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#### **Correspondence Address:**

Editor, JBUMDC, Bahria University Medical & Dental College, Adjacent PNS SHIFA,  
DHA Phase II, Karachi Pakistan

 +92-21-35319491-9

 <https://jbumdc.bahria.edu.pk>

 [editor.bumdc@bahria.edu.pk](mailto:editor.bumdc@bahria.edu.pk)

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## Pregnancy and Covid-19: Some Thing to Worry About?

Samreen Iqbal, Muhammad Majid Ali Jafri

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Pregnancy is a special time, full of excitement and anticipation, but for expectant mothers facing the outbreak of the coronavirus disease (COVID-19), fear, anxiety and uncertainty are clouding this otherwise happy time.

Coronavirus disease 2019 (COVID-19) has led to the deadliest pandemic observed in more than a 100 years.<sup>1</sup> Around 131 million women give birth annually. This population is particularly vulnerable to emerging infectious pathogens due to alterations in immune, respiratory, and cardiovascular physiology that occurs during pregnancy. Recent outbreaks of severe acute respiratory syndrome, Middle East respiratory syndrome, influenza H1N1, Ebola virus disease, and Zika virus disease resulted in high rates of maternal morbidity and mortality, fetal loss, and fetal harm. Fortunately early data regarding pregnancy outcomes in COVID-19 are reassuring: maternal outcomes are similar to non-pregnant adults; vertical transmission and neonatal infection are rare. However pregnant women remain at risk of severe disease requiring intensive care, and they deserve equity to access therapeutic options guided by rigorous scientific data.<sup>2-3</sup> More than 90% of infected mothers recovered without undergoing delivery.<sup>3</sup>

Pregnant women should follow the same recommendations as non pregnant individuals to avoid exposure to the virus such as social distancing, hand hygiene, disinfecting surfaces and wearing a mask in public. All pregnant women should be monitored for development of symptoms and signs of COVID-19, particularly if they have had close contact with a confirmed case or persons under investigation.

American College of Obstetricians and Gynecologists (ACOG) has developed algorithms to evaluate pregnant outpatients with suspected or confirmed COVID-19.<sup>4</sup> Patients having symptoms compatible with COVID-19, the severity of illness, underlying co-morbidities, and clinical status should be assessed to determine the potential need for hospitalization.

Possible vertical transmission has been reported in several cases of peripartum maternal infection in the third trimester,

suggesting congenital infection is possible but uncommon.<sup>3</sup> The placentas from COVID-19- positive pregnant women showed injury; type of injury seen in the placentas revealed abnormal blood flow between the mothers and their babies in utero, pointing to a new complication of COVID-19. An early diagnosis could help in persistent clinical monitoring of pregnant women during the pandemic.<sup>5</sup> Complications of infection include acute respiratory distress syndrome, arrhythmias, acute cardiac injury, shock, preterm birth, fetal growth retardation and perinatal mortality.<sup>6</sup> In most cases, the timing of delivery should be dictated by obstetric indications rather than maternal diagnosis of COVID-19. There is no alteration in usual timings of delivery indicated among women with suspected or confirmed COVID-19 infection early in pregnancy who then recovered.

For women with suspected or confirmed COVID-19 in the third trimester, it is advisable to postpone delivery (if no other medical indications arise) until a negative test result is obtained or quarantine restrictions are lifted to avoid virus transmission to the neonate.<sup>8-11</sup>

In general, a diagnosis of COVID-19 during pregnancy is not an indication for early delivery.<sup>12</sup> Neither is COVID-19 an indication to alter the route of delivery. Cesarean delivery is performed for standard obstetric indications, which may include acute decompensation of mother with COVID-19.<sup>7</sup> Corona virus has not been found in breast milk, however if the mother has COVID-19 infection, she can spread the virus to the infant through tiny droplets that spread when she talks, coughs or sneezes.<sup>7-12</sup>

Congenital infection in a live born infant depends on presence or absence of clinical features of infection in a newborn and mother with COVID-19 infection. In symptomatic cases, congenital infection is confirmed if the virus is detected by PCR in umbilical cord blood or neonatal blood collected within the first 12 hours of birth or amniotic fluid collected prior to rupture of membranes. In asymptomatic cases, neonatal infection is confirmed if the virus is detected by PCR in cord blood or neonatal blood collected within 12 hours of birth. Neonatal infection may be acquired intrapartum or acquired postpartum.<sup>13,14</sup>

The multidisciplinary team in contact with the newborn must wear PPE (N95 or PFF2 masks, glasses and face protectors, waterproof aprons, and sterile gloves and caps). Newborns requiring intensive care should ideally be admitted to an isolation room with the potential for negative ambient pressure or other available air filtration systems. Incubators should be kept at a minimum distance of 1.5 meters. For

### Samreen Iqbal

Assistant Professor, Department of Obsrtrics and Gynaecology, Bahria University Medical & Dental College, Karachi  
Email: drsam222@yahoo.com

### Muhammad Majid Ali Jafri

Peads Specialist  
Agha Khan University Hospital, Karachi

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newborns with indications for non-invasive ventilation (CPAP or bilevel), high-flow oxygen therapy, or invasive mechanical ventilation, precautions should be taken to avoid aerosols, droplets, and contact through the use of PPEs recommended for this purpose<sup>13,14</sup> It is satisfactory that most newborn babies infected with the virus recovered uneventfully. Unfortunately, pregnant women have systematically been excluded from clinical trials of therapeutics and vaccines. There are currently more than 300 trials exploring therapeutics for COVID-19, yet near universal exclusion of pregnant women, despite many of these trials repurposing drugs already widely, and safely, used in pregnancy. For example, hydroxychloroquine is commonly used in connective tissue disorders, and lopinavir plus ritonavir in combination is a common anti-retroviral therapy to prevent vertical transmission of HIV. Intrapartum azithromycin decreases maternal and neonatal infective morbidity. Interferon beta-1a reduces multiple sclerosis relapse. Exposure registry and post-marketing surveillance for these drugs all provide reassuring signals of safety. To conclude; pregnant women should do whatever they can to avoid getting COVID-19 infection.

**Author Contribution:**

Samreen Iqbal: Conception of Idea  
Muhammad Majid Ali Jafri: Final Proof Reading

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## Expression And Scoring Of HER2/Neu in Variants of Prostate Adenocarcinoma

Santosh Kumar Sidhwani, Madeeha Sadiq, Mubina Lakhani, Sumayyah Shawana, Raffia Siddiqui, Sobia Hassan

### ABSTRACT

**Objective:** To evaluate the immunohistochemical expression and scoring of HER2/neu in different variants of adenocarcinoma of prostate and to compared the association of HER2/neu expression with biological behavior and risk factors of prostate adenocarcinoma.

**Study Design and Setting:** Cross sectional study in which all clinically suspected prostate adenocarcinoma cases received at the laboratory Saddar Karachi during the years 2015 and 2016 were evaluated for morphological features of adenocarcinoma.

**Methodology:** This cross sectional study was carried out using prostate biopsies of clinically suspected prostate adenocarcinoma. The diagnosis of adenocarcinoma was confirmed and histological characterization was done by evaluating the morphological features. The tumors were graded according to the revised 2015 Gleason's grouping. Immunohistochemical analysis for HER2/neu expression was performed in the most representative tumor block. SPSS version 22 was used for data analysis. Mean frequency and percentages were calculated for quantitative variables, whereas chi-square test and Fisher's Exact Test were applied for qualitative variables. P-value of < 0.05 was considered as significant.

**Results:** Out of 77 biopsies only one showed moderate HER2/neu expression. Positive HER2/neu was acinar variant. No significant statistical association was observed between expression of HER2/neu and prostate cancer variants. The positive case had age more than 60 years with moderately increased serum PSA levels and was aggressive in nature at the time of diagnosis.

**Conclusion:** It was concluded from the study that HER2/neu was rarely expressed in prostate adenocarcinoma.

**Keywords:** Adenocarcinoma Prostate, Acinar, Ductal, Gleason Groups, PSA levels, Variants, HER2/neu.

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### INTRODUCTION:

Prostate cancer is second most prevalent cancer affecting males worldwide.<sup>1</sup> About every 7<sup>th</sup> man in his lifetime is diagnosed with the prostate cancer.<sup>2</sup> According to GLOBOCON 2018, the prevalence of prostate adenocar-

cinoma is 7.1% and about 1.3 million of new cases have been reported in same year with a death rate of 24.1 per 100,000 males.<sup>3</sup> Prostate cancer is known to affect the older age group with a mean age of 65 years and above.<sup>4</sup> Nations with high prevalence are New Zealand, Australia and South Africa where as lower rates have been seen in less developed countries.<sup>5</sup>

In Pakistan, an increasing trend of prostate cancer has been recorded with a prevalence of 5.3% per 100,000 in recent years.<sup>6</sup> Till now, the established causes of the prostate adenocarcinoma remained obscure, though multiple risk factors have been described which include hormones, age, family history, race, genetics, androgen receptors and many others.<sup>7</sup> The pathogenesis of prostate cancer mainly depends on cell growth and differentiation affected by the genes and androgens and their binding to their receptors.<sup>8</sup>

Diagnosis of prostate cancer mainly depends on history, clinical examination like DRE (digital rectal examination) sign and symptoms, radiological examination and PSA levels.<sup>9</sup> But still, the gold standard is biopsy and histopathological examination. Histologically, prostate adenocarcinoma exhibits neoplastic glands lined by a single layer of cuboidal cells. While the immunohistochemistry helps in diagnosis of the many cancers including the prostate adenocarcinoma.<sup>10</sup> According to recent studies, there are several immune markers expressed by prostatic tissue and

#### Santosh Kumar Sidhwani

Assistant Professor, Department of Pathology,  
Ziauddin University, Karachi  
Email: santoshkumarsidhwani@yahoo.com

#### Madeeha Sadiq

Assistant Professor, Department of Anatomy,  
Ziauddin University, Karachi

#### Mubina Lakhani

Assistant Professor, Department of Anatomy,  
Ziauddin University, Karachi

#### Sumayyah Shawana

Associate Professor, Department of Pathology  
Bahria University Medical and Dental College, Karachi

#### Raffia Siddiqui

Assistant Professor, Department of Pathology,  
Karachi Medical and Dental College, Karachi

#### Sobia Hassan

Assistant Professor, Department of Pathology,  
Altamash Dental College, Karachi

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one of them is HER2/neu.<sup>11</sup> It has been demonstrated that HER2/neu has been expressed in high pathological stage and highly aggressive prostate adenocarcinoma.<sup>12</sup>

HER2/neu expression could be targeted for the novel therapeutics intervention in prostate adenocarcinoma as implicated in other tumors like breast cancer. Several studies have postulated that HER2/neu expression in prostate cancer could be responsible for differentiation, angiogenesis and alteration in cellular proliferation migration, survival and tumor formation. In many tumors, HER2/neu is proved to be good prognostic marker thereby providing a vital therapeutic option.<sup>13</sup>

Therefore, the present study was aimed to evaluate the immunohistochemical expression of HER2/neu in different variants of prostate adenocarcinoma and to compare its expression with the different clinicopathological parameters of prostate cancer.

**METHODOLOGY:**

This study was conducted after approval from ethical review committee of Ziauddin University (Ref Number. 0110306SKPATH). All clinically suspected prostate adenocarcinoma cases received at The Laboratory Saddar Karachi during the years 2015 and 2016 were evaluated for morphological features of adenocarcinoma. We excluded the cases with benign prostatic hyperplasia, secondary cancer or metastatic to prostate, cases with other benign prostatic lesion, prostatic intraepithelial neoplasm and cases on anti-androgen therapy.

After confirming the diagnosis, 77 cases were randomly selected following informed consent along with pertinent clinical history and PSA levels. Tumor was classified into ductal and acinar variants while the representative Gleason's group was assigned by examining multiple levels of Hematoxylin and Eosin stained sections by the consultant histopathologist. The most representative tumor block bearing abundant tumor volume was selected for immunohistochemistry. The study was conducted following ethical approval from ethics review comity (ERC) of Ziauddin University Karachi. We performed immunohistochemistry

by the method described by Signoretti et al.<sup>14</sup> The paraffin embedded, formalin fixed prostatic tissue blocks were selected and cut into 3µm sections and dipped into water. After transferring the tissue to glass slides these sections were treated with citrate buffer (0.1mol/L) for 45 minutes in microwave for antigen retrieval. A mouse monoclonal antibody (HER2/neu, cell marque) was prepared at dilution of 1:50ml. Tissue sections were then treated with prepared antibody for 45 minutes followed by rinsing with buffer, followed by separately developed enzyme activity. These sections were then treated with graded alcohol and counter stained with hematoxylin for 1 minute followed by distilled water rinse and later dried at room temperature. Cover slip was applied on the slide using mounting media. Known HER2/neu positive breast adenocarcinoma slides were used as positive controls while slides incubated without primary antibody in tris buffer (TBS) were used as negative controls. These slides with immunohistochemical sections were then evaluated for stating pattern of HER2/neu by the same panel of histopathologists. The tissue sections were examined in light microscopy and sections with dark brown cytoplasmic staining were considered as positive. Statistical analysis was performed using SPSS version 22 (SPSS Inc., Chicago, USA). The association of HER2/neu expression with clinicopathological parameter, which includes; age, tumor grade and PSA levels were assessed by Chi-square test. P value less than 0.05 was considered as significance.

Table 1: Expression of HER2/neu in study subjects

HER2/neu	Prostate Adenocarcinoma
Positive	1
Negative	76
Total	77

Table 2: Statistical estimates of immunohistochemical expression of HER2/neu in different variants of prostate adenocarcinoma

Tumor Variants	HER2/neu Positive	HER2/neu Negative	P value
Acinar N=71	01	70	0.78*
Ductal N=6	00	06	

Table 3: Correlation of tumor variants with different risk factors of prostate adenocarcinoma

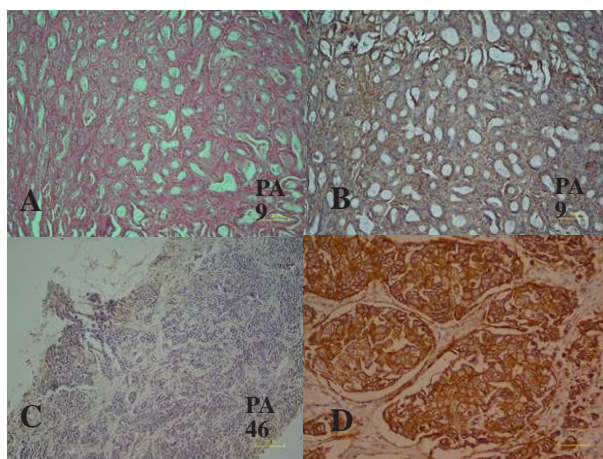
Tumor variant	Age (years)			Family history			PSA level (ng/ml)				Gleason's Group			
	≤ 60	> 60	P-value <sup>1</sup>	Sporadic	Familial	p-value <sup>2</sup>	> 4	≥ 20	> 50	P-value <sup>3</sup>	Mild Risk <sup>4</sup>	Intermediate Risk <sup>4</sup>	High Risk <sup>4</sup>	p-value <sup>4</sup>
Acinar n=71	12	59	0.34*	62	9	0.46*	67	4	0	0.71*	11	18	42	0.32 <sup>4</sup>
Ductal n=6	0	6		6	0		6	0	0		0	3	3	

\*Fisher's Exact Test, p-value for comparison of HER2/neu with <sup>1</sup>age and <sup>2</sup>family history  
<sup>3</sup>Gleason's Group 1, <sup>4</sup>Gleason's Group 2 and 3, <sup>5</sup>Gleason's Group 4 and 5, \*Fisher's Exact Test, <sup>?</sup>Pearson Chi Square test, p-value for comparison of HER2/neu with <sup>3</sup>PSA level and <sup>4</sup>Gleason's group.

## RESULTS:

According to histopathological findings, the prostate cancer were differentiated into acinar (71 cases) and ductal (6 cases) variants. The immunohistochemical expression of HER2/neu was evaluated in all 77 biopsies and we determined only one case that showed the HER2/neu expression (Table 1). Positive HER2/neu tumor showed acinar morphology (Figure 4.1). This has an insignificant statistical association with prostate cancer variants (Table 2) The strength of protein expression was observed 2 on scale of 3. The statistical comparison of variants of prostate adenocarcinoma with age revealed that most of the cases were aged 60 years and above at time of diagnosis. Mean age of patients in the present study was observed to be  $68.7 \pm 7.9$  years. Moreover, majority of the cases presented with aggressive biological behavior with high PSA levels. Unfortunately, no statistical correlation association was seen between variants of prostate adenocarcinoma and HER2/neu and these parameters. (Table 3)

Figure 1: Microscopic picture of PA 9 showing (A) H & E of neoplastic glands with variable sizes (B) moderate immunohistochemical expression of HER2/neu in atypical glands (C) PA 46 showing HER2/neu negative with neoplastic glands that are undifferentiated and (D) Membranous expression of HER2/neu membrane in control (Breast Adenocarcinoma). (H & E and IHC; 20x magnification)



## DISCUSSION:

Globally in men, prostate adenocarcinoma is found to be the second most common killer.<sup>15</sup> There is a rise in incidences of this specific type of tumor over the last few decades which makes therapeutic intervention and diagnosis challengeable.<sup>12</sup> A few previous studies demonstrated up to 53% of expression of HER2/neu in prostate adenocarcinoma while some studies failed to find any expression in their respective studies.<sup>16</sup> Therapeutic and prognostic significance of HER2/neu has been established in many cancers such as breast adenocarcinoma.<sup>17</sup> The present study however failed to generate any significant relation between prostate adenocarcinoma and expression of HER2/neu apart from

one positive case of acinar variants. These findings are in line with other several studies that showed rare or no expression of HER2/neu in adenocarcinoma prostate.<sup>18,19</sup> These differences in present study may have been attributed due to different antibodies or different technical skills used. Else genetic variation, demographic profile and exposure to different risk factors, fixation and processing of tissue may also affect the levels of immune staining.<sup>20</sup> Many population based studies with moderate and high prevalence of prostate cancer suggested advancing age as a major risk factor for prostate adenocarcinoma with mean age of 65 or above, also showing that after seventies the risk is increased by two folds.<sup>21</sup> The mean age of prostate adenocarcinoma in the present study was found to be  $68.7 \pm 7.9$  years. These findings are comparable with previous studies done on including different populations.<sup>22,23</sup> The cases recruited in the present study are hospital based due to which the conclusion drawn on advancing age and risk of prostate adenocarcinoma cannot be generalized on population.

Two variants of prostate adenocarcinoma acinar and ductal were observed in the present study. The predominant variant was acinar with a frequency of 92.2% followed by ductal with 7.8% of patients. These frequencies are in accordance with past studies.<sup>24,25</sup> However, no rare morphological variants were seen due to the limited sample size. The HER2/neu positive case had morphological features consistent with the acinar variant so it was characterized accordingly. This showed an insignificant statistical association ( $p=0.078$ ) with different pathological parameters. Low sensitivity of immunohistochemistry may be the reason behind the absent expression of HER2/neu in other variants.<sup>26,27</sup> However, FISH, PCR, gene amplification may show more reliable results due to their high sensitivity. Our results may be explained on the basis of observation of only two variants of prostate cancer in our sample.

In this study, only the acinar (mean age 68 years) and ductal entities (mean age 71 years) of prostate cancer were observed. These results showed that these two entities follow the pattern of advancing age and these findings are in agreement with previous studies.<sup>28</sup> A possible explanation is the late presentation of symptoms. It can be hypothesized that some factors like putative agents and formation of free radicals related to aging may contribute to causation of cancers in conjunction with other environmental factors such as sedentary lifestyle, family history and dietary habits. However more studies on large number of these entities are needed before any definite conclusion may be drawn regarding age and prostate cancer.<sup>29</sup>

The preoperative PSA levels of both groups were similar on comparing the pathological parameters. It was postulated that there is high risk of developing the prostate cancer before the age of 60 years in individuals having a strong family history. Such patients may be benefited from regular PSA screening compared to general population. PSA levels

and Gleason score and tumor stage are considered as best prognostic factors for prostate adenocarcinoma progression. Additionally, new Gleason grouping system provides a better comparison and better assessment of invasion, growth pattern and morphological differentiation. Furthermore, as recommended by new Gleason grouping system, prostate adenocarcinoma is categorized as low, intermediate and high risk groups which allows us to define the significant cut off points for each group. It can also be helpful in differentiating the groups with different prognosis and management needs.<sup>30,31</sup>

However, there are a few limitations to the current study. Due to small sample size, we were unable to show a significant association. Secondly, more advanced robust techniques like FISH and PCR may show different results in outcomes due to their sensitivity. Third, several potential biases have been identified that could affect our results such as patients age and PSA levels only at the time of diagnosis were taken that prevented us from making any meaningful conclusion for the serum PSA levels and age of onset of prostate adenocarcinoma. Moreover, only needle biopsies and TURP cases were included in the present study. Therefore, patients who've undergone radical prostatectomy and who may have had more advanced stage were not recruited. Furthermore, needle biopsy and TURP specimens limited us for comparative analysis of other parameters like histopathological staging. It is also likely that HER2/neu treatment strategies will be ineffective in treating prostate cancer. However, future studies with large number of cases may prove beneficial to further explore this association of HER2/neu expression with prostate cancer.

### CONCLUSION:

It was concluded from the study that HER2/neu was rarely expressed in prostate adenocarcinoma. Her2/neu expression is present in acinar variant of this tumor which is a common entity. Therefore, it was evident that HER2/neu is not expressed in the same manner like other cancers such as adenocarcinoma of breast.

#### Author Contribution:

Santosh Kumar Sidhwani: Primary Researcher  
 Madeeha Sadiq: Writer  
 Mubina Lakhani: Writer  
 Sumayyah Shawana: Evaluator of Histological Cases  
 Raffia Siddiqui: Evaluator of Histological Cases  
 Sobia Hassan: Writer, Statistical Analysis

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## Role of Magnetic Resonance Spectroscopy in Differentiating Neoplastic From Non-Neoplastic Ring Enhancing Brain Lesions Taking Surgical Findings as Gold Standard

Ameet Jesrani, Marya Hameed, Seema Nayab, Asma Javed, Sehrish Sethar

### ABSTRACT

**Objective:** To evaluate the diagnostic accuracy of Magnetic Resonance spectroscopy (MRS) in distinguishing neoplastic from non-neoplastic ring enhancing brain lesions taking histopathological findings as gold standard.

**Study Design and Setting:** The cross sectional study was conducted at Radiology department of Jinnah Postgraduate Medical Centre.

**Methodology:** Total 102 patients with ring enhancing lesions detected on MRI brain contrast studies were selected for this study. Cases were referred from Outpatient Department of Neurology Clinics who were suspected of having space occupying lesions in brain. Full history, clinical examination and laboratory investigations (Complete Blood Count and ESR) were carried out. The patients having claustrophobia, metallic implants, cardiac pacemaker and having metallic foreign body in situ were excluded from the study. Informed consent was taken from the research and MRS was performed. On MRS, lesion was categorized and final diagnosis was taken based on histopathology results. All the information was recorded into predesigned proforma. Patients Data was scrutinized by using Statistical Package for Social Sciences (SPSS 21.0). Mean + SD was calculated for age, gender, duration of symptoms and size of the lesion.

**Results:** The average age of the patients was 35.45±10.36 years. Sensitivity, specificity, PPV, NPV and accuracy of MRS was 87.5%, 93.3%, 95.5%, 89.7% and 92.1% respectively.

**Conclusion:** Magnetic resonance spectroscopy can be effective in discerning neoplastic from non-neoplastic ring enhancing cerebral lesions, thus avoiding an invasive procedure like brain biopsy.

**Key Words:** Brain lesions, Magnetic resonance spectroscopy, Neoplastic, Non-neoplastic, Ring Enhancing.

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### INTRODUCTION:

Magnetic resonance spectroscopy (MRS) is an application of MRI that early detects the abnormal chemical metabolites of brain tissue.<sup>1</sup> First clinically used in 1980s, it has proved to be useful in providing molecular information about the tumor and non tumoral cells of the brain tissue.<sup>2</sup> After true

detection of the benign or malignant lesions on MRS, many patients are saved from undergoing unnecessary surgeries.

Ring-enhancing lesions are frequently encountered neurological lesions and provide a challenge to neuroimaging. Typical location of ring-enhancing lesions is at the junction of the gray and white matter, however they can also be seen in the sub-cortical area, deep in the brain parenchyma or may even be superficial.<sup>3</sup> Cerebral ring-enhancing lesions may present as non-tumorous conditions like abscesses, tuberculomas, multiple sclerosis, resolving hematoma (age 10-21days) or even post radiation necrosis. These conditions can easily mimic primary brain tumors or metastasis.<sup>4</sup>

Some of non neoplastic lesions show changes in MRS like raised Cho/Cr ratio with a suppressed NAA peak in Alexander's leukodystrophy<sup>5</sup> while lower concentration of all metabolites, except Cr, in adult onset autosomal dominant leukodystrophy. Gupta R et al<sup>6</sup> described the presence of lipid/lactate peak in both pyogenic and tuberculous abscesses, however, more frequently in tuberculous lesions. Distinguishing neoplastic from non-neoplastic ring-enhancing and tumor mimicking lesions is extremely important which if misdiagnosed may not only lead to unwarranted neuro-

**Ameet Jesrani**  
Assistant Professor, Department of Radiology,  
Sindh Institute of Urology and Transplantation, Karachi  
Email: [ameet.jesrani@yahoo.com](mailto:ameet.jesrani@yahoo.com)

**Marya Hameed**  
Consultant Radiologist, Department of Radiology,  
Jinnah Postgraduate Medical Center, Karachi

**Seema Nayab**  
Assistant Professor, Department of Radiology,  
Liaquat University of Medical and Health Sciences, Jamshoro

**Asma Javed**  
Resident, Department of Radiology,  
Sindh Institute of Urology and Transplantation, Karachi

**Sehrish Sethar**  
Resident, Department of Radiology,  
Sindh Institute of Urology and Transplantation, Karachi

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surgery, noxious chemotherapy or harmful irradiations but also prove to be fatal in many cases. Conventional MRI shows only 61.4% <sup>7</sup>sensitivity in separating benign from malignant lesions even with the use of exceptional soft tissue contrast.

Magnetic resonance spectroscopy (MRS) significantly increases the diagnostic accuracy when used as an adjunct with conventional MRI. MRS determines the concentration of specific metabolites of different neurological pathologies in a pre-selected volume of brain tissue. <sup>8,9</sup> Therefore, in newer imaging, MRS is emerging as a capable diagnostic tool in identifying several neurological and neurosurgical disorders with sensitivity and specificity of 97.6% <sup>1</sup> and 71.42% <sup>10</sup> respectively.

The rationale of this study was the intention to determine the diagnostic accuracy of magnetic resonance spectroscopy which is cost effective, noninvasive and does not involve ionizing radiations in detecting neoplastic from non-neoplastic ring enhancing brain lesions and to standardize its use to determine the best management.

#### METHODOLOGY:

This cross-sectional study was executed from 9<sup>th</sup> January 2019 till 10<sup>th</sup> July 2019 in Radiology department of Jinnah Postgraduate Medical Centre after approval from ethical committee. Total 102 patients with ring enhancing lesions detected on MRI brain contrast studies were selected with patient's age ranging from 16 to 70 years. The mean age was 35.45±10.36 years of both genders. Cases were referred from Outpatient Department of Neurology Clinics who were suspected of having space occupying lesions in brain. Full history, clinical examination and laboratory investigations (Complete Blood Count and ESR) were carried out.

The patients having claustrophobia, metallic implants, cardiac pacemaker and having metallic foreign body in situ were excluded from the study. Informed consent was taken from the research and ethical committee of the institution. Sample size was calculated considering both the sensitivity and specificity of magnetic resonance spectroscopy to differentiate neoplastic from non neoplastic ring enhancing brain lesions. Nonprobability consecutive sampling technique was applied to collect the samples. Patient's history regarding duration of symptoms and demographic details like patient's age and gender was noted. Patients were subjected to Toshiba 1.5 Tesla MR Scanner. Various sequences were carried out with and without contrast like T1, T2 and Fluid Attenuated Inversion Recovery using a head coil. Then MRS was performed via single voxel technique using main metabolites like NAA which appears at 2.01ppm, Cho at 3.22ppm, Cr at 3.02, lipid at 0.8 to 1.3ppm and lactate at 1.32 to 1.33ppm.

Lesions with increased Choline and reduced NAA levels along with increased Cho/Cr ratio of more than 1.5 were labelled as neoplastic. While non-neoplastic lesions have reduced Cho, Cr and NAA levels.<sup>2</sup> Final results were

evaluated based on the histopathology results.

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS 21.0) as to obtain sensitivity and specificity of MRS in the differentiation of neoplastic from non-neoplastic ring enhancing brain lesions while taking histopathology as gold standard. Frequency and percentage was calculated for qualitative variables, i.e, presenting complains, detailed history of presenting complains; MRS findings and histopathological findings.

Mean ± SD was computed for quantitative variable, i.e. Age of the pateint. Taken histopathological results as gold standard, all statistical parameters, (sensitivity, specificity, positive predictive value, negative predictive value) were estimated to obtain diagnostic accuracy of MRS.

Patients Data was scrutinized by using Statistical Package for Social Sciences (SPSS 21.0). Mean + SD was calculated for age, duration of symptoms and size of the lesion. Frequency and percentage was computed for qualitative variables like gender, benign and malignant ring enhancing cerebral lesions using MRS and histopathology. With histopathology findings as gold standard; the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of magnetic resonance spectroscopy findings were calculated using 2 x 2 tables. Stratification was done on age, gender, duration of symptoms and size of the lesion.

#### RESULTS:

A total of 102 patients with ring enhancing lesions detected on MRI brain contrast studies were included in this study. There were 60.78% (62/51) male and 39.22% (40/51) female. Diagnostic precision of magnetic resonance spectroscopy in separating neoplastic from non-neoplastic ring enhancing brain lesions is presented in table 1. Sensitivity, specificity, PPV, NPV and accuracy of MRS was 87.5%, 93.3%, 95.5%, 89.7% and 92.1% respectively.

#### DISCUSSION:

Magnetic resonance spectroscopy provides useful chemical

**Table 1:** Diagnostic accuracy of MRS in segregating neoplastic from non-neoplastic ring enhancing brain lesions taking histopathology as gold standard

Magnetic Resonance spectroscopy Findings	Histopathology		Total
	Positive	Negative	
Neoplastic	42 (TP)	2 (FP)	44(43.1%)
Non neoplastic	6 (FN)	52 (TN)	58(56.9%)
<b>Total</b>	<b>48(47.1%)</b>	<b>54(52.9%)</b>	<b>102</b>
Sensitivity	87.5%		
Specificity	93.3%		
PPV	95.5%		
NPV	89.7%		
Accuracy	92.1%		





Figure 1(b): MRS of lesion in right parietal lobe shows elevated choline peak and reduced NAA peak

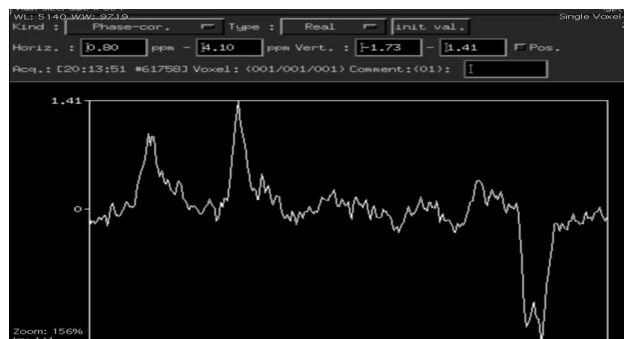


Figure 2(a): Ring enhancing lesion in left parietoccipital lobes with perilesional edema

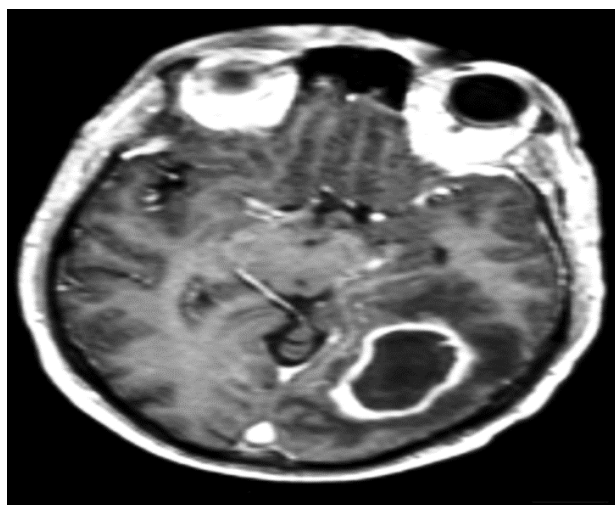
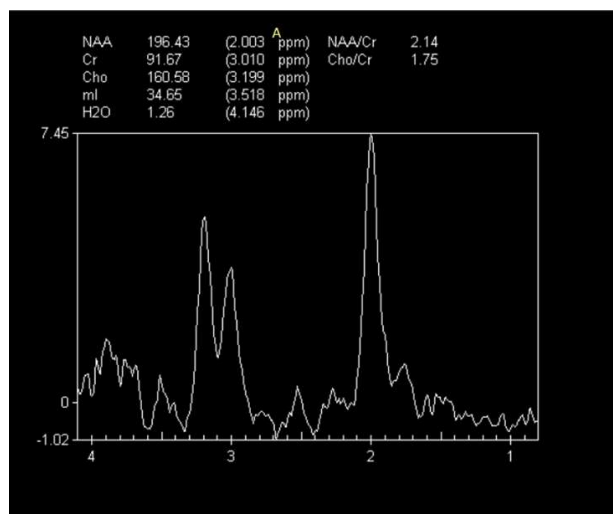


Figure 2(b): MRS of lesion in left parietoccipital lobes shows elevated lipid/lactate peak



showed diagnostic accuracy of 83% while our study revealed the diagnostic accuracy of 92.1% which signifies present study more. MRS is helpful for categorizing and classifying brain tumors.<sup>23</sup> Gliomas of each grade exhibit some specific

MRS features which again improve the diagnostic value of conventional magnetic resonance imaging.<sup>24</sup>

Few limitations apply to this study. First, this study was conducted in one center of a private hospital and, hence, a certain demographics variables were observed. Second, sample size was small hence more sample size is required to generalize the specific findings and results.

#### CONCLUSION:

By using non invasive technique of MRI like MRS, invasive procedures such as brain biopsy can be avoided in differentiating neoplastic from non neoplastic ring enhancing brain lesions thus reducing the morbidity and mortality.

#### Author Contribution:

Ameet Jesrani: Written, revised and finalized manuscript  
 Marya Hameed: Provided data  
 Seema Nayab: Revised Manuscript  
 Asma Javed: Written Manuscript  
 Sehrish Sethar: Written Manuscript

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## Needlestick Injuries among Dental Professionals in Dental Colleges of Rawalpindi, Pakistan

Batool Zara, Eruj Shuja, Nasar Um Min Allah, Muddasar Pervez, Omer Siddiquie, Sohaib Siddique

### ABSTRACT:

**Objective:** This study aimed to assess the knowledge and practices of Needlestick Injuries (NSIs) among dental professionals in various dental hospitals of Rawalpindi.

**Study Design and Setting:** It was a cross-sectional observational study conducted in four different dental colleges of Rawalpindi from January 2019 to March 2019.

**Methodology:** By using convenient sampling technique, a total of 252 dental professionals were approached for the data collection through a structured, pretested, self-designed questionnaire. SPSS version 23 was used for data analysis.  $P$ -value  $\leq 0.05$  was considered as statistically significant.

**Results:** Among 252 participants; 36 (14.3%) were dental assistants, 158 (62.7%) were dentists, 38 (15.1%) were postgraduate trainees (PGTs) and 20 (7.9%) were consultant dentists. The mean age  $\pm$  SD of participants was  $26.9 \pm 5.41$ . There were 92 (36.5%) male and 160 (63.5%) female participants. Mean knowledge score was best for consultant dentists ( $85.83 \pm 15.74$ ) followed by PGTs ( $80.70 \pm 14.71$ ) and dentists ( $76.58 \pm 15.39$ ) whereas it is lower for dental assistants ( $65.28 \pm 11.87$ ),  $p = 0.002$ . Practice response has shown that 22 (16%) of the dental assistants have never been vaccinated for Hepatitis B whereas most of the dental assistants have never reported the incident of NSIs to the concerned authorities.

**Conclusion:** NSIs continue to be a serious occupational hazard in the field of Dentistry. This study concluded that despite the mean knowledge score was highest among consultant dentists, the dental assistants and dentists have lower overall knowledge and practice indicates a need to continuing education on safe injection techniques along with the hands-on programme to prevent NSIs in hospitals.

**Keywords:** Blood-Borne Pathogens; Clinical Practice; Dental Professionals; Knowledge, Practice, Needlestick Injuries; Risk Factors

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#### Batool Zara

Assistant Professor and Head, Department of Periodontology, Foundation University College of Dentistry, Foundation University, Islamabad

#### Eruj Shuja

Assistant Professor and Head, Department of Oral and Maxillofacial Surgery, Watim Dental College, Rawalpindi

#### Nasar Um Min Allah

Assistant Professor, Department of Periodontology, Foundation University College of Dentistry, Foundation University, Islamabad  
Email: [nasar.zulfiqarali@gmail.com](mailto:nasar.zulfiqarali@gmail.com)

#### Muddasar Pervez

Assistant Professor, Department of Community Medicine, Al-Nafees Medical College and Hospital, Isra University, Islamabad

#### Omer Siddiquie

Registrar, Department of Orthodontics, National University of Medical Sciences, Armed Forces Institute of Dentistry, Rawalpindi

#### Sohaib Siddique

Senior Registrar and Head, Department of Periodontology, HBS Medical and Dental College, Islamabad

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### INTRODUCTION:

Needlestick injury (NSI) is an accidental skin pervading stab wound from a hollow-bore needle (or a sharp) contaminated by foreign blood or body fluid. In Medical settings, penetrating skin wounds caused by sharp instruments account as sharp injury.<sup>1</sup> NSI is amongst the leading health care safety issue and an integral common occupational hazard which is being faced by health care professionals around the world. The World Health Organization (WHO) reported that the annual number of NSIs among health care workers (HCWs) is four injuries per person in Africa, the Western Mediterranean, and Asia.<sup>2</sup>

NSIs are the wounds caused by sharps e.g. blood collection needles, connecting needles of intravenous (IV) sets, hypodermic needles and IV cannulas.<sup>3</sup> Healthcare professionals encounter the hazard of NSI that can lead to major infections with blood-borne pathogens such as Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or Human Immunodeficiency Virus (HIV).<sup>4</sup> Health personnel working with patients harbouring these viruses are placed at increased risk. It is estimated that 66000 HBV, 16000 HCV, and almost 1,000 HIV infections may have occurred in the year 2000 worldwide among health-care workers due to their

occupational exposure to percutaneous injuries; almost 40% of HBV and HCV, and 4.4% of HIV infections are attributable to occupational exposure to needle-stick/sharps.<sup>5,6</sup>

The oral cavity contains diverse bacterial flora<sup>7</sup> along with blood, saliva and oral secretions and norm of using sharp instruments in a dental setting, is a leading risk factor that contributes towards acquiring blood-borne infections.<sup>8</sup> Dental professionals are at high risk of being infected with various diseases transmitted by blood and body fluids (BBFs) due to frequent exposure to biological materials and patient's body fluids. Needlestick injuries and injuries due to cutting, biting, or splashing incidents are some of the ways dental professionals encounter during their daily activities.<sup>4</sup> The frequency of needlestick injuries and the high prevalence of blood-borne diseases in the general population have a great impact on the exposure of different infection agent risk among HCWs.

Prevention of NSIs is a challenge faced in nearly every medical/dental workplace. The burden of needlestick injuries can be reduced in dental settings if all the dental professionals from consultants till the dental surgery assistants abide by standard universal precautions against the NSIs. The establishment of an infection control committee that has the responsibility to work out an effective infection control programme and guide the staff of dental setups with postexposure prophylaxis is the need of time and should be an integral part of every dental hospital.<sup>9</sup> HCWs must undergo follow-up assessments for both the prevention and treatment of acute infection, such as HCV, after being exposed to BBFs. For the prevention of fluid borne infection due to its high prevalence, knowledge regarding universal precautions and safety measures should be well asserted for the prevention of such infections and constant upgrading via programmes and set regimes should be periodically implemented.<sup>10</sup>

Occupational hazards such as NSIs faced by HCWs in Pakistan<sup>11,12,13</sup>, have received significant attention, but current surveillance systems and responsiveness towards safety/preventive measures are insufficient to describe how much they are aware of such injuries as well as the kind of practices being followed in the hospital setup. Despite this, little data have been published that are assessing the knowledge and practices of dental professionals towards NSIs. This study was carried out for assessment of knowledge and practices among dental professionals about NSIs among various dental hospitals of Rawalpindi.

#### **METHODOLOGY:**

The study design was cross-sectional observational, conducted in four different dental colleges of Rawalpindi namely; Watim Dental College, Foundation University College of Dentistry, Margalla College of Dentistry and Armed Forces Institute of Dentistry, Rawalpindi over a period of three months (1st January 2019 to 31st March 2019). The ethical committee of Watim Dental College had

approved this study before data collection and ERC number was WDC/PRINCIPAL/2018/1072. The study participants were dental professionals divided into four groups i.e. Group 1: Dental Assistants, Group 2: Dentists, Group 3: Postgraduate Trainees (PGTs) and Group 4: Consultant Dentists.

Based on previous study<sup>14</sup>, Convenience sampling technique was used in which a total of 252 dental professionals who gave consent to be a part of the study were informed about the design and purpose of the study. The anonymity of the participants was maintained throughout the study. The data was collected through a self-designed, structured, pretested questionnaire consisting of closed and open-ended questions.

A pilot study was conducted with a random sample of 20 participants to ensure the feasibility and applicability of the questionnaire. The pilot study confirmed the feasibility of the main study. Subsequently, minor changes were done in the questionnaire for effective communication among the participants. Those who participated in the pilot study were excluded from the study. Face and content validity of the questionnaire was assessed by three experts in the field of public health. The reliability of the questionnaire was assessed using Cronbach's alpha (0.84).

The questionnaire was divided into the following sections: demographic data; and NSI knowledge and practice. The demographic section contains information related to age, sex, gender and designation. Knowledge parameters include information of participants knowledge on; any occupational hazards related to dentistry, exposure to infectious diseases by working in the dental profession, hazards of needle stick injuries, diseases that can be transmitted by NSIs, any awareness on NSI protocols, knowledge of universal precaution guidelines, knowledge about post-exposure prophylaxis (PEP) and safety devices to prevent NSIs. Practices parameters include vaccination status, the occurrence of NSIs, source of NSI, post-exposure Hepatitis B and C screening, sequence of events performed after NSI, and reporting of NSI incident to the concerned authorities.

The inclusion criteria include dental professionals consisting of dental assistants, general dentists, post-graduate trainees, and consultant dentists, between the age group of 18 to 60 years. Exclusion criteria include BDS undergraduate students and house officers. An informed consent was obtained from all the study participants before taking their responses.

The knowledge of the NSI was graded using a scoring system, a score of "one" for a "yes" answer and "zero" for "no" or "not sure" answer. This scoring system has been used in the previous study.<sup>15</sup> Scores of each respondent were calculated by adding the scores of all items of the knowledge. The score was converted to percentage and level. Scores for each respondent were summed up and graded as low= <50%, moderate= 50%-79% and high= 80% -100%.

The data was analysed in statistical software (SPSS for windows version 23, SPSS Inc, Chicago, USA) with a

confidence interval of 95%. No discrepancies were found in the data. Descriptive statistics like frequencies and proportions were used to summarize the data. The continuous data of knowledge score was tested for normality by using the Kolmogorov-Smirnov test. As the data were normally distributed, a parametric test; One-way ANOVA was conducted to compare the knowledge scores of needle stick injuries among four groups of dental professionals. A  $p$ -value = 0.05 was considered as statistically significant.

## RESULTS:

A total number of 252 participants were included in this study. All the participants returned the fully completed questionnaire making a response rate of 100%. The mean age  $\pm$  SD of participants was  $26.9 \pm 5.41$ . The minimum age was 19 years and maximum age was 57 years. There were 92 (36.5%) male and 160 (63.5%) female participants. Among 252 participants, 36 (14.3%) were dental assistants, 158 (62.7%) were dentists, 38 (15.1%) were postgraduate trainees and 20 (7.9%) were consultant dentists.

One-way ANOVA was performed to compare the knowledge scores about needle stick injuries among four groups: (Group 1-Dental Assistants), (Group 2-Dentists), (Group 3-PGTs) and (Group 4-Consultant Dentists). It was revealed that there was a statistically significant difference ( $p = 0.002$ ) present between knowledge scores among these groups. The mean knowledge score was highest among Consultant dentists ( $M=85.83$ ), followed by PGTs ( $M = 80.70$ ), Dentists ( $M = 76.58$ ) and Dental Assistants ( $M = 65.28$ ) as shown in Table I.

The response of the study subjects towards NSI knowledge and practices is presented in Table II and III respectively.

The results showed that the level of knowledge of NSI was low among 22 (8.7%) of participants, moderate among 80 (31.7%) and high among 150 (59.5%) of participants. The designation-wise level of knowledge about NSI is shown in Figure 1.

## DISCUSSION:

Health care workers especially doctors, nurses, and dentists are at increased risk of occupational accidental NSI because of their hazardous work environment. Hence the HCWs are at higher risk to acquire bloodborne pathogens like hepatitis B, C, HIV and other diseases.<sup>16</sup> Studies have also shown that HIV and Hepatitis B are among the important diseases transmitted by needle stick injuries.<sup>17</sup> The incidence of NSI is a common occupational hazard among dentists and it is showing an increasing trend.<sup>18</sup> Fifty percent of the dentists in Southern Thailand experienced percutaneous injuries, whereas 42% in the United Arab Emirates had minimal of one percutaneous injury in last year.<sup>19</sup> Another study conducted in Germany signifies that 62% of dentists acquired one needle stick injury at minimal mostly caused by needles, scalpels and surgical devices.<sup>20</sup>

In this study, among 252 participants, 36 (14.3%) were dental assistants, 158 (62.7%) were dentists, 38 (15.1%) were postgraduate trainees and 20 (7.9%) were consultant dentists. Frequency of needle stick injuries was found out to be 60% among dental assistants, 70% among dentists, 49% among post-graduate trainees and 10% among consultant dentists. The prevalence was high compared to previous studies.<sup>21,22,23</sup> This high percentage of needle stick injury amongst dental assistants and general dentists in our study can be attributed towards increased patient load in our region owing to our population, however further studies are needed to justify the amount of patient seen by each doctor and if there is any correlation between the incidence of needle stick injury and the number of patients seen per day. Another study conducted by Singh and colleagues indicated the prevalence of 703 per 1000 HCW (70.3%) during a complete working period and 48% of participants experienced the injury prevalence more than once in their career.<sup>10</sup> In another study conducted on HCW of Aga Khan Hospital Karachi, NSI was reported by 45% of the participants during their working tenure.<sup>24</sup>

In this study, knowledge regarding needle stick injuries was low among 22 (8.7%) of participants, moderate among 80 (31.7%) and high among 150 (59.5%) of participants. The mean knowledge score was highest among Consultant dentists ( $M = 85.83$ ), followed by PG Trainees ( $M = 80.70$ ), Dentists ( $M = 76.58$ ) and Dental Assistants ( $M = 65.28$ ). Low knowledge scores have seen amongst dental assistants in our study warrants that further investigation is required for this group as it has shown contrasting results with studies explained in references. Zafar et.al. study indicate high knowledge among HCWs regarding NSI.<sup>24</sup> A recent study has shown that only 21% of the HCWs has adequate knowledge about disease transmission by NSIs.<sup>25</sup> In another study conducted in India, a significant proportion of participants had knowledge about infectious diseases transmission through needle stick injuries.<sup>3</sup> Pavithran et al. indicates that the majority of dental professionals knew about the transmission of hepatitis B and C along with HIV/AIDS through NSI.<sup>9</sup>

This study signifies that among dental assistants, less than half of them were vaccinated against Hepatitis B, whereas most of the dentists, PGTs, and consultant dentists were vaccinated for it. The cause of under vaccination amongst dental assistants needs to be further investigated. A recent study has shown that about three in ten dental assistants experienced at least one NSI (29.8%, 95% CI 25.6–34.2%). Moreover, lack of adequate knowledge of infection control procedures and disease transmission, non-compliance with infection control protocol of vaccination against hepatitis B virus and attending 12 or a lesser number of patients daily were significantly ( $p < 0.05$ ) associated with increased risk of NSIs.<sup>8</sup> A study conducted at Aga Khan Hospital, Karachi reported the majority of HCWs vaccinated for Hepatitis B.<sup>20</sup>

Table I: Comparing the awareness scores of needle stick injuries among dental professionals

Designation	N	Mean $\pm$ SD	F (df1, df2)	p-value
Dental Assistant	36	65.28 $\pm$ 11.87	5.23 (3, 122)	0.002
Dentist	158	76.58 $\pm$ 15.39		
PG Trainee	38	80.70 $\pm$ 14.71		
Consultant Dentist	20	85.83 $\pm$ 15.74		
*One-way ANOVA				

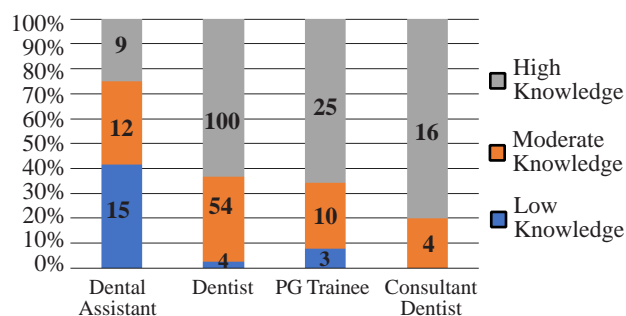
Table II: Responses of the study participants to Needle Stick Injuries knowledge

Knowledge on Needle Stick Injuries among dental professionals	No. of respondents (%)			
	Dental Assistant	Dentist	PG Trainee	Consultant Dentist
<b>Do you think there are any occupational hazards associated with dentistry?</b>				
Yes	7 (19.4)	148 (93.6)	36 (94.7)	20 (100)
No	24 (66.6)	2 (1.2)	--	--
Not sure	5 (13.8)	8 (5.1)	2 (5.2)	--
<b>Do you think working in the dental profession puts you at a higher risk of exposure to infectious diseases</b>				
Yes	6 (16.6)	12 (7.6)	4 (10.5)	12 (60)
No	18 (50)	131 (83)	34 (89.4)	8 (40)
Not sure	12 (33.3)	15 (9.5)	--	--
<b>Do you think needle stick injury is hazardous to health in any way?</b>				
Yes	8 (22.2)	133 (84.1)	36 (94.7)	20 (100)
No	21 (58.3)	25 (15.8)	2 (5.2)	--
Not sure	7 (19.4)	--	--	--
<b>Are you aware of any needle stick injury protocols?</b>				
Yes	12 (33.3)	116 (73.4)	35 (92.1)	20 (100)
No	22 (61.1)	42 (26.5)	3 (7.9)	--
Not sure	2 (5.5)	--	--	--
<b>Are you aware of "Universal Precautions Guidelines"?</b>				
Yes	7 (19.4)	139 (88)	37 (97.3)	20 (100)
No	29 (80.5)	17 (10.7)	1 (2.6)	--
Not sure	--	2 (1.2)	--	--
<b>Diseases that can be transmitted by NSIs are</b>				
Hepatitis B	2 (5.5)	62 (39.2)	2 (5.2)	1 (5)
Hepatitis C	21 (58.3)	12 (7.6)	4 (10.5)	--
HIV/AIDS	4 (11.1)	7 (4.4)	--	--
Tuberculosis	6 (16.6)	3 (1.9)	--	--
All of the above	3 (8.3)	74 (46.8)	32 (84.2)	19 (95)
<b>Knowledge on safety devices to prevent NSIs</b>				
Yes	8 (22.2)	103 (65.2)	29 (76.3)	20 (100)
No	26 (72.2)	55 (34.8)	9 (23.6)	--
Not sure	2 (5.5)	--	--	--
<b>Knowledge on post-exposure prophylaxis in the management of NSIs</b>				
Yes	4 (11.1)	111 (70.2)	37 (97.3)	20 (100)
No	30 (83.3)	44 (27.8)	1 (2.6)	--
Not sure	2 (5.5)	3 (1.9)	--	--

Table III: Responses of the study participants towards practices for the prevention and management of needle stick injuries

Practices for the prevention and management of needle stick injuries among dental professionals	No. of respondents (%)			
	Dental Assistant	Dentist	PG Trainee	Consultant Dentist
<b>When were you last tested for HBV &amp; HCV?</b>				
More than one year	4 (11.1)	68 (43)	22 (57.9)	10 (50)
Within one year	16 (44.4)	82 (51.9)	12 (31.6)	10 (50)
Never	16 (44.4)	8 (5.1)	4 (10.5)	--
<b>Have you ever been vaccinated for Hepatitis B?</b>				
Yes	14 (38.9)	142 (89.9)	36 (94.7)	20 (100)
No	22 (61.1)	16 (10.1)	2 (5.3)	--
<b>When was your last booster dose for Hepatitis B?</b>				
More than one year	8 (22.2)	106 (67.0)	30 (78.9)	16 (80)
Within one year	6 (16.7)	30 (19)	4 (10.5)	4 (20)
Never	22 (61.1)	22 (13.9)	4 (10.5)	--
<b>Have you ever been pricked within dental settings, if yes, then how many times?</b>				
4-6 times	2 (5.6)	10 (6.3)	6 (15.8)	2 (10)
3 or less times	16 (44.4)	76 (48.1)	24 (63.2)	14 (70)
Never	18 (50)	72 (45)	8 (21.1)	4 (20)
<b>What was the level of depth of needle stick injury?</b>				
Superficial/Non-Bleeding	--	40 (25.3)	26 (68.4)	13 (65)
Superficial/Bleeding	6 (16.6)	21 (13.2)	11 (28.9)	7 (35)
Deep/Non-Bleeding	--	1 (0.7)	1 (2.6)	--
Deep/Bleeding	2 (5.5)	4 (2.5)	--	--
Not Known	28 (77.7)	92 (58.2)	--	--
<b>What was the source of a prick?</b>				
Used Instrument	27 (75.0)	87 (55.0)	20 (52.6)	14 (40)
Unused Instrument	5 (13.8)	34 (21.5)	10 (26.3)	4 (20)
Unknown	4 (11.1)	37 (23.4)	8 (21.1)	2 (10)
<b>After needle stick injury did you get tested for HBV and HCV, if yes, then after how many weeks?</b>				
Within 1 week	6 (16.7)	76 (48.1)	8 (21.1)	16 (80)
After 4 weeks	2 (5.6)	4 (2.5)	4 (10.5)	4 (20)
Within 4 months	2 (5.6)	18 (11.4)	8 (21.1)	--
No	26 (72.2)	60 (37.9)	16 (42.1)	--
<b>Did you get your patient tested after needle stick injury?</b>				
Yes	6 (16.7)	86 (54.4)	10 (26.3)	18 (90)
No	30 (83.3)	72 (45.5)	28 (73.7)	2 (10)
<b>What was the sequence of events after needle stick injury?</b>				
Washed with water and bandaged	2 (5.6)	10 (6.3)	4 (10.5)	6 (30)
Washed with water and remained open	4 (11.1)	8 (5.1)	2 (5.3)	2 (10)
Washed under running water and disinfectant	20 (55.5)	28 (17.7)	4 (10.5)	6 (30)
Encouraged bleeding, washed under running water	4 (11.1)	108 (68.3)	16 (42.1)	4 (20)
Did nothing	6 (16.7)	4 (2.5)	12 (31.6)	2 (10)
<b>Are you familiar with post-exposure immunoglobulin injection for HBV?</b>				
Yes	9 (25)	80 (50.6)	26 (68.4)	16 (70)
No	27 (75)	78 (49.4)	12 (31.6)	4 (20)
<b>Did you report the injury to concerned authorities?</b>				
Yes	4 (11.1)	90 (56.9)	27 (71.0)	20 (100)
No	32 (38.8)	68 (43.0)	11 (28.9)	--

Figure 1: Designation-wise level of knowledge about needle stick injuries among dental professionals.



Less than half of the dental professionals in this study did not get tested for HBV and HCV and most of them did not get their patients tested for HBV and HCV after needle stick injury. Previously, a study conducted in India had similar findings, where more than half of HCWs did not get tested for HBV, HCV, and HIV for themselves and their patients after needle stick injury.<sup>9,26</sup>

Most of the dental professionals in this study get their hands washed after needle stick injury which is comparable to the study done earlier, in which it was observed that most of the HCWs washed their hands and allowed the wound bleeding to lower down the potential viral load after needle stick injury.<sup>20</sup> In this study, less than half of dental professionals reported their concerned authorities about the NSI and the results are found to be in agreement with previous studies.<sup>9,27,28,29</sup> Our study has pointed out the need for a centralized reporting cell to be present at every centre for such injuries as it is lacking in our hospitals.

Limitations must be considered when interpreting findings from this study. The major limitation of our study was time and region-based results i.e. the sample in this study was solicited from only four teaching hospitals in Rawalpindi. Therefore, the results of this study cannot be extrapolated to all the dental professionals in Pakistan. Due to time constraints, the data were collected in a cross-sectional study (NSI incidence rates could not be calculated) using a non-probability sampling method (convenience sampling) which has low weightage in the presentation of results. Another limitation was the recall bias that may have led to inaccurate estimation of the frequency of NSIs and accompanying risk factors. The low education level of the dental assistants' comprehension and understanding of the questionnaire was also time-consuming. Further studies are needed to develop and evaluate interventions for the prevention of NSIs among dental professionals especially dental assistants in Pakistan.

### CONCLUSION:

NSIs continue to be a serious occupational hazard in the field of Dentistry. This study concluded that despite the mean knowledge score is highest among consultant dentists,

the dental assistants and dentists have lower overall knowledge and practice indicating a need to conduct awareness programs to reduce the prevalence of NSIs in hospitals. Hospitals need to imply annual faculty awareness programs to keep knowledge of dental health professionals up to date. Also, a centralized reporting cell for reporting such injuries in dental settings is the need of time.

### Author Contribution:

Batool Zara: Study design and concept, data analysis, data interpretation and drafting of the initial manuscript,  
 Eruj Shuja: Study design and concept, questionnaire design, data collection, analysis and interpretation,  
 Nasar Um Min Allah: Data analysis, data interpretation, final drafting and critical revision of the manuscript,  
 Muddasar Pervez: Literature search, conception/design of the work,  
 Omer Siddiqui: Data collection.  
 Sohaib Siddique: Data collection.

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## Correlation between Inferior Vena Cava Diameter Assessed on Ultrasonography and Central Venous Pressure among Critically ILL Patients Admitted In Intensive Care Unit

Shabih Zehra, Atif Latif, Asiya Kazi, Syed Ijaz Hussain Zaidi

### ABSTRACT

**Objective:** To assess the correlation between inferior vena cava(IVC) diameter and central venous pressure (CVP) in critical patients admitted in ICU.

**Study Design and Setting:** The cross-sectional pilot study was conducted at Radiology Department of PNS SHIFA Hospital.

**Methodology:** 18-80 years patients were included and patients with severe orthopnea, unable to lie in supine position, morbid obese, pneumothorax, mass in mediastinum, tricuspid regurgitation and intra-cerebral bleeds were excluded.

**Results:** The mean age of 50 patients was  $41.44 \pm 16.73$  years. Mean measurement of CVP was considered as  $10.41 \pm 4.18$  mm. Mean diameter of IVC was  $12.65 \pm 2.22$  mm. The study results showed weak negative correlation between the CVP and IVC ( $r = -0.110$ ,  $p = 0.04$ ). It was also predicted that patients with age  $\leq 50$  years showed weak negative correlation between the CVP and IVC ( $r = -0.290$ ,  $p = 0.034$ ). Similarly, in patients with age  $> 50$  years there was strong negative correlation between CVP and IVC ( $r = -0.680$ ,  $p = 0.045$ ). The study results also showed that in male patients there was weak negative correlation between the CVP and IVC i.e. ( $r = -0.045$ ,  $p = 0.048$ ). However, in female patients there was moderate positive correlation ( $r = 0.685$ ,  $p = 0.001$ ).

**Conclusion:** Weak negative correlation was found between inferior vena cava diameter on ultrasonography and central venous pressure measurement among critically ill patients.

**Keywords:** central venous pressure, inferior vena cava.

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### INTRODUCTION:

The hemodynamic status of intensive care patients that are critically ill is of vital importance for critical care physicians in order to achieve appropriate goals for their patient's fluid therapy<sup>1</sup>. A variety of techniques exist which are used for this purpose, most of them include physical examination, measurement of central venous pressure (CVP), biochemical markers, estimation of vascular width, pulmonary artery catheterization and ultra-sonographic inferior vena cava (IVC) diameter assessment.<sup>2</sup> The measurement of CVP is the most commonly employed technique through the help

of preload estimation. Requisites in the measurement of CVP are insertion of a central venous catheter that can be time-consuming, expensive and could lead to complications.<sup>3</sup>

The use of ultrasonography in intensive care setups as a bed-side technique are due to easy availability but also being cheap, safe and more importantly non-invasive. Inferior vena cava visualization on ultrasound is a technique used for providing rapid and non-invasive means of gauging preload and is also needed for fluid resuscitation<sup>4</sup>. Researches have shown correlations between measurements of CVP and IVC. The rapid measurement of CVP through non-invasive means is critically important especially in intensive care setups<sup>5</sup>. Any change in volume status will be depicted through a change in diameter of IVC, whereby it can aid in differentiating between hypovolemic, cardiogenic and septic shock<sup>6</sup>.

The precision in assessing volume status is vital for patients having critical illnesses like acute renal failure, congestive cardiac failure, septic shock and acute blood loss. For instance, a study demonstrated that CVP measurement as an early hemodynamic assessment modality led to substantial improvements in patient's outcomes with septic shock and severe sepsis<sup>7</sup>. Jugular venous pulse (JVP) examination for estimating CVP is usually done as a bed-side technique. CVP refers to mean vena caval or the right atrial pressure

**Shabih Zehra**  
Resident, Department of Radiology  
PNS SHIFA Hospital, Karachi

**Atif Latif**  
Assistant Professor, Department of Radiology  
PNS SHIFA Hospital, Karachi

**Asiya Kazi**  
Senior Lecturer, Department of Pharmacology  
Benazir Bhutto Medical College Lyari, Karachi

**Syed Ijaz Hussain Zaidi**  
Associate Professor, Department of Pharmacology  
Bahria University Medical & Dental College, Karachi  
Email: col\_zaidi@yahoo.com

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(RAP) that is equal to right ventricular and diastolic pressure. Detecting elevated JVP among left-sided heart failure patients is predicted with elevations in pulmonary capillary wedge pressure, without severe pulmonary disease, indicating poor prognosis<sup>8</sup>

Nevertheless, accurately measuring JVP is seldom difficult to obtain due to poor technique of the examiner<sup>9</sup> Measuring CVP through invasive methods either by internal jugular vein or subclavian vein catheterization have reported few complications like air embolism, pneumothorax, arterial puncture, catheter associated infection and injury of great vessels. Therefore, it is important to determine CVP through a reliable and non-invasive means.<sup>10</sup> Many researches have observed fair to excellent correlations between CVP and various IVC parameters.<sup>11-13</sup> The studies used diameter of IVC greater than 10 to 20 mm as a cutoff point for high CVP. Size and shape of IVC were not only correlated to CVP but also to circulating volume of blood. Since IVC is a highly compliant vessel having no valves therefore size variations are easily seen with changes in intra-vascular pressure. Consequently, even normal respiratory movements lead to change in intra thoracic pressure that in turn influence venous return from IVC and also affect the IVC diameter<sup>14</sup>. As a result, IVC collapses during inspiration as blood gets pumped out of IVC because of negative pressure created through chest expansion. In spontaneously breathing healthy subjects, cyclic changes in thoracic pressures might result in collapse of IVC diameter by around 50 %<sup>15</sup>. Hence, measuring diameter of IVC could possibly also aid in ongoing resuscitation by providing a means for CVP measurement through non-invasive methods. Performance of bed-side ultrasonography for evaluating IVC by clinicians is a technique which potentially can provide instant and non-invasive measures of volume status which in turn can help in rapid initial assessment for guiding subsequent therapies. Multiple studies conducted outside the country but there is very little data in Pakistani population. Therefore, the objective of this study was to done to evaluate the correlation between IVC diameter and CVP measurement among critically ill patients admitted in intensive care unit in Pakistani population.

#### **METHODOLOGY:**

This cross-sectional pilot study using non-probability convenient sampling technique was carried out at the department of Radiology, PNS Shifa Hospital, Karachi for duration of 6 months from January 2018 to Jun 2018. After ethical approval from the Institutional Review Board (IRB) of the hospital, non-intubated adult patients of either gender, between the ages from 18 to 80 years, that were admitted in the intensive care unit of the hospital, and those who were able to breathe spontaneously and lie in supine position; already had CVP catheter (subclavian or internal jugular vein) in place were included in the study. Patients below 18 years of age or above 87 years, with severe orthopnea and

unable to lie in supine position, morbid obese, with pneumothorax, mass in mediastinum, tricuspid regurgitation and intra-cerebral bleeds were excluded from the study. Fifty patients were included in the study after taking informed consent from the patient's attendants. Patients were requested to lie in supine position and ultrasound machine was used to obtain ultrasonic images of IVC diameter. A portable ultrasound machine with 17 mm curved probe and cardiac transducer for IVC imaging 3.5MHz, 21 mm phase array was used. Sub-xiphoid approach was used for IVC visualization. Maximum IVC diameter (antero-posterior diameter) was measured during end expiration 2cm confluence of hepatic veins in longitudinal plane. All readings were observed (reported by two intensive care clinicians with the help of trained nursing assistant. Similarly, CVP measurement was done using catheter in place and measured by two intensive care clinicians and an assistant nurse with the help of manometer at mid-axillary level and patients in supine position. Three readings were obtained and their mean reported.

Data analysis was done using SPSS version 20.0. Correlation between CVP and IVC diameter was determined on the basis of gender and with IVC diameter of <50 mm and >50 mm using Pearson correlation coefficient keeping a P-value =0.05 as significant level.

#### **RESULTS:**

Among the total of 50 patients enrolled in the study, the mean age of the patients was  $41.44 \pm 16.73$  years with minimum and maximum ages of 22 and 67 years respectively. Total 34(68%) patients were male and 16(32%) patients were females. Male to female ratio of the patients was approximately 2:1. Out of these 50 patients, the patients with diagnosis of sepsis, severe hypertension, uncontrolled diabetes, hysterectomy, IUD and hysterectomy, MVA, and pulmonary embolism were 3(6%) for each category. The patients of drowning were 9(18%), the patients with ectopic pregnancy, IHD were 4(8%) respectively and the patients with LSCS and RTA were 6(12%) respectively for each. The mean CVP of the patients reported in the study was  $10.41 \pm 4.18$  mm with minimum and maximum values of 3 and 16 mm respectively. The mean value of the diameter of IVC of the patients in the study was  $12.65 \pm 2.22$  mm with minimum and maximum values of 10 and 18 mm respectively. (Table: I)

The study results showed weak negative correlation between the CVP and IVC ( $r = -0.110$ ,  $p = 0.04$ ). It was also predicted that in patients with age =50 years there was weak negative correlation between the CVP and IVC ( $r = -0.290$ ,  $p = 0.034$ ). Similarly, in patients with age >50 years there was moderate negative correlation between the CVP and IVC ( $r = -0.680$ ,  $p = 0.045$ ). The study results also showed that in male patients there was weak negative correlation between the CVP and IVC i.e. ( $r = -0.045$ ,  $p = 0.048$ ). However, in female patients

there was moderate positive correlation ( $r=0.685$ ,  $p=0.001$ ). (Table: II)

**DISCUSSION:**

CVP monitoring has been observed to be a mainstay for estimation of intra-vascular fluid status and cardiac pre-load in critically-ill patients. It has been criticized that the use of CVP measurement for estimating fluid responsiveness arguing that CVP as an absolute value or in terms of changes in response to fluid, do not correlate with ventricular volume or volume responsiveness.<sup>16-17</sup>

Nonetheless, the guidelines for hemodynamic management of critical patients continue to promote inclusion of filling pressure among treatment regimens. Wiryanat et al., reported a statistically significant correlations between CVP and IVC diameter<sup>18</sup>. In another study by Wiwatworapan et al, a positive correlation was reported between IVC diameter and CVP ( $r = 0.75$ ,  $p < 0.001$ )<sup>19</sup> Similarly Ilyas et al reported in 100 patients a positive correlation between CVP and maximum IVC diameter ( $r = 0.371$ ,  $p < 0.005$ ) and minimum IVC diameter ( $r = 0.57$ ,  $p < 0.005$ )<sup>20</sup> The findings of the above studies are contradictory to our observation. Nonetheless, one of the study reported a strong negative correlation of CVP measurement and IVC diameter ( $r = -0.721$ ,  $p < 0.001$ ). However, the study was performed on

only 30 patients and all the patients were diagnosed cases of shock<sup>21</sup>. Whereas in our study, the correlation is weak negative.

Factors reported to affect the diameter of IVC include elevated pressures in pulmonary artery, pulmonic or tricuspid valve disease, dysfunction of right ventricle and any other condition having an increased intra-abdominal pressure, like morbid obesity or moderate to massive ascetic fluid. Other than these issues, interpretation of ventilated patients is also a problem, but since in our study only non-ventilated patients were included, this limitation was out of question<sup>22</sup> In a study by Garg et al, a negative correlation ( $r= -0.41$ ) was reported while in a study by Airapetian et al, a strong positive correlation ( $r= 0.81$ ) was recorded, thereby confirming the fact that paucity of data persists<sup>23</sup> In another study by Attainsee et al, moderate correlation was reported, however only hypovolemic patients were included in the study<sup>24-25</sup> Ciozda et al reported that in around 21 studies seeking to evaluate the correlation of CVP and IVC diameter, found a moderate to considerable correlation between them and concluded that IVC diameter measurement could be considered as a reliable method to calculate intravascular volume as a substitute for measuring CVP among adults<sup>26</sup>

Sridhar et al reported in a study that IVC diameter and CVP were significantly correlated ( $P < 0.001$ ) to each other and their correlation was used for evaluating intravascular volume in adults. Naghipour et al also reported similar results in their study. In another study done by Naghipour et al on American patients, no such significant correlations were observed between IVC diameter and CVP. However the study was done on pediatric ICU (PCIU) patients.

Thanakitcharu P et al in another study reported positive correlation between CVP and IVC diameter. Arthur et al in a study on 95 patients mechanically ventilated under general anesthesia, found a significant relationship in-between CVP and IVC diameter. Another study by Khalil et al on 115 adult patients reported a moderately significant correlation ( $r=0.53$   $p < 0.001$ ) in-between CVP and maximum as well as minimum IVC diameter. The findings of the above studies are contradictory to our results.

Our study had potential limiting points. Firstly ventilator support patients were not included in the study; moreover most patients had CVP in place for about 24 hours. The study might not be immune from selection and observer bias. Larger sample size and aiming to focus on evaluating patient’s recovery from illness should also be measured and their values correlated.

However, the differences of gender ratio and small sample size in our study might have been a limiting factor due to which differences of correlation are reported in the studies.

**CONCLUSION:**

A negative correlation was found between inferior vena cava diameter on ultrasonography and central venous pressure

Table I: Demographic representation of patients admitted in intensive care unit

Variable		Mean ± SD/ n (%)
Age (Years)		41.44±16.73
Central Venous Pressure (mm)		10.41±4.18
Inferior Vena Cava Diameter (mm)		12.65±2.22
Gender	Male	34(68.0%)
	Female	16(32.0%)
Diagnosis	Sepsis	3(6.0%)
	Drowning	9(18.0%)
	Ectopic Pregnancy	4(8.0%)
	Severe Hypertension	3(6.0%)
	Uncontrolled Diabetes	3(6.0%)
	Hysterectomy	3(6.0%)
	IHD	4(8.0)
	IUD, Hysterectomy	3(6.0%)
	LSCS	6(12.0%)
	MVA Done	3(6.0%)
	Pulmonary Embolism	3(6.0%)
RTA	6(12.0%)	

Table II: Correlation of CVP and IVC diameter

Variable		CVP	
		r	p-value
IVC		- 0.110	0.04
IVC	<50 years	-0.290	0.034
	>50 Years	-0.680	0.045
IVC	Male	-0.045	0.048
	Female	0.685	0.01

measurement among critically ill patients admitted to the Intensive care unit. Further multi-centered large scale studies are needed to establish a precise correlation between central venous pressure and inferior vena cava diameter.

**Author Contribution:**

Shabih Zehra: Selection of topic, introduction and methodology  
Atif Latif: Abstract writing and literature review  
Asiya Kazi: Writing and discussion  
Syed Ijaz Hussain Zaidi: Data analysis

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## Comparison of Mean Efficacy of Gluma and Ultraez Desensitizer to Decrease Hypersensitivity of Vital Abutment Teeth Prepared for Full Coverage Restoration

Hamid Bashir, Shoaib Rahim, Jawad Ali Shah, Zarah Afreen, Ammarah Afreen, Eruj Shuja

### ABSTRACT

**OBJECTIVE:** To compare the mean change in hypersensitivity between Gluma and Potassium Nitrate (UltraEz) desensitizers, on vital abutment teeth prepared for full coverage restorations.

**Study Design and Setting:** Randomized experimental study conducted at Watim Dental College, Rawalpindi, from February to August 2019.

**Methodology:** Total 100 patients were included in this study. Inclusion criteria consisted of both male and female patients with age ranging from 20-40 years, consisting of vital teeth and no active carious lesion. Two hours after tooth preparation, vital abutment tooth was stimulated with a blast of air and hypersensitivity of the vital abutment was measured using Visual Analog Scale (VAS). Then Gluma Desensitizer was applied on vital abutment for one minute, air dried and then rinsed. After Gluma Desensitizer application, the abutment tooth was again stimulated with a blast of air and hypersensitivity of the vital abutment was measured using VAS. All the data was entered and analysed using SPSS version 20.0. P values of less than or equal to 0.05 was considered significant.

**RESULTS;** All the teeth before tooth preparation had zero hypersensitivity. After preparation, Mean+ SD of hypersensitivity on VAS were 8.92 + 0.77 and 8.96 + 0.75 in Group A (Gluma) and Group B (UltraEz) respectively. After desensitizers application, Mean+ SD of hypersensitivity on VAS were 4.00 + 0.75 and 2.00 + 0.72 in Group A (Gluma) and Group B (UltraEz) respectively.

**CONCLUSION:** It was concluded that both desensitizers reduce Hypersensitivity but UltraEz Desensitizer (containing Potassium Nitrate) relieves Hypersensitivity to a greater extent than Gluma Desensitizer when used on vital teeth prepared for providing conventional Fixed Dental Prosthesis

**Keywords;** Desensitizer, Gluma, UltraEz, Potassium Nitrate, Hypersensitivity

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### INTRODUCTION:

Patients with missing teeth often report to the dental clinic for their replacement. One of the treatment options to replace

missing teeth is to provide conventional partial Fixed Dental Prosthesis (FDP) in which, one tooth (abutment) anterior to the edentulous span and one tooth (abutment) posterior to it are prepared to receive full coverage crowns (retainers). These abutments are often become hypersensitive during the pre-cementation period. The pre-cementation period is the time lapse between preparation of the abutments and the cementation of the FDP or restoration that could be 01 week to 10 days. This hypersensitivity during the pre-cementation period would not only cause discomfort to the patient but also could lead to necrosis of the pulp.<sup>1</sup> The preparation of tooth or abutment removes the protective layer enamel from the tooth and leaves the dentine exposed to the oral environment. Dentine is of sensitive nature due to its close association with the pulp and is usually not revealed because enamel or cementum normally covers the dentine.<sup>2</sup>

Dentine hypersensitivity is characterized by pain that arises from dentinal surfaces in reaction to various stimuli like hot and cold stimuli. Dentine hypersensitivity is confirmed only when all other likely conditions are clinically ruled out.<sup>3</sup> The most widely acknowledged theory to explain dentine hypersensitivity is the hydrodynamic theory. This theory describes that when a stimulus is applied to the exposed

<b>Hamid Bashir</b> Consultant Prosthodontist, Department of Prosthodontics Armed Forces Institute of Dentistry, Rawalpindi
<b>Shoaib Rahim</b> Assistant Professor, Department of Prosthodontics Foundation University College (Foundation University College of Dentistry), Islamabad
<b>Jawad Ali Shah</b> Consultant Operative Dentist, Department of Operative Dentistry, Armed Forces Institute of Dentistry, Rawalpindi
<b>Zarah Afreen</b> Assistant Professor, Department of Prosthodontics Watim Dental College, Rawalpindi Email: <a href="mailto:zarahsufian@yahoo.com">zarahsufian@yahoo.com</a>
<b>Ammarah Afreen</b> Assistant Professor, Department of Operative Dentistry Watim Dental College, Rawalpindi
<b>Eruj Shuja</b> Assistant Professor, Department of Oral and Maxillofacial Surgery Watim Dental College, Rawalpindi
Received: 06-Feb-2020 Accepted: 17-Jun-2020

dentine surface, fluid flow in dentinal tubules is disturbed leading to stimulation of A- $\delta$  fibres near the odontoblasts.<sup>4</sup> This mechanism only works when dentinal tubules are opened at both ends, that is, exposed dentine surface and the pulp, and a stimulus on exposed dentine surface can stimulate the nerves near the odontoblasts through fluid flow alteration in the dentinal tubules. Sclerotic dentine, on the other hand, is non-sensitive.<sup>5</sup>

The relationship between the diameter of the dentinal tubule and the dentine hypersensitivity is described by Poiseuille law (fluid flow  $\times$  radius<sup>4</sup>) that two times increase in diameter would increase the fluid flow 16 times. Tubules in sensitive dentine are twice the diameter than that of non-sensitive dentine.<sup>6</sup> The two main treatment options for dentine hypersensitivity are either blocking the dentinal tubules or stabilizing the nerves. Gluma Desensitizer seals the dentinal tubules thus making hydrodynamic mechanism ineffective. Potassium Nitrate (UltraEz) increases the potassium ion concentration in the extracellular fluid, thereby causing the nerves to depolarize and also inhibiting their repolarization.<sup>7</sup> In a study conducted by Jalalian et al, the amount of hypersensitivity after applying Gluma Desensitizer was  $5.000 + 2.026$  (mean + S.D.) and for Potassium Nitrate was  $2.000 + 1.041$  (mean + S.D.).<sup>8</sup>

There is not much literature available regarding the efficacy of desensitizing agents on vital abutment teeth prepared for full coverage restorations. Furthermore, the effect of desensitizing agents on prepared vital teeth has not been studied in our population. Therefore; the aim of this study was to compare the mean change in hypersensitivity between Gluma and Potassium Nitrate (UltraEz) desensitizers, on vital abutment teeth prepared for full coverage restorations.

#### **METHODOLOGY:**

It was a randomized experimental study and ethical approval was obtained before study conduction from the institute. Inclusion criteria consisted of both male and female patients with age ranging from 20-40 years, consisting of vital teeth and no active carious lesion. Exclusion criteria consisted of patients having tooth hypersensitivity before tooth preparation, patients having periodontal disease associated with the abutment tooth, pregnant patients and patients using desensitizing agents or drugs like anti-inflammatory, analgesics 06 weeks before or during the study. As a protocol all patients presenting to the hospital were examined in Outpatient Department (OPD) and those patients who fulfilled the criteria were referred to Prosthodontic department.

A total of 100 patients were selected for this study based on above mentioned criteria and were asked regarding previous history of denture usage. The patients underwent history and complete oral examination after informed consent. On the basis of this information the patients were selected for the study according to the exclusion and inclusion criteria. The patients were allocated into two groups, Group A and

Group B by random allocation method (Randomization was done by a computer-generated random allocation sequence). In Group A patients, local anaesthesia was administered and tooth preparation for full coverage restoration / Retainer was carried out. Two hours after tooth preparation, vital abutment tooth was stimulated with a blast of air and hypersensitivity of the vital abutment was measured using Visual Analog Scale (VAS). Then Gluma Desensitizer was applied on vital abutment for one minute, air dried and then rinsed. After Gluma Desensitizer application, the abutment tooth was again stimulated with a blast of air and hypersensitivity of the vital abutment was measured using VAS.

In Group B patients, local anaesthesia was administered and tooth preparation for full coverage restoration / Retainer was carried out. Two hours after tooth preparation, vital abutment tooth was stimulated with a blast of air and hypersensitivity of the vital abutment was measured using VAS. Then UltraEz Desensitizer was applied on vital abutment for five minutes and then rinsed. After UltraEz Desensitizer application, the abutment tooth was again stimulated with a blast of air and hypersensitivity of the vital abutment was measured using VAS. Abutment teeth were then provided with provisional restorations. Definitive restoration was provided after two weeks. The scores recorded were filled in the Proforma.

All the data was entered and analysed using SPSS version 20.0. Descriptive statistics were calculated for both qualitative and quantitative variables. For qualitative variable like frequency and percentages were calculated. For variables like degree of hypersensitivity of teeth (before and after application of desensitizers and change in hypersensitivity) paired sample t-test was used. P values of less than or equal to 0.05 was considered significant.

#### **RESULTS:**

A total of n=100 patients were selected for this study and distributed in two equal groups, Group A and Group B, both groups having 50 patients each. The Mean + SD age of the patients  $32.13+4.76$  years. Mean + SD and the frequency of the hypersensitivity in Group A, before and after Gluma application has been illustrated in Figure-I and Figure-II respectively. Mean + SD and the frequency of the hypersensitivity in Group B, before and after UltraEz application was  $8.96+0.754$  and  $2.00+0.728$  respectively. Statistically significant difference was found in Hypersensitivity before and after desensitizer application in both Groups as illustrated in Table-I. Statistically significant difference was also found in Hypersensitivity between Group A and Group B (after desensitizer application), as illustrated in Table-II.

Statistically no significant difference was found in Hypersensitivity between males and females in Group-A before and after application of GLUMA with a p value of 0.525 and 0.710 respectively. Statistically no significant

difference was found in Hypersensitivity between males and females in Group-B before and after application of ULTRAEZ with a p value of 0.976 and 1.000 respectively. Statistically significant difference was found in Hypersensitivity between Group A Male and Group B Male, & Group A Female and Group B Female (after desensitizer application), with a p value of 0.001 for both. Group A and Group B were further stratified into two age-groups; Group 1: 20-30 years and Group 2: 31-40 years. Statistically no significant difference was found in Hypersensitivity between two age groups in Group A before and after application of GLUMA with a p value of 0.535 and 0.435 respectively. Statistically no significant difference was found in Hypersensitivity between two age groups in Group B before and after application of ULTRAEZ with a p value of 0.773

Figure-I: Histogram Illustrating Mean Hypersensitivity (Vas) Before Desensitizer (Gluma) Application In Group A Patients

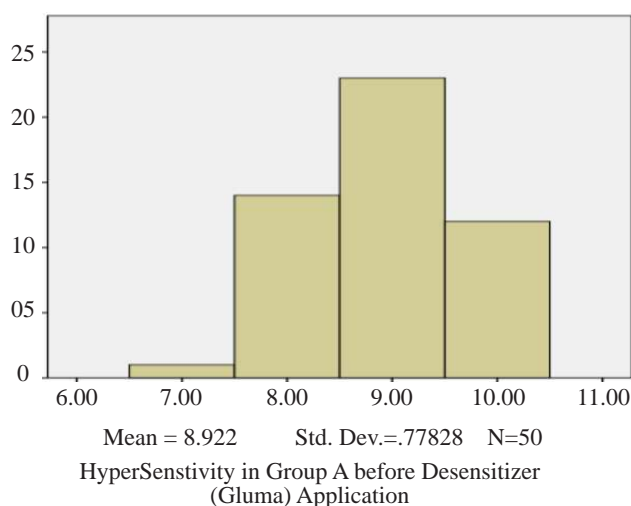


Figure-II: Histogram Illustrating Mean Hypersensitivity (Vas) After Desensitizer (Gluma) Application In Group A Patients

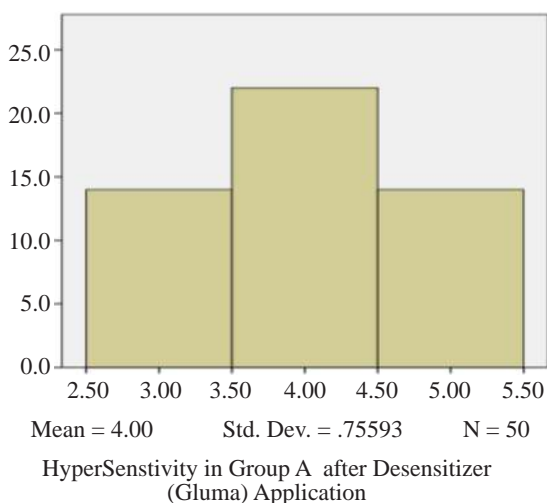


Table-I: Comparison of Mean Hypersensitivity (Vas) Before and After Application of Desensitizer

	Mean Hypersensitivity	P Value (Paired Sample t-test)
<b>Group A (GLUMA)</b>		
Before Application	8.92+0.77	0.001
After Application	4.00+0.75	
<b>Group B (ULTRAEZ)</b>		
Before Application	8.96+0.75	0.001
After Application	2.00+0.72	

Table-II: Comparison Of Mean Hypersensitivity (Vas) Between Group A And Group B After Desensitizer Application

	Mean Hypersensitivity	P value (Paired t-test)
After GLUMA Application	4.00+0.75	0.001
After ULTRAEZ Application	2.00+0.72	

and 0.429 respectively. Statistically significant difference was found in Hypersensitivity between Group A (20-30 Age Group) and Group B (20-30 Age Group), & Group A (31-40 Age Group) and Group B (31-40 Age Group) (after desensitizer application), with a p value of 0.001 both.

**DISCUSSION:**

Dentinal sensitivity is a common finding. It is often under-reported by the dental patient population or it is not diagnosed properly. The prevalence of dentin hypersensitivity has been reported to be 14.3% in all-dental patients. Maxillary premolars are found to be the most commonly affected teeth by dentin hypersensitivity. The maxillary first molars follow it with the incisors being the least sensitive. Pain and sensitivity is elicited on a vital tooth following tooth modification procedures.<sup>9,10</sup> Depending on the extent of preparation, the pain may be mild to severe. Mild pain can be managed with use of analgesics whereas severe pain may require elective endodontic procedures. Dentinal desensitizers have been introduced to counter the pain and hypersensitivity arising due to dentin hypersensitivity. Dentinal desensitizer may include lasers, calcium hydroxide and wide range of sealing systems. The nerve desensitization can be achieved with potassium nitrate, whereas agents such as HEMA and Glutaraldehyde can block dentinal tubules.<sup>11</sup> Desensitizing agents not only occlude the dentinal tubules at the surface (at the tubular orifice) but also at the subsurface (within the dentinal tubules) level thereby preventing the fluid flow. It has been suggested that prior to recording the impression, sealing of the dentinal tubules should be considered for tooth preparation on vital teeth.<sup>12</sup>

In 2009 Jalalian E et al compared three agents (Gluma, Potassium Nitrate and control) to decrease hypersensitivity



of vital teeth prepared for full coverage restorations.<sup>8</sup> Mean + SD of VAS on teeth treated with Gluma Desensitizer and Potassium Nitrate Desensitizer was 4.76 + 2.02 and 2.20 + 1.04 respectively whereas it was 3.71 + 1.00 and 1.71 + 0.91 in our study. Both desensitizers reduce the hypersensitivity significantly however ePotassium Nitrate (UltraEz) was found to be more effective in reducing sensitivity in this study as well as in our study<sup>8</sup>

In 2005, Pamir et al compared three desensitizing agents (5% Potassium Nitrate, 2% Sodium Flouride and Prompt L Pop) and found all the agents to be effective in reducing pain and discomfort with Mean +SD pain 1.6+0.3, 1.7+0.3 and 1.8+0.3 to thermal stimuli respectively. The results of this study showed that 5% Potassium Nitrate was mildly more effective than other two agents<sup>13</sup> In 2003, Frechoso et al compared two desensitizing agents (5% Potassium Nitrate Gel and 10% potassium Nitrate Gel) found the 10% potassium nitrate to be more effective and for longer duration than the 5% potassium Nitrate.<sup>14</sup> In another study three desensitizing agents were compared namely Bis Block Dentin Desensitizer (oxalate based), Systemp Desensitizer (glutaraldehyde based), and Tooth Mousse Desensitizer. Application of Systemp and GC Tooth Mousse Desensitizer resulted in 100% reduction in sensitivity level at the end of one week compared to Systemp Desensitizer (86%) .<sup>1</sup>

In 2008, Tengrungsun et al compared the desensitizing effect of GaAlAs Laser with Dentine bonding Agent and found the laser therapy to be less effective than dentine bonding agent.<sup>15</sup> In 2013, Joshi et al compared the dentinal tubules occlusion by NovaMin Desensitizer which is powder based, with Gluma Desensitizer which is liquid based under electron microscope. It was found that NovaMin Desensitizer occluded dentinal tubules almost completely and Gluma Desensitizer occluded dentinal tubules partially. Thus, NovaMin may be considered more effective in dealing with dentinal hypersensitivity compared to Gluma in relation to this study.<sup>16</sup>

In 2004, Duran et al compared five desensitizing agents including Gluma desensitizer and found VAS after gluma application to be 2.33 + 2.32 whereas it was 3.71 + 1.00 in our study.<sup>17</sup> In 2013, Larson et al compared the efficacy of Gluma Desensitizer with Potassium Nitrate in patients requiring crowns and FDPs before cementation and found Gluma to be more effective than Potassium Nitrate.<sup>18</sup> In a study conducted by Jamshed and colleagues in Altamash institute of Dental Medicine it was found that GLUMA desensitizer was statistically more effective in reducing the hypersensitivity compared to Flouride varnish with Mean+SD pain score 2.95+0.86 and 4.01+0.79 respectively.<sup>19</sup> In 2012, LMS Al-saud compared the occluding effect of Nd:YAG Laser with different desensitizers including Gluma Desensitizer. It was found that laser produced dentinal tubules occlusion in most areas whereas gluma produced dentinal tubules occlusion to lesser degree.<sup>20</sup>

The strength of our study was that it was a randomized experimental study and single operator applied the desensitizers to the subjects. The limitation of our study was that placebo effect could not be ruled out because of the absence of Control Group. Secondly, our study was limited only to conventional Fixed Dental Prosthesis. Teeth prepared for partial coverage restorations were not included in our study Similarly Resin Bonded Fixed Dental Prosthesis were also not included in the study as the amount of dentine exposed in such preparations is variable depending upon the preparation design.

## CONCLUSION:

The results of our study demonstrate that both desensitizers reduce Hypersensitivity but UltraEz Desensitizer (containing Potassium Nitrate) relieves Hypersensitivity to a greater extent than Gluma Desensitizer when used on vital teeth prepared for providing conventional Fixed Dental Prosthesis.

### Authors Contribution:

Hamid Bashir: Original Idea of research, statistics Literature Review  
Shoaib Rahim: Data collection statistics  
Jawad Ali Shah: Statistics literature review  
Zarah Afreen: Data collection literature review  
Ammarah Afreen: Data collection literature review  
Eruj Shuja: Literature review

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## Awareness of Mammographic Screening Amongst Females Visiting Breast Clinic at a Tertiary Care Hospital of Karachi

Summayyah Shawana, Sehrish Shafique, Sarah Rabbani, Sobia Hassan, Santosh Kumar Sidhwani, Rafia Siddiqui

### ABSTRACT:

**Objective:** To assess the awareness of mammographic screening among women visiting the breast clinic at a tertiary care facility in Karachi.

**Study Design and Setting:** This cross-sectional study was conducted at Jinnah Post Graduate Medical Centre Karachi over one month period from 1-10-2019 to 31-10-2019.

**Methodology:** After receiving ethical approval, relevant information from patients coming to the breast clinic over the study period, regarding age, level of education, family history, diagnosis and awareness regarding mammographic screening was recorded on specially designed proformas and was statistically analyzed on SPSS 23. P value  $\leq$  to 0.05 was considered as statistically significant.

**Results:** Out of the 100 participants included in the study 68 patients had malignant lesions, 18 had a benign diagnosis while 14 patients were undiagnosed. Only 42 had at least some knowledge of mammographic screening of breast cancers and only 15 patients actually had a screening mammogram performed. Of those aware of the screening majority were informed regarding the procedure by health care professionals or through media sources. Only 4 out of 17 participants with a positive history of breast cancer in the family had the screening done. 12 patients diagnosed with malignant breast lesions were under the age of 40 years.

**Conclusion:** Awareness of mammographic screening for breast cancer among females in our setup is still unsatisfactory and calls for improvements in the awareness programs for breast cancer screening. An early age at diagnosis for malignant breast lesions should prompt the concerned to revise the recommended lower age limit for commencing mammographic screening.

**Keywords:** Breast cancer, Mammogram, Screening, Pakistan

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### INTRODUCTION:

Breast cancer is the most common malignancy in women and is the leading cause of cancer-related deaths worldwide.

#### Summayyah Shawana

Associate Professor, Department of Pathology  
Bahria University Medical and Dental College, Karachi  
Email: shawana75@yahoo.com

#### Sehrish Shafique

Assistant Professor, Department of Medicine  
Bahria University Medical and Dental College, Karachi

#### Sarah Rabbani

Resident  
Agha Khan University Hospital  
Karachi

#### Sobia Hassan

Assistant Professor, Department of Pathology  
Altamash Institute of Medicine, Karachi

#### Santosh Kumar Sidhwani

Assistant Professor, Department of Pathology  
Ziauddin Medical University, Karachi

#### Rafia Siddiqui

Associate Professor, Department of Pathology  
Karachi Medical and Dental College, Karachi

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There were over 2 million new cases in 2018<sup>1</sup>. It was a major cause of cancer related deaths in the year 2018 with approximately 626000 deaths due to breast cancer. This figure amounts to about 15% of cancer related deaths in women worldwide in 2018<sup>2</sup>. Breast cancer is on the rise in Pakistan but due to insufficient data collection, research on this issue has been minimal. According to published data one in every nine women in Pakistan is at risk for developing breast cancer and kills approximately 40,000 women per year.<sup>3</sup> Incidence of breast cancer in Pakistani women is 2.5 times higher as compared to neighboring countries.<sup>4</sup> The prevalence of breast cancer in Pakistan and other Asian countries has been observed at a relatively younger age when compared with the western world.<sup>5,6</sup> The Shaukat Khanum Collective cancer registry report (1994-2018) has documented Breast cancer as the most common malignancy amongst all age groups.<sup>7</sup> Assimilation of genetic and environmental factors with age are the most significant risk factors as concluded by many studies. The risk of developing breast cancer increases with age. Women with first degree relatives suffering from breast cancer have been reported to be at an increased risk of developing breast cancer.<sup>8</sup>

Early detection is critical for improving breast cancer

outcomes and survival and late diagnosis is the major reason for mortality in women with breast cancer. This factor can be overcome only with early detection through an effective screening for breast cancers<sup>9</sup>. The various methods for early detection include self-breast examination, clinical breast examination and mammography. Mammography however, is considered to be a gold standard for early detection of breast cancer.<sup>10</sup> Early detection of malignant breast lesions on mammography has been observed to reduce breast cancer mortality by 20 to 35%, particularly among the women of age 50 year and above<sup>9</sup>. Mammographic screening is recommended for all women 50 years and above.<sup>11</sup> However in many countries, including Pakistan, the knowledge and acceptance of mammographic screening remains poor. Previous studies have demonstrated poor knowledge, attitudes and utilization of mammographic screening.<sup>12,13</sup>

As the knowledge regarding screening of breast cancer is still negligible in our part of the world, this study aims at contributing to the current situation regarding awareness of mammographic screening among females of our population, especially those with a positive family history of breast cancer. The present study would hopefully contribute in devising policies regarding screening programs for breast cancer.

#### METHODOLOGY:

A cross-sectional study was carried out from 1st October 2019 to 31<sup>st</sup> October 2019. A total of 100 females visiting the breast clinic at a tertiary care hospital in Karachi during the study period were included using convenience sampling. Ethical approval for the study was received from the ERC at BUMDC prior to commencing the study. Subjects were selected using convenient sampling technique. The information was collected on a structured questionnaire. Data regarding age, level of education, family history, diagnosis and awareness regarding mammographic screening was recorded on the designed proforma. The questionnaire was subjected to peer-review prior to data collection and data was entered during one to one interview. Informed consent was obtained from all the subjects before the interview. Confidentiality was maintained and names of patients were not recorded on the questionnaires. Data was entered and analyzed using SPSS 23. P value  $\leq$  to 0.05 was considered as statistically significant.

#### RESULTS:

Mean age of the patients was 47.8 + 12.1 years. The age range was 24 to 80 years. The patients reported to the breast clinic for various benign and malignant breast pathologies. Majority (82) of the patients had a diagnosed lesion while 18 were undiagnosed at the time of study. Out of the diagnosed cases 68 patients had malignant lesions while 18 had a benign diagnosis. 12 patients with malignant lesions were under 40 years of age. As far as education status is concerned majority, i.e. 45, of the patients had completed

matriculation while 22 patients had studied up to the fifth grade. 15 of the patients were uneducated. 18 patients had a positive family history of breast cancer with at least one immediate family member diagnosed with malignant breast lesion. Out of the 100 patients included in the study, 42 were aware of mammographic screening for breast cancers and only 15 patients had a screening mammogram done. Of these 42 patients, majority (23) were informed regarding mammographic screening by health professionals while 14 came to know through media sources and 5 were informed by family members or friends. Out of the 17 patients with a positive family history, 10 were aware of mammographic screening and only 4 actually underwent a screening mammography. When enquired why the patients who were aware of mammographic screening did not have a mammogram done (27 patients), majority (19 patients) said that they found the procedure embarrassing. Further among these 27 patients, majority (20) were above the age of 50 years.

#### DISCUSSION:

The present study is in line with various studies done in the country in the past and shows a general lack of awareness regarding screening procedures for breast cancers.<sup>13,14,15,16</sup> Even though 17 patients had a positive family history of breast cancer only 4 actually underwent a mammographic screening. This reveals the extreme lack of awareness and compliance

Table-1: Association of variables with knowledge and practice of mammographic screening

Variable	N=100	Knowledge of screening n=42	Underwent screening n=15
<b>Age in years</b>			
20-30	12	02	00
31-40	18	10	05
41-50	29	14	06
51-60	30	12	02
61-70	08	02	01
70-80	03	02	01
<b>Education</b>			
Uneducated	15	05	01
Primary	22	08	04
Secondary	45	17	04
Intermediate	12	07	03
Bachelors (or above)	06	05	03
<b>Diagnosis</b>			
Undiagnosed	18	05	01
Benign	14	26	08
Malignant	68	11	06
<b>Family history of Breast cancer</b>			
Yes	17	10	04
No	82	32	11
Don't know	01	00	00

to medical advice as far as screening of family members for breast cancer is concerned. Previous studies conducted in Pakistan have shown similar results and a persistent lack of awareness shown by the present study points towards an extremely poor situation as far as awareness programs for breast cancer screening are concerned<sup>17</sup>. Further, 12 patients with malignant breast lesions in the present study were under the age of 40 years. In Pakistan mammographic screening is recommended for women 40 years of age or above. An early age at diagnosis for breast cancer observed in the present and previous studies strongly argues against the recommended age limit for commencing screening mammogram in Pakistan.<sup>18</sup>The level of education was observed to influence knowledge of screening mammography, as 29 out of 42 patients who were aware of the screening procedure had at least completed matriculation. Hence one cannot emphasize enough the importance of education. Studies carried out in the developed countries show a significant reduction in breast cancer mortality with improved screening programs.<sup>19, 20</sup> Results of effective screening programs being carried out worldwide are an evidence of the utmost importance of effective awareness programs and easy access to screening procedures. The single centered nature of the study, small sample size and cross sectional nature of the study are among the limitations of the study. The various socioeconomic can be addressed to portray the real findings of the breast cancer awareness.

### CONCLUSION:

A lack of awareness of mammographic screening for breast cancer among the participant females residing in a metropolitan city of Pakistan reflects the ineffectiveness and lack of awareness programs. Further, an early age at diagnosis for malignant breast lesions should prompt the concerned to revise the recommended lower age limit for commencing mammographic screening.

#### Author Contribution:

Summayyah Shawana: Manuscript writing data collection analysis  
 Sehrish Shafique: Manuscript writing data collection  
 Sarah Rabbani: Manuscript writing data collection  
 Sobia Hassan: Manuscript writing analysis  
 Santosh Kumar Sidhwani: Data collection analysis  
 Rafia Siddiqui: Manuscript writing

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# Medical Student Syndrome: A Hypochondriacal Distress In Undergraduates– Verity Or Myth

Sana Akbar, Misbah Riaz, Lalarukh Munawar, Shazia Shakoor

## ABSTRACT:

**Objective:** The purpose of this study was to correlate the hypochondriacal concerns related to diseases with level of anxiety and depression symptoms among medical and engineering undergraduates.

**Study design and Setting:** Cross sectional study was conducted among undergraduates of final year students of BUMDC (Bahria University Medical & Dental College) and engineering students from NUST- PNEC (NUST – Pakistan Navy Engineering College).

**Methodology:** In this study; (99) final year medical students and (92) engineering students were recruited. In order to maintain consistency of age, students aging between 21–26 years were selected. Selected students were handed to fill the required ‘Self-administered Questionnaire’ comprising of demographic details, short health anxiety inventory, medical history and DASS (depression, anxiety and stress scale) which were completed on-site. Data was entered in SPSS version 21 and analyzed using Fisher’s exact test. P value < 0.05 was considered as statistically significant.

**Result:** Out of 191 students in total from both the groups n=86 (45%) were females and n=105(55%) were males. There were 99 participants from MBBS and 92 from engineering. The participants’ ages ranged from 21-26 years with a mean= 23.95 (SD±2.29), both the cohorts belonged to approximately same age group. While assessing depression the responses were not very different for both the groups. When responses of depression scale were related to visits to psychiatrists or psychologist or psychotherapist a strong relationship was observed (p=0.012) in medical students cohort.

**Conclusion:** The results of the study reflected comparable psychosocial strain at an elevated level among both student groups.

**Keywords:** Hypochondriacal symptoms, Medical Student Syndrome, cognitive, distress, student health questionnaire, DASS, incidence, prevalence, coping strategies.

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## INTRODUCTION:

Medical student syndrome is a constellation of psychosomatic symptoms resulting from studying of a disorder recently learned during lectures or encountered in hospital wards<sup>1,2</sup>. In this disorder, students noticed something innocuous about their health and they correlate their vague symptoms with the disease they have studied<sup>2</sup>. A stomach gurgle becomes appendicitis. A mosquito bite herald’s hemorrhagic fever and a minor headache becomes a brain tumor, bipolar disorder

or some serious illness.<sup>2,3</sup> Worldwide Medical student syndrome is divided into two components: Cognitive and Distress, the first one includes the thought of a student that he has the disease being studied and second one includes the anxiety due to cognitive component. Comparison of these two shows that cognitive component is present in all students which progresses from the start of their education to the senior level where as the distress component is significantly more in the younger students as older students get more knowledge with time along with the increase the maturity level<sup>4,5,6</sup>. “Hypochondriasis” a term used for medical student syndrome; and was diagnosed by using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria<sup>7</sup>. The DSM diagnostic criteria for hypochondriasis includes: Preoccupation with fears that the patient has, or will have, a serious illness based on their misinterpretation of symptoms, that fear is not relieved by appropriate medical reassurance, and that lasts for at least 6 months<sup>7</sup>. The personality features were found to be common among patients with hypochondriasis like obsessive compulsion, avoidance, self-defeating and aggression<sup>8</sup>.

The mission of medical school is to ensure the production of skillful, knowledgeable and professional graduates and

**Sana Akbar**  
Senior Lecturer, Department of Physiology  
Bahria University Medical & Dental College, Karachi  
Email: sana.rudani@gmail.com

**Misbah Riaz**  
Senior Lecturer, Department of Physiology  
Bahria University Medical & Dental College, Karachi

**Lalarukh Munawar**  
Senior Lecturer, Department of Physiology  
Bahria University Medical & Dental College, Karachi

**Shazia Shakoor**  
Professor, Department of Physiology  
Bahria University Medical & Dental College, Karachi

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for this purpose curriculum, mentoring and hands on experience is designed to raise the undergraduates but unfortunately sometimes this exposure results in negative outcome on student's individual health<sup>9</sup>. Another factor unique to medical students is the intensive clinical and pre-clinical exposure of medical knowledge. In addition to this; academic pressure causes the fear to what they have perceived after observing some harmless bodily dysfunction, either modeled after a patient they have examined during their clinical rotation, or a family member who has been ailing<sup>10</sup>.

Medical student disease is also known as noso-phobia meaning fear of disease<sup>11</sup>. It gained its attention in mid 1960s after the researchers reported that 70% students complained of various mental illnesses, they had during their psychiatry rotation<sup>12</sup>. The probable cause is stress which the medical students experiences from the beginning of the training process. This stress is thought to affect symptom detection by enhancing physical sensations through autonomic activation, making individuals more aware of their bodily state, particularly enhancing pain<sup>13,14</sup>.

A healthy body produces various "noises" including flutter, rippling and itches, but hypochondriacal concerns result when these harmless sounds are misinterpreted to indicate an illness which leads to physiological arousal of an atrocious cycle. Medical student usually develop emotional stress during cadaver dissection, exposure to death and human suffering. Exposure to real death for the first time makes the students fearful awkward, apprehensive, vulnerable and angry at the situation and may precipitate thoughts about one's own death thereby hesitating them to interact with the dying patient<sup>15</sup>.

Whether these developments are particularly pronounced in the course of medical education, Comparisons with other student groups (engineering) showed inconsistent result that is no statistically significant difference was found<sup>16</sup>. Results from other studies support that stress may not be particularly pronounced in medical education. Levels of distress were lower in medical than engineering students<sup>7</sup>. Prevalence of depression was lower or similar in both groups. Medical students spent significantly more hours studying than engineering students but it was claimed by students of non-medical course that a comparable amount of time was required for studying their subjects because of strictly-scheduled course and frequent testing system. More than a quarter of engineering students are at risk for burnout, and another quarter with reduced study motivation at the time of graduation, supports this impression of perceived stress. Therefore a comparable psychosocial strain at an elevated level in both student groups was found to be equal since there is no training for students to deal with these stresses and no systematic efforts are incorporated to reduce workload or optimize teaching conditions this might lead to higher anxiety, depression, burnout and suicide levels in both groups<sup>19</sup>.

The purpose of this study was to correlate the hypochondriacal concerns related to diseases with level of anxiety and depression symptoms among medical and engineering undergraduates. However, the evidence that this syndrome exists and is particularly more in medical than engineering students such that it contributes to an increased number of medical consultations is weak.

#### **METHODOLOGY:**

This was a cross sectional survey conducted through self-reported questionnaires among two study groups of students from a medical and engineering student. Final year medical and engineering students were recruited from Bahria University Medical & Dental College (BUMDC) and NUST – PNEC by purposive sampling technique. ERC was obtained from the ethical review committee of the institute. They research students were assured about the confidentiality of data and completed questionnaires were sealed in envelope. Data was collected over a period of two weeks. Students between the ages of 21-25 were included. Students with other tertiary education before their medical education were evicted, to maintain consistency of education level across groups. A total of 191 students were included in the study, out of which 99 were studying in a medical college whereas 92 were inducted from an engineering college. Prevalence of health anxiety among students is 30%<sup>20</sup>. Statistical condition used was proportion sampling with 95% confidence interval and 5% margin of error. Sample size was calculated from open epi software. The required sample size derived was 179 however, a sample of  $\pm 20$  was considered.

The research mean selected was 'Student Health Questionnaire' which is used internationally recognized tool for assessing mental health of students, it is a detailed performa which helps in identifying health issue along with the performance of students in their educational careers<sup>21</sup>. After thorough literature search, the questionnaire was modified for achieving the aims of the study. The questionnaire inquired about basic socio-demographic information (age, gender, university) and screening questions to investigate about year of study, course enrolled in (medical or engineering), previous tertiary education and past medical history. Questions were asked about a close relative suffering from a serious health issue, visit to a doctor in last six months and its reason and any current or previous addiction. Addiction has a strong and proven relation with depression and anxiety<sup>22</sup>. Detailed questions were asked about medical illnesses and their perception about the symptom of neurological illnesses, diseases of musculoskeletal system, dermatological problems or respiratory disorders. Similarly, few questions about mental health of students inquired about psychiatric and psychological disorders.

Anxiety refers to a mixture of general distress such as irritability, agitation, difficulty relaxing, and impatience. For assessing anxiety on DASS, participants were asked

how they would react if they see someone dying in front of them, would they become apprehensive, get panicked or would they become upset but believe that it's a part of life?

Stress was measured by asking the subjects to assume a situation where they have to face a fatal road traffic accident on their way to routine work. Subjects had to select one of the given options like over aroused, unable to relax, irritable, nervy/fidgety or would they rush the victim to hospital or call an ambulance for help. Depression, anxiety and stress scale (DASS) was used to assess the phenomena (Anxiety, depression and stress) in both the groups<sup>23</sup>. The original DASS has 42 items measuring three most important aspects of negative emotional states, namely depression (DASS-D), anxiety (DASS-A), and stress/tension (DASS-S). Depression refers to low levels of positive affect, e.g., dysphoria, hopelessness, lack of energy. A hypothetical scenario was given to subjects to assess depression, which inquired about their response when they visit a relative in hospital who is suffering from a critical illness. Data was recorded using SPSS version 21 and evaluated using Fisher's Exact test.

### RESULTS:

Out of 191 students in total from both the groups n=86 (45%) were females and n=105(55%) were males. There were 99 participants from MBBS and 92 from engineering. The participants' ages ranged from 21-26 years with a mean=23.95 (SD±2.29), both the cohorts belonged to approximately same age group. While assessing depression the responses were not very different for both the groups. The responses of both the groups according to depression scale are given in table 1. When responses of depression scale were related to visits to psychiatrists or psychologist or psychotherapist a strong relationship was observed (p=0.012) in medical students cohort. This indicated that medical students with depressive symptoms tend to visit psychiatrist/ psychologists more frequently. But the relation of depression scale with psychiatrist/ psychologist visit in engineering students was not significant (p=0.135). (Table 1) The results of anxiety scenario on DASS revealed that a large percentage of subjects (MBBS=52% and Engineering 62%) said that they would become upset but believe that it's a part of life (table 2). When the level of anxiety was related to visits to mental health care visits in both the groups the relationship was not significant. It indicates that the subjects do not tend to visit doctors for anxiety. (Table 2). When stress was observed on the same scale p value was significant (p=0.009) for both groups of the study population. Greater number of MBBS students chose responses which indicated increased levels of stress when they were asked about their reactions on seeing a fatal road accident. Stress did not show strong association with psychiatrist/psychologist visits in medical cohort whereas engineering group had a significant relation of stress with visits to mental health consultants (p=0.019). (Table 3)

### DISCUSSION:

This study is one of its kind because it compares medical to engineering students to analyze the results of two different groups and find out the relation between visits by the undergraduate students to hospital and mental health care givers. In this study the relation is assessed on depression stress anxiety scale.

The geographical situation and political instability in Karachi Pak and high prevalence rate of depressive and anxiety symptoms coupled with extensive syllabus and challenging exams adversely affect academic performance and mental well-being of a student. The finding declines to support the notion that medical students seek to acquire more medical advice for hypochondriacal health concerns.

The results showed that students do not visit physicians regarding the emotional–apprehensive component, as during the pre-clinical years, the levels of anxiety are slightly low, due to limited exposure to clinical content. However, with the advancement to clinical studies, there is a high level of anxiety with relative stability throughout the clinical years<sup>2</sup>. A study conducted in Pakistan reported that only few medical students with symptoms of depression approach a physicians or psychologists<sup>24</sup>. This study reveals that there is no significant difference between the two groups regarding perception of symptoms of diseases and help seeking behavior. Similar results were found in study of Saudi Arabia which also enforced that help seeking behavior does not depend on the type of curriculum the students are studying<sup>25</sup>. This finding is supported by another study in 2009 which states that medical students who are more prone to self-diagnosis tend to change their diagnosis with their rotations in different departments of hospital, which means self-diagnoses done by students are not a reliable criteria for labeling them hypochondriac.<sup>26</sup>

Previous studies which showed higher number of medical students with health related anxiety may be because medical students can approach doctors more easily and anxiety may have been reported in casual conversation but medical students are more specific about their self-diagnosis<sup>7</sup>. On the contrary, it was also reported in a multi-centered study that out of 45.5% of the medical students who suffered from anxiety only 3.6% had visited psychiatrists for medical assistance<sup>27</sup>. Perhaps internet is the most unreliable avenue for attaining the alarming medical information which has developed hypochondriacal concerns in them and general public. It is also known as “cyberchondria” in which people seek help from internet sources to explore about their symptoms and reach a diagnosis on their own and this can further lead to hypochondriasis<sup>28</sup>. The results of our study reflect a comparable psychosocial strain at an elevated level in both student groups. Since there is no training for students to deal with this stress adequately nor systematic efforts to reduce workload or optimize teaching conditions this might



Table 1: Comparing depression scale among medical and engineering Cohorts

		Hospital Visit In Past 3 Weeks		Total	P-value
		ENGR n(%)	MBBS n(%)		
Depression Scale	Self-disparaging	1 (2.3%)	2 (9.5%)	3 (4.6%)	0.012
	Dispirited, gloomy, blue	0 (0.0%)	2 (9.5%)	2 (3.1%)	
	Convinced that life has no meaning or value	0 (0.0%)	1 (4.8%)	1 (1.5%)	
	Pessimistic about the future	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Asking them if they need any of your help	20 (46.5%)	4 (19.0%)	24(37.5%)	
	Unable to experience enjoyment or satisfaction	2 (4.7%)	2 (9.5%)	4 (6.2%)	
	Assuring everyone that everything will be alright	20 (46.5%)	10 (47.6%)	30 (38.4%)	

Table 2: Comparison of medical and engineering students on anxiety scale

		Hospital Visit In Past 3 Weeks		Total	P-value
		ENGR n(%)	MBBS n(%)		
Anxiety Scale	Become apprehensive	1(2.3%)	0(0.0%)	1(1.5%)	0.735
	Start panicking	0(0.0%)	2(9.5%)	2(3.0%)	
	Tremble and shake	7(16.3%)	3(14.3%)	10(15.3%)	
	Become upset but believe that it's a part of life	31(72.1%)	11(52.4%)	42(64.6%)	
	Have pounding of the heart and sweatiness of the palms	1(2.3%)	4(19.0%)	4(6.15%)	
	Actively participate in the funeral proceedings	6(12.2%)	1(4.8%)	7(10.7%)	

Table 3: Responses of two study groups on the basis of stress scale

		Hospital Visit In Past 3 Weeks		Total	P-value
		ENGR n(%)	MBBS n(%)		
Stress Scale	Over-aroused, tense	1(2.3%)	2(9.5%)	3(4.6%)	0.446
	Unable to relax	0(0.0%)	2(9.5%)	2(3.1%)	
	Touchy & easily upset	1(2.3%)	0(0.0%)	1(1.5%)	
	Rushing the victim to the hospital	1(2.3%)	2(9.5%)	3(4.6%)	
	Irritable & startled	1(2.3%)	2(9.5%)	3(4.6%)	
	Nervy, jumpy & fidgety	0(0.0%)	0(0.0%)	0(0.0%)	
	Call the ambulance or for nearby help	30(90.7%)	13(61.9%)	43(66.1%)	

lead to higher anxiety, depression, burnout and suicide levels in both groups<sup>23</sup>.

It is advisable to teach about the existence and the benign nature of medical illness and the related phenomena elaborately along with correct interpretations of expanding medical knowledge. It can be explained to students that anxiety is a part of normal process of life and not a pathological one, so that the students would have better methods of coping up that would minimize a source of additional stress for already overburdened students<sup>2</sup>.

The strength of this study was to recruit the participants from two different groups of same ages but with different academic backgrounds and approach towards medical symptoms related to mental health provides a comparison. The engineering students serve the purpose of a control group.

As it was a cross-sectional study; the primary limitation is that exposure and outcome are simultaneously assessed, there is generally no evidence of a temporal relationship between exposure and outcome. Many of these study design limitations would overcome with a prospective longitudinal approach with greater sample size; which has yet to be used in researching the health concerns and reassurance seeking behavior of medical students.

However, the studies used the DASS-21 as a dependent variable. This is not reliable in validating the psychometric properties of the DASS-21 in an Asian sample, which can be compounded by social, cultural, and political variations between Asian countries. Hence without the use of confirmatory factor analysis to determine the factor structures of the DASS-21, it remains uncertain whether this scale is psychometrically sound and valid for use in Asian

populations. Therefore Medical student's disease should be regarded as a phenomenon by defining it as a normal process; one can assist in guiding students to reduce their level of anxiety and distress.

### CONCLUSION:

The results of the study reflected comparable psychosocial strain at an elevated level among both student groups. Since there is no training for students to deal with this stress adequately nor systematic efforts are there to reduce workload or optimize teaching conditions.

#### Author Contribution:

Sana Akbar: Principal investigator took part in conception and study design acquisition, analysis or interpretation of data for the work, compilation of write up and references.  
 Misbah Riaz: Took part in collection and interpretation of data.  
 Lalarukh Munawar: Took part in compilation of write up, drafting the article and worked on results and references.  
 Shazia Shakoor: Took part in reviewing it critically for important intellectual content.

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## Impeding Minocycline Induced Hyperpigmentation by Pomegranate Extracting the Epidermis of Guinea Pig

Sarwath Fatimee, Nadia Younus, Sadia Sundus, Yasmeen Mahar, Syed Munawar Alam, Syeda Bushra Ahmed

### ABSTRACT:

**Objective:** This study was planned over the hypothesis that pomegranate extract rich in ellagic acid used with minocycline could decrease its adverse effect and prolong its therapeutic use and efficacy.

**Study design and Setting:** This experimental study was done in the department of anatomy, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center, Karachi,

**Methodology:** We acquired 40 guinea pigs (male, adult, 450 – 550 gm), randomly divided them into 4 groups. Group B received 0.0003mg/g bodyweight of minocycline only, group C was given 0.0003mg/g bodyweight of minocycline with 0.4mg/g bodyweight of pomegranate, group D was given 0.4mg/g bodyweight pomegranate only; with keeping group A with no intervention at laboratory diet for 8 weeks. After the experimental period, the animals were sacrificed, H & E and DOPA-OXIDASE staining was done on harvested skin tissues for morphometric observations under light microscopy.

**Results:** The results showed that minocycline induced reduction in mean thickness of epidermis and increased melanin pigment deposition. Mean number of melanocytes decreased with pomegranate use though the difference was insignificant (P-value > 0.05) but consistent and measurable.

**Conclusions:** It was proven that by including pomegranate in our daily diet, the process of hyperpigmentation of skin induced by the broad spectrum tetracycline particularly minocycline, can be slow down by decreasing the activity of tyrosinase enzyme, thus it provides a novel pathway to fight against any other drug induced hyperpigmentation occurring due to increase activity of tyrosinase enzyme.

**Keywords:** Pomegranate, Minocycline, Epidermis, Skin, Hyperpigmentation, Tyrosinase inhibitor, Ellagic acid.

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### INTRODUCTION:

Skin is composed of epidermal units that are responsible for the production and distribution of melanin, on which the colour of skin depends. These epidermal units are composed of melanocytes surrounded by keratinocytes. Melanin

synthesis occurs in melanocytes under paracrine control. Hyperpigmentation of skin can result from increased melanin synthesis<sup>1</sup>. Drug-induced hyperpigmentation represents about 20% to 40% of all cases of acquired pigmentation. Commonly used drugs such as pain killers and antibiotics particularly sulphonamides and tetracyclines<sup>2</sup>, can also stimulate melanocytes causing increased melanin production, thus causing hyperpigmentation of skin<sup>1</sup>.

Minocycline, a broad-spectrum antimicrobial tetracycline, was mainly accepted for the treatment of tetracycline resistant inflammatory acne. It is still prescribed for acne vulgaris as oral or in topical gel formulations in moderate to severe acne cases<sup>3</sup>. It has been used as an effective, well tolerated therapy in rheumatoid arthritis<sup>4</sup>. The drug is approved by FDA (US) for the treatment of gram negative bacteria in immune-compromised and seriously ill ICU patients<sup>5</sup>.

Cutaneous hyperpigmentation is a well-recognized adverse effect of chronic minocycline therapy. Various studies have reported hyperpigmentation induced by chronic administration of minocycline in patients with acne, rosacea, and rheumatoid arthritis. It is a cosmetically concerning side effect that is also noted to occur in subcutaneous fat, nails, teeth, gingivae, oral mucosa, lips, conjunctiva, sclera, as well as various internal organs<sup>6</sup>.

Melanin pigment is synthesized by a cascade of enzymatic

#### Sarwath Fatimee

Associate Professor, Department of Anatomy  
Fatima Jinnah Dental College, JSMU, Karachi  
Email: sarwathfatimee@gmail.com

#### Nadia Younus

Assistant Professor, Department of Anatomy  
Jinnah Medical & Dental College, Karachi

#### Sadia Sundus

Assistant Professor, Department of Anatomy  
Ruth Pauff Fazaia Medical College, Air University, Karachi

#### Yasmeen Mahar

Associate Professor, Department of Anatomy,  
Bahria University Medical & Dental College, Karachi

#### Syed Munawar Alam

Assistant Professor, Department of Biochemistry  
Fatima Jinnah Dental College, JSMU, Karachi

#### Syeda Bushra Ahmed

M.Phil Scholar (Anatomy), Department of Anatomy,  
Bahria University Medical & Dental College, Karachi

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and chemical reactions. Its production is mainly controlled by the activation of tyrosinase enzyme. Thus, tyrosine as inhibitors of natural sources can be used as an essential constituent of de-pigmenting agents for the treatment of hyperpigmentation disorders<sup>7</sup>.

Natural sources including plants have recently gained interest for their anti-tyrosinase activity. Researchers do prefer inhibitors from natural sources due to their less toxicity and better bioavailability, especially for food, cosmetics and medicinal purposes<sup>8</sup>.

Pomegranate (*Punicagranatum*) is a tropical fruit and is a rich source of polyphenols such as ellagitannins and ellagic acid. Many studies have documented the beneficial effects of pomegranate consumption in the treatment of various disorders<sup>9</sup>. Recently, it was demonstrated that the skin-whitening effects of ellagic rich pomegranate are due to the inhibition of melanocyte proliferation and melanin synthesis by tyrosinase in melanocytes<sup>10</sup>. Although, other commercially available tyrosinase inhibitors such as glutathione are now used as skin whitening product intravenously for almost a decade<sup>11</sup>, pomegranate being an edible fruit, has the potential for skin whitening through inhibition of tyrosinase leading to the decreased melanin content<sup>10</sup>.

In this experimental study, it is investigated that pomegranate impedes melanin pigmentation thus reduces epidermal hyperpigmentation, a commonly occurring adverse effect observed when minocycline is used therapeutically for prolonged period.

#### METHODOLOGY:

This experimental study was done in the department of anatomy, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center, Karachi, after Ethical Review Committee approval No. F.1-2/2019/BMSI-E.COMT/075/JPMC obtained from the institute. The duration of experiment was 8 weeks. The study was conducted from April 2012 to May 2012. Forty male adult guinea pigs weighing 450 – 550 g were randomly divided into 4 groups (A, B, C and D) comprising of 10 guinea pigs in each. The animals were kept under standard conditions in the Animal House of BMSI, and were given standard laboratory diet consists of fresh cucumbers and water ad libitum. The animals were acclimatized for one week prior to the experiment. All were on 12 hrs fasting prior to the administration of compound. Group A served as control. Group B received Minocycline (Minocin, Stiefel Laboratories Pakistan Pvt. Ltd; Stiefel Laboratories Inc. Coral Gables, FL 33134. USA) 0.0003 mg/g body weight per oral, through gastric lavage, once daily for 8 weeks in the morning after 12 hours fasting. The dose was calculated based on the optimum recommended human dose 200 mg/day in 375 days being used in evaluation of its efficacy in Primary Sclerosing Cholangitis in patients for 1 year without any toxic effects.<sup>12</sup> Group C received Minocycline 0.0003 mg/g body

weight per oral and Pomegranate (Just Vitamins, England, Company No. 3991727; UK) 0.4mg/g body weight per oral after grinding and mixing in the daily early morning diet, after 12 hours fasting. The dose was calculated and based on the experimental study done by Yoshimura et al.<sup>13</sup> and prepared on recommended human dose of Pomegranate tablet of 250 mg/100g body Weight. Group D was negative control group and received only pomegranate (Just Vitamins, England, Company No. 3991727; UK) 0.4mg/g body weight orally daily mixed in the diet.

At the end of the experimental period all animals were anesthetized in a glass container under ether anesthesia and the skin was dissected out after shaving. Two fragments of two inches of skin, one from upper limb and one from lower limbs, were fixed in two types of fixatives. First fragment was fixed in 10% formalin for H&E staining and second one was fixed in 10% formalin in pH7.4 buffer (v/v) plus 0.44 M sucrose for DOPA OXIDASE Method for two days. The tissue of skin fragments were processed in automated tissue processor and sectioned then stained.

In H&E stained sections, morphology of epidermal cells was observed at 400X magnification and thickness of epidermis was measured at 100X magnification using ocular micrometre; at 5 different fields and mean thickness of epidermis was calculated. In Dopa Oxidase nuclear fast red stained sections, melanin pigment deposition in epidermis was observed at 100X magnification and melanocytes were counted at 400X magnification in Stratum Basale and other strata under light microscope with the help of ocular counting reticule in 5 different fields and mean number of melanocytes was calculated.

The melanin deposition was also observed and was graded as per following design:

Grade I: Normal melanin deposition limited till Stratum Basale with scattered distribution (+)

Grade II: Increased melanin deposition limited till Stratum Spinosum with patchy distribution (++)

Grade III: Increased melanin deposition limited till Stratum Corneum with uniform distribution (+++)

The data was entered in SPSS v.23. Mean thickness of epidermis; mean number of melanocytes per reticule for each group was calculated. The difference in the means was calculated with the use of one way ANOVA with post-hoc tukey. The results were considered statistically significant at the P –value of less than 0.05.

#### RESULTS:

In H & E stained slides, the epidermis appeared normal in all four groups with not much difference at 400X magnifications. (Figure-1a) The epidermis comprises of keratinocytes, containing rounded nuclei, arranged in five strata, from which Strata Basale, Spinosum, Granulosum and Corneum are easily identifiable; Langerhans cells with clear

cytoplasm and rounded nuclei are also seen. (Figure-1a)

The mean thickness of epidermis in upper and lower limbs was  $67.30 \pm 0.47$   $67.50 \pm 0.48$   $\mu\text{m}$  respectively in Group A. (Table-2, column 2 & 3) It was decreased  $66.10 \pm 0.47$  and  $66.50 \pm 0.38$   $\mu\text{m}$  respectively in Group B in comparison to Group A. (Table-2, column 2 & 3) It was increased  $67.30 \pm 0.47$  and  $67.5 \pm 0.47$   $\mu\text{m}$  respectively in minocycline plus Group C in comparison to Group B. (Table-2, column 2 & 3) It was increased  $66.70 \pm 0.48$  and  $66.30 \pm 0.49$   $\mu\text{m}$  respectively in Group D in comparison to Group B. (Table-2, column 2 & 3) But the difference remained statistically insignificant (P-value > 0.05) between all groups.

The melanin pigment deposition was also observed in DOPA OXIDASE with red nuclear fast red stained at 100X magnification, which was grade I that is normal (+) in Group A (Figure-1b, Table-1), was Grade II (+++) in Group B (Figure-1c, Table-1), was grade I (++) in Group C (Figure-1d, Table-1) and was normal (+) in Group D. (Table-1, column 4 & 5). In DOPA OXIDASE with red nuclear fast red stained sections, the shape of the melanocytes was ovoid to round with sparsely stained dendrites spread between keratinocytes of Strata Basal and Spinosum in Group A. (Figure-1b) The morphology of melanocytes observed in

the Group B, C and D found to be similar to the Group A. (Figures-1c & 1d).

The mean number of melanocytes per reticule was also counted in upper and lower extremities in DOPA OXIDASE stained sections; which was  $2.26 \pm 0.29$  and  $2.21 \pm 0.24$  respectively in Group A (Table-2, column 4 & 5), was decreased  $2.25 \pm 0.35$  and  $2.20 \pm 0.30$  respectively in Group B in comparison to Group A (Table-2, column 4 & 5); was decreased  $2.20 \pm 0.28$  and  $2.22 \pm 0.23$  respectively in Group C in comparison to both Group A and B (Table-2, column 4 & 5); And was almost same  $2.24 \pm 0.28$  and  $2.20 \pm 0.25$  in Group D as compared to Group A (Table-2, column 4 & 5). Though the differences between the groups were not significant (P-value > 0.05).

#### DISCUSSION:

Minocycline, a broad-spectrum antibiotic from the group of tetracyclines, is frequently prescribed for acne vulgaris and rosacea. Hyperpigmentation is a relatively common side effect of this drug and can lead to multiple unpleasant skin lesions, which are not always reversible.<sup>14</sup>

The prevalence of pigmentation secondary to Minocycline ingestion varies between 2.4% to 41% of treated individuals and is highest in patients with rheumatoid arthritis<sup>15</sup>.

Table 1: Melanin deposition and extension in epidermal layers in different groups

Group	Treatment Given	Treatment Period	Melanin Deposition	Extension
A Control	None diet Ad labitum	8 Weeks	+	Grade I*
B Minocycline Treated	0.0003 mg/g body weight / day orally	8 Weeks	+++	Grade III***
C Minocycline + Pomegranate protected	0.0003 mg/g body weight / day orally + 0.4 mg/g body weight / day orally	8 Weeks	++	Grade II**
D Pomegranate only	0.4 mg/g body weight / day orally	8 Weeks	+	Grade II*

\*Melanin deposition till stratum basale

\*\* Melanin deposition till stratum spinosum

\*\*\*Melanin deposition till stratum corneum

+ scattered distribution

++ patchy distribution

+++ uniformed distribution

Table 2: Mean thickness of epidermis and mean number of melanocytes per reticule in upper and lower limbs of guinea pigs of different groups

Groups (8 weeks)	Mean Thickness of Epidermis ( $\mu\text{m}$ )		Mean number of Melanocytes per reticule	
	Upper Limb	Lower Limb	Upper Limb	Lower Limb
A Control With Diet Ad Labitum	$67.30 \pm 0.47$	$67.50 \pm 0.48$	$2.26 \pm 0.29$	$2.21 \pm 0.24$
B Minocycline Treated	$66.10 \pm 0.38^*$	$66.20 \pm 0.39^*$	$2.25 \pm 0.35^*$	$2.20 \pm 0.30^*$
C Minocycline + Pomegranate Protected	$67.30 \pm 0.40^*$	$67.5 \pm 0.47^*$	$2.20 \pm 0.28^*$	$2.22 \pm 0.23^*$
D Pomegranate Only	$66.70 \pm 0.48^*$	$66.30 \pm 0.49^*$	$2.24 \pm 0.28^*$	$2.20 \pm 0.25^*$

KEY \* insignificant = 0.05

Figure 1a: Photomicrograph of H & E stained skin section from upper limb of control Group A showing epidermis comprising of keratinocytes with darkly stained cytoplasm and round nuclei, arranged in distinguishable stratum basale (SB), stratum spinosum (SS), stratum granulosum (SG), stratum corneum (SC) along with langerhan's cells (Lc) containing clear cytoplasm and rounded nucleus.400X.

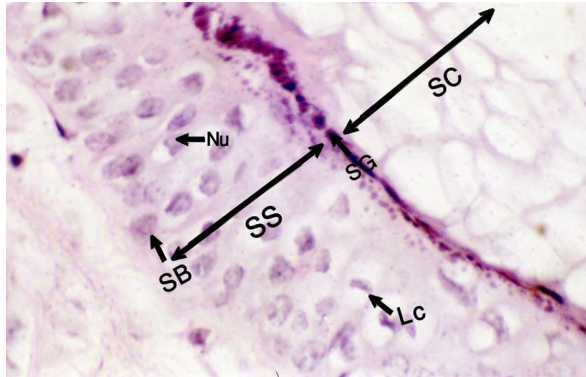


Figure 1b: Photomicrograph of DOPA OXIDASE with Nuclear Fast Red stained skin section showing melanocyte (M) located in stratum basale and melanin pigmentation (mp) limited till stratum basale in the epidermis of upper limb from control guinea Group A. 100X

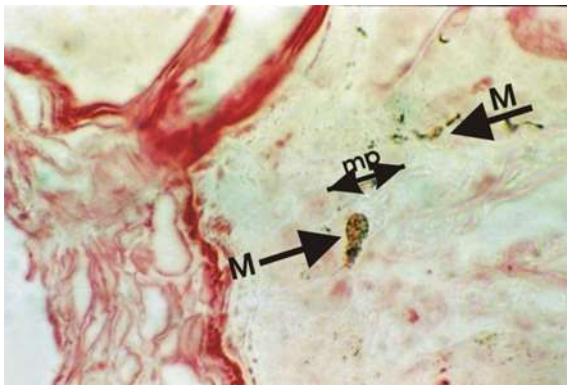


Figure 1c: Photomicrograph of DOPA OXIDASE with Nuclear Fast Red stained skin section showing melanocyte (M) located in stratum basale and melanin pigmentation (mp) limited till stratum corneum in the epidermis of upper limb from Minocycline treated Group B.100X.

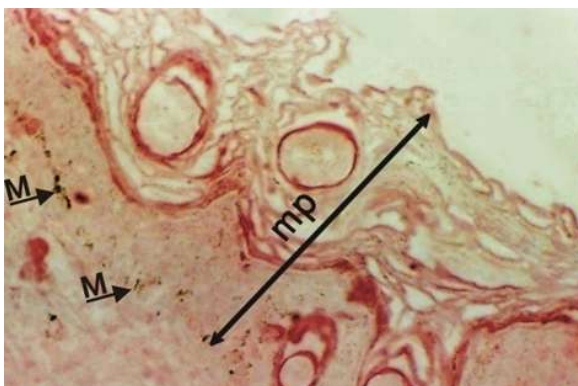
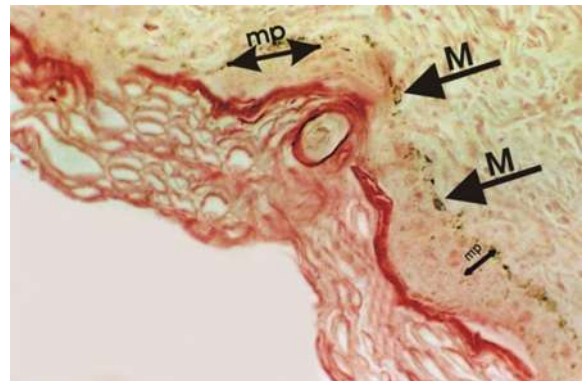


Figure 1d: Photomicrograph of DOPA OXIDASE with Nuclear Fast Red stained skin section showing melanocyte (M) located in stratum basale and melanin pigmentation (mp) limited till stratum spinosum in the epidermis of upper limb from Minocycline treated plus prevented with Pomegranate Group C. 100X



Pomegranate fruit have been used for centuries in ancient cultures for its medicinal purposes and its benefits has been attributed to the content of hydrolysable tannins (ellagitannins) including ellagic acid and ellagic acid derivatives<sup>16</sup>. Ellagic acid is present in the extract of pomegranate has been proven to exhibit the potent antioxidant and tyrosine inhibitor properties<sup>17</sup>.

In this study, the given dose of 0.0003mg of minocycline per gram body weight of a Guinea Pig was based on cumulative dose given in the clinical trial conducted by Silveria et al.<sup>12</sup> This dose is less than the cumulative dose of 0.0139 mg per gram body weight being prescribed for animals with mean bioavailability 62% any without toxic effects<sup>18</sup>. The dose of ellagic acid rich pomegranate of 0.4 mg per gram body weight was based on the experimental study conducted on mice by Youshimura et al.<sup>13</sup> A randomized controlled trial of pomegranate juice and extract was also conducted in 2019 based on the experimental animal study of Yoshimura et al on the healthy women to observe the effects against Ultraviolet B induced erythema produced in their skin without any adverse effects<sup>17</sup>.

In the present study, the minocycline treated group B showed decrease in epidermal thickness compared to control group A. This may be explained by the fact that minocycline inhibits the release of cytochrome C from mitochondria by reducing the tumor suppressing gene p53<sup>19</sup>, which in turn decreases the pro-apoptotic factors such as BAX(BCL 2-Associated X protein; B Cell Lymphoma associated), thus inhibiting the activation of caspase-9. It also decreases TNF (Tumor Necrosis Factor). These are the reasons of suppression of apoptosis as described by Kumar et al.<sup>20</sup>. That is why there is no alteration in the epidermal thickness. This is also being the findings of Guney et al. that demonstrate the anti-apoptotic effects of minocycline on fat graft and observed statistically significant apoptosis inhibition<sup>21</sup>. This has also being proven in the study conducted by Abbaszuden et al.

who found that minocycline protects neurons from caspase activation through decrease release of cytochrome C from mitochondria and also reduces the levels of TNF<sup>22</sup>.

In minocycline treated group B, the DOPA OXIDASE nuclear fast red exhibited melanin pigment deposits till Stratum Corneum when compared to control group A. This is in accordance with the findings of Hanada et.al. who reported high incidence of minocycline induced hyperpigmentation in patients with orthopaedic infections receiving long term minocycline<sup>23</sup>. In another study, the histopathological examination of skin showed increased melanin pigment deposition extending in all layers of epidermis<sup>24</sup>. The mean number of melanocytes was insignificantly increase in treated Group B as compare to control group A, this could be due to the minocycline's ability to scavenge free radicals. This have a protective effect on melanocytes against H<sub>2</sub>O<sub>2</sub> induced apoptosis<sup>25</sup>.

In pomegranate treated group C, the change in epidermal thickness is insignificant compare to control group A, due to the down regulation of TNF levels by pomegranate rich ellagic acid extract<sup>26</sup>, thus there is no significant difference between the epidermal thicknesses of pomegranate treated and control groups.

The melanin deposition in the epidermis was markedly decrease and limited till Stratum Basale (++) in Group C as compared to Group B due to the inhibitory effects on tyrosinase enzyme by ellagic acid of pomegranate preventing the process of melanogenesis. This is being proven experimentally on melanoma cells by the metabolites of dietary ellagic acid derivatives<sup>27</sup>.

The number of melanocytes was significantly decreased in Group C, (Table -2, column-4 & 5), compare to control group A. This was due to inhibition of melanocyte proliferation by ellagic acid rich pomegranate<sup>28</sup> proving that ellagic acid possesses strong inhibitory effects on proliferation of melanocytes.

The negative control group D was included in this experiment to exclude out all the probable effects of pomegranate that could occur due to its administration, on the epidermal thickness, melanin pigmentation and number of melanocytes. It was observed that no significant effects were exhibited on the mean thickness of epidermis, melanin pigmentation deposition and extension as well as number of melanocytes when compared to control group A.<sup>26,27,28</sup>

### CONCLUSION:

This experimental study had taken into account the single optimum recommended human dose of minocycline that had already been proven from the previously conducted studies, in resulting to produced hyper pigmentary effects in human epidermis, without causing any toxicity. For these reasons, this experimental study was aimed to determine the impeding effects of ellagic acid-rich pomegranate extract,

which is in human consumption for quite sometimes, against the cutaneous hyper pigmentary effects due to tyrosinase enzyme inhibition. The results obtained so far, had proven to be quite optimistic in this regard, and open a novel corridor for further research in this aspect.

### CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

### Author Contribution:

Sarwath Fatimee: Conceptualization, Methodology, Formal Analysis, Investigations, Writing-Original Draft, Referencing  
Nadia Younus: Methodology, Validation, Writing- Review & Editing Final Draft  
Sadia Sundus: Methodology, Investigations, Resources  
Yasmeen Mahar: Supervision, Resources  
Syed Munawar Alam: Conceptualization, Resources  
Syeda Bushra Ahmed: Investigations, Writing-Original Draft

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## Awareness of Denture Cleansers and its Recognition among Dental Professionals

Maria Shakoor Abbasi, Maleeha Ishfaq, Naseer Ahmed, Maryam Abdul Rahman, Yusra Kanwal,  
Naseer Ahmed, Adil Bin Irfan

### ABSTRACT:

**Objective:** To assess the awareness of denture cleansers and its recognition among dental professionals in Karachi, Pakistan.

**Study Design and Setting:** Cross-sectional study conducted at various institutes and hospitals of Karachi, over a period of 06 months from March to August' 2019.

**Methodology:** Total 200 dental practitioners were included in this study using nonprobability convenience sampling technique and according to the inclusion criteria. Those dental practitioners who were currently in practice; either at a hospital or clinic setting were included; others who were not in practice or only working as an academician were excluded. This study was conducted by administering a well-structured questionnaire, comprising of 12 close ended questions divided into two sections including demography and responses concerning the knowledge and attitude of dental practitioners regarding denture cleansers. The data was entered in SPSS version 25 for descriptive statistics for qualitative variables.

**Results:** The study showed that 86.5% dentists were aware of denture cleansers and 89% prescribe them. However, 58.5% were not aware of the adverse effects.

**Conclusion:** Our analysis has shown that the dental professionals reinforce oral hygiene instructions in their dental practice and prescribe denture cleansers according to need. However, the knowledge regarding adverse effects among the subjects should be addressed.

**Key Words:** Awareness, Denture Cleansers, Dental Professionals

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### INTRODUCTION:

Edentulism leads to a detrimental effect on one's healthy life, causing impairment of speech, aesthetics and mastication which in turn has adverse effect on the quality of life<sup>1,2</sup>. The loss of dentition is caused by a loss of periodontal support,

dento-alveolar trauma and lack of dental care. The incidence of complete tooth loss occurs more with advancing age<sup>3</sup>. In order to overcome this helpless edentulous state and enable one with better nutrition and diet, denture provision is one of the most common treatments.

Bacteria, plaque, and tartar deposition occurs on denture surface just as in our natural dentition. Accumulation of plaque and microorganisms increases the risk of oral diseases such as, dental caries, periodontal diseases and systemic diseases<sup>1,2,4-7</sup>. Therefore, it is important to emphasize on denture hygiene particularly in elderly population as they are more prone to immunity declines. Rehabilitative treatment can only achieve its desired aim if the denture wearer maintains high standards of both oral and denture hygiene by following dentist instructions<sup>3</sup>. Majority of the patients lack basic knowledge of denture maintenance due to dentist's failure, to thoroughly, instruct the patients<sup>8</sup>.

Various means can be used to clean dentures, denture cleansers being one of the most common one. Owing to their strong chemical nature, it effectively removes the collection of microorganisms on the denture surfaces<sup>9-12</sup>. An ideal denture cleanser from a patient's perspective should not only effectively remove deposits and stains from the denture surface, it should also be inexpensive and easily manageable<sup>13</sup>.

The dental professionals should be aware of denture cleansers, their chemical contents, adverse effects, the brands available

#### Maria Shakoor Abbasi

Assistant Professor, Department of Prosthodontics,  
Altamash Institute of Dental Medicine, Karachi  
E-mail: maria\_shakoor@hotmail.com

#### Maleeha Ishfaq

House officer,  
Altamash Institute of Dental Medicine, Karachi

#### Naseer Ahmed

Associate Professor, Department of Prosthodontics  
Altamash Institute of Dental Medicine, Karachi

#### Maryam Abdul Rahman

Registrar  
Altamash Institute of Dental Medicine, Karachi

#### Yusra Kanwal

House officer  
Altamash Institute of Dental Medicine, Karachi

#### Naseer Ahmed

Assistant Professor, Department of Community Dentistry,  
Altamash Institute of Dental Medicine, Karachi.

#### Adil Bin Irfan

Registrar  
Altamash Institute of Dental Medicine, Karachi

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as well as its compatibility amongst available materials<sup>13-17</sup>. Literature shows that studies which have been conducted previously to evaluate knowledge of the dental professionals regarding the composition and adverse effects of denture cleansers showed inconsistent results<sup>2,18</sup>. In addition to that, how often the dentists prescribe it and what methods of denture cleansing they consider to be the best, were also evaluated. The rationale of this study was to assess the knowledge regarding denture cleansers; this will have a positive impact on the treatment outcome. Therefore, the purpose of this study was to re assess the level of knowledge and attitude of dental practitioners regarding the use of denture cleansers in our population.

#### **METHODOLOGY:**

This cross-sectional study was conducted at various institutes and hospitals of Karachi, over a period of 06 months from March to August' 2019. The ethics and review committee of Altamash Institute of Dental Medicine (AIDM) (EC/06/2019/09) reviewed and approved the project. Open-epi epidemiological calculator was used to analyze the sample size of this study considering the least mean value of 87%<sup>2</sup> Dental professional awareness level and keeping 95% confidence interval with 80% power of test. The total sample size calculated was 200 participants. Initially 250 participants were included, 50 were excluded as they were not fulfilling the inclusion criteria or the forms were partially filled. Therefore, 200 dental practitioners were included in this study using nonprobability convenience sampling technique; Only those dental practitioners who were currently in practice; either at a hospital or clinic setting were included; others who were not in practice or only working as an academicians were excluded. A consent statement for voluntary participations was included in the questionnaire for all subjects to understand prior to their agreement. A modified form of a previously validated and reliable questionnaire<sup>19</sup> consisting of 12 close ended questions regarding denture cleansers knowledge and recognition was used as an instrument for data collection. The study questionnaire was divided into two sections. The first section of the questionnaire enquired about the respondent's demographic features along with work setup. The second section comprised of 12 close ended questions, concerning to respondent's knowledge and attitude; including awareness of denture cleansers and its adverse effects, its knowledge related to the composition, compatibility with denture base materials, methods for denture cleaning and brands available in the market. Also, questions regarding the recall for maintenance of dentures, recommendation about the use, form of denture cleansers and special brushes for denture cleaning were included. The data was finally entered into SPSS version- 25 for descriptive statistics of different variables.

#### **RESULTS:**

Out of 200 respondents, the majority 47% were aged between 20-25 years, 35.5% were between 25-30yrs, 12.5% between

30-35yrs, 4.5% were 35-40yrs and 0.5% were above 40 yrs. Males constituted 45% whereas females 55% of the sample. Out of the total respondents, 74.5% were graduates, 21.5% postgraduate trainees and 4% consultants. Regarding the recall of patients to check the maintenance of dentures 69.5% had recalled their patients. As shown in figure 1(a) and 1(b) respectively, 86.5% were aware of denture cleansers but only 41.5% were aware of the adverse effects. 61.5% of responses related to form of denture cleanser showed a preference of the tablet form, as shown in figure 2. 60.5% advocated the combination method for denture cleansing. A good 54% knew less than three brands and only 34.5% were aware of the composition. As presented in figure 3, 69% responded that denture cleansers should be compatible with the denture base material. However, 48.5% had recommended denture brushes. 42% recommended using denture cleansers once daily. 51.5% agreed that adequate knowledge was imparted during undergraduate levels. Furthermore 96.5% of the respondents stated the need to update their knowledge on denture cleansers.

#### **DISCUSSION:**

The use of dentures necessitates the establishment of a greater oral hygiene by the patients to avoid the development and accumulation of bacteria, plaque and stains on the denture which would otherwise lead to halitosis and further exacerbation of poor oral hygiene. This in turn results in a vicious cycle. This mandates the use of denture cleansers. This study was conducted to investigate the awareness of denture cleansers. In order to analyze this, a questionnaire was used, to focus on 3 main approaches: methods of denture cleansing, awareness and the need for upgrading knowledge regarding denture cleansers.

Regarding the question as to which method of denture cleaning is considered best, 12.5% of the dental practitioners considered using the chemical method, 22% mechanical, a significant 60.5% advocated the combination method and 5% did not know. This was in accordance with an analysis by Dikbas et al which reported 78.2% of the dentists recommended combination of brushing and soaking in cleansing solutions, 4.6% only recommended soaking in cleansing solutions and 11.1% recommended brushing method<sup>20</sup>. There are brushes available in the market specifically made for denture cleaning and this study found that 48.5% of the respondents had recommended these specific brushes. This was in accordance with a study done by Pasricha et al. which revealed that 72.5% of the dentists had recommended a special denture brush<sup>18</sup>.

The participants in our research were well aware of denture cleansers, our research showed that 86.5% of the dentists were aware of denture cleansers as seen in Figure (1a). This is in contrast to Hong et al.who reported that more than 59% of Chinese students and more than 86% of Indonesian students had heard only a little about denture cleansers<sup>20</sup>. This difference could be owing to the lack of presence of

Figure 1: (A) Awareness of denture cleansers and (B) Awareness of disadvantages/adverse effects of denture cleansers respectively

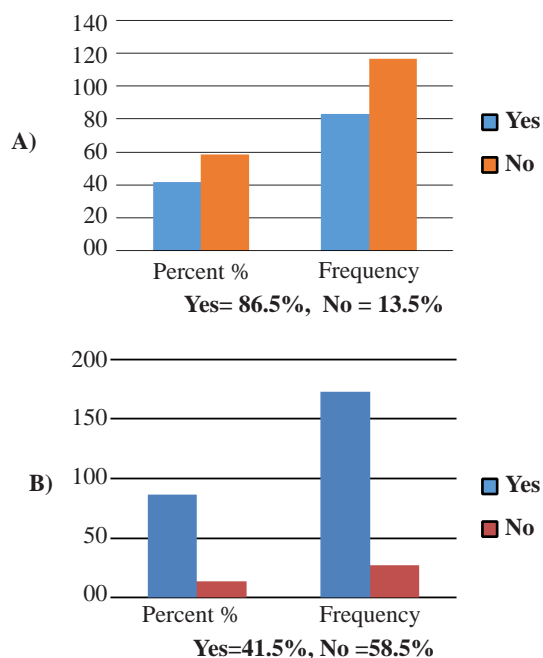
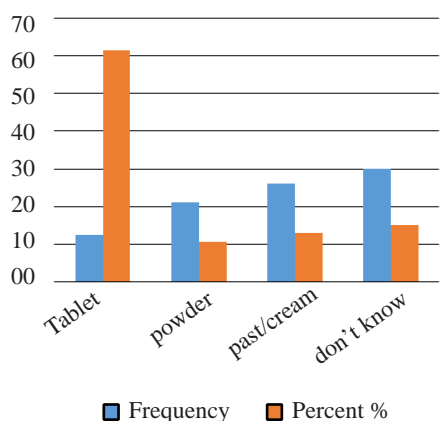
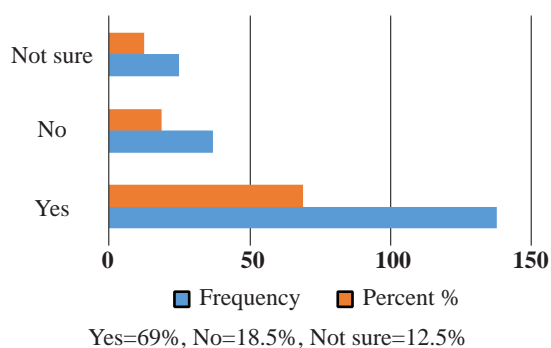


Figure 2 Recommendation of forms of denture cleansers



a) Tablet = 61.5%, b) Powder = 10.5%,  
c) Paste/cream = 13%, d) Don't know = 15%

Figure 3 Compatibility of cleansers with denture base material



denture cleansers in the curriculum of dental schools. Furthermore, our study has revealed that a significant percentage 54% of the respondents knew less than three brands, 13.5% knew more than three brands and 32.5% didn't know any brands available in the market which is in accordance with Hong et al. who reported that 74.5% of the Japanese students knew less than three brands, and 76.5% and 96.6% of the Chinese and Indonesian students answered none, respectively<sup>20</sup>.

For every dentist, it is crucial for them to have the knowledge of the composition of every medicine or paste/ cream they prescribe. This knowledge is important as patients may respond differently to certain elements. Certain patients may be allergic to certain components present in the denture cleansers thus mandating the dentists to have sound knowledge of the composition. Regarding the question on the awareness of the composition and the recommendation of the form of denture cleansers, 34.5% of the dentists were aware of the composition. In addition, denture adhesives have been introduced in various forms i.e. tablet, powder and cream forms. The various forms differ in terms of handling, effectiveness and availability. The tablet form is considered to be the most convenient in terms of handling and usage, which involves a one-step procedure compared to the latter two which involve a two-step procedure. The effectiveness is comparable, however, for the powder and paste form, it becomes dependent on the extent of accuracy of directions followed. This ease in use is further reflected by the response of the participants. As presented in figure (2) 61.5% of the dentists prefer the tablet form, 10.5% powder, 13% paste/cream. The analysis conducted by Chaturvedi et al. showed that 17% were aware of the composition. 88% recommended tablet form of denture cleansers, 8% powder and 4% paste<sup>2</sup>. Both studies revealed that the tablet form is most commonly employed, probably due its ease of use.

On analyzing the frequency of recommendation, it was found that 18% of the dentists had recommended the usage of denture cleansers twice daily, 42% once daily, 19% after every meal, 10% weekly. The application and interaction of denture cleansers with dentures can affect the durability of the dentures. Thus, the compatibility of the two is essential. As shown in figure (3) our analysis has also revealed that a striking 69% were of the view that denture cleansers are supposed to be compatible with the denture base material. Denture cleansers promote and enhance denture cleanliness. However, they can result in adverse effects due to poor instructions or misuse, such as burns, vomiting etc. as well as rashes or breathing problems due to allergic reactions. Regarding the question, on the awareness of the adverse effects of denture cleansers, 41.5% were aware while 58.5% were not (figure 1(b)). In a similar study by Saurabh Chaturvedi et al. it was found that 75% of the dentists knew about the adverse effects<sup>2</sup>. Although, denture cleansers can

result in adverse effects, properly followed directions and correct use help outweighing the advantage of improved and maintained denture hygiene.

The results have revealed that 51.5% were of the view that sufficient knowledge is imparted during undergraduate levels.

In addition, a striking 96.5% were of the view that they needed to enhance their knowledge about denture cleansers. Alqarni et al reported that 80% of the respondents felt the need to update their knowledge<sup>21</sup>. A greater in-depth knowledge of denture cleansers needs to be provided for continuing dental education, so that the dentists will be able to provide better treatment for their patients. By including graduates, post-graduates and consultants in the study, we were able to extract awareness, knowledge and practices of dentists from different educational levels. However, the study was confined to a specific demographic region and had a small sample size. A greater area coverage and larger sample needs to be considered to generalize the results.

#### CONCLUSION:

This study concluded that the dental professionals are aware of denture cleansers and also reinforce oral hygiene instructions in their dental practice. However, the knowledge regarding adverse effects among the subjects should be addressed.

#### Author Contribution:

Maria Shakoor Abassi: Conception and design  
 Maleeha Ishfaq: Manuscript writing  
 Naseer Ahmed: Manuscript writing  
 Maryam Abdul Rahman: Data Analysis, final review  
 Yusra Kanwal: Data collection  
 Naseer Ahmed: Data analysis and data collection  
 Adil Bin Irfan: Critical review

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## Role of Visfatin as a Marker for Depression in Elderly Patients

Sabeen H. Qazi, Shaista Emad, Rubina Ghani

### ABSTRACT:

**Objective:** To identify a new marker for depression amongst the elderly residing in old age institutes (OAI) of Karachi.

**Study Design and Setting:** This was a case control study which was carried out by visiting different private old age institutions in the city of Karachi, Pakistan from 2017- 2018.

**Methodology:** A total of 164 people aged 60 years or more were enrolled via convenient sampling. Basic anthropometric variables were measured, lipid profile was estimated as well as serum Visfatin was estimated via ELISA and was also estimated.

**Results:** The BMI, serum triglyceride and visfatin in depressed subjects were significant with  $p$  values  $< 0.001$  \*\*,  $< 0.004$ \* and  $< 0.001$ \* respectively. Systolic blood pressure was highly significant in depressed subjects when compared with control cases  $p$  value  $< 0.000$ \*\*. The diastolic blood pressure was significant  $p$  value  $< 0.001$ \* as well. Visfatin was found to be negatively correlated with triglycerides, BMI and LDL and it was weakly correlated with depression.

**Conclusion:** The levels of visfatin were found raised in the depressed individuals but they were statistically not significant. It is suggested that more studies on visfatin can be done to find its association in the identification of depressive symptoms in patients suffering from depression.

**Keywords:** Geriatric depression, old age institutes, lipid profile, visfatin.

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### INTRODUCTION:

Depression or major depressive disorder is a devastating condition and represents one of the leading causes of disability worldwide. It can be defined as having lack of interest in normal day to day activities, feeling of sadness as well as changes in daily sleeping and eating habits. This leads to irritable mood most of the day, as noticed by the person or observed by others. Depression hinders people from achieving their complete potential, impairs the finances and is associated with an earlier mortality from suicidal tendencies or other associated illnesses.<sup>1</sup> Depression is classified as mild, moderate or severe depending on severity as well as number of times symptoms occur. The number of cases of depression worldwide have increased by about 50%.<sup>2</sup> Half of the people affected with depression live in the South-East Asian region with an elderly predominance.<sup>3</sup> In the year 2016, a prevalence of 3% was found in Pakistan with highest depressive disorders amongst the females and elderly.<sup>4</sup>

Late life depression is often unacknowledged, which results in a poor quality of life.<sup>5</sup> Depression amongst the elderly is identified via the GDS (Geriatric depression scale). There is an enormous evidence to reinforce its reliability and validity for measurement of depressive symptoms amongst the elderly. A proposed score of 0-9 tells that the person is normal, 10-19 score is marked as mildly depressed whereas, marking of 20-30 shows severe depression.<sup>6</sup>

Pakistan is the 6<sup>th</sup> most populated country in the world. Local data has suggested that elderly population is expected to rise to about 16% by the year 2050.<sup>7</sup> People usually find it difficult to manage time for taking care of the elderly people who require a lot of attention especially the ones who are sick or have any disabilities due to their progressing age. This has resulted in the institutionalization of the old individuals into old age institutes (OAI).<sup>8</sup> It is observed that the psychosocial requirements and issues affect the mental health of the elderly.<sup>9</sup>

Visfatin also known as Pre B cell Colony Enhancing Factor (PBEF) or (NAMPT) Nicotinamide phosphoribosyl transferase was identified in 2005 and it plays a role in the salvage pathway of NAD.<sup>10</sup> Visfatin has also been suggested as a potential biomarker for early identification of cancers.<sup>11</sup> In obese diabetics and non-diabetics, visfatin was increased when compared with controls.<sup>12</sup> A positive association was observed between binge eating and visfatin.<sup>13</sup>

Many studies have already shown a bidirectional association between depression and adiposity. The Obesity-depression–inflammation cycle has been described in which a low grade inflammation is responsible for creating a link

**Sabeen H. Qazi**  
Senior Lecturer, Department of Biochemistry  
Jinnah Medical and Dental College

**Shaista Emad**  
Assistant Professor, Department of Biochemistry  
Jinnah Medical and Dental College

**Rubina Ghani**  
Professor, Department of Biochemistry  
Jinnah Medical and Dental College  
Email: [ghanimusavvir35@yahoo.com](mailto:ghanimusavvir35@yahoo.com)

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between depression and obesity.<sup>14</sup> The function of adipose tissue is no more identified as only storage of lipids but it produces adipocytokines for metabolic regulators like adiponectin, visfatin, leptin which interfere with different pathways including the immune system.<sup>15</sup> The aim of present study was to identify one of the biomarker of depression “visfatin” which was not previously studied in elderly depressed patients in our set ups.

**METHODOLOGY:**

This case control study was carried out at 4 different old age institutes located in Karachi namely Anmol Zindagi trust, Dar ul Sakoon home for elderly, Gills shelter old age home and Sahara Village old age home from September 2017 to March 2018. Elderly people aged = 60 of either sex were selected for this study. A total of (n=164) samples were collected via convenient sampling under fasting conditions. History was taken along with the Geriatric Depression scale (GDS). For the purpose of study questionnaire administration and basic anthropometric parameters were noted on all participants of the study. Blood sample of each participant were drawn for biochemical estimations of serum lipid profile and visfatin. A written consent was acquired from each participant of our study. A permission letter for conducting research was obtained from BMSI (Ref. NO. F. 1-2/2017-BMSI/JPMC). Study was conducted in accordance with Declaration of Helsinki. Elderly people aged = 60 were selected for this study. Those taking lipid lowering drugs, had diabetes, any mental diseases or any other chronic illnesses were excluded. Data analysis was done by One-way ANOVA (Bonferroni test) by using SPSS 20.0 software.

**RESULTS:**

The anthropometric analysis was carried out showing that in depressed patients, the systolic and diastolic blood pressure both were highly significant. During this study BMI was also observed to be significant in depressed whereas the age and waist to hip ratio were found to be statistically insignificant as shown in table 1.

The biochemical parameters were carried out and depressed was compared with normal subjects. The total serum cholesterol and LDL cholesterol were statistically significant in depressed cases. Visfatin was compared with controls and it was observed that it was strongly significant in depressed elderly cases as shown in table 2.

The correlation study was also carried out and we found that visfatin was negatively correlated with triglycerides, BMI and LDL as shown in figure 1, 2 and 3. Visfatin was found to be weakly correlated with depression as shown in figure 4.

**DISCUSSION:**

Pakistani society is one where we have a joint family system and elderly individuals are considered as the head of families. The advent of modern era has led to westernization, where

Table 1: Comparison of anthropometric parameters between depressed cases with controls

Variables	Controls (82)	Depressed (82)	p values
Age (Years)	67.16 + 7.76	69.10 + 8.18	> 0.05
BMI (Kg/m <sup>2</sup> )	22.96 + 3.80	26.03 + 6.89	< 0.001 **
WHR	0.91 + 0.08	0.88 + 0.08	> 0.05
Systolic BP (mm of Hg)	120.68 + 16.94	133.74 + 17.47	< 0.000 **
Diastolic BP (mm of Hg)	74.78 + 11.59	81.96 + 12.32	< 0.001 **

For statistical analysis, one-way ANOVA (Bonferroni test) was used between the controls and the depressed groups.

\*\* p value < 0.001

\* p value < 0.05

Table 2: Comparison of biochemical parameters between depressed cases with controls

Variables	Controls (n=82)	Depressed (n=82)	p values
Total Cholesterol (mg/dl) (TC)	174.11 + 65.17	206.83 + 44.22	< 0.000 **
TG (mg/dl)	143.18 + 47.44	166.84 + 48.39	< 0.004 *
HDL (mg/dl)	35.16 + 7.33	36.00 + 6.06	> 0.05
LDL (mg/dl)	117.68 + 43.00	165.88 + 70.35	< 0.000 **
Visfatin (ng/ml)	5.81 + 2.40	8.25 + 4.54	< 0.001 **

\*\* p value < 0.001;

\* p value < 0.05

Figure 1: Correlation of Visfatin with BMI.

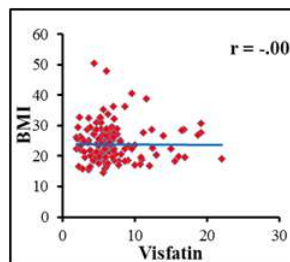


Figure 2: Correlation of Visfatin with Triglycerides

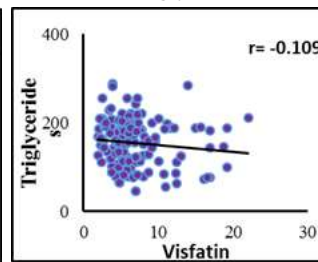


Figure 3: Correlation of Visfatin with LDL

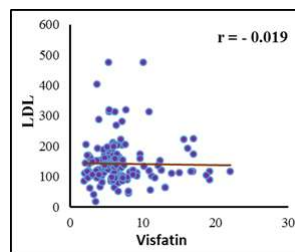
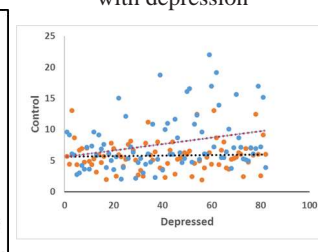


Figure 4: Correlation of Visfatin with depression



men and women both are working due to which they are unable to find time to take care of their parents. This led to the need for OAI. Elderly people become depressed and find themselves helpless and lonely although they have companions living with them of similar age group.

The proposed hypothesis of the study was the visfatin levels will be raised in depression of elderly people staying in OAI's. The results of the study were in accordance with our hypothesis as there was a significant increase in visfatin levels amongst the elderly people who were depressed.

The bridge between depression and obesity is inflammation.<sup>16</sup> Altered adipose tissue and gut microorganisms cause production of inflammatory factors, causing chronic inflammation.<sup>17</sup>

It was found that the body mass index (BMI), systolic blood pressure and triglycerides (TG) were associated with depression<sup>18</sup>, which was similar to our study where we found body mass index, systolic blood pressure, triglycerides, total cholesterol, low density lipoprotein and visfatin were significant.

During our study it was observed that increased systolic and diastolic blood pressures which might be due to depression leading to increased activation of sympathetic nervous system along with genetic influences.<sup>19</sup> It was reported that people who were depressed had a poor adherence to taking anti-hypertensive medicine causing poor control of their blood pressures.<sup>20</sup> Another study also reported that the elderly treated with antidepressants and anti hypertensives showed a decrease in depression, systolic blood pressure and diastolic blood pressure.<sup>21</sup> A meta-analysis reported a notable increase in visfatin levels in hypertensives and cerebrovascular accident patients.<sup>22</sup>

Two Chinese studies<sup>23,24</sup> and a South Korean study<sup>25</sup> are in conflict with our study as they support the "fat and jolly hypothesis" where they found that middle aged and elderly people with low BMI were more depressed so they concluded that depression leads to weight loss in elderly Asians. However another longitudinal study on community residing elderly concluded that an increase in BMI showed increased depressive symptoms, which is in concordance with our study.<sup>26</sup> A study reported raised visfatin levels in obese individuals with low HDL levels which is similar to our study.<sup>27</sup>

An extensive study was conducted on visfatin at genetic level by knocking out NAMPT gene in mice and comparing with normal gene mice. It was found that in lipid metabolism 29 out of 32 enzymes were down regulated. This explained high TG in visfatin gene knocked out mice.<sup>28</sup> A study reported that visfatin was synthesized and released from endothelial cells of human due to ongoing inflammation and since depression is also an inflammatory condition therefore we can link that increased visfatin levels would be observed in depressed individuals.<sup>29</sup>

The increased visfatin levels would be observed in depressed individuals by a study which observed that people having hypertension had raised levels of TC, TG, LDL, BMI and visfatin levels this is in agreement with our study.<sup>30</sup>

This study was carried out on adipocytokine visfatin which was not studied till date in humans with relation to depression which was indeed the strength of the study. This study had a small sample size and should be carried out on a larger sample size in future. This study detected depression via self-reported questionnaire (GDS- mild, moderate, severe depression categories valid on Pakistani population) not clinical assessment. Visfatin has been studied as the biomarker for depression. It will be beneficial to study other inflammatory mediators like C-reactive protein in depressed patients.

## CONCLUSION:

It was concluded that visfatin can be studied as a marker for depression and recommend that it should be studied on a larger sample size to predict depression in elderly.

### Author Contribution:

Sabeen H. Qazi: Principal Investigator  
Shaista Emad: Statistics  
Rubina Ghani: Supervisor

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## Awareness and Practices of Alginate Disinfection Protocol Among Dental Practitioners of Karachi City

Safia Anwer, Syed Ahmed Omer, Perveen Memon, Usman Mehmood, Hameedullah Arif, Shahid Mustafa

### ABSTRACT:

**Objective:** To determine the awareness and practices about disinfection of alginate impression among dental practitioners of Karachi city.

**Study Design and Setting:** This cross-sectional study was conducted at a private sector teaching hospital and private clinics, both located in Hamdard University Dental Hospital, Karachi from the period of April, 2017 to April, 2019.

**Methodology:** A Questionnaire was designed by subject specialist in light of Australian Dental Association guidelines for cross infection prevention and disinfection for dental offices and laboratory. The questionnaire comprised of demographic details including age, gender, years of clinical experience; awareness of disinfection protocols such as self-protection precautionary measures while pouring the alginate impressions; practices of disinfection in the Laboratory; Practice of personal protection and details regarding the attendance of CDE (Continuing Dental Educations) seminars. The data was analyzed on Statistical Package for Social Sciences SPSS version 20.

**Results:** Among total subjects of 186, 78(41.9%) male and 108 (58.06%) female participants were included in this study. In present study the awareness of disinfection of alginate was observed in 171(91.8%) subjects while 15(8.2%) were not up to the mark. Regarding precautionary measures n=142 (83.0%) participants used gloves,. Considering the preferred method and duration of disinfection 56.4% used running tap water for gross cleaning of impression for 5 minutes while 43.6% marked spraying with 2% sodium hypochlorite as preferred disinfection method.

**Conclusion:** majority of the participants of this study were aware regarding the ADA guidelines of disinfecting the alginate impressions while there was a dearth of practice observed for disinfecting the alginate impressions and were not used the prescribed disinfectant to disinfect the dental impressions.

**Key Words:** Alginate, Chlorhexidine, Disinfection. Dimensional stability, dental impressions.

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### INTRODUCTION:

Cross infection is defined as ‘the transmission of infective agents between patients as well as patients and medical staff within a clinical environment. In dentistry, the control of

cross-infection and cross-contamination has been a major concern since dental environment is constantly exposed to these agents<sup>1</sup>. Dental professionals are exposed to wide variety of microorganisms on daily basis and are at greater risk to get infected and become carrier of infections.<sup>2</sup> Even with advancing age there is a little awareness among practitioners and many despite having years of experience do not understand the importance of disinfection<sup>1</sup>.

Dental impressions obtained for various purposes are more often contaminated with microorganisms which may originate from saliva, plaque and blood. The survival rate of majority of microorganism is low unlike some pathogens which may survive for longer duration depending on protein availability from fluids outside the body. The harboring of pathogens on impressions can be easily transferred to casts which is poured for the construction of appliance or study purposes and may eventually result in cross infecting the laboratory technicians<sup>3</sup>. Dentists and dental hygienists are therefore at a high risk of exposure to various diseases like Hepatitis B, Hepatitis C, acquired immunodeficiency syndrome, herpes simplex. However, sterilization of dental impressions is not possible.<sup>3,4</sup> Some studies have demonstrated that a numbers of impressions which are sent to the laboratory are contaminated with blood, saliva and food debris.<sup>5</sup>

#### Safia Anwer

Resident, Department of Operative Dentistry  
Fatima Jinnah Medical and Dental College, Karachi

#### Syed Ahmed Omer

Assistant Professor, Department of Science of Dental Materials  
Bahria University Medical and Dental College, Karachi  
Email: omer\_kalim@yahoo.com

#### Perveen Memon

Associate Professor, Department of Oral Biology  
Liaquat University of Medical Health Sciences, Jamshoro

#### Usman Mehmood

Associate Professor, Department of Science of Dental Materials  
Lahore Medical and Dental College, Lahore

#### Hameedullah Arif

Senior Lecturer, Department of Community Health Sciences  
Bahria University Medical and Dental College, Karachi

#### Shahid Mustafa

Pathologist  
Lyari General Hospital, Karachi

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There are many methods of disinfecting the dental impressions; ideally disinfection procedures should be carried out immediately after taking the impressions of patient before sending to laboratories. There are number of reasons for poor compliance in carrying out disinfection of impressions by dental practitioners which may include: time, effort, loss of surface accuracy and dimensional stability of the impression.<sup>6</sup> There were studies carried out in order to assess the post-performance effects of disinfectant on irreversible hydrocolloid (alginate) impressions.<sup>7</sup> Results are greatly influenced on different methods and materials evaluated. Generally, the data obtained is clinically insignificant.<sup>7,8</sup>

Most of the disinfectants are irritant to body and may cause health risks to the dentist and dental auxiliaries. Moreover, these toxic disinfectants are great source of corrosion for metallic impression trays resulting in dislodgement of the impression from corroded parts of tray.<sup>9,10</sup> General standard operating procedures for cleaning and disinfection include thorough rinsing of impression under running tap water; it removes food debris and saliva. After rinsing, immersion and spraying under disinfectants is a routine recommendation for impressions. Spraying requires less solution, time and can be used for disinfecting chair side surfaces. As dentist is bound to take proper protective measures such as gloves, mask, eyewear and clinical clothing while carrying out chair side dental procedures (e.g. dental checkup, fillings) same protocol should be followed when disinfecting the impressions. All hospital and clinic staff must be trained by professionals to perform infection prevention protocols independently and dental offices must be in compliance with the Occupational Safety Health Administration (OSHA) guidelines.<sup>11</sup> The dental impressions that are exposed to patient's saliva or blood, contaminated the stone casts and serve as a source of infection to dental personnel who handle or deal with the impressions or casts.<sup>12</sup>

Safety for dentists and general population can be emphasized through conduction of awareness and appraising the reasons for poor compliance can result in acquiring large number of serious health conditions. Despite of enough studies conducted and papers being published on awareness of disinfection of impression already but still there is a gap in determining the role of various disinfection procedures over dimensional accuracy and surface standard of impressions. A local study conducted in Karachi city revealed that one third of dental practitioners had sufficient knowledge regarding disinfection of dental impressions.<sup>13</sup> Another study conducted by Saad and colleagues concluded that 93.6% of study group was aware of appropriate need of disposal of disposable impression trays however method of disposal were different. According to another study; 100% study group was sending the impression out after washing or disinfecting them which were an incredible finding.<sup>14</sup>

The aim of this study was to determine the awareness and

practices about disinfection of alginate impression among dental practitioners of Karachi city.

#### **METHODOLOGY:**

This cross-sectional study was conducted at a private sector teaching hospital and private clinics, both located in Hamdard University Dental Hospital, Karachi from the period of April, 2017 to April, 2019. The Department of Research and innovation of Hamdard University Dental Hospital issued the ethical approval letter with ERC number 112-09-03-17 approving the conduct of study. Sample size was calculated from the online software openepi.com. The statistical conditions were 95% confidence interval and 5% margin of error. Prevalence of disinfection of alginate impression material was used as 62%.<sup>13</sup> Therefore the calculated sample size was 362.

For this study the non-probability convenient sampling technique was utilized. A Questionnaire was designed by subject specialist in light of Australian Dental Association guidelines for cross infection prevention and disinfection for dental offices and laboratory. The Australian Dental Association (ADA) recommends the following disinfectants: 0.5% Chlorhexidine, 1% Sodium hypochlorite, 2% Glutaraldehyde and Iodine agents. The 1% Sodium hypochlorite has been generally accepted as the disinfecting agent of choice for alginate.<sup>15</sup> Furthermore, the American Dental Association guidelines states that impression should be rinsed to remove saliva, blood and debris and then disinfect before being sent to the laboratory personals.

The questionnaire comprised of demographic details including age, gender, years of clinical experience; awareness of disinfection protocols such as self-protection precautionary measures while pouring the alginate impressions; practices of disinfection in the Laboratory; Practice of personal protection and details regarding the attendance of CDE (Continuing Dental Educations) seminars. The responses were closed ended as yes or no for the awareness, practice of personal protection and details regarding the attendance of CDE questions. Validity of questionnaire was assessed by Cronbach's alpha test. It was found to be 0.8 (acceptable). All the dentists working in private clinics and teaching hospital at Hamdard University Dental Hospital, Karachi were approached for the study. A total number of 362 questionnaires were distributed among dental professionals, out of which 186 responded were completed in all aspects and therefore were included in the study. All participants were briefed about the rationale of the study and written informed consent was obtained from all the participants before data collection. All data were transferred on Statistical Package for Social Sciences SPSS version 20. Descriptive statistics was applied for qualitative variables.

#### **RESULTS:**

The response rate was 51.38% as total 262 forms were distributed from which 186 were completed in all sections

and were included in the study. Among total subjects of 186, 78(41.9%) male and 108 (58.06%) female participants were included in this study. In present study the awareness of disinfection of alginate was observed in 171(91.8%) subjects while 15(8.2%) were not up to the mark according to disinfection protocols as shown in Table 1. We further investigated precautionary measures while pouring the dental impression which is an important protocol to prevent cross infection among dentists and laboratory technicians. The present findings revealed that 142 (83.0%) participants used gloves, 7(4.0%), face mask and 22 (12.8%) wore goggles as medium for protection during impression taking procedures.

In present study investigation regarding type of disinfection materials was also investigated. Considering the preferred method and duration of disinfection 56.4% used running tap water for gross cleaning of impression for 5 minutes while 43.6% marked spraying with 2% sodium hypochlorite as preferred disinfection method.

Males were found to be more compliant (52.8%) than females (37.2%) with the disinfectant protocols of alginate impression. The alginate disinfection compliance were also observed among specialists and general practitioners were 13(59.1%) and 57(51.4%) respectively which was greater than assistants and hygienists 7(28.0%) and 9(32.1%) respectively (See Figure1). The participants were also asked about the continuing dental education programs (CDE), 54.3% of participants did not attend any type of CDE programs, while rest 45.7% responded that attending CDE program has improved their clinical practice.

## DISCUSSION:

This study was aimed to determine the awareness and practices about disinfection of alginate impression among dental practitioners of Karachi city. Clinical dentistry deals with majority of procedures which may cause cross infection. Dental impressions contaminated with patient's saliva and blood may cross infections. Contaminated impressions and dental casts, thus become tools for the transmission of both

Figure 1: Alginate disinfection compliance according to Designation

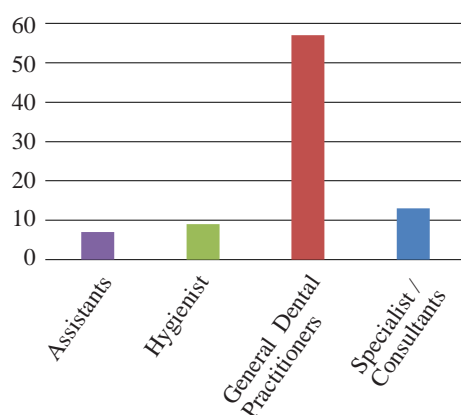


Table 1. Awareness of Alginate Disinfection (n = 186)

Awareness of Disinfection	n (%)
Yes	171(91.8%)
No	15(8.2%)
Practice of Precautionary (protective) measures while disinfecting the impression	
Gloves	142(83.0%)
Masks	7(4.0%)
Goggles	22(12.8%)

bacteria and viruses between clinics and dental laboratories.<sup>16,17</sup>

When considering disinfection method of dental impression in the current study the majority of the respondents were aware of method of alginate disinfection. Whereas another study conducted in Karachi city demonstrated the maximum numbers of subjects were unaware about the appropriate method of disinfection.<sup>11</sup>

Al Mortadi and colleagues conducted a study revealed that the most of laboratory owners (53%) believed that the dentist should disinfect the impressions before sending them to dental laboratories, while (45%) believed that disinfecting the impressions is the responsibility of the dental assistant. Moreover, about 38% of this study population reported not using gloves in their labs.<sup>18</sup>

A local study conducted by Amin F in different dental college showed that the one third of practitioners have practiced impression scrubbing after taking impression.<sup>11</sup> Present study findings also support the other studies such as Shah et al, conducted a study on cross infection control within UK orthodontics departments in which they found that the majority of departments had policy in place to decontaminate impressions and at the dental office.<sup>19</sup>

The cross-infection control has a prime importance in clinical dental practice but impression disinfection is still a widely neglected area, the proper criteria for impression disinfection includes: 1) spray or immersion (the most suitable method), Appropriate application (time of contact) and Periodic check for efficacy.<sup>15</sup>

Awareness of various methods of disinfecting the dental impression was also investigated in current study. The present study findings showed the majority of our participations washed impression under running tap water for gross cleaning of debris. A study conducted in a tertiary care hospital in Lagos Nigeria revealed the spraying 49(21.8%), immersion 89(39.5%) methods used by their subjects for alginate disinfection.<sup>20</sup> A local study conducted in Lahore, Pakistan reported that House officers and students had knowledge of infection control and were following the internationally acceptable standard procedures for dental impression disinfection.<sup>14</sup> However, a large number of

dentists in Karachi Hospital in a different study where described as having a poor knowledge about the use of disinfecting agents.<sup>11</sup>

Bacterial species like Streptococcus, Escherichia coli, Staphylococcus, Actinomyces, Pseudomonas, Klebsiella, and Candida are commonly seen in the oral cavity. Impression materials are commonly contaminated with such microorganisms. Choudhury GK, conducted study to assess the disinfection efficacy of Epimax and 0.525% sodium hypochlorite on alginate impression over a period of 10 minutes was found that both Epimax and 0.525% sodium hypochlorite can disinfect the alginate impression material against *P. aeruginosa*, *C. albicans*, and *S. aureus* strains. However, Epimax was found to be more effective against *S. aureus* as compared with 0.525% sodium hypochlorite.<sup>21</sup>

In most countries this is now being in practice to attend containing dental education for up gradation of knowledge about the subjects. Achieving good dental practice requires health care professionals to keep their scientific knowledge and skills up to date throughout their work as well as to maintain and improve their clinical performance and attitude. A cross-sectional study conducted in Eastern Province in Saudi Arabian dentists reported that about 67.3% of dentists attended CDE for personal learning needs and 66.9% for career development.<sup>22</sup> In this context our majority of subjects did not attend the continuing dental education workshops or seminars. In our opinion the attending the CDE courses will help to improve the confidence in delivery of professional services.<sup>23</sup> Therefore, dental colleges and dental education providers should highlight the importance of disinfection of impressions and also incorporate the impression disinfection protocols in their curriculum for students and dental auxiliaries. Furthermore, CDE Programs to increase awareness and reduction of risk of cross infection should be conducted frequently because practicing safe dentistry is only the road to prosperity of dentistry in Pakistan.

### CONCLUSIONS:

This study concluded that majority of the participants of this study were aware regarding the DA guidelines of disinfecting the alginate impressions while there was a dearth of practice observed for disinfecting the alginate impressions and were not used the prescribed disinfectant to disinfect the dental impressions but and were only using the washing under tap water as to remove debris from impression which is inadequate for inhibiting a microbial growth.

#### Author Contribution:

Safia Anwer: Literature Search / Review  
 Syed Ahmed Omer: Study conception and design  
 Perveen Memon: Literature Search / Review  
 Usman Mehmood: Statistical analysis  
 Hameedullah Arif: Critical Revision  
 Shahid Mustafa: Analysis and interpretation

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## Comparison of Salivary pH Among Smokers and Non- Smokers by Keeping DMFT at Unity

Usman Zafar Kayani, Hashim Bin Mansoor, Hamza Asif, Naufal Nadeem, Ayesha Aslam, Hira Zafar Kayani

### ABSTRACT

**Objective:** To evaluate the effects of smoking on salivary pH and compare it among smokers and non-smokers while keeping DMFT (Decayed Missing Filled Teeth) index at unity.

**Study Design and Setting:** Cross sectional study carried out among young male undergraduate students with age range of 19-25 years at Army Medical College (Rawalpindi) over a period of 2 months from 1<sup>st</sup> January to 1<sup>st</sup> March 2018.

**Methodology:** The sample size was 58; from which equally 29 were smokers and 29 were non-smokers. Sample size was calculated by WHO sample size calculator. Unstimulated saliva using a simple drooling method was used to collect in a sterile container from each of the subject. The pH was assessed by using a portable KETOTEK digital pH meter. DMFT was recorded by using dental mirrors and probes under illumination of dental unit. All the readings, along with demographic data were entered in performa. Data was analyzed using SPSS version 24. Descriptive statistics were calculated. Mean salivary pH between the study groups was compared using Independent sample t test.  $P < 0.05$  was taken as significant.

**Results:** Total of the 58 study subjects, 29 were smokers and 29 were non-smokers. Mean salivary pH of the whole study sample was  $7.2 \pm 0.45$ . A statistically significant difference was observed between smokers and non-smokers; whereas smoker's salivary pH was significantly lower than that of non-smoker's ( $P < 0.001$ ).

**Conclusion:** It can be concluded that, the mean salivary pH levels decreases with tobacco consumption in smoked form.

**Key Words:** DMFT, pH meter, Un-stimulated Saliva

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### INTRODUCTION:

Saliva is a major component of oral cavity and it plays a critical role in homeostasis<sup>1</sup>. Saliva performs a lubricative function, wetting food and permitting the initiation of swallowing, and protecting mucosal surfaces of the oral

cavity from desiccation. Moreover, saliva also protects the various oral tissues by its anti-bacterial action. For all the designated functions salivary pH plays a vital role<sup>1</sup>. Normal salivary pH of a non-deficient healthy person ranges between 7.1- 7.5, which is slightly alkaline.

The pH value of saliva refers to the acidic or basic content of the saliva which has an overall effect on the oral hygiene and general health of the oral cavity. The variability of the pH is dependent on many local and systemic factors. One of the local factors is tobacco smoking<sup>1</sup>, which not only deteriorates the general health of an individual but it can also lead to fluctuations within the oral cavity. One of these fluctuations is variation in the pH of the saliva. <sup>1</sup> Smoke from tobacco contains various chemical compounds which directly interact with the salivary contents. Some of these contents are oxidants while others are acidic in nature. These contents release free radicals which lead to hazardous effects on the health of the individuals.<sup>2</sup>

DMFT (Decayed Missing Filled Teeth) is directly a measure of the oral health of an individual.<sup>3</sup> DMFT is an epidemiological tool that is widely utilized in oral health surveys.<sup>4</sup> As DMFT is altered by factors such as; types of food intake, oral flora, mental status of individual etc.<sup>5</sup> Hence it could alter the salivary pH.

Salivation is a complicated process, and salivary composition and flow rate vary greatly under various circumstances and

#### Usman Zafar Kayani

House Officer Armed Forces Institute of Dentistry  
National University of Medical Sciences, Rawalpindi  
Email: [usmankiani010@gmail.com](mailto:usmankiani010@gmail.com)

#### Hashim Bin Mansoor

House Officer Armed Forces Institute of Dentistry  
National University of Medical Sciences, Rawalpindi

#### Hamza Asif

House Officer Armed Forces Institute of Dentistry  
National University of Medical Sciences, Rawalpindi

#### Naufal Nadeem

House Officer Armed Forces Institute of Dentistry  
National University of Medical Sciences, Rawalpindi

#### Ayesha Aslam

Senior Lecturer, Department of Prosthodontics  
Armed Forces Institute of Dentistry, National University of  
Medical Sciences, Rawalpindi

#### Hira Zafar Kayani

Demonstrator, Department of Operative Dentistry  
Margalla Institute of Health Sciences, Rawalpindi

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conditions.<sup>6,7</sup> An unstimulated saliva is referred to as mixture of secretions, that enter the mouth in the absence of exogenous stimuli and this unstimulated flow from salivary glands is called as basal salivary flow rate, that is protecting the oral tissue and is secreted for about 14 hours a day.<sup>8</sup> Gilmen et al. (2008) stated that the smoking habit was more frequently found in high school and university individuals with an average individual smoking till 8.4 pack years.<sup>9</sup> Moreover, the systemic review in Saudi Arabia by E Ingle suggests that the *Streptococcus mutans* had a colony count of  $46 \times 10^4$  and  $3.85 \times 10^4$  among smokers and non-smokers and DMFT score depicts a direct relationship with a decreased salivary pH.<sup>10</sup> One of the study in India stated the significant relationship of smoking to DMFT at P-value of 0.02).<sup>11</sup> According to the study conducted in Karachi 91.4% subjects had pH level of 7 in the control group (non-smokers), whereas in the experimental group (smokers), 68.6% subjects had pH of 6 while 8.6% showed pH level of 5.<sup>12</sup>

None of the previous researches in the medical or dental literature has used DMFT as a confounding factor before analyzing relationship of salivary pH with smoking and indeed it was the rationale of the study. Therefore the aim of the study was to evaluate the effects of smoking on salivary pH and compare it among smokers and non-smokers while keeping DMFT (Decayed Missing Filled Teeth) index at unity. By this the significance of the detrimental effects on the pH of saliva can be established primarily and the overall oral health ultimately.

**METHODOLOGY:**

This comparative cross-sectional study was conducted in a 2-month time frame from 1st January to 1st March 2018. The target population was young male undergraduate’s students with age range of 19-25 at Army Medical College (Rawalpindi). The ethical approval was obtained after a review of the research synopsis by the relevant ethical review committee of the Armed Forces Institute of Dentistry. A non-probability consecutive sampling design was adopted to reach the specified sample size that was calculated by WHO sample size calculator. An experimental and control group were created namely smoker (who smokes at least 5 cigarettes a day) and non-smoker respectively, both with a confounding factor (DMFT) at unity.

The DMFT was intentionally contained at 1 since literature suggests that a higher DMFT score is directly related to a lower salivary pH. An extra-oral examination was performed with after obtaining informed consent from the subjects, followed by a detailed intra-oral examination on a standard dental unit. Decayed, missing, filled teeth (DMFT) index was then noted using artificial illumination along with a dental mirror and probe. Furthermore, 10ml unstimulated saliva using a simple drooling method was collected in a sterile container from each of the subject and then pH was assessed using a portable Digital pH meter ketotek pH TDS

METER made in Xiamen, China . Each patient was first familiarized with this type of saliva collection and was educated via audiovisual aid. Data was analyzed using SPSS version 24. Descriptive statistics were calculated. Mean salivary pH between the study groups was compared using Independent sample t test. P<0.05 was taken as significant.

**RESULTS:**

The results obtained were quite significant, of the 58 study subjects, 29 were smokers and 29 were non-smokers. Mean salivary pH of the whole study sample was  $7.2 \pm 0.45$  (Table 1). A statistically significant difference was observed between smokers and non-smokers (Table 2), where smoker’s salivary pH was significantly lower than that of non-smoker’s (P<0.001).

**DISCUSSION:**

Salivation is a complicated process, and salivary composition and flow vary greatly under various circumstances and conditions.<sup>6,7</sup> The results of this study depicted that there was a significant relationship of salivary pH with the smoking habit of an individual. It was observed that there was an inverse relation of salivary pH with smoking tobacco, showing that with increase in the smoking behavior of the subject, there will be a significant decrease in the salivary pH of respective individuals. Gilmen et al. (2008) stated that the smoking habit was more frequently found in high

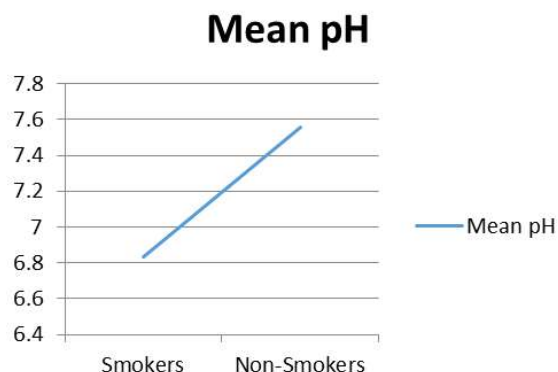
Table 1: Mean salivary pH of the study sample

Salivary pH	Minimum	Maximum	Mean ± SD
	6.4	8.0	7.19±0.45

Table 2: Comparison of Mean Salivary pH between smokers and non-smokers

Smoking Status	N	Mean Salivary pH	P value
Smokers	29	6.83±0.27	<0.001
Non-Smokers	29	7.56±0.24	

Figure 1: Shows the declining salivary pH as a comparison between smokers and non-smokers.



school and university individuals with an average individual smoking 8.4 pack years [rate ratio (RR) = 1.58, confidence interval (CI) = 1.31, 1.91].<sup>9</sup> It is important that the community workers and educationists impart the knowledge of salivary pH shift.

Moreover, the systemic review in Saudi Arabia by E Ingle suggests that the *Streptococcus mutans* had a colony count of  $46 \times 10^4$  and  $3.85 \times 10^4$  among smokers and non-smokers respectively, it further states that the DMFT score i.e. decayed, missing, filled teeth index depicts a direct relationship with a decreased salivary pH.<sup>10</sup> Similarly, study carried out in India stated that the highest mean DMFT was seen among smokers with score of  $3.65 \pm 5.78$ , whereas that of nonsmokers was  $3.01 \pm 2.66$ , and this relationship of smoking to DMFT was found to be significant ( $P = 0.02$ ).<sup>11</sup>

A similar research was conducted in Karachi and the results second the outcome of the current study, which stated that 91.4% subjects had pH level of 7 in the control group (non-smokers), whereas in the experimental group (smokers), 68.6% subjects had pH of 6 while 8.6% showed pH level of 5.<sup>12</sup>

Similarly, Pratika P. et al. (2017) also observed a lower salivary pH in smokers that was,  $6.7 \pm 0.38$  in comparison to  $7.16 \pm 0.30$  in nonsmokers. The difference was statistically significant ( $P < 0.001$ ).<sup>13</sup> Evidence proved that hypo-salivation and decreasing pH eventually facilitates the growth of opportunistic colonies in the oral cavity.<sup>14</sup> Moreover a research performed in Indonesia also supports the results of the present study qualitatively, where litmus paper was used as a screening tool for adolescent behavior of smoking. The salivary pH of smokers turned out to be more acidic than that of non-smokers and the relationship of smoking with the salivary pH came out to be quite significant ( $p < 0.005$ ).<sup>15</sup>

According to the study in India which explained the mechanism of decreasing salivary pH by the change in basal salivary flow rate and stated that SFR alters salivary pH by decreasing bicarbonate secretion and this decrease in saliva bicarbonate in turn decreases the salivary pH.<sup>16</sup> On the contrary, the study conducted by Al-Weheb showed that the mean salivary pH was higher in smokers that is, 7.32 as compared to nonsmokers that is, 7.27.<sup>17</sup>

Past research has concluded that the difference in the quality of saliva without mentioning the pH change; smokers have thick saliva and nonsmokers predominantly serous nature of saliva.<sup>8</sup> Similarly it was stated in another research that negative correlations were found between cigarette consumption and salivary flow.<sup>19</sup> Moreover, a study conducted in Karachi proved a decrease in salivary pH with increase in packs consumed per day.<sup>20</sup>

The study can be considered as a strong evidence for general education of population at large through seminars and workshops in order to critically appraise the awareness status regarding slowly deteriorating effects of smoking.

Certain limitations may have impacted review results of the study. Only DMFT was limited to unity but DMFS was not taken into consideration. Similarly, radiographic detection of caries wasn't done, only clinical eye-balling and probing was used as a diagnostic tool. Secondly, tobacco assessment was self-reported inducing a subjective bias. Since the subjective participants knew the purpose of the study, social desirability bias would be incorporated as tobacco usage would not be reported appropriately.

### CONCLUSION:

It can be concluded that smoking significantly decreases the salivary pH, further research should be conducted in order to correlate the salivary pH with various oral diseases.

### Author Contribution:

Usman Zafar Kayani: Conceived the idea; analysis of the data; principal author; final approval of the version to be published; and agreement to be accountable for all aspects of the work.

Hashim Bin Mansoor: Structuring the study design; revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work.

Hamza Asif: Interpretation of data; drafting the work; final approval of the version to be published; and, agreement to be accountable for all aspects of the work.

Naufal Nadeem: Acquisition of data; drafting the work; final approval of the version to be published; and, agreement to be accountable for all aspects of the work.

Ayesha Aslam: final analysis of data; final approval of the version to be published; and, agreement to be accountable for all aspects of the work.

Hira Zafar Kayani: detailed analysis of data; aide in data collection; final approval of the version to be published; and, agreement to be accountable for all aspects of the work

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## Role of Ultrasound in Estimation of Palatine Tonsil Volume in Obstructive Sleep Apnea Patients

Ayesha Mehwish, Ambreen Usmani

### ABSTRACT:

Sleep constitutes one-third of our life and a good sleep affects the physical, mental and behavioral aspects of an individual. Disturbance in the normal biological rhythm of an individual can disrupt one's performance. Sleep disorders are many but the type that could take one's life is obstructive sleep apnea. Therefore it is important to know the anatomy of involved structures that are responsible for the pathophysiology of the above-mentioned condition. Obstructive sleep apnea-OA is evolving as a worldwide health epidemic and is confronting an increasing prevalence especially due to the obesity pandemic. Though extensive global prevalence facts and figures are still missing, and worldwide OSA research in standings of activity, value, and socio-economic features has not yet been revealed. Ultrasound of palatine tonsil is an emerging and novel technique, as it is noninvasive and safest modality that can be used to determine severity of OSA. High frequency ultrasound is an impeccable diagnostic tool for assessment of tonsils in children and adults. It is cost effective, portable, noninvasive, painless, quick and easily accessible as compare to CT and MRI imaging.

**Keywords:** grading, obstructive sleep apnea, palatine tonsil, ultrasound, snoring

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### INTRODUCTION:

Sleep is a vital attribute of life as one-third of our lives are devoted to sleep.<sup>1</sup> A normal healthy individual sleeps for 7-8 hours.<sup>2</sup> Disturbances of normal biological processes manifests in form of individual's poor performance at work, daily routine affecting his or her physiological processes of entire life. Population-based investigations have shown that people who have extensive and reduced sleep have lesser life span.<sup>1,2</sup> Obstructive sleep apnea (OSA) is also termed as OSA-hypopnea syndrome is featured by recurrent complete or partial blockage of upper airway leading to recurrent oxyhemoglobin desaturation and altered sleep. Another known type is central sleep apnea that involves the failure of central control to initiate respirations by sending signals to muscles involved in breathing. OSA is a common sleep disorder and emerging as a "global health epidemic". It is increasingly documented to be an essential factor of medical morbidity and mortality.<sup>3</sup> Regarding global prevalence of obstructive sleep apnea reported that 936 million adults comprising age group from 30 to 69 years, men and women have this condition with mild to severe intensity, whereas 425 million adults having same age group have moderate to severe obstructive sleep apnea worldwide. The highest

figure of people reported to be affected were in China and then in USA, Brazil and India.<sup>4</sup> It is 3-7% prevalent in the general population,<sup>5</sup> occurs in male and female and includes all ages with a predominant male predisposition.<sup>6</sup> Symptoms of the disease include snoring and apnea at night and day time restlessness, somnolence and lack of attentiveness and poor performance at home and office<sup>3,5</sup>, which in turn increases the risk of cardiovascular disease, hypertension, diabetes, infertility, reduced thinking and unexpected death. Increased neck circumference, weight gain, age above 40 years are the influencing factors for the disease.<sup>5,6</sup>

Clinical evaluation of OSA requires detailed history which leads to early diagnosis of the condition. A close family member such as a spouse can give more trustworthy information than the person themselves as one is not aware of events during sleep. Careful assessment of symptoms must be included in the history like snoring, mouth breathing increased daytime sleepiness, breathlessness, choking, unrefreshing sleep, bad temper, sunrise headaches, memory loss, impotence, menopause, hormone replacement therapy, and use of alcohol, caffeine and tranquilizers.<sup>3,5,6</sup> Primary anatomical site for OSA is pharynx and nearby related structures along the respiratory tract with most likely involvement of retroglossal and retropalatal regions. Other factors include hypertrophic tonsils, uvula, tongue, narrow oropharyngeal isthmus and mandibular retrognathia. Therefore, it is important to carefully inspect all the related anatomy which is involved in the development of the disease process by an otorhinolaryngologist or sleep specialist.<sup>7</sup>

There are various subjective tools invented in the past for the assessment of OSA. One of them is Berlin questionnaire which was invented in 1996 is an easy and authentic tool

**Ayesha Mehwish** (M.Phil Postgraduate Student)  
Department of Anatomy  
Bahria University Medical and Dental College, Karachi  
Email: [aisha\\_mhwsh@yahoo.com](mailto:aisha_mhwsh@yahoo.com)

**Ambreen Usmani**  
Professor, Head of Anatomy Department  
Bahria University Medical and Dental College, Karachi

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for the estimation of sleep apnea risk in general population.<sup>8</sup> This questionnaire gained an equal importance in China for anesthesiologists of Post Anesthesia Care Unit and accepted as a screening tool to recognize subjects who are more vulnerable to develop OSA and to establish the possible reason of developing postsurgical respiratory complications. Others include Epworth Sleepiness scale and STOP-BANG questionnaire but these tools facilitates the physician in reaching diagnosis and recommended to be used in addition to physical examination and laboratory evaluations<sup>8,9</sup>

Physical examination should cover identification of risk factors such as weight gain with BMI = 28 kg/m<sup>2</sup>, neck circumference, detailed upper respiratory examination along with Muller's maneuver in which supple endoscope is passed through nasal cavity and patient is instructed to inspire with mouth and nose closed. In this way collapse of soft tissues at tongue base, above soft palate and pharyngeal obstruction can be visualized. Similarly, the disease may go unnoticed and underdiagnosed when patients visit any clinic or hospital, they are inquired about systemic disorders but not screened for OSA symptoms. Radiographs should be taken to assess craniofacial malformation or occlusion.<sup>10</sup>

The "gold standard" test for the diagnosis of OSA is polysomnography, which include the accounts for various observations like electroencephalogram, electrocardiography, electrooculogram, electromyography, pulse oximetry, nasal and oral airflow, sleep posture, blood pressure and esophageal pressure. Another type is a split-night polysomnography which is conducted in two phases first usual polysomnography test is done followed by CPAP- Continuous positive airway pressures- titrations but these tests are very expensive and require a lot of investigations of physiological processes and a night stay which in our setup is not easy.<sup>11</sup> Ultrasound is emerging as an effective and beneficial technique in estimation of tonsil volume in adults and pediatric population. Palatine tonsil is simply recognized in the pharynx through physical examination but in certain conditions, the size and position of the tongue and its base may make necessary evaluation difficult. In routine examination, tonsil grading and lateral views of x-rays are utilized to judge the area occupied by tonsils. Clinical grading of tonsils involve transverse extension of the lymphoid tissue towards the mid line. On the other hand, depth of this tissue in the oral aspect and medial margins spreading toward the pharynx are not evaluated.<sup>12</sup> Ultrasonography is frequently used to evaluate cranio-cervical growths or masses.<sup>13</sup> However, for visualization of tonsils, the usage of this modality is scant. Transcervical ultrasound was used to distinguish peritonsillar cellulitis from tonsillar abscess in adults. Its use has shown an outstanding sensitivity and specificity in order to differentiate between tonsillar infections.<sup>14, 15</sup>

Incorrect assessment of the disease condition may lead to inaccurate treatment and management that may end up in life threatening complications. Other imaging techniques

such as CT-scan neck can be used for identification of pathology but with it there is an issue of harmful exposure of radiations. Consequently ultrasound has been increasingly used for imaging purposes due to its safety and easiness and should be considered for diagnostic and preoperative assessment. Therefore, it is evident from literature that transcervical ultrasound can be an acceptable imaging technique for the evaluation of tonsillar shape, size, appearance, perfusion, pathology and as well as severity of obstructive sleep apnea by identifying pathological changes of the anatomical structures that basically cause it.<sup>16</sup> It is imperative to review literature and gather authentic information from different researches conducted worldwide to help physicians, surgeons and health care providers by providing them evidence based outcome when ordering investigations to their patients, objective ultrasound findings of tonsillar size in OSA.

#### **METHODOLOGY:**

The literature was reviewed and systemically searched from international search engines for example pub med and Google scholar. This literature search was carried out from 2000-2020. The used key words were palatine tonsil, ultrasound, grading, snoring, oropharyngeal anatomy and obstructive sleep apnea. By exploring with these key words total 72 articles were retrieved and 47 articles were filtered by focusing on the topic. In addition to the mentioned topics, more articles were further explored from the references of the filtered articles to get more literature.

#### **LITERATURE REVIEW:**

The paired palatine tonsils are positioned at the junction of the gastrointestinal and respiratory tract in tonsillar fossa between palatoglossal and palatopharyngeal arches. These lymphoepithelial organs and are the sites for continuous lymphoid cell stimulation therefore are an important part of immune system.<sup>17</sup> Tonsils undergo hypertrophy due to recurrent infections or as a part of generalized lymphoid hypertrophy. The first removal of the tonsils was explicated in the first century A.D. by Cornelius Celsus in Rome. He used his bare fingers to embrace the tonsil and remove it. If the tonsil was covered by a membrane, he used a scalpel to cut through it. Later vinegar and a layered medication were used to accomplish hemostasis.<sup>18</sup>

There are various pre- and post-operative methods for the determination of tonsil volume that how much they occupy oropharyngeal isthmus. Evaluation of its size and free pharyngeal airway is significant in clinical routine. The present valuation of palatine tonsils is made according to Brodsky's criteria for almost thirty years.<sup>19</sup> However, controversies are still present about the significance of such measured methods. In accordance with Gray's anatomy, it states that "the size of the projection of the medial border of the tonsil into the pharynx is not a true indication of the size of the organ".<sup>20</sup> Various other methods developed for

estimation of actual volume includes measurements of various parameters on excised specimens, these include Archimedes' Principle according to which water displaced by excised specimen measured as real volume. Ellipsoid formula in which total tonsil volume is calculated as product of length, width and depth of specimen, multiplied by 0.523, measured by sliding calipers and ruler. Cavalieri method involves physical sectioning of surgical specimen of equal thickness then addition of volumes of each section by incorporating values obtained in a certain formula for total volume of a specimen.<sup>21</sup> Other diagnostic measures include radiographic, ultrasonographic, CT scan and MRI images. All these modalities have certain limitations and restrictions, among them ultrasonographic assessment is the safest and innovative. It is eminent that the lateral view of skull radiograph is valuable for the assessment of adenoid hypertrophy or nasopharyngeal narrowing; on the other hand, tonsil shadow can also be seen in the skull lateral view. Furthermore this technique can be easily performed on pediatric patients in an out-patient department.<sup>22-25</sup> Correlational analysis of tonsillar grading and tonsillar volume in a prospective cohort done in adults showed the mean post-operative tonsillar volume of grades 1,2,3 and 4 was  $2.58 \pm 1.15$ ,  $4.33 \pm 1.99$ ,  $6.58 \pm 2.69$  and  $9.33 \pm 1.15$  ml, respectively as a significant relationship between them with  $p < 0.001$ .<sup>26</sup>

Another study revealed the coherent correspondence between subjective and objective tonsillar dimensions and added that Brodsky grading was more effectively linked with OSA severity than palatine tonsillar volume.<sup>27</sup> It was documented in 2015 that size of tonsil does not influence the severity of OSA with  $p$ -value = 0.32. The study was conducted on 70 children of ages between 1 to 18 years undergoing adenotonsillectomy, polysomnography was done before and after surgery. 40% (28/70) Subjects who were categorized as grade 3+ and 4+, their symptoms resolved completely after surgery. Improvement in AHI also noted from the median of  $11.8 \pm 21.7$  to  $2.0 \pm 6.1$  events/h.<sup>28</sup>

In a recent review article, authors concluded that present available anatomical treatment strategies do not provide cure to all adults suffering from OSA whereas clinical diagnosis is limited to apnea hypopnea index severity which is also not a complete criteria. There is rising attention towards anatomical and physiological phenotyping which is related to syndrome identification. Clinical evaluation of a patient must include a detailed morphological evaluation of oropharynx with supportive physiological treatment which is evolving such as oxygen, sedatives, stimulation of hypoglossal nerve that will modify therapy options for an appropriately selected patient.<sup>29</sup> Pre-surgical evaluation of palatine tonsil volume helps physicians in appropriate diagnosis as this technique is safest, noninvasive and less painful. In adults, for over 30 years trans-cervical ultrasound has been used for the detection of peritonsillar infections.

However, in the past few years use of this modality is highlighted to observe the tonsils in pediatric population.<sup>30</sup>

Trans-cervical ultrasound imaging technique is considered generally safe as it is noninvasive, devoid of harmful radiations, valuable in detection of head and neck masses in young age group. In recent times, this imaging technique has been gaining significant value because of its ability to visualize the oral cavity and pharynx with meticulousness. Effective and successful use requires a thorough knowledge of airway anatomy and ultrasound experience.<sup>12, 31-33</sup> Trans-cervical ultrasound of palatine tonsils as an adjunct to the assessment of upper airway is an alternative and complementary imaging method to magnetic resonance imaging and computed tomography which have certain limitations. Pre-surgical evaluation of tonsil anatomy with ultrasound is thought to be valuable for the estimated response to tonsillectomy and perioperative distresses.<sup>34</sup>

In the pediatric domain, Bandarkar et al reported first time use of tonsillar ultrasound of various tonsillar pathologies along with comprehensive photographic accounts. Authors of the study used this novel technique to differentiate tonsillitis, tonsillar abscess, peritonsillar cellulitis and infections. This technique determines palatine tonsils effectively and accurately as well as it is very practicable and noninvasive choice. In spite of presenting great assertion for identifying different tonsillar pathologies, authors of this research reported that there are no studies in the literature that confirm precision of this imaging technique in assessing volume of tonsil in different scopes.<sup>35</sup> An ultra-sonographic study, which is the first of its kind, performed on 26 children in which they have compared preoperative trans-cervical tonsillar ultrasound measurements with excised tonsils and volume assessment by water displacement method. The mean  $\pm$  SD ultra-sonographic size was 3.6 ml ( $\pm 2.5$  ml) and actual tonsillar size was 3.9 ml ( $\pm 2.1$  ml) having  $p$ -value 0.24 which is not significant but have correlation with real tonsillar size ( $r = 0.89$ ), these findings will help in further perioperative risk stratification of pediatric patients planned for surgery who could or not undergo obstructive sleep apnea syndrome. However, both measurement methods shows no distinction but compliance of sonographic measurements was proven.<sup>36</sup>

Kay-Rivest E et al; are the pioneers to affirm size of tonsil in three scopes can be exactly distinguished with ultrasound and relates with ex vivo specimens. In their prospective analysis they compare tonsillar ultrasound dimensions to actual pathology in 75 consecutive children going through surgery for various reasons. In general, ultrasound mildly underestimated tonsillar size. The right and left tonsils which were assessed exhibited dissimilarities between measured volumes of -0.075 and actual volume of -0.221  $\text{cm}^3$  along with confidence interval of 95%. They have concluded that high frequency ultrasound is an effective technique to evaluate acute and chronic tonsillar disease in

pediatric population.<sup>37</sup> In a study pre-surgical evaluation of subjective and actual volume after tonsillectomy were compared in which investigators of the study established that tonsil sizes were higher in the subjects who were overweight and undergoing from Obstructive sleep apnea syndrome further objective volume and clinical volume estimation through grading correlates well.<sup>38</sup>

Obesity is one of the major influencing feature for Obstructive sleep apnea. Development of this condition likely involves increase in appetite hormones triggered by disturbed sleep whereas might help mild condition but not the severe one.<sup>39</sup> A study which involves 277 pediatric cases relates pre surgical subjective grading via oral examination with post-surgical measurements of tonsil which includes width, length, height and volume. Volume was the best correlated factor in the subjective classification and actual tonsil volume was described to differ from 2.17-4.7 ml.<sup>40</sup>

Children with advanced obstructive sleep apnea have high chances of getting postsurgical airway problems.<sup>41</sup> In pediatric population the occurrence of postoperative complications is nearly four times greater in children of age less than 3-years.<sup>42</sup> In tonsillar enlargement and severe OSA subjects sonography may be used to identify and predict the severity of postsurgical complications after tonsillectomy. Anatomy of human's upper respiratory tract is highly variable, and the pathological anatomy of sleep apnea patients is even more inconstant. Furthermore the upper airway anatomy of sleep apnea patient alters over time as the condition advance or recovers.<sup>43</sup>

In a prospective clinical research that includes both children and adults in which the investigators explore the achievement of ultrasonography in the precise estimation of palatine volume. In the sample of 50 children the mean actual tonsil volume  $\pm$ SD was  $3.5 \pm 1.45$  ml which was evaluated through water displacement method and ultrasonographic volume was  $3.67 \pm 1.59$  ml with high correlation. In this study the mean actual tonsil volume in 35 adult subjects  $\pm$  SD was  $5.15 \pm 2.25$  ml. Ultrasonographic volume which was evaluated was  $5.71 \pm 2.98$  ml with moderate correlation was found between both methods.<sup>44</sup> It is well identified that endophytic tonsil lead to misrepresentative of clinical grading as compared to actual volume in adults. Those subjects with lower grades were known to have greater tonsil volume than predicted during surgery. In these type of cases ultrasound is a better option to provide true estimation of tonsil volume that may enhance considerable importance and direction on clinical follow up or operation decisions.<sup>45</sup>

Another ultrasonographic Japanese study conducted in pediatric age group, in which authors reported that tonsil size increases significantly until 3-years of age but it does not increase between 3 to 12 years of age, they also reported that tonsil size was associated with anthropometric indices like age, weight, and height, with strongest correlation with

height. Authors of the study concludes, usage of this modality in early assessment of tonsillar pathology, determination of its size and assistance in pre-surgical evaluation of its expansion in the oral cavity.<sup>46</sup> Imaging, performed predominantly by physicians and research scientists, has been essential to evaluate the morphological basis of obstructive sleep apnea. Increased collapsibility of the upper airway due to increased nasal resistance and a narrowed, elongated oropharynx leads to apnea during sleep as there is reduction in tone of the pharyngeal dilator muscles. Imaging can strongly detect this condition. The value of imaging techniques has proven its importance in assessing site, degree and reasons of airway collapsibility, its length and location of the hyoid bone.<sup>47</sup> Understanding of radiological anatomy of the normal tonsillar tissue and various peritonsillar pathologies can help the radiologist and clinicians to make the appropriate diagnosis. Correct diagnosis of the condition helps in management of cases, taking decisions and care of patients. Imaging technique like ultrasound should be considered when managing or treating obstructive sleep apnea in order to assess the airway appropriately which will in turn help in better evaluation of a patient. Though it is not the standard in care of patients, there is significant potential for the incorporation of ultrasound technology into forthcoming care of upper airway assessment.

#### CONCLUSION:

High frequency ultrasound is an impeccable diagnostic tool for assessment of tonsils in children and adults. It is cost effective, portable, noninvasive, painless, quick and easily accessible as compare to CT and MRI imaging. Also, it does not require sedation neither uses ionizing radiations. Use of this safest modality aids clinical classification and can be helpful in decisions for tonsillectomy.

#### Author Contribution:

Ayesha Mehwish: Conceiving the idea, data collection and analyzing data, literature search and writing of the article  
Ambreen Usmani: Literature search, analyzing data and writing of the article

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## Association of Diet, Quality of Life and Premenstrual Syndrome; A Review

Quratulain Javaid

### ABSTRACT

Premenstrual syndrome is a disorder experienced by the females of reproductive ages. The etiology of this common condition is unknown. The presentation of symptoms is highly variable all over the world. The variability in the presentation of symptoms could be linked to social and cultural effects of environment. There can be psychological, physical or behavioral characteristic manifestations linked to premenstrual syndrome. The presentation of premenstrual syndrome can effect a female's life. Household chores, work place tasks and interpersonal relationships are effected gravely. Dietary intake of the individuals is associated with the symptoms of premenstrual syndrome symptoms. Intake of diet loaded with whole grains, fish, fruits, vegetables, micronutrients like vitamin B1, D and E have shown to have protective effects against the development and severity of premenstrual syndrome symptoms. Intake of harmful food items like refined sugar, fast food, sweetened drinks, alcohol and chocolates are associated with increase in severity of the condition.

**Key words:** Premenstrual syndrome, prevalence, diet, quality of life

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### INTRODUCTION:

Menstrual cycle has characteristics that are variable among different females. Premenstrual syndrome (PMS) is a condition that is associated with certain physical and psychological and behavioral conditions. The term of premenstrual syndrome was first coined by Frank in the year 1931 after he observed females having certain symptoms that were relieved after the start of menstruation. It occurs in the end of luteal phase of the menstrual cycle.<sup>1</sup> It gets relieved after 3 days of the menstrual cycle.<sup>2</sup> The etiology of post menstrual syndrome is not known as yet.<sup>1</sup>

The symptoms include edema, increased weight and nervousness.<sup>3</sup> There are wide range of symptoms that can include both the psychiatric as well as somatic symptoms.<sup>4</sup> Premenstrual syndrome is associated with symptoms like bloating, muscular pain, anxiety, tetchiness, breast edema, tenderness in the breast, increase sleep or absence of sleep, increase appetite/craving of food, weight gain and mood fluctuations.<sup>5</sup> According to published standard guidelines, any one symptom from the affective category and one from the somatic category should be present in each of the three menstrual cycles that have been occurred previously to declare a female having premenstrual syndrome.<sup>6</sup>

Various researches have documented different reasons for the appearance of premenstrual syndrome. Diet, genetic factors, way of living have been identified as important factors which contribute in inducing the symptoms of this

condition.<sup>7</sup> There are various treatment options like antidepressants and serotonin reuptake inhibitors for premenstrual syndrome but the use of medicines and chemical agents has its own adverse effects. A study conducted in Qazvin University of Medical Sciences has documented that life style changes can help decrease the severity and occurrence of PMS.<sup>8</sup> Dietary modification is considered to be one of the best available options in alleviating the symptoms of PMS.<sup>9</sup>

Modification in diet is documented to have an impact on the occurrence of symptoms of premenstrual syndrome. Reduction of high saturated food, refined carbohydrate and salt are observed to be beneficial in reducing the symptoms of this condition. Inclusion of certain macro and micronutrients like high fiber diet, unsaturated fats, vitamin E and B have revealed to be of high value in controlling the severity of the syndrome.<sup>10,11</sup> Another study conducted on the females living in Sharjah has demonstrated that symptoms of the premenstrual syndrome aggravate when diet includes salt, high number of calories and increase content of fat.<sup>12</sup>

### Prevalence of premenstrual syndrome:

Variable prevalence percentages are mentioned in the literature. This could be due to the cultural and ethnic or genetic differences among the various nations of the world.<sup>13</sup> A study published in 'Journal of International Dental and Medical Research' has stated that prevalence of post menstrual syndrome is 75% to 80% in the females which are in reproductive age.<sup>14</sup> Corresponding findings in terms of prevalence of PMS was noted in a study conducted in Islamabad, Pakistan. Eighty percent of the respondents reported symptoms of premenstrual syndrome. An even higher percentage was mentioned in a study conducted in Sharjah. According to the authors, there was at least one symptom of premenstrual syndrome and it was there in 95%

**Quratulain Javaid**

Senior Lecturer, Anatomy Department  
Bahria University Medical and Dental College, Karachi  
Email: [docannie2010@gmail.com](mailto:docannie2010@gmail.com)

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of the females.<sup>12</sup> A study conducted in Karachi, Pakistan has documented that prevalence of PMS was 79.5% according to a self-reported questionnaire and 23.9% according to the guidelines given by American College of Obstetrics and Gynecology.<sup>5</sup> A research conducted in Puducherry, India has documented the prevalence of premenstrual syndrome to be 62.7% in females of reproductive age groups.<sup>13</sup> Similarly, a study conducted in Turkey has documented the prevalence of PMS to be 58.1%.<sup>14</sup> A study published in 'Brazilian Journal of Nutrition' has documented that among the study participants, PMS was present in 43.80% of individuals.<sup>15</sup> On the contrary, Akbari in her research study has stated comparatively low percentage of premenstrual syndrome. According to her, 31% of the research participants studying at a medical college in Chitradurga, India experienced PMS.<sup>16</sup> A study on secondary school students in Jeddah, Saudi Arabia has reported that one third of the research participants experienced premenstrual syndrome.<sup>17</sup>

### Variable symptoms of premenstrual syndrome

Numerous researches have documented variability in the appearance of symptoms of premenstrual syndrome. Some studies reported physical symptoms to be more common than other symptoms. A study conducted in India, has reported muscle, joint and backache to be among the most common symptoms experienced by the participants followed by abdominal pain and bloating.<sup>13</sup> Similarly, a study conducted in Turkey has documented physical symptoms to be among the most common ones other being the psychological symptoms. Among the physical symptoms, the most common was backache that was present in 73.6% of the individuals. Backache was followed by pain in the pelvis (61.3%), tiredness (55.7%), irritable mood (52.5%), bloating (49.7%), change in appetite (43.4%), tenderness in the breast (39.6%) and episodes of depression (34.9%).<sup>15</sup> As reported by a study on medical students, physical symptoms were more as compared to the psychological and behavioral symptoms. The symptoms were reported to be 95%, 75% and 43% respectively. Among the physical symptoms, the most common one was breast tenderness (60% of participants) followed by headache (40%), muscle and joint pain (30%), bloating (20%) and increase in weight (20%). Among the psychological symptoms, the most common was depression (36%), followed by anxiety (30%), sleep pattern changes (25%), guilt feeling (20%) and tearfulness (20%). Changes in behavior pattern was divided into two categories. Low academic performance was present in 76% and social withdrawal was noted in 46.7% of the participants.<sup>18</sup>

Many researches have reported psychological symptoms to be more common than others have. A study conducted on the medical students of Karachi, Pakistan has documented tetchiness to be the commonly occurring symptom (81.7%). Other reported characteristics were anger (66.9%), depressive mood changes (53.1%), anxiety (46.9%), skin issues (42.7%), tenderness of breast (39.6%), gastrointestinal issue (39.3%),

social withdrawal (37.1%), swelling of the abdomen (33.7%), sleep pattern changes (33.4%), headache (21.9%), and arm/leg swellings (8.1%).<sup>5</sup> Variability in symptoms presentation was also noted in a research study conducted in Sharjah. The most common symptom mentioned was depression (95%). Other reported symptoms were lack of energy (92%), body pain (89.3%), angry mood (85.7%) and food carvings (84.7%). Behavioral symptoms were the least common as compared to the psychological and the physical symptoms.<sup>12</sup>

### Disruption of quality of life

The premenstrual syndrome can have variable effects on the females' lives. Health related quality of life among young females of reproductive ages is effected gravely by the symptoms of PMS.<sup>19</sup> According to a research study, young girls' work efficiency, concentration and quality of work are affected by the condition adversely. Premenstrual syndrome has a disturbing effect on the females.<sup>14</sup> Similarly, a recent study has reported that PMS can adversely affect females' public as well as routine life. The work life atmosphere as well as social life of the female gets disturbed.<sup>17</sup> A study conducted in Karachi, Pakistan has reported that among participants, 60.4% have reported that their normal routine life gets disrupted due to PMS.<sup>5</sup> A study conducted on Turkish nurses has mentioned that stress was observed to be found more in those having PMS.<sup>20</sup> It was documented in an Egyptian research that because of the premenstrual syndrome, occupational work was negatively affected.<sup>21</sup>

Other than the work life, sexual life of a female is also disturbed. A study conducted in Iran has reported that there are various unfavorable effects of PMS on a woman's life. It can effect physical, behavioral and psychological health. The sexual life and henceforth relationship between couples also gets disrupted because of the severity of symptoms. Agitation is one of the features that can lead to social distancing among the females of reproductive ages.<sup>22</sup>

Premenstrual syndrome seriously effects the concentration and hence learning capabilities of the students. A study conducted on Thai high school students has documented that premenstrual syndrome effects academics. The students experiencing the symptoms of PMS have difficulty in concentrating in the classrooms. Other than that, interpersonal skills are also affected and collaborative work cannot be done in an effective manner. All these factors contribute to low academic scores.<sup>23</sup>

### Knowledge about the prevention of PMS

In the present day society, females over the world have different strategies to cope up with the symptoms of premenstrual syndrome. A study conducted in Islamabad, Pakistan has reported that 71.5% of the study participants had no clue about the prevention options available for PMS. Out of the 29.5% who had idea about the prevention of PMS, 50% believed that home remedies could prevent the

symptoms. 30% believed that supportive measures like reassurance play a part while 20% thought that medications could be helpful.<sup>18</sup> A research study conducted in Karachi, Pakistan has notified that several treatment options were adopted by the study participants. The most commonly used treatment was painkillers (41%), followed by homeopathic medicine (1.4%), supplements containing vitamins (5.1%), traditional remedies (13.8%), exercise (17.7%), antidepressants (0.3%) while 49.4% did nothing for the symptoms. The study revealed that 77.5% of the participants considered it an important issue and they were of the opinion that it should be discussed.<sup>5</sup>

### Diet helpful in prevention and severity of PMS

There are various research studies that have documented the effect of food intake and its role in development as well as severity of premenstrual syndrome. In a recent study, different vegetables were compared for their effects on PMS. It was mentioned that cruciferous vegetables (cabbages, broccoli and cauliflower) intake is associated with protective effect against the development of PMS. Vegetables like green (spinach, basil, parsley etc.), dark yellow (yellow squash, carrot etc.) and other categories do not have a significant effect on the symptoms of premenstrual syndrome.<sup>24</sup> A study has mentioned the protective effects of fruits in alleviating the behavioral, psychological and physical symptoms of PMS. The reason could be the antioxidants role which are there in enormous amounts in the fruits.<sup>12</sup> A result of a triple blind control trial conducted in Iran has concluded that intake of vitamin B1 in diet can prevent physical symptoms of PMS. According to the study, calcium intake can help prevent both psychological and physical symptoms.<sup>25</sup> A study conducted in Japan has documented that PMS can be relieved by inclusion of fish in the diet.<sup>26</sup> A study published in 'Public Health Nutrition', has documented that diet rich in eggs, tomatoes, meat, fruits, condiments and nuts is associated with alleviating the symptoms of PMS.<sup>27</sup> Bahrami has reported that intake of vitamin D is associated with protective effects that can help prevent symptoms of premenstrual syndrome.<sup>28</sup> Results of a double blind controlled trial in Iran, has stated that Vitamin D and E are both beneficial in relieving the symptoms of premenstrual syndrome.<sup>29</sup> A randomized controlled trial published in 'British Journal of Nutrition', has documented that diet has an effect on the symptoms of premenstrual syndrome. Diet rich in grains can have beneficial effects on the symptoms of this condition. The inclusion of whole grains in the diet were found to have a beneficial effect in preventing and reducing the severity of PMS. Significant decrease in mood related symptoms ( $p < 0.01$ ) and highly significant improvement in behavioral ( $p < 0.003$ ), physical ( $p < 0.001$ ) and general symptoms ( $p < 0.001$ ) was mentioned<sup>30</sup> On the contrary, in a research conducted on students of Sharjah, it was documented that complex carbohydrates do not have any effects on Premenstrual syndrome.<sup>12</sup>

### Diet causing premenstrual syndrome

Researches across the world have shown variable food items that contribute in the occurrence of premenstrual syndrome. A study in Turkey has revealed that alcohol, fast food, two or more cups of caffeine are associated with the development of premenstrual syndrome. It was also documented that breakfast skippers are also associated with PMS symptoms.<sup>31</sup> A research study has stated that while a female is having PMS, she develops the craving to eat sweetened foods.<sup>32</sup> A study conducted on the college girls has documented that food items like caffeine, junk food and high sugar content food contribute in producing the symptoms.<sup>13</sup> Parallel findings were reported in a study conducted in Sharjah. In the luteal phase of the cycle the females had craving for sweets like Baklava, Kunafa, chocolates and other sweetened food items.<sup>12</sup> Comparable findings were mentioned in a study conducted on the university students. The students with PMS have the habit of consuming refined sugar, fatty meals, fast food and chocolates. The students' diet was lacking essential vitamins and minerals.<sup>15</sup> A case control study has reported analogous findings. The western diet which includes burgers, soft drink and processed meat contributes in the development of PMS with highly significant p value of  $< 0.001$ .<sup>27</sup>

Various studies have observed the effects of caffeine in the diet. A research has documented that caffeine in the diet not only cause the PMS but also prolongs its duration. It was recommended that a week before the start of menstruation the consumption of the caffeine should be decreased or finished.<sup>33</sup> Another study conducted in Manipal, has reported that intake of caffeine contributes in the aggravation of symptoms of PMS.<sup>34</sup> Contradictory results were documented in a prospective study published in 'American Journal of Clinical Nutrition'. The research reported that caffeine intake does not effect premenstrual syndrome.<sup>35</sup> Likewise, another research has documented that caffeine was not shown to have an effect on the PMS symptoms.<sup>12</sup> A quasi-experimental study conducted in India, has reported beneficial effects of calcium intake in decreasing the effects of PMS.<sup>36</sup>

### CONCLUSION:

Premenstrual syndrome is a common condition that is experienced by majority of females in reproductive age group all around the world. The prevalence of PMS varies among females belonging to different regions of the world. The presentation of symptoms is highly variable. There can be psychological, physical or behavioral features linked to premenstrual syndrome. Dietary intake of the individuals have been linked to the premenstrual syndrome symptoms. Consumption of diet loaded with whole grains, fish, fruits, vegetables, micronutrients like vitamin B1, D and E have protective effects against the development and severity of premenstrual syndrome symptoms. Intake of harmful food items like refined sugar, increased salt, fast food, sweetened

drinks, alcohol and chocolates are associated with increase in severity of the condition.

**Author Contribution:**

- Quratulain Javaid: 1. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data  
 2. Drafting the article or revising it critically for important intellectual content  
 3. Final approval of the version to be published  
 4. Agreement to be accountable for all aspects of work in ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Pharmacologic Advancement in Schizophrenia

Hafiza Tuseef Sayyar, Afshan Siddiq

### ABSTRACT:

Schizophrenia is a disorder of mental debility characterized by abnormal social behavior in which person is unable to recognize reality. The sign and symptoms are variable and heterogeneous. Due to the diverse symptoms and variable treatment response, it is challenging to treat. Recent advancements in genomic, epidemiology and neurosciences can provide the appropriate medicines and treatments for minimizing symptoms and consequences of schizophrenia. This literature review highlights the etiology, pathophysiology, neurotransmitter system, novel treatment and management of schizophrenia. The mainstay treatment of schizophrenic patients included antipsychotic drug with psychotherapy, social rehabilitation and job training.

**Keywords:** Antipsychotic drug, Schizophrenia, Pathophysiology, Neurotransmitter system

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### INTRODUCTION:

Schizophrenia is a chronic mental ailment which disturbs the numerous areas of brain and results in inconsistency of cognitive memory and behavior. It is a diverse disorder categorized by positive, negative and cognitive symptoms, often accompanied by signs of depression. The diagnosis of schizophrenia is purely based on clinical assessment of patient psychiatric history along with group of signs and symptoms.<sup>2</sup> The major signs and symptoms included hallucination (hearing voices), delusion (having false belief) and disordered thinking. Typically symptoms start gradually, usually occur in young adulthood and in many cases never resolve<sup>3-4</sup>. Prognosis of this diseases is unpredictable and merely 20% patient showed favourable treatment results. Many patients experience a psychotic episode along with long term symptoms and insufficient response to antipsychotic drugs<sup>5</sup>

### METHODOLOGY:

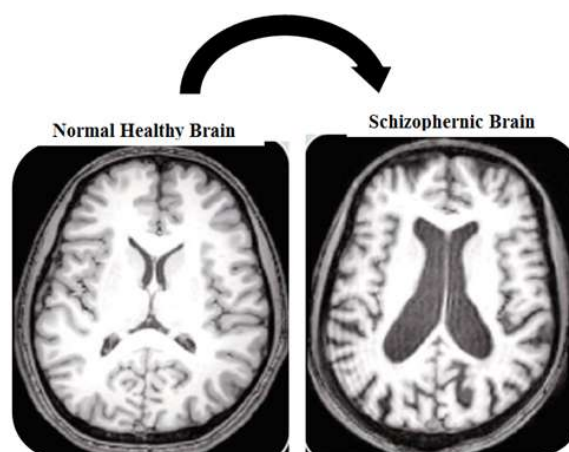
This review explained the etiology, pathophysiology and management of schizophrenia. The past 40 years literature search was employed by searching engines of Pub MED, Science direct, MEDLINE Google and Google scholar. Key word and phrases used were schizophrenia, causes, signs and symptoms, pathophysiology and treatment of schizophrenia. A total of 50 relevant articles/book chapter were used for comprehensively writing this review.

### Pathophysiology of Schizophrenia:

**Anatomical Defect:** The researches investigated the structural variations in the brain of schizophrenic patients, such as changes in volume and modifications of various parts mainly cortical, subcortical, global and white and gray matter of the brain.<sup>6</sup> Numerous neuropathological investigations and brain imaging showed changes in different areas and specific regions of brain in schizophrenic patients. Researcher investigated the delicate reductions in gray matter and irregularities of white matter in brain areas and circuits.<sup>7</sup> Many studies validated that the progression of gray matter reduction, particularly in the region of temporal lobe is associated with anti-psychotic drug treatment during the period of illness.<sup>8</sup> Several studies reported no confined anatomical variations and functional anomalies specifically associated with the disorder.<sup>9-13</sup>

**Dysfunctional Neurotransmission:** The complex pathological examination indicated abnormalities in the

Fig-1: Comparison of structural variations in Healthy versus Schizophrenic brain



**Hafiza Tuseef Sayyar**  
Senior Lecturer, (BUCPT) Department of Pharmacology  
Bahria University Medical & Dental College, Karachi  
Email: [touseef\\_sayyar@yahoo.com](mailto:touseef_sayyar@yahoo.com)

**Afshan Siddiq**  
Associate Professor  
Karachi University

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release of dopamine, serotonin, glutamate and GABA neurotransmitter that is leading cause of heterogeneous symptoms.<sup>14</sup> A number of brain imaging and pharmacological literature verified that psychotic symptoms such as delusion and hallucination are associated with dopaminergic neurotransmission dysfunction.<sup>15-17</sup> However the dysfunctional dopaminergic neurotransmission is unable to explain the complete range of this disorder because most of the schizophrenic like symptoms were also observed in other psychiatric conditions.<sup>18-21</sup> Many other pharmacological and physiological studies of brain imaging reported that cognitive dysfunctions were due to the disturbed glutamatergic function specifically NMDA-type glutamate receptor which is responsible to cause the para albumin positive interneuron dysfunction in the region of cerebral cortex and hippocampus and dysfunction of these spiking neurons may lead to cognitive dysfunction in schizophrenia.<sup>22</sup> Numerous symptoms of schizophrenia are due to unusual actions of dopamine receptor, especially at D2 site. Four main dopaminergic pathways involved to initiate these symptoms are as under.<sup>16,23</sup>

1. The mesolimbic pathway produces excessive dopamine responsible for positive symptoms of schizophrenia
2. The mesocortical pathway play role in initiating negative symptoms due to decrease in the level of dopamine.
3. The nigrostriatal pathway originating from substantia nigra and culminating at caudate nucleus
4. Tuberoinfundibular dopamine outcome blockage produces an elevated prolactin level and cause symptoms of amenorrhea, galactorrhea and decrease libido.

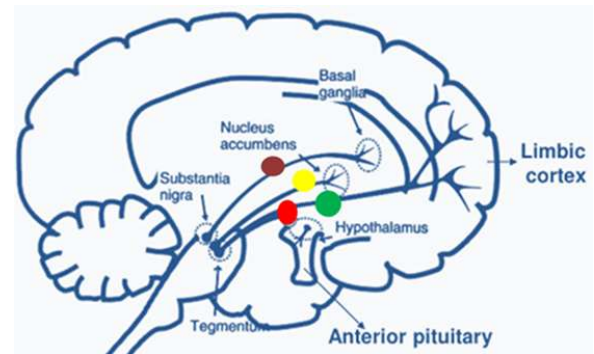
**Stress related Signaling Cascade:** The connectivity, maintenance and development of synapses is dependent on stress associated signaling cascade, especially oxidative stress and inflammatory processes. Microglia are responsible for synaptic preservation and destruction, particularly synaptic lopping during puberty, particularly synaptic lopping during puberty and the main histocompatibility complex I as well as the complement system involving synaptic plasticity are the examples of this. Moreover the investigation on preclinical models suggested piercing upsurge of parvalbumin interneurons, which are indicated mainly susceptible to produce oxidative stress and interruption of arrangement in myelination.<sup>24</sup>

**Causes of schizophrenia:** Numerous studies documented several factors such as genetic, environmental and family history (20-40%) played a role in the development of schizophrenia.

### 1. Genetic Factors

Investigations revealed that 80% development of schizophrenia is due to the hereditary difference in gene and 6.5% risk associated with this disease in first degree relative, 40% in monozygotic twins and if one parent affected; there

Fig 2: Brain pathways involved in schizophrenia



is 13% chance and if both parents then there is a 50% risk.<sup>25</sup> Many genes involved in schizophrenia showed unknown transmission and expression. Around 5% cases showed CNVs (copy number variants) specifically 22q11, 1q21 and 16p11 are comorbid with autism and intellectual disabilities. Occurrence of schizophrenia increases to 20 fold in these patients 20 fold.<sup>26-28</sup>

### 2. Environmental Factors

Many studies investigated that several environmental factors were also associated in the development of schizophrenia such as living environment, drug use and maternal stress increased the risks of schizophrenia.<sup>29-31</sup> Maternal stress causes hypermethylation in animal model lead to reduction of GABAergic neurons along with nutritional deficiencies as well as maternal obesity is also the potential risk features of schizophrenia. In both maternal stress and infection, inflammatory protein IL-8 and TNF alters the fetal neuro development.<sup>32,33</sup>

Researchers investigated that in some people intestinal tract dysfunction due to non-celiac gluten sensitivity of intestinal flora and elevated level of serum biomarkers such as anti-gliadin IgG and IgA antibodies is also accountable to cause schizophrenia.<sup>34</sup> Additional factors that play an important role are childhood trauma, being bullied or abused, critical and hostile parents, social isolation, unemployment, cultural discrimination, poor housing condition and death of parents. These are related to the increased risk of psychosis.

### 3. Drug causing Factors

Approximately half of the schizophrenic patients are drug and alcohol abusers. It has been reported that amphetamine, cocaine and minor amount of alcohol use can develop transient stimulant of psychosis via kindling mechanism. Cannabis is also the contributing factor among those at risk.<sup>35</sup>

### 4. Developmental Factors

Many other considerations such as hypoxia, stress, infection, malnourished mother during fetal development may increase the risk of schizophrenia in future.<sup>36</sup> On the other hand socioeconomic reasons, difficulty in childhood, first and second

generation immigrant credentials are also linked to schizophrenia.<sup>37</sup> Social pressure, such as financial sufferings may predispose person in the way of delusion, fearful and paranoid thoughts.<sup>38</sup> It has been proposed that most of the schizophrenic people are born in winters or spring; as there is 5 to 8% increased risk of in utero viral exposure during these seasons. Other infection such as *Toxoplasma gondii* and *Chlamydia* during pregnancy may also increase the risk of this disease.<sup>39</sup>

**Management and treatment of schizophrenia:** Schizophrenia is managed and treated with antipsychotic medication along with the psychological session, therapies, social support and rehabilitation. According to the survey report, 20% of patients showed positive result after first episode of psychosis while 35% patient showed relapse.<sup>40</sup>

**Pharmacological treatment:** Neuroleptic drug both typical (first generation) antipsychotic drug including Chlorpromazine, Prochlorperazine, Thioridazine, Haloperidol, Fluphenazine and atypical (second generation) including Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone and Ziprasidone has been used for many years for acute and long term treatment of schizophrenia.<sup>41</sup> The mechanism of antipsychotic drug to antagonize dopamine D<sub>1-5</sub> receptors, but second generation drug, particularly act on serotonin 5HT receptor to reduce neurotransmitter binding in forebrain and create feedback loop that cause the release of more dopamine after taking drug.<sup>42</sup> The goal of the antipsychotic drug treatment is to manage psychotic symptoms at the lowest possible dose because these medications cause less severe side effects. The second generation antipsychotic drug is preferable over first generation due to more benefits and less extrapyramidal adverse effects.<sup>43</sup> The physician and psychiatrist prescribe a combination of drugs with different doses to achieve best possible results. Patient willingness and cooperation is also necessary for successful treatment.<sup>44</sup>

**Psychological intervention:** Psychotherapy may help to normalize schizophrenia by individual therapy to manage this illness through thought pattern and with the help of this schizophrenic patient learn to cope with stress and early warning sign of relapse can be identified.<sup>46</sup> Social skills training can improve the communication and social interaction to provide support and educate families to deal with schizophrenia.<sup>47</sup> Vocational rehabilitation centers help and prepare people to find jobs. However, during periods of crisis severe symptoms may require the hospitalization and electro-convulsive therapy may be considered for patients having depression.<sup>48-50</sup>

## CONCLUSION:

It is important to check the contributory factors in schizophrenia patient, including genetic and non-genetic since the incidence rate of this disease is rapidly increasing. Currently, many treatment options are available to treat with schizophrenia, but future modeling is required

for the treatment resistant patient. Several treatment options are developing where newer drugs and their combination has revealed promising results with or without non pharmacological therapy. Further investigations are required to discover and implement advance remedies for the treatment of schizophrenia.

### Author Contribution:

Hafiza Tuseef Sayyar: Perceived the idea, write-up of manuscript  
Afshan Siddiq: Supervised the whole project, examined the manuscript

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## Drug Induced Hepatotoxicity – An Ongoing Challenge

Mehr Fatima, Syed Ijaz Hussain Zaidi

### ABSTRACT:

Drug induced liver injury is one of the main factor of liver failure and acute liver damage world wide with high incidence in western countries. Liver injury can be intrinsic (dose dependant) or idiosyncratic (dose independent). However idiosyncratic type is considered to be mainly responsible for drug induced liver damage. Binding of reactive metabolites of drugs to tissue proteins and oxidative stress is the possible cellular mechanism involved in this process. Moreover, some antibiotics, anti-epileptics, nonsteroidal anti-inflammatory drugs etc are more likely to induce liver damage in high risks groups that includes females, elderly and obese people. HLA halotype and variation in protein expression also plays an important role in this context. Various studies are available regarding clinical features, histopathological features, diagnosis and management related to antibiotics and acetaminophen induced liver damage. N acetylcysteine is commonly available antidote for drug induced hepatic damage. Role of other pharmacological agents as an antidote requires further studies. However, liver transplantation should be considered with drug induced lethal liver failure.

**Key Words:** Liver injury, drug induced liver damage, antibiotic, liver histopathology, liver enzymes, antidote.

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### INTRODUCTION:

Drug induced liver injury can be stated as the damage to liver tissue caused by several medicines, plants and exogenous chemicals excluding other etiological factors which affects liver enzymes and liver function. In USA, drug induced liver damage is the main contributory factor to acute hepatic damage and it accounts for 13% of acute hepatic failure cases.<sup>1</sup>

Liver is the main organ involved in detoxification of drugs. Liver health can be affected by drugs either by intrinsic (dose dependent) or idiosyncratic (dose independent manner). Some drugs like Acetaminophen can induce damage if given in excessive dosages. Idiosyncratic drug induced liver injury is thought to be unpredictable and accounts for most cases of drug induced liver injury. Patients with underlying liver diseases can have the possibility of having idiosyncratic drug induced liver damage. Data regarding drug induced liver injury cases have been found in Western as well as Asian countries. It is reported to have the annual incidence of 13.5 cases per 100,000 in France, 12 cases per 100,000 in Korea and 19.1 cases per 100,000 in Iceland.<sup>2,3</sup> Considering that information on drug induced liver injury is not available in the form of a database or national registry in Pakistan, a retrospective study conducted at a major tertiary care hospital

in Pakistan identified 31.1% cases of drug induced liver injury on the basis of Roussel Uclaf Causality Assessment Method (RUCAM), over a 7 year period.<sup>4</sup> Many drugs have been withdrawn from the market due to this reason. Since drug induced liver injury is common reason of liver failure in USA and Europe, practice guidelines have been set up by American college of Gastroenterology regarding diagnosis and management of idiosyncratic drug induced liver injury.<sup>2,3</sup>

Earlier studies showed that the drugs were either removed from the market such as Ximelagalan, Troglitazone, Bromlenac, Benoxaprofen or received black box warning such as Valproic acid, Ketoconazole, Isoniazid, Rifampin, Nicotinic acid, Dantrolene, Teletromycin, Infliximab, Nefazadone due to their hepatotoxic effects that might be dose dependant.<sup>5</sup>

Drug induced hepatotoxicity is an ongoing challenge that needs specific addressing particularly in our part of world as available literature is scanty.

### METHODOLOGY:

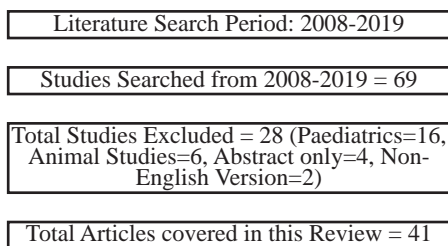
Different search engines like Google scholar, Pubmed and Cochrane library were used for writing this review. Around 69 articles were found for the year 2008-2019. From these 16 were of paediatrics, 6 were animal studies, 4 were abstract only, 2 were in non English version and therefore were excluded. A total of 41 articles are used in the write up of this review focusing on drugs that commonly caused hepatotoxicity in adults and obese individuals. The key words used were liver injury, liver enzymes, drug induced liver injury, antidote, liver histopathology and antibiotics and liver injury.

**Mehr Fatima** (M.Phil Postgraduate Student)  
Senior Lecturer, Department of Pharmacology  
Bahria University Medical and Dental College, Karachi  
Email: mehr\_fatima@yahoo.com

**Syed Ijaz Hussain Zaidi**  
Associate Professor, Department of Pharmacology  
Bahria University Medical and Dental College, Karachi

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### FLOW CHART



### LITERATURE REVIEW:

#### Risk Factors For Drug Induced Liver Injury:

Females and elderly people, patients with chronic liver disease and HIV infection are more prone to be affected by drug induced liver injury. However, data available regarding these factors is insufficient. Females are more vulnerable to the effects of some drugs. Drug induced liver damage in females have been linked to some specific drugs like Nitrofurantoin, Azithromycin, Erythromycin, Flucloxacillin, Amoxicillin, Fluoroquinolones, Minocycline and Isoniazid. Different age groups are being affected by different drugs. Isoniazid is more likely to cause liver damage in old aged patients whereas Aspirin and Valproate is a risk factor for younger age group. Since processes of pharmacokinetics including absorption, metabolism and elimination varies, in elderly might be the factor of drug induced liver injury. A prospective study conducted on Spanish population also reported increased risk of drug induced liver damage in older women which might be due to loss of cell repair and regeneration processes as the result of aging. Patients with underlying liver disease as a risk factor is arguable but patients with Hepatitis B, Hepatitis C taking anti-tubercular and antiretroviral drugs are at risk.<sup>6,7,8</sup> Alcohol intake and diabetes is another risk factor for severity of drug induced liver injury.<sup>9</sup>

Risk of drug induced liver injury is also high in obese people. Drugs like Corticosteroid, Methotrexate, Tamoxifen, Tetracycline and Nucleotide reverse transcriptase inhibitors may worsen non alcoholic fatty liver disease in these individuals. Drugs like Losartan, Ticlopidine, Acetaminophen, Omeprazole, Halothane and Isoflurane are more likely to induce acute liver damage in obese individuals.<sup>10,11</sup>

#### Mechanism of Drug induced liver injury:

Intrinsic type of drug induced liver damage occur in acetaminophen toxicity. In this type, liver is damaged is by the production of large amount of reactive metabolite which exceeds liver capacity to convert it into nontoxic compounds as well as it depletes Glutathione levels which finally leads to hepatotoxicity.<sup>12,13</sup>

Mechanism of liver injury by idiosyncratic type can be classified into two types; Hypersensitive- type reactions (immunologic) and Metabolic type of injuries.<sup>12,13</sup>

Hypersensitivity type of drug induced liver injury is reported to occur in 23 to 37% of all idiosyncratic reactions. It is produced due to covalent binding of reactive metabolites of drugs to tissue proteins which provoke immune mediated reaction and direct hepatic damage. Metabolic mechanism mainly involves mitochondrial injury and oxidative stress. Liver damage can occur as a consequence of oxidative stress. Since reactive oxygen specie damages nucleus and main enzymes, an immune mediated liver injury may happen. This can be a result of imbalance between free oxygen radical formation and cellular defense mechanism.<sup>12,13</sup>

Enzymes of phase 1 and 2 expression and cytokine expression are also linked to hepatotoxicity induced by drugs. Formation of toxic metabolites of anti tubercular drugs is related to CYP2E1 enzyme, while toxic metabolite of Diclofenac is CYP2C8 enzyme. It is also suggested that there is an association between antibiotic induced hepatotoxicity and HLA halotypes. Studies on genome showed that Amoxicillin is related to 10 times increase in risk of developing hepatotoxicity due to HLA halotypes HLA-DRB1 \*1501-DRB5, \*0101-DQB1 \*0602. Not only this, variation in protein expression of different drug transporters has been reported to contribute in hepatotoxicity induced by drugs. In this context, multi drug resistant protein and bile salt export pump have been associated with drug induced hepatotoxicity.<sup>14</sup>

#### 1) Antibiotic induced hepatotoxicity:

Studies conducted in western countries have shown Amoxicillin as the common antibiotic affecting liver conditions leading to hepatic damage.<sup>15</sup>

In a study conducted in Iceland for the period of 2 years, Amoxicillin was determined to be one of the most common drug causing liver injury. A study was conducted on 35252 patient in Iceland. 1 out of 2350 outpatients had liver injury whereas risk of developing liver injury was higher in inpatients. 1 out of 729 inpatients treated with Amoxicillin also developed liver damage. There was no obvious reason for this variation in incidence of inpatient versus outpatient amoxicillin treated groups. However limited data regarding route of drug administration is available. It was reported that Amoxicillin-clavulanate caused delayed and late type of liver injury with mean latency of 16 and 30 days from the beginning of the therapy.<sup>16</sup>

Although clinical feature of hepatotoxicity caused by Amoxicillin varies but jaundice was the most observed symptom. Other predominant symptoms were tiredness, anorexia and itching. In a large cohort study (n=1038) conducted in Spain, with 11% representing Amoxicillin induced hepatic injury being the main cause of idiosyncratic drug induced liver injury. Liver enzyme (ALT and AST) levels reached at the highest level after 4-5 days where as ALP and total bilirubin at the highest level at around 17 and 12 days. Cholestatic features were more marked on liver

biopsies. 2 participants were reported to have asymptomatic elevation of liver enzymes. Very few subjects were in need of liver transplantation.<sup>17</sup> Hepatocellular hepatic granuloma were caused by amoxicillin induced hepatic injury.<sup>18</sup>

## 2) Azithromycin:

Azithromycin belongs to macrolide class of antibiotic. It is used for the treatment of mild to moderate sinopulmonary diseases. It causes idiosyncratic hepatotoxicity with variable clinical presentation. In a prospective cohort study, the most common symptoms were jaundice, abdominal pain, nausea and pruritis. In a study, Azithromycin was given for 4 days (mean duration). Liver enzymes levels were found to be deranged 14 days after the cessation of azithromycin. Liver biopsy showed hepatocellular liver injury (56%), cholestatic (33%) and mixed pattern (11%). Antinuclear antibodies were more likely to be present in patients with hepatocellular injury than with cholestatic or mixed type.<sup>19</sup>

## 3) Fluoroquinolones:

Fluoroquinolones are a widely used antibiotic due to better coverage against microbes and good efficacy. Previous studies reported that they cause idiosyncratic drug injury. Common clinical features with liver injury caused by fluoroquinolones were rash, fever and increased eosinophilia. Fluoroquinolones caused liver damage with sudden onset. It had short latency period. Liver biopsy showed hepatocellular, cholestatic and mixed type of liver injury. Corticosteroids were effective for patients with features of hypersensitivity. Patients with Fluoroquinolones induced liver damage rarely developed acute and chronic liver failure. Moxifloxacin, Levofloxacin and Gatifloxacin causes acute liver failure with the incidence of (2.1,6.1,6.6 per 10 million prescriptions), this is less than Amoxicillin – clavulanate (10 in 1 million prescription).<sup>20</sup>

## 4) Nitrofurantoin:

A prospective cohort study reported that Nitrofurantoin induces liver injury with particular autoimmune features with female preponderance. Studies indicated that time from initiation of therapy to the identification of deranged liver enzyme level that is latency period in Nitrofurantoin induced liver damage can be quite prolonged. It differs from 4 days to more than 5 years. Liver injury patterns were mainly hepatocellular.<sup>21,22</sup>

## 5) Isoniazid:

Tuberculosis is a chronic infectious disease of respiratory system affecting 9 million people world wide. Isoniazid is the drug of choice for latent tuberculosis. Other most commonly used first line anti tubercular drugs Rifampicin and Pyrazinamide can also induce liver damage. Researchers revealed that, in most cases, no symptoms can be produced in case of liver injury caused by isoniazid. It can be identified by measuring serum liver enzyme levels. However, previous studies showed that the main features of liver injury caused

by Isoniazid were nausea, vomiting, jaundice, fever, eosinophilia, malaise and fatigue. Changes in liver enzyme levels were detected as early as 1 week and as late as 9 months. Pattern of liver injury was hepatocellular with multilobular necrosis and mononuclear infiltrate which was difficult to differentiate from viral hepatitis. In case of long term treatment, isoniazid produced lupus like autoimmune reaction with raised antinuclear antibodies. Few studies found out the association between chronic hepatitis B virus and anti-tubercular induced liver injury. Hepatitis B virus carrier had more critical liver damage with anti-tubercular drugs as compared to non-carriers.<sup>23,24</sup>

Since isoniazid is mainly metabolized by enzyme N-acetyltransferase, slow acetylators are at higher risk of having isoniazid induced injury. Based on the expression of halotypes, patients were categorized as rapid, intermediate and slow acetylors as reported by earlier studies. Slow acetylators were deprived of the NAT2\*4 allele or other rapid NAT2 alleles whereas rapid acetylators had homozygotes NAT2\*4 and intermediate acetylators possessed the NAT2\*4/\*5B, \*4/\*6A, or \*4/\*7B halotypes. NAT2\*4, \*6 and \*7 alleles were present in many Asian populations. NAT2\*7 were peculiar allele in Asians, while NAT2\*5 was commonly found in Caucasians and Africans.<sup>25</sup>

## 6) Acetaminophen induced hepatotoxicity:

Acetaminophen is widely used analgesic and is one of the main cause of acute liver failure. It is commonly available over the counter drug. Almost 30,000 people are hospitalized annually in USA for treatment of paracetamol intoxication. Paracetamol induced liver toxicity is mainly responsible for almost 48% of liver failure diagnosis. It occurs due to formation of large amount of reactive metabolite N acetyl p benzoquinone (NAPQI). This depletes Glutathione level and its capacity to convert it to non toxic metabolite.<sup>26,27</sup>

Symptoms of acute liver failure were anorexia, abdominal discomfort, jaundice and fever progressing to hepatic encephalopathy 0-7 days after the onset of jaundice in case of acetaminophen toxicity.<sup>27</sup> Studies have revealed that patients may present with the specific signs of decreased level of consciousness, increased serum level of acetaminophen and lactic acidosis several hours after acetaminophen intake. NAPQI disrupts mitochondrial function which can cause early lactic acidosis.<sup>27,28</sup>

A review study has reported differences in metabolic enzyme level due to genetic variability as the risk factor for paracetamol intoxication. Randomized control trial of 145 patients reported that there was an association in Alanine aminotransferase level at the dose of 4 g paracetamol administered for 4 days.<sup>29</sup>

Another review article has reported common hepatic damage caused by drugs. Isoniazid, disulfiram and acetaminophen causes acute hepatic necrosis. Nitrofurantoin and Minocycline causes drug induced autoimmune hepatitis.<sup>30</sup>

## DIAGNOSIS:

Diagnosis is mainly based on complete history, patient age and sex, history of drug reactions, history of liver disease and drug abuse, main disease for which the drug was prescribed, drug exposure, other medications if used for 3 months before the onset of liver injury. Signs and symptoms include weakness, abdominal pain, dark urine, presence and absence of jaundice, fever, liver tenderness etc. Abnormal liver biochemistry (Bilirubin, ALT, ALP, INR, PT), laboratory test to be done to exclude other causes (IgM anti-HAV, IgM anti-HBc, HBs antigen, anti-HCV. Antinuclear antibodies, and liver imaging (abdominal ultrasound, CT and MRI) are used to diagnose liver damage, however liver biopsy is not necessary.<sup>31,32,33</sup>

Currently many new serological, biochemical and histological biomarkers are used to detect drug induced liver damage. These included apoptosis-cytokeratin-18 fragments (CK-18Fr), soluble Fas and Fas ligand (sFas/sFasL), soluble TNF- $\alpha$  and TNF receptor related (sTNF- $\alpha$ /sTNFR), and soluble TNF-related apoptosis-inducing ligand, cell necrosis-related full-length CK18, high-mobility group protein B1, and micro RNA, specific mitochondrial biomarkers, circulating autoantibodies targeting drug-metabolizing enzymes such as cytochrome P 450, biomarkers indicating cholestasis, as well as genetic biomarkers to drug induced liver damage, such as the genetic polymorphisms of HLA, drug metabolizing enzymes and drug transport proteins. However, these markers showed poor specificities for the diagnosis of drug induced liver injury, and their value for clinical use still needs to be further tested. Moreover only acetaminophen protein adduct was a peculiar biomarker of acetaminophen related liver injury.<sup>34</sup>

## Management of Drug Induced Liver Injury:

Following are main principles of management for drug induced liver injury;

- 1) Withdrawal of drug immediately if it was not the critical drug used for the treatment of any specific disease. Timely withdrawal of the drug affecting liver is important. It was estimated that 95% of the patient responded to drug withdrawal.<sup>34,35</sup>
- 2) Based on clinical signs and symptoms, use appropriate anti-inflammatory and hepatoprotective agents to treat drug induced liver injury.<sup>34</sup>
- 3) Corticosteroids had also been used to treat drug induced liver injury. But so far no controlled trial has been reported.<sup>35,37</sup>
- 4) FDA has recommended N-acetylcysteine as the antidote for all types of drug induced liver injury in 2004. It should be administered at the dose of (50-150mg/kg) for 3 days. Previous studies reported its role in early stage of liver failure. However further investigations are required to determine its role in moderate and severe liver damage. In case of acetaminophen induced liver damage, use of N

-acetylcysteine within 24 hours of acetaminophen ingestion is found to be effective.<sup>35,36,37</sup>

5) Liver transplantation is required for those cases of drug induced acute liver failure who presented with decompensated cirrhosis, hepatic encephalopathy or coagulation disorders.<sup>34</sup>

6) In an immune mediated liver injury, role of glucocorticoid and uricosuric agents were not yet clear. Moreover, in patients with no improvement after drug withdrawal, corticosteroids may be effective with allergic features of drug induced liver injury.<sup>38</sup>

7) In case of non acetaminophen induced liver injury, use of N acetylcysteine is restricted. Molecular adsorbent recirculating system and plasma exchange in management of drug induced liver injury has demonstrated its effectiveness but it still requires further work up.<sup>39</sup>

8) The active ingredient of milk of thistle, Silmyrin has shown protective effects in such patients.<sup>40</sup>

So far, few preclinical studies have also revealed the role of some medicinal herbs and food in preventing drug induced liver injury which is an open avenue for future.<sup>41</sup>

## CONCLUSION:

Since drug use can lead to hazardous and troublesome effects for body tissues, especially liver which can be fatal, therefore, drug use should be rationalized in order to prevent drug induced liver damage. Moreover, early diagnosis and management of individuals who are either at high risk or exposed to drugs, might be helpful in preventing serious consequences of liver damage. Furthermore, studies regarding drug induced liver damage in our setup are lacking and more research work should be carried out in order to explore role of drugs and their antidotes. Thus, the matter of drug induced hepatotoxicity is an on-going challenge for health professionals at preventive, diagnostic and management horizons.

### Author Contribution:

Mehr Fatima: Selection of topic, introduction & literature review  
Syed Ijaz Hussain Zaidi: Abstract writing, conclusion and methodology

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# Joubert Syndrome Diagnosed at 16+6 Weeks Gestation and Molar Tooth Sign by 3D Modality

Prabha Sinha, Shabnum Sibtain

## ABSTRACT:

Joubert's syndrome is a rare genetic disorder. It is an autosomal recessive neuro-developmental disorder involving mid and hind brain. This report describes a fetus at gestational age 16weeks+ 6 days, who presented with characteristic Molar tooth sign on the antenatal scan. This sign is a salient feature of Joubert syndrome (JS). Mostly the diagnosis of JS is made after birth. Few cases are diagnosed prenatally by ultrasound.

**Key words:** Joubert syndrome, mortality, genetic disorder, brain malformation

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## INTRODUCTION:

Joubert syndrome (JS) is a rare autosomal recessive genetic disorder.<sup>1</sup> It affects the area of brain involved in balance and coordination. It is clinically heterogeneous associated with retinitis pigmentosa and multiorgan involvement. JS affects 1 in 80,000-100,000 newborns.<sup>2,3</sup> It is likely to be underdiagnosed. Variety of genes disorder cause Joubert's syndrome. It is commonly found in Arab, Jewish, French, Canadian, and Netherland populations. It is autosomal recessive but it can rarely be inherited as an X-linked recessive pattern. The recurrence risk is 25% in most families.<sup>4</sup>

Joubert syndrome is primarily nervous system disorder with cerebellar vermis hypoplasia or absence. There is malformation of brain stem. This leads to defect in axon signals. In addition to neurological symptoms there may be hypoplastic phallus, renal cysts, cleft lip or palate, polydactyly and tongue abnormalities. Prenatal sonographic findings are relatively nonspecific. The molar tooth sign is observed on 3D ultrasound or MRI scan; and is a salient feature of this disease.

**Case:** A 28-year-old, G8 P5+2 had consanguineous marriage. History was significant for gestational diabetes, controlled on diet. She has four healthy children and one child with Vermis Agenesis and Polyhydramnios. The family history was noteworthy for recurrent fetal loss with hydrocephalus.

She was referred to Fetal Medicine Unit for early anomaly scan at 16 weeks + 6 days due to previous history. On ultrasonography scan; characteristic molar tooth sign, absent

cerebellum and vermis, frontal bossing with hypertelorism, dilated anterior horn of the lateral ventricle, enlarged cisterna magna with posterior encephalocele, kyphoscoliosis and bilateral renal pelvic dilatation were observed. The diagnosis of Joubert syndrome was made based on these findings and the history of previously affected child. The couple was counselled about the findings and outcome. Parents decided for termination of pregnancy at 17 weeks of gestation. Sample from aborted fetus was consistent with the diagnosis of Joubert syndrome type 21. Genome sequencing confirmed CSPP1 (NM\_024790.6; exon 17,) homozygous likely pathogenic variant c.2131\_2132del p. (Ser711Leufs\*11)

## DISCUSSION:

Joubert syndrome a genetically heterogenous disorder was first described in 1968.<sup>5</sup> The disorder is characterized by molar tooth sign<sup>6</sup> due to thickened cerebellar peduncles. A cleft is visualized between the cerebellum. The sign can be visualized on a 3D ultrasonography scan or MRI scan. This syndrome is a result of malformation of the brain. The diagnosis of this condition is based on the physical symptoms and radiological findings, and confirmed by testing for specific genetic mutations. The symptoms of the disease present in very early childhood, primarily involving neuromuscular system along with developmental delay. Other associations are disorders of kidney, liver and eyes. Mutation of 21 genes has been observed in relation to JS.<sup>7</sup> Early prenatal genetic testing is advised for at risk couples. Fetal brain imaging can provide useful information in the last trimester.<sup>4,8</sup>

The management of this syndrome is multidisciplinary. The neonates have respiratory and feeding difficulties and these problems need to be addressed as priority. Cognitive behavioral therapy is required in young patients for neuropsychological support and rehabilitation.

The prognosis of JS varies and is dependent on the extent and severity of organ involvement. Mostly the diagnosis of JS is made after birth. Few cases are diagnosed prenatally by ultrasound. The diagnosis is usually missed because of

**Prabha Sinha**  
Consultant Tawam Hospital  
Abu Dhabi, UAE.

**Shabnum Sibtain**  
Assistant Professor  
Azra Naheed Medical College, Lahore, Pakistan  
Email: s\_sibtain@hotmail.com

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nonspecific features that can occur in Dandy-Walker malformation and other cranial syndromes.<sup>9</sup> The ultrasound is the primary screening method to detect posterior fossa abnormalities and diagnosis of JS is confirmed on MRI.<sup>10</sup> The ultra-sonographer may just observe the nonspecific features due to lack of knowledge and rarity of this syndrome.

There is lack of enormous data on the long-term outcome of children affected by JS. Children with associated complications have poorer outcome. The sonographic findings in fetuses with JS are relatively nonspecific in the prenatal period. In this case molar tooth sign was identified at 16+6 weeks in 3D scan. The pregnancy was terminated at 17 weeks because of poor outcome. Early diagnosis is of great value in Islamic country as termination of a pregnancy is not feasible beyond 18 weeks gestation. Previous history with ultrasound findings helped to formulate early diagnosis. Careful history is important to assess risks of JS and optimal management is multidisciplinary. Our findings of JS in early stages are mostly the same as found in literature to date. The risk of recurrence is 25% in most families.<sup>11</sup>

**CONCLUSION:**

Early prenatal detection of JS can lead to early termination of pregnancy. This can reduce the emotional and financial stress on the couple. These prenatal sonographies can also

help the differentiate mid and hind brain abnormalities. Therefore, a protocol to monitor the pregnancies at risk of JS should be followed. It can be achieved by serial ultrasonography performed by a specialist followed by MRI. The prenatal genetic analysis of couple and fetus is useful in making a definitive diagnosis. The affected couple should be counselled in this regard. JS is associated with high mortality, identifying the cause and time of death will help in development of guidelines to improve the outcome of JS.

**Author Contribution:**  
 Prabha Sinha: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work  
 Shabnum Sibtain: Drafting the work or revising it critically for important intellectual content

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Figure 1: Molar Tooth sign on Ultra-sonography scan

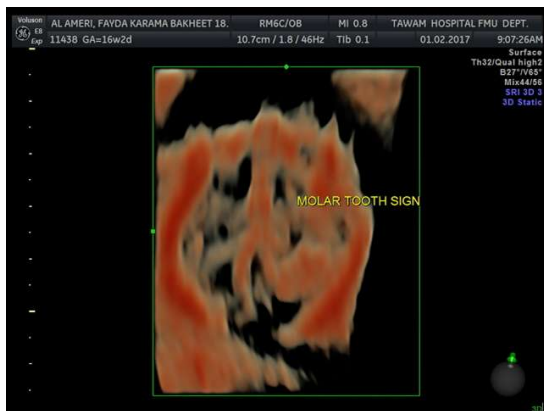


Figure 2: Fetal Ultrasound at 16+6 weeks Gestational age showing agenesis of vermis.





## Covid-19: The Wuhan Pandemic

Tooba Masood

### ABSTRACT:

Coronavirus belongs to a large family of viruses that usually cause respiratory illness in human beings that can be mild and severe depending upon the strain. In 2002, the outbreak of SARS (severe acute respiratory syndrome) reported more than 8000 infected cases with 774 mortalities. In 2012, the outbreak of MERS (middle east respiratory syndrome) infected around 2494 people and 858 deaths were reported according to the WHO. In January 2020, a new strain of coronavirus named 2019-nCoV has been identified in China. The number of confirmed cases has been increasing reaching 5,593,631 cases worldwide with 353,334 deaths up till 28<sup>th</sup> May 2020 according to WHO situation report-129. Concerned authorities are working on minimizing its spread. Prevention guidelines have been released by WHO, hoping to control the transmission and save the world from the effects of this novel virus.

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### INTRODUCTION:

Coronaviruses are a large group of viruses named for the crown-like spikes on their surface. There are four main sub-groupings of coronaviruses, known as alpha, beta, gamma, and delta. The identification of human coronavirus was first seen in the mid-1960s. The coronaviruses that are common and can infect people include 229E, NL63, OC43, HKU1. Other human coronaviruses are MERS-CoV (causes Middle East Respiratory Syndrome), SARS-CoV (causes Severe Acute Respiratory Syndrome) and 2019 Novel Coronavirus (2019-nCoV) that has been recently identified in China.<sup>1</sup>

### OUTBREAK OF NOVEL CORONAVIRUS (2019-nCoV):

On 31<sup>st</sup> December 2019, WHO was informed about the growing cases of pneumonia in Wuhan City, Hubei Province of China. The causative agent was not identified till 7<sup>th</sup> January 2020 when Chinese authorities isolated and confirmed the virus which was identified to be a Coronavirus and named as Novel Coronavirus “2019-nCoV” because it’s a new strain that was previously not identified in humans. Later, WHO renamed it to SARS-CoV-2 to relate it to the disease symptomatology. On 12 January 2020, China shared the genetic sequence of the novel coronavirus for countries to use in developing specific diagnostic kits.

It was suspected that the outbreak of this virus was initially associated with the exposure in one seafood market in Wuhan. The exact host was not identified then but, its spread has thought to be viral from the improper handling of animals which is further transmitting among humans.<sup>2</sup> Later, the origin of the SARS-CoV-2 genome has been linked to bats akin to the SARS-CoV-1 and MERS-CoV viruses.<sup>3</sup>

After SARS and MERS outbreak in the past, SARS-CoV-2 is the third coronavirus to emerge in the human population in the past two decades — an emergence that has put global public health institutions on high alert.<sup>4</sup>

The number of lab-confirmed cases of Coronavirus is increasing since then and reaches beyond the border of China involving 213 countries and territories around the world. The statistics about the number of confirmed cases globally by 28<sup>th</sup> May 2020 reported by WHO situation report-129 is given below in the table.<sup>5</sup>

### VIROLOGY:

SARS-CoV2 is from the beta Coronavirus family, single-stranded RNA, enveloped virus about 50-200 nm in diameter. It contains an encoded structural protein called Spike Glycoprotein (S) that bind to angiotensin-converting enzyme 2 (ACE2) receptor on type II pneumocyte. The entry of SARS-CoV-2 into the type II pneumocyte is via endocytosis and then multiplies in the cytoplasm further leading to apoptosis. The RNA from the SARS-CoV-2 will be recognized by the pattern recognition receptor or toll-like receptors leading to a chemokine surge which causes neutrophil migration and activation. This causes the destruction of the alveolar-capillary walls and fluid leaks into the alveolar sacs.<sup>6</sup>

### MODE OF TRANSMISSION:

COVID-19 is thought to be transmitted from improper handling of animals to humans and further spreading to other humans directly or indirectly.

- Direct transmission to other person can be through respiratory droplets (> 5-10 mm in diameter) and can easily infect others in close contact of 1 meter distance when the infected person cough or sneeze.
- Indirect transmission can be through touching the surfaces or objects in the immediate environment of an infected individual and touching either their mouth, nose or eyes without washing hands properly.

**Tooba Masood**  
Lecturer, Department of Physiology  
Bahria University Medical and Dental College, Karachi  
Email: [toobamasood@live.com](mailto:toobamasood@live.com)  
Received: 29-Jan-2020  
Accepted: 25-Jun-2020

**Situation in numbers (by WHO Region)**  
Total (new cases in last 24 hours)

<b>Globally</b>	5,593,631 cases (104505)	353,334 deaths (4221)
<b>Africa</b>	89,592 cases (3777)	2370 deaths (62)
<b>Americas</b>	2,556,479 cases (60,254)	148,412 deaths (2584)
<b>Eastern Mediterranean</b>	461,824 cases (12,234)	11,621 deaths (169)
<b>Europe</b>	2,079,924 cases (18,096)	177,331 deaths (1105)
<b>South-East Asia</b>	227,611 cases (9088)	6630 deaths (271)
<b>Western Pacific</b>	177,460 cases (1056)	6957 deaths (30)

• Airborne transmission may be possible in specific circumstances and settings in which procedures or support treatments that generate aerosols are performed; i.e., endotracheal intubation, bronchoscopy, open suctioning, manual ventilation before intubation, tracheostomy, and cardiopulmonary resuscitation etc.<sup>7</sup>

**SYMPTOMS:**

Symptoms may appear in 2-14 days after exposure to the virus and include:

Fever, cough, sore throat, dyspnea, runny nose, muscle pain, headache, malaise, new loss of taste and smell, nausea and vomiting. If the infection spreads into the lower respiratory tract it can develop pneumonia, sepsis and can lead to death.<sup>8</sup>

**SUSCEPTIBILITY OF INFECTION:**

Patients with heart disease, weak immunity, infants or older adults > 60 years of age are more prone to get this infection.<sup>9</sup>

**INVESTIGATIONS AND DIAGNOSIS:**

As the coronavirus causes respiratory illness, the laboratory tests are done on respiratory specimens (nasopharyngeal swabs, sputum etc) and serum used to detect human coronavirus. Its been reported that the previous outbreak of SARS and MERS were also confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR). So, SARS-CoV-2 is also reported to be diagnosed by the genetic code sequencing via RT-PCR.<sup>10</sup> Although the sensitivity of PCR is around 66-80% which is one of the reasons of having false negative results.

In one of the largest research carried out in China showed CT-chest had a 95% sensitivity in making an early diagnosis of COVID-19 through the identification of ground-glass opacities. But it has some cons including huge economic burden on the healthcare resources and the potential to contaminate the CT scanners.<sup>11</sup>

**PREVENTION:**

There is no vaccine available for SARS-CoV-2. Following three steps altogether will help prevent the spread of COVID-19.

1. Social distancing.
2. Hand washing.
3. Wearing mask.

Social distancing will help keep a healthy person less prone to get infection.

Washing hands with soap and water and using alcohol-based sanitizer will further add protection against this disease.

Wearing mask will keep an infected person from spreading the virus to healthy individual and also helps in keeping your hands away from touching your face (indirect route of infection).

Using a disinfectant to clean the frequently used objects by the infected individuals will add sugar on top.<sup>12</sup>

**TREATMENT:**

There is no specific antiviral treatment or vaccine for this new strain virus. In mild cases, only supportive care can help relieve symptoms i.e; resting, adequate hydration, gargling and the use of antipyretics.<sup>13</sup> In severe cases, use of supplemental oxygen at 5L/min and SaO<sub>2</sub> of > 90% should be maintained. According to the WHO situation report-129, the use of antibiotics for treatment of acute co-infection in mild to moderate COVID-19 cases has not been recommended. Antivirals including interferon  $\alpha$  (IFN- $\alpha$ ), lopinavir/ritonavir, chloroquine phosphate, ribavirin, arbidol, favipiravir, remdesivir and darunavir should not be administered as treatment of COVID-19 outside the context of clinical trial. In hospitalized patients, prophylactic administration of heparin according to local and international standards to prevent venous thromboembolism can be helpful.

Hoping to have an effective drug or vaccine against this new virus soon.<sup>14</sup>

**SCHOOL'S OUT, BUT CLASS'S ON: ROLE OF SOCIAL DISTANCING IN EDUCATIONAL INSTITUTES**

As it has been cleared from all the guidelines provided by the WHO and CDC, that maintaining social distance and staying at home will keep a person at a very low risk of attaining the COVID-19. COVID-19 has become a challenge for the education system as well, affecting all the students globally. In order to prevent the spread of disease rapidly, government has decided to keep the institutes closed till further notice depending upon the country's situation. To contain this virus from further spreading we mainly need to avoid gatherings and completely follow social distancing.

To keep students at a low risk, we can't gather them in such large numbers in their educational institutions. Hence, online education has become trendy these days to overcome the academic loss of students due to this pandemic. If education can be gained online sitting at home in safe environment then it should be promoted atleast till things fall into place.<sup>15</sup>

**CONCLUSION:**

Coronavirus is a large family virus whose outbreak as SARS and MERS caused an increased mortality rate in less time span. The new strain identified recently in January 2020 is spreading throughout the world. Looking at the statistics update, the number of infected cases and deaths is continuously increasing. It is crucial to minimize its spread and find the cure as soon as possible otherwise we will see an abnormally increased number in statistics of these cases which can affect the world badly.

**Author Contribution:**  
 Tooba Masood: Selection of Topic, writing abstract, introduction, history, mode of transmission, signs and symptoms, investigations & diagnosis, prevention, treatment & conclusion.

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## Challenges of Health Care Providers During the Crisis of Covid-19 Pandemic

Nadia Khalid, Kiran Mehboob Bana

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The world is facing the sweeping effects of COVID 19 that has started from Wuhan City. It exponentially spread globally and turned out to be an outrageous event for the economy and global health.<sup>1</sup> The major challenge for the health care professionals is to cope with mental and physical stress while dealing COVID-19 patients in hospitals.<sup>2</sup>

We would like to highlight the challenges that are faced by our front line workers and how they are trying to cope with these situations in Pakistan. Safety of health care workers from being infected with the virus and facing aggressive behavior from attendants of patient simultaneously is one of the main challenges. Until now, a number of cases have been reported on daily basis where doctors and paramedical staffs are beaten and injured due to aggressive actions of attendants. This attitude reflects the inaccessibility of hospitals and unavailability of appropriate health care services; from which provision of ventilator is the basic requirement for the severe cases of COVID-19. For this reason doctors' community is in favor of complete lock down to break the chain of transmission and to lessen the burden on health care systems. However, for country with poor resources it is very difficult to implement lock down and social distancing due to socioeconomic challenges.

Frontline health workers are facing impractical expectations while managing the patients of COVID 19. Without sufficient safety measures; it is difficult to keep them motivated. The exhaustive workload drained the professionals physically, mentally and emotionally.<sup>3</sup> They are at high risk of anxiety, stress, insomnia and constant fear of being exposed to infection. Therefore it is essential to take care of their health and safety by providing them a safe and conducive environment which ultimately leads to quality patient care.<sup>4</sup>

Strategic plan should be enforced and implemented by the government and all stake holders to prioritize the effective measures to control the infection spread among health care providers.<sup>5</sup> All frontline workers should be equipped with ample support from government and from the administration

of hospitals. In this context; mandatory trainings for COVID-19 preparedness and provision of PPEs are basic requirements. Psychosocial support plays a vital role to maintain the moral of health care professionals to cope with the pandemic. Focus should be given to raise the awareness among general public regarding the management of corona virus at home and when to bring patient to hospital in order to lessen the burden in hospitals as majority of patients are recovered with symptomatic treatment.<sup>6</sup> For this purpose, electronic and social media platform should be used to stop all misinformation and provide correct information through medical experts in terms of signs and symptoms, management and psychological support associated with COVID-19.

### Author Contribution:

Nadia Khalid: Conception of idea

Kiran Mehboob Bana: Final editing and prof reading

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### Nadia Khalid

Senior Lecturer, Department of Community Health Sciences  
Bahria University Medical and Dental College, Karachi

### Kiran Mehboob BANA

Senior Lecturer, Department of Community and Preventive  
Dentistry, Bahria University Medical and Dental College,  
Karachi  
Email: [kiranbana291@gmail.com](mailto:kiranbana291@gmail.com)

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