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MGM Journal of Medical Sciences

1. Aims and Scope

MGM Institute of Health Sciences (Deemed University) recognizes the urgent need for promoting medical education in the country, so that the quality of life for individuals and community could be improved by promoting health, preventing and curing diseases, advancing biomedical and clinical research and educational programs for tomorrow's physicians and scientists. The University is committed to creativity, innovation and excellence in every sphere of its working. The University will transform lives and serve the society by educating, creating knowledge and putting knowledge to work. In this endeavor, the University has launched a quarterly peer-reviewed scientific journal 'MGM Journal of Medical Sciences' to encourage investigators to publish their research findings for wider dissemination with the aim of applying those for the benefit of the society.

The peer-reviewed quarterly journal would cover full spectrum of the specialties in biomedical and clinical research. Its eighth issue would be released in February 2016. The journal aims to publish articles arising out of original research, specialized topics, review articles, editorials, and description of new diagnostic and therapeutic techniques and technologies. In addition, the journal will include pictorial reviews, letters to the editors, book review, and notices of meetings and courses. In this endeavor, the journal hopes to provide a forum for the stimulation of new developments, clinical practices and research in the field of health and allied sciences. The salient feature of the journal would be to bring out from time to time special issues focusing on specific themes of national relevance including the outcome of scientific meetings, etc. A section would be devoted exclusively to young researchers and students in order to encourage them to publish their innovative ideas and research findings. **In fact, it will be a 'student-friendly' journal.**

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From Editor's Desk

This issue contains an interesting article entitled: 'In Silico-based Study of Cytochrome P450 and Multidrug Resistance Protein 1 from Docking Perspective to Understand Kidney Failure' by Vasudha Satalkar et al about novel ways of finding nephrotoxic potential of drugs by Bioinformatics Data Analysis. About 75% of metabolism of drugs is carried out by cytochrome P450 enzymes which are membrane-associated proteins located in mitochondria and endoplasmic reticulum of human cells. If the active sites of these enzyme molecules are blocked by a drug, the metabolism of that drug will be slowed resulting in increase in its concentration in blood to toxic levels. With their 'In Silico' studies, the authors found that known nephrotoxic drugs have higher binding scores and therefore block the active sites on cytochrome P450 molecules more effectively. Higher the binding scores, greater is their nephrotoxicity potential. This is an interesting field of study of safety of drugs. It is possible that in near future, fewer clinical trials of newly introduced potentially nephrotoxic drugs may be required to establish their safety. Presently, pharmacogenetics is being routinely used in some advanced cancer treatment centers to predict efficacy and toxicity of chemotherapeutic drugs at individual level, thereby helping in tailoring most effective and least toxic drug regimen for a particular patient.

Of course, in addition to this original article, there is usual mix of papers from various disciplines of health sciences which, we are sure, will interest all our esteemed readers.

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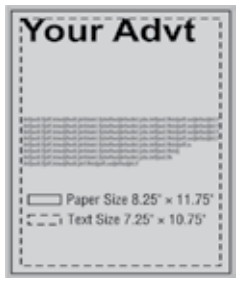

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ORIGINAL ARTICLE

In Silico-based Study of Cytochrome P450 and Multidrug Resistance Protein 1 from Docking Perspective to Understand Kidney Failure

[1]Vasudha Satalkar, [2]C Selvaa Kumar, [3]Mansee Thakur, [4]Dattatraya Shankar Joshi

ABSTRACT

Background: The need to identify causes of drug induced kidney failure has been underscored by International Conference on Harmonization (ICH) regulated agencies. In our earlier studies on adverse drug reaction (ADR) reported in Canada Vigilance Adverse Reaction Online Database it was observed that drugs azathioprine, clozaril/clozapine, diclofenac sodium, diflucan/fluconazole, furosemide, indomethacin, metformin, micardis/telmisartan, viread/tenofovir, and zyprexa/olanzapine lead to kidney failure.

Method: Attempts have been made to understand the physiological process via bioinformatics perspective. This was done by active site identification for cytochrome P450 along with multidrug resistance protein 1 (MRP1). Docking against the drugs in these proteins that are categorically involved in drug binding based on their pharmacological actions are as per drug bank annotations.

Results: Cytochrome P450 2C19 protein showed better interactions with drug indomethacin with a maximum score of –119.2 kcal/mol followed by drug clozaril with a score of –102.5 kcal/mol. This was finally followed by of drug zyprexa with a score of –101.0 kcal/mol. The residues which are actively involved with the drug indomethacin include Arg97 and Arg433. Drug clozaril shows interaction with Ala297. For drug zyprexa the residues like Arg97, Ala297 and Cys435 interact with the protein. For MRP1, even though it showed better binding scores for drugs azathioprine, indomethacin, diflucan and furosemide. But still, they are not able to interact within the pocket, leaving it empty during docking studies.

Conclusion: Through this study, it was possible to identify active site pocket in the related proteins and the interacting amino acid residues of cytochrome P450 that may contribute to drug induced kidney failure.

Keywords: Cytochrome P450, Docking, Renal failure, Virtual screening.

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INTRODUCTION

One of the top 10 causes of death in the US is drug induced toxicity that results in substantial health care costs.[1] Mortality due to acute kidney failure is estimated at about 40 to 80% and is constantly rising while mortality due to acute myocardial infarction is decreasing worldwide.[2] Kidney failure occurs when the kidneys cannot function properly. This results in buildup of waste and fluid in the body. Acute kidney failure may develop suddenly due to drugs or other reasons. Chronic kidney failure develops gradually over years. End-stage kidney disease causes anemia, high blood pressure, bone disease, heart failure, and poor mental functioning.[3]

Acute kidney failure caused by nephrotoxic drugs is estimated at around 19 to 25% of critically ill patients. These drugs injure kidney either by their hemodynamic effect, direct cellular toxicity, osmotic cellular damage, precipitation/crystallization or interstitial damage. The need for diagnostic tools to identify drug induced nephrotoxicity has been emphasized by the International Conference on Harmonization (ICH) regulated agencies.[4] In addition to this, transport mechanism is important in understanding renal drug clearance, which is sum of rates of glomerular filtration and tubular secretion minus the rate of tubular reabsorption.[5]

Role of transporters in absorption, distribution, metabolism and excretion (ADME) is very important. Elimination of drugs is directly related to the uptake rate mediated by transporters. Pharmacological or toxicological effect depends on transport of drugs to and from the tissue.[6] The ATP-binding cassette (ABC) transporters are major membrane proteins involved in transport of drugs across biological membranes. These proteins dictate the reabsorptive and excretory capacity of the kidneys.[7] The multidrug resistance associated protein 1 (MRP1), a member of the ATP-binding cassette family, plays an

important role in modulating the absorption, distribution, metabolism, excretion and toxicity of drugs.[7] Medications are a major source of acute kidney injury, especially in critically ill patients. Two cases where CYP deficiencies could have played an important role in acute kidney injury have been reported by Leung, Nelson et al. They performed genetic testing of their patients for the detection of CYP polymorphism.[8]

The food and drug administration (FDA) made it mandatory in the USA to indicate CYP2C19*2 allele frequencies for different populations in medication guides highlighting the fact that the effectiveness of the drug varies among patients.[9] The metabolism and elimination of many drugs is mediated the enzyme cytochrome P450 2C19 (CYP2C19) which is an isoenzyme of the cytochrome P450 super family.[10] The clinical impact of the CYP2C19 of the enzyme depends on if a drug is activated or inactivated by it. Involvement of metabolic pathways and other nongenetic factors like other medicines taken can also influence the pharmacological/toxicological outcome.[10] The involvement of enzyme in drug clearance depends on the structure of the site of metabolism that allows it to select and bind with the drugs. Its substrate and inhibitor profile depends on the amino acids that shaped the substrate binding cavities.[11]

Glomerular filtration, tubular secretion and tubular reabsorption are the three major processes by which drugs get eliminated via the kidney. Tubular secretion and reabsorption involve both passive and active transport processes across the membranes. Drug filtration is a diffusional passive process. The tubular secretion of drugs is mediated by many active transporters, which take up compounds from the kidney interstitium and efflux them into the tubular lumen. Organic anion transporters (OATs) and organic cation transporters (OCTs) are the two major classes of uptake transporters, but OCTNs and OATPs can also be found in the kidney. Efflux transporters, such as P-glycoprotein and MRPs are also found in the kidney tubule.

Cytochrome P450 enzymes are present in many mammalian organs, such as kidneys, lungs and intestines with the majority in the liver.[12] The CYP450 monooxygenase metabolites play an important role in renal regulatory mechanisms by modulating the activities of the Na^+/K^+ ATPase, Na^+ $K^+/2Cl^-$ cotransporter, and K^+ channels in various segments of kidney nephrons. CYP450 hydroxylase metabolites, epoxygenase metabolites also make important contributions to integrate kidney function by directly affecting tubular ionic transport processes, vascular tone, and cellular proliferation.[13] Many ligands bind to proteins via tight, cooperative interactions, that is, 'lock and key' mechanisms. However, other, looser interactions also occur and may have physiological significance (e.g. in multidrug resistance).[14]

Here attempts have been made to study drugs reported with the fatal patient consequence due to kidney failure as suspected ADR from the open source Canada Vigilance Adverse Reaction Online Database. The drugs suspected to cause kidney failure with the fatal patient consequence were docked with two proteins cytochrome P450 2C19 and MRP1 to find the active sites and interacting amino acid residues.

METHODOLOGY

Medical Data Analysis

Data collection: To begin with, Canada Vigilance Adverse Reaction Online Database[15] an open source was considered for the data source. All the drugs selected were reported to have an adverse reaction 'renal failure acute (RFA)' and 'renal failure chronic (RFC)' which dates back from 1965 till 2012.

Data cleaning: All the records downloaded from Canada Vigilance Adverse Reaction Online Database and were imported into MySQL for cleaning purpose. Two separate databases were created for Acute Renal Failure and chronic renal failure. The raw data consisted of a total of 55574 records for RFA and 8364 records for RFC. Only records reported as suspects for an adverse event RFA and RFC were selected. Duplicate records were removed. Total of 1573 RFA suspects and 358 RFC suspects were found after removal of duplicates.

Data analysis: A total of 577 drugs were reported to cause RFA and 147 drugs were found to cause RFC. The frequency of each drug in both tables was calculated. There were 276 incidences of drug induced death due to RFA and 55 incidences of death due to RFC reported in the database. Counts of top ten drugs found in both databases are listed in Table 1.

Table 1: Top ten drugs causing renal failure acute and renal failure chronic

Renal failure acute		*Renal failure chronic*	
Counts	*Drug*	*Counts*	*Drug*
56	Gentamicin	45	Zyprexa
23	Vioxx	30	Aclasta
21	Celebrex	29	Fleet phosphosoda oral laxative
21	Metformin	14	Eprex sterile solution
20	Remicade	6	Prednisone
20	Furosemide	4	Prograf
20	Vancomycin hydrochloride for injection	4	Clozaril
18	Vasotec	4	Cyclosporine
18	Lipitor	4	Revlimid
17	Crestor	—	—

Drugs suspected to cause both acute renal failure as well as chronic renal failure where death has been reported as patient outcome were found to be azathioprine, clozaril/clozapine, diclofenac sodium, diflucan/fluconazole, furosemide, indomethacin, metformin, micardis/telmisartan, viread/tenofovir, and zyprexa/olanzapine.

Common proteins are involved in pharmacological actions for all the ten drugs.

Some observations on the ten drugs reported to cause death due to kidney failure as suspected ADR from the drug bank[16] database are as follows:

- All drugs contain N atom in their chemical formula.
- There are total of 104 proteins functioning either as targets, enzymes, transporters, carriers, etc. associated with the ten drugs shortlisted above.
- Six drugs are metabolized by enzyme 'cytochrome p450 2c19': clozaril, diclofenac sodium, diflucan, indomethacin, micardis, viread, zyprexa.
- Same 6 drugs are transported by 'multi drug resistance protein 1'.
- Four drugs share 'glucuronide' as a metabolite for 4 drugs: diclofenac sodium, furosemide, micardis and zyprexa.
- Three drugs share 'desmethylated metabolite' as metabolite clozaril, indomethacin and zyprexa.
- Four drugs share carrier 'serum albumin' diclofenac sodium, furosemide, indomethacin, zyprexa.
- Three drugs share transporter 'solute carrier family 22 member 6': diclofenac sodium, furosemide, indomethacin.
- Three drugs share transporter 'canalicular multi-specific organic anion transporter 1': furosemide, indomethacin, micardis.
- Two drugs share transporter 'multidrug resistance associated protein 1': diclofenac sodium, indomethacin.
- Three drugs share transporter 'solute carrier family 22 member 8': diclofenac sodium, furosemide, indomethacin.
- Three drugs share transporter 'solute carrier family 22 member 11': diclofenac sodium, furosemide, indomethacin.
- Two drugs share same targets-related to dopamine, 5 hydroxytryptamine, alpha-adrenergic, muscarinic acetylcholine, prostaglandin G/H are clozaril and zyprexa also called clozapine and olanzapine are both antipsychotic agents.

Bioinformatics Data Analysis

Crystal structure retrieval: The coordinate files required for docking studies, like cytochrome P450 (CYP) 2C19 with PDB Id: 4GQS (considered as wild type) and structure of the human MRP1 nucleotide binding domain 1(PDB Id: 2CBZ) were downloaded from Protein Data Bank (http://www.rcsb.org/pdb/home/home.do).[17] Both the structures were individually considered for docking against drug molecules azathioprine, clozaril, diclofenac, diflucan, furosemide, indomethancin, metformin, micardis and zyprexa. Structures of all the drugs were retrieved from Pubchem (http://pubchem.ncbi.nlm.nih.gov/search/search.cgi.).[18]

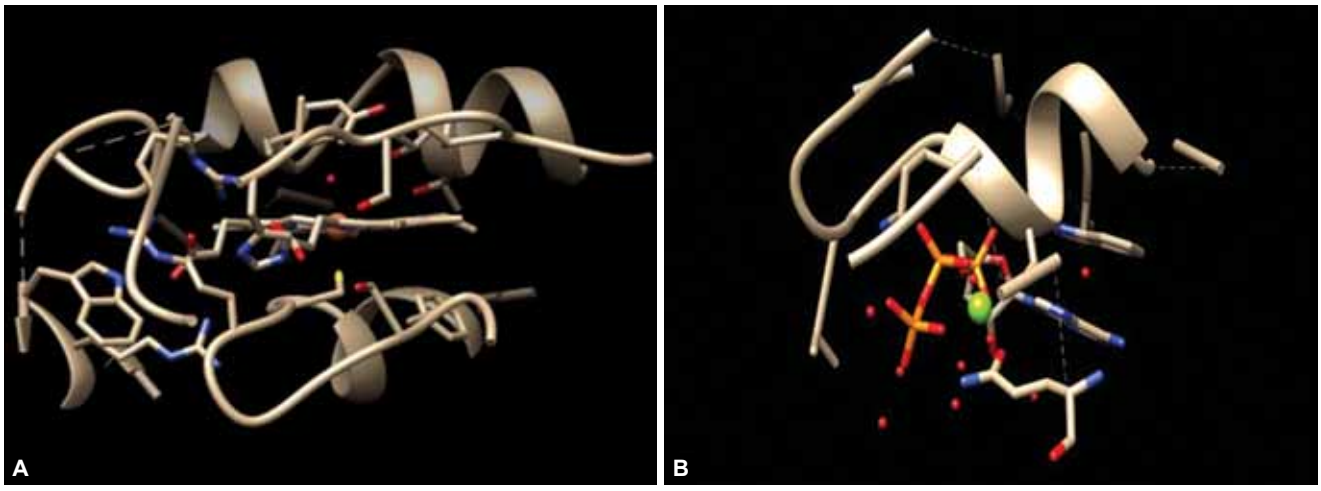
Pocket identification: The volume of the active sites was investigated using POCASA 1.0 software http://altair.sci.hokudai.ac.jp/g6/service/pocasa/[19] which was further confirmed using iGEMDOCK http://gemdock.life.nctu.edu.tw/dock/[20] These pockets were separately investigated for their overall volume both in wild and the mutant, which includes 4GQS and 2CBZ respectively.

Docking studies: Both the downloaded structures of 4GQS (wild) and 2CBZ (multidrug resistance: MDR) were considered for docking. The drug molecules considered here were already retrieved from Pubchem database. The software iGEMDOCK (Yang and Chen, 2004) was then used to dock the proteins and drugs to find the binding affinity and the residual interactions. This tool generally computes a ligand conformation and orientation relative to the binding site of target protein based on the generic evolutionary method (GA). Further, they opt for better post screening analysis and pharmacological based interaction instead of mere residual interactions. Additionally, this software is also involved in forming binding pockets with specific physiochemical properties of the target protein. This docking study followed the rough docking protocol, which is fast with their population size of 150 with the number of generated solution = 1. The generation number was maintained at 70.

RESULTS

Identification of pocket size: To begin with, the coordinate files of cytochrome 450 in wild and mutant state was considered for docking. But before that, the active site was identified using POCASA 1.0 the volume of the cavities were 412Å^3, 48Å^3 and 30Å^3 in wild type (4GQS). Next, the multidrug resistant protein (2CBZ) shows a pocket size of 70Å^3. Thus, there is a reduced pocket cavity observed in multidrug resistant protein which may not allow the binding of the drugs in to the pocket. But a better understanding of this could be only possible through docking studies. The overall active site cavity of 4GQS and 2CBZ is shown in (Figs 1A and B).

Protein-ligand docking: Docking studies were instigated using iGEMDOCK software. Both wild (4GQS) and the MDR CYP450 (2CBZ) were considered as the receptor proteins. In addition to this, the downloaded drugs were



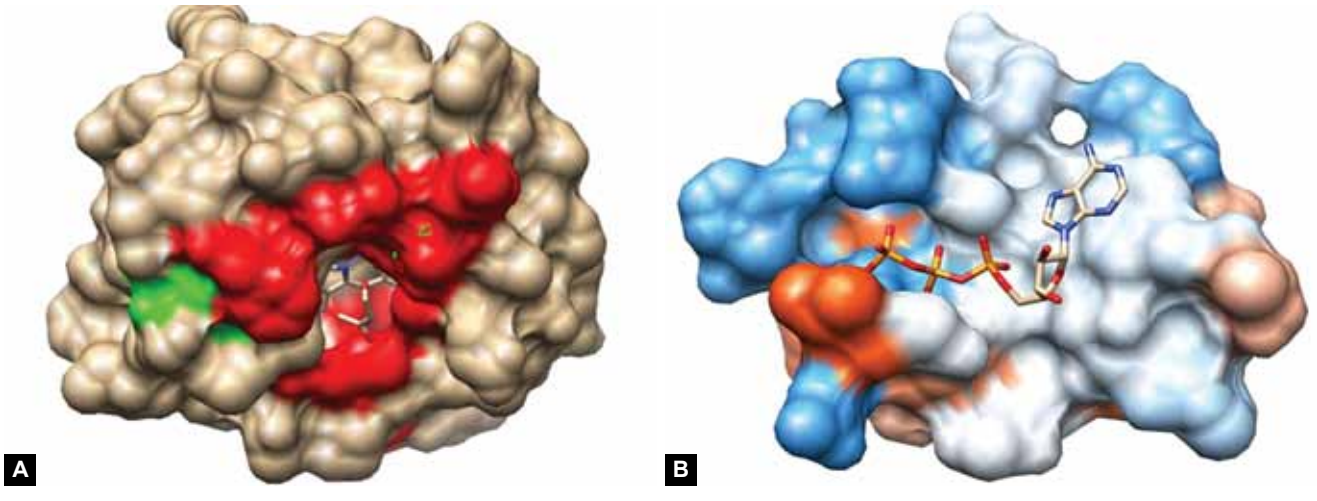
Figs 1A and B: (A) Active site for protein 4GQS and (B) cav2CBZ_ATP.pdb

targeted against these receptors through rigid docking methods. Here all the selected ligands will be docked against the warfarin and ATP binding site of wild and DR receptors respectively.

Residual interactions: For MRP1, even though it showed lesser binding scores for drugs azathioprine, indomethacin, diflucan and furosemide. But still, they are not able to interact within the pocket, leaving it empty during docking studies. Residual interactions between mutant protein 2CBZ MRP1 and drugs are shown in Table 2. Figure 2B shows the surface structure of the cavity after docking with protein 2CBZ with their active

Table 2: Residual interactions with wild protein 4GQS and mutant protein 2CBZ

Drug	*Binding energy in kcal/mol for protein 4GQS*	*Residual interactions in 4GQS*	*Binding energy kcal/mol for protein 2CBZ*	*Residual interactions in 2CBZ*
Azathioprine	– 87.5	Arg 97; Ser 365; Pro 427; Arg 433	– 82	Gln 713; Gln 774; Asp 793; Ser 796
Clozaril	– 102.5	Ala 297	– 68.5	Lys 818; Asp 836
Diclofenac	– 78.6	NA	– 78.2	His 827
Diflucan	– 79.5	Ala 297; Thr 301; Pro 427; Cys 435; Gly 437	– 78.9	Val 708; Leu 727; Phe 728; Arg 780; Ala 781
Furosemide	– 74	Asp 293; Leu 295; Gly 296	– 72.3	Ser 828; Ser 830; His 872
Indomethacin	119.2	Arg 97; Arg 433	– 79.9	Gly 762; Lys 773
Metformin	– 67.3	Ala 297; Gly 298; Thr 301; Thr 302; Glu 444; Gly 437	– 63.8	Leu 795; Ser 796; Val 798; Asp 799
Micardis	1267.4	Phe 114; Asp 360; Ile 362	822.2	Ala 693; Pro712; Gln 714
Zyprexa	– 101	Arg 97; Ala 297; Cys 435	– 71.5	Gly 671; Lys 818; Asp 836



Figs 2A and B: (A) Surface structure of the active site cavity of CYP 450 2C19 with interfacial residues in red color and noninterfacial residue in soluble domain (in green color) and (B) the active site of protein 2CBZ with bound ATP

site docked with ATP. For the mutant protein MRP1, all the drugs have binding affinities range between –60 and –90 kcal/mol except Micardis which is a non binding drug and an outlier.

During this study, the wild type protein cytochrome P450 showed better interactions with drug indomethacin with a maximum score of –119.2 kcal/mol followed by drug clozaril with a score of –102.5 kcal/mol. This was finally followed by of drug zyprexa with a score of –101.0 kcal/mol. The residues which are actively involved with the drug Indomethacin include Arg97 and Arg433. This was followed by drug clozaril which shows interaction with Ala297. For drug Zyprexa the residues Arg97, Ala297 and Cys435 interact with the protein. Residual interactions between wild protein cytochrome and all the drugs is shown in Table 2. For the wild protein, drugs with binding affinities ranges between –60 and –90 kcal/mol are metformin, furosemide, diclofenac, diflucan and azathioprine. Drugs with binding affinities ranges between –91 and –120 kcal/mol are zyprexa, clozaril and indomethacin. Micardis with score of positive 1267.4 kcal/mol is a nonbinding drug and an outlier.

Surface structure of the active site cavity of CYP 450 2C19 with interfacial residues in red color and non-interfacial residue in soluble domain (in green color) is shown in Figure 2A. The functional site as predicted by SPPIDER http://sppider.cchmc.org/[21] showing solvent accessibility based protein-protein interface identification and recognition of the iGEMDOCK predicted residues is shown in Table 3 with the coloring same as Figure 2A.

The surface structure of the active site of the protein MRP1 (2CBZ) with bound ATP molecule is shown in Figure 2B. The red color denotes negative residues, blue color positive residues and white color neutral residues.

DISCUSSION

Drugs with reported kidney failure associated with mortality is due to protein like 'cytochrome p450 2c19'. In the present study, docking studies showed some interesting binding patterns in the protein. For wild type, drugs like clozaril (clozapine), indomethacin and zyprexa (olanzapine) showed better binding scores due to larger binding site. However, in MDR, due to smaller cavity, all these drugs could not bind effectively. This study has shown that the increase in volume or size of cavity allows drugs to bind with a better binding score compared to the smaller cavity. With better binding, the active site gets blocked, hence the toxicity increases. The compounds with better binding score exhibits higher binding energy and more hydrogen bonds are the potential inhibitors of the enzyme cytochrome which agrees with the previous report.[22] If the binding is strong the active site is blocked, hence the toxicity increases. The compounds which have a high binding score, high binding energy and have more hydrogen bonds are the best inhibitors of the enzyme CYP2C19 which agrees with the previous report.[22] More studies are needed to further understand the role that cytochrome P450 plays in renal injury.

Table 3: Functional site predicted

Details of the type of interactions for residues of 4GQS						
Residue number	97	114	293	295	296	297
Amino acid	R	F	D	L	G	A
Average probability	44	95	96	97	97	96
Number of neural networks voted	3	10	10	10	10	10
Type of interaction	Noninterfacial residue in soluble domain	Interfacial	Interfacial	Interfacial	Interfacial	Interfacial
Residue number	298	301	302	360	362	365
Amino acid	G	T	T	D	I	S
Average probability	92	85	0	88	88	52
Number of neural networks voted	10	10	0	10	10	5
Type of interaction	Interfacial	Interfacial	Buried residue	Interfacial	Interfacial	Interfacial
Residue number	427	433	435	437	444	—
Amino acid	P	R	C	G	E	—
Average probability	75	40	90	79	80	—
Number of neural networks voted	10	3	10	10	10	—
Type of interaction	Interfacial	Noninterfacial residue in soluble domain	Interfacial	Interfacial	Interfacial	

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ORIGINAL ARTICLE

Geriatric Depression and Associated Risk Factors: A Cross-sectional Study in an Urban Setting

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ABSTRACT

The geriatric population in India is steadily rising over the past years. The healthcare sector in India has been focusing on somatic age related diseases, neglecting psychological disorders faced by this population. Depression is the most common psychiatric disorder in this group and is frequently under diagnosed because its symptoms are not reported considering them to be age related. Changing cultural traditions and emergence of nuclear families in urban areas of India has left the elderly lonely and insecure, making them more prone to depression. In this view, a study was conducted to assess the prevalence of depression in apparently healthy elderly living in a city and to find the associated risk factors.

A cross-sectional study was conducted where 100 elderly (≥ 60 years) were interviewed by visiting old age homes and residential areas located in Panvel, Navi Mumbai. The geriatric depression scale-short form (GDS-SF) was used to assess their depression status. Various sociodemographic factors were analyzed to see their association with depression.

In this study, 31% of the participants suffered from depression (GDS score >5). A significant association was observed between depression and the risk factors: age, education, place of residence and comorbid conditions. No significant association was observed with gender, marital status, family type or financial status.

The study shows that the prevalence of geriatric depression is moderately high even in urban settings in India. With increasing geriatric population, there is a need for greater attention toward the elderly and formulation of welfare services toward their betterment.

Keywords: Depression, Geriatric depression scale, Geriatrics, Urban population.

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INTRODUCTION

India is in a phase of demographic transition as the percentage of elderly population (≥60 years) has been steadily rising over the past years and has gone up from 6.0 to 8.3 % respectively during 1991 to 2012.[1] With increasing geriatric population, the burden of geriatric health problems is also increasing. The healthcare sector in India has been focusing on somatic age related diseases like hypertension, diabetes mellitus, coronary artery disease, etc. However, the psychological disorders faced by elderly are neglected majority of the times, considering them to be a by-product of the natural process of ageing. Among these psychiatric problems, depression is the most common as found in a number of studies.[2,3] World Health Organization (WHO) reports that in 2004 there were 0.5 million adults aged ≥60 years with moderate or severe depression in high income countries and 4.5 million in low and middle income countries.[4] Studies have revealed that the prevalence rates for depression in community samples of elderly in India vary from 6 to 50%.[5] Nevertheless, depression in elderly is under diagnosed because its symptoms are erroneously assumed to be age related and are not reported. These patients hardly ever seek medical attention and often suffer from the consequences of depression, such as poor quality of life, impairment in activities of daily living, cognitive decline, increased non-suicide mortality, increased use of health and home care services, etc.[6]

With a change in social scenario and cultural traditions in urban areas of India, elderly who were once the most respected and cared for members of the family are now increasingly facing problems. Moreover, the emergence of nuclear families has left the elderly lonely and insecure, making them more prone to depression. There have been a number of studies which show that depression in elderly is not a part of ageing but a disorder which can be treated or prevented by addressing the risk factors leading to it.[7,8] In this view, this study was conducted to assess the prevalence of depression in apparently healthy elderly living in urban areas and to find the association of geriatric depression with sociodemographic characteristics, place of residence and other risk factors like multiple comorbidities.

METHODS

A cross-sectional, observational study was conducted in Panvel City of Navi Mumbai, Maharashtra, during the months of June and July 2014. In this study elderly have been defined as those above 60 years of age. The presence of factors like chronic pain, severe limitation of mobility or inability to communicate with others due to audiovisual handicap is often a cause of depression in elderly. In order to eliminate bias due to the above mentioned factors while determining the association of depression with sociodemographic characteristics and place of residence, an inclusion and exclusion criteria was formulated and the study population was limited to the elderly who were able to perform the activities of daily living (ADL) with minimal assistance. Those who were above 90 years of age, bedridden, and suffering from severe debilitating disease or audiovisually handicapped were excluded from the study.

The study area has a geriatric population of 33417. For calculation of sample size, previous studies were considered which show prevalence rates varying from 6 to 50%.[5] Hence, sample size was calculated considering the prevalence of depression to be 6%. A sample size of 100 was calculated at 95% confidence limit and ± 4.65% as desired level of accuracy. Consenting participants were interviewed by visiting three randomly selected old age institutions located in the city and by conducting door to door visits in the residential areas of the city. Forty elderly residing at the old age institutions matched our inclusion and exclusion criteria and the remaining 60 were obtained from the community.

A predesigned questionnaire was used to evaluate sociodemographic characteristics of the participants and the geriatric depression scale-short form (GDS-SF) was used to assess their depression status.[9-11] The GDS was interpreted by taking a score of 0 to 5 as normal and a score greater than 5 as suggestive of presence of depression. A score greater than 10 was taken to be suggestive of severe depression. Cognition of the participants was assessed by performing a simple 4 word recall test and those who were unable to recall more than one word after the distractor activity were excluded from the study as the GDS cannot be used in the cognitively impaired elderly. Various sociodemographic factors like age, gender, marital status, education, place of residence, type of family, financial status and comorbidities were analyzed to see whether they have any association with depression.

STATISTICAL ANALYSIS

Data were entered in Microsoft excel and analyzed. Chi-square test was used to find the association between variables. A p-value of < 0.05 was considered to be statistically significant.

RESULTS

The sociodemographic characteristics of the participants have been presented in Table 1. Out of 100 participants who consented for the study, majority belonged to the age groups 71 to 80 years (38%) and above 80 years (40%) and only 22% were in the age group 61 to 70 years. The number of males (47%) and females (53%) was comparable. Forty-four percent of the participants were married and 41% were either widowed or had separated from their spouse. Majority of the participants had received secondary schooling or less (44%) and one third (33%) were graduates. In the present study, approximately 60% of the participants stayed with their family and 40% stayed in old age institutions. More than half of the elderly (56%) belonged to a joint family and 65% were financially independent. The participants were interviewed regarding chronic comorbidities like hypertension, diabetes, coronary artery disease, insomnia, joint pain, constipation, asthma, frequent micturition and it was found that 63% suffered from hypertension and more than one third suffered from joint pain, insomnia

Table 1: Sociodemographic characteristics of the participants

Variable		*Total % (n = 100)*
Age	61–70 years	22
	71–80 years	38
	81–90 years	40
Gender	Male	47
	Female	53
Marital status	Married	44
	Unmarried	15
	Separated/widowed	41
Education	Up to secondary School	45
	Matriculate or up to high school	22
	Graduate and above	33
Place of residence	Family	60
	Old age institution	40
Family type	Joint/with children	56
	With spouse	26
	Alone	18
Financial status	Dependant	35
	Nondependant	65
Number of chronic comorbidities	≤2	48
	3–4	22
	≥5	30

and heart disease. Forty-eight percent of the participants suffered from 2 or less comorbidities and 30% suffered from more than 5 comorbidities.

Out of the total elderly participants interviewed, 31% of the participants suffered from depression (GDS score >5) and 69% were normal (Table 2). Out of 100, 16 participants (16%) suffered from mild depression (GDS score 6–9) and 15 participants (15%) suffered from severe depression (GDS score >10).

The association of geriatric depression with various sociodemographic variables is summarized in Table 3. Depression was more common in the age groups 81 years and above (40%) and 71 to 80 years (34.2%) and the association of depression with age was statistically significant (p = 0.036). Depression was significantly higher in elderly who were illiterate or who had received secondary schooling only (46.6 %) as compared to those who had matriculated (22.7%) or graduated (5%) (p = 0.007). Place of residence also had significant association with geriatric depression (p = 0.042) which was higher in those who were staying away from their family in old age institutions (42.5%). The presence of chronic comorbidities was significantly associated with geriatric depression (p = 0.004), with more number of depressed in the group of participants having >5 comorbidities (56.6%) and 3 to 4 comorbidities (31.8%). No statistically significant association was observed between depression and other variables assessed in this study, such as gender, marital status, family type or financial status.

Table 2: Assessment of depression in elderly on the basis of geriatric depression score

Depression assessment based on GDS score		*n (%)*
Depression present	Depressed (score >5)	31 (31%)
	Mildly depressed (score 6–9)	16 (16%)
	Severely depressed (score ≥10)	15 (15%)
Depression absent	Normal (score ≤5)	69 (69%)

DISCUSSION

The prevalence of depression in this study was 31%. Studies have revealed that the prevalence rates for

Table 3: Comparison of depressed and nondepressed elderly and their association with various risk factors

Variable		*Depression present- GDS ≥ 5*	*Depression absent- GDS < 5*	*Chi-square*	*p-value*
Age	61–70 years	2 (9.0)	20 (90.9)	6.63	0.036*
	71–80 years	13 (34.2)	25 (65.7)		
	81–90 years	16 (40.0)	24 (60.0)		
Gender	Male	17 (36.1)	30 (63.8)	1.10	0.290
	Female	14 (26.4)	39 (73.5)		
Marital status	Married	10 (22.7)	34 (77.2)	2.68	0.260
	Unmarried	5 (33.3)	10 (66.6)		
	Separated/widowed	16 (39.0)	25 (60.9)		
Education	Up to secondary school	21 (46.6)	24 (53.3)		
	Matriculate or up to high school	5 (22.7)	17 (77.2)	9.74	0.007*
	Graduate and above	5 (15.1)	28 (84.8)		
Place of residence	Family	14 (23.3)	46 (76.6)	4.121	0.042*
	Old age institution	17 (42.5)	23 (57.5)		
Family type	Joint/with children	18 (32.1)	38 (67.8)		
	With spouse	5 (19.2)	21 (80.7)	3.28	0.198
	Alone	8 (44.4)	10 (55.5)		
Financial status	Dependent	12 (34.2)	23 (65.7)	0.27	0.60
	Independent	19 (29.2)	46 (70.7)		
Number of chronic comorbidities	≤2	8 (16.6)	40 (83.3)	15.29	0.0011*
	3–4	7 (31.8)	15 (68.1)		
	≥5	17 (56.6)	13 (43.3)		

*Statistically significant at p < 0.05 (*Note*: Figures in parenthesis show the percentages)

depression in community samples of elderly in India vary from 6 to 58%.[5,12-14] A meta-analysis of various study reports done found the median prevalence rate of depression among Indian elderly to be 21.9%.[7] A study done in Surat city reported a prevalence rate of 39.04%[12] while another study done in urban Pune found a prevalence rate of 21.2%.[15] Our study reported a lower prevalence rate of depression as compared to studies done in rural areas which report rates as high as 47%[16] and 61%.[13] This may be due to the exclusion of severely ill and audiovisually handicapped elderly from the study and a small sample size. Other factors like higher educational qualification, lower rates of financial dependency, more awareness, better availability of health services and better quality of life in urban areas may also be a reason for this finding.

In the present study, the prevalence of depression was found to increase significantly with increasing age. The prevalence of depression was only 9% in the age group 61 to 70 years, 34.2% in the age group 71 to 80 years and as high as 40% in the above 81 years age group. Similar findings were seen in a study already published where high prevalence of depression was seen especially after 69 years of age.[16] This may be because, with increase in age there are increased difficulties in performing activities of daily living which lead to dependency on others for assistance. Also, increased age is accompanied by increased health problems and increased widowhood.

Depression showed no association with gender in our study which is in contrast to a number of studies in India which suggest that prevalence of depression was higher in females.[13] A quantitative meta-analysis of relevant articles published from January 1967 to June 2001 revealed female gender to be one of the 5 risk factors for depression in the elderly.[17] This contrast may be due to the fact that this study was performed in urban population where females were better educated and less financially dependent.

Our study showed that those who were widowed/ separated from their spouse showed high prevalence of depression (39%) as compared to only 22.7% in married elderly. Unmarried elderly also showed a high prevalence of depression (33.3%). However, the difference was not statistically significant. Similar results have been seen in other studies.[12-13,15] This is because those who were married felt a sense of companionship in sharing the experiences of old age and were less lonely.

As seen in another study, level of education was associated with depression in our study as well.[16] The prevalence of depression was lowest in those who had completed their graduation (15.1%), slightly higher in those who had matriculated or attended high school (22.7%) and highest in those who were illiterate or had only received secondary schooling (46.6%). This may be attributed to higher financial dependency of the illiterate elderly. Also those who have received higher education, have more means of leading a productive life by keeping themselves engaged even after retirement.

Depression was found to be more common in those living in old age institutions (42.5%) as compared to those living with their family (23.3%). This is in accordance with a study which showed that more than half of the inhabitants of old age institutions suffer from one or the other mental problems.[2] It had been observed in a study that depression is more common in old age homes (25.71%), followed by those living in the affluent areas (22.8%) and those living in the slums (11.4%).[12]Another study conducted in the old age homes of Lucknow city showed a prevalence rate of 37.7%.[2] The reason could be restricted environment of institutions, lack of family support, insecurity and loneliness.

In this study, 44.4% of those living alone were depressed as compared to 32.1% of those living in joint family and 19.2% of those living with spouse. However, family type could not be proved as a statistically significant risk factor for depression as the sample size was small. Similar results were seen in another study.[15] Higher prevalence of depression among those living alone as compared to those living in a joint family may be due to perceived loneliness, less sociability and lack of support from family members who can act as caretakers in times of need.

No significant association of depression could be traced with financial status while conducting the study. However, a few studies reveal that higher rates of depression are associated with financial dependency.[15,16] This may be because most of the participants in our study belonged to monetarily sound urban families and were mostly financially independent (65%).

A majority of those who suffered from multiple chronic comorbidities suffered from depression as well. More than half of those who suffered from >5 comorbidities (56.6%) suffered from depression and 31.8% of those having 3 or 4 comorbidities suffered from depression. Thus, depression showed a strong correlation with presence of multiple comorbidities supporting the findings of other studies which report that depression is often accompanied by minimum 2 to 3 other clinical diagnoses.[2,5,13,15] This may be due to the stress caused by chronic pain, social and physical restrictions that result in isolation, financial burden of treatment, and decreased quality of life.

LIMITATIONS

This study may have over-estimated the prevalence of depression since no formal method of diagnosis was employed. The tool used for assessment of depression in this study GDS-SF is merely a screening tool and cannot be used to replace clinical diagnosis. A number of factors were found to be significantly associated with depression in this study. Since the sample size of this study was very small the findings may not be generalized for the entire Indian urban population and studies on a larger scale are needed to substantiate the observations.

CONCLUSION

The study shows that the prevalence of geriatric depression is moderately high even in the urban population of India. A definite association between risk factors such as; age, education, place of residence, comorbid conditions and depression has been established from this study. With the ever increasing geriatric population of India, there is a need for greater attention toward the physical as well as psychiatric problems faced by this group. More studies need to be conducted in the urban elderly population and these risk factors need to be looked into while formulating welfare services for the elderly.

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ORIGINAL ARTICLE

Aortic Stenosis in Elderly—A Clinical and Two-dimensional Echocardiogram Correlated Study

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ABSTRACT

Introduction: Aortic valve stenosis (AS) is a common disease in elderly. The prevalence of severe AS in the general population is 2% in 72 years and increases to 8% in 85 years old. With the aging of the population, these patients will be seen more and more in clinical practice. Several clinical factors have been found to be associated with the presence and the progression of the stenosis.

Aims: To study clinical and echocardiography (ECG) profile of aortic stenosis in elderly.

To evaluate etiologies of aortic stenosis in elderly.

To study comorbidities in association with aortic stenosis in elderly.

Method: Randomized prospective study of 100 patients.

Conclusion: Though increasing age is likely to increase the degenerative changes, elderly patients of 61 to 71 years are the commonest group with aortic stenosis (symptomatic as well as asymptomatic) in the present study. Male sex is more associated with aortic sclerosis and stenosis. There are significant correlation of past smoking, and present smoking in development of aortic sclerosis and stenosis. Hypertension, coronary artery disease, diabetes mellitus are common comorbidities associated with aortic sclerosis and stenosis.

Keywords: Aortic sclerosis, Aortic stenosis, Hypertension, Left ventricular hypertrophy.

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INTRODUCTION

Aortic valve stenosis (AS) is a disease of the heart valves in which the opening of the aortic valve is narrowed. The aortic valve is the valve located between the left ventricle of the heart and the aorta, the largest artery in the body, which carries the entire output of blood to the systemic circulation.[1] Aortic valve stenosis is a common disease in elderly. The prevalence of severe AS in the general population is 2% in 72 years and increases to 8% in 85 years old. With the aging of the population these patients will be seen more and more in clinical practice.[2]

Age-related calcific (formerly termed senile or degenerative) AS of normal trileaflet valve is now the most common cause of AS in adults.[7,8] In a population-based echocardiographic study, 2% of persons 65 years of age or older had frank calcific AS, whereas 29% exhibited age-related aortic valve sclerosis without stenosis, defined by Otto et al[3] as irregular thickening of the aortic valve leaflets detected by echocardiography (ECG) without significant obstruction. Aortic sclerosis is the initial stage of calcific valve disease and, even in the absence of valve obstruction, is associated with a 50% increased risk of cardiovascular death and myocardial infarction. Several clinical factors have been found to be associated with the presence and the progression of the stenosis.[4,13-15]

The stenotic process is usually gradual in onset and progression, giving the heart ample opportunity to respond. The left ventricular myocardium becomes hypertrophic, which leads to a greater pressure during systole, which in its turn forces blood past the mechanical obstruction. As a result, the cardiac output and left ventricular end-diastolic volume are maintained for a prolonged period despite the presence of a systolic pressure gradient between the left ventricle and peripheral arterial system.[11,12] However, as hypertrophy continues to progress, the left ventricle becomes less compliant. Left ventricular end-diastolic pressure can become elevated even though the ventricular size remains normal.[2]

Elderly patient with AS remains asymptomatic for a long time despite the obstruction and the pressure overload. Once the patient has developed one of the typical symptoms angina,[17] syncope or shortness of breath, life expectancy is limited. The only possible treatment is replacement of the calcified valve by a mechanical or bioprosthesis, a major procedure in these patients.[16,18,19] Clinical decision making, however, can be very difficult.[4,5]

Though there are ample studies regarding aortic stenosis in elderly population in western countries, similar studies in Indian subcontinent are lacking. In

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view of this the present study is undertaken to evaluate aortic stenosis, the common valvular disease in elderly patients which is growing exponentially.

AIMS AND OBJECTIVES

- To study clinical and echocardiographic profile of aortic stenosis in elderly.
- To evaluate etiologies of aortic stenosis in elderly (degenerative/rheumatic/congenital/other).
- To study comorbidities in association with aortic stenosis in elderly.

METHODOLOGY

Material

This prospective randomized study includes a total of 100 outpatients and inpatients from all departments, in age group of 60 years and above including both sexes.

On 1st visit:

Enrolment of the patient

Consent of the patient

History

Clinical examination:

Basic lab investigations, X-ray chest and ECG

Plan for the follow-up visits

On 2nd visit:

Lab investigations review

Performance of 2D ECG and color Doppler study and Interpretation of the results according to severity of aortic stenosis. (Aortic valve area and mean pressure gradient across the stenotic valve).[24]

Inclusion and Exclusion Criteria

Sample size: Hundred patients attending MGM Hospitals, Kamothe, as outpatients and inpatients of all wards/departments on the basis of the inclusion and exclusion criteria.

The study has been conducted for a period of 2 years from November 2012 to October 2014.

Inclusion Criteria

- Age 60 years and above
- Ejection systolic murmur in aortic area.

Exclusion Criteria

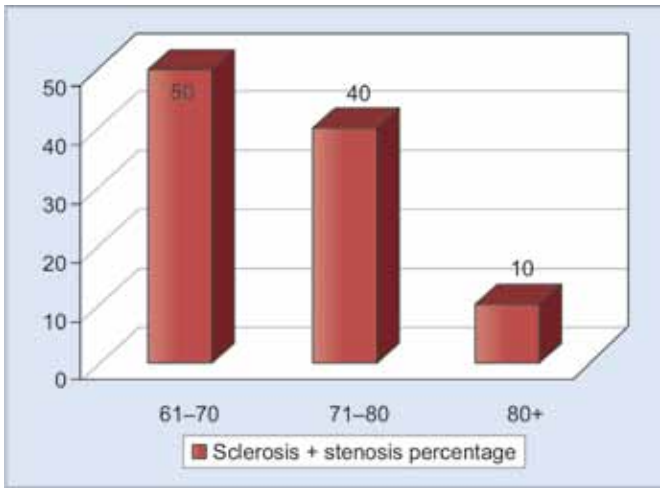
- All the patient below the age of 60 years
- Any known case of cardiomyopathy.

RESULTS

Out of total 100 patients having ejection systolic murmur in aortic area, 67 patients of aortic sclerosis and stenosis are found. In our study 33 patients (50%) are in the age group 61 to 70, 27 patients (40%) are in the age group 71 to 80 and 7 (10%) above the age above 80 years. Out of total 67 patients with aortic stenosis, 35 patients (52%) are males, 32 patients (48%) are females. Remaining 33 patients had systolic murmur at aortic area which could not be attributed to pathology at the aortic valve *per se*. Out of 67 patients, 23 patients had true aortic stenosis evident on ECG while other 44 patients had sclerotic aortic valve without significant obstruction (Graph 1).

In our study, 32 patients (47%) are having dyspnea as presenting symptom, 10 patients (15%) angina, 5 patients (7%), syncope respectively (Table 1). Total 39 patients (58%) are smokers, 31 patients (46%) are past smokers and 8 patients (12%) are current smokers respectively. Total 29 patients (44%) are hypertensive, 38 patients (56%) are non-hypertensive.

Eleven patients (17%) are diagnosed to have diabetes. 27 patients (40%) have coronary artery disease (CAD), 40 patients (60%) are normal. The mean high-density lipoprotein (HDL) observed is 54 with systolic dysfunction (SD) 15.3, the mean low-density lipoprotein (LDL) is 95 with SD 20.2 respectively. Seven patients (10%) have serum creatinine levels > 2, 60 patients (90%) have creatinine levels < 2 respectively. Hypertension (HT), CAD, diabetes mellitus (DM), left ventricular (LV) SD, chronic obstructive pulmonary disease (COPD), renal dysfunction is the major, comorbidities associated with aortic sclerosis and stenosis in present study (Graph 2).

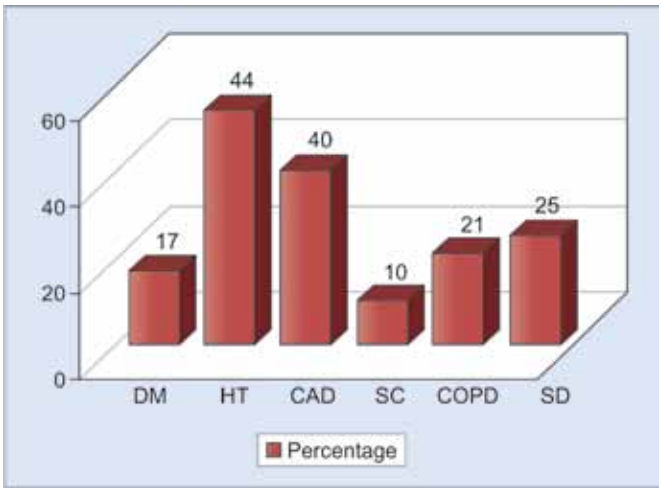


Graph 1: Distribution of data by age-group of sclerosis + stenosis

Table 1: Distribution of data by symptoms

Symptoms	*Number of cases*	*Percentage*	*p-value*	*Result*
Dyspnea	32	47	0.000	HS
Angina	10	15	0.004	S
Syncope	05	7	0.06	NS
Total	47	69		

HS: Highly significant; S: Significant; NS: Not significant



Graph 2: Percentage distribution of associated comorbidities

Mitral regurgitation (26%) and aortic regurgitation (20%) are mainly associated valvular diseases associated with aortic sclerosis and stenosis in present study.

Out of total 23 patients of aortic stenosis, 9 patients (40%) have mild stenosis, 11 patients (47%) have moderate stenosis and 3 patients (13%) have severe stenosis. Forty patients (60%) have normal ejection fraction, 27 patients (40%) have ejection fraction < 50% (Table 2). Sixty patients (89%) have degenerative causes, 7 patients (11%) have other causes of development of aortic sclerosis and stenosis.

Echocardiography changes with left ventricular hypertrophy (LVH) and strain pattern is seen in 22 (34%) patients. Age group of the patients is compared with severity of aortic stenosis. Severe aortic stenosis is seen in 10% patients between the age 61 and 70, 11% in the age 71 and 80, 50% in above 80 (Table 3) Clinical and two-dimensional echocardiogram (2D echo) correlation shows age of patients has significant correlation with degenerative changes and development of aortic sclerosis and stenosis (p = 0.001). There is significant correlation between age of the patients and symptoms associated with aortic sclerosis and stenosis (p = 0.001), 2D echo changes and aortic sclerosis and stenosis (p = 0.001).

Table 2: Distribution of data by 2D echo

2D echo	*Number of cases*	*(%)*	*Aortic jet velocity (m/s)*	*p-value*	*Result*
Mild	9	40	2.6–2.9	0.003	S
Moderate	10	47	3.0–4	0.001	HS
Severe	4	13	> 4	0.004	S
Total	23	100			

S: Significant; HS: Highly significant

Table 3: Distribution of data by age-group and severity of aortic sclerosis and stenosis

Age group	*Mild stenosis*	*Moderate stenosis*	*Severe stenosis*	*p-value*	*Result*
61–70	6	3	1	0.06	NS
71–80	3	5	1	0.07	NS
80+	0	2	2	0.002	S
Total	9	10	4		

NS: Not significant; S: Significant

DISCUSSION

Our study includes total 100 patients above the age 60 years with ejection systolic murmur in aortic area. Patients with cardiomyopathy were excluded. We found total 67 patients of aortic sclerosis and stenosis age, sex, smoking, hypertension, diabetes mellitus, CAD, serum creatinine, cholesterol, LV ejection fraction were studied as clinical factors and comorbidities associated with development of aortic sclerosis and stenosis in each patients. Causes, symptoms associated with aortic sclerosis and stenosis with their percentage distribution are studied. Two-dimensional echocardiogram findings in each patient were studied individually. Valvular heart diseases associated with aortic sclerosis and stenosis is studied. Correlation between various variables like age, 2D echo findings, and symptoms shows significant association. In our study, 17% patients are diabetic, 52% patients are hypertensive, 40% patients are affected by CAD, serum creatinine is >2 in 10% patients, 21% are affected by chronic obstructive pulmonary disease, LV systolic dysfunction in 25% patients. The findings regarding comorbidities are consistent with the previous studies.[3,5,21,23]

With regard to the degree of stenosis, the moderate stenosis has been observed in 30% patients in the age group 61 to 70, 67% in the age group 70 to 80, 50% in the age group above 80. Severe stenosis has been found in 10% patients in age group of 61 to 70, 11% in age group of 71 to 80 and 50% in age group above 80. These findings are similar to findings of euro heart survey.[9,10]

Faggiano[6] et al show marginal revenue (MR) in 32.5% patients, Lindroos et al[2] show 27% patients with average revenue (AR). In our study, 26% patients above the age 75 are affected by MR, 20% with AR respectively. Sixty patients (89%) have degenerative causes, 7 patients (11%) have other causes of development of aortic sclerosis and stenosis.

Echocardiography changes with LVH and strain pattern is seen in 22 (34%) patients. Clinical and 2D echo correlation shows age of patients has significant correlation with degenerative changes and development of aortic sclerosis and stenosis (p = 0.001). There is significant correlation between age of the patients and symptoms associated with aortic sclerosis and stenosis (p = 0.001), 2D echo changes and aortic sclerosis and stenosis (p = 0.001).

CONCLUSION

The aims and objectives of our study was to study the prevalence, clinical and ECG profile of aortic stenosis in elderly. Though increasing age is likely to increase the degenerative changes, elderly patients of 61 to 71 years are the commonest group with aortic stenosis (symptomatic as well as asymptomatic) in the present study. Male sex is more associated with aortic sclerosis and stenosis. There are significant correlation of past smoking, and present smoking in development of aortic sclerosis and stenosis.

Hypertension, CAD, diabetes mellitus are common co-morbidities associated with aortic sclerosis and stenosis. High levels of HDL and LDL, S. creatinine, Low ejection fraction though associated with aortic sclerosis and stenosis in other studies, no significant role in present study is found.

Moderate and severe stenosis is commonly seen in present study. Dyspnea and angina are mainly the significant presenting symptoms. With the increase in age of the patients, there is worsening of symptoms and the severity of aortic stenosis (moderate, severe) increases as seen in present study.

Degenerative changes are the commonest etiology in development of aortic stenosis in present study. Association of smoking, mitral regurgitation, hypertension, CAD, and diabetes mellitus signifies the role of degenerative and atherosclerotic changes in presence study.

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ORIGINAL ARTICLE

Anthropometric Profile in Relation to Playing Position of Elite Indian Soccer Players

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ABSTRACT

Background: Previous literature has demonstrated that each specialized playing position may have unique physical and physiological requirements. Body fat is highly related to playing position of football players.

Purpose: The purpose of the study was to examine differences among positions in body size and percent body fat of elite football players prior to the start of regular season.

Subjects: The subjects of this study were 34 (10 forwards, 10 midfielders, 10 defenders, 4 goalkeepers) normal, healthy elite football players without any orthopedic, respiratory or cardiovascular problems.

Methods: Anthropometric profiles of the subjects were determined by measuring height, weight, body mass index (BMI) and percent body fat. The prediction formula used to calculate percent body fat using BMI was: body fat % = (1.20 × BMI) + (0.23 × age) – (10.8 × gender) – 5.4 (R2 0.79, standard error estimate = 4.1% BF%), taking age and gender (male = 1, female = 0) into account.

Results: The results demonstrated significant differences ($p < 0.005$) in the percent body fat among the players of different playing positions. Goalkeepers possessed highest values for body fat percentage followed by defenders and forwards while midfielders had the least body fat percentage.

Conclusion: The study suggests that anthropometric characteristics differ in players of different playing positions. The differences found despite similar training protocol might be due to the physiological adaptations in the players.

Keywords: Anthropometric profile, Body mass index, Percent body fat, Playing position.

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INTRODUCTION

Soccer is the most popular and widely played sport globally.[1,2] There is a growing interest for this sport in India as well. However, the Indian national team is currently ranked 166 of 207 according to the Fédération Internationale de Football Association (FIFA). The ranking suggests that Indian playing standards need to be improved in line with three key areas namely physical, technical, and tactical skills. The sport is characterized by short sprints, rapid acceleration or deceleration, turning, jumping, kicking, and tackling.[3,4] The physiological demands of a given position in the team may not be linked directly to absolute fitness. The tactical role assigned to a player in that position is probably dictated by the physical capacity of that player. It is assumed that the game has developed to become faster, with more intensity and aggressive play than seen in the past. Elite soccer is a complex sport, and performance depends on a number of factors, such as physical fitness, psychological factors, player's techniques, and team tactics.

Team games are sports where body size, shape, body composition and level of fitness, all play an important part in providing distinct advantages for specific playing positions particularly at the highest level of performance where there is a high degree of player specialization.[5] Since the physiological as well as physical characteristics are important consideration in player performance,[6] the review focuses on the anthropometric and physiological characteristics of elite soccer players. A starting point in the search for outstanding talent is the use of profiles established for those who have been successful. These multifactorial profiles are sketched from observations on anthropometric, physiological and performance measures. Knowledge of these characteristics can provide clues as to the existence of biological prerequisites for playing at the highest standard. The degree to which physiological indices of performance capability prevail through growth and into adulthood is open to discussion. Physiological characteristics that have been reported as essential for football players are aerobic fitness, agility, muscle strength, speed, and explosive jumping

power.[7] One aim of body composition assessment is to differentiate and quantify different body compartments. In professional soccer, assessments are used alongside fitness measurements to determine physical preparedness for competition and to monitor the effects of training and dietary interventions on body composition status.[11]

Excess fat mass acts as a dead weight in activities in which the body is lifted repeatedly against gravity.[12] The fat-free compartment, which includes lean muscle mass and bone mineral mass, is important for the production of speed, strength and power, and for injury prevention.[13,14] Few descriptive studies are available that use quantitative analyses for body fat and % body fat) (e.g. underwater weighing) in National Football League (NFL) players, thus providing a further need for documentation of NFL players' body size and composition. Body fat is highly related to playing position of soccer players, as previous studies have demonstrated.[15] This is because of the different speed and movement demands of each position.

In the general population, differences in body composition are evident based on age,[16] gender,[17] physical activity,[18] ethnicity,[19,20] and disorders, such as metabolic and wasting diseases.[21] Previous research with elite soccer players has highlighted differences in body size and composition between individuals according to playing position, although the most notable differences were found between goalkeepers and outfield players, with only minor differences reported between outfield players.[22-24] The goalkeepers tended to be taller and heavier, with relatively more fat mass and less lean mass, than the outfield playing groups. These investigations used skin fold thickness or bioelectric impedance techniques to assess body composition, and results have yet to be confirmed using a more complex and sensitive measure, such as underwater weighing.

The database of physique and performance qualities of the players throughout the country is very important to make a national team. It is a fact that in India, there is still limited information of soccer players regarding physique and physiological profiles and performance according to the playing positions.

The purpose of this study was to find out the differences in the anthropometric characteristics of soccer players according to their respective playing positions.

SUBJECTS AND METHODS

Thirty-four healthy elite football players (10 forwards, 10 midfielders, 10 defenders, 4 goalkeepers) had furnished their consent to serve as subjects in the study. The procedure, benefits, and potential risks of study were explained to the participants before signing the informed consent form and starting the test. The study was approved by the Institutional Ethics Committee of Faculty of Sports Medicine and Physiotherapy, Guru Nanak Dev University, Amritsar.

The inclusion criteria included for the study were: subjects agreed with the purpose of the study, subjects had no existing musculoskeletal problems, such as lower limb fracture and sprain/strain, subjects had no recent injury to lower limb, subjects had no existing neurologic problems and subjects had no existing respiratory or cardiovascular system problems. The data collection was undertaken during the period of August to December 2013 in Guru Nanak Dev University Campus, Amritsar.

Body mass was measured to the nearest 0.1 kg with an electronic scale (Atco, India). Subjects were weighed in minimal clothing with bare foot. Height was measured with a Harpenden stadiometer (Holtain Ltd., Crymych, UK) to the nearest mm. Subject was asked to stand bare foot on horizontal surface. Heel touched the ground. Counter board of Stadiometer was brought down till it touches the vertex. The height of the subjects was recorded. Body mass index (BMI) was calculated from height and weight.[25]

Body fat percentage (BF%) of the participants was determined by anthropometric characteristics using BMI, taking age and gender (males = 1, female = 0). The prediction formula used was:

Body fat percentage = (1.20 × BMI) + (0.23 × age) – (10.8 × gender) – 5.4 25.

Independent test was used to find out the means, standard deviation and standard error mean for the studied physiological and physical characteristics of players of different playing positions. One way analysis of variance (ANOVA) (SPSS Inc., Chicago, IL version 17) was used in order to find out the differences among different playing positions. All significant differences reported were at $p < 0.01$.

RESULTS

The anthropometric characteristics of players of different playing positions have been illustrated in Table 1. The results of this study revealed statistical significant difference ($p < 0.001$) in the anthropometric characteristics among the players of different playing positions. The results demonstrated significant differences ($p < 0.001$) in the percent body fat among the players of different playing positions (Table 2). Goalkeepers possessed highest values for body fat percentage followed by defenders and forwards while midfielders had the least body fat percentage (Table 2).

Table 1: Anthropometric profile of players at different playing positions

	Forward (n = 4) mean ± SD	*Defender (n = 10) mean ± SD*	*Midfielder (n = 10) mean ± SD*	*Goalkeeper (n = 10) mean ± SD*
Age (years)	20.5 ± 1.84	19.9 ± 1.29	20.0 ± 0.67	21.0 ± 1.41
Weight (kgs)	59.5 ± 3.50	62.3 ± 3.02	57.4 ± 2.79	71.25 ± 6.29
Height (cms)	167.6 ± 2.84	169.8 ± 2.57	168.7 ± 1.42	171.0 ± 5.48
BMI	21.19 ± 0.83	21.58 ± 0.73	20.16 ± 1.11	24.15 ± 0.68

Table 2: Comparison of body fat percentage of players at different playing positions

	Forward (n = 4)	*Defender (n = 10)*	*Midfielder (n = 10)*	*Goalkeeper (n = 10)*
Mean ± SD	13.95 ± 1.04	14.27 ± 0.90	12.59 ± 1.37	17.60 ± 0.57

DISCUSSION

The data illustrated significant percent body fat differences among the players of different playing positions. The results supported our hypothesis that there exists significant difference in the anthropometric profile in relation to playing positions in elite Indian soccer players.

The results of this study postulated that goalkeepers possessed the highest body fat percentage compared to other playing positions. Defenders possessed the second highest body fat percentage followed by forwards. Midfielders had the least percent body fat compared to other playing positions. The findings may be because midfielders are more mobile throughout the game and covers greater distance of the ground compared to other playing positions. Goalkeepers being steady for the most part of the game justify their higher percent body fat than other playing positions.

The results of this study support the findings[22,24] that reported significant differences in the body composition of soccer players of different playing positions, with most differences being observed between goalkeepers and the outfield players. The goalkeepers were the tallest and heaviest of the soccer players, and demonstrated greater percent body fat than the outfield players.[11] The results of this study also support the findings[12] that investigated body fat with respect to playing position in soccer. They found very little difference in body fat percentage among the different outfield positions, although midfielders tended to have lower body fat levels. The percentage body fat values of the present groups were found (forwards: 21.5267 ± 0.90779, defenders: 26.5500 ± 2.22153, midfielders: 17.7333 ± 1.7382, goalkeepers: 31.8700 ± 3.21269). Midfield is a position in which players need to be mobile, as they are involved in many aspects of play. They cover more ground than their defensive and offensive team mates.

The distance covered by a group of soccer players was investigated.[26] The team was divided into midfielders and defensive and offensive players. Midfielders covered more ground [9137 (977) m] than defenders [8523 (1175) m] and offensive players [8490 (673) m]. Thus, present study showed the similar results that midfielders possessed lowest values for body fat percentage among all. Significant differences in age, stature, body mass and body mass index have been recently identified between elite players of different positions suggesting that players of particular size and shape may be suitable for the demands of the various playing positions. In this respect, positional role appears to have an influence on VO_2 max of an individual.

The study confirms that body fat is highly related to playing position of football players as demonstrated in previous studies. This is because of the different speed and movement demands of each position. The study demonstrated that each specialized playing position may have unique physical and physiological requirements. Knowledge of these characteristics can provide clues as to the existence of biological prerequisites for playing at the highest standard. Therefore, understanding the profile of successful players is valuable for talent identification; ensuring players are assigned to their optimal positions, and provide assistance in the design of conditioning programs.

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REVIEW ARTICLE

Tertiary Prevention of Ischemic Heart Disease: Post Coronary Artery Bypass Surgery

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ABSTRACT

Coronary heart disease is more prevalent in Indian urban populations and there is a clear declining gradient in its prevalence from semi-urban to rural populations. Epidemiological studies show a sizeable burden of coronary heart disease in adult rural (3–5%) and urban (7–10%) populations. Thus, of the 30 million patients with coronary heart disease in India, there would be 14 million who are in urban and 16 million in rural areas. In India, about 50% of coronary heart disease-related deaths occur in people younger than 70 years compared with only 22% in the West. Extrapolation of these numbers estimates the burden of coronary heart disease in India to be more than 32 million patients. In India, there are large spectrums of patients who present at tertiary stage when first examined. These patients are left with very little margin of safety. Heart disease is one of the commonest causes of mortality and morbidity worldwide. Coronary artery bypass graft (CABG) surgery is a frequently used cardiothoracic revascularization to treat coronary artery disease (CAD).

In addition to physical impairments and activity restrictions in the immediate postoperative period, patients encounter some obstacles to exhibit improvements in quality of life in the long run. Cardiac tertiary prevention programs generally consist of the prevention of disease progression and patient suffering. Aim of these interventions is to reduce the negative impact of disease by restoring function and reducing disease-related complications and therefore, include the rehabilitation of disabling conditions. Cardiac rehabilitation programs are interventions aimed to reduce mortality and morbidity of patients with ischemic heart diseases through promoting a healthier lifestyle among patients. These programs are used to restore, maintain, or improve both physiologic and psychosocial outcomes and finally the quality of life in patients through a combination of exercise, education and psychological support.

Keywords: Cardiac surgery, Cardiac tertiary prevention programs, Coronary artery bypass grafting, Coronary heart disease.

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INTRODUCTION

Coronary heart disease is more prevalent in Indian urban populations and there is a clear declining gradient in its prevalence from semi-urban to rural populations. Epidemiological studies show a sizeable burden of coronary heart disease in adult rural (3–5%) and urban (7–10%) populations. Thus, of the 30 million patients with coronary heart disease in India, there would be 14 million are in urban and 16 million in rural areas.[1-3] In India about 50% of coronary heart disease-related deaths occur in people younger than 70 years compared with only 22% in the West. Extrapolation of these numbers estimates the burden of coronary heart disease in India to be more than 32 million patients.[4] In India there are large spectrum of patients who present at tertiary stage when first examined. These patients are left with very little margin of safety. Heart disease is one of the commonest causes of mortality and morbidity worldwide. Coronary artery bypass graft (CABG) surgery is a frequently used cardiothoracic revascularization to treat coronary artery disease (CAD).[5] In addition to physical impairments and activity restrictions in the immediate postoperative period, patients encounter some obstacles to exhibit improvements in quality of life in the long run. Cardiac tertiary prevention programs generally consist of the prevention of disease progression and patient suffering. Aim of these interventions is to reduce the negative impact of disease by restoring function and reducing disease-related complications and, therefore, include the rehabilitation of disabling conditions.[6-8] Cardiac rehabilitation programs are interventions aimed to reduce mortality and morbidity of patients with ischemic heart diseases through promoting a healthier lifestyle among patients. These programs are used to restore, maintain, or improve both physiologic and psychosocial outcomes and finally the quality of life in patients through a combination of exercise, education and psychological support.

Literature Search Methods

A literature search was performed in Medline, Google, PubMed, using the following headings: 'Cardiovascular disease-related mortality in India', 'primary, secondary and tertiary prevention of coronary heart disease', 'tertiary prevention of coronary heart disease', 'coronary artery bypass grafting', and 'cardiac surgery'.

Literature Search Results

To evaluate patients' quality of life, the short form 36 (SF-36) questionnaire (Persian standard version) was completed for all patients at an average time of 23.4 months afterward CABG. The reliability and validity of the Persian version of the SF-36 have been well established.[9,10] Short form-36 is a 36 item scale that generates scores for eight items which can finally establish physical and mental component summary scores. Physical component summary score includes physical functioning, role limitations due to physical health, bodily pain, and self-perception of general health. Mental component summary score includes vitality, social functioning, role limitations due to emotional problems, and mental health. Short form-36 scores were calculated according to the methods determined by the authors of the questionnaire.[11,12] A questionnaires was used to collect data on age, sex, medical history and attendance in cardiac tertiary prevention programs.

Patients in CR group were attended in a cardiac tertiary prevention program 10.6 ± 1 weeks after operation at Isfahan Cardiac Research Center.[13] The program was at least 8 weeks long and consisted of exercise training and dietary and psychological counseling.

Morbidity and mortality were assessed via telephone interviews approximately 23.4 ± 1 months after CABG.[14-17] The interview was comprised of questions related to the recurrence of angina, subsequent cardiovascular associated hospitalization and/or contact with the healthcare system, such as emergency department. During this interview, participants were asked about chest pain and shortness of breath on the basis of the NYHA, and the occurrence of any neurological symptoms representative of transient ischemic attack or stroke. Patients were also questioned regarding their level of activity, their employment status and their restoration to previous level of performance in social activities after surgery.

Statins appear to exert several beneficial, non-lipid related actions in many cardiothoracic surgical operations, namely CABG, valve surgery, heart and lung transplantation, pulmonary lobectomy/pneumonectomy and thoracic aortic aneurysm surgery.[18] Current evidence suggests that a large percentage of cardiothoracic surgical patients are under treated with respect to statins. This has considerable implications for perioperative, as well as long-term morbidity and mortality rates.[19,20] In the last few years, there is accumulating evidence that statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) exert several non-lipid related actions.[21,22] Statins have an established role in primary and secondary prevention of cardiovascular events. Besides this, however, a number of studies suggest that statins exert pleiotropic actions in patients undergoing percutaneous or open surgical procedures.[23] Early studies showed that atherosclerosis frequently develops in saphenous vein coronary bypass grafts leading to occlusion rates as high as 40% at 10 to 12 years.[24, 25] Following an observational study following up 1041 post-CABG patients for 20 years showed that one in five patients underwent repeat CABG and another 7% had percutaneous transluminal coronary angioplasty during this time period.[26,27] These progressive atherosclerotic obstructive changes are especially common in patients with hyperlipidemia. The key role of managing hyperlipidemia in these patients was demonstrated in the post-CABG trial.[28] Compared with moderate lipid-lowering treatment with lovastatin [target low-density lipoprotein cholesterol (LDL-C): 132–136 mg/dl],[29] aggressive lovastatin treatment aiming at target LDL-C levels < 100 mg/dl[30] resulted in a reduced percentage of grafts per patient with angiographically detected atherosclerosis progression after a mean follow-up of 4.3 years (39 *vs* 27%, respectively; $p < 0.001$). Similar results were reported regarding the mean percentage of grafts per patient with occlusion or new lesions. The post-CABG trial was designed to have adequate power to detect treatment-related differences in angiographic characteristics but not in clinical events. As a result, a reduction in the number of clinical events was not seen. Nevertheless, a 29% lower rate of revascularization procedures was observed in the aggressive compared with the moderate treatment group ($p = 0.03$).[31] In an extended follow-up report of the post-CABG trial evaluating the long-term (7.5 years) effects of moderate as compared with aggressive lipid-lowering treatment with lovastatin, the initial 29% difference in the revascularization rates between the two groups[31] increased to 42% (or 30% increase; $p = 0.0006$).[32] Similarly, a significant 24% difference was observed in the composite end-point (death from cardiovascular or unknown causes, non-fatal myocardial infarction (MI), stroke, CABG or percutaneous transluminal coronary angioplasty) between the moderate and aggressive lipid-lowering groups (40.4 *vs* 32.0%, respectively = 0.001).[32] The long-term clinical benefit in post-CABG patients assigned to aggressive lipid-lowering treatment provides rationale

for postoperative initiation of high-dose statin treatment in these patients. Following the post-CABG trial, several other studies on patients undergoing CABG showed that statin treatment is beneficial in these patients with respect to the incidence of postoperative adverse cardiovascular outcomes (unstable angina, MI, arrhythmia, stroke and cardiac death). The possible mechanisms through which statins exert their beneficial actions in CABG are reviewed elsewhere.[33-35] Briefly, these include reduction of inflammation and oxidative stress, improvement of vascular endothelial function and management of postoperative hyperlipidemia/dyslipidemia.[33-35] Lipid-lowering in post-CABG patients is crucial; hyperlipidemia is responsible for the development of atherosclerotic changes in vein grafts eventually leading to graft occlusion.[34,35] Preoperative statin therapy in CABG patients improves postoperative myocardial perfusion of bypassed areas.[36] It also significantly reduces cytokine release [such as interleukin (IL-6[37-39] and IL-8[37])] and neutrophil adhesion to the venous endothelium via a nitric oxide-mediated mechanism. Preoperative statin treatment is also associated with improved perioperative mortality rates[40-43] and reduced risk of postoperative thrombocytosis and thrombotic complications.[44] Postoperative thrombocytosis occurs in 20 to 30% of the patients undergoing CABG and it is associated with an increase in late thrombotic complications.[45] Furthermore, pre-CABG statin use is associated with a 33% reduction in the odds of developing a postoperative infection and a 20% reduction in the odds of requiring a prolonged post procedural hospitalization.[46] Another beneficial action of statins in CABG patients is stroke prevention,which is one of the most serious complications of this procedure,[47] a recent prospective study showed that, compared with non-use, statin treatment for at least 4 weeks prior to surgery was significantly and independently associated with a lower risk of perioperative cerebrovascular events [odds ratio (OR) 0.26; 95% confidence interval (CI) 0.06–086; p = 0.027].[47] Acute renal failure occurs in 1 to 5% of the patients following CABG surgery.[48-50] It is associated with mortality rates as high as 60%[48,49] and substantial increases in the lengths of intensive care and hospital stay.[48-50] A large, multi-center trial including 19,625 patients undergoing isolated CABG surgery showed that patients with preoperative non-dialysis-dependent renal dysfunction had significantly higher in-hospital mortality (adjusted OR 3.0; p < 0.001), stroke (adjusted OR 2.0; p = 0.33), atrial arrhythmia (adjusted OR 1.5, p = 0.003), prolonged ventilation (adjusted OR 2.1; p < 0.001), postoperative hospital stay > 6 days (adjusted OR 2.6; p < 0.001) and follow-up mortality rates (adjusted OR 2.7; p < 0.001).[51] A retrospective cohort study including 1802 CABG patients suggested that preoperative statin therapy might be renoprotective in patients undergoing CABG.[52] By multivariate analysis, preoperative statin use was associated with an almost 50% lower incidence of new postoperative renal insufficiency (OR 0.54, 95% CI 0.18–0.82; p = 0.047).[52] Statins exert several beneficial actions on saphenous venous bypass graft patency rates. A 4-year prospective study with a median follow-up of 32 months (mean: 38.54–0.54 months) investigated predictors of symptom recurrence (recurrent angina, MI and congestive heart failure) and adverse cardiac events (MI, coronary reintervention and any cardiac-related mortality including sudden cardiac death) in 591 patients undergoing CABG.[53] Following the procedure, statins were used in 391 patients (66.1%). Postoperative statin use was associated with both decreased symptom recurrence [hazard ratio (HR) 0.157, 95% CI 0.075–0.330; p < 0.0001] and adverse cardiac events (HR 0.178, 95% CI 0.076–0.418; p < 0.0001).[53] Similar results were also reported in other studies;[31,54-58] statins improve endothelial cell function and inhibit smooth muscle cell proliferation in human saphenous veins, thus, effectively decreasing progression of atherosclerosis in the vein grafts used in CABG.[31,54-58] An interesting study evaluated the predictive role of preoperative C-reactive protein (CRP) levels in the long-term outcome of 843 patients undergoing CABG.[59] Among operative survivors (753 patients with low CRP (<1.0 mg/dl) and 87 with high CRP (1.0 mg/dl),[60] patients in the low CRP group had significantly better 12-year overall survival rate (74.1 *vs* 63.0%; p = 0.004) and survival freedom from fatal cardiac events (86.7 *vs* 78.1%; p = 0.008).[61-64]

DISCUSSION

Primary, secondary and tertiary prevention are three terms that map out the range of interventions available to health experts. Prevention includes a wide range of activities aimed at reducing risks or threats to health. Primary prevention aims to prevent disease or injury before it ever occurs. Secondary prevention aims to reduce the impact of a disease or injury that has already occurred. This is done by detecting and treating disease or injury as soon as possible to halt or slow its progress, encouraging personal strategies to prevent injury or recurrence, and implementing programs to return people to their original health and function to prevent long-term problems. Examples include: regular examinations and screening tests to detect disease in its earliest stages, low-dose aspirins and/or diet and exercise programs to prevent further heart attacks, suitably modified work so ill workers can return safely to their jobs. Aim of tertiary prevention is to soften the impact of an ongoing illness that has long-lasting effects. This is done by helping

people manage long-term health problems. In order to improve as much as possible their ability to function, their quality of life and their life expectancy by cardiac rehabilitation programs. Examples include: cardiac rehabilitation programs, chronic disease management programs. Support groups that allow members to share strategies for living well and vocational rehabilitation programs to retrain workers for new jobs when they have recovered. The burden of cardiovascular disease and its risk factors in India calls for a effective public health approach to stop the epidemic. Efforts to put in place an intervention program. Intervention program should be complemented with a robust surveillance mechanism so as to monitor, evaluate and guide policies and program. It has been demonstrated in a pilot mode that it is possible to establish surveillance for cardiovascular disease risk factors at community levels. It has been scaled up to the national level, and is now included in the National Programme for Prevention and Control of Diabetes and Cardiovascular Diseases. The future of surveillance systems lies in its timeliness, systems approach and enduring partnerships with public. Consolidating on the gains will push the path for the forward. Two systematic reviews that analyzed[48] randomized controlled trials reported a 20% decrease in all-cause mortality and a 27% reduction in cardiac mortality in participants of cardiac rehabilitation programs at 2 to 5 years after surgery. The improvement in general health status has been shown 5 years after CABG. It has been demonstrated that patients who attended cardiac rehabilitation recognized their health and overall life situation to be better. There was no difference in the incidence or severity of cardiac associated symptoms and hospitalization between cardiac rehabilitation attendants and non-attendants corroborating the results from another study that investigated the impacts of attendance at cardiac rehabilitation on the outcomes after myocardial infarction.

As patients' perceptions of their health despite of the physical health, determine the likelihood of their return to work after CABG, it is conceivable to observe that cardiac rehabilitation program participants had returned to their previous level of performance in society more than control group. Similar reports in the literature have shown that more rehabilitation participants returned to work and fewer dropped out afterwards cardiac rehabilitation.

CONCLUSION

While rehabilitation participants are not healthier than their control counterparts, they appear to have a better perception of their health problems and are thus, able to cope better. These findings are comparable with the results of above mentioned randomized studies reporting better self-perception of health status and viewpoint of overall life situation among post-CABG patients who participated in cardiac rehabilitation programs.

Although, the results of current observational study should be interpreted with caution, and also considering that self-selection of patients participating in cardiac rehabilitation programs may be redolent of their better motivation, the improved health-related quality of life of patients who participated in cardiac rehabilitation after CABG can be interpreted as evidence of the positive effect.

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REVIEW ARTICLE

Rising Maternal Mortality in Mumbai Metropolitan Region: Need for Action

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ABSTRACT

Data from the past suggest that maternal deaths mostly occurred due to obstetric complications, like postpartum hemorrhage, sepsis or maternal morbidities, like eclampsia and cardiac diseases. This trend, however, has changed over a period of time in developing countries, like India where increasing number of maternal deaths have been attributed in recent years to preventable infectious causes, such as hepatitis, tuberculosis and malaria. Rising maternal mortality ratio (MMR) due to infections indicates there are several loop holes in the basic healthcare system at various levels in their prevention and control. Although maternal mortality worldwide is decreasing progressively, curbing maternal deaths in certain developing regions of the World including few parts of India and Mumbai Metropolitan Region at a faster rate is essential in order to achieve the United Nations Fifth Millennium Development Goal of 2015.

Keywords: India, Infections, Maternal mortality, Millennium development goal 2015, MMR, Mumbai metropolitan region, Preventable.

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INTRODUCTION

Maternal mortality remains an issue of concern worldwide, even today. Measurement of maternal mortality in the form of maternal mortality ratio (MMR) is an important indicator for assessing the quality of health care system in any community. Maternal mortality ratio is calculated as the number of maternal deaths during a given time period per one lakh live births during the same period due to complications arising from pregnancy or childbirth.[1]

Maternal mortality ratio is considered to be low if it is <100, moderate if >100 to 299, high if it is ≥300 to 499, very high if it is > 500 to 999 and extremely high if it is ≥1000.[1] The Fifth Millennium Development Goal (MDG) put forth by the United Nations aims to improve maternal health with the target of reducing MMR by 75% between 1990 and 2015 and achieve universal access to reproductive health by 2015.[1] While most countries aspire to achieve the target by 2015 and there has been a decreasing trend in maternal mortality across the World, some developing regions with very high or extremely high MMR continue to lag behind in this race and are unlikely to attain this goal.[1]

This article presents an overview on recent trends in maternal mortality—globally, in India, in the state of Maharashtra and Mumbai Metropolitan Region. The estimates are from recent data from the World Health Organization (WHO)—the United Nation Childrens Fund (UNICEF), United Nation Population Fund (formerly United Nations Fund for Population Activities) (UNFPA), United Nations population division report (2013) on global MMR, sample registration system (SRS) maternal mortality data of 2013 to 2014 in India and Brihan Mumbai Municipal Corporation (BMC) data of maternal deaths (2013).

Worldwide Trends in Maternal Mortality

A country is considered to be 'on track' for achieving the Millennium Development Goal 2015 if MMR of 1990 was >100 and the average annual percentage decline between 1990 and 2013 is 5.5% or more. Only 11 countries are 'on track' according to the WHO 2013 data, which includes countries like Maldives, Nepal and Bhutan.[1]

If the average annual decline in MMR is between 2 and 5.5%, the country is considered to be 'making progress'. Sixty-three countries including India and USA are in this category.[1] Countries with an average annual decline of less than 2% are considered to have made 'insufficient progress' which includes 13 countries mostly in the Sub-Saharan African region.[1]

Globally, there were an estimated 289000 maternal deaths in 2013, a 45% decline since 1990, which recorded 523000 maternal deaths. Similarly, the global MMR has reduced from 380 in 1990 to 210 in 2013 yielding an average annual decline of 2.6%. Developing countries accounted for 99% (286000) of the global maternal deaths in 2013.[2] The Sub-Saharan Africa with 179000 maternal

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deaths contributed alone to 67% of all maternal deaths globally in 2013 and continues to be a high risk region for maternal mortality due to its very high MMR of 510.[1] Out of the 40 countries with the highest MMR in 2013, Sierra Leone is the topper with an extremely high MMR of 1100, followed by Chad (980), Central African Republic (880) and Somalia (850).[1] Other countries with high MMR are Afghanistan, Tanzania, Pakistan, Bangladesh, Iraq and Russia.[1] India—50,000 and Nigeria—40,000 together accounted for one-third of all global maternal deaths in 2013.[9] In contrast, China with the largest population in the world recorded only 5900 maternal deaths in 2013 due their 'one child policy'.[3]

United States of America (USA) estimated a total of 800 maternal deaths in 2013 (MMR increased from 7.2 in 1987—18.1 in 2013) most of which were due to hypertensive disorders of pregnancy, uncontrolled diabetes, heart diseases, postpartum hemorrhage or obstructed labor.[1] The best performing countries with the lowest MMR in 2013 are—Estonia, with only two maternal deaths in 2013, Sweden, Norway (MMR-4), Denmark, Greece (MMR-5) Australia, Netherlands (MMR-6), France and United Kingdom (MMR-8).[1]

The low MMR in these countries is attributed to efficient leadership, innovation, development of short and long-term strategies promoting safe motherhood and nutrition, adaptation to change for sustained progress and good quality healthcare.[1]

MATERNAL MORTALITY AND HIV-AIDS

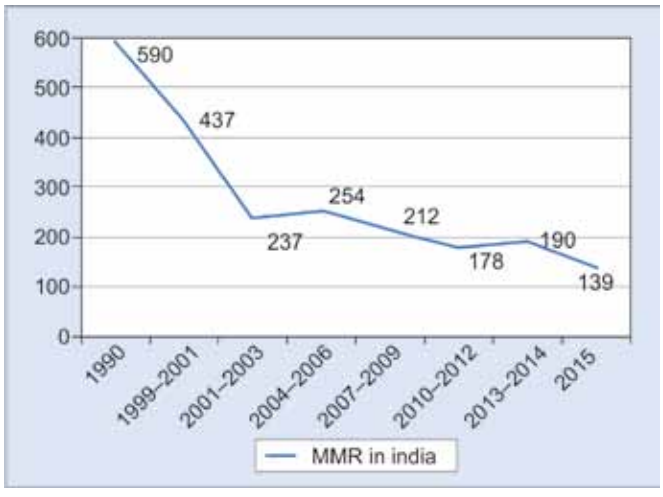
There is an aggravating effect of pregnancy on human immunodeficiency virus (HIV) and the interaction between pregnancy and HIV is the underlying cause of maternal death. These deaths are considered as acquired immune deficiency syndrome (AIDS)-related indirect maternal deaths.[2] In 1990, there were nearly 1700 AIDS-related indirect maternal deaths. Following the HIV epidemic, maternal deaths increased, peaking in 2005 at 12000, but then declined in 2010 when an estimated 8500 AIDS-related maternal deaths occurred.[2] In 2013, 7500 (2.6%) out of total 289000 maternal deaths were attributed to AIDS-related indirect maternal deaths. Out of these, Sub-Saharan Africa accounted for 6800 deaths (91%).[2] The rapid roll out of antiretroviral therapy over recent years in regions with high HIV prevalence has reduced the number of maternal deaths and the number of people on retroviral therapy has increased.[2]

Maternal Mortality in India

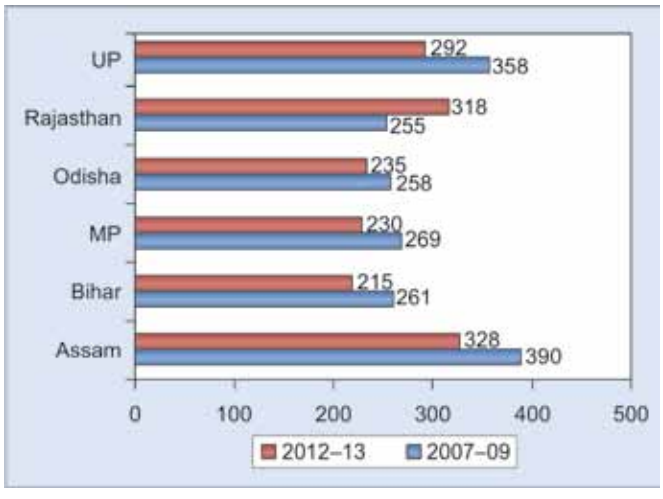
According to WHO data, MMR in India is 190 in 2013 in contrast to 590 in 1990. Despite its noticeable progress in decreasing MMR over recent years (65% drop in MMR since 1990) India is still lagging behind the MDG target of bringing a 75% decline in MMR till 2015.[4] Maternal mortality ratio in India is decreasing at the rate of 4.5% annually. In order to meet the 2015 target, this reduction should be accelerated to 5.5% annually.[3]

As shown in the Graph 1, the MMR in India has been declining steadily since 1990. According to the Sample Registration System report of 2013, only three states in India have achieved MMR reduction to double digit in 2013. Kerala has been a consistently best performing state with MMR of 66 in 2013 followed by Maharashtra (MMR-87) and Tamil Nadu (MMR-90).[5] But there has been considerably high MMR in few states like—Assam which has recorded the highest MMR in 2013 (328) followed by Rajasthan (318), Uttar Pradesh (292), West Bengal (235), Madhya Pradesh (230) and Bihar (215) as shown in Graph 2.[4]

These are low performing states mainly because of lesser proportion of institutional deliveries (less than 25%), illiteracy, lack of information regarding importance of antenatal care and complications of home deliveries,



Graph 1: Sample registration system, Office of Registrar General India report



Graph 2: High MMR states in India (2012–13) as per sample registration system report—2013

social issues like young age at marriage or childbirth, poverty, and high prevalence of infections.[3]

Although India has been successful in curbing maternal deaths since 1990, the high MMR of the above mentioned states is a major reason why India still has a long way to go to achieve the 2015 target.[4]

Maternal Mortality in Maharashtra

Maharashtra has been among the only three states in India, to have achieved a double digit MMR of 87 in just 3 years, bringing it to second position after Kerala in 2013.[7] There has been a progressive fall in maternal mortality in our state, more importantly due to the Janani Suraksha Yojana (JSY), a centrally sponsored scheme, which is a safe motherhood intervention under the National Rural Health Mission launched in 2005 in all states and union territories of India with an objective of reducing maternal deaths. It provides monetary benefit to those below poverty line in the first two deliveries to promote institutional deliveries in rural and urban areas of states with less than 25% institutional deliveries like UP, Uttarakhand, Bihar, Assam, Odisha, MP, Chhattisgarh, Jharkhand, Rajasthan and Jammu Kashmir and in rural areas of the remaining states. Beneficiaries are escorted by the Accredited Social Health Activists (ASHAs) for delivery at health center along with provision of cost reimbursement for transport and cash incentive to the ASHA for encouraging women for institutional deliveries. This cash incentive policy was perceived to attract, motivate and support the needy pregnant women with special focus on the low performing states mentioned above.[11]

Currently, the MMR is below 80 (2014–2015) in Maharashtra as there have been 96% institutional deliveries throughout the state—in private or government hospitals under proper medical attention.[10] For the low income group, there are Anganwadi centers throughout the state for free vaccinations, supplements and medicines during pregnancy, free checkup every 3 months and post pregnancy checkup. Maharashtra which currently fares second, aims to surpass Kerala in achieving the lowest MMR in India by next year.[6]

Maternal Mortality in Mumbai Metropolitan Region

While Maharashtra has achieved reduction in its MMR, Mumbai continues to have a rising incidence of maternal deaths (Table 1).[7] An update from Hindustan Times in May 2015 stated that maternal deaths in Mumbai have increased 40% over the past 5 years.[7] Maternal mortality ratio in Mumbai has reached an alarming 158 this year. This is almost two times the mortality ratio of Maharashtra.[9] The exact total number of mortalities in the year 2015, however, is not yet known.

Table 1: The increasing maternal deaths in Mumbai since 2010 as per BMC data

Years	*BMC death review committee data—total maternal deaths in mumbai*
2010–11	222
2011–12	259
2012–13	278
2013–14	260
2014–15	319

Data from the civic body which record these deaths every month revealed that the top cause of maternal deaths in Mumbai is tuberculosis, an infectious disease that is curable.[7] The emergence of multi-drug resistant (MDR TB) and also extensively drug resistant cases (XDR TB) has proved significant.[7] Early diagnosis and initiation of treatment can prevent maternal deaths due to untreated tuberculosis. After TB, hepatitis A and E which are foodborne infections have emerged as common causes of maternal mortality and are easily preventable by simple household methods like boiling water prior to drinking.[7] Severe maternal anemia, again a preventable cause of mortality reflects poor antenatal care and follow up in the rural areas. This situation is in contrast to other parts of the country and world where maternal deaths are mostly due to postpartum hemorrhage, hypertensive disorders, cardiac diseases and septicemias.[8]

One of the major reasons for the rising maternal mortality is, untimely referral of severely morbid patients from neighboring districts of Thane, Kalyan, etc. to tertiary referral centers in Mumbai for critical management.[8] The time lapse during referral results in deterioration in patients condition, further decreasing the chances of survival. The high numbers of referred patients brings out the inadequacy in antenatal, intrapartum and immediate postpartum care and health infrastructure at peripheral centers.

Weaknesses in the JSY scheme also contribute toward the rising MMR. According to an article in the Indian Express in 2014, there has been a decline of 82.6% in the number of women beneficiaries under JSY as most women find it difficult to access the cash incentive due to absence of bank accounts and Aadhaar cards.[9] Some women receive the cash several days after delivery or often in instalments, and have to travel to the nearest institution for it which is in contravention of the JSY guidelines. It was also found that ASHAs have underperformed in encouraging more women from low socioeconomic classes for institutional deliveries.[10] Moreover, the scheme is provides financial assistance only in rural areas of high performing states like Maharashtra. Hence, Mumbai with a majority of urban population is hardly supported by

JSY. Also, the incentive amount of Rs. 700 provided to beneficiaries is not enough for delivery expenses at health centers in the metropolitan cities as a result of which, fewer women are attracted toward the cash benefit and do not avail the facility. Utilization rate of the JSY services has been found to be lower in metropolitan areas and there is scope for improvement.[11]

Lack of access to transportation, fewer antenatal visits of the urban-poor due to language barriers and overcrowded hospitals, increasing numbers of home deliveries, inability of traditional birth attendants (dais) to conduct safe deliveries and recognize complications leading to late referral are other challenges in peripheral parts of Mumbai.[7]

Maternal Mortality at our Set up

Recent trends in maternal mortality at MGM Hospital which is a tertiary referral center at Kalamboli, Navi Mumbai, have been similar to those observed all over Mumbai. There has been an increase in maternal deaths in recent years due to infections.

In 2014, a total of six maternal mortalities were recorded of which three (50%) were due to hepatitis E. 2015 has so far recorded five maternal deaths of which two were attributed to hepatitis E, one to H1N1 positive swine flu and one to severe anemia. Though majority of these patients were referred from Rural health centers, these mortalities could have been prevented by timely referral, and antenatal precautions like early diagnosis of anemia, iron supplements, boiling of drinking water, avoiding roadside food, improved sanitation and H1N1 vaccination in susceptible cases.

CONCLUSION

The earlier belief that most causes of maternal mortality are not much within our control is slowly fading away as a result of the shift of this spectrum in recent years from obstetric causes toward preventable and curable medical causes like tuberculosis and hepatitis, in most developing countries of the world including India. Putting an end to these preventable deaths is the need of the hour.[12]

The first step should be taken to correct fallacies of the healthcare system in early identification and reporting of infections leading to maternal mortality. Health services must be strengthened at the grass-root level in order to bridge the gap between healthcare professionals and below poverty line areas. This can be achieved through strategies, such as adoption of remote villages and improvement of their sanitation and health infrastructure. Better utilization of JSY should be stressed upon by creating more awareness regarding the scheme, increasing the incentive amount by a sufficient margin to meet requirements in urban-poor areas of metropolitan cities like Mumbai, ensuring that the entire amount reaches the beneficiaries without unnecessary delay, availability of free and accessible transportation, timely referral to higher centers and provision of all services free of cost at the health facilities.

While all Millennium Development Regions of the world are experiencing a decline in their MMR and although India and Maharashtra have done exceedingly well in decreasing maternal mortality, Mumbai continues to lag behind. It is indeed a paradox that the financial capital of our country having advanced tertiary health-care still has a rising incidence of maternal deaths. There is certainly a need for action.

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CASE REPORT

Acquired Cold Urticaria: An Under-reported Entity

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ABSTRACT

Acquired cold urticaria (ACU) is a subtype of physical urticaria which may be primary (idiopathic) or secondary to underlying infections or cryoproteins. In addition to complete history and thorough physical examination, the diagnosis is dependent on a positive cold stimulation time test (CSTT) which is the minimum time of cold contact stimulation required to induce an immediate coalescent wheal. Although idiopathic type is seen in 96% of the cases, it is important to rule out cryoprotein by an intricate yet simple test for cryoprecipitate. The identification of cold exposure as the likely trigger for urticaria is vital because systemic anaphylactic reactions are common in patients with cold urticaria, occurring in roughly 1 in 3 patients. In addition to preventive counseling and avoidance of critical cold exposure, H_1-receptor antagonists form the first line of treatment. However resistant cases may require cyclosporine, danazol or omalizumab. No individual case reports of ACU appear in Indian literature. Therefore, the authors attempt to highlight the diagnostic work-up and therapeutic options for this not so uncommon cause of chronic urticaria.

Keywords: Acquired cold urticaria, Cold stimulation time test, Ice cube test, Physical urticaria.

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INTRODUCTION

Acquired cold urticaria (ACU) is a subtype of physical urticaria characterized by the development of wheal-and-flare type skin reactions and/or angioedema resulting from stimuli, such as direct contact with cold, ingestion of cold foods or beverages, handling cold objects, and to a lesser degree, exposure to ambient cold.[1]

CASE REPORTS

Case 1

A 39 years old, male came with 4 months old history of cold sensitivity, characterized by the development of red itchy solid and raised evanescent lesions following exposure to cold air, cold objects and especially cold water bath. He described similar, but less severe symptoms after exercise. He denied history of fever, headaches, sore throat, joint pain, dizziness, palpitations, fluid filled lesion, wheezing, abdominal symptoms, swelling of lips or periorbital area. There was no history of atopy or similar complaints in family. Dermographism was negative, and Raynaud's phenomenon could not be elicited. On the basis of his symptoms, a working diagnosis of ACU was made. Cold stimulation time test (CSTT), i.e. application of an ice pack, for 5 minutes produced erythematous edematous plaques in the area of contact (Fig. 1A) followed by the appearance of wheal at the same site (Fig. 1B). Complete blood count, comprehensive metabolic profile, urine and stool routine, ANA, autologous serum skin test (ASST), HIV ELISA, HBsAg, HCV antibody, VDRL and cryoglobulins (Fig. 2) were either normal or negative. He was prescribed 10 mg of cetirizine and 180 mg of fexofenadine orally per day, and his symptoms were under control in 1 week. The same treatment was continued and there was no recurrence of lesions while the patient was on follow-up for the next 6 months.

Case 2

A 23 years old man complained of reddish evanescent lesions appearing shortly after taking a shower regardless of the temperature of water since month. Lesions were small in nature, appeared predominantly on the trunk

Figs 1A and B: (A) Patient 1 ice pack applied to normal skin and (B) enlarging wheal 5 minutes later

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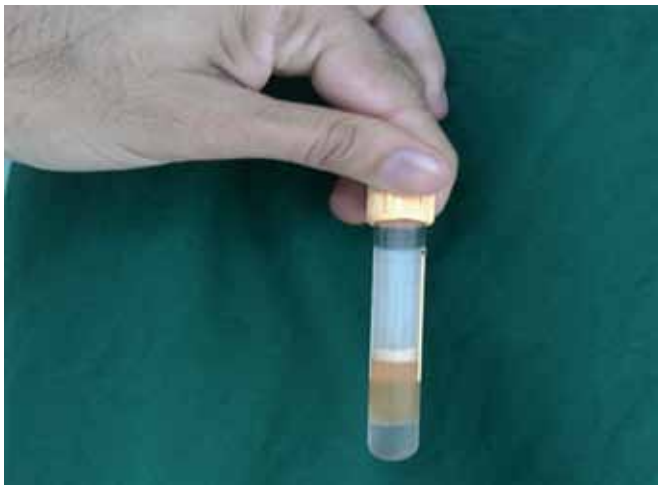

Fig. 2: Serum of patient 1 negative for cryoprecipitate

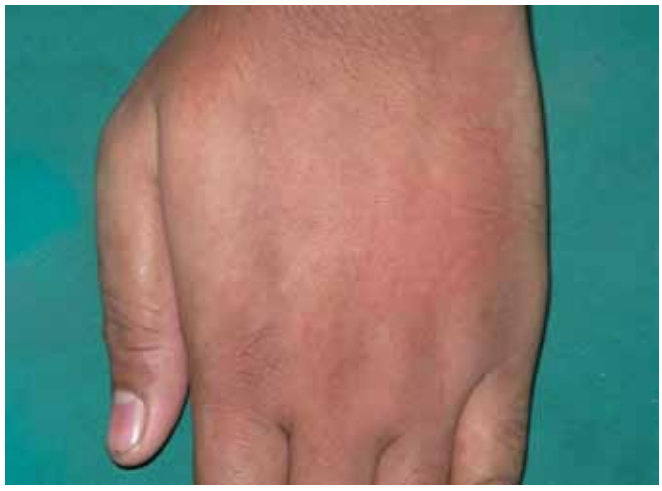

Fig. 3: Wheals on dorsum of hand of patient 2

and upper extremities within 10 minutes of contact with water, lasted for 15 minutes and resolved spontaneously. His symptoms were not triggered by other conditions such as cold weather, exercise, sweating, stress, or sunlight. He had no history of atopy or similar complains in family. On examination, ill defined, erythematous wheals were seen on dorsum of hand (Fig. 3). The diagnosis of primary ACU was confirmed by CSTT. Exercise test, ASST and laboratory work-up similar to the previous case were negative or normal. He was prescribed oral antihistamines (10 mg of cetirizine and 180 mg of fexofenadine) daily which failed to induce satisfactory response. The dose of antihistamines was escalated further and this reduced the induction of wheals, but pruritus persisted even after 1 month of therapy. We finally added oral danazol 200 mg twice daily following which the patient achieved complete remission of symptoms and remained so for the next 3 months of follow-up.

DISCUSSION

Chronic urticaria accounts for approximately 1 to 3% of all cases of cold urticaria (CU)[2] and have been reported in studies on CU like Shankar et al[3] who found 3 (2%) cases attributable to this subset. But to our surprise, no individual case reports appear in Indian literature.

Acquired cold urticaria may be primary (idiopathic) or secondary to underlying infections or cryoproteins.[2] An array of infectious diseases have been associated with ACU, including toxoplasmosis, Epstein Barr virus, *Helicobacter pylori*, hepatitis C virus and HIV.[4] In addition, cryoglobulinemia, cryofibrinogenemia, and cold agglutinins have all been reported.[5] We failed to demonstrate any underlying cause in our patients and hence categorized them as idiopathic which represents 96% of all cases of ACU.[2] Both our patients were young adults which are the most commonly affected age group, but pediatric cases are not uncommon.[2,4]

In addition to complete history and thorough physical examination, the diagnosis is dependent on a positive CSTT which is the minimum time of cold contact stimulation required to induce an immediate coalescent wheal.[6] A cold (0–4°C) stimulus is applied to the subject's forearm for 5 minutes following which the skin is allowed to re-warm to normal skin temperature. If the test is negative after a 10 minutes ice challenge, the patient probably does not have typical ACU.[6]

The identification of cold exposure as the likely trigger for urticaria is vital because systemic anaphylactic reactions are common in patients with CU, occurring in roughly 1 in 3 patients.[2,7] In addition to anaphylaxis, even death has been reported subsequent to water immersion.[8] The extracutaneous site of reaction may be respiratory tract (hoarseness, dyspnea and wheezing), gastrointestinal system (duodenal ulcers and abdominal pain), or cardiovascular system (hypotension, tachycardia and arrhythmia). Our patients did not report any history of angioedema, nor did we elicit any systemic involvement.

In addition to laboratory studies suggested by history and examination, it is important to test for cryoglobulins and cold agglutinins. Although cryoproteins form the perpetrator in a very small percentage of cases of ACU, a positive cryoprecipitate can reflect an underlying diagnosis of essential mixed cryoglobulinemia, hepatitis, autoimmune disease or lymphoma.[4] Motyckova and Murali[9] have described the intricate process of testing for cryoprecipitate which we followed. Around 10 ml blood drawn in tubes without anticoagulant was allowed to clot for 1 hour at 37°C followed by separation of serum in a 37°C water bath. Alternatively, a warm centrifuge can also be used subject to availability, but the temperature should not be allowed to fall below 37°C. The serum was then kept at 4°C and analyzed after 72 hours. Both our patients tested negative for cryoprecipitate (Fig. 2).

A complete understanding of the pathogenesis of ACU has not been realized. The activation of mast cells and subsequent release of histamine and other inflammatory mediators (PGD2, LTE4, chemotactic factors, PAF, platelet factor 4, TNF-α, IL-3) subsequent to cold challenge is thought to play a central role.[10] However, the mechanism by which the cold stimulus is transformed into a signal for molecular and cellular activation has not been elucidated. Wandere and Hoffman[6] have reviewed the differentials for ACU. They suggested that very rare sub-forms of ACU where symptoms occur from exposure to unique environmental conditions and cannot be diagnosed by CSTT should be classified as atypical ACU.

The therapeutic options have been highlighted in Table 1. In addition to preventive counseling and avoidance of critical cold exposure, H_1-receptor antagonists form the first line of treatment and high doses (upto four times) may be required for complete resolution of symptoms.[11] H_2-blockers, leukotriene antagonists and ketotifen may have additive benefit to antihistamines.[12] Occasionally, insufficient response to antihistamines may warrant the use of cyclosporine,[13] omalizumab[4] or danazol.[14] Cautious induction of cold tolerance may be successful (desensitization) by gradually hardening the skin to cold conditions and then exposing the skin to it regularly, e.g. by taking regular cold showers. Life-threatening or shock-like symptoms necessitate carrying a self-administered injectable epinephrine and oral corticosteroid.

Table 1: Therapeutic options for cold urticaria

Drug	*Comments*
H_1-receptor antagonists	Most effective symptomatic therapeutic option, many patients require high dosing of up to four times the daily recommended dose
H_2-receptor antagonists	In combination with H_1-receptor antagonists
Doxepin	Has combined H_1- and H_2-receptor antagonist activity
Leukotriene antagonists (Zafirlukast)	In combination with H_1-receptor antagonists
Ketotifen	Established efficacy in double-blind trial
Cyclosporine	Individual case reports show good response
Omalizumab	Monoclonal antibody against IgE, gives excellent response, can be used in refractory cases
Danazol	Synthetic derivative of testosterone, isolated case reports show efficacy, established treatment for hereditary angioedema may justify use in CU, should be reserved for severe refractory cases in view of its side effects
Corticosteroids	No suppressive therapeutic effect in primary or secondary ACU, may have role in anaphylaxis or systemic symptoms

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CASE REPORT

Nonspecific Computed Tomography Presentation of Gossypiboma

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ABSTRACT

A gossypiboma also known as 'textiloma' or 'cottonoid' is a term used to describe a foreign object (nonabsorbable surgical material), that is left behind in a body cavity during an operation. The manifestations and complications of gossypiboma are so variable that diagnosis may be difficult and patient morbidity is thus significant. Moreover, such foreign bodies can often mimic tumors or abscesses. Here we discuss a case of pelvic gossypiboma that presented as a mass in the pelvis associated with abdominal pain in a post ovarian cystectomy case. The diagnosis was suggested on computed tomography (CT). The diagnosis was confirmed on surgery and the gossypiboma was retrieved successfully.

Keywords: Foreign body granuloma, Gossypiboma, Hypodense mass, Postovarian cystectomy, Retained sponge.

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INTRODUCTION

Gossypiboma is due to surgical complication resulting from accidental placement of the sponge within the patient's body. The true incidence of gossypiboma is not known as the cases may be misdiagnosed and/or not declared due to medicolegal implications. The incidence is more common in abdominal operations and found to be one in 3000 to 5000 operations.[2] It generally presented as an abdominal mass comprising of sponge surrounded by foreign body granuloma.[2]

CASE REPORT

A 35-year-old lady presented with a mass in hypogastrium associated with pain and discomfort in abdomen predominantly in the hypogastrium since 1 week. There was no history of fever, vomiting, diarrhea, bleeding or white discharge PV. The patient had past history of ovarian cystectomy 2 months ago.

On examination, vital signs were normal and a round mobile mass was palpable in the hypogastrium.

Ultrasonography of abdomen done outside suggested that the mobile mass could represent recurrent neoplastic lesion of ovary.

Hence, the patient was referred for computed tomography (CT) scan for further characterization of the lesion. Plain and contrast CT scan of the abdomen and pelvis was performed on 64 slice brilliance philips CT scanner with 1 mm slice thickness which revealed a well-defined hypodense mass in the hypogastrium with thin enhancing wall and central non-enhancing hyperdense contents within (Fig. 1). The distal ileal loops were seen to be displaced superiorly and posteriorly by the mass. No spongiform/sleeve/interlacing mass pattern was seen (Figs 2 and 3). Rest of the small bowel loops were normal.

Exploratory laparotomy revealed an encapsulated sponge surrounded by omentum (Fig. 4), which was removed. Few of the distal ileal loops appeared to be adhered to the lesion. Partial distal ileal resection and end to end ileal anastomosis was done. There was no e/o intestinal obstruction or fistula. Postoperative course was uneventful.

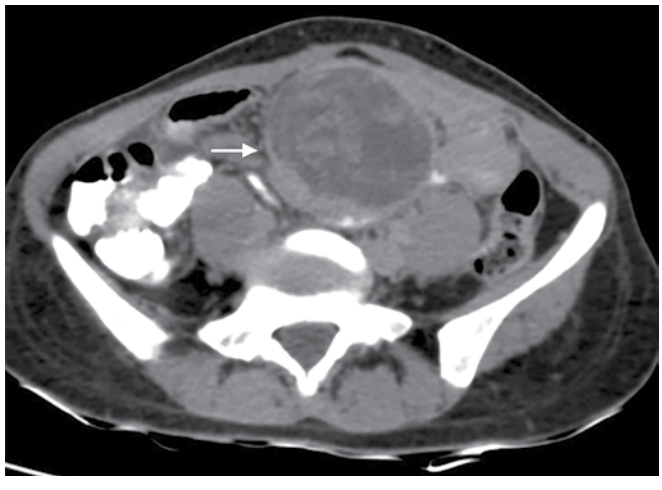

Fig. 1: Axial reconstructed image of venous phase represents well-defined hypodense mass with thin enhancing wall and central non-enhancing hyperdense and hypodense contents within (white arrow)

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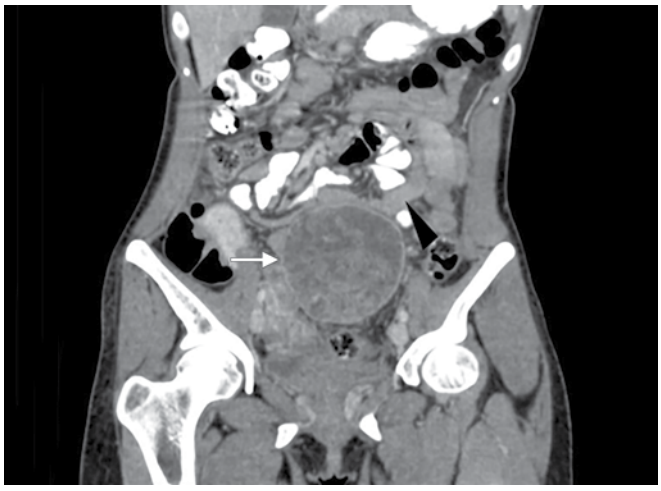

Fig. 2: Coronal reconstructed image showing the gossypiboma (white arrow) and displacement of ileal loops superiorly (black arrow head)

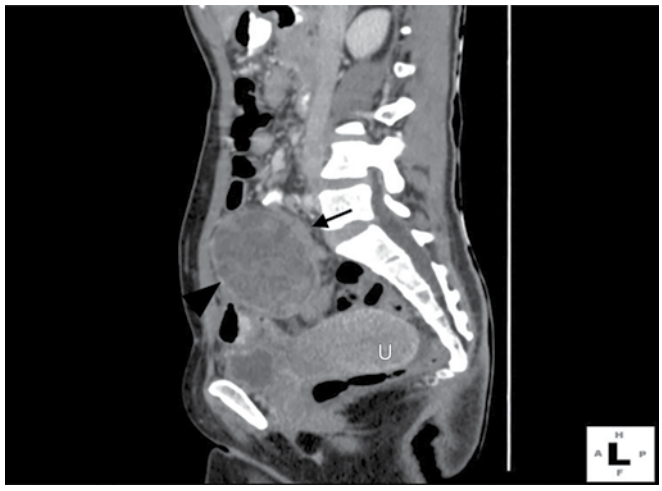

Fig. 3: Sagittal reconstructed image showing gossypiboma (black arrow head) causing posterior displacement of ileal loops (black arrow) with maintained fat plane with uterus (U)

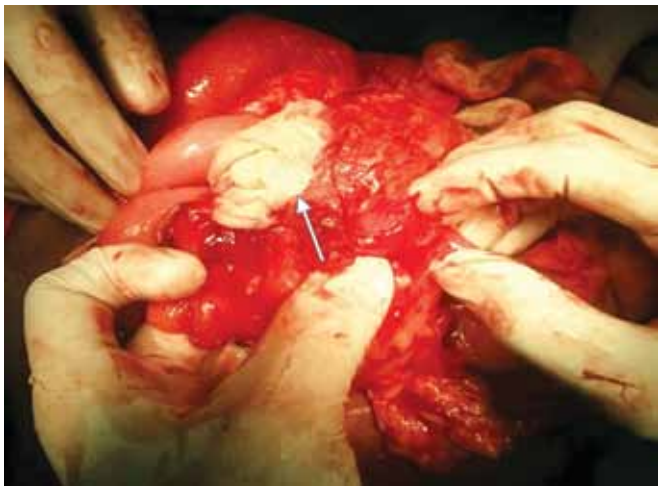

Fig. 4: Intraoperative specimen showing the gauze piece (white arrow)

DISCUSSION

Gossypiboma/textiloma/cottonoid is a term used to describe surgical complications resulting from non-absorbable surgical material accidentally left inside a patient's body during surgery. The first case of gossypiboma was reported by Wilson in 1884.[2-4]

The term gossypiboma is derived from two words the Latin word 'gossypium' meaning cotton (as it is the most common foreign body culprit), and the Swahili word 'boma', which means place of concealment, pertaining here to retained sponge in the surgical bed.[3,4]

Likewise 'textiloma' is derived from textile (surgical sponges made of cloth) and the suffix '-oma', meaning a tumor or growth.[1] Frequent sites of gossypiboma formation include: abdominal cavity (most common), intrathoracic (pleural or pericardial cavities), extremities, CNS, breast.

Risk factors for gossypiboma include GI tract surgery and gynecologic surgery (which account for about 75% of reported cases), long and difficult procedures, especially those with nursing/personnel changes, changes in operative field, emergency procedures, large body habitus, hemorrhagic procedures.

Patients with intra-abdominal gossypiboma usually present with abdominal pain, an abdominal mass, subacute intestinal obstruction, fistulae, free perforation or even extrusion.

Angiosarcoma is a rare but reported possible complication of gossypiboma.[5]

Gossypibomas typically have an inconsistent radiologic appearance determined by the time *in situ*, the type of material and the anatomical location.[6] Two major types of reactions are seen with gossypibomas; acute inflammatory reaction presenting as an abscess or chronic type foreign body granulomatous reaction presenting as a fibrinous response followed by encapsulation and adhesions.[2,5]

On plain radiographs 'Whirl-like' pattern of sponge or a calcified mass may be seen.[7]

Ultrasound may be helpful, but often non-diagnostic. It may show echogenic 'wavy' structure (sponge) within a mass with acoustic shadowing.[7]

Computed tomography can also be disguising as it shows ring enhancement, which is indistinguishable from an abscess or tumor.[5] In long standing cases, air bubbles, calcification of the cavity wall as well as contrast enhancement of the rim may be seen in gossypibomas. These CT findings may be indistinguishable from intra-abdominal abscess.

However, CT scan is one of the important diagnostic techniques. Gossypibomas show wide array of features on CT scan including a well-defined mass with soft-tissue attenuation with a thin enhancing capsule (nonspecific but common), whorled appearance, spongiform appearance with gas bubbles (typical but uncommon),

calcifications along the architecture or within the wall of the foreign body.[5]

Prevention as always said is better than cure even in case of gossypibomas. A simple way of prevention, a method, was codified into recommended guidelines in the 1970s by the Association of Perioperative Registered Nurses (AORN).[8]

According to this method, to prevent gossypiboma, sponges are counted by hand before and after surgeries. Four separate counts are recommended: the first when instruments and sponges are first unpackaged and set up, second before the beginning of the surgical procedure, third as closure begins, and a final count during final skin closure.

In most countries, surgical sponges contain radiopaque material that can be readily identified in radiographic and CT images, facilitating detection.[1] However, in developing Asian countries, the sponges do not contain such radiopaque material.

In our patient, CT scan did not show typical features of gossypiboma. Hence, other possibilities of complex ovarian cyst or cystic neoplasm of ovary were considered. However, in view of history of recent intra-abdominal surgery, high index of suspicion was kept for gossypiboma.

CONCLUSION

Gossypiboma though an unusual diagnosis, should always be kept in mind in patients with abdominal complaints and history of surgery done even when CT scan findings are nonspecific and atypical.

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CASE REPORT

Report of a Rare Case: Ligamentum Flavum Cyst

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ABSTRACT

A rare case of ligamentum flavum cyst of the lumbar spine in an elderly male is reported. The patient presented with low backache and features of bilateral radiculopathy of a sudden onset. The cyst was lying in the extradural space. After surgery, the patient reported complete relief of symptoms.

Keywords: Etiology of lumbar canal stenosis, Extradural lesion, Ligamentum flavum cyst.

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BACKGROUND

Different etiologies for cystic lesions in the lumbar spinal canal have been reported in the literature, among them are hemorrhagic cysts, perineural cysts, dermoid cysts, and parasitic cysts.[4] The most common lesion seems to originate from the facet joints: the synovial cyst, which represents a protrusion of the synovial membrane into the surrounding tissue. The literature remains imprecise about the histopathologic nature of cystic lesions in the lumbar region of the spine. Some authors differentiate between the terms 'synovial cyst' (with a synovial lining) and 'ganglion pseudocyst' (without any synovial lining). Others proposed the term 'juxtafacet cyst,' simply representing both. Also, evolution from a synovial cyst into a ganglion pseudocyst has been questioned. Ligamentum flavum pseudocyst, as a cystic lesion in the lumbar spine, has only rarely been mentioned.[4,5,7,25,28,29]

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CASE PRESENTATION

A 68-year-old male presented to us with sudden onset of lower back pain with bilateral radiating pain to lower limb associated with difficulty in walking which was progressive in nature also complaining of weakness in both lower limbs. He was operated for cervical myelopathy in 1995. At present, there was no history of trauma or other constitutional symptoms.

Clinical examination revealed weakness (grade 3/5) of the both lower limbs ankle dorsiflexion and flexion and extension of the left great toe. Otherwise, motor examination of the other muscle groups was normal. Sensation of both lower limbs was intact. The knee reflexes were present and ankle reflexes were mute.

Plain radiographs of the lumbosacral spine showed degenerative changes. Blood parameters showed normal white cell count (WCC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (Figs 1 to 3). Magnetic resonance imaging (MRI) scan showed a cystic lesion (where it is found to be mentioned), T1 hypointense and T2 hyperintense.

Posterior decompression by L3 to L5 laminectomy was performed. Intraoperatively, a cyst was noted in the epidural space spanning the whole of ligamentum flavum in a transverse and craniocaudal direction at L3/4 level. The dorsal side of the ligamentum flavum cyst extended up to L5 level space. The cauda equina was decompressed by excising the dorsal cyst wall and drainage of clear fluid inside dura repair done. The ventral wall could not be separated from the dura and was left *in situ*. Further decompression of bilateral lateral canals was performed by undercutting of the facet joints. Histological examinations suggestive of fibrocollagenous tissue with inflammatory cell infiltration (Fig. 4).

Postoperatively, the patient showed relief from the spinal claudication symptoms and improvements in ankle dorsiflexion, left great toe flexion and extension power to grade 3+/5. He could walk with stick with foot drop splint in bilateral lower limb. Bowl and bladder are intact.

DISCUSSION

Several studies have shown that the usual aging process of the ligamentum flavum causes thickening and loss of elasticity.[11] Change in proteoglycans, loss of elastic fibers,

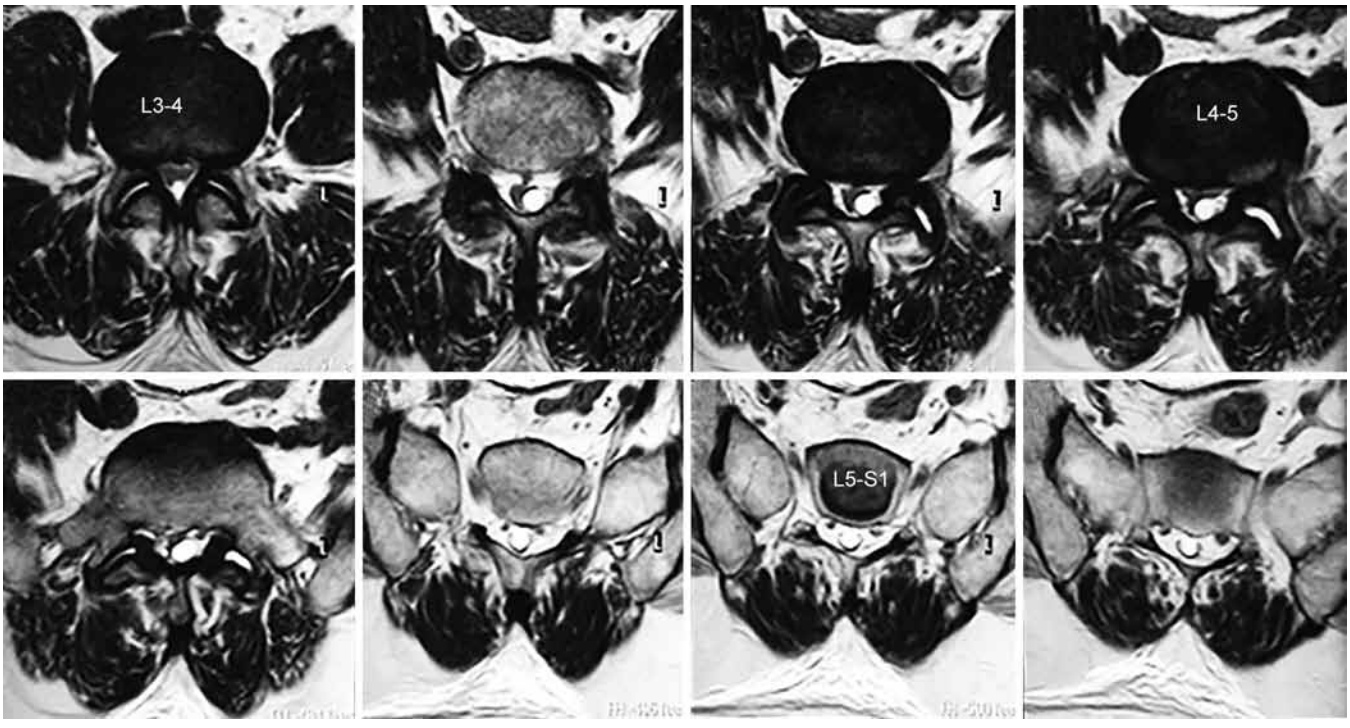

Fig. 1: T2 weighted image extradural cyst in axial view hyperintense signal extension from L3–L4 disk level to L5 shows body level

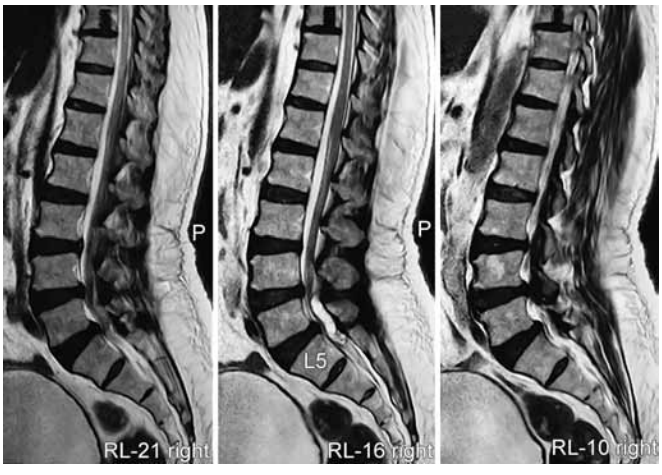

Fig. 2: T2 weighted image shows cystic mass over L4–L5 vertebral level

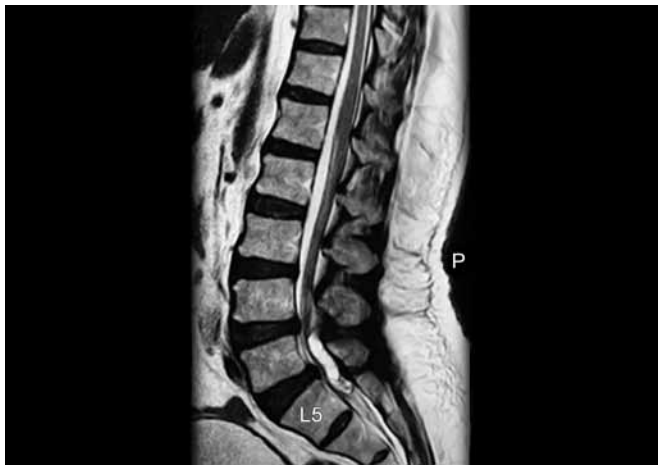

Fig. 3: T2 weighted image shows it is extradural cyst

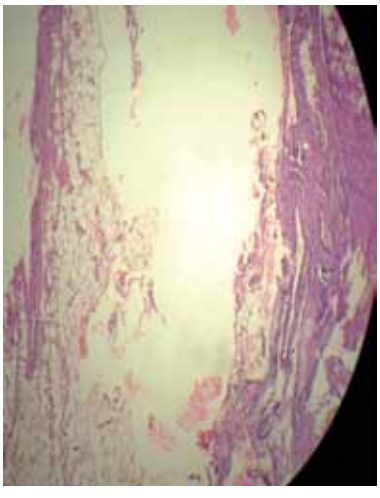

Fig. 4: Histopathology slide of cyst

and increase in collagen tissue and chondroid metaplasia due to mechanical stress have been described.[22] Additionally and closely related to age, amyloid can accumulate within the ligamentum flavum.[25] This amyloid deposition has been reported in only a few cases to be associated with systemic amyloidosis.[24] Similarly, age-related calcification of the ligamentum flavum can occur.[26] A diffuse form of calcification contributing to the loss of elasticity and the thickening and a focal form of calcified material accumulation as well as granulomatous inflammation and tophaceous depositions of calcium pyrophosphate crystals can occur. These depositions have been ascribed to decreasing cellularity of the ligamentum flavum with age and resultant diminished calcification

inhibiting factor production by fibroblastic-like cells.[21] The tophaceous type of lesion seems to be closely related to previous degeneration of the affected ligament by minor trauma predisposing to calcium deposition. Activity of proteolytic enzymes within the ligament, produced by neutrophils localizing to calcified nodules, has been found.[9] Wildi et al[30] found only four patients with calcium pyrophosphate depositions, suggesting that they play a minor role in the pathogenesis of ligamentum flavum pseudocysts. In addition to calcification, ossification of the ligamentum flavum might occur. This seems to follow a sequential process of chondroid metaplasia and eventual enchondral ossification mainly at the insertion site of the ligament. All these factors, resulting partially from mechanical stress, seem to contribute to loss of the natural structure of the ligamentum flavum, making them again susceptible to new mechanical stress, forming a vicious circle. The degenerated bony structure of the lumbar spine and the facet joints suggest a major pathogenic role of degenerative segmental instability in pseudocyst formation of the ligamentum flavum, as found by other authors too.[18] Most ligamentum flavum cysts reported in the literature were also located laterally within the spinal canal. While possibly a consequence of chronic bony degenerative disease, this phenomenon may be further elucidated in certain cases by the observation that the yellow ligaments are not as thick laterally as they are medially. Furthermore, they form posterior recesses bilaterally to the vertebral bodies. These recesses are filled with epidural fat[16] and offer an area of decreased resistance and may, as a result, tolerate cyst formation.

The pathogenesis of ligamentous degeneration remains to be elucidated, but it may be considered in the context of degenerative spinal changes. The spine is divided into alternating mobile and fixed segments, and the transitional zones between the mobile and fixed regions incur the most severe stress during motion. The anatomic disposition, histologic characteristics, and biomechanical properties of the ligamentum flavum indicate that it is markedly different from other spinal ligaments.[10] The ligamentum flavum is a well-defined elastic structure composed of 80% elastic and 20% collagen fibers.[31] This composition of dense connective tissue with elastic fiber predominance is rarely seen in other tissues, although it can be seen in the vestibular folds of the larynx and the media of large arteries.[31] When a change occurs in the ligamentum flavum, regeneration of elastic fibers that includes the formation of collagen fibers and degenerative changes occurs, and this regenerative process leads to decrease in elasticity. Moreover, this process in the ligamentum flavum is markedly different from other spinal ligamentous reactions.[10] Thus, chronic irritative or degenerative changes of the ligamentum flavum in the area of the cyst could predispose it to mechanical stress, even after a minor repeated injury.[8]

Cysts of the ligamentum flavum have myxoid degeneration and arise from or are partially embedded in the inner surface of this ligament, and in contrast to juxta-articular cysts, are not related to the facet joint cavity. Pathogenesis of the cyst formation is secondary to ligamentous and fibrocollagenous tissue degeneration and hypermobility of the spinal segment, mainly at the transitional zones between the mobile and the fixed segments of the spine.[14] These degenerative changes represent a histologically distinct entity different from ganglion or synovial cysts. Pathologic ligamentum flavum cysts can contain hemorrhage, and previous degeneration of the ligament may create conditions for the formation of hematoma. Rupture of vessels in degenerated lumbar ligamentum flavum may develop secondary to stretching forces on the back. The pathogenesis of the hematoma may originate from minor acute or chronic trauma, such as minor back injury, physical exertion or heavy lifting.[20,26]

Intraspinal ligamentum flavum cysts are rare; they occur preferentially in the lower lumbar region,[5,15,32] while cervical localization is uncommon.[17] In most of the cases, ligamentum flavum cysts in the lumbar spine occur at L4–L5, the most mobile segment within the lumbar spine, and are frequently associated with lumbar degenerative spondylolisthesis. Cervical cysts are preferentially located in the cervicothoracic junction.[29] Continuous stress to the ligamentum flavum due to minor chronic trauma, such as listhesis may predispose to the formation of the cyst.[8] Only in a few cases is the localization of cysts C6–C7, C3–C4, and C5–C6 levels.[29] No reports have described the appearance of these cysts in any region other than the mobile spine. The T2–T10 vertebrae mainly act with the ribs to form the thorax and are not generally considered to be part of the mobile spine (Table 1).

There are no specific clinical symptoms for ligamentum flavum cyst. Cysts in the spinal canal can impinge upon and displace neural structures and can lead to neurologic symptoms. The majority of symptomatic cysts usually presents with radiculopathy, such as sciatica in the case of lumbar cysts, and can mimic symptoms related to intervertebral disk herniation.[15] In the study of Wildi et al,[30] 97% patients complained of radicular pain, 39% showed motor deficits, 55% had sensory changes, 18% had abnormal reflexes, and 33% showed a positive Lasèque sign. Our patient presented with gradually developing right-sided radicular pain involving mostly the L4 distribution with patellar reflex loss on the same side.

Table 1: Reported cases of ligamentum flavum cysts occurring in the spine

Literature: Reported cases of ligamentum flavum cysts occurring in the spine	*N*
Cervical	
Takano et al[27]	1
Yamamoto et al[32]	2
Hatem et al[17]	1
Gazzeri et al[14]	1
Cervicothoracic	
Chan et al[8]	1
Lunardi et al[19]	1
Lumbar	
Haase[15]	1
Abdullah et al[1]	4
Vernet et al[29]	6
Savitz et al[25]	6
Baker and Hanson[4]	1
Bloch et al[6]	6
Mahallati et al[20]	1
Bärlocher and Seiler[5]	1
Terada et al[28]	1
Cakir et al[7]	1
Wildi et al[30]	33
DiMario et al[9]	4
Asamoto et al[2]	1
Gazzeri et al[13]	1
Ayberk et al[3]	2
Our case	1

Neuroimaging is helpful in diagnosing cyst of the ligamentum flavum. On myelography, these lesions are recognized as intraspinal extradural masses and on postmyelogram computed tomography as a faint cyst adjacent to the ligamentum flavum.[32] Magnetic resonance imaging provides the best images[14,20,25,28]: on T1-weighted images, the cysts have a variable signal, and on T2-weighted images, the cysts have a high-intensity signal.[20,28] Differential diagnosis of imaging studies between ligamentum flavum cysts and synovial cysts is useful to the surgeon, as the latter are more difficult to resect, requiring exploration of the facet joint. Magnetic resonance imaging, in some cases of synovial cysts, reveals demonstrable communication with the facet joint with enhancement of the synovial cyst wall and of the adjacent facet joint. Synovial cysts often have a calcified rim, while ligamentum flavum cysts do not.

Differential diagnosis of intraspinal extradural mass lesions includes ligamentum flavum cyst, juxta-articular cysts (ganglion and synovial cysts), arachnoid cyst, perineural cyst, dermoid cyst, infectious cyst, schwannoma, meningioma, and metastasis or nont-umorous-type mass lesions including neurofibromas, fibrous dysplasia, ependymal cyst, and rheumatoid arthritis pannus.[15,20,23] The nomenclature of cysts in the spinal canal is somewhat unclear in the literature. Most intraspinal cysts reported are juxta-articular cysts. Ligamentum flavum and juxta-articular cysts can be definitely distinguished only by their pathological findings.

Conservative therapy appears to have no success.[15,20] Most conservative therapies are temporary and have varying success in the short-term. Surgical removal is the first-choice therapy. The goal of surgery is spinal decompression as well as resection of the cyst and affected ligamentum flavum. Complete excision at the base of the ligamentous insertion of the cyst assures a minimal rate of recurrence. Wildi et al[30] reported recurrence of the cyst in the remaining ligamentum flavum in two patients 1 year after surgery. While nearly 95% of all operated cysts can be removed in their entirety, a major reported intraoperative difficulty lies in the presence of adhesions to the dural wall, which is the main causative factor of incomplete resection.[9]

Complete removal of pseudocystic lesions generally has excellent results.[2,9,14,27,28,30] Our patient showed complete postoperative resolution of symptoms. He is neurologically intact and symptom free to date.

CONCLUSION

To summarize, ligamentum flavum cysts represent a rare cause of lumbar nerve root compression or spinal stenosis. The lumbar ligamentum flavum undergoes lifelong mechanical stress. Similar to bony structures in this region, it degenerates with age. The degenerative changes in the lumbar ligamenta flava can be followed by cystic changes. Histologically, these degenerative changes represent a distinct entity different from ganglion or synovial cysts. Magnetic resonance imaging provides the best images. Radical removal of pseudocyst guarantees in nearly all cases complete relief of radiculopathy and seems to prevent recurrence of such a lesion at the same level.

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CASE REPORT

Fine-Needle Aspiration Cytology Findings of Mucinous Carcinoma of Breast

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ABSTRACT

Pure mucinous carcinoma (MC) of the breast is a relatively uncommon variant of breast carcinoma with distinctive histological and cytological features. Knowledge of the distinctive cytomorphological appearance of MC would enable correct identification of these lesions as malignant and prompt treatment that could further enhance the survival of these prognostically good breast cancers.

Keywords: Breast neoplasms, Fine-needle aspiration cytology, Mucinous carcinoma.

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INTRODUCTION

Mucinous lesions of the breast represent a broad spectrum of entities, which may pose a diagnostic challenge on fine-needle aspiration cytology (FNAC). Mucinous carcinomas (MCs) are so bland cytologically that they may be misdiagnosed as benign lesions, especially in cellpoor samples with ample mucin. Mucinous carcinoma of the breast is a distinctive, well-differentiated type of adenocarcinoma, constituting 2 to 5% of breast cancers.[1,2] Pure MC of breast has been reported to have a more favorable prognosis than other well-differentiated adenocarcinomas of breast, with a lower frequency of auxiliary node metastasis and excellent short-term prognosis, especially when the tumor measures less than 5 cm in diameter.[3] Fine-needle aspiration has been described to yield copious amounts of mucinous material with a variable proportion of tumor cells. The tumor cells have been described as being generally small and fairly uniform with minimal atypia, and this may give a false impression of bening.

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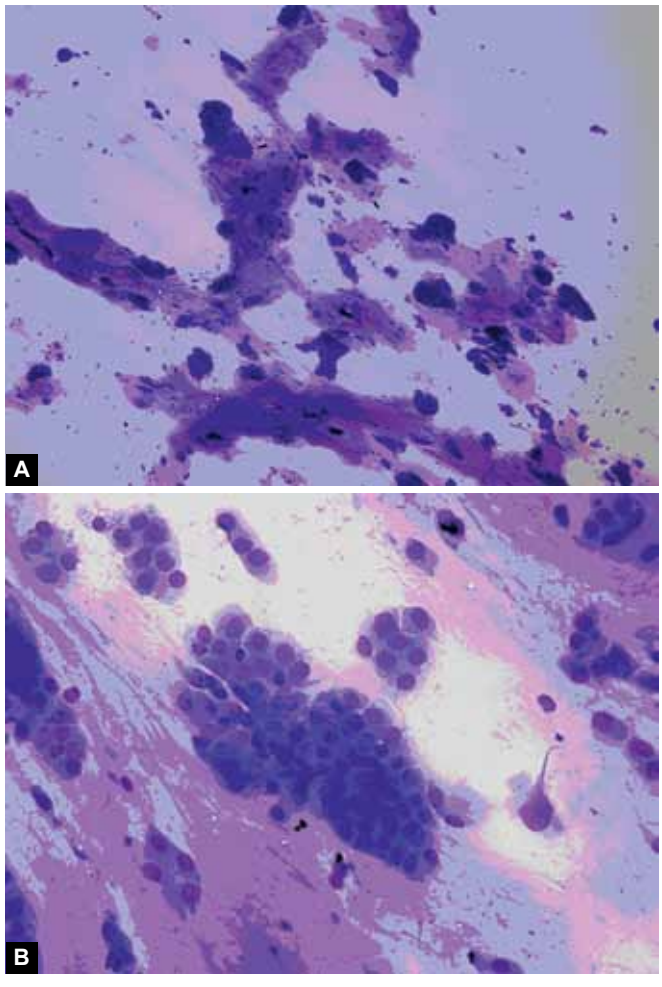
CASE REPORT

A 50-year-old Indian woman complained of left breast mass for 6 months. Her past medical record and family history were unremarkable. Sonography revealed a partially ill-defined and lobulated tumor about 3.4 × 2.5 cm in dimension.

Fine-needle aspiration smear was moderately cellular with clusters of tumor cells against a rich mucinous background (Figs 1A and B). The tumor cells were bathed in wispy or colloid-like mucin material. Tightly cohesive three-dimensional (3D) cell balls and angulated clusters were noticed. The tumor cells exhibited mild to moderate nuclear atypia with small nucleoli.



Figs 1A and B: (A) Moderately cellular with clusters of tumor cells against a rich mucinous background and (B) tumor cells were bathed in wispy or colloid-like mucin material

DISCUSSION

Breast lesions with mucin represent a broad spectrum of entities, including fibrocystic change (FCC) with luminal mucin, mucocele-like lesion (MLL), pure or mixed type of, and other conditions accompanied by mucin-like material. Among these mucinous lesions, MLL is an uncommon tumor initially described by Rosen as a benign process of breast.[4] The subsequent reports on MLLs disclose a spectrum of pathologic lesions from benign tumor, atypical ductal hyperplasia, carcinoma *in situ* to invasive carcinoma, further complicating the diagnostic problem. Mucinous carcinoma is a variant of breast cancer, characterized by the accumulation of abundant extracellular mucin around invasive carcinoma cells. In practice, a carcinoma should not be classified as pure MC if more than 10% of the invasive component is nonmucinous, or if the nonmucinous invasive component is poorly differentiated cytologically. Mucinous carcinoma may appear clinically and radiologically benign and FNAC plays important role in the correct preoperative diagnosis. Significant nuclear pleomorphism and necrosis, in addition to extracellular mucin suggests mixed MC invasive ductal carcinoma.[5] In general, pure MCs have a favorable prognosis, and the 10-year survival ranges from 80 to 100%.[6]

The cytologic features of MC are well established. However, aspirates with abundant extracellular mucinous material originating from other mammary lesions, especially those with increased cellularity, may pose a diagnostic challenge on FNAC. Cytologic features, such as cellularity, shape of the epithelial cell nests, nuclear pattern, background and stromal component are helpful in the differential diagnosis.[7,8] The mucinous material in MC appears thin and wispy or thick and resembling colloid on aspiration biopsy smears. In general, the cytologic pattern is highly variable from predominantly dyscohesive single epithelial cells floating in a mucinous background to predominantly cohesive sheets and 3D aggregates. Cellular atypia is mild to moderate. A distinct feature of MC is the presence of thin-walled capillaries, either free-floating or coursing through the thick mucin. Caution must be taken in diagnosing any malignant mucinous lesion with a high nuclear grade specifically as MC, because these lesions most likely will harbor ductal carcinoma, not otherwise specified (NOS) component. It is recommended that paucicellular lesions lacking cytologic atypia, whether representative of FCC or mucocele-like lesion, be considered for conservative surgical excision based on the lack of reliable malignant features.

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CASE REPORT

Pulmonary Thromboembolectomy in Chronic Thromboembolic Pulmonary Hypertension: A Case Report and Review of Literature

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is an important cause of severe pulmonary hypertention (PH) resulting in significant morbidity and mortality. Chronic thromboembolic PH occurs when a pulmonary embolism fails to undergo complete thrombolysis leading to vascular occlusion and pulmonary hypertension. Despite the fact that CTEPH is a potential consequence of pulmonary embolus, diagnosis requires a high degree of vigilance as many patients will not have a history of thromboembolic disease. The ventilation perfusion scan is used to evaluate for the possibility of CTEPH although right heart catheterization and pulmonary artery (PA) angiogram are needed to confirm the diagnosis. Pulmonary thromboendarterectomy is the first-line treatment for patients who are surgical candidates. This case report and review describes the pathophysiology, risk factors, diagnosis, and management of CTEPH. As it is a potentially curable cause of PH, its accurate diagnosis is vital. The gold standard and effective treatment for CTEPH is pulmonary endarterectomy (PEA). Pulmonary endarterectomy is an uncommon procedure with less than 50 years of experience worldwide. Research on the development of new surgical approaches is essential. In the present case, a new successful surgical technique for PEA was introduced.

Conclusion: The surgical procedure used on the present patient was a unique technique. We do not claim that our technique is better than the original San Diego technique, but it is suggested as a modification that may improve patient survival. However, this procedure has its own limitations and cannot be used for clots that are located distally. Therefore, further experience should be obtained in order to overcome the limitations and improve the applicability of the technique.

Keywords: Chronic obstructive pulmonary disease, Chronic thromboembolic pulmonary hypertension, Interstitial lung disease, Pulmonary artery angiogram, Pulmonary endarterectomy, Pulmonary thromboendarterectomy.

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INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is an important cause of severe pulmonary hypertention (PH) resulting in significant morbidity and mortality. As it is a potentially curable cause of PH, its accurate diagnosis is vital. The gold standard and effective treatment for CTEPH is pulmonary endarterectomy (PEA).[1] Pulmonary endarterectomy is an uncommon procedure with less than 50 years of experience worldwide. Research on the development of new surgical approaches is essential. In the present case, a new successful surgical technique for PEA was introduced.

CASE REPORT

A 45-year-old woman presented with a chief complaint of dyspnea and fatigue. She had a history of dyspnea and exertional chest pain for 6 months, which had worsened in the last few months (New York Heart Association functional class III). She had no history of orthopedic surgery, deep vein thrombosis, being bed ridden, or long air travel. Physical examination revealed an elevated neck vein, loud P2, tachypnea, and light edema of the feet.

In evaluations performed previously in another medical center, an echocardiographic study revealed normal left ventricular systolic function and size, severe pulmonary arterial hypertention (PAH), Grade 1 tricuspid regurgitation, and dilated inferior vena cava with minimal collapsibility. Based on echocardiographic data, the estimated systolic pulmonary pressure was 130 mm Hg.

As the chest X-ray and the pulmonary function test were normal, it seemed that the patient's PH was not related to chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD). A lung computed tomography (CT) scan with contrast angiography

was performed. It revealed a filling defect compatible with chronic pulmonary thromboembolism in the right pulmonary artery (RPA) leading to its complete obstruction (Fig. 1). It was also decided to perform right heart catheterization to measure the patient's hemodynamic parameters in order to confirm CTEPH.

All findings were suggestive of CTEPH, therefore, surgical embolectomy was recommended. Evaluation of the patient prior to surgery excluded predisposing factors of CTEPH including antiphospholipid antibodies, anticardiolipin antibodies, lupus anticoagulant, and inflammatory bowel disease.

Surgical Technique

The patient was intubated, and after inserting monitoring devices, the median sternotomy was performed. Cannulae were inserted into both the vena cava and the ascending aorta encircled with tapes. Cardiopulmonary bypass was established under moderate (26°–31°C) hypothermia. The aorta was clamped, and a cold cardioplegia solution was infused into the aortic root with subsequent infusions of the same solution every 20 minutes. During cooling, the superior vena cava (SVC) was immobilized to the level of innominate vein, but the azygos vein was not divided. Right pulmonary artery was mobilized by retracting the vena cava laterally and the aorta medially by using encircling tapes. After establishing cardiac arrest, on the RPA, a 4 cm incision was taken. A plane was established using a sharp dissector, and thromboembolectomy was done. Establishing the correct plane is important as a very deep plane will result in perforation of the vessel and a plane that is too superficial will result in inadequate embolectomy. After completing the dissection in the distal part of the RPA, the incision on the proximal part was extended, and then, the embolous material was removed (Fig. 2). Finally, the RPA incision was repaired with Prolene 5-0.

The cardiopulmonary bypass duration was 1 hour 10 minutes, and the aortic clamp duration was 50 minutes. After re-warming and heart beat restoration, cardiopulmonary bypass was discontinued, the cannulae were removed, and the rest of the surgery was completed under standard conditions. The patient was transferred to the intensive care unit. She was hospitalized for 7 days and discharged in good general condition. The postoperative day 2 echocardiogram showed a significant decrease in the size of the right heart chambers, decreased systolic pulmonary pressure (from 130 to 60 mm Hg), improved right ventricular (RV) function, and reduced tricuspid valve regurgitation. The lung CT scan with contrast angiography showed complete reopening of the RPA and its lobar branches.

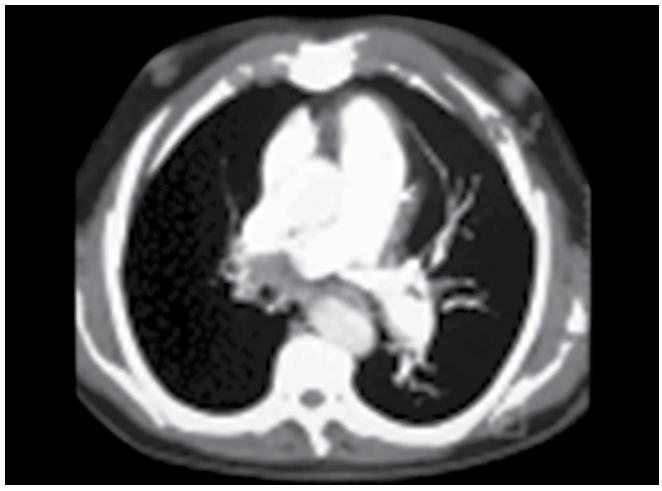

Fig. 1: Lung CT scan with contrast angiography showing a filling defect in the RPA leading to complete obstruction

Fig. 2: Macroscopic view of the endarterectomy specimen

Literature Search Methods

The literature search of electronic databases, such as MEDLINE, EMBASE, Cochrane Library, Canadian Medical Association InfoBase, and National Guideline Clearinghouse, etc. were undertaken by way of combining heading terms and text search terms like, 'pulmonary thromboendarterectomy', 'chronic thromboembolic pulmonary hypertension', 'chronic pulmonary embolism', and 'PEA in order to identify the body of published evidences on chronic thromboembolic PH.

Literature Search Results

Pulmonary embolism is a common condition. Some patients subsequently develop CTEPH. Many care gaps exist in the diagnosis and management of CTEPH patients including lack of awareness, incomplete diagnostic assessment, and inconsistent use of surgical and medical therapies. Asymptomatic patients postpulmonary embolism should not be screened for CTEPH. In patients with PH, the possibility of CTEPH should be routinely evaluated

with initial ventilation/perfusion lung scanning, not CT angiography. Pulmonary endarterectomy surgery is the treatment of choice in patients with surgically accessible CTEPH, and may also be effective in CTEPH patients with disease in more 'distal' PAs. The anatomical extent of CTEPH for surgical PEA is best assessed by contrast pulmonary angiography, although positive CT angiography may be acceptable. Novel medications indicated for the treatment of pulmonary hypertension may be effective for selected CTEPH patients. Chronic thromboembolic PH is defined as follows:

- A mean pulmonary arterial pressure (mPAP) of 25 mm Hg or greater and pulmonary vascular resistance (PVR) of 3 Wood units (240 dyne × sec/cm^5) or greater
- Persistent angiographic pulmonary arterial thrombotic obstruction despite at least 3 months of effective, uninterrupted anticoagulation.

Clinical recognition and management of CTEPH are important for several reasons. First, CTEPH is believed to be one of the most common causes of PH. Second, CTEPH is a serious, progressive and often fatal disease. Patients with untreated CTEPH experience significantly increased mortality—observational studies[2,3] have estimated the median survival rate in severe CTEPH patients to be as low as 10 to 20% at 2 to 3 years. Third, CTEPH is potentially curable with PEA surgery. Finally, CTEPH patients may also benefit from treatment with novel PH-specific medications that are currently available for patients with other types of PH such as PAH.

DISCUSSION

Chronic thromboembolic pulmonary hypertension is a disabling disease referred to a late onset complication of pulmonary thromboembolism that decreases the patient's functional status and reduces the patient's chance of survival. The main cause of death in such patients is usually RV failure.[4] Chronic thromboembolic pulmonary hypertension is misdiagnosed in many cases as occurred for our patient at his first visit. The patient's dyspnea had been previously attributed to COPD or ILD. As no positive findings were obtained by chest X-ray and pulmonary function test (PFT), performing the lung CT scan with contrast angiography indicated a filling defect compatible with chronic pulmonary thromboembolism in the RPA leading to its complete obstruction.

The available treatments for CTEPH include medical therapy, PEA, and pulmonary transplantation.[5] Lung transplantation is not recommended as the first step due to its unsatisfactory results: a postoperative mortality rate of 20% and a 5-year survival rate of 50%.[6] Medical therapy is appropriate only in patients with inoperable or residual postoperative CTEPH. The treatment of choice for CTEPH is surgical PEA leading to normal pulmonary hemodynamics in 80% of the patients.[7] The pathophysiology of PH and RV overload in many CTEPH patients is related to the presence chronic, organized thrombotic vascular disease at the level of the larger proximal PAs including the main, lobar and segmental PAs. By definition, such disease is not treatable with simple anticoagulation because the occlusive material is believed to have evolved from a thrombus to more organized or fibrotic tissue. No medications have been shown to be effective in treating this occlusive pulmonary arterial disease.

The current surgical procedure for PEA as a standard approach to the treatment of CTEPH was first developed in the late 1980s at the University of California at San Diego (California, USA) by the team led by Dr Ken Moser.[8] Since the initial reports, there have been several modifications to the surgical approach to PEA. Approximately 4000 procedures have been completed in specialized centers in many countries worldwide.[9,10]

The accepted approach to the PAs is through a median sternotomy using central cannulation with cardiopulmonary bypass. Due to bronchial artery hyperplasia in CTEPH,[11] PEA is usually performed under deep hypothermic circulatory arrest or low-flow bypass to minimize bleeding, and to optimize visualization and the quality of the PA dissection. After aortic cross-clamping and the administration of myocardial protection with cardioplegia, the right and left main PAs are sequentially approached through arteriotomies extending out close to the pericardial reflection. The RPA is approached from the space between the SVC and the aorta. Once the blood vessel is opened, an appropriate endarterectomy plane is developed in the posterior wall of the vessel using blunt dissection. The specimen is prepared circumferentially, with subsequent careful dissection distally into the lobar and segmental vessels of each lung. The periods of circulatory arrest are generally limited to a maximum of 20 minutes, with corporeal reperfusion for 10 minutes between periods of arrest.[12] Two 20 minutes period are usually required for complete excision of bilateral specimens. After the specimen has been completely removed, the PA is closed, and the patient is subsequently rewarmed and weaned from cardiopulmonary bypass. Postoperative care is usually in an intensive care unit setting with routine clinical and hemodynamic monitoring.

Most probably, the first PEA was performed in May 1962 by Dr Charles Hufnagel.[13] In 1970, Nina Braunwald performed the first operation using a right lateral thoracotomy and cardiopulmonary bypass at the University of California San Diego (UCSD).[14] Since

then, the technique has been modified progressively, including the use of median sternotomy and hypothermic circulatory arrest, more proximal incisions, an approach to the right side beneath the SVC rather than above it, and the avoidance of more than one arteriotomy on each side. The technique for endarterectomy was mainly developed by Dr W Jamieson at UCSD. In the routine procedure, after circulatory arrest is established, an incision is made in the PA between the aorta and the SVC. Any loose thrombotic material debris, if present, is removed. The correct plane is established with a sharp dissector, and intima and a part of media are removed. Then, the fibrotic material is grasped gently with a pair of forceps while sweeping away the outer vessel wall layer with an aspirating dissector resulting in the progressive withdrawal of the endarterectomy specimen.[15]

Although PEA is the gold standard of treatment, its perioperative mortality is about 10% (4–24%).[16-20] Yet, PEA remains an unusual procedure. The method does not support complete clot removal, and the outcome is highly dependent on the degree of thrombotic specimen extraction and damage to the PA bed. The aspirating dissector can be harmful for the PA and may cause perforation in the PA. Pulmonary endarterectomy is the best treatment for patients with CTEPH. Traditionally, PEA has been performed utilizing deep hypothermic circulatory arrest to provide a bloodless field, but some recent reports have challenged this concept. We reviewed our experience with selective extra suctions as the initial strategy of controling bronchial collateral flow to avoid complete circulatory arrest in patients undergoing PEA.

In our center, PEA was done as mentioned above with the exception that extra suctions were used instead of an aspirating dissector. The modification seems to be safe and convenient. In conclusion, the surgical procedure used on the present patient was a unique technique. We do not claim that our technique is better than the original San Diego technique, but it is suggested as a modification that may improve patient survival. However, this procedure has its own limitations and cannot be used for clots that are located distally. Therefore, further experience should be obtained in order to overcome the limitations and improve the applicability of the technique.

CONCLUSION

Pulmonary endarterectomy has become the standard of care given the dramatic hemodynamic and clinical improvements that have been observed in many CTEPH patients. This is in contrast to the poor prognosis for survival that has historically been associated with CTEPH.[1,4] For example, survival at 2 years was less than 20% when mPAP exceeded 50 mm Hg in non-surgically treated CTEPH patients in one study from an era before the availability of PH-specific medications.[2] A significant mortality of 32% was also found in CTEPH patients with less severe hemodynamics.[3]

Key Evidence

Although approximately 4000 PEA surgeries have been performed worldwide in the past 30 years, not all of these patients' outcomes are reported in the published literature. A large number of observational reports have described the effects of PEA surgery on pulmonary hemodynamics,[21] cardiac size and function,[22,23] clinical parameters and other important outcomes, such as survival.[9,24,25] However, there are no RCTs that directly compared PEA surgery for patients with surgically accessible CTEPH with either conservative management alone (e.g. diuretics, oxygen and anticoagulation) or with conservative management plus novel PH-specific medications without PEA.

In the vast majority of reports, there is an immediate improvement in hemodynamics after PEA including an increase in CI and significant decreases in PVR and PAP both on arrival to the intensive care unit and over the ensuing few days.[9] Right ventricular remodeling also occurs quite rapidly after PEA.[26,27] There is an immediate decrease in right-sided chamber sizes, a marked reduction in tricuspid insufficiency, with normalization of valve geometry, decreased leftward shift of the interventricular septum, increased left ventricle (LV) end-diastolic area and reduced LV eccentricity.[28-30] Clinical improvement after PEA is likely related to improvement in pulmonary hemodynamics,[31,32] blood flow and RV function following removal of pulmonary arterial obstructive material[29,33] but may also be due to reversal of pulmonary vascular remodeling.[34,35]

In experienced hands, perioperative (30-day) mortality ranges from 4 to 10%, with the most common cause of early death related to persistent PH.[24,25,29,36] In the largest series,[36] PEA perioperative mortality between 1998 and 2002 was 4.4% (22 of 500). Increasing surgical experience, technical refinements and better patient selection likely explain the improvements in perioperative mortality during the past 15 years. However, the purported benefits of PEA suffer from potential publication bias, and outcomes[37-39] may vary significantly from center to center depending on experience and surgical expertize.

Among survivors of PEA, there is evidence that patients can expect significant improvement in long-term outcome. A comprehensive follow-up conducted in San Diego (California, USA) between 1970 and 1994 reported a survival rate of 75% 6 years after surgery in 514 PEA patients. The most common cause of late death

was residual PH post-PEA, with death in this subgroup occurring at a mean of 2.73 years after surgery. More recent series have found 2-year survival to be in the 85 to 90% range[24,40-42] in striking contrast to the natural history studies of nonsurgically treated CTEPH patients.[1]

Studies have also reported significant post-PEA improvements in long-term health-related quality of life (HRQoL),[40,48] exercise tolerance as measured by six-minute walk distance (6MWD),[24,25,44,45] peak oxygen consumption and functional capacity[24,43,46,47,49] The improvements in these clinical parameters have often been correlated with pulmonary hemodynamic improvement post-PEA.

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SHORT COMMUNICATION

Better Visualization of Red Blood Cells by Adding Leishman's Stain to Hayem's Fluid

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ABSTRACT

The visualization of red blood cells (RBCs) was compared by the modified method and the conventional method. The RBCs were seen better with the modified method.

Keywords: Hemocytometer, Leishman's stain, RBC diluting fluid, Red blood cells count.

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INTRODUCTION

Presently, the students are using hemocytometer for doing total red blood cell (RBC) count which contains Neubauer's chamber and the RBC pipette. The dilution fluid used is Hayem's fluid which is colorless. The principal of this method is on the basis of diluting the blood with Hayem's fluid and then counting the RBC's. Students face difficulty in counting the RBCs as RBCs are not seen properly as they are not stained. Students will find it more easy to identify the RBCs if they are stained. Therefore, counting also become more easy.

In view of this, the modified method is proposed for better visualization of RBCs.

MATERIALS AND METHODS

Materials

(1) Hemocytometer; (2) Hayem's fluid-with composition of sodium chloride—2 gm, sodium sulfate—4.4 gm, mercury chloride—1 gm, distilled water—400 cc[1,2] purchased from Fisher Scientific Qualigens company; (3) Leishman's stain-contains methyline blue and eosine—0.15 gm of dry stain slowly madeup to 100 ml with acetone free methyl alcohol from Ranbaxy fine chemicals limited; (4) sterile needle, and (5) microscope.

Methods

In modified method, two drops of Leshman's stain were added to 2 ml of Hayem's fluid and mixed well. This mixture is used as diluting fluid. With aseptic precautions finger prick is done and blood is collected. It was diluted by conventional method using Hayem's fluid and by modified method using mixture of Hayem's fluid and Leishman's stain. Two Neubauers chambers were charged. One Neubauers chamber charged with the blood sample diluted with Hayem's fluid and second Neubauers chamber charged with the blood sample diluted with Hayem's fluid containing Leshman's stain. Then both Neubauers chamber were observed under the microscope using 40× objective lens. The photographs were taken.

RESULTS

Red blood cells with the conventional and modified methods under 40× magnification were observed (Figs 1A and B). Out of these two methods, the RBCs were seen comparatively better with the modified method.

DISCUSSION

In conventional method of RBC count, Hayem's fluid which is colorless, is used only as diluting agent which provides poor visualization of RBC whereas in modified method, the Eosin present in the Leishman's stain stains the RBCs. Because of the staining, the RBCs are relatively seen well.

CONCLUSION

In a nutshell, the application of modified method (Leishman's stain mixed with Hayem's fluid) is highly recommended for optimum visualization of RBCs.

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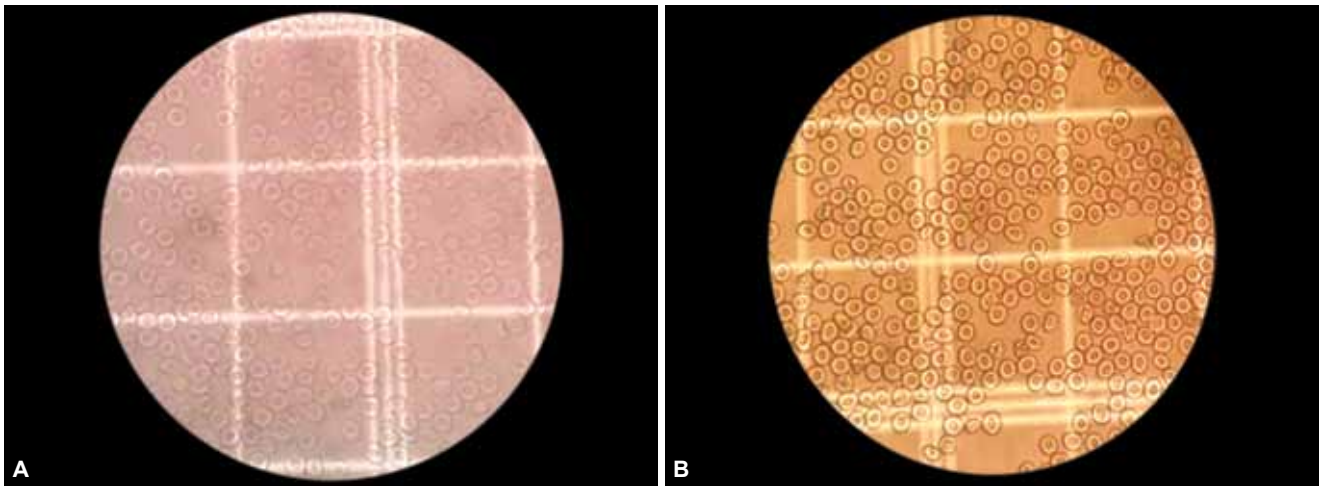

Figs 1A and B: The RBCs with the conventional and modified methods under 40× magnification

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