and percentage.

Results

The study results showed 59% of the people were above 60 years of age and 76% of them were females. Most of them were Hindu and married with a monthly family income of Rs.5000. There were 97.8% of people with cancer among the subjects requiring palliative care. Their place of diagnosis and treatment was the Private sector with a duration of illness of more than 6 months as per the characteristics given in Table 1.

Constraints of palliative care patients were divided into sections like constraints of palliative care patients, constraints in diagnosis and treatment, and insurance schemes. The constraints of palliative care patients were:

- Difficulty in travel (66%),
- Difficulty in crossing the check-post at the borders of the state while assessing for treatment (87%),

Table 1 — *Socio-demographic details and morbidity profile of study participant (n= 92)*

Socio-demographic Data		Frequency	Percentage
Age	< 60 years	37	40.22
	> 60 years	55	59.78
Gender	Male	22	23.91
	Female	70	76.09
Religion	Hindu	86	93.48
	Muslim	5	5.43
	Christian	1	1.09
Marital Status	Single	1	1.09
	Married	86	93.48
	Widowed	2	2.17
	Divorced	1	1.09
	Separated	2	2.17
Monthly family income	< 5000	87	94.57
	5000 – 10000	3	3.26
	10000 – 30000	2	2.17
	> 30000	0	0
Disease condition	Cancer	90	97.83
	Trauma/injuries	2	2.17
Place of diagnosis	Government	37	40.22
	Private	55	59.78
Duration of illness	< 6 months	24	26.09
	> 6 months	68	73.91
Place of treatment	Government hospital/ Medical colleges	30	32.61
	Private hospital/ Medical colleges	60	65.22
	Home-based treatment	2	2.17

- Difficulty to avail food during the travel (86%),
- Emotional constraints and social issues during accompanying the person during pandemic were 89% and 91 % respectively as stated in Fig 1.

Constraints in diagnosis and treatment were segregated into 5 divisions like:

- Difficulty in undergoing initial screening (65%),
- Delay in treatment initiation (53%),
- Delay in initial investigations (45%),
- Delay in diagnosis and change in the treatment plan was 41% and 14% respectively as per Fig 2.
- Constraints in insurance schemes were expressed as 97% of patients had a delay in the application of insurance scheme for treatment, change in treatment plan due to non-availability of schemes (83%), and change in financial expenses (94) respectively as given in Fig 3.

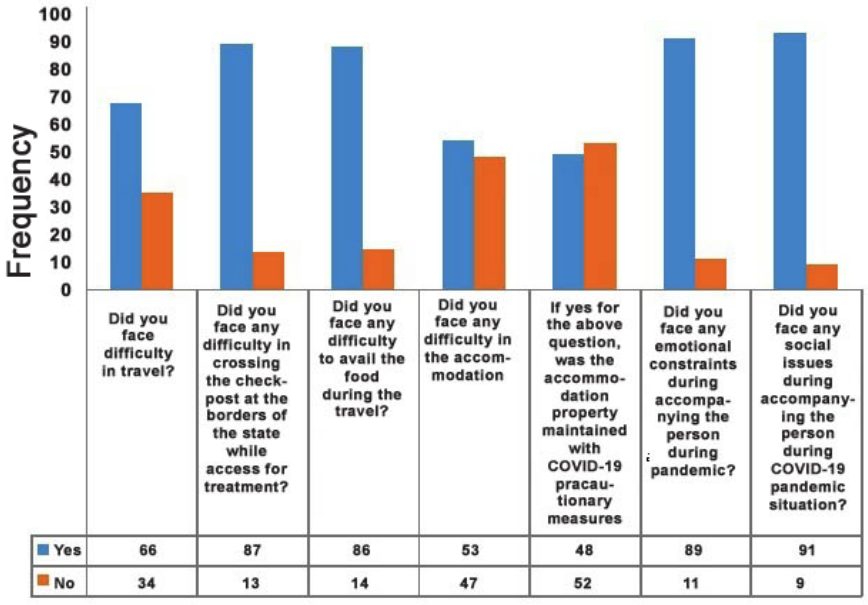

Fig 1 — Constraints of palliative care patients (n=92)

Discussion

Based on the objective of the study which is to address the challenges and the solution exploration on the challenges faced by the Palliative care patients during the Pandemic, our study showed 97.8% of people with cancer among the subjects were requiring Palliative care. Their place of diagnosis and treatment was the Private sector with the duration of illness of more than 6 months.

Our study showed the constraints of palliative care patients were difficulty in travel, difficulty in crossing the check-post at the borders of the state while assessing for treatment, difficulty to avail food during the travel, emotional constraints and social issues during accompanying the person during the Pandemic. A study stating similar features regarding the Palliative care services during COVID-19 pandemic is as follows: "An exploratory study done on Palliative care interventions from a social work perspective and the challenges faced by patients and care-givers during COVID-19" showed that in COVID pandemic, patients and caregivers are left more vulnerable at this time. It highlights on the physical and emotional distress due to the lack of care, access to treatment and interruption in treatment.

In our study, we captured the constraints in diagnosis and treatment and segregated them into 5 divisions like difficulty in undergoing initial screening, delay in treatment initiation, delay in initial investigations, delay in diagnosis and change in the treatment plan. We also captured the constraints in insurance schemes and among them the majority of patients had a delay in the application of insurance scheme for treatment, change in treatment plan due

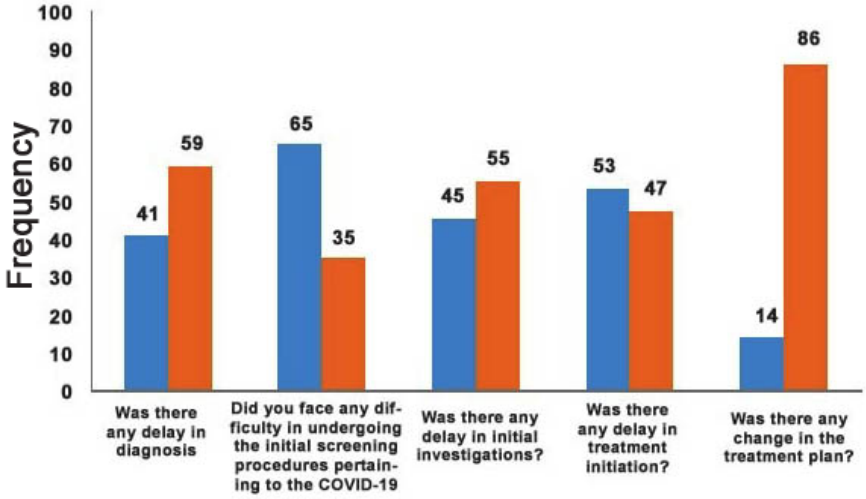

Fig 2 — Constraints in diagnosis and treatment (n=92)

to non-availability of scheme, and change in financial expenses. "A study on Palliative care challenges and strategies for the management amid COVID-19 Pandemic in India: Perspectives of Palliative care nurses, cancer patients, and care-givers" showed the similar results that the COVID-19 pandemic is increasing day by day that makes the patients still live with a fear of getting infected and compromised family life. The lockdown has brought a lot of challenges to the patient and family members to cope with the difficult situations. Adequate resource allocation can make a significant change in patient care which would ensure safe and effective practice for the nurses. Financial challenges and insurance schemes were the more important component among them.

Hence, our study findings mainly highlighted that there are many constraints like difficulty in the accessibility of health care facilities, delay in diagnosis, and application of insurance schemes due to COVID-19 which made the Palliative care patients postpone their treatment and prefer the private sectors and to increase their stay in hospitals.

Conclusion

- Accessibility of health care facility, delay in diagnosis and application of insurance schemes are the most common challenges faced by Palliative care patients during COVID- 19 pandemic.
- This led to the postponement of treatment, privatization of the health sector and increased hospital stay.

Recommendations :

- Government should necessarily recognize the integration of Palliative care with various health schemes.
- Digital health care may support Palliative care for patients living in remote areas.
- With increasing needs, more Palliative care center initiatives can be done at the community level to increase awareness.

Authors' Contribution :

- All authors read and approved the final article. MM participated in the design of the study, analyzed data, interpreted results and drafted the initial article. KR revised the article. KV analyzed the data. BPS revised again the article for the intellectual content in it.

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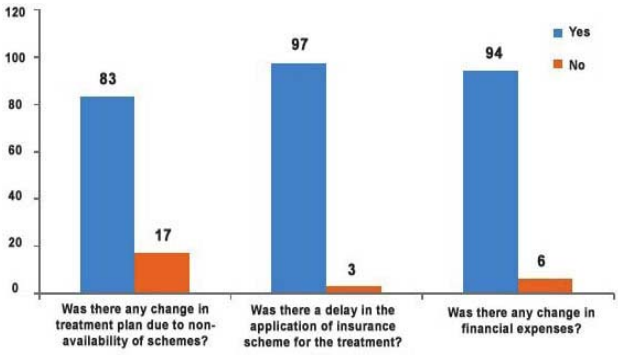

Fig 3 — Constraints in insurance schemes (n=92)

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Original Article

Health Decline in Older Adults

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Background : While it is widely recognized that health declines with an increase in age, the rate of this decline may depend not only on the host but also on several environmental factors. Variability in health status and the risk for adverse outcomes for people of the same age are also recognized as frailty. The rate of health decline is an important consideration for functional healthy ageing. The present cohort study evaluated the rate of health decline in older adults and explored the factors associated with a faster decline.

Methods : Older adults visiting our clinic were included in a dynamic cohort and were evaluated on a 74-point score of previously identified indicators over a period of one year. Various clinical and biochemical factors associated with a faster health decline were further assessed in a logistic regression model analysis.

Observations : A total of 101 participants (51 males and 50 females) with a mean age of 65.4 (±5.4) years and a BMI of 22.2 (±3.2) kg/m^2 participated in the study. The median count of negative health indicators was nine (IQR; 5,13) which increased to ten (IQR; 5, 14) at the end of one year. The medial change was one (IQR; 0, 2). Frailty score, Deficit count and Depression score at baseline were associated with a faster health decline.

Conclusion : A knowledge of factors associated with a faster health decline allows appropriate resource allocation to ensure healthy ageing.

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***Key words* : Frailty, Frailty score, Rate of health decline.**

Morbidity in older individuals is due to the accumulation of health deficits and may not be directly related to the numerical biological age of the individual. Initial impressions have indicated that a decline in an individual's health is closely related to progressive ageing because increasing age is closely related to the accumulation of health deficits[1]. Worldwide, the proportion of the elderly population has risen rapidly from 6 per cent in 1990 to 9 per cent in 2019; is said to rise further to 16 per cent by 2050[2]. In India, the older individuals grow at a rate three times higher than the population as a whole[3]. It is estimated that the rapidly ageing population's economic burden in terms of health-related needs as well as retirement programs is estimated to impact the tax revenue making it 11% higher by 2050[4]. However, the adoption of approaches toward healthy ageing could offset this anticipated expense to the exchequer[5].

Editor's Comment :

- We calculate the rate of accumulation of health deficits in older adults, which is rarely studied.
- We explore the factors associated with rapid health deficit accumulation.
- *Why does this paper matter ?* Knowledge about the rate of accumulation of health deficits as well as clinical and biochemical factors associated with a faster rate will develop targeted therapies for the older population. Thus, reducing frailty and its associated economic outcome

World Health Organization (WHO) has defined healthy ageing as "the process of developing and maintaining the functional ability that enables wellbeing in older age" ,according to WHO, the concept of healthy ageing revolves around two key discussions, *Diversity* and *Inequity*[6]. Diversity highlights the broad range of functioning capacity in individuals from the same age group; while inequity implicates this diversity in functioning to the variable factors in a person's life. Additionally, the WHO describes five domains to assess the Quality Of Life (QOL): Physical and Functional abilities, Social Interactions, Psychological

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status, Religious and spiritual status and Economic and Vocational status[7]. Focusing on factors that impact QOL as well as knowledge of deficient accumulation rate coupled with factors associated with rapid accumulation, could guide in preventing and handling complex health problems in an ageing population.

Frailty is defined by Fried, *et al* acts as an independent risk factor for poor health outcomes[8]. In a systematic review, Collard, *et al* found that the prevalence of frailty in community-dwelling older people varies from 4.0% to 59.1%[9]. In studies that used broad definitions or measurement instruments, the overall weighted average prevalence has been calculated as 10.7% (95% CI = 10.5-10.9%; 21 studies; 61,500 participants)[9]. An Indian study, including 250 older hospitalized subjects identified 83 (33.2%) frail participants who had a higher median hospital stay with multiple co-morbid conditions and higher mortality[10]. Random molecular damage that progressively accumulates with age is responsible for the process of ageing. Mechanisms for frailty include damage at the cellular level causing tissue dysfunction, by reactive oxidative species, exposure to UV light, and toxins. Concomitant factors like epigenetics, genetics, diet, social interaction and physical activity also impact the rate of deficit accumulation. Variability in these factors explains heterogeneity in functioning and disease states of people from the same age group[11]. However, the rate of accumulation of health deficits has been seldom studied and factors associated with the rapid deterioration remain unexplored.

It has been suggested that an individual's health status can be represented by the number of health deficits (broadly defined by biological and clinical characteristics) as they accumulate. Counting deficits allows health to be conceptualized in a single number, the Frailty Index (FI). This method appears to be robust since inferences do not depend on whether the data use self-reported, clinical or performance-based frailty indices. The current study aimed to calculate the rate of accumulation of health deficits in an Indian community-dwelling population while also attempting to identify the clinical and biochemical factors associated with a faster rate of accumulation.

Materials and Methods

Subjects older than 60 years visiting the outpatient clinics for one or more comorbid conditions requiring monitoring or therapy were included in a dynamic cohort after a due informed consent process. Acutely ill patients who could not be evaluated and those needing hospitalization were excluded. Those who could not provide a viable also phone number for future contact were excluded (Fig 1).

Health indicators were determined at the time of recruitment and during follow-up visits. Subjects were assessed with the aid of a pre-designed performa which included the count of 74 previously defined health indicators. The participants were also graded based on the Fried frailty phenotype[8]. The health indicators included a mix of subjective, objective and laboratory characteristics. It has been shown earlier that a frailty index derived from a deficit count has always predicted mortality better than the simple use of age and this approach has been independently validated[12,13]. The questionnaire developed included standard items like examination of Blood Pressure, Pallor, Oedema, Heart Rate, Crepitations, Ascites, Murmur, Neurological Weakness, Medication History Including Pill Burden, Mmse Score, Body Mass Index (BMI), Get-up-and-go test and Barthel's score[14-19].

Laboratory parameters included estimation of Haemoglobin, Total Leucocyte Count, Blood Urea, Serum Creatinine, Fasting Blood Sugar, Serum Calcium, Serum Bilirubin, And Total Cholesterol. To indicate severity, each parameter was not restricted by its nature to two values (ie, 0 or 1 for absence or presence, respectively) and was assigned three (0, 0.5, or 1)

The statistical analysis was done on Stata version 13 (StataCorp, TX, USA). The baseline characteristics were presented as mean (Standard Deviation) or number (percentage). Differences between baseline and one-year measures were evaluated using paired t-test or Chi-square test, as appropriate. The decline in health was reported by counting the newly accumulated indicators over baseline at the end of one year. The relation between health decline and other parameters was evaluated using regression techniques. The distribution of change as estimated

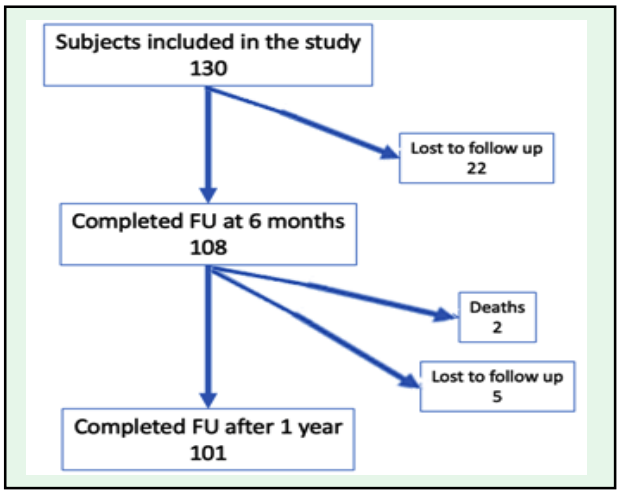

Fig 1 — Flowchart of Study

by the subtraction was studied using histograms and a value at the 90th percentile in the data was considered to define the *fast accumulation* of deficits. The change in the count was modelled as the dependent outcome variable in logistic regression analysis and the baseline count was with other independent risk factors.

Results

Baseline Characteristics :

A total of 101 community living participants older than 60 years, with comorbidities visiting our outpatient clinics for medications, completed one-year follow up in a dynamic cohort. The mean age of the study subjects was 65.4 (±5.4) years with a maximum age of 80 years. There were 51 males and 50 females. The mean BMI of the participants was 22.2 (±3.2) kg/m^2.

The median deficit count noted at baseline was 9 (IQR; 5, 13). A total of 13 (12.9%) participants were frail at baseline with three or more features on the Fried phenotype score[8]. A similar number (13, 12.9%) had features of depression. The median number of pills being taken by the participants was 6 (IQR; 4, 9).

Health Decline in One Year :

At the end of one year, the median deficit count was ten (IQR; 5,14). A total of 23 (22.8%) were now found to be frail and 21 (20.8%) had features of depression. The median pill burden increased to seven (IQR; 5,9). The details of the baseline characteristics of all participants and the changes acquired in one year are presented in Table 1.

Significant changes were noted over one year in Depression Score, Pill Burden, Get-up-and-go Test, Walking Speed, QOL Score, Frailty Score, Deficit Count, Haemoglobin, TLC, Blood Urea, Fasting Blood Sugar, and Serum Calcium. There were no significant changes in BMI and hand-grip strength.

Speed of Health Decline or Rate of Accumulation of Deficits :

The distribution of the total deficits was assessed at each follow-up visit and we recorded that the 90th percentile of the observations was 3 (range -2, 6). Most subjects were found to have accumulated 3 or fewer additional health deficits over baseline in one year. For our analysis, we surmised that if the change in deficit count was more than three, this was considered a '*fast change*' or rapid accumulation of deficits. If the change in deficit count was less than or equal to three, this was regarded as *slow change* or a relatively 'stable' condition.

Table 1 — *Baseline Distribution of variables and changes over time*

Variable	Baseline Mean (SD)	FU 6 months Mean (SD)	FU 1 year Mean (SD)	P value
BMI	22.55(3.20)	22.57(3.21)	22.68(3.22)	0.168
Depression score	0.65(1.39)	0.78(1.38)	0.94(1.37)	<0.001*
Pill burden	6.58(3.17)	6.72(3.10)	7.00(3.09)	<0.001*
Get-up-and-go test	12.42(3.26)	13.12(3.38)	13.19(3.65)	<0.001*
Hand-grip strength	26.90(8.76)	26.89(8.80)	26.22(8.66)	0.064
Walking speed	6.3(2.1)	6.5(2.3)	6.8(2.4)	<0.001*
QOL score	87.82(10.86)	87.43(10.94)	86.97(10.90)	<0.001*
Frailty score	0.97(1.19)	1.08(1.25)	1.37(1.37)	<0.001*
Deficit count	9.47(6.25)	9.84(6.64)	10.64(7.21)	<0.001*
Hb	12.32(1.13)	12.92(1.22)	13.05(1.65)	<0.001*
TLC	7988.30(2238.37)	7076.60(1931.37)	6464.15(1633.66)	<0.001*
FBS	96.08(31.88)	109.48(30.32)	99.26(33.20)	<0.001*
Urea	17.26(4.66)	26.17(7.64)	26.53(12.59)	<0.001*
Calcium	9.14(0.56)	9.27(0.51)	9.30(0.54)	0.028*

*significant change over one year; BMI - Body Mass Index; QOL - Quality Of Life; Hb - Hemoglobin; TLC - Total Leucocyte Count; FBS - Fasting Blood Sugar; FU - Follow-up

Factors Associated with Faster Health Decline :

The various clinical and biochemical parameters were compared within the fast and slow change group. We found that the Baseline Frailty Score, Baseline Deficit Count and Baseline Depression Score were significantly associated with a more rapid accumulation of health deficits. The details of the comparison are presented in Table 2.

In a logistic regression analysis for faster health decline with baseline deficit count as the exposure of interest, we included age, sex and other risk factors as independent variables. We found that the baseline count of health indicators was significantly associated with a faster health decline after adjusting for measured confounders. The details of the logistic regression analysis are presented in Table 3.

Discussion

We examined the rate of decline of health by counting the rate of accumulation of health deficits in an Indian community-dwelling population over a one-year follow-up and found that the Frailty Score, Deficit Count and Depression Score assessed at baseline, were significantly associated with a faster accumulation of deficits. Further, we found that the rate of decline in health is independently associated with the number of established deficits.

Several authors have reported an age-related decline in health over time across the Globe. In a cohort study, Rockwood, *et al* included 17,276 community-dwelling respondents (15-102 years of age) in Canada and assessed changes in fitness and frailty using a Frailty index in a two-yearly follow-up study[20]. They found the prevalence of frailty in various age

Table 2 — *Comparison of health indicators between subjects with faster health decline and those relatively stable*

Baseline Variables	Slow Change group (n=82)		Fast Change group (n=19)		P Value
	Mean	SD	Mean	SD	
Age	65.30	5.34	66.00	5.70	0.615
BMI	22.28	2.83	23.71	4.38	0.189
Income	9402.44	6239.28	11368.42	9226.84	0.264
Depression Score*	0.51	1.24	1.26	1.82	0.033*
Pill Burden	6.34	3.08	7.63	3.44	0.111
Get-up-and-go test	12.13	3.11	13.63	3.70	0.071
Hand-grip Strength	27.20	8.27	25.63	10.78	0.486
Walking Speed	6.18	1.86	6.89	3.05	0.340
MMSE	25.56	5.59	24.53	6.22	0.478
Barthel's ADL score	19.83	0.68	19.58	0.96	0.294
QOL	88.01	10.94	87.00	10.77	0.716
Overall QOL	6.85	1.16	6.47	1.26	0.208
Frailty Score*	0.76	1.04	1.89	1.37	0.002*
Baseline Deficit Count*	8.41	5.93	14.00	5.66	<0.001*
Hb	12.35	1.06	12.07	1.42	0.324
TLC	7906.10	2248.42	8016.67	2024.92	0.848
FBS	95.76	31.15	96.16	34.47	0.960
Urea	17.52	4.71	15.42	4.05	0.075
Calcium	9.17	0.54	9.07	0.65	0.494

*significant association with fast change

Table 3 — *Logistic regression analysis for fast change*

Variable	Model 1 Crude rates OR (95% CI)	Model 2 With confounders OR (95% CI)	Full Model OR (95% CI)
Baseline deficit count	1.14(1.05-1.24)*	1.20 (1.08-1.32)*	1.21 (1.01-1.46)*
Age		0.98 (0.89-1.09)	1.03 (0.91-1.16)
Sex		0.26 (0.07-1.01)	0.28 (0.04-2.15)
Income		1.00 (1.00-1.00)	1.00 (1.00-1.00)
Pill Burden			0.98 (0.22-4.25)
Get-up-and-go test			1.10 (0.71-1.71)
Handgrip strength			1.06 (0.94-1.19)
Walking speed			0.82 (0.43-1.58)
Feels less active			2.00 (0.28-14.14)
MMSE score			0.86 (0.72-1.03)
Barthel's ADL Score			1.00 (0.43-2.34)
QOL score			1.04 (0.97-1.12)

OR-Odds Ratio, CI-Confidence Interval, * significant association with fast change

groups. They reported a prevalence of 2.0% among those younger than 30 years, 22.4% for those older than age 65, including 43.7% for those 85 and older. Additionally, they found that a larger proportion of frail individuals were users of healthcare services while relatively fit people performed better over time.

Diehr, *et al* recruited Medicare-eligible individuals from four American communities, in a cohort of 5,201 participants and 687 African Americans[21]. They compared the 5-year change to measure the rate of decline in 13 measures of Physical, Mental and Functional Health. They reported a 5-year change in standardized health varied from a decline of 12 points (out of 100) for hospitalization to a decline of 17 points for gait speed.

Similarly, Armstrong, *et al* studied the deficit accumulation in a male cohort of 3,801 older Japanese-American men and calculated Frailty Indices (FIs) across six waves and the distribution at each wave were evaluated to see the pattern between FI and age[22]. At each wave, frailty was nonlinearly associated with age and acceleration was noticed in later years of life. The distributions of the FIs were skewed with long right tails. Despite the increased mortality in each successive wave, the 99% submaximal limit never exceeded 0.65. The risk of death increased with increasing values of the FI (eg, the hazard rate increased by 1.44 [95% CI = 1.39-1.49] with each increment in the baseline FI grouping). Depending on the wave, the median survival of people with FI more than 0.5 ranged from 0.84 to 2.04 years.

Our results augment the previously reported association between baseline health and the speed of further decline with acceleration in later years. In addition, we have quantified the rate of decline using a time-sensitive analysis in our study. We had a relatively younger set of participants in our cohort who were followed for a year while evaluating an increment on 74 health variables in a deficit count. We found that the Baseline Frailty Score, Baseline Deficit Count and Baseline Depression Score were significantly associated with a faster rate of accumulation of further deficits. Ours is the first Indian study to record a change in health by measuring the deficits in a cohort of older people and associating this with baseline counts as well as component individual deficits by applying a regression analysis approach.

Our study was limited by the inclusion of a convenience sample of relatively healthier older individuals visiting the hospital for chronic ailments who were relatively easier to follow. Less robust individuals were not able to visit the hospital and consequently were not included. Logistic considerations restricted our sample size while our results do indicate a need for a larger study to explore the nuances of the associations we have uncovered.

Conclusion

The knowledge around the rate of decline in health by way of accumulation of health deficits and factors associated with this decline allows healthcare workers to focus on therapies to promote healthy and functional ageing strategies for older persons. This will not only help target therapies to older individuals based on their

baseline health function but also reduce the economic burden on society by improving the dependence requirements.

Ethical Standards : The experiments and practices associated with this study comply with the current laws of the country in which they were performed.This study could proceed only after the approval of the Institutional Ethics Committee - Human Research Cell of the University College of Medical Sciences. University of Delhi, Delhi

Disclosure of Conflict of Interest : No funding sources (grants or institutional or corporate support) for the submission. There is no conflict of interest associated with this submission. This paper has not been published as a preprint.

Impact Statement : The rate of accumulation of health deficits has been seldom studied and factors associated with the rapid deterioration remain unexplored. Our study is aimed to calculate the rate of accumulation of health deficits in an Indian community-dwelling population while also attempting to identify the clinical and biochemical factors associated with a faster rate of accumulation. This helps target therapies to older individuals based on their baseline health function but also reduces the economic burden on society by improving the dependence requirements.

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Original Article

Cardiovascular Diseases Risk Assessment of Healthcare Professionals

Devendra Prasad Singh[1], Manish Kumar[2], Ajay Kumar Sinha[3], B P Singh[4]

Aim : This study aimed at assessing the Cardiovascular risk factors among Healthcare Professionals mainly in Bihar/Jharkhand states of India.

Method : The participants were asked to answer a questionnaire electronically pertaining to their demographic characteristics, personal and medical history.

Result : It was found that 33% of study subjects had Hypertension, 24% had Diabetes and 15% had a combination of both Hypertension and Diabetes. 30% of all diabetics had their HbA1c above optimal levels. 16% of Doctors were smokers and 17% had Dyslipidemia. 70% of Doctors were doing exercise for >150 minutes/week, however only 15% were sleeping for 7 hours or more.

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Key words **: Cardiovascular Risk, Doctors, Healthcare Professional, Self Care.**

Cardiovascular diseases are the leading cause of mortality in India contributing to almost 25% of all deaths[1,2]. India has undergone a rapid epidemiological transition from predominantly infectious diseases to non-communicable diseases. Certain aspect of this CVD epidemic in India is of grave concern like early age of onset, rapid progression and a high case fatality rate.

Doctors involved in clinical care are one of the most important pillars of the Health Care System. They are expected to have a good knowledge on the disease and its outcome which should affect their attitude and practice. This could influence the prevalence of lifestyle diseases such as Hypertension and Diabetes among them. However, quite commonly they have a sedentary and stressful lifestyle and fail to maintain ideal healthy diet or exercise schedule. There is a paucity of data on the prevalence of lifestyle associated disorders among Doctors in India.

There is strong evidence to support that specific self care behaviour such as healthy diet, regular exercise and avoidance of tobacco and alcohol help in prevention and management of Cardiovascular Diseases[3].

Editor's Comment :

- Physicians should lead by example to combat the epidemic of obesity and cardiovascular diseases.

Materials and Methods

The data was collected from Doctors of mostly Bihar and Jharkhand states of India by the means of a questionnaire which was answered by them electronically. Apart from the demographic details, data regarding personal, family and medical history was recorded. The data was compiled and analysed in Microsoft Excel. The statistical analysis was done using chi square calculator.

Results

The total number of participants in the study were 213 (n) with 188 males (88%) and 25 females (12%) Table 1. The most common age group of participants was 60-69 years (26%). A total of 26 Doctors (12%) were from outside Bihar/ Jharkhand in this study. The average age of the participants in the study was 48 years. 68% of the study subjects were more than 40 years of age. The average weight of study subjects was 73.6 kg and average BMI was 27.

A large percentage of Doctors 69%, were either overweight or obese according to the WHO criteria. However according to the Modified criteria of BMI for

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Table 1 — *Demographic variables*

Age Range	Total No (n)	Percentage %
20-29	16	8
30-39	46	21
40-49	50	23
50-59	43	20
60-69	53	25
70-79	4	2
80-89	1	1
Sex	N	%
Male	188	88
Female	25	12
BMI CATEGORIES (WHO Classification)	N	%
UNDERWEIGHT <18.5	3	1.4
HEALTHY WEIGHT 18.5-24.9	63	30
OVERWEIGHT 25-29.9	103	48
OBESE >30	44	20.6
Combined Overweight & Obese	147	69
BMI Modified Criteria for Asian Indians	N	%
OVERWEIGHT (23-24.9)	42	18
OBESE (>25)	144	68
Combined Overweight & Obese	186	86

Age group	Total (n)	BMI >23 (%)	Doing Exercise(%)	Smoking(%)
<40	65	54 (84)	35 (54)	9 (14)
40-60	86	78 (89)	66 (76)	14 (16)
>60	59	56 (91)	47 (77)	20 (16)

Asian Indians even a greater number of Doctors 86%, were either overweight or obese. The percent of people doing exercise increased with age, however BMI also increased with age.

The percentage of hypertensive individuals was 33% and 24% were diabetics. 30% of diabetics had poor control of blood sugar levels. Dyslipidemia was reported by 17% of doctors. 15% of the study subjects were smokers.

70% of Doctors did Exercise or Yoga for at least 150 minutes in a week. Most of the Doctors (83%) in the study took heart healthy diet (i.e. plenty of nutrient-rich foods—fruits and vegetables and avoiding saturated fats, trans fats, and excess sodium and sugar). Table 2.

Discussion

The study was conducted among 213 doctors, mostly from Bihar and Jharkhand states of India. 30% of the Doctors were at high risk due to physical inactivity or sedentary lifestyle. This is similar to other studies done on Health Professionals in India by Hegde, *et al*[4] (30%) and Gopal, *et al*[5] (25%). In the present study, 17% were at high risk based on their dietary assessment which is similar to the study by Hegde, *et al*[4] (14.4%). 24% of the Doctors in this study had Diabetes which is significantly less as compared

Table 2 — *Self reported Cardiovascular risk factors*

	Total (n)	%
Hypertension	71	33
Diabetes	51	24
Hypertension & Diabetes	32	15
HBA1C >7	15	7
Smoker	34	16
Smoker with Hypertension	15	7
Dislipidemia	37	17
Hypertension+Diabetes+Dyslipidemia	13	6
History of CAD	16	7.5
Family history of CAD	65	30.5
Exercise/ Yoga < 150mins /week	64	30
Sleep < 7hrs/ day	180	85
Not taking “Heart healthy Diet”	37	17

to other study by A.Ramachandran, *et al*[6].

Notably 69% of Doctors had high BMI and were either in overweight or obese category. But according to the modified criteria of BMI for Asian Indians 86% were above the normal weight recommendation[7,8]. Only 30% of the Doctors had healthy weight, in spite of the fact that 70% were physically active and 83% were taking heart healthy diet. This could be due to either insufficient exercise or unhealthy dietary habits. According to the 2007 Physician Health Study 63% of the physicians were above the normal weight range[9]. Studies have shown that Physicians BMI may be related to the effectiveness of counselling patients regarding obesity. The patients are more ready to accept advice regarding Diet and Exercise from normal weight doctors[10].

The American Heart Association has outlined seven basic self care activities that are most important in the prevention of CVD and stroke called “Life’s simple, 7". They include cessation of smoking, maintenance of a healthy BMI, Healthy diet, Physical activity, maintaining normal Blood pressure, cholesterol and Plasma Glucose levels[3]. The present study incorporated the above 7 goals for assessment of risk for CVD. Similarly the “Know your numbers” campaign by American Heart Association was intended to encourage people to raise awareness regarding their risk for CVD[11,12].

The seeds of Cardiovascular Disease and other non communicable diseases are planted very early in life. A shift in focus from care of acute events to prevention by means of awareness and self care is the need of the hour.

The doctors are involved in taking care and educating people regarding CVD. However, more often than not they forget to practice what they preach and neglect their self care.

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Original Article

Antiviral Effect of Doxycycline against Dengue 2, Influenza A (H1N1), Influenza B, Human Rhinovirus 17, Human Adenovirus, and Human Respiratory Syncytial Virus : An *In-vitro* Study

Hemant Thacker[1], Mayank Ravindra Dhore[2], Snehal Muchhala[3], Monil Gala[4], Arti Sanghvi[5], Swathi Bhureddy[6], Mahesh BN[7], Bhavesh Kotak[8]

Objective : The purpose of this study was to determine *in-vitro* antiviral activity of Doxycycline against Dengue 2, Influenza A Virus (H1N1), Influenza B Virus, Human Rhinovirus 17 Virus, Human Adenovirus and Human Respiratory Syncytial Virus in a cell infection model (Prophylactic method and Co-culture method) by the MTT Assay.

Methods : *In-vitro* cell lines culture of Dengue 2, Influenza A Virus (H1N1), Influenza B Virus, Human Rhinovirus 17 Virus, Human Adenovirus and Human Respiratory Syncytial Virus in a cell infection model used (Prophylactic method and Co-culture method) and antiviral activity determined using cytotoxicity test by the MTT Assay.

Result : The *in-vitro* cytotoxicity test was performed for Doxycycline upto 2250µM. The *in-vitro* antiviral activity of Doxycycline against Dengue 2 was performed and the IC_{50} was 135.5 µM in the Prophylactic method and 114.5 µM in the co-culture method, Activity against Influenza A Virus (H1N1) the IC_{50} was 262.3 µM in the Prophylactic method and 184.1 µM in the Co-culture method. Activity against Influenza B Virus was 330.9 µM in the Prophylactic method and 286.4 µM in the Co-culture method, Human rhinovirus 17 and the IC50 was 387.3 µM in the Prophylactic method and 325.9 µM in the Co-culture method. Activity against Human Adenovirus and the IC50 was 146.5 µM in the prophylactic method and 106.6 µM in the co-culture method and activity against Human Respiratory Syncytial Virus the IC50 was 225.5 µM in the Prophylactic method and 165.2 µM in the Co-culture method. Doxycycline exhibits antiviral activity against selected virus in both Prophylactic method and Co-culture methods using the MTT testing was observed.

Conclusion : This study provides valuable insights into the antiviral activity of doxycycline against selected viruses. This antiviral property of Doxycycline will prove beneficial in minimizing secondary infections and complications especially when used as an adjunct.

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Key words **: Doxycycline, Cell Line study, Co-Culture Method, CTT, MTT Assay, Prophylactic Method.**

Viral infections, such as Dengue, Influenza (H1N1), Influenza B, Human Rhinovirus 17, Adenovirus, and Respiratory Syncytial Virus, cause global public health concerns due to their morbidity and mortality rates. Dengue 2 virus is a mosquito-borne pathogen that poses a severe health risk in tropical and subtropical regions[1]. Influenza viruses, including H1N1, result in seasonal outbreaks and pandemics[2]. Human Rhinovirus 17 causes the common cold, while Human Adenovirus leads to respiratory, ocular and gastrointestinal infections as main manifestation[3,4]. Human Respiratory Syncytial Virus mainly affects infants and young children, causing severe respiratory infections[5].

Doxycycline, a tetracycline antibiotic, possesses antimicrobial and anti-inflammatory properties[6]. It is Food and Drug Administration approved antimalarial drug[7]. Besides bacterial infections, doxycycline has

Editor's Comment :

- Doxycycline is a broad-spectrum antibiotic with anti-inflammatory activity, evidence suggest that doxycycline also has antiviral property and was used during COVID-19 pandemic for saving life. This study provides valuable insights into the antiviral activity of doxycycline against viruses causing Flu. This evidence with Doxycycline will prove beneficial in minimizing secondary infections and complications especially when used as an adjunct in patients suffering from viral infections.

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also shown antiviral properties against herpes simplex, dengue and retroviruses[8]. It inhibits the replication of Vesicular Stomatitis Virus and the entry and replication of the Chikungunya virus[9-11]. In silico analysis suggested that doxycycline could potentially act as an inhibitor of the nucleoprotein of the Crimean-Congo hemorrhagic fever virus, a crucial Protein involved in viral replication[12]. These findings highlight the broad-spectrum antiviral potential of Doxycycline across different viral families and its ability to target distinct stages of the viral replication cycle.

Investigating Doxycycline's antiviral effects on various viruses, including Human Rhinovirus 17, Human Adenovirus, Human Respiratory Syncytial Virus, Dengue 2, Influenza A (H1N1), Influenza B and Human Rhinovirus 17, could clarify its potential as a broad-spectrum antiviral therapy. Such research may reduce the global burden of viral illnesses and provide new management approaches.

Materials and Methods

The study utilized Doxycycline, Ribavirin, Fetal Bovine Serum, D-PBS, DMEM, EMEM, MTT Reagent, and DMSO obtained from HiMedia and Sigma. A 96-well plate from Corning was used for cell culture along with viruses and cell lines. The solubility of Doxycycline was by dissolving an adequate quantity of DMSO to produce a Master Stock (MS) solution with a concentration of 225,000 µM. The MS solution was diluted to obtain a series of Working Stock (WS) solutions, as indicated in Table 1 with an assay volume of 200 µl, and the final concentration of DMSO in the assay was maintained at 1%.

Virus Preparation :

A concentration of 100 TCID50/ml or the quantity of virus needed to produce cytopathic effects (CPE) in 80% of infected cells, was obtained by thawing and diluting the frozen viral stock.

Preparation of Cell Line :

A vial of working stock cells was thawed and added to a complete medium, centrifuged, and resuspended in a T-25 flask. The flask was incubated until cell confluency reached around 80%. The cells were then transferred to two T-75 flasks and once cell confluency reached 80-90%, the flask was used for the assay after detaching the cells using trypsin EDTA.

Cytotoxicity Test :

Cells were seeded in a 96-well plate with 200 µl of cell suspension (in complete medium with 10% FBS) without the test agent and allowed to grow for approximately 24 hours. After incubation, spent media in the wells of a 96-well plate was decanted, washed with DPBS and Treatment media (1% pen-strep and 2% FBS) containing appropriate concentrations of Doxycycline were added. The plates were then incubated at 37°C in a 5% CO2 atmosphere for 3 days (72 hours) and an MTT test was performed.

Antiviral activity Test (Prophylactic Method (PM) / Pre-treatment strategy) :

Cells were seeded in a 96-well plate and incubated for 24 hours. After removing the spent media, the cells were treated with the Doxycycline and incubated for an additional period. Then, the virus was added and incubated. After removing the virus, a fresh medium was added and the plates were observed daily for CPE. Once there was 85-90% CPE in the virus control, an MTT assay was performed[13,14].

Antiviral activity Test (Co-culture method (CCM) / During and after the adsorption) :

Cells were seeded with complete media containing 10% FBS in a 96-well plate and allowed to grow for 24 hours. Then, the spent media was removed and 100 TCID50/ml of the virus was added and incubated for 2 hours. After that, a complete medium with a Doxycycline was added and plates were incubated for 72 hours. The plates were checked daily for CPE and if there was no CPE, the incubation period was extended. An MTT assay was performed after there was 85-90% CPE in the virus control[15,16].

Results

Various cell lines were employed to evaluate the efficacy of doxycycline against Dengue 2, Influenza A

Table 1 — *Details of Viruses and Cell Lines*

Name of Viruses	ATCC number of Viruses	Name of cell lines	ATCC number of cell lines	Media
Dengue 2	ATCC® VR-1584™	BHK-21	ATCC® CCL-10™	DMEM
Influenza A Virus (H1N1)	ATCC®VR-219™	MDCK	ATCC® CCL-34™	DMEM
Influenza B Virus	ATCC®VR-1735™	MDCK	ATCC® CCL-34™	DMEM
Human Rhinovirus 17 Virus	ATCC®VR- 1663™	H1HeLa	ATCC® CRL-1958™	EMEM
Human Adenovirus	ATCC®VR-5™	HeLa	ATCC® CCL-2™	EMEM
Human Respiratory Syncytial Virus	ATCC® VR-1540™	HEp-2	ATCC® CCL-23™	EMEM

ATCC: American Type Culture Collection, BHK-21: Baby Hamster Kidney- 21, MDCK: Madin- Darby Canine Kidney, HeLa: Henrietta Lacks, Hep-2: Human Epithelial Type 2 cells, DMEM: Dulbecco's Modified Eagle's Medium, EMEM: Eagle's Minimal Essential Medium

Virus (H1N1), Influenza B Virus, Human Rhinovirus 17 Virus, Human Adenovirus and Human Respiratory Syncytial Virus, employing both the Prophylactic Method (PM) and Co-culture Method (CCM).

Using the PM for Dengue 2 Virus in the BHK-21 cell line, Doxycycline generated an IC_{50} of 135.5 µM, Imax of 85%, and mean inhibition of CPE ranging from 6.5% to 84.9%, whereas, using the CCM, it produced an IC_{50} of 114.5 µM, Imax of 87% and mean CPE of 13.2% to 86.7%. The vehicle control exhibited an Imax of 5.2% and mean CPE of 5.2 ± 0.5% by the CCM, whereas an of Imax of 3.3%, and mean CPE of 3.3 ± 0.5% by the PM for different concentrations.

Doxycycline exhibited a dose-dependent reduction using the PM for Influenza A Virus (H1N1) in the MDCK cell line with an IC_{50} of 262.3 µM, Imax of 75% and mean CPE ranging from 8% to 74.8% whereas, using the CCM, it produced an IC_{50} of 184.1 µM, Imax of 80% and mean CPE of 6.9% to 79.5% The vehicle control produced an Imax of 6.9% and mean CPE of 6.9 ± 0.9% by the CCM and an Imax of 6.8% and mean CPE of 6.8 ± 1.0% by the PM for different concentrations.

Furthermore, when tested against the influenza B Virus in an MDCK Cell Infection Model, Doxycycline generated a mean CPE of 9.2% to 71.0%, IC_{50} of 330.9 µM, and an Imax of 71%, by the PM, whereas it produced a mean CPE of 13.3% to 68.2%, IC_{50} of 286.4 µM and an Imax of 68%, by the CCM. The vehicle control produced a mean CPE of 9.2±0.3% and an Imax of 9.2%, by the PM, whereas it produced a mean CPE of 7.4 ± 1.0%, and an Imax of 7.4%, by the CCM.

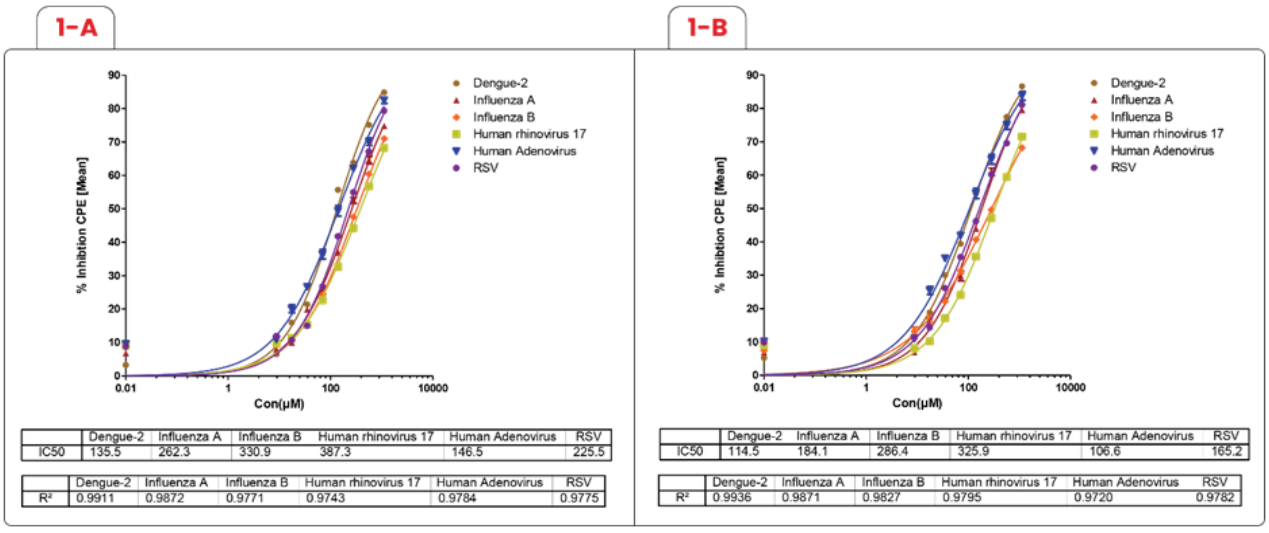
When examined against Human Rhinovirus 17 (HRV-17) in H1HeLa cell lines, Doxycycline generated mean CPE of 9.7% to 68.3%, IC_{50} of 387.3 µM and an Imax of 68.3%, by the PM, whereas it produced mean CPE of 8.2% to 71.6%, IC_{50} of 325.9 µM and an Imax of 71.6%, by the CCM. The vehicle control produced a mean CPE of 9.1 ± 1.3% and an Imax of 9.1%, by the PM, whereas it produced a mean CPE of 9.0 ± 0.3% and an Imax of 9%, by the CCM.

Doxycycline generated a mean CPE of 11.0% to 82.5%, IC_{50} of 146.5 µM and an Imax of 82.5%, by the PM, whereas it produced a mean CPE of 11.1% to 83.8%, IC_{50} of 106.6 µM, and an Imax of 83.8%, by the CCM when observed against Human Adenovirus in the HeLa cell line. On the other hand, vehicle control produced a mean CPE of 9.7±0.5% and an Imax of 9.7%, by the PM, whereas it produced a mean CPE of 10.2 ± 0.6% and an Imax of 10.2%, by the CCM.

Similarly, when examined against the Human Respiratory Syncytial Virus (HRSV) in the HEp-2 cell line, Doxycycline generated mean CPE of 12.0% to 79.3%, IC_{50} of 225.5 µM and an Imax of 79%, by the PM, whereas it produced mean CPE of 11.2% to 81.1%, IC_{50} of 165.2 µM, and an Imax of 81%, by the CCM. The vehicle control produced a mean CPE of 8.8 ± 0.6%, and an Imax of 8.8%, by the PM, whereas it produced a mean CPE of 9.9 ± 0.9% and an Imax of 10.2%, by the CCM.

The CCM generally produced higher mean values for CPE inhibition compared to the PM. These results indicated in Table 2 suggest that Doxycycline may be a more potent drug as it exhibited a dose-dependent reduction than the vehicle control. Also, it did not produce any significant cytotoxicity effect up to 2250 µM. Similarly, the vehicle control had negligible cytotoxic effect.

Fig 1 depicts the antiviral activity of Doxycycline against six different viruses. The IC50 values indicate



	Dengue-2	Influenza A	Influenza B	Human rhinovirus 17	Human Adenovirus	RSV
IC50	135.5	262.3	330.9	387.3	146.5	225.5

	Dengue-2	Influenza A	Influenza B	Human rhinovirus 17	Human Adenovirus	RSV
R²	0.9911	0.9872	0.9771	0.9743	0.9784	0.9775

	Dengue-2	Influenza A	Influenza B	Human rhinovirus 17	Human Adenovirus	RSV
IC50	114.5	184.1	286.4	325.9	106.6	165.2

	Dengue-2	Influenza A	Influenza B	Human rhinovirus 17	Human Adenovirus	RSV
R²	0.9936	0.9871	0.9827	0.9795	0.9720	0.9782

Fig 1 — Antiviral activity of Doxycycline in prophylactic (1-A) and Co-Culture (1-B) methods

the concentration of Doxycycline required to reduce viral replication by 50% *in- vitro*. The lowest IC50value was observed for Human Adenovirus (146.5µM), followed by Dengue-2 (135.5µM), Influenza A (262.3µM), Influenza B (330.9µM) and Human Rhinovirus 17 (387.3µM) by PM (1-A) while Graph 1B depicts the IC50 values for Human Adenovirus (106.6 µM), followed by Dengue-2 (114.5 µM), Influenza A (184.1 µM), Influenza B (286.4 µM) and Human Rhinovirus 17 (325.9 µM) for CCM.

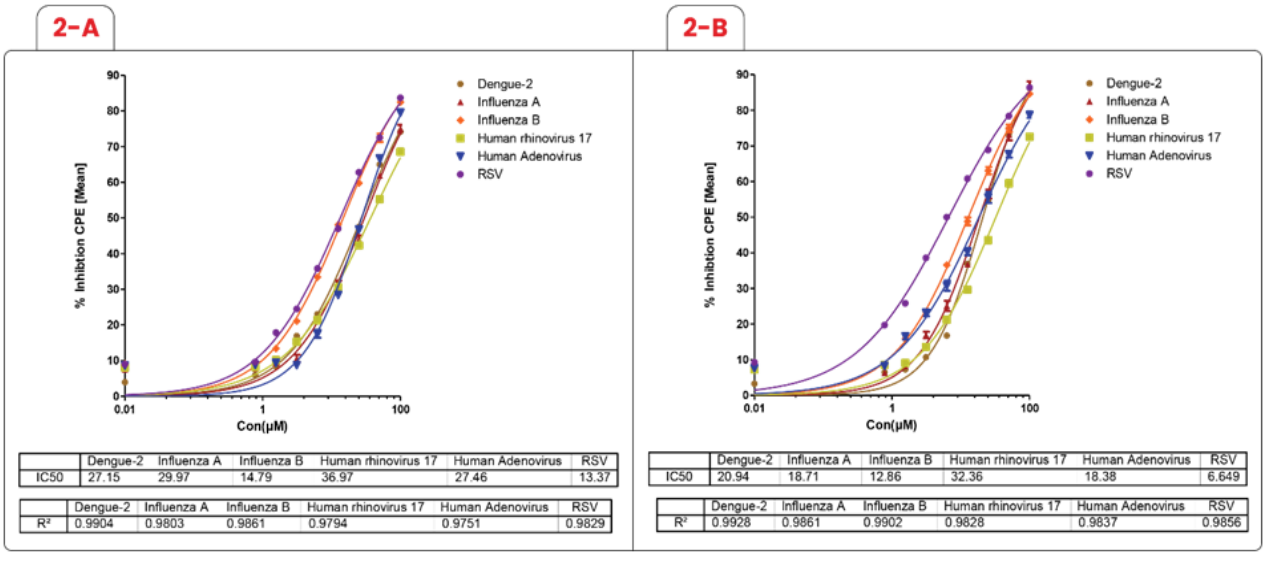
Similarly, Fig 2 depicts the antiviral activity of Ribavirin against the same viruses. The IC50value was observed for Human Adenovirus (27.46 µM), followed by Dengue-2 (27.15 µM), Influenza A (29.97 µM), Influenza B (14.79 µM) and Human Rhinovirus 17 (36.97 µM) by PMin graph 2-A while 2-B graph depicts the IC50 values for Human Adenovirus (18.38 µM), followed by Dengue-2 (20.94 µM), Influenza A (18.71 µM), Influenza B (12.86 µM) and Human Rhinovirus 17 (32.36 µM) for CCM.

Discussion

The study employed two methods, PM and CCM to evaluate the antiviral activity of Doxycycline. In PM, cells were cultured together and allowed to interact directly, while in CCM, different cell types were cultured in the same medium without physical contact, relying on the transfer of soluble materials for interaction. The Co-cultured cells were divided into target cells and helping cells, working together to form functional tissues and perform essential tasks. This co-operative interaction between different cell types in CCM influenced their behavior and activities[17].

The results showed that Doxycycline exhibited antiviral activity against all the tested viruses, although its effectiveness varied depending on the virus and the method used for testing. The PM was involved in treating the cells with the compounds before infecting them with the virus, while the CCM was involved in treating the virus and the cells with the compounds simultaneously. In the PM, Doxycycline exhibited IC50 values ranging from 114.5 to 387.3 µM. The R^2 values were high, indicating a strong correlation between the tested concentrations and the observed antiviral activities.

Ribavirin is an established antiviral agent with a known mechanism of action, specifically inhibiting viral replication (Table 3). It is widely recognized for its broad-spectrum antiviral activity[18]. On the other hand, Doxycycline, although primarily known as an antibiotic, has shown promising antiviral properties in recent studies. While the exact mechanism of Doxycycline's antiviral action is not fully understood, its potential as an adjunct treatment for viral infections is increasingly recognized. By harnessing its antiviral properties, Doxycycline could serve as a valuable therapeutic option to complement existing antiviral agents and minimize complications in patients with viral infections[10-12]. Another recent study observed the pathogenesis involved to attenuate Influenza Virus by inhibiting matrix metalloproteinases within the Neutrophils[19]. The findings of this study suggest that Doxycycline has the potential to be an antiviral drug for the treatment of viral infections and provides valuable insights into its antiviral activity against six different viruses, although its effectiveness varies depending on the virus and the method used.



	Dengue-2	Influenza A	Influenza B	Human rhinovirus 17	Human Adenovirus	RSV
IC50	27.15	29.97	14.79	36.97	27.46	13.37

	Dengue-2	Influenza A	Influenza B	Human rhinovirus 17	Human Adenovirus	RSV
R^2	0.9904	0.9803	0.9861	0.9794	0.9751	0.9829

	Dengue-2	Influenza A	Influenza B	Human rhinovirus 17	Human Adenovirus	RSV
IC50	20.94	18.71	12.86	32.36	18.38	6.649

	Dengue-2	Influenza A	Influenza B	Human rhinovirus 17	Human Adenovirus	RSV
R^2	0.9928	0.9861	0.9902	0.9828	0.9837	0.9856

Fig 2 — Antiviral activity of Ribavirin in prophylactic (2-A) and Co-Culture (2-B) methods

Table 2 — *The antiviral activity of Doxycycline against different viruses and cell lines*

Virus and Cell Lines	1-PM	1-CCM	2-PM	2-CCM	3-PM	3-CCM	4-PM	4-CCM	5-PM	5-CCM	6- PM	+6-CCM
Group (μM)	Mean Inhibition CPE [%] ± SD											
Vehicle control	3.1± 0.5	5.2± 0.5	6.8±1.0	6.9±0.9	9.2±0.3	7.4±1.0	9.1± 1.3	9.0± 0.3	9.7± 0.5	10.2± 0.6	8.8 ± 0.6	9.9 ± 0.9
8.79	6.5±0.8	13.2±0.9	8.0±0.4	6.9±0.8	9.2±0.5	13.3±2.0	9.7±0.6	8.2 ±1.6	11.0±0.6	11.1±1.4	12.0±1.5	11.2±0.5
17.58	16±2.6	18.9±1	9.9±1.0	15.2±0.6	10.9±1.0	16.9±1.7	11.4± 0.7	10.2±1.1	20.1±2.0	25.5±2.1	10.7±0.1	14.3±1.0
35.16	21.4±1.2	30.1±1.5	19.9±0.5	23.1±0.4	15.7±1.3	22.2±1.4	15.4±1.4	17.2±1.3	26.7± 0.4	35.1±1.3	15.0±1.1	26.1±1.5
70.313	36.6±0.9	39.4±1.6	25.6±1.9	29.8±2.6	24.4±1.1	31.4±1.5	22.7±0.8	24.1±0.6	36.4±2.5	41.9±1.1	26.8±2.1	35.5±1.2
140.63	55.7±1.4	54.5±1	36.9±0.5	44.0±0.9	32.8±0.8	40.7±0.3	32.7±1.6	35.6±0.3	49.4± 2.7	54.5± 2.6	41.8±1.0	46.2±2.7
281.3	63.8±1.4	65.1±0.9	52.6±1.6	61.0±1.9	47.6±1.4	49.6±1.3	44.2±1.0	47.2±0.8	62.1±1.1	64.7±2.5	55.0±0.2	60.2±1.8
563	75.2±0.9	77.5±1.5	64.6±2.0	69.8±0.7	60.5±0.6	59.7±0.7	56.8±1.4	59.4±1.1	70.1±1.9	74.9±2.1	67.1±2.4	69.6±1.8
1125	84.9±1.7	86.7±0.7	74.8±0.8	79.5±0.8	71.0±0.5	68.2±0.7	68.3±1.0	71.6±0.7	82.5±1.6	83.8±2.4	79.3±0.3	81.1±1.6
IC50	135.5 μM	114.5 μM	262.3 μM	184.1 μM	330.9 μM	286.4 μM	387.3 μM	325.9 μM	146.5 μM	106.6 μM	225.5 μM	165.2 μM
Imax	85%	87%	75%	80%	71 %	68 %	68.3%	71.6%	82.5 %	83.8 %	79%	81 %

1: Dengue 2 virus in BHK-21cell line; 2: Influenza A Virus (H1N1) in MDCK cell line; 3: Influenza B Virus in a MDCK Cell Infection Model; 4: Human Rhinovirus 17 in H1HeLa cell line; 5: Human Adenovirus in HeLa cell line; 6: Human Respiratory Syncytial Virus in HEp-2 cell line, PM: Prophylactic Method, CCM: Co-culture Method, SD: Standard Deviation, CPE: Cytopathic Effect

Table 2 — *The antiviral activity of Ribavirin against different viruses and cell lines*

Virus and Cell Lines	1-PM	1-CCM	2-PM	2-CCM	3-PM	3-CCM	4-PM	4-CCM	5-PM	5-CCM	6- PM	+6-CCM
Group (μM)	Mean Inhibition CPE [%] ± SD											
Vehicle control	4.0±0.5	3.3±0.5	7.5±0.8	7.3±1.3	9.1±1.0	7.5±1.2	8.1±0.9	7.3±0.8	8.7±0.6	7.7±0.5	9.0±0.4	9.2±1.1
8.79	6.0±0.3	6.5± 0.8	7.7±0.6	6.4±0.9	8.6± 0.4	8.5±0.9	8.2±1.0	8.6±0.6	8.8±0.1	8.3±0.4	9.6±0.7	19.8±1.9
17.58	8.3±1.8	7.3±0.7	9.9±1.9	8.2±0.5	13.4±1.0	15.9±0.7	10.2±0.9	9.1±0.9	9.4±0.1	16.6±1.5	17.8±1.2	25.8±1.9
35.16	17.0±0.8	10.7±1.9	10.6±1.8	16.9±1.6	21.1±1.2	23.4±1.4	15.3±1.1	13.6±0.2	8.7±0.3	23.2±1.7	24.5±2.4	38.6±1.3
70.313	23.1±2.7	16.8±1.4	21.2±1.4	25.1±2.5	33.4±0.2	36.6±0.8	21.4±1.6	13.6±0.2	17.6±1.9	30.8±2.6	35.8±2.7	50.0±0.9
140.63	31.4±1.7	36.9±2.1	31.5±1.7	36.8±1.1	48.1±1.1	48.8±1.9	30.4±1.8	29.7±0.9	28.4±0.5	40.4±1.8	47.0±2.1	60.9±2.2
281.3	47.5±1.9	54.6±1.5	43.9±2.0	56.5±2.2	59.8±1.2	63.1±1.8	42.3±0.7	29.7±0.9	46.8±1.5	55.6±2.7	62.8±0.9	68.9±1.9
563	65.0±0.9	73.2±0.9	61.9±1.4	73.2±2.8	72.5±2.0	75.0±1.9	55.3±1.3	59.5±1.6	66.8±0.4	67.7±1.6	72.5±2.9	78.4±1.2
1125	74.2±0.7	86.3±0.8	75.0±1.9	87.2±1.6	82.5±0.5	84.7 1.2	68.6±1.4	59.5±1.6	79.6±0.9	78.8±1.5	83.7±2.4	86.4±0.7
IC50	27.15 μM	20.94 μM	29.97 μM	18.71 μM	14.79 μM	12.87 μM	36.97 μM	59.5 1.6	27.46 μM	18.38 μM	13.37 μM	6.64 μM
Imax	74%	86%	75%	87%	83 %	85 %	68.6%	72.6%	79.6%	78.8%	84%	86 %

1: Dengue 2 virus in BHK-21cell line; 2: Influenza A Virus (H1N1) in MDCK cell line; 3: Influenza B Virus in a MDCK Cell Infection Model; 4: Human Rhinovirus 17 in H1HeLa cell line; 5: Human Adenovirus in HeLa cell line; 6: Human Respiratory Syncytial Virus in HEp-2 cell line, PM: Prophylactic Method, CCM: Co-culture Method, SD: Standard Deviation, CPE: Cytopathic Effect

The limitations of this study include that the antiviral activity of Doxycycline *in-vitro* may not accurately reflect the Doxycycline's effectiveness in an *in-vivo* or clinical setting. Furthermore, the study was conducted using cell cultures and a limited number of viruses that may not replicate the complexity of viral infections *in-vivo* and clinically. The study did not explore the mechanisms underlying Doxycycline's antiviral activity, which limits our understanding of how the drug works against viruses.

The strengths of the study are that a Doxycycline was examined against a broad range of viruses that provide a comprehensive understanding of its antiviral properties. As this was an *in-vitro* analysis performed in laboratory settings, this approach provided more controlled and consistent results than clinical studies, which can be affected by confounding factors. Since Doxycycline produced effective antiviral activity at higher doses without toxicity against the viruses tested in this study, it could be repurposed as a readily available and cost-effective treatment option for viral infections, particularly in resource-limited settings where access to specific antiviral agents is limited after further analysis and randomized controlled trials.

Conclusion

In conclusion, the findings of this research offer important new information regarding the antiviral activity of Doxycycline against a total of six distinct viruses, however, the degree to which the drug is successful varies not only with the virus but also with the method that was applied. The antiviral impact of Doxycycline was observed when compared to the effects observed with vehicle control.This antiviral property of

Doxycycline will prove beneficial in minimizing secondary infections and complications especially when used as an adjunct.

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Conflict of Interest : All authors declare no Conflict of Interest.

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Original Article

Maternal Occupational Exposure and Risk for Orofacial Clefts : A Prospective Study

Pinki Pargal[1], Jharna Verma[2], Eldo Varkey George[3], Pallavi Nigam[4]

Background : Raising a child with an Orofacial Cleft is one of the most challenging responsibilities faced by a new parent. It has a great impact not only on the social competence of a child but also has psychological implications on their families who suffer both physical and emotional stress which require holistic family-based treatments. Even after successful treatment, it remains a matter of concern for the affected families and they find it difficult to cope with the situation. So to lessen both financial and emotional burdens it becomes altogether more important to search for the aetiologic factors which are responsible for these Orofacial Defects. Though the aetiology of these defects is not fully understood, recent studies have shown the involvement of genetic as well as certain environmental factors which include Smoking[1], Maternal Alcohol Consumption[2], Diabetes[3], Teratogenic Medicines[4] and Maternal Occupational Exposures[5]. More knowledge of these pre-disposing risk factors better in future will be the option for prevention, treatment and prognosis for individuals with these clefts.

Materials and Methods : A prospective study was conducted in the Department of Plastic Surgery at Christian Medical College, Ludhiana. All the patients with Orofacial Clefts who visited the OPD from 1st September, 2019 to 31st August, 2022 were included in the study. The medical records were analyzed and details regarding the demographic profile, occupation of the mother and occupational exposure during the periconceptional period were noted. The nature of the defect was noted following Nagpur classification[6]. Statistical analysis of the data obtained was analyzed by using proportions & chi-square tests.

Results : In our study which included 278 patients, 24.46% patients had mothers working as Housekeepers, 15.46% of patients had mothers working in the agricultural industry, 12.58%of patients had mothers working in the textile industry and 1.43% patients had mothers working in hair salons. A total of 53.93 % of patients' mothers had exposure to different chemicals which included Biocides, Pesticides, Dyes, Aldehydes & Lead Compounds.

Conclusions : With the increasing number of women now coming out from their homes to do various jobs, especially the poor strata working in the labour market, and in factories to improve the financial conditions of their families, it is important to identify various teratogenic factors in the workplace so that these can be avoided. We can decrease the chances of Oral [c]lefts in offspring, saving the child & their families from future agony & pain. However, larger studies are needed to confirm the findings.

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***Key words* : Cleft Lip, Cleft Palate, Maternal Occupational Exposure, Pesticides, Biocin, Working Women.**

Raising a child with an Orofacial Cleft is one of the most challenging responsibilities of a new parent. It has psychological implications both for the patients and their families. Cleft Lip (CL) and Cleft Palate (CP) are one of the most common types of Orofacial Cleft malformations that cause child disability and morbidity[7]. The incidence of Cleft Lip Palate is about 1 to 2 per 700 live births in developed countries. A Cleft Lip is two times more common in males than females where an isolated Cleft Palate is more commonly seen in females[8]. In India, the number of infants born with Cleft Lip, Cleft Palate and Cleft Lip Palate together is 28,600 per year. Since India is the second highest populated country in the World, it may consist of the highest number of cleft cases if no further steps are taken to control its occurrence[9]. The aetiology of Orofacial Clefts is not fully understood

Editor's Comment :

- This study was done in view to know the various occupational risk factors which are associated in causing the orofacial clefts.
- This will help the medical professional to properly guide the women to avoid the exposure to the causative agents and henceforth this may help to reduce the incidence of disease in near future.

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but various studies have shown the association of various genetic and environmental factors. Large population-based case-control studies suggest a relationship between environmental factors like Maternal Smoking[10], Maternal Alcohol Consumption[11], Maternal Pregnancy Body Mass Index[12], Maternal Occupational Exposure[13] and risk of offspring with an Orofacial Cleft.

Increasing outdoor jobs especially by women to improve their financial conditions is exposing them to various teratogenic chemicals. Women working as industrial labourers who are more exposed to various chemicals like Biocides, Pesticides, Dyes, Aldehydes and Lead Compounds have increased association with Orofacial Clefts. Henceforth, it is important to know about the exposure of the various teratogenic compounds at the workplace. Prevention is always better than cure. Better knowledge of the possible aetiologic variants will open doors for better preventive measures, treatment facilities and the best prognosis for the individual with these defects. The present study was conducted in the Department of Plastic Surgery, CMC Ludhiana to find possible maternal risk factors and their association with clefts in patients.

Materials and Methods

A prospective study was conducted in the Department of Plastic Surgery CMC Ludhiana from 1st September, 2019 to 31st August, 2022. It included all the patients registered during this period of one year. The medical records were analyzed and details regarding the demographic profile, occupation of the mother and occupational exposure during the periconceptional period were noted. All the patients were grouped into various types of cleft as per the Nagpur Classification of Cleft Lip and Palate.

Statistical Analysis :

Statistical analysis of the data obtained was analyzed using proportions and Chi-square.

Results

A total number of 278 patients were included in the study. The patients of the study were divided as per the Nagpur classification of Cleft Lip and Cleft Palate. Group I included 28 patients, Group IA had 36 patients, Group II included 109 patients and 105 patients were included in Group III. In our study, the minimum age of the patient was one month with a maximum age of 8 years. Of the total 278 patients included in the study, 181 patients were males and 97 patients were females. Group II mainly included isolated Cleft Palate and Group I and IA included Cleft Lip of the 278 patients included in the study the maternal occupations were analysed (Table 1).

Group I :

- 7 patients' had non-working mothers
- 6 patients' mothers worked in housekeeping
- 4 patients' mothers worked in the agricultural industry
- 10 patients' mothers worked in the textile industry.
- 1 patient's mother worked in a hair salon.

Group IA :

- 21 patients' had non-working mothers
- 12 patients' mothers worked in housekeeping
- 3 patients' mothers worked in the agricultural industry

Group II :

- 51 patients' had non-working mothers
- 23 patients' mothers worked in housekeeping
- 22 patients' mothers worked in the agricultural industry
- 10 patients' mothers worked in the textile industry
- 3 patients had mothers working in hair salons

Group III :

- 49 patients had non-working mothers,
- 27 patients' mothers worked in housekeeping
- 14 patients' mothers worked in the agricultural industry
- 15 patients' mothers worked in the textile industry

Of the 278 patients included in the study occupational exposure to chemicals was included in the analysis. Chemicals included in the study were Biocides, Pesticides, Lead Compounds, Aldehydes and Dyes. Group I included 16 patients with mothers having no history of occupational exposure. In 14 patients with a history of maternal exposure to Biocides. 6patients with history of maternal exposure to

Table 1 — *Maternal Occupation*

Occupation	Group I	Group IA	Group II	Group III	Total
Non-working mothers	7	21	51	49	128 (46.04%)
Housekeeping	6	12	23	27	68 (24.46%)
Agriculture	4	3	22	14	43 (15.46%)
Textile industry	10	0	10	15	35 (12.58%)
Hair salons	1	0	3	0	4 (1.43%)
Total	28 (10.07%)	36 (12.94%)	109 (39.20%)	105 (37.76%)	

Pesticides. In 2 patients with mothers with a history of exposure to Lead Compounds Aldehydes or Dyes. Group IA included 19 patients with mothers having no history of maternal occupational exposure, 12 patients with mothers having a history of occupational exposure to Biocides and 7patient with mothers having history of maternal occupational exposure to Pesticides. 3 patients with mothers with a history of exposure to Lead Compounds Aldehydes or Dyes. Group II included 39 patients having mothers with no history maternal occupational exposure, 20 patients with mothers with a history of maternal occupational exposure to Biocides, 21 patients with having mothers with occupational exposure to Pesticides, 6 patients with mothers having a history of occupational exposure to Lead Compounds, Aldehydes and Dyes. Group III included 53 patients having mothers with no history of maternal occupational exposure, 29 patients with mothers having a history of maternal occupational exposure to Biocides, 15 patients with a history of mothers having maternal occupational exposure to Pesticides, 16 patients with a history of mothers having maternal occupational exposure to Lead Compounds, Aldehydes and Dyes (Table 2).

Table 2 — *Occupational Exposure*

Occupational exposure	Group I	Group IA	Group II	Group III	Total
No exposure	16	19	39	53	134 (48.20%)
Biocides	14	12	20	29	67 (24.1%)
Pesticides	6	7	21	15	48 (17.26%)
Lead compounds, Aldehydes and Dyes	2	3	6	16	29 (10.43%)
Total	38 (13.67%)	41 (14.74%)	86 (30.93%)	113 (40.64%)	

Discussion

Orofacial Clefts are the most common Oral congenital deformities worldwide. Various studies have been done to evaluate clinical profile of Cleft Lip and Cleft Palate patients and have identified various predisposing risk factors. In the present study total of 278 patients were evaluated. In our study, out of 278 patients, 65.1% were males and 34.89% females. Similar results were seen by Angulo Castro, *et al*[14] in their study which included 66.66% males and 33.4% females. In our study, out of the 278 patients included in the study, 128 (46.04%) patients had non-working mothers, 68 (24.46%) patients had mothers working as housekeepers, 43 (15.46%) patients had mothers working in the agriculture industry, 35 (12.58%) patients with mothers working in the textile industry and 4 (1.43%) patients had mothers working in hair salons. In 128 (46.04%) patients had non-working mothers, hence no history of occupational exposure, 68 (24.46%) patients had mothers working as housekeepers, thus, with a history of exposure to Biocides and 43 (15.46%) patients had mothers working in the agriculture industry, thus history of exposure to pesticides. 35 (12.58%) and 4 (1.43%) patients had mothers working in the textile industry and hair salons respectively with a history of exposure to dyes, Aldehydes and Lead Compounds.

Lorente, *et al*[15] evaluated the maternal occupation in the 1st trimester of pregnancy of the women in the housekeeping profession 25% had children with cleft Lip and Cleft Palate. Of the mothers in the agricultural profession 16% had an offspring with CL with/without CP. Of the mothers working in the textile industry, 16.6% had mothers with children with Cleft Lip with/without Cleft Palate. In a study conducted by Lorente, *et al*[15] evaluated occupational exposure in the 1st trimester of pregnancy in 100 women, 19.6% of the women had a history of exposure to Biocides, 1.2% had a history of exposure to Pesticides and 6.5% of the mothers had a history of exposure to Lead Compounds, Aldehydes and Dyes. In a study done by NykeSpinder, *et al*[13]a total of 387 cases were studied. Oral Clefts had significantly increased odd ratios of maternal occupational exposure to Pesticides and Dust. Prevalence of maternal occupational exposure to all agents was 43.9 % and 41%/ 37.7% among cases and control respectively. Yang, *et al*[16] in their study also found a positive relationship between herbicide exposure and Oral Clefts. However,Romitti, *et al*[17] found small increases in risk with maternal exposure to organic solvents. Maternal occupations related to transportation and communications were significantly associated with Oral Clefts (OR: 1.94; $p < 0.05$) in a study by Hemminki, *et al*[18], who analyzed a potential association between parents' occupation and these three groups of malformations (Central Nervous System and Muscular-skeletal) in their offspring. Referring to solvent use, Holmberg, *et al*[19]indicated that mothers of cases were more exposed to this heterogeneous group of substances than mothers of controls, especially to aliphatic and aromatic hydrocarbon and their mixtures.

Conclusions

Working women especially those working as labourers in industries, factories or as housekeepers

are at increased risk of exposure to harmful organic solvents and mineral dust which are exposed in the form of Biocin, Pesticides, Dyes, Lead etc. Preventive measures should be taken at workplaces to avoid maternal exposure. This small effort from our side will not only save society from the trauma of a child with Orofacial Cleft but also help in reducing the financial burden on poor families in developing countries.

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Review Article

One-hour Post load Hyperglycemia : A Powerful but Underestimated Marker of Incident Diabetes and Related Complications

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Purpose of Review : Type 2 Diabetes and related complications, due to Hyperglycemia, are increasing in number Worldwide. Early identification of subclinical disease in the form of hyperglycemia can offer early intervention and delay the progression of irreversible micro and macro-vascular complications. The aim of this review article is to narrate the usefulness of One-hour post load Hyperglycemia in terms of prompt identification and timely management of glucose dysregulation.

Recent Findings : Literature has described that Hyperglycemia itself is an independent factor which can produce various complications, similar to Diabetes. Studies have shown that glycated haemoglobin is less superior in recognizing early Hyperglycemia and can miss a transient rise in blood glucose which subsequently gives rise to reactive oxygen species. This oxidative stress generates endothelial damage and dysfunction. Raised blood glucose levels form advanced glycation end products and generates sub-clinical inflammation, which cause pathological alteration in the vessel wall and increased process of Atherosclerosis. Fatty liver formation and progression to non-alcoholic Steatohepatitis is enhanced due to chronic relative insulin deficiency, reflected by post load Hyperglycemia. One-hour Hyperglycemia can identify β-cell dysfunction at an early stage. Recently, 30-minute plasma glucose value measurement was found to be successful in predicting overt Diabetes in limited trials.

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***Key words* : One-hour Post load Hyperglycemia, Glucose Tolerance Test, Insulin Resistance, Diabetes Related Complications.**

Pre-diabetes or intermediate hyperglycemia is an increment of Plasma Glucose (PG) levels exceeding the normal range which is less than the diagnostic cut-off for Diabetes. This deviation is usually missed with the current diagnostic markers and may lead to future diabetes and various irreversible complications. Diabetes mellitus and pre-diabetic dysglycemia / hyperglycemic abnormalities are increasing worldwide, owing to the rapid rise in obesity in both adults and adolescents. Around 366 million people in the world will be affected with diabetes by 2030[1]. The magnitude of this burden of Diabetes and pre-diabetes needs timely intervention to flatten the rising disease curve.

Elevated glucose levels to glucose load or impaired glucose tolerance starts with insulin resistance or decreased response to insulin by peripheral tissues, which occur due to Hyperglycemia itself, inflammation and obesity[2]. Individuals with Hyperglycemia or deranged PG tolerance are at danger for the evolution of overt Type 2 Diabetes Mellitus (T2DM) and related complications later in the future, and clinical studies have described that both lifestyle changes and appropriate timely pharmacological interventions prevent the advancement from impaired glucose tolerance to T2DM[3].

Editor's Comment :

- One-hour Post-load hyperglycemia is a superior marker in identifying glucose dysregulation and related complications at an earlier stage and can provide an important time frame, in which, intervention can delay or halt the progression of disease. It gives an advantage to recognize individuals at risk of growing related complication, when other markers are within normal range.

It is well-known that the β-cell numbers are reduced to 40% when an individual develops impaired fasting glucose[4]. Hyperglycemia to glucose loading and insulin resistance worsen over time, causing a continuous reduction in β-cell function that expands the chances of developing Type 2 Diabetes. In epidemiological studies, it is demonstrated that about 40% of those who develop T2DM in the future, had normal glucose tolerance at baseline[5]. Redefining threshold values of current diagnostic tools and incorporation of one-hour PG (1h-PG) levels may improve sensitivity of recognizing high-risk individuals earlier enough before advancement to permanent Dysglycemia.

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Currently, the utility of 1h-PG to predict overt Diabetes and related complications, including Nephropathy, Retinopathy, Neuropathy, Atherosclerosis, Fatty Liver and associated Mortality is underestimated while clinically evaluating metabolic Disease. This review may clarify the potential of 1h-PG in predicting Diabetes and subsequent complications and support its measurement in routine practice in an attempt to reduce the burden of Metabolic Dysglycemia.

Mechanism and Pathogenesis of Hyperglycemia related complications :

Long term exposure to unapparent chronic Hyperglycemia is now an identified marker for initiation of the pathogenesis of diabetic complications. Continuous glucose monitoring has shown that diabetic and pre-diabetic individuals have PG variability with one half of individuals having baseline hyperglycemic state[6]. We know that microvascular complications like retinopathy, nephropathy and neuropathy are majorly due to capillary endothelial dysfunction by chronic Hyperglycemia or glucose toxicity[7]. Hyperglycemia causes some major changes in a large vascular compartment that potentially promote accelerated Atherosclerosis, leading to macro-vascular complications. Sustained mild rise in glucose levels may also result in micro and macro-vascular complications. Presently, three crucial processes have arisen, that causes the majority of the patho-physiological alterations as detected in the vascular anatomy of diabetic individual : (1) Glycosylation of lipids and protein particles by non-enzymatic method, (2) Oxidative stress and (3) Activation of protein kinase C[8]. Oxidative stress occurs due to excess NADH and $FADH_2$ production by high glucose levels, leading to increased ATP/ADP ratio and mitochondrial dysfunction[9,10]. All these stress factors lead to end organ damage by direct or indirect mechanism.

Atherosclerosis and Endothelial Dysfunction :

The vital mechanism responsible for macro-vascular complications including Atherosclerosis in Hyperglycemia is the formation of advanced glycation end products by non-enzymatic interaction between glucose and lipoproteins or protein substances in arterial walls. Unusual activation of signalling cascades (such as protein kinase C), upgraded reactive oxygen species production and aberrant stimulation of hemodynamic regulation systems (such as the renin-angiotensin system) are another crucial mechanism[11-13]. Advanced glycation end products in non-haematopoietic cells have been linked with this complication[14]. Further, Flynn, *et al* demonstrated that Hyperglycemia is capable to start pathological alteration in bone marrow, leading to Myelopoiesis, monocytosis and accelerated plaque formation; even in the absence of overt diabetes or insulin resistance[15]. High glucose levels lead to activation of Intercellular Adhesion Molecule (ICAM)-1 and Vascular Cell Adhesion Molecule (VCAM)-1 due to hyperosmolar environment, which begin vascular endothelial dysfunctions[16]. Other than this, sub-clinical inflammatory process due to high PG also causes aberrant endothelial function[17]. All these mechanisms are associated with accelerated Atherosclerosis and microvascular complication, due to endothelial dysfunction.

Fatty Liver Disease :

Hyperglycemia leads to hepatic fat accumulation by various mechanisms and causes generation of fatty liver. Non-alcoholic Fatty Liver Disease (NAFLD) includes a bunch of liver disorders characterized by hepatic fat deposition (also called Steatosis) in the absence of insults like alcohol abuse and viral hepatitis, and is usually associated with a broad spectrum of the metabolic syndrome like impaired glucose tolerance or overt diabetes, visceral obesity, hypertension and dyslipidemia. Insulin resistance leads to free fatty acid release from adipose tissue, which leads to imbalance of lipid metabolism in the liver and hepatic mitochondrial dysfunction, causing hepatic inflammation and the development of fatty liver[18]. As Hyperglycemia is an indirect marker of insulin resistance, it is associated with fatty liver formation.

β-cell Dysfunction and Insulin Resistance :

Recently, Hyperglycemia is also associated with the development of insulin resistance. Hyperglycemia starts with β-cell dysfunction and this generates a pathological cycle, which leads to further β-cell abnormality and persistent raised PG levels. The mechanism for this β-cell dysfunction due to Hyperglycemia includes enhanced hexosamine flux, increased reactive Oxygen species, decreased Pdx-1 expression and increased pancreatic endoplasmic reticulum stress[19-22]. Impaired Pdx-1 activity leads to decreased insulin biosynthesis and increased β-cell apoptosis[23]. Even mild Hyperglycemia can promote β- cell dysfunction, due to changes in genetic structure and altered gene expression by glucose toxicity[24]. Madonna, *et al* have described that high glucose concentration and related hyperosmolar state can directly induce insulin resistance[25].

Importance of Unapparent Hyperglycemia :

American Diabetes Association sorted glucose intolerance on the ground of PG levels after a single 75-gm Oral Glucose Tolerance Test (OGTT). Pre-diabetes designated as fasting PG between: 100–125 mg/dl (Impaired Fasting Glucose) or impaired glucose tolerance with fasting PG levels <126 mg/dl but two-hour post load PG140–199 mg/dl and HbA1c between 5.7-6.4%[26]. It is superior to evaluate postprandial PG by 75gm OGTT than ordinary meal, because glucose rise after a meal is depending on the amount and type of the food which does not occur with OGTT. However, recent data has shown that even normal glucose tolerant individuals (individuals with normal two-hour post load plasma glucose) tend to have elevated cardio-vascular risk, as depicted by a worse plasma lipid levels, thickened intima-media, and hypertrophy of the left ventricular chamber[27]. Normal glucose tolerant individuals can have chronic Hyperglycemia, which can be missed by traditional tests like two-hour PG (2h-PG) level and HbA1c measurement. This continuous mild hyperglycemia is a prime precursor in the formation of biochemical and vascular abnormalities by inducing various functional, structural and metabolic derangements.

Hyperglycemia leads to a negative impact on β-cells of Pancreas, which is referred asglucotoxicity[28]. This deteriorates the secretory capability of β-cells[29,30]. Severe hyperglycemia affects β-cells more than milder Hyperglycemia[31]. In a study, subtle physiological Hyperglycemia led to deterioration in β-cell function and insulin resistance[32]. Another study showed that this insulin resistance due to chronic Hyperglycemia is largely irreversible[17]. Observations have also shown that insulin sensitivity in tissue was found to be 17% lower in individuals with upper levels of normal fasting PG range (90-97 mg/dl) compared with fasting PG <90 mg/dl[33]. Also, a progressive drop of initial first-phase insulin response can occur with fasting PG values between 90-97 mg/dl and further decline in late-phase insulin response at levels >108 mg/dl[34].

A study from Israel regarding glucose intolerance, Obesity and Hypertension with follow up for 24 years, demonstrated that individuals with a 1h-PG levels ≥155 mg/dl but with 2h-PG <140 mg/dl had significantly increased risk for both diabetes development and pre-diabetes conditions[35]. In the same study, 1h-PG levels >155 mg/dl was also established to anticipate mortality even when the 2h-PG was <140mg/dl. Myocardial damage and fatal ischemic heart disease and risk of microvascular complications like retinopathy were also considerably higher among individuals with elevated 1h-PG values.

A study by Succurro, *et al* found that one-hour post load PG levels >155mg/dl was an atherogenic condition and this cut off is useful in identifying high risk individuals[36]. Tanaka, *et al* using intimal medial thickness as a surrogate marker for Cardio-vascular disease demonstrated that deranged PG at one-hour was associated with increased intimal medial thickness more firmly than PG at two-hours, even in the absence of chronic Hyperglycemia[37]. These studies strongly represent the correlation of raising 1h-PG with cardiovascular complications.

Superiority of One-hour Post load Hyperglycemia:

Tabak, *et al* described a multilevel model theory related to an extended compensatory time interval prior to the clinical diagnosis of diabetes[38]. In this interval, insulin secretion in the body rises to compensate the ongoing development of resistance and this keeps PG values within normal range as a result of physiological adjustment. This leads to β-cell compensatory adaptation and later, generation of a brief unsteady time spell with a sharp rise of PG leading to overt diabetes. PG levels are within the normal physiological range for about 2-6 years during this period, before crossing the actual diagnostic cut-off for overt diabetes. Post load PG value, especially at one-hour may uncover the inconspicuous yet significant damage to β-cells in this time period.

Jagannathan, et al in their study, highlighted how HbA1c is an inferior marker, in terms of correlation with insulin sensitivity and β-cell function than single determinations of PG levels at one-hour[39]. The same study also explained that the 1h-PG value above 155 mg/dl had finer descriptive capability to point out high risk subjects, when compared with the present cut-off criteria for HbA1c. Also the Veterans study showed that the association of HbA1c with insulin sensitivity and β-cell dysfunction was a nonlinear association within the Mexican-American population[40]. This tells the ineffectiveness of HbA1c in the prediction of insulin sensitivity.

Similarly, studies have demonstrated that post prandial hyperglycemia is a causal factor in significant numbers of individuals with impaired glucose tolerance with normal levels of HbA1c, leading to increased cardiovascular morbidity[41,42]. It has been elucidated how subjects with an HbA1c level of 5.7-6.4% (pre-diabetic) and one-hour post load PG value above 155 mg/dl have a remarkably excess risk of hepatic steatosis when differentiated with subjects having pre-diabetic HbA1c levels, but one-hour post load PG value below 155 mg/dl[43]. This shows the inferiority of HbA1c

in terms of predicting fatty liver like complications. As HbA1c is an average of glucose values of the past 2-3 months, it cannot describe the daily post prandial rise or fluctuation in PG and this drawback can be abolished by using post load PG values.

Priya, *et al* found that both β-cell function and insulin sensitivity are altered among subjects with elevated 1h-PG values[44]. Sato, *et al* study suggested an abnormality in β-cell stimulus-secretion coupling process in the presence of an elevation of post challenge PG levels[45]. These studies promote the use of 1hPG for assessment of β-cell function. And it has been increasingly realized that, normal glucose tolerant individuals who have elevated 1h-PG >155 mg/dl, may have accelerated fatty liver disease development, subclinical inflammation and early atherosclerotic changes[36,46].

Yet another study has revealed that glycemic parameters measured by OGTT were more accurate in describing individuals with deranged β-cell function and described that the 1h-PG is better than HbA1c for this β-cell dysfunction[47]. The superiority of early Hyperglycemia identification is also proven by indirect evidence of complication reduction, after controlling hyperglycemia. Early diagnosis of dysglycemia or hyperglycemia can reduce relative risk of cardiovascular morbidity by 29% and all-cause mortality by 17% after 5 years[48]. Early detection of high-risk individuals is very crucial step to prevent the hyperglycemic injury and is imperative in younger individuals as they show a faster progression to diabetes than adults and have more life span[49]. Evaluating the young obese individuals with raised PG values at one-hour, may identify complications like Cardiomyopathy, neuropathy, nephropathy, atherosclerosis, and fatty liver at primordial stages. This strategy might prove crucial in maintaining and preserving β-cell function. Other than this, one-hour post load plasma glucose value measurement is easy and a feasible tool in developing countries and limited resource setting.

30-minute Post load Plasma Glucose : Another Emerging Marker :

Recently, Post load PG value at 30-minute has been evaluated to diagnose diabetes early and to assess its correlation with different end organ complications. A study on Japanese population showed that individuals with higher 30-minute post-load PG have increased risk of future diabetes development[50]. The study also described that the addition of 30-minute plasma value in standard OGTT can improve the future prediction. A study from India recently described the same finding and illustrated the predictive power of 30-minute PG value[51]. The study suggested that the 30-minute PG value of >188mg/dl was associated with future diabetes emergence, especially in obese population and with positive family history of diabetes. Further, one more analysis of Indian population including 753 participants illustrated the association of 30-minute post load PG and future diabetes development[52]. The study also observed that 30-minute PG value was an independent marker of future diabetes, superior to 2h-PG and HbA1c levels. These limited studies clearly indicate the importance of intermediate Hyperglycemia. However, more prospective studies and randomized trial are required for better insight regarding the use of 30-minute PG value and its incorporation in routine evaluation.

Conclusions

This review focuses on the correlation of after one-hour post load glycemic values with development future T2DM and its related various complications. Different observations have shown that one-hour Post-load Hyperglycemia is a better tool to distinguish the risk of diabetes development. This marker also carries the potential to identify high risk individuals earlier than other diagnostic markers like HbA1c and 2h-PG value. Deranged 1h-PG value reflects insulin resistance, an early step to abnormal fat metabolism and the formation of fatty liver. Studies have demonstrated that individuals with raised 1h-PG are pre-disposed to early Atherosclerosis development due to atherogenic lipid profile formation in the body and subsequent damage to the vessel wall. Individual with raised 1h-PG is also prone to the generation of reactive oxygen species and damage to the organs like liver, heart, kidney and retina. Currently, the 30-minute plasma glucose value is also emerging as a novel marker of future diabetes, but proper data is still less and require more extensive investigations. In this study, it is clear that one-hour post load Hyperglycemia is a strong marker in diagnosing diabetes and related complications and management of this parameter can independently prevent important organ damage.

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Case Series

Thoracoabdominal Flap Coverage after Excision of Locally Advanced Breast Carcinoma

Arghya Bera[1], Amit Roy[2], Gaurab Ranjan Chaudhuri[3], Sudip Das[4], Ramita Mukherjee[5], Risabh Dagra[5]

Excision of locally advanced breast carcinoma which is not responding to neo-adjuvant chemotherapy, leads to wide anterior chest wall defect with difficult closure of wound also delayed adjuvant radio-chemotherapy. The Thoracoabdominal flap (TA flap), a fascio-cutaneous rotation advancement flap quite better option for local tissue coverage of the wide defect in same stage. Here we present four patients with locally advanced breast carcinoma with no response to neo-adjuvant chemotherapy. The tumors were excised along with the local surrounding tissues and axillary dissection. Those defects were covered with TA flap (laterally based) derived from the same side of thorax and abdomen. One case developed marginal congestion of the flap managed by skin grafting. The anterior chest wall have few options of donor vessel. The TA flap having its blood supply from thoracolumber vessels and it does need a microsurgical procedure. The mean duration of hospital stay, postoperatively, is shorter in the TA flap, no difficulty in shoulder movement. Patients take adjuvant radio-chemotherapy earlier. A TA flap is a better coverage option for a wide defect following excision of locally advanced chemo-radio resistant breast carcinoma.

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Key words **: Thoracoabdominal flap, Locally advanced, Breast carcinoma, Chemotherapy.**

Excision of locally advanced chemo-radio resistant breast carcinoma leads to wide chest wall gap. Some times radical resection may need removal of anterior chest wall muscles. Following excision, reconstruction of chest wall needed. Skin grafting is the simplest one. Skin grafting usually fragile and not durable if adjuvant radiation indicated. Various loco-regional myo-cutaneous, fasciocutaneous, dermofat flaps were previously used for healing and potentially covering the defect after cancer excision[1-3]. Loco-regional flaps, either medially based (thoracoepigastric) or laterally based (thoracoabdominal) flaps are commonly used fasciocutaneous flap. Thoracoabdominal flap resulted in lesser complications even with larger flap[4]. It's a locally rotation advancement flap.

Case 1

A 52-year-old female patient comes with history of ulcerofungating growth on her left breast for a duration of 8-10 months. On physical examination a hard mass, size around 8x10 cm, immobile which appeared to be attached with the Pectoralis Major (PM) muscle fascia. There was a skin ulceration around 4-5 cm with everted margins. Patient was khown case T2DM and hypothyroidism, taking oral medication.

On core-needle biopsy proved it invasive ductal carcinoma of breast with staging of T4bN1M0. She received 3 cycles of NACT, without downstaging or downsizing. Another 3 cycles of taxen based NACT taken with no effect on stage and size. Patient undergone MRM with partial removal of PM muscle, creating a gap of 18x12 cm. the gap was covered with Thoracoabdominal flap. A Thoracoabdominal incision made through midline starting from medial corner of the defect to umbilicus. The skin and subcutaneous tissue from Mastectomy flap's lower margin is also raised from anterior rectus sheath. Dissection continued laterally on suprafacial layer. As flap is raised, most of perforators from lateral intercostal arteries, subcostal arteries and lumber artereis are preserved for flap circulation, whereas sacrificing most of superior epigastric perforators for

Editor's Comment :

- Thoracoabdominal Flap reconstruction is technically easy, can be done by fellows, no need of expertise help.
- Local tissues used for defect coverage, take less operative time.
- Larger defects easily get covered.
- We can avoid skin grafting related complications, where Radio-therapy almost needed.

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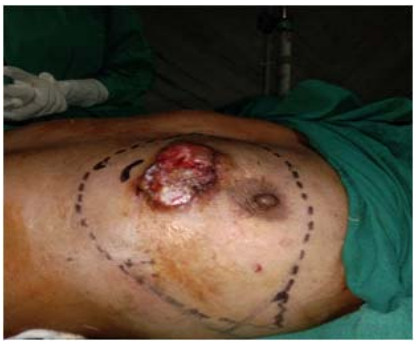

Fig 1A — Pre-operative breast lump 8x10 cm

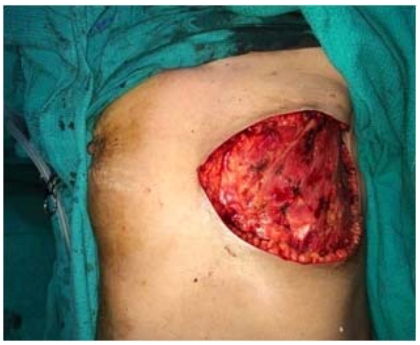

Fig 1B — After modified radical mastectomy defect 12x18cm

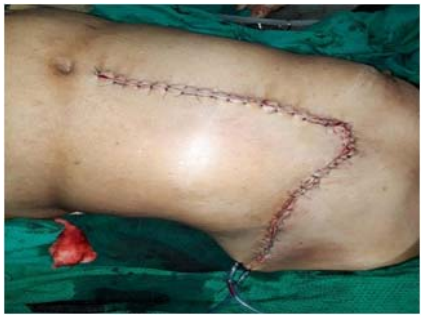

Fig 1C — Immediate Postoperative picture after covering with TA flap

Fig 1D — Follow up of 10 months

maximizing flap's reach. Closure starts from medial side with flap rotation-advancement, with dog ear management at lateral side. The patient's shoulder movement was normal. The patient was followed for 2 year postoperative period and remaintumor free.

Case 2

A 45-year-old female presented with a history of large mass on her left breast for a duration of 6-7 months. On physical examination a hard irregular mass, size around 9.5 x11 cm, immobile that appeared fixed to PM fascia. Mass was located at upper and lower inner quadrant. She also had family history of same carcinoma.

On FNAC proved it invasive ductal carcinoma of breast, with staging of T4bN2M0. She received 3 cycles of NACT, without any downstaging or downsizing. Patient undergone MRM with partial removal of PM muscle, leaving gap of 12x15 cm. The gap was covered by the TA flap as in Case 1. After 72 hours there was slight venous congestion at most distal part of flap. Following that distal part of flap get necrosed. Wound was managed by debridement, small skin grafting and opposite breast flap. The patient's shoulder showed free range of movement. The patient having no recurrence oftumor till date.

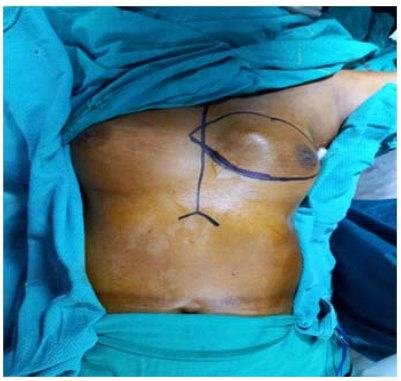

Fig 2A — Pre-operative breast lump 9.5x11cm

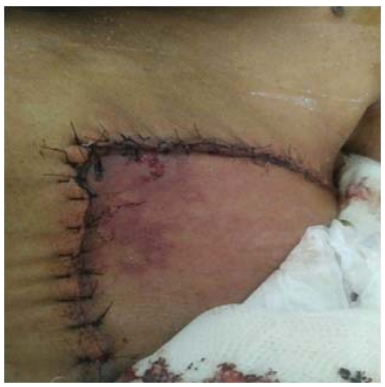

Fig 2B — Postoperative day 5

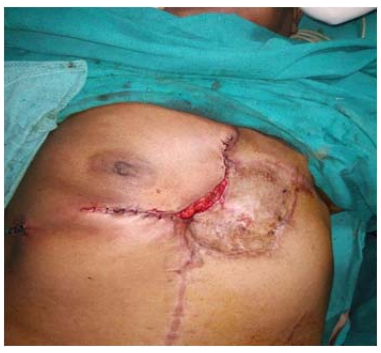

Fig 2C — Debridement of necrotic part with skin grafting and opposite breast flap

Case 3

A 53-year-old male patient came with a growth at his right breast for few months. On examination, it revealed that a 6x7-cm hard growth at his right breast that seems to be hard to firm on palpation. CT showed a subcutaneous growth around a size of 6x7 cm in.

The tumor excised with approximately 4 cm of surrounding underneath PM fascia and the skin subcutaneous tissue, creating a gap of 11x12 cm. The gap was covered by the TA flap.

Case 4

A 60-year-old male patient presented with a lump on his right breast for 8 months. On physical examination a 8x10-cm mass on his right breast that feel hard on palpation. On true cut biopsy, it proved lobular carcinoma of breast.

MRM was done along with a margin of 5 cm. All level of axillary lymph node clearance was also done.

Resulting defect was around 13x15 cm in the maximum diameter. The huge defect was reconstructed by laterally- based thoracoabdominal flap.

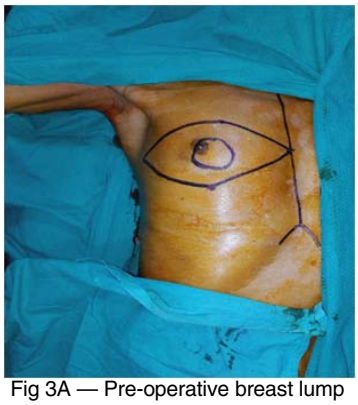

Fig 3A — Pre-operative breast lump

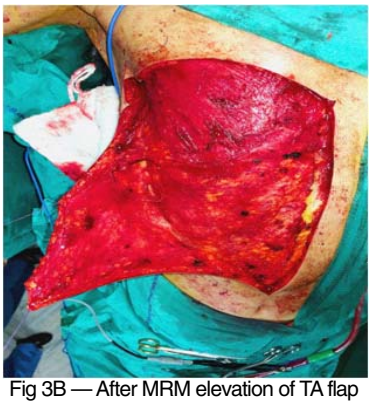

Fig 3B — After MRM elevation of TA flap

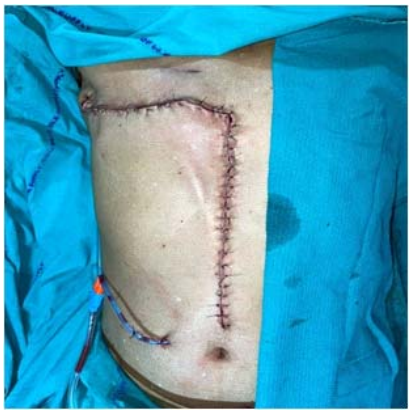

Fig 3C — Immediate postoperative stage

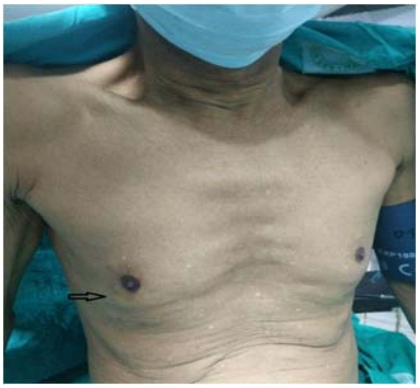

Fig 4A — Lump in right breast

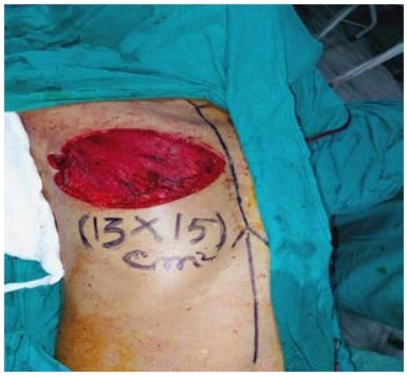

Fig 4B — Defect of 13x15cm after excision

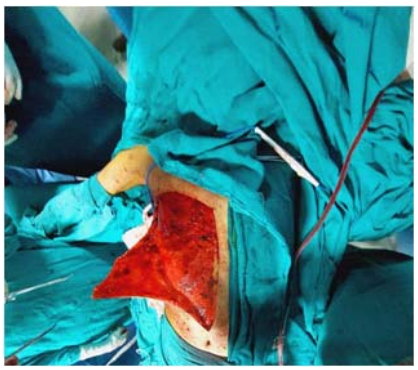

Fig 4C — Elevation of TA flap

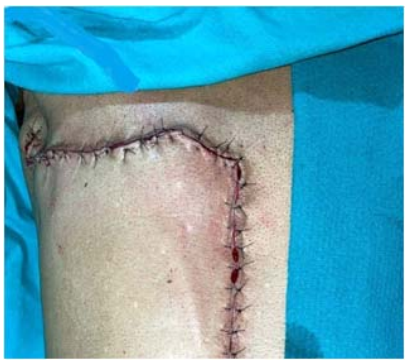

Fig 4D — 48 hours postoperative period

Discussion

Advanced and chemo-radio resistant breast CA often needs wide excision, including all breast tissue. Soft tissue reconstruction remain always a problematic following wide-area excision. Before skin grafting era post radical mastectomy wounds were allowed to heal by secondary epithelialization alone[5].

The TA flap is a fasciocutaneous rotation advancement flap. TA flaps in late 1970s when medial- and lateral-based flaps were both described[2,3] lateral intercostal vessels for several advantages. Medial-based usually did not reach to most distal defect or leads to partial necrosis of the flap. Lateral-based TA flaps have robust circulation even with fewer vessels in a hatchet shape or transversely oriented design.

In our presentation, TA flaps were used for coverage after excision of advanced breast carcinoma in 4 patients. Among them only one patient had partial necrosis of flap that was managed with debridement followed by skin grafting and opposite breast flap.

The TA flap has an axial blood supply, and the procedure is quite simple, safe to dissection and requiring no microsurgical procedure. The mean duration of hospital stay, postoperatively, was less in the TA flap, no difficulty in shoulder movement. Patients take adjuvant radiotherapy earlier.

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Case Report

An Unusual Case of Bisalbuminemia in a 61-year-old Male Patient

Neepa Chowdhury[1], Suparba Chakrabarti[2], Anannya Ghosh[2]

Bisalbuminemia is an uncommon protein aberration presenting with two distinct fractions of albumin on Serum Protein Electrophoresis. It reflects the presence, of a normal albumin and a modified albumin, in the same individual. Bisalbuminemia may be either hereditary or acquired. Hereditary type is permanent but the acquired form may be transient and is usually observed in diabetes mellitus, sarcoidosis, nephrotic syndrome, chronic kidney disease, multiple myeloma, Waldenström's macroglobulinemia and observed during treatment with beta-lactams. Here we are reporting the case of a 61-year-old male, who, is a patient of chronic kidney disease and diabetic and the electrophoresis performed on Capillary Electrophoresis revealed a bisalbuminemia. Through this work, we wish to present an uncommon case of bisalbuminemia in order to familiarize clinicians and laboratory personnel with this protein anomaly, to throw some light on its physiopathological and practical aspects.

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Key words **: Bisalbuminemia, Electrophoresis, Monoclonal Gammopathy.**

Bisalbuminemia is an uncommon protein aberration presenting with two distinct fractions of albumin on Serum Protein Electrophoresis. It reflects the presence, of a normal albumin and a modified albumin, in the same individual. Bisalbuminemia may be either hereditary or acquired. Hereditary type is permanent but the acquired form may be transient and is usually observed in Diabetes Mellitus, Sarcoidosis, Nephrotic Syndrome, Chronic Kidney Disease, Multiple Myeloma, Waldenström's Macroglobulinemia and observed during treatment with beta-lactams. Here we are reporting the case of a 61-year-old male, who, is a patient of Chronic Kidney Disease and Diabetic and the Electrophoresis performed on Capillary Electrophoresis revealed a Bisalbuminemia.

Through this work, we wish to present an uncommon case of Bisalbuminemia in order to familiarize clinicians and laboratory personnel with this protein anomaly, to throw some light on its physiopathological and practical aspects.

Bisalbuminemia or Alloalbuminemia is an uncommonly presented serum protein anomaly which may be acquired or inherited. It is characterized by the presence of double peak pattern of electrophoresis in the albumin fraction detected on Serum Electrophoresis. It can be seen as a bicuspid mountain with two albumin heads in densitometry scanning. These mutant albumins are also called Alloalbumins. They can be classified into either (slow type variants) or (fast type variants) depending upon their decreased or increased electrophoretic mobility[1]. The accumulative frequency of inherited Bisalbuminemia is typically 1:10000 to 1:1000[2-4], with an autosomal codominant inheritance[5]. Although there are no pathological or therapeutic implications in case of inherited bisalbuminemia, interest lies in finding out the characteristic functional differences in the protein, including altered protein binding affinity for thyroxine, steroid hormones and several dyes[6]. Acquired or transient Bisalbuminemia have been found to be associated with various conditions including Diabetes Mellitus, Nephrotic Syndrome, Chronic Kidney Disease, Sarcoidosis, Pancreatic Pseudocyst, Alzheimer's disease, Waldenström's Macroglobulinemia, multiple myeloma and also in patients receiving high doses of penicillin.

We recently encountered a case of a 61-year-old male patient, who has a chronic history of type 2 Diabetes Mellitus, Dyslipidaemia and Chronic Kidney Disease (Stage- III).

The patient was referred to our center to rule out any Monoclonal Gammopathy. Serum Capillary Electrophoresis by Sebia Capillary Electrophoresis System revealed no band suggestive of M-spike but

Editor's Comment :

- Bisalbuminemia is an uncommon protein aberration which may be hereditary or acquired. This may be an incidental finding or associated with co-morbidities like diabetes mellitus, sarcoidosis,nephrotic syndrome, chronic kidney disease, multiple myeloma, etc. Though bisalbuminemia does not influence disease process, it may be mistaken as an abnormal globulin peak while screening suspected or confirmed cases of monoclonal gammopathies. This entity must be kept in mind and then interpreted with caution.

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revealed a distinct bifid peak of Serum albumin zone.

A laboratory examination of other parameters revealed in Table 1.

We got the picture (Fig 1) on Serum Capillary Protein Electrophoresis.

So, in this case, we got an incidental finding of Serum Bisalbuminemia. Patient was ordered this test for the first time and therefore, we could not identify the nature of the Alloalbumin that whether it is an inherited or an acquired condition.

We suggested the patient to follow-up after 6 months to rule out any acquired aetiology of this condition as the patient has multiple co-morbidities which may be related to the acquired cause of this appearance of Alloalbumin.

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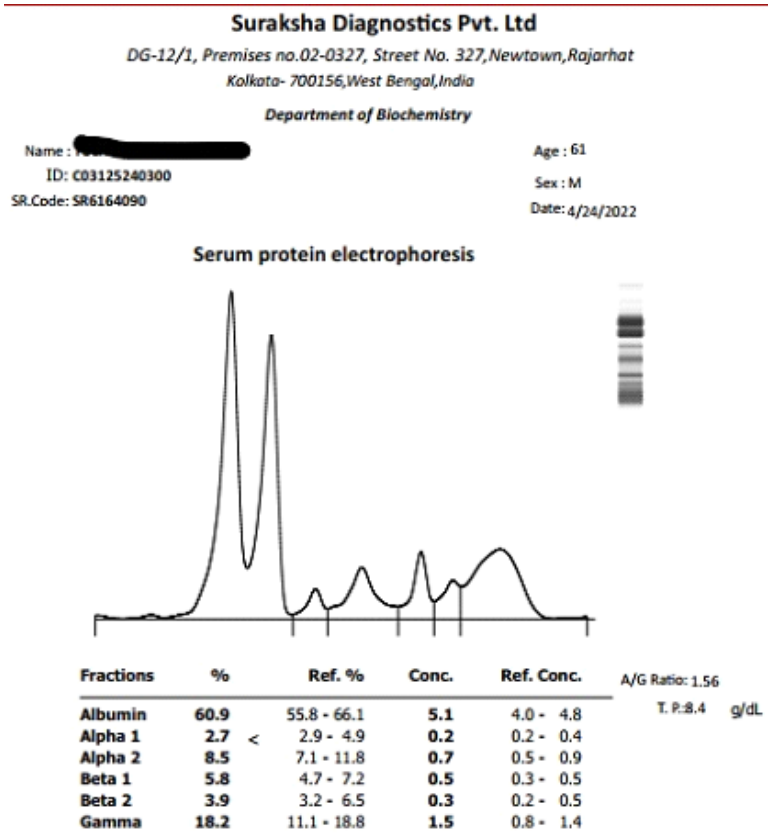

Fig 1 — Serum protein electrophoresis showing bifid albumin peak

Table 1 — *Results of the patient's biological assessment*

Parameters	Results	Biological reference Interval
Fasting Plasma Glucose	109 mg/dL	≤126 mg/dL
PP Plasma Glucose	169 mg/dL	≤200 mg/dL
Serum Creatinine	1.98 mg/dL	0.7-1.3 mg/dL
Serum Calcium	9.40 mg/dL	8.7-10.4 mg/dL
Serum Uric acid	5.9 mg/dL	3.5-7.2 mg/dL
Serum Phosphorus	4.5 mg/dL	2.4-5.1 mg/dL
HbA1c	7.4 %	≤ 6.5 %

Case Report

A Unique Case of Pulmonary and Hepatic Hydatidosis

Harshit Jain[1], Shivmohan Sarraf[2], Bhavya Atul Shah[3], Arti Julka[4]

Hydatid disease or Hydatidosis is a rare infectious disease of human being that is caused by Echinococcus and can involves multiple organs. We report a case of multiple pulmonary and hepatic hydatid cysts in a 35-year-old female, admitted in our hospital with complaints of Cough with expectoration, Hemoptysis, Breathlessness, Chest and Abdominal pain with swelling and fever since 7 month. Chest X-ray revealed multiple rounded opacities of varying size in both lung field with some showing air fluid levels. Computed tomography scan of thorax showed multiple cystic lesion in both lungs and liver with air-fluid level in few cyst. Cystic fluid was aspirated that showed scolex of Echinococcus granulosis. Albendazole was started for the patient with relief in symptoms.

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Key words **: Hydatid disease, Hydatid cyst, Echinococcus granulosis, Scolex, Albendazole.**

Hydatid disease is caused by ingesting embryonated eggs of cystode tapeworm of the genus Echinococcus. Human beings are incidental hosts and get infected by contamination from infected animals which leads to development of hydatid cyst in various organ, but most common site is liver followed by Lung. Here we present a case of 35 year old female, belonging to rural area who was found to have disseminated hydatid cysts of Lung and Liver.

Case Report

A 35-year-old homemaker was admitted to our hospital with symptoms of Cough with expectoration, loss of appetite and weight since 7 months, Hemoptysis, Breathlessness, Right sided chest pain and also Abdominal pain and swelling since 6 month. Fever which was low grade on and off since 3 months. She also gave history of occasionally having a salty taste in the mouth with grape skin like material in expectoration. She had a history of recurrent hospitalization for similar complaints since past 3 years and had also received a course of Anti Tuberculous treatment empirically. On examination of chest, two visible soft fluctuant cystic swelling were present over 9th and 10th intercostal space in posterior axillary line on the right side of chest. She was to found to have crepitations and rhonchi bilaterally. Chest X-ray revealed multiple rounded opacities of varying size in both lung field with some showing air fluid levels. Ultrasonography of abdomen showed multiple well defined cystic lesion of variable size (5.6x5.2x4.9cm) in liver. HRCT thorax revealed multiple cystic lesions in both lung and in liver with air-fluid level in few cyst which appear to be communicating with the bronchi. Her complete blood count showed a low Hemoglobin of 8 gm%, neutrophilic leukocytosis of 15650/cu mm, erythrocyte sedimentation was raised 85mm/hour and newly diagnosed Type 2 Diabetes Mellitus (HBA1c-7.1). The pain over the swelling was relieved by aspiration of a clear fluid which revealed scolex of Echinococcous granulosis. The patient was started on albendazole 400mg (two times a day). She was also given bronchodilators and antibiotics for the secondary infection. The patient improved symptomatically. However, due to disseminated disease, surgery was not considered and patient continued on medical therapy with regular follow up (Figs 1&2).

Editor's Comment :

- Hydatid disease is a rare infectious disease of human being that is caused by Echinococcus and can involves multiple organs and have various presentation in the body. As in our case cyst was protruding out from chest wall in the form of a swelling that help in making diagnosis.

Discussion

Hydatid cyst are caused by parasite known as Echinococcus which is particularly endemic in cattle/ sheep-raising rural area. Echinococcus granulosus species is the the most common among human (>95%). In endemic region, human incidence rate can reach more then 50 per 100000 person-year, and prevalence level as high as 5%-10%. The annual incidence in India is varying, 1 to 200 per 100000 population[1]. The hydatid cyst tend to involve the Liver

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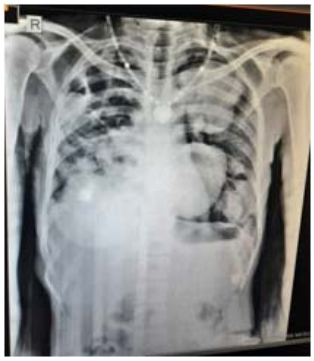


Fig 1 — Chest X-ray showed multiple bilateral opacities with air-fluid level.

Fig 2 — Aspirated fluid showed Scolices of Echinococcus Granulousus

(50-70%), Lung (20-30%) but can be found in other organs like Brain, Heart, Bone, Kidney etc. except Hair, Teeth and Nails.

The ingested eggs are ruptured in digestive tract and larvae reached the Liver by portal system and pass through sinusoids and right chamber of the heart and eventually reside in the Lung. They grow in parenchyma and produce hydatid cyst. Cyst are made up of 3 layer (pericyst, ectocyst, germinal/endocyst). Daughter vesicle originate from germinal. Hydatid fluid is clear or pale, neutral pH, Contain Sodiumchloride, Proteins, Glucose, Ions, Lipids and Polysaccharides. The fluid is antigenic and may contain scolices, hooklets and hydatid sand[2].

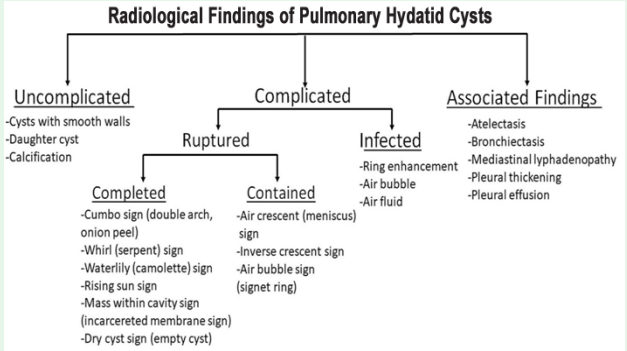
Individual may remain asymptomatic for a long time. The pressure symptoms of the enlarging cyst produce pain in chest and abdomen as was seen in our case. Cyst rupture, secondary infection, suppuration and pneumothorax are common complication of pulmonary hydatid cyst. Cyst rupture may cause sudden cHest Or Abdominal Pain, Hemoptysis, Cough, Fever and Salty taste in mouth as was seen in our case too. This can also lead to anaphylaxis[3].

Diagnosis is by medical history, physical examination, IgG antibody by ELISA and indirect hemagglutination test. Chest radiograph of the pulmonary cyst show the sharply defined, round to oval homogenous opacities of variable sizes. Ultrasonography of abdomen shows solitary or multiple cyst in Liver as was seen in our case. Computed tomography features shows smooth wall of variable thickness 1-20mm and homogenous internal content of water with various sign like "the crescent" or "the meniscus sign" which are reliable sign but not pathognomonic sign of pulmonary hydatid cyst. Radiologically, ruptured hydatid cyst is called double-arch, combo sign, iceberg sign, sign of rising sun, serpent sign and whirl sign. If the parasitic membrane float on fluid surface, this produce the "water lily sign" or "Camelot sign". If all parasitic contents are aspirated, only the pericyst remains, known as "empty cyst sign"[4].

Surgery is the treatment of choice. Drug of choice is albendazole (group-benzoimidazole),10 -15mg/kg/day in two divided doses given for 3-6 month. Hydatid disease should be treated with either albendazole only or albendazole and surgery like PAIR(Puncture, Aspiration, Injection of scolicidal agent and Re-aspiration) to extract cyst without complication. Management of disseminated echincoccal disease is complex, which require a multidisciplinary approach[5].

In our case, due to extensive dissemination, the cysts were inoperable so medical therapy with albendazole was continued with close medical follow up and serial imaging studies.

Table 1 — *Radiological manifestation of thoracic hydatid cyst*



Taken from - Gamze Durhan, Aziz Tan, Selin Ardali Duzgun, Selcuk Akkaya and Orhan Macit Ariyrek. Radiological manifestation of thoracic hydatid cyst: pulmonary and extrapulmonary findings. Durhan et al. insight into imaging (2020) 11:116. https://doi.org/10.1186/s13244-020-00916-0.

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Case Report

Post COVID Rhino Orbital Mucormycosis with Pulmonary Mucormycosis : A rare case report

Pritam Chatterjee[1], Debasish Barman[2], Sudip Kumar Das[3], Arunabha Sengupta[4], Somnath Kundu[5]

Mucormycosis is an acute and fulminant fungal infection caused by fungi of family Mucoraceae, seen usually among immunocompromised or decompensated diabetic patients. Post COVID upsurge of Mucormycosis have been a well-documented entity witnessed in last year affecting several states of India after second wave in form of an epidemic. Disseminated form which indicates involvement of two or more Non-contagious Organ System is extremely rare and generally occurs in severely immunocompromised patients with disseminated Mucormycosis, often discovered in autopsy. Pulmonary and Rhinoorbital forms in a same patient without systemic dissemination is rarely reported.

[*J Indian Med Assoc* 2023; **121(6):** 64-6]

Key words **: Mucormycosis, Rhino orbito Cerebral mucormycosis, Pulmonary mucormycosis, COVID.**

Mucormycosis is an acute and fulminant fungal infection caused by fungi of family Mucoraceae, seen usually among immunocompromised or decompensated diabetic patients[1]. Post COVID upsurge of mucormycosis have been a well-documented entity witnessed in last year affecting several states of India after second wave in form of an epidemic.

Mucormycosis may manifests in six different forms: Rhino-Orbito-Cerebral (ROCM), Pulmonary (PM), Cutaneous, Gastrointestinal, CNS or others[5]. ROCM is mostly associated with Uncontrolled Diabetes Mellitus (DM). Pulmonary Mucormycosis (PM) is more commonly associated with hematological malignancies rather than DM. Disseminated form which indicates involvement of two or more non-contagious organ system is extremely rare and generally occurs in severely immuno-compromised patients with disseminated mucormycosis, often discovered in autopsy[7]. PM and ROM in a same patient without systemic dissemination is rarely reported.

Case Report

An 18-year-old male was referred to ENT emergency of our Tertiary Care Facility on 08/08/21 with complaints of swelling, redness and dimness of vision of left eye for the last 6 days with Non-productive cough & Irregular fever for the last 20 days (Fig 1). He had no record of COVID positivity in recent past but suffered from COVID like symptoms. There was no other comorbidity except newly developed Diabetes Mellitus (DM).

Editor's Comment :

- Early diagnosis and adequate early treatment leads to better prognosis.
- Judicious use of steroids.
- Screening should be done for diabetic immunocompromised patients with non resolving dyspnoea and ROCM cases with Chest CT and bronchoscopic KOH smear keeping pulmonary mucor as differential diagnoses.
- Imaging, KOH Smear and biopsy proven disease can be treated with aggressive adequate surgical debridement, which prevents disease progression and eslablishes vascularisation for better penetration of anti-fungal medications, which in turn improves prognosis and survival chances.

Patient was alert, conscious and cooperative on admission. Initial laboratory studies showed mild Leukocytosis with low Hemoglobin. Ophthalmic examination showed Proptosis of left eye, drooping of upper eyelid, Chemosis and Edema with loss of Perception of Light (PL). During hospitalization on second day patient developed Dyspnea and productive Cough. Physical examination revealed tachypnea and coarse basal crepitations in both Lungs along with falling Oxygen saturation near about 89%. Sputum for AFB, HIV antibody test and RT-PCR for COVID-19 were negative.

Chest X-ray showed multiple rings like opacities in both the Lungs (Fig 2). HRCT thorax revealed multiple large thick walled cavitary lesions in both Lungs and septae like structures within. Multifocal ground glass opacities were noted in Right Upper Lobe and basal segment of Left Lower Lobe (Fig 3). USG abdomen was normal.

Diagnostic Nasal Endoscopy (DNE) showed black crusts on left middle turbinate. Sample taken for KOH smear, culture and biopsy. Bronchoscopic suction done and lavage material sent for KOH smear and culture. Both the specimens showed broad aseptate hyphae.

MRI of Nose, Paranasal sinuses, Orbit and Brain were done in sequences of T1, T1 with contrast and T2 with

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Fig 1 — Patient at presentation with nasal discharge and facial cellulitis with orbital cellulitis

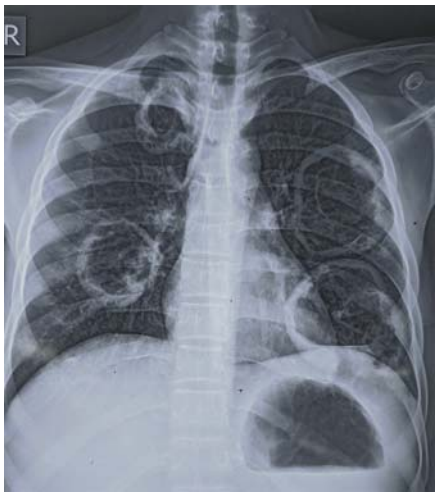

Fig 2 — Chest X-ray showing multiple ring like opacities in both the lungs

FSE, DWI and GRE. The MRI findings are suggestive of – Heterogenous areas with mucosal thickenings involving ethmoids, spheroids, left maxillary antrum and adjacent left frontal sinus. Postcontrast study showed marked heterogenous enhancement. Such heterogenous areas were also seen involving retro-ocular portion of left orbit and adjacent peri orbital region with enhancement in post contrast study. Left ocular bulb showed loss of morphology with extra ocular muscles involvement. Left Optic Nerve also had signal changes. Enhancement of para-seller carotid more on left side was also seen on MRI.

Management was done as per Institutional mucormycosis guideline. On clinical suspicion for Post COVID Mucormycosis, patient was started on Amphotericin B (liposomal) 1mg/kg body weight from day 2 of admission awaiting histopathological confirmation. Adequate antibiotic & anti-inflammatory coverage along with medical therapy was also initiated to stabilize underlying metabolic derangement.

After diagnosis was confirmed, surgical management in form of endoscopic endonasal wide local debridement of all sinuses, pterygopalatine fossa and drilling of pterygoid wedge along with eyelids sparing exenteration of left eye done under General Anesthesia on 4th day of admission (Fig 4). Postoperative period was uneventful. Postoperative histological examination showed inflammatory tissue invaded with broad aseptate hyphae with irregular branching pattern at right angles suggesting Mucormycosis.

Regular endoscopic suction clearance, removal of crusts and amphotericin washes were given to the Postoperative cavity. After 25 days of injection Amphotericin B, he was started on oral Posaconazole 300 mg once daily. Patient was discharged on day 29 on Posaconazole. At the time of discharge patient was hemodynamically stable, CRP level was 20 mg/l and blood sugar were well controlled with insulin therapy. On follow up after 2 weeks eyelids stitches were removed. Postoperative cavity of sinonasal & orbital areas was well epithelized and Chest X-ray became normal. During successive follow up for 8 months no recurrence was seen. Patient is still under our supervision with oral Posaconazole.

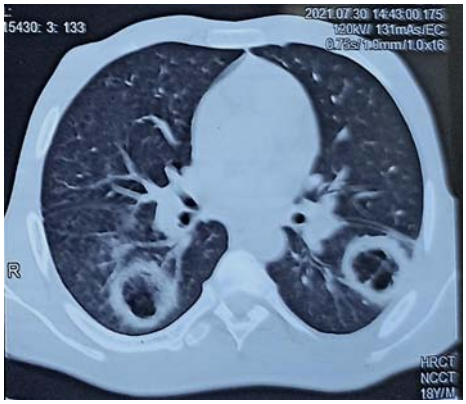

Fig 3 — HRCT thorax revealing multiple large thick walled cavitary lesions in both lungs and septae

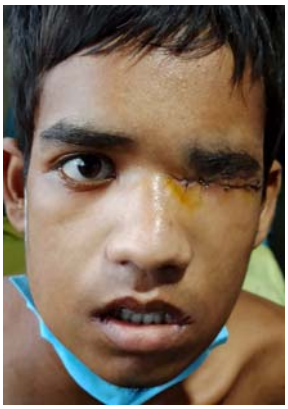

Fig 4 — Postoperative photograph prior stitch removal where patient has undergone endoscopic endonasal wide local debridement of nasal component of mucor along with orbital exenteration

Discussion

Mucormycosis is an opportunistic infection caused by Mucorales. Such fungal infection mainly occurs in patients with immune system deficiency, though it can rarely attack immunocompetent patients. Such a massive involvement in an immuno-competent patient at such a younger age is an extremely rare entity, which is possibly due to post COVID immunosuppression. Still the patient probably survived due to timely interventions and more importantly due to well-maintained immune status.

Rhino-orbital Mucormycosis begins with nonspecific nasal complains like Rhinorrhea, Nasal blockage, Headache, Deep seated retroorbital pain, which rarely alarms clinicians. It's generally the visual compromise, facial cellulitis or check hypoesthesia which warrants the Otorhinolaryngologist for a Nasal

Endoscopy or MRI and possibly a biopsy demonstrating mucorales for diagnosis. Similarly, non-specific symptoms such as Fever, Cough, Dyspnoea, Haemoptysis and Chest pain are presenting features of Pulmonary Mucormycosis. The definitive diagnosis of Pulmonary Mucormycosis also comes from identification of typical hyphae through bronchoalveolar lavage culture, needle biopsy and resected lung tissue biopsy. Variable presentations make it difficult to distinguish Rhino-orbital and Pulmonary Mucormycosis from other sino-nasal or pulmonary pathologies. Mucormycosis should be suspected in patients with normal immune function with fulminant progression, especially when routine anti-infective treatments fail. Invasive procedures in decompensated patients are always dilemmas. Culture takes longer time and culture positivity rates are near about one-third. Such limitations delays diagnosis and systemic antifungal therapy, which worsen prognosis and increase the risk of death.

The Post COVID mucormycosis is still an enigma. The virus spreads from the Nasopharynx to the Lungs or inhaled directly to both separately, where it can cause intense inflammatory response with alveolar edema and may result in the Acute Respiratory Distress Syndrome and to other tissues that expresses the ACE- 2 receptor, including the blood vessels[2]. The locoregional spread pathway of ROCM has not been adequately described. Pterygopalatine fossa acts as a reservoir of the disease through which it can spread to the neighboring structures including the retro-global space of the orbit and Infratemporal Fossa (ITF)[3]. Mucor causes angioinvasion and its ability to cause tissue necrosis and dissemination through bloodstream is well established[4]. Dissemination most commonly affects the Brain (ROCM), but can affect any other organ like Lungs (PM), Spleen, Heart and Skin.

Diagnostic nasal endoscopy shows characteristic eschars, discharge or necrotic mucosa which directs surgeon to collect biopsy and conduct KOH smear. MRI of Nose, Paranasal sinuses & Orbit shows devitalized and involved tissues for surgical planning. The patient developed ptosis, ophthalploplegia and visual loss on left side. Loss of vision probably due to cavernous sinus involvement. Cavernous Sinus Thrombosis usually results from spread of infection from orbital apex or sphenoid sinus. A through Ophthalmic examination is required for deciding fate of the eye. Radiologic signs can suggest Pulmonary Mucormycosis in an appropriate clinical setting[8]. Halo sign on CT, a ring of ground glass opacity surrounding a nodular infiltrate which pathophysiologically represents a region of ischemia. Reverse Halo sign on CT (atoll sign) represents an area of ground glass opacity surrounded by a ring of consolidation are pathognomonic of Pulmonary Mucormycosis (Fig 5).

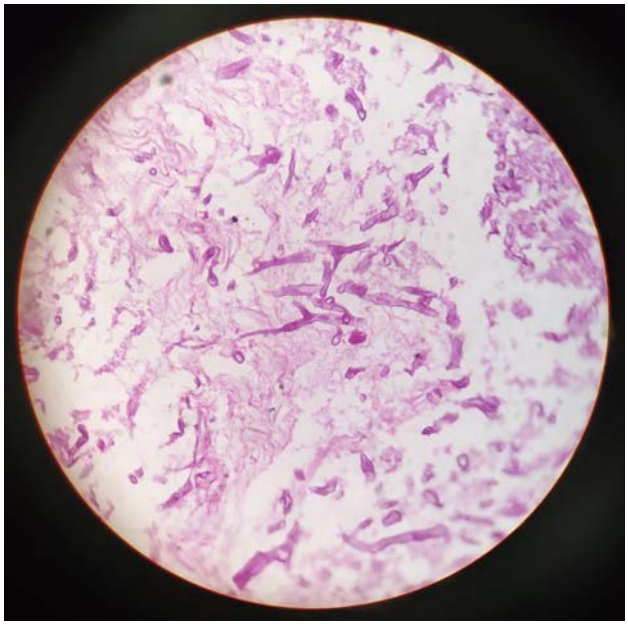

Fig 5 — KOH smeer from tissues obtained from endoscopic nasal biopsy

Conclusion

Key to successful outcome is early diagnosis and initiation of systemic antifungal in form of Amphotericin B based on clinical judgement. KOH smear has role in early diagnosis. Prompt and adequate surgical debridement of involved areas reduces disease load, slows down disease progression and establishes vascularization for penetration of anti-fungal which in turn results in better prognosis & survival chances.

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View Point

"Tunnel of Love" in Whipple — In the Pursuit of the Proposer

Utpal De[1], Kaushik Bhattacharya[2], Riya Agrawal[3]

"Tunnel of Love"(TOL) in Whipple surgery of Pancreatic Tumours is the cleavage plane over the superior mesenteric vein and behind the pancreas. While the term is well known in operative surgery textbooks since ages, the reason behind such a terminology and the creator of this term TOL has never been investigated or explored. This is probably the first initiative in surgical literature to decode the term TOL with various postulations.

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Key words **: Pancreaticoduodenectomy, Tunnel of Love, Portal vein.**

Pancreaticoduodenectomy for Periampullary Cancer is a challenging operation. One of the key steps for operability is the creation of a clear "Tunnel of Love" ie, the space behind the neck of pancreas and anterior to portal vein (Fig 1)[1]. Successful creation of the tunnel is a key determinant for further progression and completion of the Whipple operation with complete clearance of the tumour.With the advancement in radiology and based on multi-detector Computed Tomography reports even borderline cancers are resectable wherein a portion of portal vein can be sacrificed and anastomosed. These are usually done in dedicated high volume centers. A review of the literature shows that the percentages of patients who underwent surgery at very low-, low-, high-, and very high-volume centres were 29%, 19%, 23%, and 29%respectively[2]. So approximately 48% of the operations are performed in either a low volume or very low volume center where advanced radiology is inaccessible. Moreover, technical support and expertise of portal vein excision and reconstructionis inaccessible. So,surgeons have to rely on the safe dissection of "Tunnel of Love" as sole criteria for progress of the operation. But the question is how such a complicated operation with such a crucial step could be associated with the idea of "Love". Further, a search of medical literature failed to identify the surgeon who named it or the reason behind naming that step as the 'tunnel of love' in pancreatic tumour surgery.

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Possible Postulations :

(A) Of the many meanings of 'love' according to Oxford dictionary includes intimacy or attachment[3]. It could have been named because of intimate relation between the portal vein and posterior pancreas. But how can one attribute its naming to making a tunnel which is akin to breaking love as love is inseparable and eternal. Neither is any structure created rather the tunnel is dismantled and laid open for further anastomosis.

(B) It could have been named by some surgeon in the name of "Dr Love" posthumously, but a search of

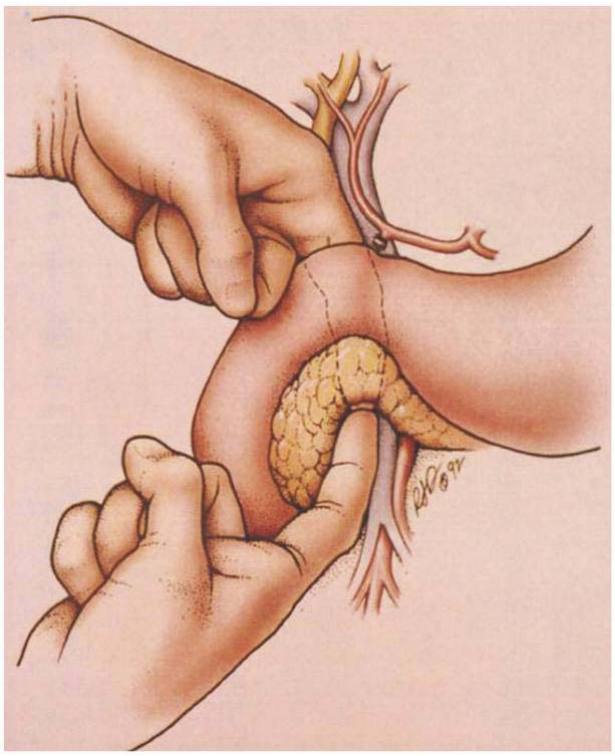

Fig 1 — Per-operative picture of "Tunnel of Love" during Whipple

history of medical literature failed to provide any such possible evidence.

(C) A broad Goggle search with search words "tunnel of Love" reveals amusements rides to music albums but all of them are recent development long after pancreatico-deodenectomy was in vogue. The section of industrial railway located near Klevan, Ukraine, that links it with Orzhiv[4]. It is a railway surrounded by green arches and is three to five kilometres in length (Fig 2). It is known for being a favourite place for couples to take walks since trains pass thrice a day. The tunnel of trees is so dense it is difficult to see outside from within the structure and the natural light that penetrates the canopy from above makes the space soothingly dark.However, there is not much attention given to the tunnel as a tourist attraction despite the obvious potential and the fact it is a naturally occurring space. Tourist legends says that couples who ride together through the green tunnel and make a wish will get what they want. The Idyllic tunnel of love was created in collaboration by nature and man. The above explanation seems more realistic. "TOL" is obscure hidden behind the head of pancreas and once the two fingers meet (one from above and one from below) it's for sure that in all probability the operation could be completed.

(D) Another probable reason of creating the term " Tunnel of Love" in Whipple surgery may be was to warn the surgeon and the assistants to be gentle and perform dissection with utmost care and love in that area to avoid any type of catastrophe, injury or bleed.

Conclusion :

Thus though the mystery behind the term "TOL" remains unsolved, it's a mysterious excitement in the wild dreams of Pancreatic Surgeons holding back the adrenergic drive while traversing through this surgically challenging yet adventurous tunnel, each time thinking about the passionate "proposer". It also speaks volumes about the humour and wit of the proposer. Like many other hidden and buried surgical history it is ardent that we unravel the truth behind the name and pay homage to the great surgeon who has paved the way for saving many lives of patients who are benefitting from Pancreaticoduodenectomy.

Fig 2 — Picture of "Ukraine" Tunnel of Love

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Image in Medicine

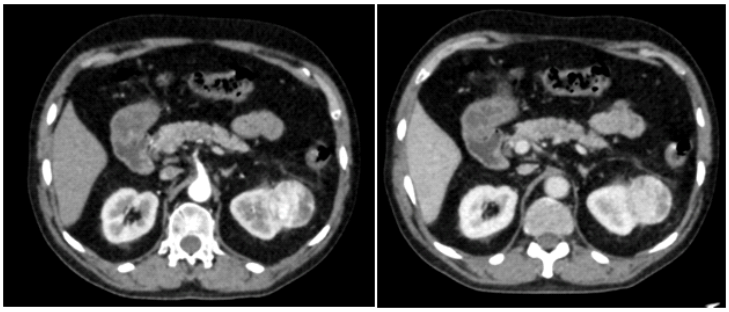
Bhoomi Angirish[1], Bhavin Jankharia[2]

Quiz 1

A 48-year-old male presented with haematuria and loin pain since 10 days.

Questions :

(1) What is the diagnosis 2 ?
(2) What are the hereditaryassociations ?
(3) What is RENAL nephrometry scoring system ?



Answers :

(1) A well defined enhancing partly exophytic lesion is seen arising from lateral cortex of left kidney suggestive of renal cell carcinoma.

(2) Hereditary renal cell cancer syndromes include Von Hippel Lindau syndrome, tuberous sclerosis, Birt-Hogg-Dube syndrome, sickle cell disease.

(3) The RENAL nephrometry scoring system is used to categorize renal masses into low, intermediate and high complexity. Its purpose is to aid in decision making, patient counseling, surgical planning, and patient follow-up, as well as academic reporting. It includes the following parameters:

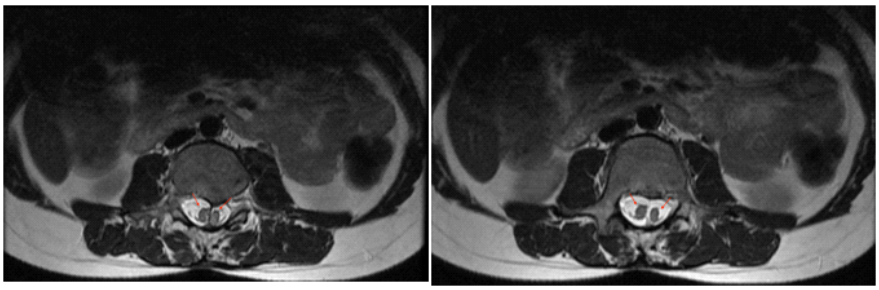
a) Radius (maximum diameter) in centimeters (cm) in any axis
b) Exophytic/endophytic tumor location.
c) Nearness to the renal collecting system or renal sinus measured in millimeters (mm) as the shortest distance from the deepest point of the tumor.
d) Anterior or posterior location - assessed on the axial view.
e) Location relative to the renal poles

Quiz 2

A 18-year-old female presented with tingling and numbness in both lower limbs.

Questions :

(1) What is the diagnosis ?
(2) What is the classification?
(3) What are the common associations of this condition?



Answers :

(1) A longitudinal split is seen in the cord separated by a septum, suggestive of diastematomyelia.

(2) Diastematomyelia or split cord malformations are divided into two types according to the presence of septum and single vs dual dural sac. Type I has duplicated dural sac with common midline spur which can be fibrous or osseous. Type II is a single dural sac containing both hemicords.

(3) Diastematomyelia is frequently associated with other anomalies such as meningocele, neurenteric cyst, dermoid cyst, spinal cord lipoma.

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In Memoriam

JIMA deeply mourns the sad demise of Dr M. Abbas, veteran leader and Past National President of IMA, who breathed his last on 15th June, 2023, evening.

He was a life member of IMA Cuttack Branch. His contribution to the Medical Association as well as to the Medical Profession shall be remembered for times to come. He was the State Secretary of IMA Orissa for long 13 years.

We convey our heartfelt condolences to the members of the bereaved family.

His demise is an irreparable loss to the Association, Medical fraternity as well as to the society.

May Almighty give enough strength to the loved ones to bear with this irretrievable loss!

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