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EDITORIAL

NEGLECTED PATIENTS, THE PHYSICIANS

Physicians in general have better health than the general population, but they do not take as good care of themselves. Many physicians in good health often do not undertake routine screening tests or physical examination which is mandatory for their age and is being conducted by them on their patients on daily basis. These physicians settle for curb side diagnoses or consultations and then treat themselves albeit with incomplete diagnosis and poor compliance.

Physicians with impairments usually maintain their occupational functioning at an adequate level until their problem becomes more advanced and their ability to care for their patients deteriorates. One of the most important highlights of revised Geneva declaration is the duty of a physician to attend to his own health, well-being, and abilities in order to provide care of the highest standard.

Physician impairment is a public health issue as it not only affects the affected individual himself but also puts the lives of his patients at risk of being ignored and mistreated. A physician is said to be impaired if he is unable to fulfill professional and personal responsibilities because of a physical or mental illness, alcoholism, or drug dependency. Although concern about physical health issues has started to improve but the ignorance and denial of mental health issues is increasing amongst physicians. Suicide rate amongst health professionals is highest amongst all professions and is rising even further every passing day. Similarly, substance abuse problems remain undetected for several years before being brought to attention and treatment undertaken.

It is so strange that physicians who are the front-line treatment providers for health related issues don't always recognize the value of mental health professionals for their own mental health needs. They prefer to discuss mental health problems with family or friends instead of seeking formal or informal advice, citing reasons such as career implications, professional integrity, and perceived stigma of mental health problems.

If we carefully examine these three reasons as root cause of ignorance of personal mental health issues, then these appear to be themselves flawed.

Foremost reason which is usually reported as cause of not reporting mental health issues is its impact on career. Many organizations tend to not hire professionals who are known to have a psychiatric illness and many more try to discard physicians who report to have mental health issues. If an organization is going to deny you career advancement because you're being honest about a mental health condition, perhaps that's a sign you need to find another organization to work for. Or work to change such mid-century, backwards thinking from within the organization.

Another commonly reported concern is loss of professional integrity by reporting to have mental health issue. Doctors need to be honest with themselves about their own lack of treatment for treatable mental disorders. Another main reason is stigma of having a mental health issue. Here again doctors don't realize

they are only perpetuating the cycle of stigma, by avoiding such treatment themselves. And whether they admit it or not, such thinking can't help but influence the way they portray mental health issues to their patients.

Last but not the least is issue of breach of confidentiality and so they are afraid that by seeking treatment within the same system, it will be used against them in the future. That's a legitimate concern, and one that could be easily corrected by adding additional privacy protections for such professionals.

It's high time for physicians in general and impaired physicians in particular to work toward ridding our world of such stigma and ignorance, and stop the discrimination against professionals who have a mental health concern.

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Major General Muhammad Salim Jehangir, HI(M)
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EDITORIAL**PREVENTIVE AND STRATEGIC APPROACHES FOR REDUCING THE BURDEN OF NON-COMMUNICABLE DISEASES IN PAKISTAN**

According to World Health Organization (WHO), about 40 million people die due to Non-communicable (NCDs) diseases every year, accounting for 70% of total deaths. Majority of these deaths occur in low and middle income countries. About sixteen million deaths below 70 years of age occur globally due to NCDs. The annual mortality due to NCDs includes; cardiovascular diseases (17.5 million), cancers (8.2 million), respiratory diseases (4 million) and diabetes (1.5 million). Most common reported risk factors of NCDs were consumption of tobacco, alcohol, high fat diet and lack of physical activity.¹

NCDs, Injuries and Mental health issues contribute to half of the disease burden in Pakistan. Injuries account for more than 11% of the total Burden of Diseases, the contributing factors include; road traffic accidents, violence and rapid urbanization. Pakistan ranked 7th in the world for diabetes prevalence and every fourth adult above 18 years of age is found hypertensive. Tobacco smoking prevalence is high, one third of population is suffering from high cholesterol level, one fourth of the population over 40 years of age suffers from a cardiovascular disease. Disability due to blindness or other causes is also high, and disabled population is neglected and compromising their quality of life due to lack of special service provision. The Burden of Diseases is on rise due to increasing population, Pakistan is sixth most populous country in the world. The health system functions are compromised due to acute crises such as floods, droughts, earthquakes, man made emergencies as well as disease outbreaks such as Dengue and Measles. The chronic factors which affects the health systems include; low GDP allocation to social sector, overall slow economic growth, ongoing conflict in several areas of the country, and over-arching governance challenges affecting the public sector. Moreover, official development assistance (ODA) from the donors is quite low.²

Now the question arises what is the solution to combat this epidemic of NCDs? The prevalence rates of obesity, diabetes mellitus, and hypertension is on the rise in young and old population. The answer is complex as we have to fight this battle from multiple ends; community, organization and country level. Prevention of risk factors of NCDs causing obesity in children is important, because obesity shortens an individual's life span, affects quality of life, leading to lifestyle diseases like stroke, blindness, diabetes and its complication like amputations, and kidney failure.³ Screening of the high risk population is extremely important as it detects the disease early so that prompt treatment is applied. Modern diagnostic and treatment facilities should be available for those who have developed the disease to prevent complications of chronic NCDs.

Pakistan's Health policy and health system development is the key to improve the health status of Pakistani population and combating NCDs. Improvements in policy-making and governance can be made through policy assessment and analysis and review of the health system with a view to outline gaps and propose solutions as part of the national health strategy. Pakistan needs to improve service delivery through development of an integrated framework for the provision of comprehensive and equitable health care to the population. WHO is supporting Prime Minister's Health Insurance Programme and has advocated for more

adequate budget allocations to the health sector. Pakistan should be given opportunity to increase external resources to support critical aspects of health sector, reform at provincial level and promote coordinated approaches in view of the devolution process. Developing public–private partnership and managing human resources for health, developing an integrated health information system and promoting and supporting applied research are other components to strengthen Health policy and system development in Pakistan. According to WHO strategic cooperation agenda 2011-2017 strategic priority number 4 emphasizes the development of national non-communicable control strategy minimizing negative impacts of risk factors and advocating multi-sectorial public policies. Strengthening public-private partnership and accelerating implementation of the provisions of the WHO Framework Convention on Tobacco Control can be of great help. Efforts should be targeted to integrate mental health and substance abuse into primary health care services.² By adopting these strategies we can fight the battle against non-communicable diseases before it goes beyond our control and leads our nation to a catastrophic situation. Monitoring and surveillance is another aspect which provides internationally comparable assessments of trends in NCDs and provides foundation for policy development to reinforce political commitment.

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EDITORIAL

ROAD TO UNIVERSAL HEALTH COVERAGE (UHC)

Universal health coverage (UHC) is about ensuring that everyone gets quality health services, wherever & whichever one needs them, without suffering from financial hardship. UHC cuts across all of the health-related Sustainable Development Goals (SDGs) and is key to people's and nations' health. The idea is often viewed as utopian but an extension of Plato, Socrates and other philosophers' concepts of social justice. It is this same idea which is embedded in Islamic principles of “Adal and Ehsan”.

In its present sense, UHC is based on the WHO constitution of 1948 declaring health a fundamental human right and “Health for All agenda” set by the Alma Ata declaration in 1978. Since the pronouncement of MDGs in 2000, low-income countries remained underperformers in providing affordable health services and reducing out-of-pocket costs to patients. UHC needs a strong, efficient and well run health system that meets peoples' priority needs. The system relies on well trained and motivated staff with medicines and technologies in place at an affordable cost addressing the social determinants as well. The type of services to be included has to be according to public affordability and time needs.

A journey from MDGs to SDGs provided us with a six action line “2030 Agenda for Sustainable Development”. It gives us an opportunity to build better systems for health, because strengthened systems would help us to achieve UHC. This 2030 Agenda points out inter-sectoral action, scientific research, innovation and M&E (Monitoring & Evaluation) as important action lines.

Universal Health Coverage and Public health constitute an essential combination for ensuring parity and complementarity. The best service by public health would be to improve data on public health spending and to expand the scope of evaluations. Both clinical services and public health interventions are critical to health systems and population health. In the context of universal health coverage, the concepts of health care and health care services deserve to be clearly distinguished. The focus on clinical services is evidenced and supported by the UHC vocabulary, “access to services” and financial risk protection related to “out of pocket expenditures” align poorly with public health interventions such as tobacco taxes, informational campaign on healthy diets and public health capacities for epidemic preparedness and response. Keeping in view the competing economic interests for services we need to guard against marginalization of cost-effective, population based interventions while dovetailing the individualized public health preventive services like Vaccinations. Public health must not lose focus on long term population based interventions which are ultimately going to promote Universal Health Coverage.

At national level, it would be worthwhile to suggest pursuing two parallel objectives of PH interventions and UHC, each complementing the other. In order for successful achievement of UHC alongside PH, it is important to develop quality data on surveillance of national and international public health spending (Total

Health Expenditure -THE). This would clarify the effect on life expectancy at birth and per capita expenditure. Accurate data on expenditure on public health vis-a-vis clinical services are essential for debating, and improving a balance.

Moreover, though it is important to have health benefits measured in terms of economic gains, Public health interventions provide benefits beyond mere economics and include educational effects and these render them far superior to clinical services; for example school lunch programs improve health status as well as school attendance. Same is the case for interventions that affect social determinants of health which have a broader socioeconomic uplift effect. This brings to fore the fact that appraisal of public health interventions must include non-health outcomes and distributional impacts to ensure right priorities in action and spending.

WHO and World Bank UHC Measurement Framework (2014) helps all countries in measuring UHC, taking an account of population coverage with equity indicators, health services coverage indicators, financial protection and a subset of performance indicators.

Pakistan has seen progress in access to health care services. Government has documented universal health coverage as its prime agenda for the health sector. Gains are uneven across different service areas as out of pocket expenditure is still around 70%. The National Health Vision 2016-2025 strives to provide a responsive unified national direction to confront various health challenges, while ensuring adherence to Universal Health Coverage as its ultimate goal.

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KNOWLEDGE AND AVAILABILITY OF HOUSEHOLD FIRE SAFETY EQUIPMENT AMONG DOCTORS AND VISITORS OF HOLY FAMILY HOSPITAL (HFH)

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ABSTRACT

Objective:

To assess the knowledge and availability of fire safety equipment in different household fires among doctors and visitors of HFH.

Design:

It was a cross sectional survey.

Place and duration of study:

This study was conducted in OPD of Holy Family Hospital, Rawalpindi during the months of April-May 2016.

Subjects and methods:

Data was taken from doctors and visitors in Holy Family Hospital OPD. Data was collected using questionnaires with questions related to their demographic details, availability of household fire safety equipment in homes and knowledge about their use in different types of fires. Data was entered and analyzed in SPSS version 21.

Results:

Majority of our respondents i.e. 55.7% had emergency numbers available in their homes. Fire exits, water sprinkler and sand were present in 31.4%, 31.4% and 34.3% homes respectively. Least available equipments were fire extinguishers especially dry chemical powder (2.9% prevalence). Majority respondents (75.7%) knew how to extinguish fire from furniture/ clothing/ paper. Least knowledge was observed for extinguishing fire from cooking oil i.e. only 2.9%.

Conclusion:

Majority of the respondents did not have fire safety equipments available in their house and their knowledge about use of fire safety equipment was found to be inadequate.

Keywords:

Fire Safety, Fire Extinguishers, Fire Exits, Water Sprinkler, Smoke Alarm

INTRODUCTION

Residential fires are common due to multiple factors present in homes. More than 2,000 deaths occur annually in US. Lifetime expenditure due to fire injuries is almost \$1.2 billion.^{1,2} In 2015, domestic fires made up 77.4% of all fires in US.³ Almost 63% fire deaths occur in homes without a

smoke alarm.⁴

Center of Disease Control recommends using smoke detectors in homes, fire extinguisher in the kitchen for small fires & fire escape plan.⁵ This is especially important in flats and houses in multiple occupation. In US, it is mandatory to maintain fire safety in houses under the Housing Act 2004 & Fire Safety Order 2005, which recommends the use of a simple multi-purpose extinguisher, fire blankets ('light duty' type) in kitchens & smoke alarm in house and also fire safety advice at the start of new tenancy.⁶

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It's an accepted fact that with presence of sprinklers, smoke alarms, and fire extinguishers risk of injury is much reduced in case of fire.^{7,8,9} US has made improvement in reducing fires by extensive use of smoke detectors (>90%), fire sprinkler systems by fire safety education and home inspection programs.^{5,10,11,12} An essential aspect of this fire safety education is to train people how to react to different fire types, i.e. which fire extinguisher to use in which type of fire.¹³

Many studies are being conducted in US on fire safety situation,¹⁴ but no published literature was available from other countries including Pakistan. In Pakistan, every year 16,500 people die and 164,000 get injured in fire accidents but still the government has no National Fire Safety Policy to prevent these accidents.¹⁵

As no national publication has been found regarding this topic so we aimed to find facts about the situation of fire safety prevention in our population. This study will not only help in assessing the knowledge of literate people but also sensitize them about this growing public health issue. The information revealed from this research can be helpful for concerned higher authorities to consider fire safety education as a neglected issue which is an effective measure for fire and burn prevention.

MATERIALS AND METHODS

This study was conducted in the month of April and May 2016, in Holy Family Hospital (HFH) OPD. Doctors and visitors (including patients and their attendants) in OPD were included in our study population using non-probability consecutive sampling. Sample size was calculated using sample size calculator. Taking prevalence of fire extinguisher use 18%, margin of error 9%, confidence level 95%, sample size came out to be 70.¹ Inclusion criteria was that respondent should be 20-60 years of age and at least primary pass. Visitors coming from rural area were excluded from the study population due to communication barrier. Data was collected by researchers using questionnaires, which were filled by the researchers after interviewing the respondents. Questionnaire was close-ended, semi-structured and in English language. Questions were related to age, gender, education (under-matric, under-graduates, graduates, and post-graduates), occupation

(doctors/ non-doctors), prevalence and availability of fire safety equipment in homes. Options were given for each question. Availability was assessed by asking respondents whether they had these fire safety equipment available in their homes or not; water sprinkler, fire extinguisher (CO₂ filled), dry chemical powder extinguisher, foam filled fire extinguisher, water mist extinguisher, smoke alarm, fire exit, fire blanket, sand, emergency numbers. Options given were 'yes' and 'no'. Later for each respondent we categorized, the availability of these equipment as; poor=no equipment present in home, satisfactory=1-5 equipments, good=>5 equipments. Knowledge was assessed by asking which fire safety equipment to use in the different types of fires. Options were given and choosing answer only from correct options was considered correct answer. They were allowed to choose more than one options. For example, in fire from furniture/ plastic/ clothing/ paper (class A fire), correct answer will be dry chemical powder extinguisher/ water/ water mist extinguisher/ foam extinguisher. Any other answer was incorrect. In case of fire from oil/ petrol (class B fire), correct answer was CO₂ filled extinguisher/ dry chemical powder extinguisher/ water mist extinguisher/ foam extinguisher. In fire from gas leakage (class C fire): correct answer was dry chemical powder extinguisher. Fire from electrical equipment (class E fire): correct answer was CO₂ filled extinguisher/ dry chemical powder extinguisher. In fire from cooking media (class F fire): correct answer was wet chemical extinguisher/ water mist extinguisher. We then categorized knowledge as poor=no correct answer, satisfactory=1-2 correct answers, good=>2 correct answers. Informed written consent was taken from study subjects and confidentiality of respondents was assured. These variables of knowledge and prevalence of fire safety equipment were compared in relation to age, gender, education and occupation and were tested for statistical significance using chi-square test. Statistical analysis was done using SPSS Version 21.

RESULTS

Demographic details are shown in table I. In our study, majority people were of age 20-30 years (68.57%). Proportion of males was 37.1% and of females was 62.9%. A majority i.e. 58.6% was undergraduates. Doctors were 38.6% and 61.4% were non-doctors.

Table I: Demographic and educational characteristics (n=70).

Variable	N (%)
Age	
20-30 years	48 (68.57)
31-40 years	11 (15.71)
41-50 years	7 (10)
51-60 years	4 (5.71)
Gender	
Male	26 (37.1)
Female	44(62.9)
Education	
Under-matric	8 (11.4)
Under-graduates	41 (58.6)
Graduates	15 (21.4)
Post-graduates	6 (8.6)
Occupation	
Doctors	27 (38.6)
Non-doctors	43 (61.4)
Total	70 (100)

Availability of fire safety equipment in homes of our study population is shown in table II. More than half of our study population (55.7%) knew emergency numbers. Fire exits, water sprinkler and sand were present in 31.4%, 31.4% and 34.3% homes respectively. Least available equipments were fire extinguishers especially dry chemical powder (2.9% prevalence). Knowledge about use of fire safety equipment in different types of fire is also shown in table II. Majority of our study population (75.7%) knew how to extinguish fire from furniture/ clothing/ paper. Least knowledge was observed for extinguishing fire from cooking oil i.e. only 2.9%.

Table II: Availability and knowledge of fire safety equipment in homes (n=70).

Variable	Yes N (%)	No N (%)	Total N (%)
Availability of equipment in home :			
Emergency numbers	39 (55.7)	31 (44.3)	70 (100)
Fire exits in all rooms	22 (31.4)	48 (68.6)	70 (100)
Water sprinkler	22 (31.4)	48 (68.6)	70 (100)
CO2 filled fire extinguisher	3 (4.3)	67 (95.7)	70 (100)
Dry chemical extinguisher	2 (2.9)	68 (97.1)	70 (100)
Foam filled extinguisher	6 (8.6)	64 (91.4)	70 (100)
Water mist extinguisher	3 (4.3)	67 (95.7)	70 (100)
Fire blanket	17 (24.3)	53 (75.7)	70 (100)
Smoke alarm	6 (8.6)	64 (91.4)	70 (100)
Sand	24 (34.3)	46 (65.7)	70 (100)
Knowledgeable about use of equipment in:			
Fire from furniture/ clothing/ paper/ plastic	53 (75.7)	17 (24.3)	70 (100)
Fire from petrol/ grease	26 (37.1)	44 (62.9)	70 (100)
Fire from gas leakage	7 (10)	63 (90)	70 (100)
Fire from electrical equipment/ short circuiting	11 (15.7)	59 (84.3)	70 (100)
Fire from cooking oil	2 (2.9)	69 (97.1)	70 (100)

We made categories of our study population according to the level of availability and knowledge. Those having good knowledge comprised 18.6% of our study population, 60% had satisfactory knowledge and 21.4% had poor knowledge. Majority had satisfactory availability of equipment i.e. 80% but only 4.3% had good availability and 15.7% had poor availability of equipment in home. Comparison was also done between doctors and non-doctor population as shown in table III. p-value was calculated using Chi-square test. This comparison was statistically non-significant (p-value >0.05).

Table III: Comparison of doctors and non-doctor population with respect to availability and knowledge.

Variable	Doctors	Non-doctors	P-value
<i>Availability</i>			
Poor	2 (7.4%)	9 (20.9%)	0.301
Satisfactory	24 (88.9%)	32 (74.9%)	
Good	1 (3.7%)	2 (4.7%)	
<i>Knowledge</i>			
Poor	6 (22.2%)	9 (20.9%)	0.992
Satisfactory	16 (59.3%)	26 (60.5%)	
Good	5 (18.5%)	8 (18.6%)	
Total	27 (100%)	43 (100%)	

DISCUSSION

In Pakistan, no published literature was found discussing prevalence of fire safety equipment and knowledge about their use. Our study showed that only 1/4th population knew well about which fire extinguisher to use in which type of fire. But fire extinguisher was present only in 12.8% homes. This result goes in line with a study of New York where only 18% had fire extinguisher in homes.¹⁶ This low prevalence may be because people are not conscious about fire safety. However in another American study this prevalence was 69%.⁵ In America this prevalence may be high because of implementation of laws made for fire safety in US.

In our study, only 8.5% had smoke alarm present in their homes. However, the prevalence of smoke alarm in New York study was 63%.¹⁶ Smoke alarms are less prevalent than fire extinguisher in our population which may be because they are not necessary for extinguishing fire and their preventive role is ignored by our society due to lack of awareness and legislation.

Other studies of US showed prevalence of smoke alarm in houses ranging from 82 to 86%.^{11,17} Respondent age was associated with having working smoke alarms.¹⁷ In another study, education was linked with presence of smoke alarm in home.¹⁸ Education has been established as a strong factor determining fire accidents in many studies.^{19,20} But in our study there was no such positive relation. Reason might be lack of fire safety education in our setup and the general careless attitude of educated people.

In our study, water sprinkler was present in 31% homes. Also in a study of Durham, USA water sprinkler was present only in 42% homes.²¹ This low usage of sprinkler may be because common practice is to throw water in buckets instead of using any sprinkler in case of fire.

In our study 31% had fire exits in their rooms. Whereas 60% of all households in USA had made a fire escape plan.¹⁸ Their fire accident preparedness is better may be because of frequent fire safety campaigns run in schools and in high risk population.¹⁴ Moreover, fire preparedness is worse in low income regions of world.

CONCLUSION

Majority of the respondents did not have fire safety equipments available in their house. Also their knowledge about which fire safety equipment to use in different types of fire was found to be poor.

RECOMMENDATIONS

Community awareness campaigns should be run regarding fire safety for prevention of fire accidents. Demonstrations should be given regarding how to use fire extinguisher. Which fire extinguisher to use in which type of fire. Legislation should be made for using fire safety equipment in homes. Surveys should be conducted in homes to check presence of fire safety equipment and those not keeping these equipment should be fined. Incentives should be given on purchase of these equipments and its access should be enhanced. Presence of these equipment should be mandatory for sale of house.

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KALONJI (*NIGELLA SATIVA*) AND VITAMIN B-3 FOR PREVENTION OF DYSLIPIDEMIA

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ABSTRACT

Objective of the study:

Kalonji and vitamin B-3 lowers plasma lipids variably in hyperlipidemic patients. To evaluate hypolipidemic efficacy of vitamin B-3 and kalonji, the study was conducted at Ghurki trust teaching hospital, Lahore Pakistan from January 2012 to August 2012.

Methodology:

Ninety patients with diagnosed dyslipidemia were enrolled from cardiology department of the hospital. Exclusion criteria was patients suffering from any kidney, liver and thyroid related disease. Name, age, gender, occupation, residential address, phone/contact number, previous medical history, disease in family history was kept in specified proforma. Written and well explained consent was taken from all participants. They were divided in three groups, one placebo therapy, another on kalonji and third one on Vitamin B3. Their lipid profile was estimated and determined at pathology laboratory of the hospital before treatment and at day-45. Biostatistical analysis of the data was done using SPSS version 10. Serum LDL-cholesterol was calculated by formula ($LDL\text{-Cholesterol} = Total\ Cholesterol - (Triglycerides/5 + HDL\text{-Cholesterol})$). Serum HDL-cholesterol was determined by using kit Cat. #3022899 by Eli Tech Diagnostic, France.

Results:

After one and half month, kalonji reduced 12.93 mg/dl, and increased 3.38 mg/dl LDL, and HDL respectively, which are significant changes. Vitamin B-3 reduced LDL-C 27.04 mg/dl, and increased HDL-C 3.49 mg/dl. These changes are significant when analysed statistically.

Conclusion:

We concluded from this research work that kalonji and vitamin B-3 decrease LDL-C highly significantly in hyperlipidemic patients (with $p\text{-value} < 0.001$) but both hypolipidemic agents increase HDL-C significantly (with $p\text{-value} < 0.05$).

Keywords:

Hyperlipidemia, Coronary artery disease, Vitamin B-3, Kalonji

INTRODUCTION

Coronary artery disease (CAD) is not only a disease, rather it comprises of multiple pathological events occurring in human body with age. Patients who are obese with hyperlipidemia may suffer hypertension, hyperglycemia, leading to suffer from metabolic syndrome. The syndrome starts due to abnormally high plasma lipid levels,

especially low density lipoprotein cholesterol (LDL) which get interacted with free radicals ie; Reactive Oxygen Species (ROS). Oxidized forms of LDL attract monocytes, leukotrienes, fibrinogen, platelets, and other chemotactic factors to form foamy cells i.e.; atherosclerotic plaques which get deposited to endothelial walls of blood vessels. When this abnormal deposition of atherosclerotic plaques occur in coronary vessels, it is then called coronary artery disease (CAD).¹⁻⁵ CAD can cause hypertension, congestive cardiac failure, and heart attack. One of the important preventable factor for CAD is to lower blood lipids, and lipoproteins specially LDL-C.⁶ There are four

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drug groups in allopathic discipline of therapeutics to lower plasma lipids and lipoproteins ie; Statins, Fibrates, Niacin or Vitamin B-3, and bile acid binding resins (BABRs).⁷ Vitamin B-3 increases formation of apoproteins apo-AI and apo-CII in hepatocytes. Along with others, these two apoproteins are integral part of HDL (high density lipoproteins) which removes cholesterol from extrahepatic tissues and systemic circulation. Vitamin B-3 also decreases action of lipoprotein lipase in adipose tissues preventing movement of free fatty acids to liver to synthesize triglycerides (TG). When there is low TG synthesis in hepatocytes, very low density lipoproteins (VLDL) are not required to be mature enough for carrying TG from liver to systemic circulation, so IDL will not be formed, and so the result is decreased LDL synthesis in blood circulation.^{8,9} Well established hypolipidemic medicinal herb *Nigella sativa* or Kalonji contains amino acids, crude fiber, flavonoids, unsaturated fatty acids, sterols, carbohydrates, thymoquinone, migellamine, proteins, minerals, saponin, and alkaloids. Many of these chemical compounds decrease cholesterol synthesis in liver like Statins or HMG-CoA reductase inhibitors.¹⁰ Thymoquinone found in Kalonji alters genes involved in regulation of enzyme HMG-CoA reductase for synthesis of cholesterol from Acyl-CoA, free fatty acids, and choline. Kalonji contents also regulate genetic expression of apoprotein A-1, apoprotein C-1, C-II, apoprotein E, all are integral part of good cholesterol ie; HDL.^{11,12} Aim of this study work was to compare hypolipidemic potential of kalonji and vitamin B-3 when used in specific ethnic group-related patients suffering from mild to moderate hyperlipidemia.

MATERIALS & METHODS

The research design was placebo controlled study. The research study was conducted at Ghurki trust teaching hospital, Lahore Pakistan. Ninety hyperlipidemic patients were selected for the study. Written, already approved and well explained consent was taken from all participants. Inclusion criteria were male, female, obese, age range from 20-60 years, primary and secondary hyperlipidemic patients. Exclusion criteria were patients suffering from any kidney, liver and thyroid related disease. Name, age, gender, occupation, residential address, phone/contact number, previous medical history, disease in family history, drug history were

recorded in specific Performa. Three groups I, II, and III were made (30 patients in each group). Group-I was allocated for placebo, to take placebo capsule once daily, after breakfast for six weeks. Group-II patients were advised to take 2 tea spoons of *Nigella sativa* seeds (4 grams) after breakfast for six weeks. Group-III was on Niacin (1 niacin tablet 250 mg) 2 grams in divided doses ie; 750 mg (3 tablets of 250 mg) at morning after breakfast, 750 mg with lunch and 500 mg with dinner for 6 weeks.¹³ Their base line LDL-cholesterol and HDL-cholesterol levels were estimated at the start of research work. Serum LDL-cholesterol was calculated by Friedewald formula¹⁴ (LDL-Cholesterol=Total Cholesterol-(Triglycerides/5 +HDL-Cholesterol). Serum HDL-cholesterol was determined by using kit Cat. # 3022899 by Eli Tech Diagnostic, France. Their serum was taken at follow up visits, fortnightly for determination of lipid profile. Results were written as the mean \pm SD and 't' test was applied to determine statistical difference in results by using SPSS version 10. A p-value > 0.05 was considered as non-significance, p-value <0.05 was considered as significant change and p-value < 0.001 was considered as highly significant change in the tested parameter.

RESULTS

Numerical values and results of all parameters of participated patients were analyzed biostatistically. In placebo group, LDL-cholesterol decreased from 189.14 \pm 3.91 mg/dl to 186.74 \pm 2.07 mg/dl, change in the parameter is 2.40 mg/dl. This difference in pretreatment and post treatment value is non-significant, ie; p-value > 0.05. HDL-cholesterol in placebo group increased from 36.11 \pm 2.11mg/dl to 37.17 \pm 1.51mg/dl. The difference in parameter was 1.06mg/dl. Statistically this change in parameter was nonsignificant, ie; p-value > 0.05. In *Nigella sativa* group, out of 30 hyperlipidemic patients, 27 patients completed over all study period. LDL-cholesterol in this group decreased from 202.46 \pm 1.54mg/dl to 189.51 \pm 2.21mg/dl. The difference in pretreatment and posttreatment mean values is 12.93 mg/dl. Statistically this change in two mean values is highly significant, with p-value < 0.001. HDL-cholesterol in this group increased from 38.81 \pm 3.90 to 42.19 \pm 3.32mg/dl. Change in two mean values was 3.38mg/dl. Statistically this change is significant, with probability value <0.01. In group III, 28 patients completed the research. LDL-cholesterol in this group decreased from

212.65±2.32 to 185.61±3.43 mg/dl in six weeks treatment. Change in pre and post treatment mean values is 27.04mg/dl. Statistically this change is highly significant, i.e., p-value < 0.001. HDL-cholesterol increased from 39.19±2.01 to 43.00±3.07 mg/dl in six weeks. Change in two parallel values is 3.49mg/dl, which is significant with p-value<0.01.

KEY: HDL and LDL are measured in mg/dl, n stands for sample size, p-value >0.05 indicate non-significant, <0.01 indicate significant and <0.001 indicate highly significant change in basic values

Normal LDL value= less than 100 mg/dl

Normal HDL value= 40-50 mg/dl

3.98 mg/dl which also matches with our results. Results of our study are in contrast with results of research work conducted by AH BH and Blunden G.¹⁷ They explained that some active ingredients of *Nigella sativa* are hypolipidemic but their hypolipidemic potential is low. Their results showed only 2.11 mg/dl change in LDL-C and 0.92 mg/dl increase in HDL-C of 38 rats. Difference in results may be genetic variants in human and rats.

Brown BG et al.,¹⁸ also described phenomenon of genetic variation in pharmacological effects of *Nigella sativa*. They stated that black people reduce LDL cholesterol in low ranges by utilizing kalonji due to their ethnic relation and genetic changes. Burits M & Bucar F¹⁹ has also mentioned

Table 1: LDL, HDL's mean values (pre and after treatment) and their biostatistical significance

Groups (No. of patients)	Day-0 values	Day-45 values	Change in mean values	Statistical significance
Placebo (30 pts)	LDL -c=189.15±3.90 HDL -c=36.11±2.11	LDL=186.74 ±2.08 HDL=37.17±1.51	2.40 mg/dl 1.06 mg/dl	> 0.05 > 0.05
<i>Nigella sativa</i> (27 pts)	LDL -c=202.45±1.54 HDL -c=38.81±3.90	LDL=189.52±2.21 HDL=42.19±3.32	12.93 mg/dl 3.38 mg/dl	< 0.001 < 0.05
Vit B3 (28 pts)	LDL -c=212.65±2.32 HDL -c=39.19±2.01	LDL=185.61±3.43 HDL=43.00±3.07	27.04 mg/dl 3.49 mg/dl	< 0.001 < 0.05

RESULTS

Treatment with six weeks, *Nigella sativa* decreased LDL-cholesterol 12.93 mg/dl in 27 hyperlipidemic patients. HDL-cholesterol in this group increased 3.38 mg/dl by taking kalonji for six weeks. The changes in both parameters were significant. In placebo group, LDL-C reduction was 2.40 mg/dl and increase in HDL-C was 1.06 mg/dl with p-value>0.05, which proves non-significant change in tested parameters of placebo group. These results match with Akhondian et al.,¹⁵ who did prove that *Nigella sativa* is very effective hypolipidemic drug. They tested the drug on 120 hyperlipidemic and diabetic patients for one month. Their results were highly significant when compared with placebo-controlled group. Our results also match with results of Gillani AH et al.,¹⁶ who proved LDL-Cholesterol reduction from 201.61±3.11 mg/dl to 187.16±2.10 mg/dl in forty hyperlipidemic patients. Their HDL-C increase was

nonsignificant effects of *Nigella sativa* in Australian people due to different genetic make ups. Our results also match with results of research work of Dehkordi FR & Kamkhah AF²⁰ and El-Dakhkhany M.²¹ They all observed significant effects of kalonji in hyperlipidemic patients regarding effects on LDL-C and HDL-C. Same mechanism of action of drug *Nigella sativa* is described by El-Din K et al.,²² that kalonji affects gene expression of apo A-I and apo E, causing formation of more HDL particles. In our research Niacin reduced LDL-cholesterol from 212.65±1.19 mg/dl to 185.61±1.65 mg/dl in six weeks. This reduction in LDL-C was 27.04 mg/dl, which is highly significant change, when analyzed statistically. These results match with results of research work conducted by Afilalo J et al.,²³ who proved almost same change in LDL-C in 32 hyperlipidemic patients who were cases of secondary hyperlipidemia and they used Niacin 2 grams daily for two months. Their LDL-C reduction

was 25.55 mg/dl. Their HDL-C increase was 6.65 mg/dl in 2 months. In our results HDL-C increase was 3.81 mg/dl in six weeks use of Niacin. Our results also match with results of research conducted by Whitney EJ et al.,²⁴ who proved 27.77 mg/dl reduction in LDL-C in 19 hyperlipidemic patients. Ginsberg HN et al.,²⁵ also support our results, as they proved 4.0 mg/dl increase in HDL-C when two grams of Niacin was used in 34 hyperlipidemic patients for six weeks. Our results do not match with results of research conducted by Boden WE et al.,²⁶ who proved that 2.5 grams Niacin decreased 10.99 mg/dl LDL-cholesterol. HDL-C increase was only 1.11 mg/dl. These differences may be considered due to lack of physical exercise and no restriction of use of lipids in their diet. Taylor AJ et al.,²⁷ used Niacin 1.5 grams in 29 hyperlipidemic patients for 3 weeks. These patients reduced their LDL-C from 189.88 ±1.11 mg/dl to 187.87±0.99 mg/dl. Difference in their results and our results is due to less sample size, lesser duration of exposure of patients to drug and small amount of drug given in their patients. Baigent C et al.,²⁸ explained that Niacin inhibits the peripheral mobilization of free fatty acids, which decreases the substrate available for hepatic synthesis of triglycerides and very low-density lipoprotein (VLDL) particles.

CONCLUSION

We concluded from this research work that *Nigella sativa* and vitamin B-3 decrease LDL-C highly significantly in hyperlipidemic patients (with p-value <0.001) but both hypolipidemic agents increase HDL-C significantly (with p-value <0.05) as compared to results achieved by placebo.

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ROLE OF TRANS-ABDOMINAL COLOR DOPPLER ULTRASOUND IN PRE-OPERATIVE DETECTION OF OVARIAN MALIGNANCIES

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ABSTRACT

Objective:

To determine the role of trans-abdominal ultrasound Doppler in detection and characterization of ovarian malignancies using resistive index (RI) as a yardstick.

Place and duration of study:

A prospective study was done at department of Radiology of Fauji Foundation Hospital, Rawalpindi, Pakistan from Jan 2012- Jan 2016.

Materials and Methods:

Consenting female patients from age 16-75 years with clinical suspicion of ovarian masses were included in the study through non-convenient probability sampling. Patients underwent color Doppler ultrasound for evaluation of these masses. RI index was calculated in masses with positive blood flow and they were suspected as benign or malignant using an RI of 0.4 as cut off. Histopathology was later done for accurate diagnosis. Data was assembled using SPSS version 21. Results were interpreted in the form of frequencies, percentages, sensitivity and specificity. Positive and negative predictive values for RI of ultrasound Doppler was found.

Results:

Of a total of forty two subjects, thirty four had benign lesions and eight had malignant lesions diagnosed on histopathology. For malignancies only one subject had an RI of less than 0.40. Sensitivity of RI was 12.5% and specificity was 88.23%. Positive and negative predictive values of 25% and 81.08% were found, respectively.

Conclusion:

Resistive index is not a reliable scale for screening ovarian masses and clinical decisions about ovarian masses should not be based on RI alone. Combining CA-125 with Ultrasound Doppler may improve sensitivity in diagnosis of ovarian malignancies.

Keywords:

Ovarian malignancies, Resistive index(RI), Ultrasound Doppler

INTRODUCTION

Ovarian malignancy is the third leading cancer in Pakistani females.¹ The incidence of ovarian malignancies is increasing in this region.² Given the vague nature of symptoms of ovarian malignancies there is often diagnostic delay which contributes to the high mortality rate for these cancers.³ The

efficacy, relative low cost and safety of trans-abdominal ultrasound has made it a good tool for screening ovarian adnexal masses. While trans-vaginal ultrasound may be uncomfortable for some patients, trans-abdominal ultrasound is feasible in the conservative social set up of our country. The gross features of ovarian masses on ultrasound might help to differentiate between benign and malignant masses, there is however, a substantial risk of over-diagnosing these masses as malignant ones based on the gross features alone.⁴ It is suggested that adding ultrasound Doppler and using the resistive index (RI) of blood flow might

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help in accurately diagnosing and differentiating benign from malignant masses.⁵ This affects clinical management. For benign masses, conservative approach and laparoscopy seems to be the plan of choice. It is certainly not the case with ovarian malignancies which need a more intensive approach consisting of emergency laparotomy and oncological management.⁶ The role of ultrasound Doppler is controversial in medical literature.⁷ We aimed at determining that whether or not, the resistive index on trans-abdominal ultrasound Doppler can be used for pre-operative detection of ovarian malignancies among ovarian masses

MATERIALS & METHODS:

Study Design:

A prospective study was done at department of Radiology of Fauji Foundation Hospital, Rawalpindi, Pakistan from Jan 2012- Jan 2016. Ethical approval from ethics and research committee of the medical college affiliated with hospital was obtained. Non-convenient probability sampling was done.

Inclusion and Exclusion Criteria

All patients ranging from 16-75 years of age with clinical suspicion of ovarian masses were referred to radiology department for transabdominal color doppler ultrasound. Only consenting patients were included. Patients' medical records were followed through the hospital registration number. Patients with adnexal masses who did not undergo surgery and diagnosis by histopathology were excluded from the study.

Lesions detected were assessed both on gray scale and colour Doppler ultrasound. On gray scale, lesion size, presence of septa (thin and thick) and solid components was recorded. With regards to Doppler, assessment was done by colour as well as spectral Doppler; RI was taken in all patients with positive flow.

Equipment Used

Toshiba Xario Colour Doppler ultrasound machine was used.

RESULTS

Data was assembled using SPSS version 21. Results were interpreted in the form of frequencies, percentages, sensitivity and specificity. Positive and negative predictive values of ultrasound

Doppler was found. The cut off limit of 0.40 was taken for RI to differentiate malignant from benign lesions.⁷

RESULTS

Of forty two patients belonging to age group of 16-75 years, mean age was found to be 42.9 SD 12 years. The distribution of patients in age groups is given in Figure 1.

Frequency of various lesions on histopathological diagnosis is given in Table 1.

True negative were taken as benign lesions having an RI of more than 0.40 and true positive as malignant lesions having an RI of less than 0.40. Thirty lesions were true negative and only one malignant lesion was true positive i.e. having RI of less than 0.40. False positive were lesions considered malignant on RI but were benign on histopathology. Four benign lesions were false positive whereas, remaining six lesions were false negative i.e. malignant considered benign on RI. (Figure 2).

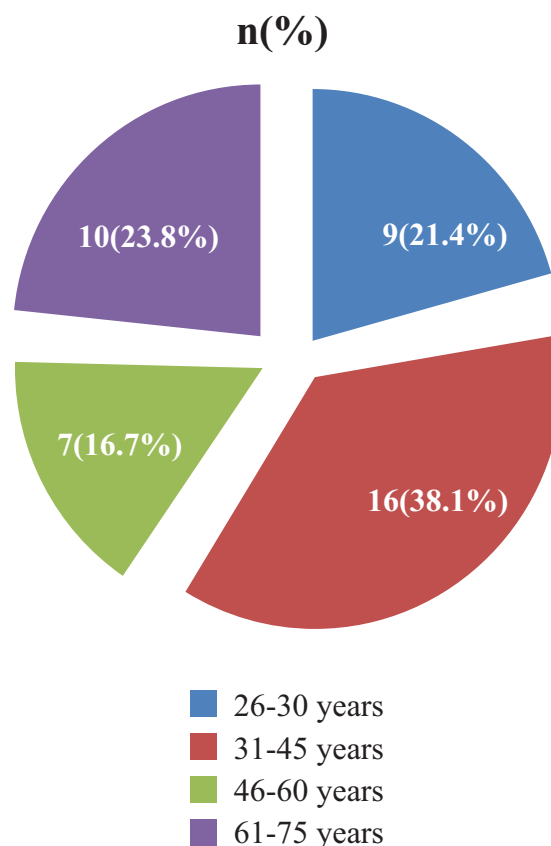


Figure 1: Distribution of patients in age groups (n=42)

Table 1: Frequency of tissue diagnosis (n=42)

Serial No.	Diagnosis on histology	N (%)
A	Benign lesions	34(80.95%)
	Serious cyst adenoma	11(26.19%)
	Mucinous cyst adenoma	10(23.8%)
	Endometriosis	9(21.42%)
	Dermoid cyst	3(7.14%)
	Torsion	2(4.78%)
B	Malignant lesions	8(19.04%)
	Cyst-adenocarcinoma	7(16.66%)
	Granulosa cell tumor	1(2.38%)

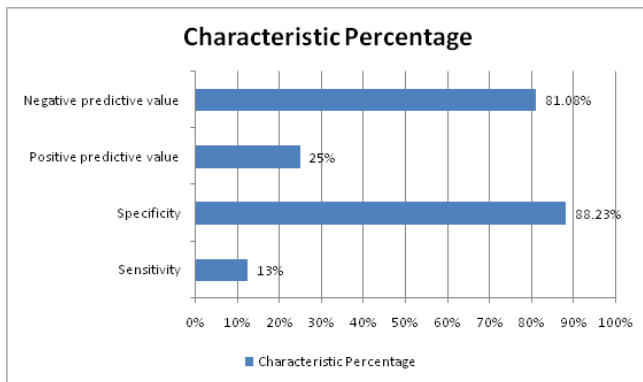


Figure 2: Sensitivity, specificity, positive predictive value and negative predictive value of RI



Figure 3: A high grade cystic adenocarcinoma of ovary having an RI of 0.68, well above the cut off value (0.4)

DISCUSSION

The prevalence of ovarian malignancies among ovarian masses ranges from 13.7% to 25%.^{8,9} The management of ovarian masses with suspicion of malignancy is surgery.¹⁰ Various methods have been proposed in pre-operative detection of ovarian malignancies including morphological features on gray scale ultrasound.¹¹ This has certainly proved beneficial however, gray scale US features have a high sensitivity and low specificity which means, many patients with benign masses may be subjected to invasive surgical procedures.⁴ Resistive index is another technique used to identify malignancies by characteristic low resistance to blood flow. We used a low cut off RI of 0.40 as advocated by Majeed et al, to increase sensitivity of RI in detecting ovarian malignancies.⁷ It is hypothesized that a lower cut off of RI will help labeling the malignant lesions without including benign lesions, since, benign masses have high blood flow resistance.⁷ However, despite use of a low RI cut off a sensitivity as low as 12.5% has been observed. This is in contrast to the findings of Shah et al., who reported a sensitivity of 97.5%. However, the specificity found is quite near to that reported by Shah i.e. 88% as compared to 84.1%.¹² A local research from Karachi has recently thrown light on the discrepancy in results on validity of RI in ovarian cancers. In the quoted study, the sensitivity of 18% and specificity of 84.61% is reported.⁷ A study from Bangladesh reports around 92% sensitivity in detecting ovarian cancers and 89% specificity.¹³ The positive predictive value or PPV was found to be as low as 25% whereas the negative predictive value was around 81%. Antonic and Rakar have found a PPV and NPV of 79% and 75% respectively.¹⁴ Majeed et al., have reported a PPV of around 33% and NPV of about 71%. Thus, the finding of our paper are much consistent with Majeed.⁷ Based on literature review the best that can be said about resistive index is that specificity i.e. detection of ovarian benign lesions is good, while the use of RI in screening the ovarian malignancies is not as sensitive as it is thought. In our research out of eight malignant masses seven had their RI above the threshold of 0.40, labeling them falsely as benign. Hence, there is current need of discouraging decision making for opting operative management of ovarian masses based on RI alone. Adding gray scale US features or CA-125 along with RI might increase sensitivity and thus help in choosing right candidates for operative management.¹⁴

However, it should be noticed that this is a single center experience, comprising of a small sample size of 42 patients. A multicenter research on this topic, including a representative sample is recommended.

CONCLUSION

Resistive index is not a reliable tool for screening ovarian masses and clinical decisions about ovarian masses should not base on RI alone.

RECOMMENDATIONS

Combining CA-125 with Ultrasound Doppler may improve the sensitivity in detecting ovarian malignancies.

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CONFLICT OF INTEREST

None

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THE PATTERN OF SKELETAL DISCREPANCY REPORTING TO ORTHODONTIC DEPARTMENT, FOUNDATION UNIVERSITY COLLEGE OF DENTISTRY: AN ESTIMATE OF FREQUENCY OF MALOCCLUSION

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ABSTRACT

Introduction:

The frequency and types of malocclusion reporting to a tertiary care facility define many parameters in terms of treatments and expertise offered case allocation for residents and future research directions. Orthodontics department can offer better treatment options and training if the cases are recorded and analyzed for research purposes. Hence the present study aims to establish the frequency of skeletal malocclusions among patients reporting to Orthodontics Department at Foundation University College of Dentistry.

Materials & Methods:

It was an observational cross-sectional study conducted between January 2014 and December 2016 at Department of Orthodontics, Foundation University College of Dentistry. 170 patients reporting for Orthodontic treatment were considered for the study. The lateral cephalometric analysis was used for classifying types of skeletal malocclusions. SPSS version 20 was used to assess the frequency and percentage of occurrence of different types of malocclusion prevailing in the group of patients selected.

Results:

The frequency of Skeletal class I, II and III malocclusion was found to be 31.0%, 68.0% and 1.0% respectively.

Conclusions:

The present study indicates the prevalence of oral malocclusions reporting to our institute. Class 2 malocclusion was most common malocclusion among patients included in this study.

Keywords:

Frequency, Sagittal Discrepancy, Skeletal Malocclusion

INTRODUCTION

There has been a steady increase in demand for orthodontic treatment over the years to improve facial esthetics and malocclusions. Malocclusion is a variation from ideal occlusion which may be considered aesthetically unpleasing but it is not unhealthy.¹ The etiology is multifactorial and both genetic and environmental factors play an

important role.

Numerous studies have been conducted in the past to determine the frequency of various malocclusions in different populations and they show great variability.²⁻⁹ It is essential for Orthodontists to have epidemiological data of their region and determine the frequency of a specific malocclusion reporting more than others to their hospitals. Such studies are necessary for allocation of resources towards orthodontic treatments and provide information regarding the malocclusions encountered more frequently in a certain population.¹⁰ Cephalometric indicators are used to analyze the maxillary and mandibular skeletal

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positions. Angular and linear measurements have been proposed in the assessment of skeletal relationship of both jaws.¹¹

The objective of this study was to determine frequency of reporting malocclusions, and to determine the most common type of malocclusions among orthodontic patients of this region.

MATERIALS AND METHOD

A cross-sectional study was conducted on patients reporting for orthodontic treatment at Orthodontic department, Foundation University College of Dentistry from January 2014 to December 2016. A total of 170 patients of both genders between 12 to 25 years of age were included in this study. Informed written consent was obtained. Patients' records included dental and medical history, radiographs including Lateral Cephalogram, Orthopantomogram (OPG) taken in natural head position with unstrained lips and teeth in centric occlusion. Patients having significant past medical history, previous Orthodontic treatment, history of trauma, syndromic patients and those with history of Cleft lip and palate were excluded from the study. Cephalometric analysis was done to determine the type of malocclusion. Two authors examined the Cephalometric readings twice to avoid misinterpretation.

Cephalometric landmarks were traced on Acetate sheets for each patient's cephalogram. The points were identified using definitions given in literature and skeletal relations of jaws were established by tracing Lateral Cephalometric X-rays.^{12,13} The skeletal relationship of maxilla and mandible with cranial base was measured by constructing angles SNA and SNB on lateral Cephalogram. The difference between the two angles (ANB) classifies the type of malocclusion (Figure 1). This is as follows;

SNA: 80-84 degrees: Orthognathic Maxilla (<80 degrees = Retrognathic Maxilla and >84 degrees = Prognathic Maxilla)

SNB: 78-82 degrees: Orthognathic mandible (< 78 degrees = Retrognathic mandible and > 82 degrees = Prognathic mandible)

ANB: 0–4°: Skeletal class I (>4°= Skeletal Class II and <0°= Skeletal class III)

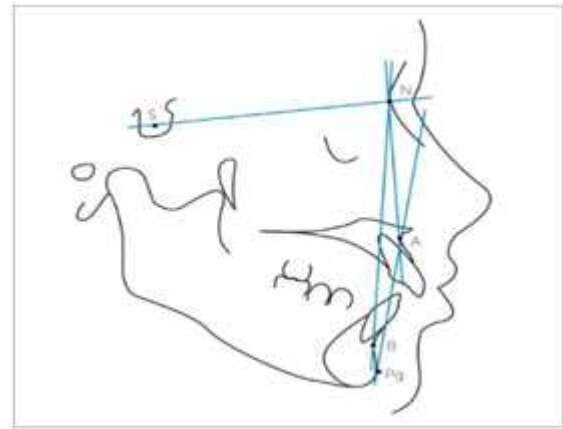


Figure 1: Horizontal Cephalometric Variables (SNA, SNB)

The data was gathered and analyzed using Statistical Package for Social Sciences (SPSS Version 20). The frequency/percentages of different types of malocclusion prevalent in the sample were calculated. Ethical approval was taken from the Ethical Review Committee.

RESULTS

Total 170 patients reported from January 2014 to December 2016 out of which 45 were Class I, 98 being Class II and 27 Class III. The highest frequency of malocclusion which reported to the Department was Class II malocclusion (68%) (Figure 2).

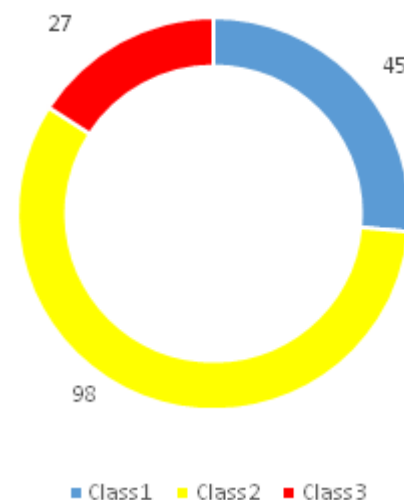


Figure 2: Frequency of Skeletal malocclusions

DISCUSSION

The frequency of malocclusions varies in different populations. Evidently the types of malocclusion

reporting give valuable information for research and planning towards even better treatment options.

According to the results from the present study, Class II malocclusion was the most prevalent category of malocclusion. Skeletal class II can be due to prognathic upper jaw or retrognathic lower jaw or a combination of both. These results are in accordance with previous studies conducted in Pakistan.^{14,15,16} Abida also reported a greater frequency of Class II.¹⁷

Despite concordance with the local results, present study differs from international data. Sari et al., reported that 61.7%, 28.1% and 10.2% to be Class I, II and III in a representative sample of Turkey¹⁸ Similarly in a sample of Saudi population the estimates were 53.8% Class I, 33.3% Class II and 12.9% bearing Class III malocclusions.¹⁹ Iranian population was also had a different frequency with the prevalence of Class I, II and III malocclusions being 52.0%, 32.6% and 12.3% respectively.²⁰

The differences in the present study and many other local or international data can be due to the fact that Foundation University College of Dentistry caters for patients coming in from multi ethnic backgrounds and report from all over Pakistan. The community catered for by FUCD will most probably be having Class II malocclusion according to the findings of this research. The future directions might be to find out the factors leading to this high prevalence in Pakistan.

The present study has certain limitations. The sample size was small and might not be a true reflection of the population. This study was only conducted on patients reporting for orthodontic treatment. Inclusion of non-orthodontic population might give a clearer depiction of skeletal malocclusion.

CONCLUSIONS

The study showed that skeletal Class II malocclusion was most frequently recorded, whereas class III was the least frequent. This study would help in assessing the more frequent type of malocclusion prevalent in this region. This is a new teaching hospital therefore Orthodontics students should receive more education and training in the management of Class II malocclusion as according to this survey, class II

is the most commonly reported type of malocclusion. The study shows an increase in the number of patients reporting every year so this research should be followed up and a longitudinal study should also be carried out to further authenticate our results.

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ATTITUDES OF POSTGRADUATE TRAINEES WITH PHARMACEUTICAL REPRESENTATIVES AND EFFECTS OF THEIR GIFTS ON PRESCRIPTION PATTERN AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Background:

Postgraduate trainees have their interactions with pharmaceutical representatives during working in hospitals. Medical trainees are often offered small gifts such as pencils, table calendars, tissue boxes, books and paper weights along with offers of free lunch or dinner as a drug promotion tool. In developing countries like Pakistan the ethical impact of these kinds of incentives and their effects on medical trainees has little data when searched in literature. Our survey about this aspect was done to investigate the attitudes of postgraduate trainees about the physician-pharmaceutical interaction and their unethical offers.

Methods:

A part of well validated survey questionnaire previously used in a study was modified a little according to local circumstances was formulated for assessing the behavior of postgraduate trainees towards pharmaceutical representatives was distributed among postgraduate trainees at Fauji Foundation Hospital Rawalpindi after taking the informed consent and telling them the study design and its significance. Questionnaire included various aspects like acceptance of pharmaceutical gifts, sponsored CMEs and conferences fees, and effects of these incentives on drug prescription pattern. Trainees reflections on questionnaire were recorded as agree, disagree or neutral. These responses were later then scored according to the AMSA (American Medical Students Association) guidelines for physician pharmaceutical interaction

Results:

Our study included 53 postgraduate trainees out of which 51 trainees returned the Performa (96.2% response). Our data showed that 21% trainees agree that there should be no interaction with drug companies in hospital working hours. On the other hand 79% trainees were in favor of drug companies sponsors for conferences/CME activities in hospitals. Almost one-third of our postgraduate trainees consider minor gifts of drug companies acceptable. As a whole our study results showed important unethical facts about physician pharmaceutical interaction. Furthermore 84.2% of our trainees agreed for revised teaching curriculum and incorporation of guidelines for physicians about pharmaceutical interaction to be taught at undergraduate and postgraduate level.

Conclusions: Our study clearly indicates that postgraduate trainees in big tertiary care institutions are not aware of proper ethical guidelines to handle pharmaceutical representatives and are easily caught by their incentives therefore this aspect of learning should be included in their curriculum.

Keywords:

Drug companies, Free dinners, Pharmaceutical gifts, Postgraduate trainees.

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INTRODUCTION

Pharmaceutical interaction with working doctors in hospital is getting problematic day by day in developing countries like Pakistan. As searched in

previous literature, 85-90% of physicians in USA, Canada, UK and almost all other developed countries are in contact directly or indirectly with pharmaceutical representatives.¹ This relationship is further creating a lot of controversy in developing countries like Pakistan. Pharmaceutical representative are basically salesmen and they approach doctors to present their low quality, old and sometimes even fake research to convince doctors for their products.² Besides this they offer various other incentives like free lunch, gifts and recreational trips for family either local or sometimes even international.³ Pharmaceutical representatives put their best efforts to confuse or corrupt physicians for sale of their products. Various offers given may be free product samples, pens, birthday cards and cakes, expansive gifts and sponsorship of local and international conferences.⁴

Our doctors and postgraduate trainees are not well taught to handle with these kinds of offers and are easily trapped by companies to promote sale of their

products. They forget their primary duty of prescribing better and cheap medication to their poor and needy patients and start writing expansive or low quality drugs in order to compensate for pharmaceutical incentives.⁵ There are three key elements which need to be considered while having doctors-pharmaceutical relationship: the justification to accept these incentives, writing product of a particular pharmaceutical company in order to compensate the gifts and looking independently the indications, cost and often fake research presented in favor of product.⁶ These unethical offers of drug companies for physicians and its negative influence on drug prescriptions led to need of some ethical boundaries to handle various emerging problems.⁷ There is an urgent need to create awareness among physicians and trainees to be careful while accepting incentives of pharmaceutical companies and to guide tertiary care institutions to ban pharmaceutical sponsored CMEs and free dinners. Considering the above

Table 1: Questionnaire for assessing attitude and understanding of postgraduate trainees towards pharmaceutical industry

Question	Disagree	Neutral	Agree	P-value
Gifts from drug companies in any form are unacceptable	17 (33.3%)	20 (39.2%)	14 (27.5%)	0.443
Are you comfortable with minor offers like free lunch, penlight, stethoscope, textbook, watches or mobile phone	15 (29.4%)	14 (27.5%)	22 (43.1%)	0.824
Are you going to write a product from a company which gave you some gift	28 (54.9%)	11 (21.6%)	12 (23.5%)	0.429
Trainees should interact with drug companies in hospital	17 (33.3%)	10 (19.6%)	24 (47.1%)	0.449
The research given by company about effectiveness of drug is unreliable	7 (13.7%)	21 (41.2%)	23 (45.1%)	<0.05
Is it acceptable for trainees to get commission on sales of a specific drug	43 (84.3%)	2 (3.9%)	6 (11.8%)	<0.001
Is it acceptable to take sponsors for events/educational seminars in a teaching hospital from pharmaceutical companies	11 (21.6%)	8 (15.7%)	32 (62.7%)	0.597
If is acceptable to pay for the printing cost of prescription pads and file folders of specialists in a teaching hospital by drug companies with their logos and product names on it	19 (37.3%)	8 (15.7%)	24 (47.1%)	0.175
Is there any necessity for making guidelines about physician-pharmaceutical interaction for implementing in hospitals and teaching in undergraduate and postgraduate curriculum	2 (3.9%)	5 (9.8%)	44 (86.3%)	<0.001

background we did a study in our hospital to see the attitude and current practices of postgraduate trainees towards pharmaceutical industry.

METHODS

This is an observational study done at Fauji Foundation hospital Rawalpindi in December 2017 at four major departments exposed to pharmaceutical representatives. Postgraduate trainees of Medicine, Surgery, Pediatrics and Gynecology were recruited for this study after explaining the purpose of study and taking informed consent. Post graduate trainees in first year were excluded from the study as having immature knowledge of physician-pharmaceutical interaction. Trainees from other departments like Radiology, Pathology were also excluded as not exposed directly to pharmaceutical representatives. A total of 53 PGTs were given a questionnaire out of which 51 trainees returned the Performa for statistical analysis. Both female and male PGTs working at above mentioned clinical departments were included in the study. For assessing trainee's preferences for drug companies at our hospital, we used a previously validated questionnaire with little changes from a study done on postgraduate trainee doctors by Joseph Barfett et al. On our constructed questionnaire, we analyzed the various aspects about trainee's attitude and their exposure with the drug companies with their current level of understanding to accept various incentives from drug companies.

We made a few changes in survey questionnaire as we are having different local norms and social setup of our trainees as compared with international studies (most of our trainees are working honorary or on very less pay during training). These changes were found important as this topic is not well studied in our hospital setting previously. Moreover knowledge of the way our trainees behave with drug companies and its impact on drug prescription pattern is lacking locally.

Our questionnaire comprised nine questions and for maintaining trainee's confidentiality, they were not asked any personal bio data on questionnaire. Our questionnaire was designed to ask about various aspects of trainee's perceptions about drug company's offers and the ways they approach physicians. The task was completed by creating hypothetical statements and then asking about their

potential responses under those circumstances. Our questionnaire comprised of predefined answers of "Agree", "Neutral" and "Disagree". So far there are no guidelines for postgraduate trainees in our hospitals about how to interact with drug companies, AMSA (American Medical Students Association) guidelines were taken for defining trainee's attitude as inappropriate or appropriate. Trainee's response with favorable attitude towards drug companies was given score of 3, neutral response was scored as 2 and response with very strictness towards pharmaceutical companies was recorded as 1. Both male and female trainees were approached in the Fauji Foundation Hospital canteen while they take some rest for tea and snakes. They were explained in group about purpose of study and its significance and were given written consent forms to fill in before taking part in study. All trainees who gave consent were then given study questionnaire and asked to fill in easily in privacy and with freedom and return on next day. After their responses the completed questionnaire was taken and deposited to chief investigator to keep it safe and enter data for analysis. All of the data was entered and analysis was done on SPSS version 16.0 and simple frequencies were calculated for different individual questions.

RESULTS

Out of a total of 53 Postgraduate trainees 51 trainees returned the questionnaire which lead to a good total response of 97.7%. Among our study participants, 18 trainees were male and 33 were female. In our study response rate for each question also varied among male and female trainees. Table shows the level of perception and acceptance of drug company's incentives and gifts and whether or not PGs should interact with them. These responses indicate that although most of our PGs were in favor of not interacting with pharmaceutical companies and their representatives but they were not sure what type of incentives or interaction is acceptable. Similarly most of them declared that it is not justified for a doctor to accept any "personal incentive" from pharmaceutical representative but they are not aware of exact code of ethics as most of them consider printing of prescription pads and cards from pharmaceutical companies are acceptable. Minor gifts like pens, stethoscope, torches and free lunch were considered ethical by most of our trainees. Moreover, while trainee were

inquired that whether you yourself accept any personal incentive, almost one-third of the participants denied but in many international studies it is evident that many physicians do accept gifts when they are asked indirectly about their colleagues and not themselves. More than 50% of our PGs believe that sponsors for conferences and seminars are acceptable from pharmaceutical industry although there are specific guidelines about accepting these offers. Most of our PGs were aware of the fact that research given by a drug company about their product is untrustworthy and should be independently sought out. Although in our study trainees showed a general increased level of acceptability for incentives, only 23% of participants declared that they will prescribe a product which was being introduced to them in the form of gifts (Details are shown in Table 1).

DISCUSSION

Previous data suggest that physician's interactions start with pharmaceutical companies to some extent during their teaching years in medical colleges.⁹ As more and more clinical based learning is now started in most of medical colleges of Pakistan, students while attending clinical OPDs and wards start exposure to pharmaceutical free lunches and seminars/conferences.¹ Most of these studies on this topic are available from nations with well-organized healthcare systems but data from under developed countries is lacking in international literature. Students and Postgraduate doctor's attitudes toward pharmaceutical interactions need much more awareness and learning about this aspect. Our study results showed that postgraduate trainee's level of awareness for the working with pharmaceutical industry was unclear and they were not sure about the ethical justification for physicians to accept any incentive from a drug company. Previous available literature about this aspect shows that there is difference in level of exposure to drug companies and acceptance of their incentives by trainees between clinical years from year one onwards¹⁰, but due to small number of trainees we have not studied this effect in our study. In a study done at Agha Khan University Hospital it was found that postgraduate trainees in 5th year of their training were accepting such incentives more as compared to PGs in 3rd and 4th year of training.¹ There was also some difference in the social status of the trainees which may be the reason of increased

acceptability of gifts from pharmaceutical industry as most trainees with good family background or getting good pay are at lesser risk as compared to trainees belonging to poor families or doing honorary training due to deficient training slots.¹¹

Unfortunately in Pakistan, there are no guidelines of Government rules to control the pharmaceutical promotional activities and the level of acceptable interaction of physician with drug company representatives in order to control the influence on attitude and prescription pattern of physicians. Approximately 90% of doctors worldwide believe that drug promotional activities have a definite impact on prescriptions for patients.¹² Regarding this study about 44% postgraduate trainees believe that information provided by drug companies is not trustworthy and must be independently sought out from other sources rather believing on their fake research.

All over the world this is a well-known fact that participating in pharmaceutical funded conferences/local meetings and traveling abroad for international conferences or recreational trips is followed by a much increase in prescription pattern of that company's medication.¹³ In our study it is obvious that a large number of trainees expressed willingness in accepting drug company sponsors for CME activities. Similarly as shown in literature a general practitioner is also at higher risk for unethical interaction with some drug company as he has left teaching and learning about ethics a long time ago and now belongs to common general public which is not well aware of promotional tools of drug company's products.¹⁴ Therefore GPS are easily caught by the unethical promotional tactics by some drug company via contributions for their personal clinics or various fake doctors' societies.¹⁵ Local guidelines should be established to draw limitations and some boundary for these unethical doctors' interactions with pharmaceutical industry and to make it a healthy relationship but keeping physicians within their limits ethically and morally as defined by various associations internationally like AMSA. Many study results in our research have insignificant p-value which might be due to small number of participants involved in our study but this idea will give us a new foundation revealing the fact of a high acceptability of postgraduate trainees for drug companies offers. There should be some immediate attention to make guidelines for this

controversial issue as exact incidence of this unhealthy and unethical relationship in developing countries like Pakistan is so far little studied. There is need to do some study on a large scale with involvement of various institutions from all over the country with larger sample size for verifying these facts and results and also to guide and change attitude of postgraduate trainees towards pharmaceutical industry. There are deficiencies in institutional policies regarding limitations for pharmaceutical interactions with physicians.¹⁶ Since our study was is a simple observational research we can't conclude or comment in a definite way about results of our study but we have generated a new aspect about this problem and recommend further prospective and interventional studies to be done confirm the findings and future concerns are required to clarify such concerns. Large multicenter studies are needed to look into the matter thoroughly about the behavior of postgraduate trainees all around our country by involving trainees from different institutions and from different backgrounds.

CONCLUSION

Due to a rapidly growing pharmaceutical business in our country and more and more people joining medical profession especially due to private medical colleges there is chance of malpractice if no proper ethical guidelines are taught or implemented in our busy hospitals. Due to a well-known role of pharmaceutical industry in development of new molecules we can't ban their visits and interactions with doctors but there is need to develop an ethical and healthy relationship of drug industry with doctors. Our study results match to some extent with findings from some other parts of the world. Postgraduate trainees involved in our study had poor pre-existing knowledge regarding appropriateness of pharmaceutical dealing showed increased acceptance of gifts offered to them. On basis of our study results it is obvious that every medical college should make and implement guidelines about a healthy physician-pharmaceutical interaction to which postgraduate trainees should be aware of so that our future physicians must be well equipped to handle these problems. More research on larger sample size should be carried out to identify the exact prevalence rate of these interactions.

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FREQUENCY OF PULMONARY IMPAIRMENT AMONG PATIENTS WITH STROKE

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ABSTRACT

Objective of Study:

To measure the frequency of pulmonary impairments in post stroke acute & Sub-acute stage. To evaluate the frequency of post stroke cases who are receiving cardiopulmonary exercise training for respiratory impairments.

Methodology:

This cross-sectional study was conducted at Women Institute of Rehabilitation Sciences Abbottabad from September 2015 to December 2015. The study enrolled 80 patients of stroke calculated through Epitool at outdoor and indoor patient department from Ayub Teaching Hospitals Abbottabad, District Head Quarter Hospital and Women Institute of Rehabilitation Sciences Abbottabad. Data was collected by using self-structured questionnaire, dyspnea scale and diaphragmatic excursion test through purposive convenient sampling and analyzed using SPSS 20.

Results:

Among 80 approached cases 44 patients met the inclusion criteria and were recruited in the study after informed consent from the patients. Participants diagnosed with pulmonary impairments were 19 and those who did not seek cardiopulmonary physiotherapy were 18. The frequency of pulmonary impairments in stroke patients was 43.1% and the frequency of patients who were not receiving cardiopulmonary exercise training for respiratory impairments was 40.90%.

Conclusion:

Based on the findings, the current study suggests that cardiopulmonary physical therapy have a greater influence on the frequency of pulmonary impairments among stroke patients. As early cardiopulmonary physical therapy lowers the chances of pulmonary impairments among patients with stroke.

Keywords:

Activities of Daily Living, Diaphragmatic Excursion Test, Modified Medical Research Council, Neuromuscular Diseases, Physical Therapy Treatment

INTRODUCTION

The World Health Organization (WHO) defines stroke as suddenly developing clinical manifestations of deteriorating sensory motor functions, lasting more than 24 hours after vascular disruption of central nervous system.¹

Respiratory muscles dysfunction is the major cause of morbidity and mortality in patients with stroke. This leads to ineffective cough, poor lung & chest wall compliance, reduction in forced expiratory and inspiratory reserved volumes, decrease in vital capacity and consequently respiratory failure. Therefore cardiopulmonary rehabilitation has significant effects on lungs function in patients with acute and sub-acute stage of stroke.²⁻⁴ In acute stage of stroke dysphagia is a common complication and it is responsible for lethal respiratory events of asphyxiation and aspiration pneumonia due to respiratory muscle weakness.⁵

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In developed countries stroke is the third most common cause of death, hospital admission and disability.¹ Prevalence of pulmonary impairments with Stroke is five to ten times higher in Asian countries as compared to United Kingdom. In South Asia there is a highest burden of cardiopulmonary diseases.⁶

To measure the frequency of pulmonary impairments in post stroke acute & Sub-acute stage. To measure the frequency of post stroke cases who are receiving cardiopulmonary exercise training for respiratory impairments.

MATERIALS AND METHODOLOGY

A cross sectional study was conducted in Women Institute of Rehabilitation Sciences, Abbottabad. The sample size was 80 patients Acute and sub acute stage of stroke calculated through Epi tool. Non-probability Convenient sampling technique was used for the data collection. Duration of study was 03 months.

Data was collected by using Self-structured questionnaire, Modified Medical Research Council Dyspnea Scale (0-4) and Diaphragmatic Excursion Test was used. Self-structured questionnaire comprising of demographics, subjective confirmation\rejection about shortness of breath (SOB), cough, effect of breathlessness on speech and consultation of cardiopulmonary physiotherapy management for respiratory issues. Modified Medical Research Council Dyspnea Scale (0-4 Points) was used to categorize the patients according to their degree of breathlessness. Diaphragmatic Excursion Test (DET) was performed on patients using measuring tape. Diagnosed criteria of pulmonary impairment included presence of SOB, cough, speech affected due to SOB, scoring of ≥ 2 on MMRC dyspnea scale and distance of less than 3 cm on DET. Participants who were immobile/partially or completely dependent for transfer and mobility were assessed only on 4th point of Dyspnea scale. Reporting presence of 4th point was considered positive for

the scale. Data was analyzed through SPSS 20.

RESULTS

Among 80 approached cases 44 patients met the inclusion criteria and were recruited in the study after proper consent from patient. These participants were then assessed on dyspnea scale and diaphragmatic excursion test out of which 19 participants had positive findings and were labeled to have pulmonary impairment. Eighteen patients did not seek the cardiopulmonary physical therapy. The frequency of pulmonary impairments in stroke patients was 23 % and the frequency of patients who were not receiving cardiopulmonary exercise training for respiratory impairments was 22.5 % as given in table below.

DISCUSSION

The aim of this study was to find out the frequency of pulmonary impairments and cardiopulmonary physical therapy treatment among patients with acute and sub-acute stage of stroke. The results clarify and further support the significant extent to which the respiratory complications occur in post stroke cases, therefore it highlights the importance of cardiopulmonary physical therapy including breathing exercises and chest physical therapy to prevent complication in stroke survivors.

The major predictor of pulmonary complication and mortality is the shortness of breath and aspiration pneumonia with frequency being reported in literature is 7%-33%.⁷ The frequency of cough (66.2%) with in this study identify the respiratory complications due to weak respiratory musculature. However the frequency of positive Diaphragmatic Excursion Test (45.4%) was considered to be higher than 41% reported by Khedr, E.,O.El Shinawy, et al.⁸ In the current study the higher rate of positive diaphragmatic excursion test may be accounted for higher frequency (40%) of the post stroke patients who did not receive cardiopulmonary physical therapy for the pulmonary complications.

Table 1: Cross tabulation of stroke & cardiopulmonary physical therapy

Disorder	Physical therapy treatment			Total Approached cases of stroke
	Patients met the inclusion criteria	Diagnosed cases of pulmonary impairment	Patients who did not seek CPT treatment	
stroke	44	19	18	80

Table 2: Pulmonary impairments among stroke

Disorder	Shortness of breath	Cough	Effect of breathlessness on speech	Total approached cases of stroke	Frequency of Patients fulfilling inclusion criteria
Stroke	67	53	44	80	44

Table 3: Pulmonary impairments on MMRC dyspnea scale & DET

Disorder	Participants assessed for pulmonary impairment	MMRC Dyspnea scale >2	MMRC Dyspnea scale <2	DET Positive	DET Negative
Stroke	44	32	12	20	24

The present study supports that post stroke cardiopulmonary physical therapy decrease the pulmonary complications of dyspnea, increase the diaphragmatic excursion, improve cough quality and speech which are affected due to weak respiratory musculature. Thus appropriate cardiopulmonary rehabilitation Programme effectively prevents the patients morbidity and mortality rate. Future studies must be designed to evaluate the role of rehabilitation in long term morbidity and mortality.

CONCLUSION

Based on the findings, the current study suggests that cardiopulmonary physical therapy have a greater influence on the frequency of pulmonary impairments among stroke patients. As early cardiopulmonary physical therapy lowers the chances of pulmonary impairments among patients with stroke and reduce the morbidity & mortality rate due to respiratory complications.

RECOMMENDATIONS

- Study design with large sample size would improve the statistical strength of these findings.
- These data suggest that further research is necessary to determine whether early cardiopulmonary physical therapy prevents respiratory complications in acute & sub-acute stage of stroke.

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HISTOMORPHOLOGICAL DEVELOPMENT OF PANCREAS AND ITS MOLECULAR REGULATION IN CHICK EMBRYO

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ABSTRACT

The pathogenesis of different congenital anomalies can be explained by understanding the process of development and the role of different factors involved. The chick pancreas shares many similarities with mammals regarding its structure and development. Thus it can serve as an effective experimental model. We review the histomorphological development of pancreas in chick and its molecular regulation. This is to clarify, how failure of molecular regulation in any stage is related to different congenital pancreatic anomalies, which can be well applicable to humans.

Keywords:

chick pancreas, histomorphological, molecular regulation

EMBRYOLOGY OF CHICKEN PANCREAS:

The chick pancreas has a posterior (dorsal), anterior (ventral), third and splenic lobes. All of these lobes are morphologically distinct. Dorsal, ventral and third lobes are large lobes whereas splenic lobe extends as an isthmus from the 'third' lobe towards the hilum of spleen.¹

The pancreas is of endodermal origin because it develops from the embryonic foregut. Pancreatic development begins from three distinct endodermal primordia, one dorsal and two ventral pancreatic primordia. These evaginate from the gut in close proximity of the liver primordium. The dorsal pancreatic bud evaginates from the dorsal wall of the gut on the third day of incubation, while the ventral pancreatic bud appears as a pair of diverticula from the ventral wall of the gut on the fourth day of incubation.¹ These pancreatic buds begin to fuse at day 7 of embryonic development², which results in the formation of definite pancreas. This eventually differentiates into four principal lobes characteristic of adult chick. The dorsal primordium differentiates into a third and a splenic lobe. The dorsal lobe is derived from right ventral bud whereas the ventral lobe from left ventral.¹ Each lobe communicates with the foregut through a

duct, which opens into duodenum at the end of its ascending part. These ducts are arranged in the same manner as in the adult, and correspond to the pancreatic ducts of the third, dorsal and ventral lobes of the adult, respectively.¹

CYTOGENESIS AND ISLETS FORMATION:

The pancreas has two histologically separate glandular components namely, exocrine and endocrine. The exocrine part comprises of tightly packed acini. These acini drain into an extensively branched system of ducts.³ The endocrine component consists of microscopic cellular units referred to as the 'islets of Langerhans', after their discoverer. Within the islets, three distinct cell types can be distinguished. These are A, B and D cells capable of secreting glucagon, insulin and somatostatin respectively. There is also a fourth type of endocrinal cells, PP or 'F' cells which secretes avian pancreatic polypeptide (APP). These cells do not participate in the formation of islets and spread throughout the exocrine pancreas.^{1, 3-6}

'A' cells at first appear at the tip of dorsal pancreatic bud at the day 3 of incubation. These increase in number to form the alpha islets at day 4 to 6 of incubation. By further increase in number and size, huge and complicatedly diverged alpha islets form during day 6 to 10 of incubation. From the beginning of development, the alpha islets remain restricted to dorsal pancreatic bud and then to its derivatives (third and splenic lobes) throughout the life.¹

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'B' cells first appear in the primitive beta islets in the tip of the dorsal pancreatic bud at day 4 of incubation. Beta islets become complicatedly organized from day 6 to 10 of incubation. After day 11 of incubation, they spread into the dorsal and ventral lobes.¹

At day 4 of incubation, D cells appear in the periphery of cell masses in the tip of the dorsal bud. They join the alpha islets at day 5 of incubation and beta islets at day 9 of incubation and increased in numbers thereafter and also spread in exocrine portion. However, these remarkably decrease in number after hatching.¹

APP cells appear sporadically in all lobes at day 9 of incubation. After day 11 of incubation, spread throughout the exocrine pancreas, and do not participate in the formation of islets.¹

MOLECULAR REGULATION OF DEVELOPMENT OF PANCREAS:

The organogenesis occurs by an intricate interaction between cells and tissues. A tissue or a group of cells can influence the fate of other tissues or cells to evolve into a new organ. The process involved in this influence is called "induction". The process of induction follows the principle of cell/tissue-to-cell/tissue signaling.

In embryo, the endoderm forms the lining epithelium of gastrointestinal tract, respiratory tract and urinary bladder and parenchyma of the different glands including the thyroid, parathyroid, thymus, pancreas and liver.⁷ Thus, how the endoderm is patterned to form the pancreas is crucial for understanding the development of pancreas.

During embryonic development, sonic hedgehog (Shh), is a strong intercellular prefiguring signal. It is uniformly expressed in the endoderm of the primordia of organs proximal or distal to pancreas, however is amazingly absent in the endoderm of pancreas. In the gut tube of embryo, the mesoderm which surround the gut tube differentiate into specific mesodermal derivatives of the small intestine and pancreas under the influence of differential expression of Shh.⁸

For the development of pancreas in the chick, endoderm required notochord signals.⁹ The notochord has repressive effects on the expression of Shh in the adjacent embryonic endoderm of pancreas. This is in contrast to its inductive effects

on the expression of Shh adjacent neuroectoderm.¹⁰

Notochord produces Fibroblast growth factor 2 (FGF2) and activin- β B (a TGF- β family member) both of which have repressive effects on the expression of Shh in endoderm of gut intended to form the dorsal pancreatic bud.¹⁰ In chicks as well as in human, inhibition of expression of Shh in pre-pancreatic dorsal endoderm is essential for allowing initial steps of development of pancreas.^{7,9,10} This is done by intercellular signals like activin and FGF.^{7,9,10}

Subsequently, down regulation of Shh expression permits expression of many transcriptional factors of pancreas including Islet1 (Isl1), Pdx1 and Pax6.¹⁰ These factors in turn are essential for further differentiation of cells and expression of those genes essentially needed for normal functioning of pancreas such as secretion of insulin, glucagon and digestive enzymes like amylase etc.¹¹⁻¹³

The endoderm of ventral pancreatic is not adjacent to notochord and therefore does not depend on signals from notochord.⁹ The ventral bud is induced by splanchnic mesoderm. As a result, expression of Pdx1 gene is up-regulated. Later signals from the mesenchyme to the endoderm permit subsequent development of both dorsal and ventral pancreatic buds, which later fuse.

Though all the factors which influence the development of pancreas have not been discovered, but it is apparent from the review of previous studies that specification of lineage of endocrine cells depends on the expression of the Pax 4 and Pax 6 genes. The cells that express Pax4 and Pax6 become B (insulin), D (somatostatin), and PP (pancreatic polypeptide) cells, and the cells which express only Pax6 become A (glucagon) cells.^{7,11-13} Molecular regulation of development of pancreas can be summarized in Figure 1.

PAX (Paired box) GENES

The PAX are genes that control development by encoding a group of nuclear transcription factors which have fundamental part in differentiation of cells and early development of embryo. These have been conserved throughout the phylogeny through millions of years of evolution. PAX proteins have been implicated as key factors in maintaining pluripotency of stem cell populations during development and as regulators of organogenesis.¹⁴

targeting and embryologic experiments.

PAX6 is a crucial for regulation of transcription of pancreatic islets hormone gene and is essential for normal development of pancreatic islets in mice, chick and human.¹¹⁻¹³ It is expressed in pancreas in α , β and γ cells of the pancreatic islets.¹² PAX6 also controls eye and brain morphogenesis.^{17, 22} During early developmental phase of ocular tissues it is expressed on the surface and neuroectoderm, later in the differentiating cells of the cornea, ciliary body, lens, and retina. In addition, PAX6 is also required in the transition from presumptive nasal ectoderm to placode.²³ In the central nervous system, it is expressed in telencephalon, cerebellum, thalamus, pituitary & pineal glands and spinal cord.^{24, 25} PAX6 heterozygous mutations in humans, result in several congenital anomalies of eye including aniridia, iris hypoplasia, Peters' anomaly, corneal opacification, isolated foveal hypoplasia, congenital cataracts and glaucoma.²⁶⁻²⁸

Whitsel et al exposed 142 chicken embryos to Valproic acid in ovo and demonstrated Pax-6 and Pax-2 protein expression was qualitatively reduced in the eye. Decreased expression of both of these proteins resulted in formation of multiple ocular defects. These included incomplete closure of the choroid fissure, aniridia, pigment anomalies, microphthalmia, cataracts and lens displacement.²⁹

Pax6 mutations in rats and mice result in Small eye (Sey) phenotype.³⁰ Heterozygous mice show anomalies similar to human Seys with aniridia, hypoplasia of iris, partial separation of the lens from the cornea and cataracts.^{31,32} Homozygous mice with Sey show perinatal mortality and are genetically homologous with the human aniridia gene mutation, and accompanied with anomalies such as absence of eyes, nasal and craniofacial defects.³³ As PAX6 is prerequisite for the development of both eye and pancreatic islets, PAX6 mutation has also been found as a genetic factor common to aniridia and glucose intolerance.³⁴

ROLE OF PAX4 AND PAX6 IN THE SPECIFICATION OF ENDOCRINE PANCREATIC LINEAGES:

In pancreas, specification of lineage of endocrine cells depend on an intricate balance between PAX6, PAX4 and other key controllers. These genes play a central role in the development of different types of endocrine cells in the pancreas. PAX6 expression is

detected in early pancreatic endoderm, and later it marks all endocrinal pancreatic cells during development and ultimately in the adult. It is essential for glucagon-producing α -cells. In its absence the structure of pancreatic islets is disturbed. Likewise, PAX4 is also initially expressed in cells of early pancreatic endoderm and is later down regulated in α -cells. Its absence result in the developmental failure of insulin-producing β -cells and somatostatin- producing δ -cells, whereas expansion of the number of α - and γ -cells. So PAX6 and PAX4 are essential for determining the cell fate in the lineage of endocrinal pancreatic.²¹

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RHEUMATOID VASCULITIS; A WIDESPREAD AND SUB ACUTE PRESENTATION IN A SERONEGATIVE PATIENT

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ABSTRACT

Introduction:

Rheumatoid Arthritis is a systemic disease which is not only confined to joints but can almost involve any part of the body including the blood vessels leading to a serious complication; the rheumatoid vasculitis. Rheumatoid vasculitis is usually associated with longstanding, erosive and almost always seropositive disease. Circulating immune complexes, expansion of cytotoxic CD28 T cells and circulating pro-inflammatory cytokines play a central role in the pathogenesis. Central nervous system involvement in rheumatoid arthritis is infrequent but when it occurs the most usual manifestations are peripheral neuropathy along with cervical spinal cord compression due to subluxation of the cervical vertebrae. Cerebral rheumatoid vasculitis is a rare and serious complication that can be life threatening.

Case Presentation:

A 48 years old lady, who was a known case of rheumatoid arthritis for 25 years who had developed joint deformities over the course of this disease, presented with bilateral lower limb weakness for last 2 weeks and a history of bluish discoloration of her toes for 3 days. Her condition deteriorated very rapidly and she developed quadriplegia, autonomic dysfunction and areflexia. MRI brain and spinal cord with T2 sequence showed high intensity foci in deep cortex, upper pons and cervical spine suggesting extensive systemic vasculitis.

Conclusion:

Cerebral vasculitis as a part of systemic rheumatoid vasculitis, is an infrequent complication especially in seronegative patients which is associated with high morbidity and in some cases it can be life threatening. Early assessment and a high index of suspicion to recognize such complications are essential in management of these patients.

Keywords:

Cerebral vasculitis, Rheumatoid vasculitis

BACKGROUND

Rheumatoid vasculitis is destructive inflammatory process that always involves blood vessel walls. It is associated with significant morbidity & mortality with up to almost 40% of patients dying within 5 years of diagnosis due to both the organ damage from the disease process and consequence of the treatment.^{1,2} The inflammatory process affects wide range of blood vessels, from medium sized muscular arteries to smaller post-capillary venules. It is more common in men and typically

occurs in patients with long standing disease usually more than 10 years.³ Predictors of vasculitis in patients with rheumatoid arthritis (RA) include clinical, genetic factors and smoking.^{4, 5, 6} Rheumatoid vasculitis (RV) is associated with an increased mortality as compared with that in patients with R.A.⁷ Low serum complement levels are negative prognostic markers.² The increased mortality may be due to a high risk rate of cardiovascular comorbidity^{8,9} and severe infections.¹⁰ Although immunosuppressive treatment with cytotoxic drugs and corticosteroids predisposes to life-threatening septicemia in such patients, there also appears to be an increased risk of infections that is independent of treatment. We had a middle aged lady with longstanding, seronegative RA who presented with signs of evolving digital gangrene. She suddenly developed

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neurological signs mimicking G B S and was found to have extensive vasculitis involving vessels supplying cortex, brainstem and spinal cord. Although plasmapheresis improved the central component but bilateral above knee amputation had to be done for progressive wet gangrene.

CASE PRESENTATION

A 48 years old woman suffering from RA for 25 years, presented with a history of pain and numbness of all four limbs for 2 weeks and bilateral lower limb weakness along with bluish discoloration of toes for 3 days. She was on a combination of disease modifying anti rheumatic agents (DMARDs) including Sulfasalazine 1g twice daily, hydroxychloroquine 200mg once daily and Leflunomide 20mg once daily. She had been a smoker in past. She was also a diabetic, hypertensive and osteoporosis for almost 4 years. Initial examination revealed a pulse rate of 72 beats/minute, blood pressure 130/90mmHg, respiratory rate 20 breaths/minute and she was afebrile. Examination of her hands revealed rheumatoid deformities in both hands. She had 10 tender and 6 swollen joints with a pain score on visual analogue scale (VAS) of 8 .Her disease activity score (DAS-28) was 5.77 (high activity). There was bilateral bluish discoloration of toes. Bilateral peripheral pulses were palpable. On neurological examination, there was sensory loss in glove and stocking distribution where as on motor examination, power was 4/5 in all four limbs. Lower limb arterial Doppler scan revealed arteriosclerotic changes [fig 5].

On day 2 of her hospital stay, she suffered a hypertensive crisis (systolic Blood Pressure 220 mm Hg) for which prompt management was started with Calcium Channel blockers and Angiotensin Receptor Blockers. It was followed by worsening of her neurological symptoms. Her neurological examination at that time revealed Glasgow coma scale (GCS) 15/15, power 2/5 in all limbs with areflexia, sluggish pupillary response, opsoclonus, decreased Rt sided palatal movement. Intravenous (IV) pulse methylprednisolone and IV cyclophosphamide following NIH protocol was started. A working diagnosis of Rheumatoid Vasculitis was made. MRI brain stem and cervical spine demonstrated bilateral vasculitis/ischemic changes in upper pons/lower mid brain and spinal cord at CV-3 level with few bilateral hyper intense foci in deep cerebral white matter. Cervical

spondylosis with multi level degenerative changes more marked at CV 3-5 levels were documented [fig 6] Cerebrospinal Fluid analysis was normal.

The next day she developed diaphoresis on left side of body, fluctuation in blood pressure and oxygen saturation with altered mental state. Discoloration of the toes progressed to gangrene and it started involving her upper limb digits as well. Power in all limbs was 0/5. The blood test profile at this time is depicted in Table 2. Blood cultures were sent; intravenous antibiotic tazobactam was started empirically. DMARDs were withheld on suspicion of septicemia. She was shifted to intensive care where she required non-invasive assisted ventilation and had 5 sessions of plasmapheresis. Her condition stabilized while undergoing plasmapheresis and ocular signs resolved over next 7 days. Unilateral diaphoresis persisted. Power in upper limbs improved to 1/5 and was 2/5 in lower limbs. Despite this, gangrene extended up to calves and also involved 3 fingers on right hand, 2 fingers on left hand and tip of the nose [fig 1,2 and 4 respectively]. Pus culture from a swab taken from leg ulcer revealed *Providentia* Sp. sensitive to Meropenem. Bilateral above knee amputation was done for rapidly spreading wet gangrene. After amputation patient was discharged with a regular follow up in Rheumatology and Rehabilitation department along with artificial limb centre. Unfortunately despite all the vigorous efforts and treatment strategies, she acquired opportunistic infection leading to septicemia and death 2 months after her initial presentation.



Fig 1 : Gangrene of finger tips right hand

Fig 2: Left hand



Fig 3: Gangrene B/L lower limbs.

Fig 4: Tip of nose



Fig 5: Doppler scan of lower limb arteries



Fig 6: MRI scan brain stem and cervical spine

Table 1: Lab profile during hospital stay

Lab test	Day 0	Day 4	Day 6	Day 12	Day 18	Day 24
Hb	10.4	11.9	8.8	10	11.4	10
TLC	28.3	49.7	45.97	27.5	15.5	22.29
Plt	496	399	218	271	267	265
Urea	4.1	7.6	4.8	3.5	6.9	4.0
Creatinine	75	103	78	79	87	77

Table 2: Culture specimens done during hospital

Culture	Day 4	Day 7	Day 16
Blood	No growth	Acintobacter baumann ii	
Urine	No growth		Proteus
Pus			Providentia
Csf		No growth	

Table 3: Serological tests

Hep serology	-ve
Anti CCP	-ve
RA factor	-ve
ANA	-ve
Anti ds DNA	-ve
Anti cardiolipin Ab	-ve

DISCUSSION

It is well documented that connective tissue diseases such as systemic lupus erythematosus (SLE), Sjogren's and Behcet's are often complicated by cerebrovascular disorders¹¹ but it occurs seldom in R A.¹² Incidence of cerebral vasculitis in patients of R A is 1-8%.¹³ Tradition ally RV has been desc ribed in long-standing, erosive seropositive RA with subcutaneous nodules and extra articular manifestations.¹⁴ Few cases of vasculitis have been reported in seronegative patients manifesting as aseptic pleuritis and peripheral gangrene.¹⁵ Another case report was about digital vasculitis in seronegative RA that responded well to Adalimumab.¹⁶ Vasculitis may involve any blood vessel bed in the body, including cerebra l, mesenteric, and coronary arteries.¹⁷ Frank infarctions of the digits and mononeuritis multiplex are more severe features of rheumatoid vasculitis.^{18, 19, 20} Circulating immune complexes and cryoglobulins have been correlated with severity of RA and arteritis and clinical improvement has been observed with their lowered levels. Plasmapheresis has been shown to reduce the levels of rheumatoid factor in patients of RA along with CICs. Studies have revealed clinical improvement in most of patients with limited plasmapheresis.²¹ Our patient did not have nodular disease. She was a smoker and had RA for 25 years. Peripheral vasculitis was revealed by digital gangrene of all limbs and then the central component progressed as indicated by development of CNS signs including quadriplegia and autonomic dysfunction. Areflexia and autonomic dysfunction raised a suspicion of Gullian Barre syndrome, which was ruled out by MRI scan and C S F studies. Her MRI brain stem and cervical spine demonstrated bilateral vasculitis/ischemic changes in upper pons/lower mid brain and spinal cord at C V-3 level, few bilateral hyper intense foci in deep cerebral white matter and cervical spondylosis with multi level degenerative changes more marked at CV 3-5 levels [fig 6] and CSF studies were normal. Plasmapheresis, being beneficial in both cases, was considered for urgent management and it was effective in remission of autonomic dysfunction. Subsequent sessions lead to some improvement in neurological manifestations such as power of limbs and ocular signs.

CONCLUSION

RV normally presents in settings of long standing RA. It can be limited to digits or can have florid

involvement of multiple organs as in above-mentioned case report. Immediate initiation of treatment is the corner stone of successful management. Nonetheless, risk benefit ratio must be weighed and management tailored according to individual cases, as patients are prone to acquired infections owing to aggressive immunosuppressive therapy.

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PSEUDO-ANEURYSM OF BRACHIAL ARTERY – A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Pseudo-aneurysm of the brachial artery is an uncommon entity. The authors present a case of an elderly male with pseudo-aneurysm of right brachial artery following an intravenous injection causing right upper limb ischemia. He was managed by vascular reconstructive surgery consisting of an autologous reverse saphenous vein interposition graft. As it is a limb saving procedure, which can be carried out even in a peripheral hospital, all surgeons should develop the expertise of vascular anastomosis.

Keywords:

Brachial artery, Pseudo-aneurysm, saphenous vein interposition graft, vascular surgery

INTRODUCTION

An aneurysm is a localized arterial dilatation more than 50% of the normal diameter.¹ A true aneurysm contains all layers of the arterial wall. A pseudo-aneurysm is a false aneurysm because it does not contain the components of arterial wall, rather it is a hematoma that forms due to a leak in the artery and is enclosed within an envelope of fibrous tissue formed in adventitia due to compression by the pulsating hematoma.² Blood flow communicates between the artery and the hematoma through the rent in arterial wall and there is a high risk of increase in size or spontaneous rupture.

Pseudo-aneurysms can occur at any site or age as they are a result of direct penetrating trauma, and at times minor blunt trauma to the involved artery.³ Pseudo-aneurysms are also known to occur in the splenic artery if it ruptures into a pancreatic pseudocyst due to autodigestion of a small part of arterial wall after moderate to severe pancreatitis.⁴ Iatrogenic injuries to vessels may lead to pseudo-aneurysm formation. While femoral artery is involved in most iatrogenic injuries⁵, pseudo-aneurysms of brachial artery may also be encountered due to invasive medical procedures like arterial line placement and in those who

indulge in intravenous drug abuse.⁶

Most pseudo-aneurysms present early as sequelae to penetrating injuries or blunt injuries in the form of fractures and dislocation of joints. There are some patients who, as in our case, present years after the trauma.⁷

CASE REPORT

A 63 year old male presented with weakness in right forearm and hand since 1 month ago and a lump in right cubital fossa for the last 15 years. The patient complained of weakness in his right forearm about a month back which was rapidly followed by weakness in his right hand as well. Weakness became more pronounced on exertion. It was not associated with pain in his right upper limb. He gave history of a painless lump in his right cubital fossa for the last 15 years which appeared after an intravenous injection at that site. The swelling was initially small but rapidly increased to the size of a lemon over the past one month.

He was receiving medication for asthma since his teens and was being treated for hypertension for more than a decade. He was also suffering from hepatitis C. He used to be a smoker with a history of 14 pack years but had quit smoking for the past 6 months. He also gave history of opium intake 7 months back.

On examination, the patient was stable hemodynamically. Right hand showed wasting of thenar and hypotenar eminences and was slightly

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cooler than the left hand. There was no sensory deficit and power in the right hand was 4/5. A firm lump was present in the right cubital fossa which was 2.5 x 3 cm in its widest dimensions. It was non-fluctuant, immobile, with smooth surface and regular margins. No bruit, thrill or pulsation could be detected. Right brachial pulse was palpable about 2.5cm proximal to the lump. Right radial and ulnar pulses were absent. No cardiac, respiratory or abdominal abnormality could be detected.

Arterial Doppler study of right upper limb showed significant reduction in blood flow in right radial and ulnar arteries. On CT angiography (Figure 1), right brachial artery was opacified up to the level of capitulum. A well-defined rounded outpouching was noted in distal part of brachial artery at the level of elbow joint with partially calcified walls and non-opacified lumen. Non-opacified segments of brachial artery were seen proximally and distally to the outpouching, measuring approximately 8.7mm and 18mm respectively. Radial and ulnar arteries were well-opacified most likely through collateral flow seen along the lateral aspect of forearm. They showed normal caliber and course. CT angiography features were suggestive of aneurysmal dilatation of distal part of brachial artery with thrombus formation extending some distance into the brachial artery proximal and distal to aneurysmal dilatation.

Based on the available findings, diagnosis of pseudo-aneurysm of right brachial artery was made and exploration of right cubital fossa was planned under general anesthesia. A sigmoid incision was made over the swelling extending about 5cm

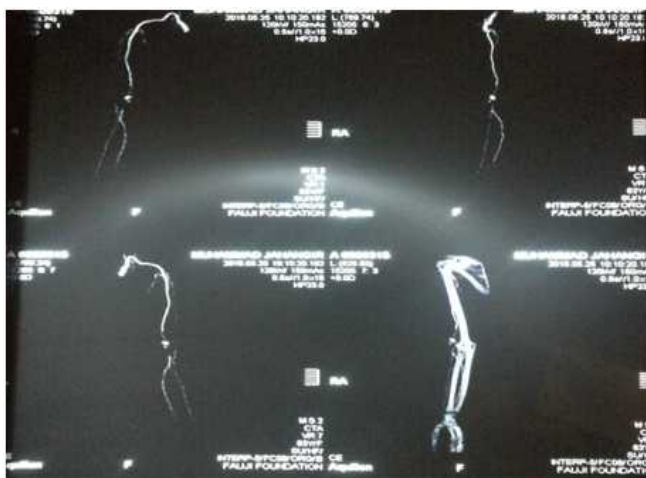


Figure 1: CT Angiogram of right upper limb

proximally and distally. Aneurysmal sac was seen in association with distal third of right brachial artery. It was partially calcified and thrombosed. Brachial artery was exposed about 5 cm proximally and distally up to the bifurcation. Proximal and distal control of the artery was obtained and the aneurysm and thrombosed parts of the artery were resected (Figures 2 and 3).

Long saphenous vein, harvested from the right groin, was reversed and interposed as a graft between normal parts of brachial artery using polypropylene 6/0 (Figure 4). Closure was done in layers after placing a sub-fascial drain.

After surgery, his radial and ulnar pulses became palpable. He was prescribed oral Aspirin 75mg daily. Follow up after one month showed palpable pulses and no signs of ischemia.

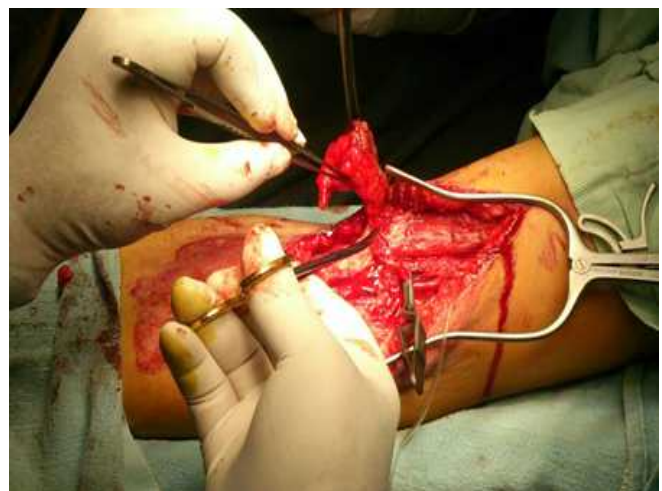


Figure 2: Resection of the pseudo-aneurysm



Figure 3: Resected specimen of pseudo-aneurysm showing thrombus inside



Figure 4: Reversed long saphenous vein interposition graft between ends of brachial artery.

DISCUSSION

Amongst all aneurysms, cumulative incidence of iatrogenic pseudo-aneurysms is approximately 1-3.2%.³ Patients with pseudo-aneurysms may either present early after trauma or many years after that. In early cases, the clinical presentation may be a pulsatile, painful mass or ischemia in the distal limb. Immediate diagnosis and treatment is necessary in order to salvage the limb.

In late cases the usual presentation is that of an asymptomatic mass but it may become symptomatic when complications arise. This was the situation in our case too. Thrombosis in the sac or calcification in its wall may occur in which case the swelling may not be pulsatile. Thrombus in the sac can throw emboli in the distal circulation leading to limb ischemia.⁸ In some cases, a missed or delayed diagnosis of pseudo-aneurysm may lead to nerve compression and neuropraxia. Pseudo-aneurysms may resolve spontaneously, keep on expanding, rupture externally or become thrombosed.⁹

Prompt diagnosis and treatment is required to prevent any serious limb-threatening situation. A focused history and thorough clinical examination will clinch the diagnosis in almost all cases. The diagnosis is confirmed by colour Doppler study and aneurysm can be evaluated by CT angiography.

Various non-surgical approaches have been tried and are being advocated for the treatment of pseudo-aneurysms. They all aim at occluding the hole in the injured artery. Percutaneous

ultrasonographically guided thrombin injection (PUGTI) has been introduced for the treatment of pseudo-aneurysms. Doppler-guided 0.5-1 ml of thrombin injection, ultrasound-guided compression of the aneurysm or a combination of the two is used to cause thrombosis in pseudo-aneurysms of peripheral arteries, particularly femoral artery. Drawbacks of PUGTI include thrombosis of the main arterial lumen if lumen of aneurysm is not effectively isolated. Other complications are anaphylaxis and distal embolization.⁹

Injection of biodegradable collagen, coil embolization and covered stents are other percutaneous methods used to plug the hole in the artery.¹⁰ Covered stent is a metallic stent covered with polytetrafluoroethylene (PTFE). It remains in place permanently and prevents continuous flow of arterial blood in the pseudo-aneurysm, which then thromboses. This technique has a high success rate. Stent fracture, migration and infection are possible complications.¹⁰ Endovascular techniques have been introduced in recent past for aneurysmal repair and may be considered in patients who are unsuitable for conventional surgery.¹¹

Surgery is considered to be the best treatment option of a symptomatic or complicated pseudo-aneurysm. Operative treatment is a must if there is an impending rupture of aneurysm. Surgery is also mandatory in cases of limb ischemia or when there are signs of compression of vein, artery or nerve. Failure of non-surgical management, large aneurysm diameter, an aneurysm causing overlying skin ischemia and presence of infection are other indications of surgery.¹²

The principles of aneurysmal repair remain the same in all peripheral arteries regardless of its etiology. The pseudo-aneurysm is excised and the arterial continuity restored by using grafts. Some long-standing aneurysms may form dense adhesions with the surrounding structures. Extensive dissection in such cases may entail danger to adherent structures. Partial resection of aneurysm and a bypass procedure may be prudent in such a situation.¹²

Placement of an interposition conduit either in the form of a saphenous vein or a prosthetic graft, is used to restore arterial continuity. Autologous reversed saphenous vein interposition graft is the preferred conduit for use in brachial artery

pseudoaneurysms.¹³

Pseudo-aneurysm may require prompt treatment to prevent permanent damage to the limb. Non-surgical methods require specialist expertise, is available in specialized centers only, and may end up in complications or treatment failure. Saphenous vein interposition graft is a procedure that can be performed in any peripheral hospital by a surgeon who is skilled in vascular anastomosis. Therefore, all surgeons must be skilled in performing this limb saving procedure.

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METHOTREXATE INDUCED PANCYTOPENIA IN A PATIENT WITH TAKAYASU'S ARTERITIS A CASE REPORT

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ABSTRACT

Introduction: Methotrexate is one of the most commonly medications in rheumatology setups. One needs to keep a watch on its side effects by regular monitoring.

Case Scenario: This is a case report of Methotrexate induced pancytopenia within a few weeks of initiation in a patient with Takayasu's arteritis. Despite vigilant monitoring, patient had severe pancytopenia and associated sequelae. Unfortunately patient lost her life.

Conclusion: Methotrexate and DMARDs need regular monitoring for the adverse events.

Keywords:

Methotrexate, Pancytopenia, Takayasu's arteritis

INTRODUCTION

Methotrexate is one of the most commonly used disease modifying anti rheumatic drug (DMARD). Methotrexate (MTX) is employed as a gold standard while starting treatment in rheumatoid arthritis as well as in other arthritis and vasculitis. It is prescribed both as a monotherapy and in combination with other DMARDs. The prevalence of methotrexate induced hematological toxicity is around 3 - 5% and the incidence around 1.4%.^{1,2} This includes leucopenia, thrombocytopenia, anemia as well as pancytopenia. Amongst these; pancytopenia in context of MTX remains an under reported yet life threatening issue.

We hereby present a case report of patient who faced severe pancytopenia following methotrexate therapy.

CASE REPORT

A 32 year old lady, teacher by profession came in with history of myalgia, weight loss and intermittent fever along with arm claudication

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especially while doing overhead activities like writing on board. Examination revealed absence of radial, brachial and carotid pulse on left side along with carotid bruit. Blood pressure was immeasurable in left arm and was 170 systolic in right arm. Computed tomography (CT) angiogram confirmed the diagnosis of takayasu's arteritis. Doppler USG abdomen revealed small shrunken right kidney with a normal sized left kidney. Once disease activity status was documented and baseline laboratory profile was done; treatment was initiated with steroids (1 mg/kg) along with MTX 10 mg/week. Patient was advised monitoring initially fortnightly for one month followed by monthly visits for first three months.

MTX was built up to 15 mg/week over next four visits. At next follow-up, patient came in with complaints of pedal edema, puffy face and rash involving upper limbs and back of chest. Patient was admitted at once. On examination, the patient looked weak, pale and had petechial blanching rash present all over the trunk and upper limbs. Chest and abdominal examination was also unremarkable.

Investigations revealed pancytopenia with all three cell line depressed. Follow up of these laboratory findings during hospital stay is as follows

Table I: Lab profile done during hospital stay

	DAY 1	DAY 3	DAY 5
Hemoglobin(Hb) gm/dl	9.8	7.9	7.1
Total leucocyte count(TLC) cu.mm	3000	450	345
Platelet count	50,000	19,000	14000
Neutrophils%	21.4	5.5%	4.8%
Lymph%	78.6	-	-
Urea (m.mol/l)	20	30	32.8
Creatinine(m.mol/l)	269	398	457
ALT (iu)	42	35	40

Bone marrow examination revealed depressed erythropoiesis, myelopoiesis with markedly reduced megakaryopoiesis and a hypo-cellular bone marrow consistent with features of bone marrow suppression.

Methotrexate was withheld immediately on day 1 of admission. Patient was shifted to isolated unit. Barrier nursing was adopted. Supportive treatment with IV daily transfusion of platelet concentrate was initiated on day 3. Recombinant granulocyte colony stimulating factors (G-CSF) (filgrastim) 300 µg subcutaneous injections was given daily for 5 days. Antibiotic coverage with neutropenic regimen started after correcting the dose for renal compromise. Red cell concentrate was given from third day of admission. Renal support was sought from the nephrology department.

Patient became dyspneic on day 5, and had to be shifted to ICU facility. A repeat chest x-ray showed soft patchy infiltrates over bilateral lung fields. Patient was immediately put to inhaled oxygen therapy. On day 6, the counts started to improve in response to aggressive supportive therapy. Total leucocyte count rose to 2500, platelets increased to 4200 and hemoglobin went up to 8.6. Despite this, patient went in to respiratory distress and chest findings worsened owing to acute respiratory distress. Patient was put to ventilator support but she succumbed to a cardiac arrest.

CASE DISCUSSION

Methotrexate (MTX) may lead to isolated

decrements in either red cell, white cells or platelets without affecting other cell lines, but pancytopenia when all lineages are affected is particularly life threatening complication.³ Profound pancytopenia has been mentioned as early as after a single dose of MTX in a case report.⁴ However, it is usually seen later in the course of MTX therapy resulting from cumulative dose.

The risk of pancytopenia may increase with daily dosing errors, folic acid deficiency, hypoalbumenia, concomitant infections like parvo virus infection, dehydration, renal insufficiency and co-administration of other drugs like cotrimoxazole.⁵ For patients with renal impairment dose adjustment should be done with complete avoidance of MTX if creatinine clearance <30 ml/min.⁶ The reason for pancytopenia in our patient was also likely an antecedent viral infection and renal impairment. Therefore American College of Rheumatology suggests that periodic routine peripheral blood count should be performed (every four to eight weeks).⁷

Methotrexate by its action as a folic acid antagonist with an average half-life of 6-8 hours; becoming undetectable in serum by 24 hours. But after take up inside the cell, methotrexate is converted in to polyglutamate derivatives (MTXglu) which prolongs its intracellular stay (median half- life of 3 weeks).⁸ This accounts for the chronic toxicity associated with MTX. Concomitant administration of folic acid (1 to 3 mg/day) halts the toxicities.⁹

In a case series, Lim et al 10 describe that prolonged exposures to high dose of MTX is responsible for the toxicity rather than achieving the peak plasma levels at one time. Similarly in another case report patient mistakenly took 20 mg daily for two weeks leading to supra threshold concentrations in tissues and hence, mucositis, gastrointestinal and myelotoxicity¹¹. Hence the cause of such toxicity in individual patient should be determined with a primary focus on management.

The management of MTX induced pancytopenia is mainly supportive with stopping the offending drug

at the first instance. Folinic acid (leucovorin) should be given to all; most effective if administered 24 to 48 hours after the last dose of MTX. Afterwards, Folinic acid might not work as the cellular uptake of the offending drug is already complete. Supportive therapy includes fluid support; blood component replacement, antibiotics and antifungal administration. The availability of Recombinant growth factors like granulocyte colony stimulating factor (G-CSF)^{12,13} also improve outcomes in such patients. In our case both Folinic acid and supportive measures including G-CSF were adopted with complete avoidance of antifungals as our patient had marked renal impairment. The mortality despite all these measures remains high (28%).¹⁰

CONCLUSIONS

Methotrexate induced pancytopenia is a serious and fatal complication that needs timely detection and prevention. Physicians need to be aware of the potential toxicity of MTX. They should follow their patients with regular monitoring with complete blood counts, liver and renal function tests to avoid sequelae of pancytopenia and other related toxicities.

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SPLENIC CYST – A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Cystic disease of spleen is a rare entity. We report here a rare case of non-parasitic cyst in a young adult male patient who presented with left hypochondrial fullness with uncertain origin. Radiological investigations showed it to be a splenic cyst involving the whole of spleen which was confirmed on laparotomy. Splenectomy was done. Histopathology showed epidermoid cyst of spleen.

Keywords:

Epidermoid Cyst, Splenectomy, Splenic Conservation, Splenic Cyst

INTRODUCTION

Splenic cyst is rarely encountered in surgical practice.¹ Classified into parasitic and nonparasitic cysts, majority of the splenic cysts are hydatid cysts caused by *Echinococcus granulosus* and are common in endemic areas. Nonparasitic cysts are rather uncommon and may be true (primary) cysts or pseudocysts (secondary). True cyst has an epithelial lining which may be epidermoid, dermoid or mesothelial in origin or they may have an endothelial cover such as hemangioma or a lymphangioma. Secondary cysts are pseudocysts or nonepithelial and are mostly traumatic in origin.

Primary cysts are mostly encountered in children or young adults.² Most of these cysts may remain silent for long periods but may increase to a considerable size eventually and present as fullness in the flank. Treatment of choice for such cysts is splenectomy. Some complications have been reported, including rupture, hemorrhage and infection.² However in younger patients, splenic conservation to avoid post splenectomy infections is now a preferred approach.³ We report here a case of primary splenic cyst of epidermoid variety in a young man.

CASE REPORT

A 27 years old young male presented with 3 months

history of left hypochondrial pain and occasional vomiting. He had noticed a mass in his abdomen which was initially painless but later became painful. The patient gave no history of trauma. On examination there was a huge, non-tender mass in left hypochondrium (LHC) that moved on respiration. Chest was clear on auscultation and radiography. Abdominal ultrasound suggested an abscess in LHC. CT scan showed a large cystic subphrenic lesion extending from the upper pole of the spleen measuring 14 x 16 x 17.5 cm with a volume of 2047 ml with dense internal contents giving suspicion of haemorrhagic fluid. Aspiration yielded clear fluid and its cytology revealed no malignant cells. *Echinococcus* antibodies were negative. Exploratory laparotomy revealed a large encapsulated splenic cystic compressing the parenchyma all around it. Multiple adhesions were separated and splenic pedicle was ligated. Splenectomy was carried out leaving behind a single spleniculus. The patient had an uneventful postoperative recovery. Histopathology of the



Figure 1: Intra-operative view of the splenic cyst

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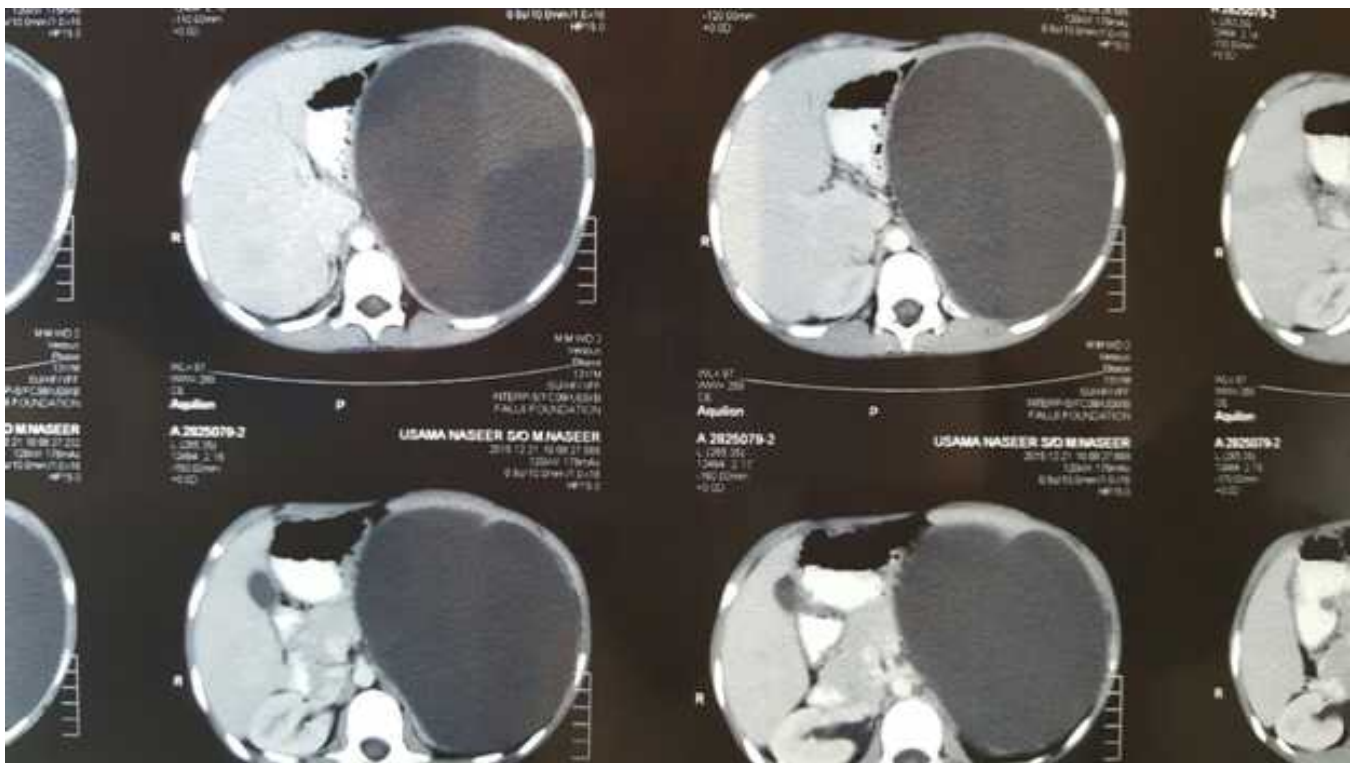


Figure 2: CECT scan showing huge splenic cyst

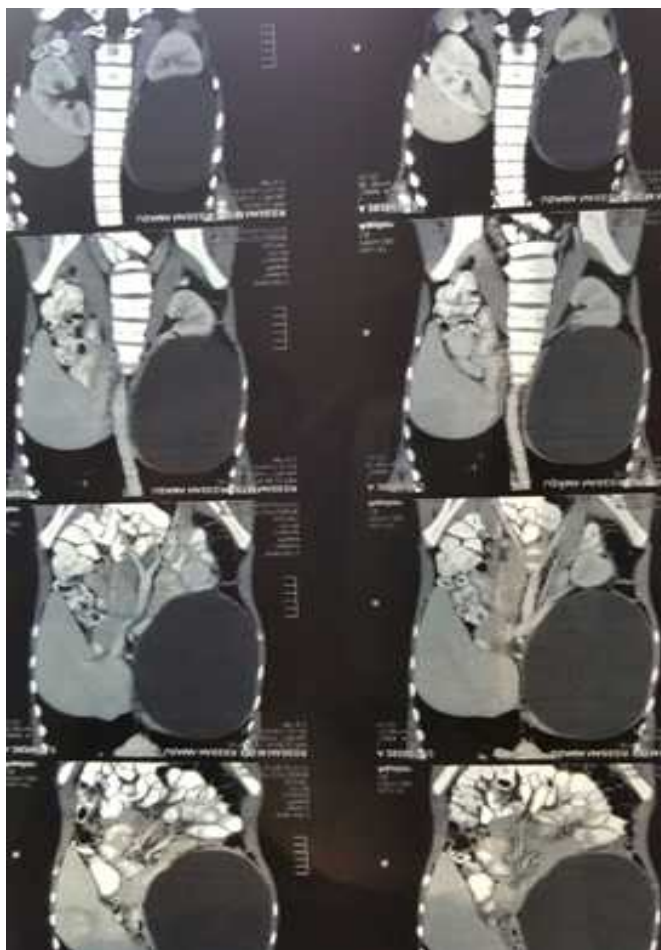


Figure 3: CECT Scan showing huge splenic cyst

DISCUSSION

True non-parasitic lesion of spleen cannot be differentiated from other types of cysts by clinical assessment alone. True cyst has an epithelial lining whereas a pseudocyst, which is mainly due to trauma or hematoma, has an inner lining of connective tissue. Infections, malignancy or metastatic degenerative disorders may also give rise to pseudocysts. Only 10% of the true, benign, non-parasitic cysts are epidermoid in origin.² Epidermoid cysts are usually congenital in origin with more than 80% occurring under the age of 20.⁴ Both epidermoid and pseudocysts, however, have similar composition of proteinaceous material mostly consisting of cholesterol crystals and fat-laden macrophages.⁵ In our case histopathology showed stratified squamous epithelium which was suggestive of epidermoid cyst.

Cysts that are less than 5 cm in size are mostly asymptomatic. Larger cysts have been reported to present with symptoms mainly in 2nd or 3rd decade of life.² Our patient also presented in 3rd decade of life. Usual presentation is a dull ache and fullness in left hypochondrium or epigastrium. The patient may present with nausea, vomiting or flatulence due to pressure effects. Rarely, cardiopulmonary

symptoms like pleurisy, dyspnea, or cough due to diaphragmatic irritation may occur. In our patient, despite a large cyst, there were no such symptoms.

When the patient presents with a lump in LHC, ultrasonography should be carried out to determine its origin. In majority of cases, particularly when the cyst is small sized, the diagnosis is confirmed. Larger cysts may have to be differentiated from a pancreatic cyst. It also needs to be differentiated from splenic hydatidosis, as an epidermoid cyst, splenic abscess, pseudocyst and cystic neoplasm of the spleen may also appear similarly. Even in the case of negative serology, hydatid disease of the spleen may be differentiated on the basis of calcification present in the cyst wall, the presence of daughter cysts or similar lesions in the liver or other organs.⁶ In our case, imaging studies could not determine the origin of the cyst because of large size and dense adhesions between the cyst and pancreas. As hematological, biochemical, cytological and serological tests turned out to be negative, the diagnosis was only confirmed on laparotomy.

Any cyst less than 5 cm in size, asymptomatic cyst or one with regular margins is best left untreated. However larger cysts with symptoms, presence of a solid component or irregularity of the cyst wall may require surgical treatment.² Aspiration of a cyst or use of sclerotic agents have no proven evidence of providing complete cure and result in frequent recurrence.³ Laparotomy with splenectomy is the treatment of choice for any cyst that is involving the whole of spleen, if it is located at the hilum, if multiple cysts are encountered or in case of anomalous anatomical relationship with the surrounding tissues.² Cysts that are symptomatic or over 5 cm in diameter should be removed by partial splenectomy or near-total cystectomy (decapsulation) either by the open or laparoscopic approach as such cysts increase the risk of rupture leading to life-threatening hemoperitoneum.³ In our case, splenic parenchyma was stretched thin over the cyst and pushed to the periphery.

In situations other than these, more conservative approaches are preferred due to the concerns of overwhelming sepsis especially in children. Partial splenectomy is performed for cysts situated at the poles leaving behind about 25% of the splenic tissue for immunological functions and which also

minimizes the risk of recurrence.⁷ This can be carried out laparoscopically⁸ with the major indications being cysts located at the poles of the spleen and the cavity being deep.⁸

Marsupialization and deroofting are other conservative approaches. Although safer and associated with shorter hospital stay, especially if performed laparoscopically, these approaches increase the risk of recurrence.⁹

Patients who have undergone splenectomy carry a lifetime risk of up to 5% for the development of Overwhelming Post-Splenectomy Infection (OPSI) with a mortality rate of 38-69%.¹⁰ Thus due to the increasing awareness of immunologic function of spleen and to avoid the rare but life-threatening risk from OPSI, such salvage procedures have gained momentum to preserve the spleen including cyst excision with partial splenectomy to cyst marsupialization with partial cyst wall excision.¹¹

CONCLUSION

True splenic cysts are rare. Cysts causing symptoms or those larger than 5 cm should be treated surgically with the main focus being the preservation of some splenic parenchymal tissue behind to cater for the immunological function and reduce the risk of OPSI. Laparotomy with splenectomy is treatment of choice for large cyst involving the whole parenchyma and in which intractable bleeding occurs from the spleen. Laparoscopic approach for smaller cysts is preferred due to benefits of minimal invasive surgery.

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RARE INHERITED DISORDER – OSTEOPETROSIS

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ABSTRACT

Osteopetrosis is a descriptive word that refers to a rare genetic disorder, representing a heterogeneous group of inherited bone dysplasia caused by osteoclast dysfunction resulting in generalized sclerosis. Osteopetrosis is opposite of a condition 'osteoporosis' in which bone mass density decreases. In Osteopetrosis the bone density increases to such an extent that it can lead to brittle bone fractures. Here is a case report of Osteopetrosis in a 44 year old female.

Keywords:

Brittle bone fracture, Generalized sclerosis, Inherited bone dysplasia, Osteogenesis imperfecta, Osteopetrosis, Osteoporosis

INTRODUCTION

Osteopetrosis can be introduced as stone bone, which is also called marble bone disease. Osteopetrosis was described in 1904 by Albers-Schönberg so the disease is also called Albers-Schönberg disease caused by malfunctioning of osteoclasts.¹ Mild form of osteopetrosis shows no symptoms. However, serious disease shows short growth, increase fracture risk and deformities.² Any disease that produces osteosclerosis can be considered in the differential diagnosis of osteopetrosis.³ Osteopetrosis has different forms so before the treatment, a correct diagnosis is more important. Osteopetrosis can be in autosomal dominant form which is asymptomatic or in autosomal recessive form which may even cause death in early age. Treatment is predominantly supportive with some literature suggesting good outcome with stem cell transplantation.¹

Incidence of osteopetrosis is around 1 case per 100,000-500,000 population.⁴ The disease rate was found out to be higher in Costa Rica (3.4:100,000).⁵

CASE SUMMARY

A 44 year old female was referred to Rheumatology Out Patient Department with pain in both hip joints

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for the last three months. There was no history of fever, rash, arthritis, weight loss, anorexia, etc, however patient had a history of spontaneous fractures since the age of five years which were managed conservatively without any internal fixation. There were no previous records or Xrays available. Multiple fractures of legs resulted in progressive difficulty in walking. Pain in lower limbs affected the patient's physical activity over time, leaving the patient bed-bound. There was no history of any co-morbid condition. Family history was positive for spontaneous fractures in the patient's brothers as well. On examination patient had normal vital signs, short stature, abnormal dentition, tenderness around right hip joint, restricted and painful bilateral hip movements. Patient's FABER test (Flexion, abduction, external rotation) for the hips was positive bilaterally. Examination of rest of the joints was completely normal. Baseline investigations were normal as shown in Table 1.

Table 1: Baseline Lab Report

ESR	26mg/dl
CRP	<6mg/l (negative)
Serum calcium	2.0mmol/l
Vitamin D	80
Serum parathyroid hormone	26.67



Figure 1 : Radiographs showing bones of spine, skull, hands and hip joints.

Radiographs showed fracture of proximal end of right femur. Bones of the spine, hands and the skull appeared hyper-dense and sclerotic with thickened cortical borders suggesting increase bone density. On DEXA Scan, T-Score was 3.4 (increased bone mineral density).

Ocular examination was done by the ophthalmology department to rule out Osteogenesis Imperfecta, results of which were found to be normal. On the basis of recurrent fractures, increase bone density, radiological images and excluding other congenital bone diseases like osteogenesis imperfecta, the diagnosis of 'Osteopetrosis' was made. Pain was adequately being controlled with NSAIDs (non-steroidal anti-inflammatory drugs) and opioids. Patient was counselled in detail about the disease and was managed conservatively with physiotherapy, rehabilitation, occupational therapy and was referred to Artificial Limb Centre for brace

treatment and Orthopaedic department for further management of the fractures.

DISCUSSION

Osteopetrosis is a heterogeneous condition, which can be asymptomatic or may even cause death in early age.⁶ The primary defect is malfunctioning of osteoclasts. The major problems are linked with bones including scoliosis, fractures, osteomyelitis, etc. It can also affect mandible.⁷

Osteopetrosis can be divided into three types: The adult type is mild, which is mostly diagnosed when a person is in adulthood. The intermediate type is found in children with age less than ten. This type is more severe than the adult form, but less than the malignant infantile form. The malignant infantile form show signs and symptoms at birth, is severe with a shorter lifespan.⁸

Infantile osteopetrosis occurs at the time of birth or early age of life. It is most severe out of all the types. If not given any treatment, patient may die because of the disease. In this type the number of osteoclasts are more. Intermediate osteopetrosis shows no symptoms at birth, but starts appearing in first ten years of life. The patients show short stature and also suffer fractures. Adult osteopetrosis usually occur in late phase of life. Patient usually shows no symptoms. The diagnosis can be made by seeing radiographic images of bones.

X-rays plays a diagnostic role by showing several characteristic features: Bones appear hyper dense and sclerotic with thickened cortical bones, narrow canal, and layer cake change in vertebral bodies (density at upper and lower edges are more and reduced in middle), widened bone ends and zebra-like pattern (alternating dark and light density shadows), bone in bone appearance (endobones) and transverse fracture.⁹

Differential diagnosis of increase bone density with fractures include Cranio-metaphyseal Dysplasia, Pyknodysostosis, Hypoparathyroidism, Osteoblastic Metastasis, Sclerosteosis, Diaphyseal Dysplasia, Osteopathia Striata.¹⁰

Treatment options can be Bone Marrow Transplant in severe cases, Interferon Gamma-1b delays disease progression, Calcitriol stimulates osteoclasts, Steroids to improve cell counts (in case of bone marrow suppression). All the treatments are still under debate and researches are going on as the disease is very rare.¹¹ Physical and occupational therapy, balanced diet, orthopaedic care for fractures, monitoring of visual and ENT (ear, nose and throat), good dental care to avoid dental abscess or caries are also considered.¹²

CONCLUSION

We conclude that in Young adults coming with recurrent fractures and increase bone density osteopetrosis should be considered one of the important differentials.

CONFLICT OF INTEREST

None.

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The manuscript should be typed in double spacing on 8” x 11” white bond paper with one inch margin on both sides. There should be no more than 40 references in an Original Article and no more than 60 in a Review Article. The CD containing soft copy of the article should be sent with the manuscript.

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Tables and illustrations should be merged within the text of the paper, and legends to illustrations should be typed on the same sheet. Tables should be simple, and should supplement rather than duplicate information in the text; tables repeating information will be omitted. Each table should have a title and be typed in double space without horizontal and vertical lines on an 8 1/2” x 11” paper. Tables should be numbered consecutively with Roman numerals in the order they are mentioned in the text. Page number should be in the upper right corner. If abbreviations are used, they should be explained in foot notes and when they first appear in text. When

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Abstracts of original article, comprising of upto 250 words, should be in structured format with following sub-headings.

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Review article, case reports and others require a short, unstructured abstract.

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This should include the purpose of the study. The rationale for the study should be summarized. Only pertinent references should be cited; the subject should not be extensively reviewed. Data or conclusions from the work being reported should not be presented.

METHODS

Study design and sampling methods should be mentioned. The selection of the observational or experimental subjects (patients or experimental animals, including controls) should be described clearly. The methods and the apparatus used should be identified (manufacturer's name and address in parentheses), and procedures described in sufficient detail to allow other workers to reproduce the results. References to established methods should be given, including statistical methods; references and brief description for methods that have been published but are not well known should be provided, new or substantially modified methods should be described, giving reason for using them, and evaluating their limitations all drugs and chemicals used should be identified precisely, including generic name(s), dose(s) and route(s) of administration.

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Results should be presented in a logical sequence in the text, tables and illustrations. All the data in the tables or illustrations should not be repeated in the

text; only important observations should be emphasized or summarized.

DISCUSSION

The author's comment on the results supported with contemporary references. Critical analysis of similar work done by other workers, its comparison with own work with possible reasons for any differences found should be included.

CONCLUSION

Conclusion should be provided under separate heading and highlight new aspects emerging from the study. It should be in accordance with the objectives.

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PEER REVIEW

Every paper will be read by two staff editors or members of the editorial board. The papers selected will then be sent to 2-3 reviewers. If statistical analysis is included, further examination by a statistician will be carried out.

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