Editorial

PAKISTAN COMBATING CORONA PANDEMIC: ARE GOVERNMENT POLICIES ENOUGH?

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Coronavirus is known to cause epidemics globally. Severe Acute Respiratory Syndrome (SARS-COV) and Middle East Respiratory Syndrome (MERS-COV) are well-known epidemics caused by the coronavirus family.[1] The most recent variety is Novel Coronavirus known as COVID-19. COVID-19 began as an epidemic in Wuhan, China in Dec. 2019 and has by now infected more than 200 countries.[2] Initially, it was reported as a public health crisis of international concern, and with an alarming increase in involvement of a large number of countries, World Health Organization (WHO) declared it a pandemic on Mar. 11 2020.[3] The patient presents with pneumonia like symptoms beginning with mild cough, dyspnea, fatigue, low-grade fever and causes mortality specifically in people with any underlying comorbidity like diabetes asthma or kidney disorders.[4]

According to the World Health Organization, by Jun. 12, 2020, there were over 7,355,981 confirmed cases worldwide and over 416,891 deaths on record.[5] This virus advanced rapidly from China to Thailand, South Korea, and the United States within the very month of Jan.[6] Because of the geographical relation to Iran and China, Pakistan was most vulnerable to the spread of this disease. The first case in Pakistan emerged on Feb. 26, 2020, in Karachi, Sindh.[7,] And by Jun. 12, 2020, total confirmed cases in Pakistan were 125,933, and total deaths were 2463.

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The province with the greatest number of cases in Sindh, with confirmed cases 46,828 and deaths 776. Then comes Punjab with confirmed cases 47,382 and deaths 890. Islamabad has 6699 confirmed cases and 65 deaths according to data provided by the government of Pakistan.[8]

Pakistan shares a border with Iran, and the first case which led to the outbreak was a result of contact with pilgrims returning from Iran without proper precautions.[9] The government took timely steps to contain the Pandemic. They set quarantine centers near the Taftan border (Pak-Iran border) for the pilgrims to be kept in isolation for 14 days.[10] As the disease unfurled and more cases were reported Sindh, and Balochistan government announced a lockdown on Mar. 23 till Apr. 7 while Punjab government-imposed lockdown on Mar. 24 till Apr. 6 .[11]

Under this partial lockdown termed as "smart lockdown," all educational institutions were closed down.[10] All ongoing and upcoming exams were delayed until further notice. Some public and private sector offices were closed down as well. Shopping malls and areas of public gatherings like cinemas, banquet halls, restaurants were shut down. Travelling and trade were halted temporarily. Even mosques and congregations have stopped some people, yet despite the government's strict orders went to pray and attend religious gatherings.[12] Only pharmacies, hospitals, and grocery stores remained open. Since the majority of the Pakistani population is a daily wager, this whole situation was a great blow to them, so in regard to their necessities, the government announced a relief package of Rs.12000/- on a monthly basis. This period was somewhat

better as the number of patients did not spike up as estimated. The mortality rate was low, too.[12] The major setback occurred as soon as the government declared "ease" in the lockdown near Eid-ul-Fitr. Small markets or shops were opened with Standard Operating Procedure (SOPs) issued by the government like wearing masks, using sanitizers, using thermal scanners for the customers, which was not followed by the majority. The government set a specific time for the opening of shops from 9 am to 5 pm. Offices were reopened.[12] Public transport, as well as special national and international flights, were operable again. This lead to the incoming of thousands of overseas Pakistani and with them a brisk increase in the number of patients.[13]

The government policies seemingly failed after Eid as the total number of people infected from Feb. 26 to May 23 were 52,437 and total deaths 1,101, while after Eid within two weeks, i.e., from May 23 to Jun. 6 the total number of cases increased swiftly and reached 93,983 and total deaths 1935.[14] As Pakistan is a developing country with much fewer resources including safety kits, ventilators and hospital beds to accommodate such a large population.[15] This makes health care workers more vulnerable to developing the infection. Even life-saving drugs have become scarce. All these prove to be major causes of the rapidity of the infected cases. Apart from this, one significant factor is the lack of awareness regarding viruses in public, which leads to ignorance of the safety measures. Despite the comparatively moderate mortality rates of COVID patients in Pakistan, the number of those getting infected on a daily basis is increasing swiftly.

Globally speaking New Zealand is the first country to have eliminated COVID-19. No new cases have emerged almost after a month since its strict lockdown began on Mar. 23, 2020.[16] The first case in New Zealand was recorded on Feb. 28.[17.] Their immediate and timely action was an absolute ban on travel which wasn't alleviated despite the pressure from other countries. Their period of "strict lockdown" included different alert levels. Level 1 attributed to setting up border policies. Level 2 included more strict implementation of these measures as well as prohibiting any public or private gatherings. Level 3 included shutting down businesses that could be carried out from home and closing of schools and universities.[6] Level 4 included the concept of "bubble" living. This type of living encompassed single household but was expanded later. If any person in the bubble was symptomatic the whole bubble was quarantined.[18] Such strong strategies lead to elimination of COVID-19 from New Zealand.

WHO has recommended the Pakistani government to implement a lockdown for two weeks to contain the rampant growth of infected cases. Besides precautionary measures like a complete ban on travel, more strict policies are to be made for the border areas. The government should ensure the public is well versed with the safety measures that are necessary, like social distancing, coughing protocol, and benefits of wearing masks. The government should provide safety kits to Health care professionals. Hospitals should ensure the thermal scanning of patients, as well as attendants, proper sanitization of hospital premises, and tools, should be considered. Strict implementation of the law is needed and not just some smart lockdown to ensure the number doesn't increase with as much rapidity as of now. It is the need of the hour to save human lives rather than the economy as even before this Pandemic Pakistan was experiencing an economic slowdown[19] and experts say millions of people will be rendered unemployed during this pandemic.[20]

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Original Article

CAREER PREFERENCES AND BRAIN DRAINING THREATS AMONG YOUNG MEDICAL GRADUATES OF SERVICES INSTITUTE OF MEDICAL SCIENCES, LAHORE.

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ABSTRACT:

Objectives: To determine the career preferences and to assess the brain drain threats among young medical graduates of the Services Institute of Medical Sciences (SIMS) Lahore.

Material and Methods: This cross-sectional study was carried out in students of final year MBBS and house officers of Services Hospital Lahore. A detailed questionnaire was used to collect data and face to face interview was also conducted.

Results: A total of 310 students, including 144 final year students and 166 house officers, with (61.29%) male and (38.71%) female. (70.97%) of the respondents were intended to migrate abroad to pursue the training. UK and US were the most preferred destinations. The reasons cited for migration abroad were quality of training (63.64%), economic prospect, after training (15.91%), salary during training (9.09%), professional prospect, after training (9.09%), and desire to settle abroad (2.27%). For respondents who had no plan of migrating abroad, the most important reason for staying in Pakistan was family ties (44.44%), followed by a desire to serve the nation (33.33%), professional satisfaction (11.11%), desire to live in Pakistan (5.56%) and lack of resources (5.56%). Surgery was the first choice by 41.9% of the graduates, followed by Internal Medicine (24.2%), General Medicine/Family Medicine (9.7%), Psychiatry (6.5%), Pediatrics (4.8%), Obstetrics and Gynecology (4.8%) while (3.2%) selected dermatology.

Conclusion: Improvement in the health care system and medical education should be made along with the policy settings to attract young doctors to settle down in Pakistan and to opt high-priority disciplines so that imbalances encountered would be minimal in the future.

Key Words: Brain Drain, Medical Education, Career Preferences

INTRODUCTION:

The transfer of skilled human resources to foreign countries is called brain drain.[1] Many countries are facing this problem. The aim of migration may be to get more salaries and improve the quality of life, access to advanced technology, and to live in stable political conditions.[2]

The four preferred countries for migration are United States, United Kingdom, Australia, and Canada. About 23-28% of doctors working in these countries are International Medical Graduates (IMGs). About 40-75% of these IMGs come from low salaried countries, like Pakistan, which contributes about one third. The percentage of physicians serving abroad (emigration ratio) from Pakistan varies from 13.5% to 17.6%.[3]

The factors important for medical students to choose their future career may be broadly classified into two major types – Intrinsic and Extrinsic. The intrinsic factors are related to personal preferences, whereas the extrinsic factors are related to work environments.[4] The effects of these factors are different in different settings. In the UK, the students are attracted by fewer practice

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hours and other peoples' perception of the job.[5] In other countries like India, Taiwan, and Saudi Arabia, the doctors are more influenced by their personal likings of the specialty.[4,6,7] Careers are chosen according to the specific gender "schemas." Male doctors' preferences are surgical subjects whereas females usually prefer Obstetrics and Gynecology and Pediatrics.[4]

An online cross-sectional survey was carried out among all Irish medical students studying in their own country. A total of 2273 medical students responded with a 37% response rate. Out of these, 1519 medical students had completed their secondary school in Ireland. 88% of these students gave their intention for migration after graduation or completion of the pre-registration intern year. 40% were of the view of returning to Ireland within five years. The causes for their decision to migrate were career opportunities 85%, working conditions (83%), and lifestyle (80%).[8] Another research conducted in Canada showed that job satisfaction, post-training lifestyle, and impact on the patient were the three predominant factors related to the choice of a specialty. Both genders considered Family Medicine, Pediatrics, and Emergency Medicine at the top of nonsurgical specialties. The least popular choice for both genders were auxiliary departments.[9]

In Saudi Arabia, a study was conducted among 220 medical graduates to determine the factors affecting the career specialty preferences. Out of these, 13.2% opted for general surgery as a major subject, 10.9% pediatrics, and 8.2% for internal medicine. A minute percentage of students opted for Genetics, Oncology, Emergency Medicine, Forensic Medicine, Pathology, Pediatric Surgery, Neurology, etc, while about 10.9% of students were not sure about their career specialty. One hundred seventy students, 53.1% chose their major specialty that matches with their own capabilities. As many as 37.2% of students were of the opinion that opting subspecialty in medicine was a confounding factor influencing their specialty selection. Two students said that their family friends selected their specialty. Female students opted for major specialties according to their preferences. Only two female students selected specialty because their friends and family preference.[10]

A study was carried out in Mayo Hospital Lahore, which depicted that various political conditions and socio-economic factors were influencing the migration of doctors from Pakistan. 83% of the doctors pointed out the poor salary package and professional infrastructure of the health department as a major factor in doctors' brain drain. 81% claimed that persistent political instability and threats of terrorism are the causes of the emigration of doctors. 84% of respondents considered fewer available opportunities of postgraduation which is responsible for their migration.[11]

The Irish Hospital Consultants Association declared that patients would be forced to remain on waiting lists until the Government makes concrete efforts to stop the brain drain of doctors from their country.[12]

The present study identifies the brain-draining threat among young medical graduates of the Services Institute of Medical Sciences, Lahore (SIMS). This will help to sensitize the concerned authorities to adopt policies to discourage such movements from Pakistan to developed countries.

MATERIAL AND METHODS:

It was a cross-sectional study of 310 participants studying in final year MBBS in SIMS and House Officers serving in Services Hospital, Lahore. Non-probability convenient sampling was used to collect sample. A structured self-administered questionnaire was used to collect basic demographic details about career preferences, factors influencing their choices of specialty, intention for postgraduate going abroad, and the chosen country. The analysis was done in a statistical package for social sciences (SPSS) version 23. Categorical data were presented by frequency and percentage. The percentage of more than 50

was considered significant for influencing career preferences.

RESULTS:

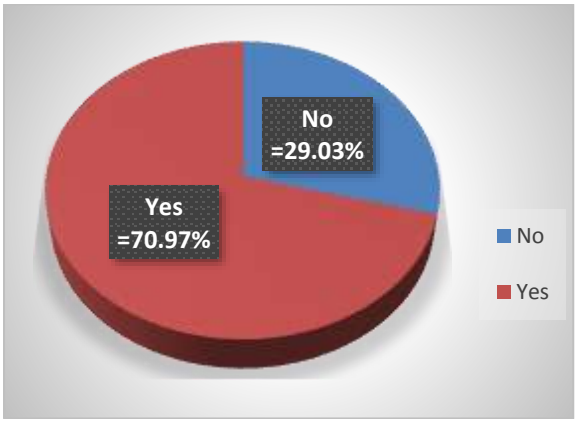

FIGURE-1: Plan of migrating abroad to pursue training.

Figure 1 reveals that 70.97% of the respondents intended to migrate abroad to pursue postgraduate training, while 29.03% had no plan of migrating abroad.

Table-1: Preferred country for migrating abroad

Country	Frequency	Percentage (%)
UK	120	54.545
USA	90	40.909
Australia	5	2.273
Canada	5	2.273
Total	220	100.0

Table 1 shows that out of 220 medical graduates, 54.54% of respondents intended to migrate to the UK, 40.91% to the USA, and 2.27% each to Australia and Canada.

Table-2: Reason for migrating abroad to pursue training

Reason	Frequency	Percentage (%)
Quality of training	140	63.636
Economic prospect after training	35	15.909
Salary during training	20	9.091
Professional satisfaction	20	9.091
Desire to settle abroad	5	2.273
Total	220	100

The most common causes for migrating abroad were quality of training (63.64%), economic prospect after training (15.91%), salary during training (9.09%), professional prospect after training (9.09), and desire to settle abroad (2.27) as depicted in table 2.

Table-3: Weaknesses of training in Pakistan

Weaknesses	Frequency	%Age
Poor working environment	110	50
Poor salary	50	22.73
Long working hours	40	18.18
Poor postgraduate examination system	20	9.09
Total	220	100

Table 3 reveals that the most important weaknesses in training in Pakistan are poor working environment (50%), low salary (20.73%), long working hours (18.18%), and poor postgraduate examination system (9.9%). Poor working conditions refer to the hostile attitude of seniors and less good feedback for good work.

Table–4: Frequency distribution of chosen specialties

Specialty	Frequency	Percentage (%)
Surgery	130	41.9
Internal medicine subspecialty	75	24.2
General medicine/family medicine	30	9.7
Psychiatry	20	6.5
Orthopedic Surgery	15	4.8
Pediatrics	15	4.8
Obstetrics and Gynecology	15	4.8
Dermatology	10	3.2
Total	310	100.0

Out of 310 respondents, 130(41.9%) respondent chose Surgery, 75(24,2%) Internal Medicine, 30(9.7%) General

Medicine/Family Medicine, 20(6.5%) Psychiatry, 15(4.8%) selected Pediatrics and Obstetrics and Gynecology and 10(3.2%) chose Dermatology (Table 4).

Table-5: Factors affecting career preferences

Reason for choosing a specialty	Frequency	Percentages (%)
Interest in the clinical work of the specialty	192	62
Rewarding to work in the specialty	192	62
Highly respected in society	186	60
Encounter with role model teachers	186	60
Aptitude for the specialty	186	60
Interested in surgical procedures or technologies	186	60
Prospect for further development in the specialty	180	58
Attainable lifestyle	180	58
Interest in the research or scientific aspects	177	57
Interest in the organ of the specialty	177	57
Advice/Expectation of parents	174	56
Job availability	174	56
Congenial atmosphere at the specialty department	174	56
Advice from teachers/consultants	171	55
Received excellent teachings	171	55
Interest in the targeted population	161	52
Ease of opening practice	155	50
Working hours	149	48
Influence of friends	130	42
Friend/family suffer(ed) from the disease of the specialty	130	42
Expectation to inherit practice of parents/relatives	124	40
Suffer(ed) from the disease of the specialty	115	37

Table 5 depicts the different factors influencing the specialty preference of the respondents. The most common reasons cited for affecting the specialty preference are interested in the clinical work of specialty (62%), rewarding nature of specialty (62%), respect in society (60%), and encounter with role model teacher (60%). Similarly, having an aptitude for specialty 59%, interest in surgical procedures (59%), the prospect for further development (58%), attainable lifestyle (57%), interest in research, interest in the organ of specialty (57%), parents' advice (56%), job availability (56%), comfortable atmosphere (56%) were also the reasons for choosing a particular specialty. Likert scale for career preferences was interpreted in terms of percentages.

DISCUSSION:

This study revealed that surgery was the residency of choice by 41.9% respondents, followed by Internal medicine (24.2%), general medicine/family medicine (9.7%), psychiatry (6.5%), pediatrics (4.8%), obstetrics and gynecology (4.8%) while 3.2% selected dermatology. This finding of our study is in concordance with the result of studies from Saudi Arabia.[13] This preference of general surgery among medical students might have a great effect on health-care policymakers while planning for future health infrastructure.

In Canadian research, "job satisfaction," "lifestyle following training," and "impact on the patient" were the three predominant factors inferring choosing a specialty. The top three non-surgical specialties ranked first by both genders combined were family medicine, pediatrics, and emergency medicine. Auxiliary specialties remained the least popular choice for both genders.[9]

Whereas in a study done in Turkey, predominant factors were financial opportunities and prestige, and personal interest in the specialty was on the fifth.[14]

In the current study, interest in the clinical work of the specialty was the most important factor influencing the choice of specialty. It was found that 70.97% of the medical students and house officers included in this study were interested in going abroad for specialty or subspecialty training. This percentage is higher as compared to a survey of 166 final year students of Indian medical schools in 2004 where 59% intended of

training abroad[15] while about one-half of South African medical graduates also go abroad.[16]

CONCLUSION:

Improvement of health care and medical education should be made along with incentives to attract young doctors to settle down in Pakistan and to opt high-priority disciplines so that imbalances encountered would be minimal in the future.

AUTHOR'S CONTRIBUTION:

NR: Conceived and presented idea
UM: Collection of data
ZQ: Data analysis
SJ: Writing of article
TN: Data analysis
MS: Editing

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Original Article

COMPARISON OF INTER-CANINE AND INTER-MOLAR WIDTHS IN ANGLE'S CLASS I, II AND III MALOCCLUSIONS; STUDY OF LOCAL POPULATION OF LAHORE

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ABSTRACT:

Objective: To assess the inter-canine and inter-molar widths amongst Angle's class I, II, and III Malocclusion groups.

Material and Methods: This study was carried out at Children's Hospital and Institute of Child Health Lahore. Fifty patients within the age range of 10-15 years were selected for study with all three classes of Malocclusion. Arch width measurements were made using dental casts of patients, and the findings were noted in specially designed Performa. Data was analyzed using SPSS 20.

Results: Mean maxillary inter-molar widths were 45.2mm, 46 mm, 46.02mm, 46.8mm, and 44.1 mm for class I, class II div 1, class II div 2, class II sub-div and class III groups respectively. Mean values for mandibular inter-molar widths were 42.7 mm, 44.09 mm, 44.6 mm, 43.5 mm, and 44.07 mm for class I, class II div 1, class II div 2, class II sub-div and class III groups respectively. Statistically insignificant differences were seen for the inter-molar widths of maxilla and mandible among the Malocclusion groups. Mean maxillary inter-canine widths were 31.8 mm, 32.6 mm, 33.0 mm, 32.0 mm and 30.7 mm for class I, class II div 1, class II div 2, class II sub-div and class III groups respectively. Mean mandibular inter-canine widths were found to be 25.00 mm, 26.7 mm, 27.7 mm, 26.5 mm and 26.0 mm for class I, class II div 1, class II div 2, class II sub-div and class III groups respectively. Significant difference was observed in the inter-canine widths of maxilla and mandible in Angle's Malocclusion.

Conclusion: Inter-canine width was found to be least in class I and widest in class II div 2.

Key Words: Malocclusion, Orthodontist, Molar

INTRODUCTION:

Arch width refers to the measured distance between the canines, bicuspids, and the first molars. The inter-canine, inter premolar, and intermolar distance may be cited as the arch width.[1] Dental arches attain full dimension at the eruption of canines and molars. The factors affecting the dimensions of dental arches include genetics, bone growth, tooth eruption, tooth inclination, muscular forces, and muscular functions, environmental factors also included. Individual variations occur at inter-canine width and intermolar width.[2]

When the jaws get closed, and teeth of two arches come close in a relationship which is not aligned in an appropriate way, this is called Malocclusion. The orthodontist who introduced this term was Edward Angle.[3] The mesiodistal relation of teeth, dental arches, and jaws were used as basis of his classification. He classified Malocclusion into three classes mainly. The dentition should fit on the occlusal line, which is a curve running over central fossae of molars and cingulum of the canines and incisors in the upper arch and in lower arch the curve running from buccal cusps of the posterior teeth and incisal edges of the anterior teeth. Changes in position of this curve leads to different types of Malocclusion.

The abnormal relationship between two teeth or a number of teeth is termed as interact

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Malocclusion. These Malocclusions can occur in sagittal, vertical and transverse plane.[4] Misalignment along the transverse plane is one of the most common reasons of Malocclusion, and this can be assessed by arch width.[5]

A study was led by Uysal et al in which he compared the widths of dental and alveolar arches in class I and class III malocclusion and the values of mandibular inter-canine, intermolar and alveolar widths were found to be considerably larger than class I.[6] Huth et al piloted a study in which he linked the arch widths of both divisions of class II malocclusion and class I and the results they got showed that maxillary arch widths for class II div 2 were smaller than normal occlusion and larger than class II div 1 group. Mandibular inter-molar widths were similar in both divisions of Class II, and both are smaller than normal occlusion.[7]

Mahmod et al showed in a study in which he compared values of class II div I Malocclusion with those with normal occlusion, and the values for both intermolar and inter-canine widths were found to be greater in former.[8] In other studies, the comparison was done between class II div 2 mal-occlusion and subjects with normal occlusion and values of former were greater as compared to normal subjects. Inter-premolar width showed insignificant difference between the two groups.[9,10]

Mushtaq et al. carried out the comparison of inter-canine and intermolar width in all types of Angle Malocclusions. They found inter-canine width highest in class II div two and mandibular inter-molar width highest in-class III.[5] This study was planned to assess the inter-canine and inter-molar widths amongst Angle's Class I, II and III malocclusion groups.

Therefore, early observation of pattern of occlusion development is crucial for timely interventions.

MATERIAL AND METHODS:

This was a cross-sectional study. Sampling was carried out by using a non-probability purposive sampling technique. A total of 50 samples were selected over a period of 3 months from October 2014 to December 2014 by following inclusion and exclusion criteria. We included good quality casts showing only mild crowding (1-4mm) in either or both maxillary and mandibular arches, all permanent teeth present from right 1st molar to left 1st molar. Cases having any dental anomaly, any extraction, large restorations that could change the mesiodistal and buccolingual dimensions of the teeth, subjects with previous orthodontic treatment, attrition of occlusal surfaces of the teeth, prosthetic replacements, severely crowded/ spaced arches, craniofacial anomalies, trauma, impactions, asymmetric arches, congenitally missing teeth and periodontally compromised dentition were all excluded. All casts were evaluated, and inter-canine and intermolar widths were noted using a vernier caliper. Maxillary and mandibular inter-canine widths were, and maxillary and mandibular intermolar widths were measured by measuring distance between mesiobuccal cusp tips of right and left permanent 1st molars. Data was analyzed using SPSS 20. For categorical variables, frequency and percentages were measured while for numerical variables mean, standard deviation and range were measured. An ANOVA test was applied. p-value lesser than 0.05 was significant.

RESULTS:

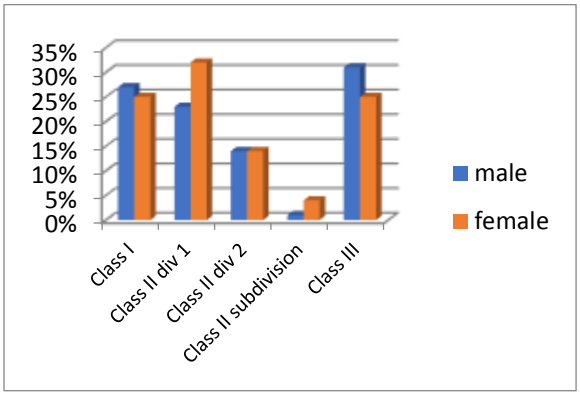
The mean age was 12.3±1.522 years. Males were 22 (44%), and females were 28 (56%) with male to female ratio 0.786:1. There were 13 (26%) Class I cases, 14 (28%) class II div 1 case, 7 (14%) class II div 2 cases, 2 (4%) class II sub-div, and 14 (28%) class III cases. ANOVA shows that a significant difference exists in the inter-canine width (p-value 0.028) among five classes of Malocclusion. (Table-1).

Analysis of variance shows a highly significant value in inter-canine width in the mandible (p-value 0.000). (Table-2).

ANOVA shows that statistically, an insignificant difference exists in the intermolar width of the maxilla (p-value

0.323) among five classes of Malocclusion. (Table-3).

Statistically insignificant difference (p-value 0.440) exists in the inter-molar width of the mandible for the five classes of Malocclusion. (Table-4).



Graph-1: Frequency of different types of Malocclusion among males and females

Table-1: Comparison of inter-canine width in different classes of Malocclusion in the maxilla.

Types of malocclusion	No. of cases	Mean	St. Deviation	Min.	Max.
Class I	13	31.793	1.1701	30.00	34.50
Class II div. 1	14	32.620	2.6591	29.47	39.00
Class II div. 2	7	32.964	1.2405	31.00	34.90
Class II subdivision	2	32.000	1.1313	31.40	33.00
Class III	14	30.721	0.9752	29.30	32.20
Total	50	31.905	1.8416	29.30	39

Table-2: Comparison of inter-canine width in different classes of Malocclusion in the mandible.

Types of malocclusion	No. of cases	Mean	St. Deviation	Min.	Max.
Class I	13	24.900	0.5196	24.20	26.30
Class II div. 1	14	26.748	1.4049	25.21	30.00
Class II div. 2	7	27.729	0.5529	27.00	28.50
Class II subdivision	2	26.500	0.7071	26.00	27.00
Class III	14	26.025	0.9423	25.10	29.00
Total	50	26.192	1.3241	24.20	30.00

Table-3: Comparison of inter-molar width in different classes of Malocclusion in maxilla.

Types of malocclusion	No. of cases	Mean	St. Deviation	Min.	Max.
Class I	13	45.239	2.2149	43.50	52.20
Class II div. 1	14	45.939	3.3825	41.92	51.00
Class II div. 2	7	46.021	3.5383	44.00	54.00
Class II subdivision	2	46.750	4.5962	43.50	50.00
Class III	14	44.121	0.6554	43.00	45.30
Total	50	45.292	2.6438	41.92	54.00

Table-4: Comparison of intermolar width in mandibular classes of Malocclusion.

Types of malocclusion	No. of cases	Mean	St. Deviation	Min.	Max.
Class I	13	42.654	2.0891	41.10	48.90
Class II div. 1	14	44.094	3.4499	40.85	51.00
Class II div. 2	7	44.648	2.8491	43.09	51.00
Class II subdivision	2	43.450	2.1920	41.90	45.00
Class III	14	44.075	1.4714	43.20	49.00
Total	50	43.766	2.5288	40.85	51.00

DISCUSSION:

The current study was performed to see inter-canine and intermolar widths of different types of Malocclusion, and comparison was done amongst the findings for different classes. We took 50 casts of patients with ages ranging from 10-15 years. Results showed statistically significant values in the inter-canine widths of maxilla and mandible (p=0.028 and 0.000, respectively). Our results are close to the study carried out by Ahmed et al.[2]

The mean value of maxillary Inter-canine width for Angle's class I malocclusion in our study was found to be 31.793±1.17 while Azeem et al[11] found the inter-canine width for normal occlusion orthodontic patients was reported 35.21±3.31 mm. The difference in the value of inter-canine width for the normal

occlusion may be because of the difference in the ages of the patients included in the study. The mean age for our study was 12.3±1.522 years while the mean age in the study conducted by Azeem et al was 19.11±3.13 years.[11]

In the present study, for mandible, inter-canine width for class I malocclusion was 24.9±0.519 and intermolar width was 42.65±2.089. Rabbani, et al.[12] found the inter-canine width for mandibular class I malocclusion in males 25.9±2.6 and 25.6±1.7 in females. They found mandibular intermolar width for class I in males 45.2±2.8 and 42.7±2.5 in females. the results are comparable to our study.

Azlan et al, 2019[13] reported the average maxilla intermolar widths for males and females 49.36mm and 46.75mm respectively, while the average mandibular intermolar widths for males and females were 43.17mm and 40.5mm. Our study showed the maxillary intermolar width 45.239±2.215 and mandibular intermolar width 42.654±2.089. These values are lesser than the normal arch values described by Azlan et al showing that there is difference in maxillary and mandibular intermolar width of normal arch dimensions and Class I dimensions.

In our study, comparison of inter-canine width for five different classes of Malocclusion in the maxilla showed statistically significant value by ANOVA (p-value 0.028). Gurjar and Purohit,[14] showed the results similar to our study and described the statistically significant value for the inter-canine width for all five classes of malocclusion by applying ANOVA. Similarly, comparison of inter-canine width for the Angle's malocclusion classes of mandible was found to be significant (p-value 0.000) just like reported by Gurjar and Purohit, 2018.[14]

In the present study, inter-canine width in maxilla for Class II div 1 was 32.620±2.659 which is comparable to 33.1±2.0 reported by Patel, et al.[15] For mandible, we found inter-canine width for class II div 1 26.74±1.4 while Patel, et al[15] 2015 reported inter-canine width 25.6±1.8 which is comparable to our results.

The results of our study were compared to a study conducted by Mushtaq et al.[5] They concluded that there is no statistical significant differences in the intermolar and inter-canine widths among the five malocclusion groups while we found the significant result for inter-canine width of both maxilla and mandible among five malocclusion groups while intermolar widths in this study were found insignificant for both arches.

Qamar and Ahmad.[10] described that mandibular intermolar width was larger in class II div 2 but no significant differences were documented for maxillary Inter-canine widths in contrast to our study as we found the statistically significant results for maxillary inter-canine widths.

Hashim et al[16] concluded that class III malocclusion showed wider arch dimensions than that in Class I and Class II while in our study class II div 2 showed wider dimensions for both maxillary and mandibular inter-canine and intermolar widths among all five malocclusion classes.

CONCLUSION:

Statistically, insignificant data difference was found between values for the intermolar widths of maxilla and mandible among different classes of Malocclusion while values for the mean inter-canine widths of maxilla and mandible in class I, class II div 1, class II div 2, class II sub-div and class III group patients were found to be statistically significant. Therefore, these values need consideration in treatment planning.

AUTHOR'S CONTRIBUTION:

SA: Conception of idea and supervision
RS: Study design
ZA: Data collection
SW: Data analysis
VJ: Drafting of article
AT: Critically review

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Original Article

FREQUENCY OF DYSPHAGIA AMONG HEAD AND NECK CANCER PATIENTS RECEIVING 3-D RADIOTHERAPY

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ABSTRACT:
Head and neck cancers are ranked sixth among all cancers globally with reported new patients (630,000) identified per year. Males are more prone to head and neck cancers than females across the Pakistani population.
Objective: In the current project, the goal was to determine the frequency of acute side effects in terms of dysphagia during and immediately post-irradiation period in patients receiving concurrent 3-dimensional radiation-therapy at Institute of Nuclear Medicine and Oncology (INMOL) Hospital, Lahore.
Study design: It was a descriptive case series.
Material and Methods: Current study was carried out on 106 enrolled patients from December 2019 to May 2020 at the Department of Radiation Oncology Inmol hospital following ethical approval. All patients received radiotherapy as per clinician advice and hospital protocol. All patients were evaluated at pre radiation time, at weekly intervals during treatment and at 11 weeks from 1st radiation fraction. Data was entered and analyzed by Statistical Package for Social Sciences (SPSS software, version 20). Chi-square and Fisher's exact test was applied as p-value ≤ 0.05 was considered significant.
Results: In the present study, there was a gradual increase in grades of dysphagia among all patients after treatments till 7 weeks. After one month of post-treatment, all grades of dysphagia improved among all patients.
Conclusion: Acute side effects like dysphagia occurred among all patients receiving 3-D Radiation-therapy with overall good the treatment response. No death was reported during the current study. Although, we concluded 3-D Radiation-therapy has a high incidence of treatment-related toxicities.

Key Words: Head and Neck Cancer, Radiation, Radiotherapy.

INTRODUCTION:

Today's one of the health problems is head and neck cancer (HNC) globally. Its management is a challenge for the health community. It originates from any site like lips, oral cavity, and larynx, etc. in the head and neck region. Due to its versatile involvement, its clinical presentation is variable that ranges from hoarseness to neck mass.[1]

Most cases (90%) are squamous cell carcinomas (HNSCC). It is ranked sixth among all cancers globally.[2] In the United States, approximately 10,000 people die due to its high incidence. Human papilloma-virus (HPV) infection caused a drastic increase in oropharyngeal cancer incidence.[3] Males are more prone to head and neck cancers than females across Pakistani population.[4,5]

Many factors lead to its emergence as reported in many previous studies. Risk factors like genetics, environmental influence, occupation, and adopted lifestyle affect its incidence greatly.[6] Loco-regional control in squamous cell cancer has been achieved by concurrent radiation therapy (RT) with cisplatin. It is now the basic component of a multi-disciplinary approach for head and neck cancer treatment. Different RT modalities damage tumor maximally with

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minimum side effects. Though it has many short-term and long-term side effects.[7,8]
Due to the increased incidence of head and neck cancers among our Pakistani population nowadays and with lack of data regarding 3D-RT acute side effects, we planned the current study to see the frequency of dysphagia associated with 3D-RT in head and neck cancers treatment among patients. It gave a useful insight into its incidence with proper management.

MATERIAL AND METHODS:

After approval from the institutional ethical review committee, a total of 106 patients (both genders) undergoing 3D-radiotherapy, were enrolled from December 2019 to May 2020 in the Department of Oncology, INMOL, Lahore, fulfilling the all patients with H and NCA who were receiving radiotherapy or chemotherapy, age of 25-70 years, stage I-III, ECOG status 1 and 2 and both genders were included in inclusion criteria.[9] Informed written consent was taken from each patient and patients were given identifiable codes for traceability. All patients were given radio-therapy or chemo-radiotherapy as per clinician advice and hospital protocol. The Sample size (106) cases were calculated with a 95% confidence level, 9% margin of error, and taking an expected percentage of dysphagia with 3D radiotherapy as 33.3%. Patients were enrolled by non-probability consecutive sampling. In the current study both females (62) and males (44) in ratio of 1.4:1 were included. Exclusion criteria involved patients who were unable to give informed consent, any second malignancy and pregnant ladies. All patients were evaluated at pre radiation time, at weekly intervals during treatment and at 11 weeks from 1st radiation fraction. Grades of dysphagia in current study were taken according to toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer.[10]
Data was entered and analyzed by Statistical Package for Social Sciences (SPSS software, version 20). Quantitative data like age (in years) and total radiation dose were presented as Mean± S.D. The categorical data like gender, site of cancer, and dysphagia were offered as frequency and percentages. Chi-square and Fisher's exact test was used to compare the frequency of dysphagia among different, based on gender and the site of cancer. p-value ≤ 0.05 was considered significant**.**

RESULTS:

Age ranged from 25-70 years among 106 enrolled patients. All these parameters were noted at the time of enrollment. Demographic parameters like age and dose of radiation as mean± S.D are described in the table-1 below.

Table-1: Descriptive statistics of patients with respect to age and total radiation dose

	Mean ± S.D	**Minimum**	**Maximum**
Age (years)	57.8 ± 8.3	39	70
Hemoglobin (g/dl)	10.7 ± 1.24	9.0	13.0
Total (Grays) radiation dose	62.8 ± 7.4	30	70

The most common site was oral cavity 31(29.2%) and the least common site was larynx 8 (7.5%) (Table-2).

Table-2: Distribution of participants with respect to gender, site of cancer and stages of cancer

Variable	**Category**	**Frequency**	**Percentage (%)**
Gender	Male	44	41.5
	Female	62	58.5
Site	Pharynx	23	21.7
	Hypopharynx	22	20.8
	Larynx	8	7.5
	Nasopharynx	22	20.8
	Oral cavity	31	29.2
Cancer	Stage 1	41	38.7
	Stage 2	46	43.4
	Stage 3	19	17.9

There was a gradual increase in grades of dysphagia among patients after treatments with 3-D RT till 7 weeks. After one month of post-treatment, grades of dysphagia among all patients improved. At the 7th week

of treatment, dysphagia of grade 4 was observed in 40 (37.7%) patients, dysphagia of grade 2 and 3 was observed in 19 (17.9%) and 47 (44.3%) patients respectively (Table-3).

Chi-square and Fisher's exact test was used to compare the frequency of dysphagia grades between male and female patients. There was no significant difference in the frequency of dysphagia grades between any week of treatment (Table-4).

Chi-square and Fisher's exact test was used to compare the frequency of dysphagia grades among sites. No significant difference was observed in the frequency of dysphagia's grades among sites at 1st, 7th, and 11th week of treatment (Table-5).

Table-3: Distribution of patients according to the grade of Dysphagia

Week	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
1st	106(100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2nd	42(39.6%)	64(60.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3rd	5(4.7%)	61(57.5%)	40(37.7%)	0 (0%)	0 (0%)	0 (0%)
4th	0 (0%)	65(61.3%)	41(38.7%)	0 (0%)	0 (0%)	0 (0%)
5th	0 (0%)	22(20.8%)	44(41.5%)	40(37.7%)	0 (0%)	0 (0%)
6th	0 (0%)	1(0.9%)	23(21.7%)	82(77.4%)	0 (0%)	0 (0%)
7th	0 (0%)	0 (0%)	19(17.9%)	47(44.3%)	40(37.7%)	0 (0%)
11th	42(39.6%)	24(22.6%)	40(37.7%)	0 (0%)	0 (0%)	0 (0%)

Table-4: Comparison of grades of dysphagia between both genders

Week	Gender	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	p-value
1st	Male	44(100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.345
	Female	62(100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
4th	Male	0 (0%)	25(56.8%)	19(43.2%)	0 (0%)	0 (0%)	0 (0%)	0.423
	Female	0 (0%)	40(64.5%)	22(35.5%)	0 (0%)	0 (0%)	0 (0%)	
7th	Male	0 (0%)	0 (0%)	11(25.0%)	14(31.8%)	19(43.2%)	0 (0%)	0.069
	Female	0 (0%)	0 (0%)	8(12.9%)	33(53.2%)	21(33.9%)	0 (0%)	
11th	Male	0 (0%)	18(40.9%)	7(15.9%)	19(43.2%)	0 (0%)	0 (0%)	0.345
	Female	0 (0%)	24(38.7%)	17(27.4%)	21(33.9%)	0 (0%)	0 (0%)	

Table-5: Comparison of the grade of Dysphagia among sites

Week	Site	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	p-value
1st	Pharynx	0 (0%)	11(47.8%)	12(52.2%)	0 (0%)	0 (0%)	0 (0%)	0.134
	Hypopharynx	0 (0%)	13(59.1%)	9(40.9%)	0 (0%)	0 (0%)	0 (0%)	
	Larynx	0 (0%)	6(75.0%)	2(25.0%)	0 (0%)	0 (0%)	0 (0%)	
	Nasopharynx	0 (0%)	11(50.0%)	11(50.0%)	0 (0%)	0 (0%)	0 (0%)	
	Oral cavity	0 (0%)	24(77.4%)	7(22.6%)	0 (0%)	0 (0%)	0 (0%)	
7th	Pharynx	0 (0%)	0 (0%)	2(8.7%)	10(43.5%)	11(47.8%)	0 (0%)	0.265
	Hypopharynx	0 (0%)	0 (0%)	2(9.1%)	11(50.0%)	9(40.9%)	0 (0%)	
	Larynx	0 (0%)	0 (0%)	2(25.0%)	4(50.0%)	2(25. 0%)	0 (0%)	
	Nasopharynx	0 (0%)	0 (0%)	5(22.7%)	6(27.3%)	11(50.0%)	0 (0%)	
	Oral cavity	0 (0%)	0 (0%)	8(25.8%)	16(51.6%)	7(22.6%)	0 (0%)	
11th	Pharynx	0 (0%)	6(26.1%)	6(16.1%)	11(47.8%)	0 (0%)	0 (0%)	0.094
	Hypopharynx	0 (0%)	6(27.3%)	7(31.8%)	9(40.9%)	0 (0%)	0 (0%)	
	Larynx	0 (0%)	5(62.5%)	1(12.5%)	2(25.0%)	0 (0%)	0 (0%)	
	Nasopharynx	0 (0%)	10(45.5%)	1(4.5%)	11(50.0%)	0 (0%)	0 (0%)	
	Oral cavity	0 (0%)	15(48.4%)	9(29.0%)	7(22.6%)	0 (0%)	0 (0%)	

DISCUSSION:

Radiation Therapy (RT) was planned for patients with head and neck carcinoma (HNSCC). Acute side effects related to RT are not reviewed routinely in our setups so we planned to see the frequency of acute side effects in terms of dysphagia during and immediately post-irradiation period (upto11 weeks from the first fraction) in patients receiving concurrent 3-dimensional radiotherapy. Thus we examined the efficacy and safety of RT in non-metastatic, stage I to stage III HNSCC patients.[11]

In the current study, sample size of the patients was 106 which was comparable to another study comprising of 221 patients who presented with symptoms of head and neck cancer.[12] In contrast, one study carried on the Brazilian population included 30 head and neck cancer patients.[11]

Age (mean ± SD) of enrolled patients in our study was 57.8 ± 8.3 years (Table-1) years in conformity with the previous study where age (mean ± SD) of enrolled head and neck cancer patients among European population was 64 ± 12 years. In past researches, the median age was 53 years (37–68) rather than mean of age.[13]

Both males and females were recruited in our work as in other previous studies. Females were 58.5% (62) while males were 41.5% (44) (table-2) paradoxically to the fact that males (21%) suffer more from head and neck cancers than females (11%) across Pakistani population respectively as well as globally.[14] Selection of gender among subjects was paradoxical to our study i.e 83% males and 17% females in one Brazilian population.[15]

In this project, acute side effect like dysphagia was seen during and immediately after post-treatment at 4 weeks interval. There was a gradual increase in grades of dysphagia in all patients after treatments till 7 weeks in our current study. Dysphagia of grade 1 was observed in only 64 (60.4%) patients after 2 weeks of treatment. At 4th week after treatment, Dysphagia of grade 1 and 2 was observed in 106 (100.0%) patients. At the 7th week of treatment, Dysphagia of grade 4 was observed in 40 (37.7%) patients, Dysphagia of grade 2 and 3 was observed in 19 (17.9%) and 47 (44.3%) patients respectively. After one month of post-treatment, a decrease in grades of Dysphagia in all patients was observed. Dysphagia of grade 3 was observed in 40 (37.7%) patients. However, Dysphagia of grades 1 and 2 was observed in 42 (39.6%) and 24 (22.6%) patients respectively as shown in table-3. Our work was in line with a previous study carried on the Dutch population showing similar results.[15]

LIMITATIONS:

This study had several limitations like financial constraints and fewer resources. We did not perform Positron Emission Tomography (PET) scan and genetic study to see genetic variability among enrolled subjects.

CONCLUSION:

Dysphagia of different grades appeared among all patients receiving 3-D Radiation-therapy although the treatment response was good. Hence, we concluded 3-D Radiation-therapy has a high incidence of treatment-related toxicity.

AUTHOR'SCONTRIBUTION:

SZ: Write up and literature review.
SN: Literature review help in write-up.
AB: Literature review help in write-up.
MSY: Collecting and arranging the data
SS: Analysis literature review, help in write up.
AA: Overall supervision and write up.
MR: Review critically

ACKNOWLEDGEMENTS:

I would like to acknowledge the hard work of the Department of Oncology, INMOL, Lahore. I am thankful to Allah, all my colleagues, and teachers for their help.

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Original Article

FREQUENCY AND ASSOCIATED RISK FACTORS OF URINARY INCONTINENCE AND IT'S IMPACT ON LIFE OF WOMEN.

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ABSTRACT:

Objective: The study was conducted to determine the frequency of urinary incontinence, its types, associated risk factors, and its impact on the life of women.

Material and Methods: This cross-sectional study was conducted in the gynaecological out patient department (OPD) of Akhtar Saeed Trust Teaching Hospital from July 2018 to December 2018. The patients of age 18 or more who complained of involuntary loss of urine were selected from gynae OPD, and after informed consent, they were further questioned about the problem according to the questionnaire. The data was analyzed on SPSS version 17.

Results: Out of 1425 patients, 210 patients answered yes to the complaint of urinary incontinence. 198 patients who agreed to participate were interviewed according to the questionnaire. The overall frequency of incontinence was 13.8 % (198). Stress incontinence was the most common type of incontinence found in 127 patients (64.1%), urge incontinence was seen in 37 patients (18.7%), and mixed incontinence was present in 34 patients (17.2%). Urinary incontinence was found to be markedly high in women above 40 years of age (69.7%). One hundred seventy-nine patients (90.4%) belonged to poor socioeconomic status, 17 patients were from the middle class, and two patients (1%) belong to upper socioeconomic status. Incontinence especially stress incontinence, was associated with increasing parity as 81 patients (40.9%) were grand multipara making it a significant risk factor for urinary incontinence. Other risk factors were vaginal delivery (85.4%), increased BMI that is > 25 per kg/m^2 (47%), constipation (51%), history of prolapse (34.8%), and chronic respiratory disease (10%). Urinary incontinence was seen more in postmenopausal women (48%) and in those having a habit of tobacco/tea coffee intake (60.5%). Urinary incontinence greatly affected women's quality of life as 71 patients (35.9%) avoided going out of the house due to this problem, 38 patients (19.2%) had reduced sexual relationships, and 23 patients (11.6%) had to use sanitary towels.

Conclusion: Urinary incontinence is a common health issue which is usually under-reported though it greatly affects the quality of life of women, especially above 40 years of age.

Key Words: Urinary Incontinence, BMI, Parity

INTRODUCTION:

According to the international continent society, urinary incontinence (UI) is defined as "involuntary loss of urine".[1] Urinary incontinence is an under-reported health problem, although it is a common problem. It causes both physical and psychological nuisance to a woman and significantly affects one's quality of life, which can lead to segregation from society.[2] Urinary incontinence is classified into three types, i-e. Stress, urge, and mixed incontinence.[3] Prevalence of stress urinary incontinence is the highest compared to urge, and mixed incontinence and research reveals that its incidence increases in the 5th decade of life.[4] Potential risk factors for UI include increasing age, parity, vaginal deliveries, obesity, surgery, constipation, and chronic respiratory problems such as cough.

Most of the studies on this topic had been carried out in developed countries but limited data is available in underdeveloped

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countries like Pakistan. An updated data of UI in the underdeveloped country will be of great importance to help to formulate strategies for prevention and control for urinary incontinence.

MATERIAL AND METHODS:

This is a cross-sectional study conducted in Gynae OPD of Akhtar Saeed Trust Teaching Hospital from July 2018 to December 2018.

The patients in Gynae OPD were asked about any experience of involuntary loss of urine. The women with such complaints were categorized as patients of urinary incontinence and were included in the study after informed consent. The age of the participants was 18 years and above. Subsequently, the participants were asked a standard questionnaire for the clinical and demographic profiles. The types of urinary incontinence are stress, urge, and mixed types. Stress incontinence is the involuntary loss of urine on sneezing, coughing, laughing, or lifting heavy weight. Involuntary loss of urine on sudden or strong urge is classified as urge incontinence. If someone has symptoms of both stress and urge incontinence are classified as having a mixed type of incontinence.

All patients who attended the Gynae outpatient department for any gynecological complaint were included in the study and exclusion criteria included pregnancy, active pelvic and urinary tract infection. Descriptive statistics were presented in the form of tables.

RESULTS:

The frequency and percentage of variables were determined. Out of 1425 patients attending Gynae outdoor department, 210 patients answered yes to the complaint of urinary incontinence. One hundred ninety-eight patients who agreed to participate were interviewed according to the questionnaire. The overall frequency of incontinence was 13.8 % (198). The most common type of urinary incontinence was stress incontinence (64.1%), urge incontinence was seen in 37 patients (18.7%), and mixed incontinence was present in 34 patients (17.2%). (Table 2)

Urinary incontinence was found to be more common in women of 40 years of age (69.7%). Among these, 37.4% of patients were in their fourth decade of life (41 to 50 years).

Urinary incontinence was more common in multiparous (33.3%) and grand multiparous patients (40.9%). Regarding educational status, 73 patients (36.9%) were illiterate, 74 patients (37.4%) were educated up to the primary, 39 patients (19.7%) were educated up to matric, and 6% of patients were graduate or postgraduate (Table 1).

Table-1. Frequency and percentage of demographic characteristics in patients presenting with urinary incontinence**.**

Parameters	No.	Percentage (%)
Age		
20 to 30 years	15	7.6
31 to 40 years	45	22.7
41 to 50 years	74	37.4
51 to 60 years	36	18.2
61 or above	28	14.1
Parity		
Nuliparous	8	4.0
Para 1	4	2.0
Para 2-3	39	19.7
Para 4-5	66	33.3
Para 6 and above	81	40.9
Education		
Uneducated	73	36.9
Primary	74	37.4
Matric	39	19.7
Bachelors	7	3.5
Master/Higher	5	2.5
Social Class		
Poor	179	90.4
Middle	17	8.6
Upper	2	1.0

Table-2. Frequency and percentage of different types of urinary incontinence.

Type of urinary incontinence	Total	No	Percentage (%)	% of those with UI
Total patients of incontinence	1425	198	13.8	
Stress incontinence	1425	127	8.9	64.1
Urge	1425	37	2.5	18.7
Mixed	1425	34	2.3	17.2

Out of one hundred and ninety-eight patients, one hundred and seventy-nine (90.4%) belonged to lower socioeconomic status, 17 patients (8.6%) were from the middle class, and two patients (1%) from upper socioeconomic status. With increasing parity stress, incontinence was found to be higher as 81 patients (40.9%) were grand multipara making it an important risk factor for urinary incontinence. Other risk factors were vaginal delivery (85.4%), increased BMI more than > 25 (53%), constipation (51%), history of prolapse (34.8%), and chronic respiratory disease (10%). Urinary incontinence, including its all types, was found to be more common in postmenopausal women (48%) and those having habit of tobacco/tea coffee intake (60.5%) (Table 3).

Urinary incontinence affected women's quality of life to a great extent (Table 4), 71 patients (35.9%) had avoided going out of the house due to this problem, 38 patients (19.2%) had reduced sexual relationship, and 23 patients (11.6%) had to use sanitary towels.

Out of 198 patient only 48 patients had ever consulted for their problem and rest of 150 patients (75.8%) did not consult for their problem due to different reasons like 62 patients (31.3%) did not consider it a problem, 63 patients (31.8%) did not consult as they felt ashamed, 22 patients (11.1%) did not think that this problem has a solution and three patients (1.5%) did not consult due to some other reason.

Table-3. Frequency and percentage of risk factors for urinary incontinence.

Risk Factors	No.	Percentage (%)
Age > 40 years	138	69.7
Parity >3	147	72.7
Vaginal Delivery	169	85.4
Postmenopausal	103	52
BMI >25 per kg/m^2	105	53
Asthma	21	10.6
Tobacco/Tea/Coffee	120	60.5
Constipation	101	51

Table-4. Impact of urinary incontinence on women's quality of life.

Risk Factors	No.	Percentage (%)
Limit Going Out of House	71	35.9
Reduced Sexual Relation	38	19.2
Use Sanitary Towels	23	11.6

DISCUSSION:

In this cross-sectional study, urinary incontinence was said to be present if the answer to the leading question about the presence of involuntary loss of urine was found to be yes. This study gives the opportunity to determine frequency types, its associated risk factors, and the impact of this problem on the quality of life of the patient.

Out of 1425 Gynae patients, 210 patients on asking a leading question answered yes to the complaint of urinary leakage, 12 patients refused to participate in the study, and the rest of 198 patients agreed and were enrolled. Thus the overall frequency of urinary incontinence was 13.8%. The frequency of stress, urge, and mixed type of incontinence in our study was 8.9%, 2.5%, and 2.3%, respectively, similar to many other studies[5-7] in which the commonest type was stress incontinence. Our study showed a low frequency of urinary incontinence (7.6%) in women with young age (18-30 years), which is very close to an Indian

study[8] in which the figure was 9% whereas this figure is very high in studies reported by Nemir and Middleton[9] which quotes the figure of 54% and 51%, conducted on college students. High frequency of urinary incontinence in women > 40 years is similar to the prevalence in most studies[10,11] where it ranges from 42-46%. The relationship between parity and incontinence in our study was similar to that in previous studies. A definite trend of increased frequency of all types of urinary incontinence with increasing parity proposes cumulative effect of the injury to innervations of the pelvic floor which occurs during normal deliveries.[12]

Pregnancy and childbirth are considered as commonest environmental determinants of urinary incontinence, and more than 60% of women with incontinence link its onset with pregnancy, childbirth or postpartum period, however, the impact of birth mode on urinary incontinence and whether the c-section has its protective role or not remains the subject of ongoing debate. Our study showed the frequency of urinary incontinence higher in a group with vaginal delivery (85.4%) as compared to that in nulliparous (4%), and with c-section (3.5%), this is in agreement to many studies[13,14] showing increased prevalence of urinary incontinence associated with vaginal deliveries. Urge and mixed types of urinary incontinence had less association with vaginal deliveries in our study.

In this study, urinary incontinence was found to be more common in women having habit of smoking and tea intake. Norwegian EPINCONT study[15] also evaluated the effect of tea intake, and the conclusion of the study was that tea intake was associated with slightly increased risk for all types of incontinence.

The limitation of this study is the fact that it is a cross-sectional study, and it was conducted in women at a single location.

CONCLUSION:

Urinary incontinence is a common health issue that seriously affects the quality of life of women, especially above 40 years of age, but remains under-reported.

AUTHOR'S CONTRIBUTION:

AM: Conceived and designed the study
NS: Critically reviewed
NS: Literature review
US: Data collection
DN: Drafting the article
FF: Data anaylsis and critical review

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Original Article

ASSOCIATION OF SERUM C- REACTIVE PROTEIN (CRP), CYSTATIN C AND HOMOCYSTEINE WITH DIABETIC RETINOPATHY IN PATIENTS OF TYPE 2 DIABETES MELLITUS

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ABSTRACT:

Objective: The aim of this study was to investigate the association of levels of serum cystatin C (Cys C), CRP and Homocysteine (Hcy) with diabetic retinopathy (DR) associated with type 2 diabetes mellitus and elucidate their clinical prognostic significance.

Material and Methods: A total of 485 patients of type 2 diabetes were recruited, and their levels of serum cystatin C, Homocysteine (Hcy), and C-reactive protein were measured by using a high sensitivity latex-enhanced immunoturbidimetric method. Type 2 diabetes was diagnosed as per the criteria of the American Diabetes Association 2012 and 1999 World Health Organization. Venepuncture was performed after an overnight fast, and venous blood of all patients was drawn. Fundus fluorescein angiography (FFA) was performed on all patients, and the procedure was carried out by the opthalmologist. Age-related macular degeneration (AMD) was diagnosed by FFA and optical coherence tomography (OCT). All participants were divided into four groups. Group 1 included patients with no Diabetic Retinopathy (NDR) and AMD (n=60, Age 55.1±9.11); Group 2 included patients suffering from Non-Proliferative Diabetic Retinopathy (NPDR) (n=180, Age 56.7±6.21); Group 3 comprised of patients suffering from Proliferative Diabetic Retinopathy (PDR) (n=160, Age 57.1±10.07) and Group 4 consisted of AMD (n=85, exclude patients with NPDR or PDR, Age55.9±6.27).

Results: Levels of serum CRP, Cys C, and Hcy were significantly distinctive between specific groups. The levels of serum Cys C in the PDR and AMD groups were significantly elevated as compared to NPDR and control groups ($p<0.05$,$p<0.01$, respectively). The levels of serum CRP in the PDR and AMD group were elevated as compared to NPDR and control group ($p<0.05$, $p<0.01$ respectively) and the levels of serum Hcy in PDR and AMD group were elevated significantly as compared with NPDR ($p<0.01$) and control group($p<0.01$).

Conclusion: It is concluded that during the clinical implications of diabetic retinopathy (DR) in patients with type 2 diabetes, the serum levels of C- reactive protein, Cystatin C, and Homocysteine play an important role.

Key Words: Cystatin C, Homocysteine, Macular degeneration

INTRODUCTION:

The most frequent complication of diabetes in microvascular disease is the Diabetic Retinopathy that affects nearly 93 million people[1] and causes leading numbers of blindness and poor vision worldwide.[2]

It is a global public health problem with physical, psychological, and socioeconomic consequences. In Asia itself, the prevalence of diabetes varies from 15.8-43.1% in different demographic studies.[3-5] If the prevalence of DM continues to rise dramatically in Asian continent[6] in concomitance with the aging population, the socioeconomic disease burden will likely increase exceptionally in the future.

Hence, the search for biomarkers and risk factors of DR is of paramount importance in order to prevent disease progression. Therefore, we investigated the role of

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Cystatin C, which is a member of cystatin superfamily, a family of cysteine proteinase inhibitors; nucleated cells mainly produced Cystatin C and is also present in urine, serum, cerebrospinal fluid, semen, colostrum, and semen in a relatively lower concentration.[7] It has been proved that the levels of serum or plasma cystatin C are independent of weight, age, gender, dietary factors, liver diseases, and infections, but few studies discovered its possible relation with age. It was emphasized that levels of serum cystatin C are increased at 50 years of age[8] and some studies have revealed that diabetes, inflammation, and BMI also affect Cystatin C levels irrespective of kidney functions.[9]

Recent clinical trials have proved that there is strong evidence of correlation of serum levels of Cystatin C and prognosis of Diabetic Retinopathy[10] and serum Cystatin C levels were also well correlated in age-related macular degeneration (AMD).[11] The higher levels of serum cystatin C have also been correlated with prediabetes.[12] A recent clinical trial based in China has suggested that elevated levels of serum Cystatin C were associated with the severity of DR, along with diabetes duration, and HbA1c levels are an important risk factor.[13] Therefore levels of serum Cystatin C can be useful as a prognostic factor in patients for higher risk of DR associated with type 2 diabetes mellitus (T2DM).

Among several markers of inflammation, the levels of serum C-reactive protein (CRP) were greatly elevated in patients with diabetes. CRP is an acute-phase reactant that is produced as a result of ongoing infection or inflammation. It also plays a unique role in innate immunity. Increased inflammatory activity in diabetic retinopathy, as reflected by significantly elevated levels of CRP, is associated with endothelial dysfunction. Moreover, CRP was also found to be elevated in patients with macular degeneration.[14]

Homocysteine (Hcy), which is formed by the demethylation of methionine, is a sulfur-containing amino acid. Several scientific studies have proved the complex interaction between the levels of blood Hcy and DR prevalence, especially PDR. The incidence of DR is also high in diabetic patients with hyperhomocysteinemia. Therefore, the total plasma level of Hcy can be used as an important prognostic biomarker in patients of DR irrespective of other factors associated with T2DM.[15]

MATERIAL AND METHODS:

A total of 485 patients were recruited in this study from February 2014 to January 2018 at Jinnah hospital. All recruited patients were diagnosed with type 2 diabetes. The protocol of the study was approved by the respective research committee. All participating patients provided written informed consent. Patients with type 1 diabetes, patients with acute complications of diabetes, patients with diagnosed diabetic nephropathy or secondary nephropathy or complicated T2DM with infections such as rheumatoid arthritis, systemic lupus erythematosus (SLE), diabetic nephropathy, presence of any psychological or neurological disorder and the presence of ocular diseases like glaucoma, uveitis, pigment degeneration, tumor, and wet age-related macular degeneration were excluded from the study. All participants were subjected to standard interviewer questionnaires, systemic and ocular examinations along with standard baseline blood investigations.

The relevant data of age and diabetes duration of all participants was collected. Type 2 diabetes was diagnosed based on the American diabetes association criteria of 2012 and 1999 World Health Organization standards. Blood pressure was measured after the participants were seated and relaxed for at least 5 minutes. Venepuncture was used to draw venous blood of all patients after an overnight fast. Immunoturbidimetric method enhanced with high sensitive latex was used to measure the levels of serum C-reactive protein (CRP) cystatin C (Cys C) and homocysteine (Hcy). Fasting plasma glucose (FPG), glycosylated hemoglobin

(HBA1c) were also estimated by the name of the method by using age and sex-adjusted models.

Ophthalmologist performed fundus fluorescein angiography (FFA) on all participants. Optical coherence tomography (OCT) and FFA were used to diagnose diabetes-related macular degeneration. Participants were grouped into four groups. Group 1 patients with no AMD and no Diabetic retinopathy (NDR) (n=60, Age 55.1±9.11); Group 2 patients suffering from Non-Proliferative Diabetic Retinopathy (NPDR) (n=180, Age 56.7±6.21); Group 3 patients suffering from Proliferative Diabetic Retinopathy (PDR) (n=160, Age 57.1±10.07) and Group 4 AMD (n=85, exclude patients with NPDR or PDR, Age55.9±6.27).

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 16.0 software package. The presentation of data was mean±standard deviation (SD). One-way ANOVA was used to make comparisons between pairs of groups. A two-tailed P value of <0.05 was regarded as statistically significant.

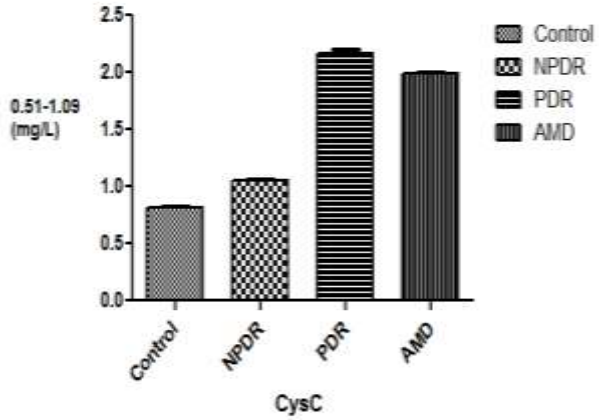
RESULTS:

We recruited a total of 485 patients and divided them into four groups. Table 1 presents the clinical features of all four groups. We observed no critical differences in the age, sex, duration of diabetes.

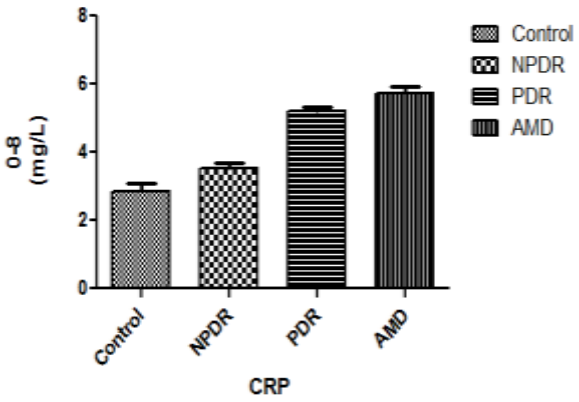
Table–1: Characteristics of the study population

	G1	G2	G3	G4
N	60	180	160	85
Mean±SD Age (years)	55.1±9.11	56.7±6.21	57.1±10.07	55.9±6.27
M/F ratio	30/30	101/89	85/75	40/45
Duration of diabetes (years)	13.1	13.7	14.5	14.1
HbA1c (%)	8.1	7.9	8.2	8

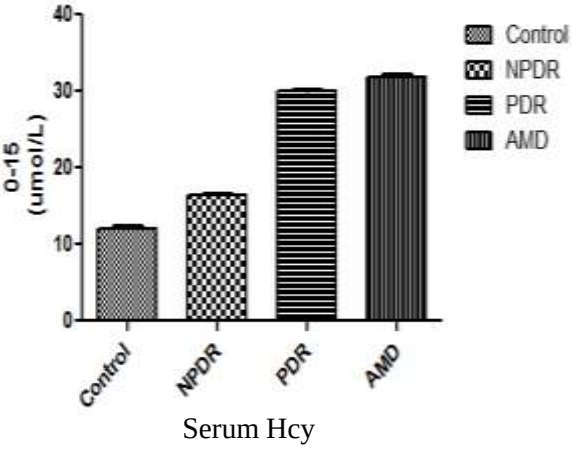
Serum CRP, Cys C, and Hcy levels among the following groups are presented in figures 1-3.



Fig–1: The serum levels of Cys C in four groups



Fig–2: The serum levels of CRP C in four groups



Fig–3: The serum levels of Hcy in four groups

Regarding the serum levels of Cys C in the four groups, there were no differences between the NPDR group and the control group. But the levels of serum Cys C were elevated in PDR and AMD groups compared with the control group ($p<0.01$), but in comparison with the NPDR group, we also found the levels of Cys C in PDR and AMD were increased significantly ($p<0.01$, $p<0.05$, respectively), but we did not find any differences among the PDR and AMD groups ($p>0.05$). (Table – 2)

The levels of serum CRP in the NPDR and control groups showed no differences. Serum CRP levels were remarkably elevated in the PDR and AMD group than the control group ($p<0.01$). In comparison with NPDR group, serum levels of CRP in PDR and AMD were found to be elevated ($p<0.05$, $p<0.01$, respectively), but no statistical difference was found among the PDR and AMD groups ($p>0.05$) (Table – 2).

There was no difference in serum Hcy between control and NPDR groups. The levels of Hcy were considerably higher in the PDR and AMD groups than the control ($p<0.01$).In comparison with the NPDR group, we also found the levels of Hcy in PDR and AMD significantly higher than the NPDR group ($p<0.01$), but there was no statistically significant difference among PDR and AMD groups ($p>0.05$) (Table – 2).

Table–2: Comparison of serum cyctatin–C, C–reative protein and homocysteine levels between four groups

Parameter	Comparison between groups					
	Control & AMD	Control & NPDR	Control & PDR	AMD & PDR	AMD & NPDR	PDR & NPDR
Serum cystain C	p<0.01	p>0.05	p<0.05	p>0.05	p<0.05	p<0.01
Serum CRP	p<0.01	p>0.05	p<0.01	p>0.05	p<0.01	p<0.05
Serum Hcy	p<0.01	p>0.05	p<0.01	p>0.05	p<0.01	p<0.01

p<0.05 Significant
p>0.05 Insignificant

DISCUSSION:

Serum levels of CRP, Cys C, and Hcy in patients were found to be elevated with advanced stages of Diabetic Retinopathy (PDR and AMD), which implies a common pathophysiological mechanism consisting of an interplay of chronic inflammation, cell injury and degenerative neuronal pathology.[16] This further implies that Diabetic Retinopathy is not just a vascular disease but a neurovascular disease.[17]

Cystatin C is a strong inhibitor of cysteine proteinase of lysosomal and extracellular substances and is expressed invariably in a wide variety of human cells such as fibroblasts, glial cells, pancreatic islet cells, and endothelial cells. The major site for Cystatin C secretion is retinal pigment epithelium that is located in the posterior eye and has a crucial role during the process of macular degeneration.

Moreover, it was hypothesized that Cystatin C proved to be an important factor during the remodeling of arterial blood vessels wall, neovascularization, inflammatory, and degenerative neuronal pathology.[18] Similarly, the DR results in abnormal pathophysiologic accumulation of fluid and subsequent edema of the macula, which causes inflammation, optic neuropathy, retinal neovascularization, and excessive expression of glial cells.[19] Furthermore, Cystatin C and DR share common mechanisms, and that explains their close connection.[11]

C- Reactive Protein (CRP) is considered as a chronic marker of several pathological conditions such as preclinical atherosclerosis, arterial wall inflammation, systemic endothelial dysfunction, impaired fibrinolysis and subclinical inflammation that leads to further progression of diabetic retinopathy that may exacerbate further tissue damage.[19,20]

The pathogenesis of DR includes the hyperhomocysteinemia which causes accelerated cell injury in retinal capillaries[21] by producing reactive oxygen species (ROS) and inducing oxidative stress and

abnormal generation of nitric oxide species that leads to abnormal proliferation of smooth muscle cells of the vessels and alteration of vasomotor activity.[22,23]
Considering the fact that there are many factors that have a role in the progression and development of DR, instead few still remain unclear. As we had explained the data analysis and mechanisms above, we believe that elevated Cystatin C, CRP, and Homocysteine are strong causative factors for DR, mainly in the progression of retinopathy not subjected to other factors.

CONCLUSION:

Serum Cystatin C, CRP, and Homocysteine levels are potential and useful biomarkers in predicting and analyzing the progression of DR. Taking into consideration the ever-increasing financial burden of diabetes, CRP, Cystatin C, and Homocysteine assays can prove to be more beneficial to estimate the progression and prognosis of DR.

RECOMMENDATIONS:

Further studies should incorporate possible thresholds and common pathophysiological mechanisms between the blood levels of these biomarkers and the separate degrees of DR in a larger number of patients. Besides, these markers are easy and more economical to measure as compared to optical coherence tomography (OCT), and high-quality fundus fluorescein angiograms.

AUTHOR'S CONTRIBUTION:

MQ: Conception of idea and article writing
MG: Data collection and revision of article
HJQ: Review critically
MSA: Data analysis and editing
AF: Data collection
SM: Data analysis

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Review Article

GROWING ANTIBIOTIC RESISTANCE IS A MASSIVE THREAT TO HEALTH SYSTEM

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ABSTRACT:
Antibiotic resistance has become a worldwide problem and a massive threat to the health system, particularly in developing countries. A number of factors such as excessive use of antibiotics in the dairy industry, poultry industry, dosage effect, non-professional doctors especially in rural areas, self-medication, and misuse of antibiotics are contributing towards antibiotic resistance. The astonishing genetic capacity of bacteria to resist antibiotics is due to over usage of antibiotics and transmission of resistant genes to further generations through horizontal gene transfer. The basic mechanisms of antibiotic resistance are the degradation of different drugs used against bacteria by enzymes, changes in proteins that have to be targeted by antibiotics, and alterations in permeability of membrane toward different antibiotics. The growing antibiotic resistance is a problem not only in underdeveloped countries but also in developed countries. This review addresses different aspects of antibiotic resistance, mechanisms, factors involved, and future impact of growing antibiotic resistance.

Key Words: Antibiotics, Antibiotic Resistance, Enzymes

INTRODUCTION:

Antibiotics can be defined as agents that are used to kill or stop the growth of bacteria.[1] No doubt, antibiotics have revolutionized the field of medicine, but today one of the most emerging problems is antibiotic resistance. The resistance to antibiotics has not only resulted in an increased rate of mortality but has dramatically increased the cost of treatment. Antibiotic resistance can also be defined as a process in which bacteria becomes resistant to specific antibiotics, and the antibiotics no longer kill or inhibit the growth of bacteria. Whenever the antibiotics are administrated, there are three possible outcomes; the bacteria will be killed, growth will be inhibited, or they will continue to multiply and will increase in number.[2] There are many factors that lead to antibiotic resistance through different mechanisms such as, i.e., natural selection, plasmid transfer, and mutation.[3]

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Plasmid transfer is a mechanism in which bacteria can transfer their genetic material directly between each other as this ability is not present in other bacteria. Plasmids are small extrachromosomal circular rings of DNA that function as a vehicle in order to transfer resistance among bacterial species. Plasmids have the capability of spreading bacterial resistance in different regions of the world. The mutation is another phenomenon that leads to resistance in bacteria. Bacterial genome regularly changes in response to the employment of antibiotics. The regular usage of antibiotics causes an increase in mutational levels that leads to an increase in the level of bacterial resistance.[4] Bacteria to get resistance by the degradation of different drugs using enzymes; changes in proteins which have to be targeted by antibiotics and alterations in permeability of membrane toward different antibiotics.

The mechanism of resistance in bacteria has been studied extensively at the molecular level, and there are different mechanisms for the development of resistance in microbes.[5] Some of the most important known mechanisms are described here.

Genetic Jugglery:

Genes of β-lactamase enzymes are most widely distributed, and mutations in these genes result in broad-spectrum resistance in different bacteria toward antibiotics.[6] The genes of β-lactamase are ancient, and these have been found in different environmental conditions[7] with different substrates, which provide sufficient evidence for its contribution toward resistance in bacteria. CTX-M is a novel β-lactamase demonstrated as the first enzyme with the ability to hydrolyze cephalosporin at a high level.[8] CTX-M and its variants are one of the most important factors which are contributing to the potential threat of antibiotics resistance worldwide.[9]

Intrinsic Resistance:

Intrinsic resistance is a mechanism in which resistance results due to the presence of specific genes in a bacterial genome, i.e., quasi and proto resistance. The advancements in recombinant DNA technology, different mutagenic techniques helped to discover the role of these intrinsic genes in bacteria and their microbial resistance. One of the most important routes which cause resistance to trimethoprim[10] and sulphonamides[11] in bacteria is gene amplification. It has been shown that specific resistant strain is produced when there is overexpression of the wild-type gene.

Transmission of Resistant Gene:

It has been documented that accessory genetic elements of the bacterial genome have the ability to take resistant genes and transmit. Mutations that make the bacteria resistant toward antibiotics are transferred at a high rate through horizontal transfer.

Regardless of differences that exist between gram-positive and gram-negative bacteria, the transmission through plasmid is the most common method for transmission of resistant genes.[12] The transmission of resistant genes through conjugation is studied extensively. The rate of transmission varies greatly in different environmental conditions, and the frequency of transmission is quite high in the natural environment as compared to laboratory conditions.[13] Recently, a large number of antibiotic-resistant genes have also been documented in human gut microbes.[14] The interchange of both virulent and pathogenic genes is most frequent in meningococci, streptococci, and their related genera, with transformation being the mechanism for transmission.[15,] Acinetobacter species are most competent to transfer DNA directly from the environment or through horizontal gene transfer.[16] Various mechanisms involved in the transmission of antibiotic resistance genes have been studied in the laboratory, and it is observed that the genetic transmission can take place by methods other than transformation by bacteriophages and plasmids. In complex communities of bacteria, the transmission of resistant genes can take place through the fusion of cell wall.[17] However, gene transmission efficiency and its selective expression are important limitations. On the other hand, the low genetic expression provides them protection from different antagonists.[7] There is enhanced antibiotic resistance when sub-inhibitory concentrations of antibiotics are used. In this case, the activation of the SOS response system of DNA repair system facilitates the transfer of genes.[18]

Risk Factors of Antibiotic Resistance:

Dairy and Poultry Industry

Same types of antibiotics are being used to treat animals and human infections, which is contributing towards increased antibiotic resistance.[19] Since the 1950s, antibiotics are used routinely in the feed of cattle, poultry, and swine to stimulate rapid growth and to avoid infections that may occur in animals that reside in congested and unsanitary conditions.[20] Nowadays, there is an increasing trend of usage of antibiotics in livestock, as almost 80% of all antibiotics are sold for livestock. Tetracyclines, Macrolides, Sulfonamides, and Streptogramins are used in cattle, poultry and swine feed. Penicillins,

Aminoglycosides, and Lincosamides are used only in the poultry and swine feed industry. Antibiotics are being routinely provided to animals regardless of their sickness. Due to this regular provision of antibiotics to animals, bacteria that reside in the gut of animals, skin, and respiratory tract become resistant to those antibiotics.[21] These bacteria can spread to people from livestock operations in different ways, i.e., food, environment, and workers. Antibiotic resistance bacteria are also found on fresh meat.[22]

Dose Effect and Overuse:

Usage of antibiotics contributes to antibiotic resistance, whether the use is appropriate or inappropriate.[23] Antibiotics that help in treating patients suffering from various diseases can be categorized as appropriate antibiotics, while antibiotics that do not help patients in coping against diseases are termed as inappropriate antibiotics. A number of studies predict that usage of antibiotics and antibiotic-resistant bacteria are interrelated.[24] It is also a fact that if we lower the usage of antibiotics, the number of antibiotic-resistant bacteria also decreases significantly.[25] If someone fails to complete the course of antibiotics, some of the infecting bacteria survive and become most resistant to that specific antibiotic. The bacteria that survive give rise to a number of bacteria more resistant to that antibiotic as compared to normal bacteria. So, the infection cannot be treated with that antibiotic.[26] Later on, antibiotics eradicate competitors that are sensitive to drugs and leave behind resistant bacteria that reproduce as a result of natural selection.

Non-Professional Doctors in Rural Areas

Non-availability of highly qualified and professional doctors in rural areas[27] is a common factor for antibiotic resistance in some developing countries. They do not advise patients to have a laboratory test before prescribing any antibiotic and prescribe inappropriate antibiotics.[28] Incorrect antibiotics can contribute to increasing the number of antibiotic-resistant bacteria.[29] Correct prescription of antibiotics is really important because incorrect prescription of antibiotics may pose serious threats, and patients become exposed to many other complications.[30] Another factor contributing to increased resistance in bacteria is the false advertisement of antibiotics by just profit earner people.

Self-Medication of Antibiotics:

The attainment and self-administration of antibiotics in order to treat a perceived infection is known as self-medication.[31] The antibiotics are self-administrated not only in underdeveloped countries but also in highly developed countries.[32] The prescribed antibiotics can also be used for self-medication.[33] People use self-medication with antibiotics in order to save time, money, to avoid consultation of doctor, past successful use for family and friends and leftover medicines.[31] In Pakistan, amoxicillin and metronidazole are the most commonly used self-medicated antibiotics while self-medication with antibiotics is mostly used for complications like fever, pain and respiratory problems.[31,34]

Misuse of antibiotics:

Misuse of antibiotics is widely practiced in developing countries, and this practice is recognized as a serious threat to our public health.[35] Superbugs are a kind of harmless bacteria that can cause serious infection as they have the ability to become resistant to multiple antibiotics.[36] The misuse of antibiotics along with overuse of fluoroquinolones causes an increase in the number of antibiotic-resistant bacteria, and it becomes really difficult to treat infections with antibiotics.[37] Fluoroquinolones when used as a first-line antibiotic, antibiotic sensitivity has decreased with negative effects such as those related with cystic fibrosis.[38]

Inappropriate Prescription:

Inappropriate prescription is another factor that is contributing to increased antibiotic

resistance. Worldwide different reports have demonstrated that duration, treatment indication, and choice of antibiotic is improper in 30% to 50% of cases.[39] It was reported in the U.S that pathogen was detected only in 7.6% out of 17,435 patients who were hospitalized with Community-Acquired Pneumoniae (CAP).[40] Moreover, 30 to 60% of antibiotics which are used in ICU are inappropriate, suboptimal, or incorrect. The sub-therapeutic concentration of antibiotics enhances antibiotic resistance through genetic alterations such as mutagenesis, Horizontal Gene Transfer (HGT) and alterations in genetic expression. Increased virulence is associated with alterations in genetic expression while HGT and mutagenesis enhances the antibiotic resistance and their transmission.[41]

Least or less of new antibiotics:

One of the most effective methods to overcome the resistance in bacteria was the development of new antibiotics which has been delayed due to many regulatory and economic problems.[40] Diversity of research teams has also reduced to significant level due to merges between different pharmaceutical industries.[42] Antibiotics are not considered economically more feasible by pharmaceutical companies because of their short duration of usage as compared to drugs which are used to treat chronic and life-threatening diseases such as gastroesophageal reflux, psychiatric disorders, asthma etc.[43-45] Because medicines used for the treatment of chronic disorders provide more profit to pharmaceutical companies and they prefer to invest in them.[44] Another factor associated with decreased availability of new antibiotics is their low price. The price of new antibiotics is a maximum of 1 to 3 thousand dollars per course as compared to hundreds of thousands of dollars of chemotherapeutic drugs.[44,45] Moreover, when the new antibiotic comes in the market, physicians usually treat it as the last option and prescribe older drugs.[43,44] This behavior leads to decreased use of new antibiotics and thereby reduced investment by companies.[42] Ultimately, when new antibiotics are used, the appearance of resistance can be predicted, but the bacterial evolution is quite uncertain; therefore, the timeline of resistance cannot be predicted. Therefore, manufacturers that invest in the development of new antibiotics may assume that profits are reduced to a significant level when resistant develop against that antibiotic.[44] One additional complication is that suppliers of most antibiotics are generic drug manufacturers, and these drugs are usually off-patent.[45] Due to these and many other factors, only a few antibiotics are being made. Infectious Disease Society of America (IDSA) has reported in 2013 that few new antibiotics are in phase 2 or phase 3 of development with activity against resistance developed in gram-negative bacteria such as Pseudomonas aeruginosa, Enterobacteriaceae and Acinetobacter baumanni.[46]

One of the major problems in the development of new antibiotics is regulatory approval.[42, 44] The approval for antibiotics has been reduced to a significant level between 1983 and 2007.[44.] The most usual difficulties in getting regulatory approval are different requirements of clinical trials in different countries, bureaucracy, clarity issues, inappropriate communication, and changes in licensing and regulatory rules.[42] Different changes in standard made by FDA during two decades have made clinical trials of antibiotics quite challenging.[45] Production of antibiotics is also considered uneconomical because a very large population sample is required.[42,45] In order to fill the gap which is present between discovery and development of antibiotics, small companies are coming forward, but they cannot accomplish the financial demands at phase 3 of clinical trials. Merck in December 2014 attained Cubist Pharmaceutical, which is proposed to speed up the regulatory approval and study of antibiotics.[47] In order to continue the discovery and development of new antibiotics there is need of new regulatory

approaches.[44] The new regulatory pathway for approval (LPAD) has been proposed by IDSA which has gained positive comments from the public. This model will help in fast, smaller and cost-effective clinical trials.[40]

Challenges:

Increased resistance of antibiotics due to their inappropriate usage to treat the patients suffering from chronic and vulnerable diseases is presenting a challenging situation. The rate of death has also risen greatly due to increased resistance, and it has been reported that in 2006, round about 50,000 people died due to increased resistance in two bacterial strains, which cause pneumonia and sepsis.[30] Another challenge associated with increased resistance of antibiotics is the increasing trend of self-medication, especially in developing countries. It has been noted that in Asian countries, even educated people are relying on self-medication.[48,49] Even after a chronic disease has been diagnosed, people consider themselves capable of maintaining their health, and in most cases, they do not take professional advice, and even if they take, they do not take it seriously. It has also been demonstrated that the use of some drugs such as topical corticosteroids, oral contraceptives, histamine H_2-receptor blockers, and antifungals is increasing day by day without any professional advice, which also shows that there is also lack of awareness.[50] The healthcare facilities are expensive in developing countries, and at the same time, these are not upto the mark; therefore, people do not prefer to go to professionals. So, to raise the standard of these health care centers and to make them accessible for everyone is another challenge.[51]

One of the great challenges for the government is to raise the awareness of antibiotics, the consequences of their misuses, and their possible side effects. It is also necessary to educate people about difficulties in the treatment of those diseases which are caused by pathogens in which resistance to different antibiotics has developed. The antibiotic resistance problem is not only a matter of concern for healthcare departments, but it may also damage the economy of the country.[52]

The lack of facilities and funding for the development of new antibiotics is another challenge which is currently faced by many pharmaceutical industries, and the efficacy of antibiotics which are currently available is in grave danger because the bacteria are becoming more and more resistant to them and as result of this resistance, the infections will become fatal. Two major problems associated with the development of new antibiotics are strict regulatory requirements and a shortage of monetary incentives.[30] Also, it has been noted that due to increased resistance in bacteria, the antibiotic therapies are becoming more and more complex and also in serious cases they are quite useless.[50]

Future Perspectives:

At this time, the world is moving toward the post-antibiotic era, and the different infectious diseases which were once considered treatable will not be able to manage again due to enhanced antibiotic resistance in bacteria. At present, around 70,000 people die worldwide annually due to enhanced antibiotic resistance. Due to the overconsumption of antibiotics in Pakistan, the resistant strains are spreading at a very high rate, and the adaptation of bacteria toward these antibiotics is also increasing day by day. The antibiotic usage in animals is increasing day by day in agriculture and poultry, and it has been reported that in order to meet the needs of the growing world the antibiotic usage will increase by 70% till 2050.

Due to increased antimicrobial resistance, there is an increase in the number of patients with such infectious diseases that cannot be treated. Also, there is a significant increase in the number of pathogens that are resistant to different drugs at the same time. Therefore it must be highlighted that is the need of time to develop new antibiotics to which bacteria and pathogens are not resistant.[53]

One of the key factors which are leading toward increased resistance of antibiotics is diagnostic uncertainty, which results not only in an increased number of resistant strains but also increased selection pressure.[54] The absence of appropriate techniques to detect and diagnose at early stages has also made it difficult to initiate therapy at appropriate time especially for those diseases which can be life threatening.[55]

It is proposed that in the future, the selection problem may be reduced by improving the diagnosis of bacterial infections. The indication to start and end the treatment by the development of a new diagnostic test would be a greater accomplishment.[56,57] Also, in the future, diagnostic accuracy can be increased by molecular diagnostics, which would enable the use of more appropriate antibiotic drugs. A scenario has been described by Dunne et al. in which he proposes that by 2050, the clinical samples would be analyzed and detected automatically by the development of sophisticated platforms with real-time amplifiers, and it will enable us to detect any pathogen within 30 minutes.[58] It has also been proposed that through the development of new tools it will be possible to distinguish between different viral and bacterial infections.[59]

The need for antibiotics and ultimately the resistance in antibiotics can be eliminated by developing conjugate vaccines, for example, those which are based on pneumococcus and encapsulated H. influenza. But at the same time, it has also been demonstrated that different problems may be associated with the development and delivery of these conjugate vaccines. Also in immunocompromised people, the commercial strains can be transformed into pathogenic strains and the vaccine activity against these bacteria could result in the destruction of natural immune system.

CONCLUSION:

The importance of antibiotics cannot be denied, and we depend completely on antibiotic therapy for the treatment of many infections. The antibiotics are used not only for the treatment of bacterial infections but also in other processes such as organ transplants. But excessive use of antibiotics results in antibiotic resistance that has threatened the benefits which have been achieved through the usage of antibiotics. There are many factors which are contributing to increased resistance of antibiotics, such as their extensive use in dairy and poultry, poverty, inappropriate prescription, regulatory barriers, over-dosing, lack of medical facilities, and many others. Many pharmaceutical companies are not making new antibiotics, mainly due to a lack of funds. The increased resistance toward antibiotics has also resulted in an increased burden on the economy of countries. It has also been also demonstrated that the rate of inappropriate prescription of antibiotics had been raised up to 88.9%. People usually do not consult doctors or other professionals, and they rely on self-medication. In order to overcome all of these issues, there is a need for increased awareness about the usage of antibiotics, health effects, and resistance. The government should also make new policies to overcome these challenges. Legislative amendments in Pakistan Medical & Dental Council (PMDC) ordinance should be made to prevent misuse and self-medication.

AUTHOR'S CONTRIBUTION:

MSA: Concept and design of the study
MSQ: Editing and final approval of the version
PI: Revision of article
SA: Drafting the article
IG: Data collection and drafting
ZA: Design of study
AH: Critical revision of article

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Case Report

SPONTANEOUS CLOSURE OF VESICOUTERINE FISTULA: A CASE REPORT

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ABSTRACT:
Vesicouterine fistula is a rare variety of urogenital fistula, representing about 1-4% of all cases, and caesarean section is the most common cause. The clinical presentation is variable and mainly includes a triad of cyclical hematuria (memoria), amenorrhoea, and urinary continence termed as Youssef's syndrome. The mainstay of treatment is surgical excision, and only less than 5% of patients respond to conservative therapy. Laparoscopic and robotic-assisted surgery is also gaining popularity. The case reported here was a young multiparous woman with previous four lower segment caesarean sections and had her elective fifth caesarean section and bilateral tubal ligation. The bladder was high up and badly adherent to the previous scar. She developed hematuria in the immediate postoperative period. Retrograde cystography confirmed the diagnosis of small vesicouterine fistula. The Patient responded to conservative management by catheterization for six weeks. Healing of fistula confirmed by repeat cystogram, and the Patient is having normal menstruation with no urinary problem.

SPONTANEOUS CLOSURE OF VESICOUTERINE FISTULA: A CASE REPORT

Key Words: Uterus, Urinary bladder, Fistula

INTRODUCTION:

Vesicouterine fistula is a rare variety of urogenital fistula representing 1-4% of all urogenital fistulas.[1] Vesicouterine fistula is a pathological communication between epithelial surfaces of bladder and uterus or cervix.[2-4] Only a few cases are reported in the literature, and most common cause is caesarean section.[5-6] Almost 83-88% of cases of vesicouterine fistula are due to caesarean section.[3, 7] The incidence is almost double after repeat caesarean section.[7]

Causes of vesicouterine fistula are mainly divided into four categories. Surgical, obstetrical, radiation necrosis and malignancy.[8] Obstetrical causes include caesarean section, obstructed labor, dilatation and curettage, induced abortion, forceps delivery, placenta percent, and vaginal birth after caesarean section.

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The classical clinical presentation is termed as Youssef's syndrome as first described by Youssef in 1957.[9] It included triad of cyclical hematuria (menouria), absence of vaginal bleeding (amenorrhoea), and complete urinary continence. The first case of the vesicouterine fistula was described by Knipe in 1908.[10.] In 2000, Jozwik and Jozwik proposed another classification of Vesicouterine fistula (VUF), based on the route of menstrual flow.[11] According to Jozwik, there are three types of Vesicouterine fistula. Type 1 is a triad of amenorrhoea and menouria and complete continence of urine (Youssef's syndrome). Type 2 is a dual menstrual flow via both bladder and vagina. Type 3 is normal vaginal menses and a lack of menouria. In some patients, the only presentation of Vesicouterine fistula is urinary incontinence.[12]

Diagnostic modalities include Cystoscopy, Cystography, and Hysterogram.[8] Treatment modalities include conservative, medical, and surgical management.

Here we report a case of the iatrogenic vesicouterine fistula, which healed spontaneously by bladder catheterization.

CASE SUMMARY:

My Patient, 27 years old, G6P4A1, previous four caesarean sections, and three alive issues. The last section was done two years back. Her expected date of delivery was Aug 22, 2019. Her pregnancy was uneventful. She was admitted on Jul 24, 2019, at 35 weeks and four days for elective lower segment caesarean section. During surgery, it was noticed that the bladder was high up and badly adherent to the previous scar. Dissection of bladder tried, but bleeding started so bleeding points diathermic and incision given on lower segment of uterus 2cm above bladder adhesion. The outcome was a 2.8 kg baby boy with a good Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score. Uterus was closed in two layers, bilateral tubal ligation was done, and the abdomen was closed. The Patient had hematuria in the immediate postoperative period, so it was decided to retain a foleys catheter for seven days. Her hematuria got settled in 48 hours with smooth recovery, so the foleys catheter was removed on the 7th postoperative day (Aug 1, 2019). She again started hematuria after removing the foleys catheter, and there was no vaginal bleeding. The urologist was consulted, and keeping in mind the possibility of vesicouterine fistula; the Foleys catheter was inserted on the same day for six weeks. Her baselines investigations were repeated, and abdominopelvic ultrasound was done to rule out any collection, and broad-spectrum antibiotics were started. To confirm the diagnosis of vesicouterine fistula, a retrograde cystogram was done, and it showed small vesicouterine fistula. (fig 1)

Her hematuria got settled after two days, and stitches were removed on the 10th postop day with a healthy wound. She was discharged with Silicon Foley's catheter 18FR, oral analgesics, and antibiotics. She suffered from amenorrhoea after her caesarean section. She presented with urinary tract infection twice afterward, and antibiotics were given after culture and sensitivity reports. Her Foley catheter was changed after two weeks and removed on Sep 16, 2019. She remained asymptomatic after that with no hematuria. As she was suffering from amenorrhoea, so progesterone was given for withdrawal bleeding to rule out menouria. She had vaginal bleeding with no menouria. She had regular cyclical bleeding after that. Her retrograde cystogram was repeated on Jan 14, 2020, and it confirmed the spontaneous healing of the fistula. (Figure 2)

Anteroposterior view **Lateral view**

Fig-1: Retrograde cystogram showing spillage of dye from bladder into uterus (Vesicouterine fistula)

AP view **Lateral view**

Fig-2: Retrograde Cystogram showing healed Vesicouterine fistula

DISCUSSION:

Vesicouterine fistula is a rare variety of urogenital fistula. In developing countries, it can occur after previous caesarean section, prolong and obstructed labor, forceps

delivery, uterine rupture, manual removal of placenta, abnormal implantation of placenta, inflammatory bowel disease and pelvic radiations.[8, 13] In developed countries lower segment caesarean section is the main iatrogenic cause of this condition.

Clinical presentation is variable, including the clinical triad of Youssef's syndrome (menouria, amenorrhoe and urinary continence).[9] Patient can also present with recurrent urinary tract infections and some with urinary incontinence.[2]

Diagnostic modalities include cystoscopy, cystography, hysterosalpingography, contrast-enhanced CT Scan, Magnetic Resonance Imaging (MRI) and Transvaginal ultrasound.[12-14]

Management options include conservative, medical, and surgical. If the fistula is small and diagnosed early, then bladder catheterization for 4-6 weeks helps in spontaneous healing of fistula, and this conservative management was successful in our case study. The overall success rate of conservative management is less than 5%.[15] In some patients, such lesion present with lochiuria in puerperium and resolve spontaneously before diagnosis.[16,17]

In 1999, Jozwik and Jozwik reported a case of spontaneous closure of the vesicouterine fistula. This was 41st Patient with spontaneous closure. He reviewed literature and found out that the total 796 cases reported until December 1997. Out of these, he identified 40 cases of spontaneous resolution of Vesicouterine fistula making success rate of less than 5%.[18]

Medical management includes the use of oral contraceptive pills, Progestogens, and GnRH analogs for induction of amenorrhoea, and there are case reports of a successful outcome with medical management.[19, 20]

Surgical management is the treatment of choice in most of the cases. Various surgical approaches include vaginal, transvesical, transperitoneal, laparoscopic, and robotic procedures.[21] It is recommended to delay fistula repair surgery for three months after iatrogenic surgery. It will help in spontaneous closure of small fistulas and in the resolution of inflammation before surgical repair of large fistulas. Although there are case reports of a successful outcome with early surgical repair of Vesicouterine fistula.[22]

Many case series and case reports are published in literature with satisfactory results of surgical repair of Vesicouterine fistula. In 2013, Rajamaheswai N et al. reported a 100% success rate of treatment of Vesicouterine fistula in 17 patients.[14] Rao MP and colleagues reported excellent surgical outcomes in 12 patients.[23] Transvaginal repair of Vesicouterine fistula is less preferred route because of the higher location of the fistula. Recently Milani R et al managed a case of Vesicouterine fistula successfully with transvaginal repair and stressed that this route should be used by only experienced surgeons.[13]

Laparoscopic and robotic repair of Vesicouterine fistula is gaining popularity due to reduced blood loss, less postoperative pain, and shorter hospital stay. In 2013, Abdel Karim et al. reported the largest series of laparoscopic Vesicouterine fistula repair.[24] He managed 11 females with no complications. In 2009, Hemal AK et al. reported the first successful case series of robotic repair of Vesicouterine fistula in 3 cases.[25] Overall pregnancy rate after Vesicouterine fistula surgical repair is from 25% to 37.5%.[15,23] In our case bilateral tubal ligation of the Patient was done.

CONCLUSION:

The incidence of caesarean sections is increasing worldwide, so doctors need to be aware of this possible complication, especially in cases of repeated caesarean sections. Patients should be informed about the risk of Vesicouterine fistula before repeat caesarean section, and informed consent should be taken. Repeat caesarean section should be performed by a senior obstetrician. Women with genitourinary fistulas lead a miserable life. Not only they have personal hygiene problems but are shunned by family and society. Women do

not come forward for treatment and continue to suffer in silence. Hence, there is a need to create awareness not only among masses but also in the the medical community.

AUTHOR'S CONTRIBUTION:

FF: Conception of idea
DN: Data collection
YA: Data analysis
SJR: Editing

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