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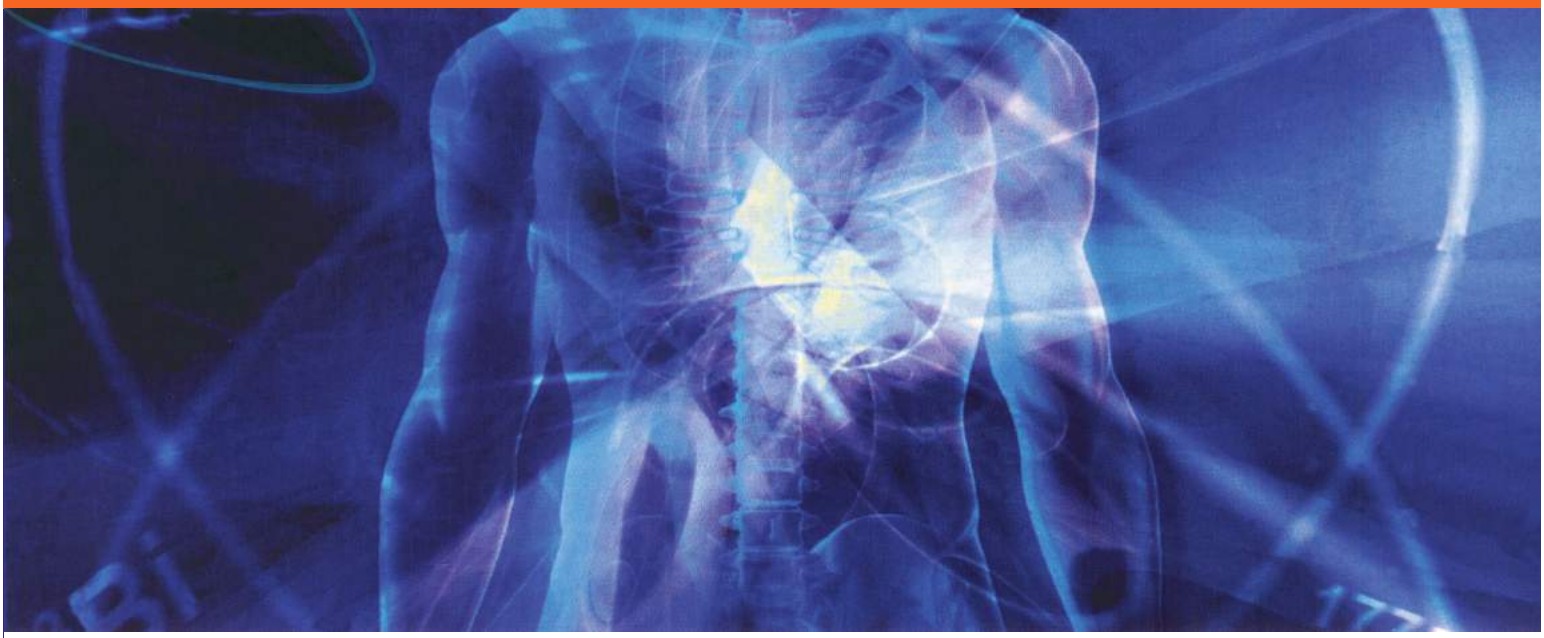

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EDITORIAL

Disaster Management

Syed Sanowar Ali

All cities are in one way or another vulnerable to some form of disaster. In particular, cities that are located in seismically active regions are vulnerable to earthquakes and volcanoes, while others are vulnerable to hurricanes, typhoons, floods, or tsunamis. Therefore, emergency and disaster management, which consist both of pre-emergency and post-emergency measures, are the important components of maintaining safety and security of the people.

What is Disaster?

This is a serious disruption of the functioning of a community or a society. Disasters involve widespread human, material, economic or environmental impacts, which exceed the ability of the affected community or society to cope with them using their own resources.

Types of disasters:

There is no country that is immune from disaster, though vulnerability to disaster varies. There are four main types of disaster.

- **Natural disasters:** including floods, hurricanes, earthquakes and volcano eruptions that have immediate impacts on human health and secondary impacts causing further death and suffering from floods, landslides, fires, tsunamis etc.
- **Environmental emergencies:** including technological or industrial accidents, usually involving the production, use or transportation of hazardous material, and occur where these materials are produced, used or transported, and forest fires caused by humans.
- **Complex emergencies:** involving a break-down of authority, looting and attacks on strategic installations, including conflict situations and war.
- **Pandemic emergencies:** involving a sudden onset of contagious disease that affects health, disrupts services and businesses, brings economic and social costs.

Any disaster can interrupt essential services, such as health care, electricity, water, sewage/garbage removal, transportation and communications. The interruption can seriously affect the health, social and economic networks of local communities and countries. Disasters have a major and long-lasting impact on people long after the immediate effect has been mitigated. Poorly planned relief activities can have a significant negative impact not only on the disaster victims but also on donors and relief agencies. So it is important that physical therapists should also join and establish programs rather than attempting individual efforts.[1]

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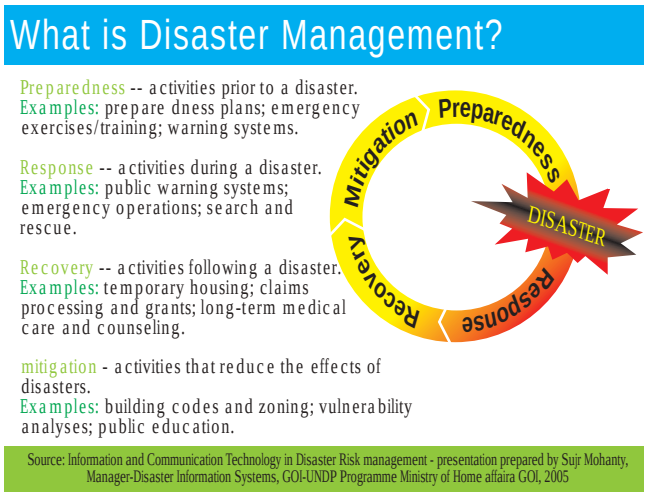
Principles of disaster management:

In 2007, Dr. Wayne Blanchard of FEMA's Emergency Management Higher Education Project, at the direction of Dr. Cortez Lawrence, Superintendent of FEMA's Emergency Management Institute, convened a working group of emergency management practitioners and academics to consider principles of emergency management. This was the first time the principles of the discipline were to be codified. The group agreed on eight principles that will be used to guide the development of a doctrine of emergency management. Below is a summary:

1. Comprehensive – consider and take into account all hazards, all phases, all stakeholders and all impacts relevant to disasters.
2. Progressive – anticipate future disasters and take preventive and preparatory measures to build disaster-resistant and disaster-resilient communities.
3. Risk-driven – use sound risk management principles (hazard identification, risk analysis, and impact analysis) in assigning priorities and resources.
4. Integrated – ensure unity of effort among all levels of government and all elements of a community.
5. Collaborative – create and sustain broad and sincere relationships among individuals and organizations to encourage trust, advocate a team atmosphere, build consensus, and facilitate communication.
6. Coordinated – synchronize the activities of all relevant stakeholders to achieve a common purpose.
7. Flexible – use creative and innovative approaches in solving disaster challenges.
8. Professional – value a science and knowledge-based approach; based on education, training, experience, ethical practice, public stewardship and continuous improvement.[2]

Disaster management comprises of (Figure 1) following main steps:

Figure: 1



Disaster prevention: These are activities designed to provide permanent protection from disasters. Not all disasters, particularly natural disasters, can be prevented, but the risk of loss of life and injury can be mitigated with good evacuation plans, environmental planning and design standards. In January 2005, 168 Governments adopted a 10-year global plan for natural disaster risk reduction. It offers guiding principles, priorities for action, and practical means for achieving disaster resilience for vulnerable communities.

Disaster preparedness: These activities are designed to minimize loss of life and damage – for example by removing people and property from a threatened location and by facilitating timely and effective rescue, relief and rehabilitation. Preparedness is the main way of reducing the impact of disasters. Community-based preparedness and management should be a high priority in physical therapy practice management.

Disaster relief: This is a coordinated multi-agency response to reduce the impact of a disaster and its long-term results. Relief activities include rescue, relocation, providing food and water, preventing disease and disability, repairing vital services such as telecommunications and transport, providing temporary shelter and emergency health care.

Disaster recovery: Once emergency needs have been met and the initial crisis is over, the people affected and the communities that support them are still vulnerable. Recovery activities include rebuilding infrastructure, health care and rehabilitation. These should blend with development activities, such as building human resources for health and developing policies and practices to avoid similar situations in future.[3]Local, regional, national and international organizations are all involved in mounting a humanitarian response to disasters. Each will have a prepared disaster management plan. These plans cover prevention, preparedness, relief and recovery.[4]Various organizations are working at international and national forums to manage disasters.

International Organizations:are (1) The International Emergency Management Society(TIEMS)(2)International Association of Emergency Managers (3)The International Recovery Platform (IRP) (4)The International Red Cross and Red Crescent Movement etc.[5]

National Disaster Organizations: In Australia, New Zealand, Canada, Germany,Russia,USA Somalia, UK, India, Pakistan etc and in some other countries organizations that deals with various types of disaster have been made[6,7,8]

NDMA-Pakistan: In Pakistan the National Disaster Management Authority NDMA, is an indepen-dent, autonomous, and constitutionally established disas-ter preparedness federal institution. It has been given mandate and is responsible to deal with whole spectrum of disaster management and preparedness in the country.The NDMA formulate and enforces national disaster policies at federal and provisional levels and collaborate closely with various government ministries, military forces, and United Nations-based organizations to jointly coordinate efforts to conduct its disaster management, search and rescue, and wide range of humanitarian operations in the country and abroad. The NDMA aims to develop sustainable operational capacity and professional competence to undertake its humanitarian operations at its full capacity.[9]Codified under the Article 89(1) of the Constitution of Pakistan, the institution is chaired by the appointed chairman, either civilian or military officer, and directly reports to the Prime Minister of Pakistan as its chief operations coordinator. The functions and duties of NDMA are defined and set by the Constitution of Pakistan in Article 239I in Chapter1. The Commission is charged with the following duties: (1)To act as the implementing, coordinating and monitoring body for disaster management (2)To prepare the National Plan to be approved and implement coordinate and monitor the implementation of the National policy (3)To provide necessary technical assistance to the Provincial Governments and the Provincial Authorities for preparing their disaster management plans in accordance with the guidelines laid down by the National Commission (4)To coordinate response in the event of any threatening disaster situation or disaster[10]

Riaz and Asim have highlighted two major natural disasters encountered by Pakistan- the earthquakes and the floods. They have recommended that (1) seismic provisions of Building Code of Pakistan should be strictly implemented in the design and construction of structures in the seismically active areas (2) the earthquake vulnerable structures should be strengthened by suitable retrofitting techniques (3) flood infrastructure should be monitored and necessary maintenance should be carried out on regular basis (4) flood forecasting system should be improved by installing more gauge stations and (5) seminars, workshops and training programs should be arranged to increase the awareness of people regarding these hazards.[11]

Thus Disaster management or emergency management is the creation of plans through which communities reduce vulnerability to hazards and cope with disasters. Disaster management does not avert or eliminate the threat, instead it focuses on creating plans to decrease the impact of disasters. Failure to create and implement a plan effectively could lead to damage to assets, human mortality, and lost revenue.[12]

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REVIEW ARTICLE

Vasculo-Protective Cover: A Novel Action of Metformin

Rabia Arshad [1], Nasim Karim [2]

ABSTRACT:
Type 2 diabetes is associated with multiple changes/complications in the body that affects almost every organ and system. In the cardiovascular system main pathology lies in the vascular endothelium leading to atherosclerosis and arteriosclerosis. Different treatment options are available for diabetes including both oral and injectable drugs. Oral drugs have better compliance like Sulfonylureas, Alpha glucosidase inhibitors, Glitazones and Maglitinides. These groups of anti-hyperglycemic drugs maintain blood glucose level, providing diabetics cost effective better life through a physiological route. However, it has been documented that these drugs do not delay vascular complications in diabetic patients. Metformin is the first line oral anti-diabetic drug from biguanide group used to treat type 2 diabetes mellitus. It is a euglycemic agent which decreases glucose levels and have additional benefit of decreasing the progression of vascular effects in multiple ways.

Keywords: Type 2 diabetes, Oral anti-diabetic drugs, Metformin ,Vasculo-protective effects, Endothelial dysfunctions

INTRODUCTION:

Diabetes Mellitus is a group of metabolic diseases characterized by increase in blood glucose levels. The pathophysiology of diabetes includes defects in insulin secretion, insulin action, or both. Chronic hyperglycemia of diabetes is associated with damage, malfunction and failure of various organs including eyes, kidneys, nerves, heart, and blood vessels[1].

Global prevalence of diabetes has increased up to 6.6% in recent years. Almost 285 million, people around the world are affected with this disease.142 million affected people are males and remaining 143 million are females. Out of 285 million approximately 108 million have age range of 60-79 years, 132 million 40-59 years and 44 million 20-39 years of age[2]. Pakistani nation is ranked 6th with diabetic burden in the population.[3] Changes in body due to hyperglycemia and hyperinsulinemia in diabetes can lead to athero-thrombic deposition as well as lethal changes in the vessels that causes 70-75% deaths in diabetic patients due to cardiovascular events[4,5] Multiple treatments have been used for patients of Type 2 Diabetes Mellitus. Oral drugs include several groups such as Sulfonylureas, Biguanides, Glitazones, Maglitinides, DPP-4 inhibitors etc. If control of hyperglycemia is not attained by oral drugs alone then injectable agent insulin is also prescribed. Some drugs which are common in use, are sulfonylureas and biguanide- metformin, have better compliance than others. Oral drugs maintain blood glucose level, providing diabetics cost effective better life through a physiological route. Metformin is the first line oral anti-diabetic drug used in type 2 diabetes. It is a euglycemic agent with additional benefit of decreasing the progression of vascular adverse effects caused by hyperglycemia[6]. Multiple electronic databases PubMed, Science direct, Google.com and Google scholar were searched by using key words, terminologies and phrases of diabetes type 2, oral hypoglycemic agents, metformin, euglycemic agent, metformin effects on vessels, vasculo-protective effects, endothelial dysfunction, atherosclerosis, fibrinolysis, carotid intima, and lipoprotein lipase. Literature search of abstracts, original articles, review articles and case studies published in past 13 years (September 2000 - September 2013) was carried out and is incorporated in the preparation of this review article after using the filter vasculo-protective effect.

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LITERATURE REVIEW:

The vascular endothelium is an important site for control of almost all vascular events and functions[7]. Many crucial vasoactive endogenous products like prostacyclin, thromboxane, nitric oxide, angiotensin, endothelium derived hyperpolarizing factors, free radicals, and bradykinins are formed in the endothelial cells of vessels to control the proper functioning of vascular smooth muscles and of circulating blood cells[8]. Many at times endothelial dysfunctions precede and predict clinical micro vascular diseases. Multiple studies have proven the fact that endothelium is both a target and mediator of atherosclerotic changes leading to cardiovascular diseases[9]. Different pathological events occurring with diabetes such as change in cholesterol levels, hypertension, increase in homocystine levels and visceral fat accumulation are also associated with endothelial dysfunction[10].Other risk factors for vascular diseases in diabetes could be increase in plasminogen activator 1, increase in clotting factor 7, decrease in HDL levels, increase in triglyceride levels and micro albuminuria[11] which further worsen the condition in vascular wall in type 2 diabetics. The most important of these vasoactive substances is nitric oxide which is a vasoprotective agent as it inhibits inflammation, oxidation and proliferation of vascular smooth muscles. Bioavailability of nitric oxide plays a very important role in regulation of events in vessels[12]. Early markers of endothelial dysfunction

can be decrease in amounts of nitric oxide leading to abnormal vasomotor response and subsequently micro and macro vascular pathology. Different studies have also indicated the fact that endothelial dysfunction can be induced by abnormality in the insulin signaling pathway, that can be a result of deprivation of endothelial nitric oxide synthase. When taken together it is evident that in type 2 diabetes, insulin resistance and endothelial dysfunction are related to each other. Treating these two previous issues would definitely improve the latter ones and therefore the functioning of vascular system[13.]

Metformin: Metformin is one of the important agents for controlling hyperglycemia in type 2 diabetes these days. It has a botanical source, obtained from Galegia Officianalis; known as goats rue and French lilac. It acts as a euglycemic agent by decreasing the carbohydrate absorption and increasing its utilization by decreasing the insulin resistance.[14]

Metformin is slowly absorbed from the gut with elimination half life of 3-6 hours which occur through kidneys. It does not increase the body weight and can be used as mono-therapy.[15] The side effects encountered with metformin are metallic taste, anorexia, nausea, flatulence, abdominal cramp, occasionally diarrhea and vomiting. All these features usually tend to disappear with the continuation of therapy. Rarely lactic acidosis can occur in patients with renal and hepatic insufficiency. This can be prevented to a large extent by having LFTs and renal profile of the patients before starting the therapy.

Metformin mode of action:

Metformin reduces blood glucose level without increasing the production of insulin, and has greater glucose lowering efficacy as compared to other anti-diabetic agents.[16] The anti hyperglycemic effect of metformin is explained by several mechanisms that collectively balance insulin resistance and improve glucose homeostasis.[17, 18] The two main mechanisms are inhibition of gluconeogenesis, and improvement in glucose uptake by decreasing insulin resistance.[19] Metformin along with some life style modifications and weight reduction can be useful for improving the endothelial function and decreasing the risk of CVS diseases in diabetics.[20, 21]

1. Effect of Metformin on smooth muscles :

Many studies have proven the fact that defective insulin signaling is a factor for vascular problems in type 2 diabetic patient. In insulin resistance this pathway gets disturbed and finally there is no nitric oxide dependent relaxation of vascular smooth muscles leading to stiffness and shortening of diameter in these vessels. Metformin has shown vasculo-protective effects by inhibiting these above mentioned mechanisms. Metformin improves the skin capillary reactivity, functional capillary density and also stimulates slow wave arteriolar vasomotion.[22,23] Different animal studies have shown improvement in nitric oxide activity and probable relaxation of pre-contracted aortic ring in streptozotocin induced diabetic rats.[24,25] Administration of metformin in the rat tail arteries causes arterial relaxation due to decrease in activity of intracellular calcium ions. Metformin potentiate the production of nitric oxide by increasing local nitric oxide synthase which again decreases the response of calcium ions in the smooth muscles of the vessels. Finally metformin decreases constriction and enhances the post ischemic perfusion of capillary beds.[26]

2. Effect of metformin on vascular endothelium:

Other than vascular smooth muscles in vessels, endothelium is also an important part where vascular deformity is noticed at an early stage in diabetics. In recent years insulin resistance and endothelium has been of great interest to the researchers due to a strong relationship between diabetics and endothelial abnormalities. Metformin increases endothelial dependent vasodilation, independent of its glycemic control properties. The main mechanism behind this effect is the increase in nitric oxide synthase and nitric oxide precursor L-arginine which is an amino acid.

3. Effects of metformin on monocyte adhesion:

Metformin also inhibits monocyte adhesion to the endothelium which is one of the factors causing arthrosclerosis in the vessels. It decreases the adhesion molecule expression in the endothelium including Vascular Cell Adhesion Molecule 1 (VCAM 1), Intracellular Adhesion Molecule 1 (ICAM 1) and E- selection[27.]

4. Effects of Metformin on haemostatic factors:

In patients with type 2 diabetes, metformin improves the markers of endothelial dysfunction and inflammatory activity including von-willebrand factor, selectin tissue type plasminogen activators and plasminogen activator inhibitor 1.[6, 28] It is also found to improve the endothelial regulators of hemostasis (vWf), leukocyte adhesion molecules (SE selectin , VCAM 1) and fibrinolytic agents (tPA, PAI).[29]

5. Effects of Metformin on platelets:

The anti atherosclerotic and cardio protective effects of metformin by its action on platelets have recently been confirmed in both prospective and retrospective studies. Metfomin has direct effect on two important component of an arterial thrombus that is fibrin and platelets. It acts by inhibiting two important platelet activating factors; PAF4 and B7G thus causing decrease in platelet plug formation.[30,31]

6. Effects of Metformin on fatty acids:

The storage of free fatty acids in the endothelium is increased in insulin resistance state. Metformin in turn promotes free fatty acid oxidation in the endothelial tissue by its ability to activate endothelial AMP protein kinase.[5, 32] Metformin decreases lipoprotein lipase production and thus decrease the breakdown of LDL into VLDL, accounting for further vasculoprotective effects. LDL is taken up by liver due to presence of its receptors on hepatocytes thus decreasing VLDL in blood. It also reduces endothelial permeability and edema and thus improves capillary functions[33.]

7. Effects of Metformin on inflammation:

Metformin along with other effects, also decreases inflammatory mediators such as tissue plasminogen activator (tPA), antigen factors 7 and 13, and C-reactive protein (CRP) levels[34].

8. Additional effects of Metformin:

Type 2 diabetes mellitus patients being treated with metformin have shown slowing of annual progression of carotid intima indicating that this drug decreases the normal carotid changes in these patients.[35] It has been documented that metformin treatment produces significant reduction in multiple factors leading to decrease in brachial artery diameter at base line; brachial artery diameter after reactive hyperthermia, abnormal flow mediated dilation and increased intima media thickness.[36, 37] In addition, plasma concentration of endothelin 1 which is one of the main biological markers of endothelial function is significantly altered in polycystic ovarian syndrome patients, has been found to decrease with metformin therapy.[38] At cellular level specifically in mitochondrial chain, it also prevents apoptosis, which is another mechanism to explain the long term vascular protection afforded by metformin.[39] A study on obese insulin resistant cases has documented that metformin promotes a prolonged post prandial fall in the plasma levels of the gut hormone "ghrelin" which stimulates food intake and encourages adiposity .Thus metformin decreases caloric intake and helps in total weight reduction in type 2 diabetes.[40]

CONCLUSION:

Metformin provides vasculo-protective cover and delays the vascular changes in type 2 diabetic patients in addition to provision of good control of glycemic levels with least side effects. These vasculo-protective effects make metformin a novel drug in the class of oral anti-diabetics.

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ORIGINAL ARTICLE

Total Sialic Acid (TSA) Level as a Tumor Marker in the Diagnosis of Oral Cancer

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ABSTRACT:
Objective: To estimate serum Total Sialic Acid **(**TSA) levels in different grades of oral squamous cell carcinoma and to access it`s utility as a tumor marker in this cancer.
Materials and Methods: This study was conducted in 68 adult subjects equally divided into two groups, healthy individuals and patients with oral squamous cell cancer. Under aseptic precautions venous blood was drawn and serum was separated.Estimation of serum total sialic acid level was done according to Spectrophotometeric method of Plucinsky. Statistical analysis was carried out by using SPSS 19.
Results: Total subjects in the study included were 58.82% males and 41.17% females. Mean age of oral cancer patients was 48.05 ± 8.82 years. There was significant male predominance with P<0.05. Oral cancer was most common in Tobacco+ Chaliya + Areca nut and Gutka+pan groups. Mean serum total sialic acid (TSA) level in control group was 60.2 ± 4.27 mg/dl, whereas it was 99.1 ± 18.30 mg/dl in oral cancer group. It was significantly increased in oral cancer group when compared to control group with P value < 0.01. There was progressive elevation in mean serum TSA level in oral squamous cell carcinoma,
Conclusion: Estimation of serum total sialic acid level (TSA) in different grades of oral squamous cell carcinoma showed positive relation with stage of malignancy, specifically with the tumor burden**.** It can be used as a diagnostic biomarker in oral squamous cell cancers.
Keywords: Oral cancer, Squamous cell carcinoma,Different grades, Serum total sialic acid, Tumor marker.

INTRODUCTION:

Worldwide, the oral cancer accounts for 2%–4% of all cancers. The prevalence of oral cancer is higher, reaching to 10% of all cancers in Pakistan.[1,2,3]More than 95% of carcinomas of oral cavity are of squamous cell type in nature. [4,5,6]Oral cancer is a major cause of morbidity and mortality in Southeast Asian countries because more than 600 million people chew areca nut and its products like pan, gutka, panmasala etc. worldwide and 85% of these live in Southeast Asian countries.[7,8] Therefore oral cancer is a major health problem and cause of death in developing countries. Other etiological factors are; Tobacco and lime chewing; Tobacco related habits, smoking, Alcohol consumption, Nutritional deficiencies, exposure to Sunlight and other miscellaneous factors.[9,10,11,12] Early detection of lesions in the oral cavity is very important because there are more chances of treatment outcomes which will reduce the rate of morbidity and mortality.[13] In this respect tumor markers are very important because they help in the screening, diagnosis and prognosis in monitoring the response of the disease to the treatment.[14,15,16]

Tumor markers are naturally occurring or modified molecules and can be measured in serum, plasma and other body fluids like saliva.[17,18]In presence of cancer their concentration may be changed. Substances changing quantitatively in the serum during tumerogenesis are collectively called tumor markers or biomarkers.[19] Actually, a biomarker is synthesized by the tumor and released into circulation in large quantities.[20,21]In oral cancer various biomarkers have been studied and one of such markers is Sialic Acid (SA). Sialic acid is an acetylated derivative of neuraminic acid. It is attached to the non-reducing residue of the carbohydrate chain of glycoproteins and glycolipids.[22,23,24,25]SA is a glycoprotein component of cell membrane which is synthesized in liver and it exists in conjugated form on the external surface of cell membrane[26]. Altered glycosylation of glycoconjugate is one of the important molecular changes in the malignant transformation.[27,28,29] Considering the high prevalence of oral malignancy in Pakistan, present study was conducted to evaluate serum TSA levels in different grades of oral cancer patients and also to validate its importance as a tumor marker in oral cancer patients.

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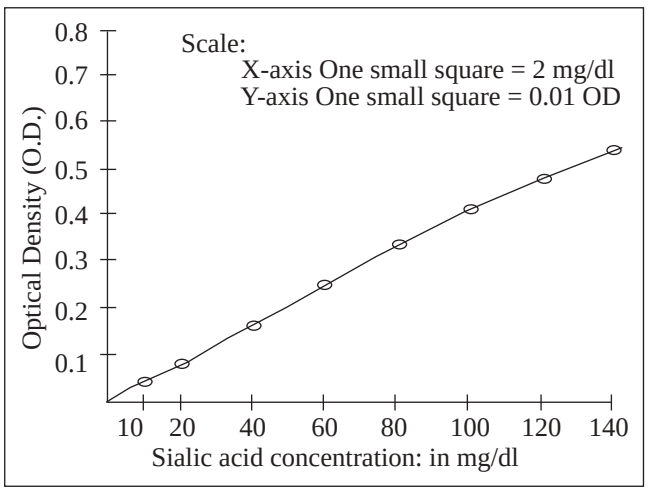
MATERIALS AND METHODS:

After approval from BASR of Karachi University, present study was conducted in the department of Biochemistry BMSI-JPMC. A total of 68 adult subjects were included in the study, 34 diagnosed cases of oral cancer from the clinical oncology ward of Jinnah Postgraduate Medical Centre, Karachi, and 34 healthy subjects were taken from general population, for comparison. Out of 34 diagnosed cases 23, 11 and 01 were of well differentiated squamous cell carcinoma (WDSCC), moderately differentiated squamous cell carcinoma (MDSCC) and poorly differentiated squamous cell carcinoma (PDSCC) respectively. Subjects having diabetes mellitus, hepatobiliary disorders, depression, premalignant neoplasms, renal disorders, cardiovascular disorders and other malignancies were excluded from the study.

Measurement of Total sialic acid (TSA): Serum total sialic acid level was determined by the Spectrophotometericmethod of Plucinsky as mentioned by Joshi and Kadam[19,21]. 20ìl of serum was diluted with 980 ìl distilled water. After treatment with resorcinol reagent the blue chromophore was extracted by butyl acetate/n-butanol (85:15) (v/v) and determined spectrophotometrically at 580nm and sialic acid was determined by the use of standard curve of N-acetyl neuraminic acid(Figure 1).

Statistical analysis: The data is expressed as mean ± SD. The statistical significance of the results was analyzed using a student's t test, Chi-square and Anova. Values of P<0.01 were considered as significant.

Figure: 1
Standard curve of sialic acid



RESULTS:

Total subjects in the study included 58.82% males and 41.17% females.The mean age of oral cancer patients was 48.05 ± 8.82 years. These values indicate that individuals above 40 years are at high risk for oral cancer. The sex ratio was evaluated by Chi-square test, which was significant (P<0.05) showing the male predominance in oral cancer, this could be because the habits like tobacco chewing, smoking alcohol consumption are more common in males.

Details of habits of oral cancer patientsare mentioned (Table 1). Oral cancer patients were using tobacco in one or the other way. Oral cancer was most common in Tobacco+ Chaliya + Areca nut and Gutka+pan groups.

Table: 1
Habits of oral cancer patients

Habits	Number of patients (n)
Tobacco + Pan with lime	03
Tobacco + gutka	04
Tobacco + Chaliya +Areca nut	06
Naswar + Pan	04
Gutka + pan	06
Beeri + Hucka	05
Cigarette + Naswar	05
Naswar+Gutkha	01

The mean serum total sialic acid (TSA) level in control group was 60.2 ± 4.27 mg/dl, whereas it was 99.1 ± 18.30 mg/dl in oral cancer group. It was significantly increased in oral cancer group when compared to control with P value < 0.01. It means that serum TSA level should be considered along with other traditional diagnostic tools for the accurate diagnosis of oral cancer (Table 2). Mean serum total sialic acid (TSA) level in WDSCC group was 80.8 ± 19.65 mg/dl, whereas it was 96.0 ± 15.86 mg/dl and 105.4 ± 22.3 mg/dl in MDSCC and PDSCC group respectively.Difference in values of mean serum TSA levels was statistically significant between WDSCC, MDSCC and PDSCC in oral cancer with P value < 0.01(Table 3).The significant elevation of mean serum TSA levels in oral cancer patients was also noted when compared to controls with P value<0.01. However, the difference between cases of MDSCC and WDSCC was again significant, which proves the role of serum TSA as an ideal biomarker of oral cancer. Because of the independent clinical significance of various tumor markers their serum concentrations are incorporated in clinical grading of the malignancies**.**

Table: 2
Comparison of serum TSA levels among case and control groups

Study groups	Mean serum TSA	SD	P-Value
Control group	60.2	4.27	0.001
Oral cancer group	99.1	18.30	

Table:3
Comparison of mean serum TSA levels in various histopathological grades of OSCC patients

OSCC patients	No	Mean TSA (mg/dl)	SD	P-Value
WDSCC	22	80.8	19.65	0.001
MDSCC	11	96.0	15.86	0.001
PDSCC	01	105.4	22.03	0.001

ANOVA utilized.(p<0.01) statistically significant

DISCUSSION:

Recently, tumor markers are receiving more attention in early detection as well as predicting prognosis of the lesion[11]. In the last few decades, considerable research efforts have been focused on defining the changes in cell surface membrane molecules in the neoplastic transformation, particularly the cell surface glycoproteins which contribute for malignant transformation of a cell. Among these glyco-conjugates, sialic acid is present up to 30% in various glycoproteins[19].

With reference to oral squamous cell carcinoma, many workers have found significantly elevated levels of mean serum TSA as compared to healthy subjects.[30]. They have also noticed increased levels of TSA when correlated with the different grades of oral squamous cell carcinoma. Present study has also shown the comparison of mean serum TSA levels with different grades of oral cancer[5]. We have also correlated TSA level with histopathologic grading of tumor. Histopathologic grading of oral squamous cell carcinoma (OSCC) was done according to the degree of differentiation as per Broder'sclassification as mentioned by Joshi[19].The TSA levels according to histopathologic grading[31]in present study are evaluated.There is significant rise of TSA level with the advancing stage of tumor. This means that TSA level is directly proportional to the tumor burden. The values we found are closely related to those of Taqi[16]and Rajpura.[29]When mean serum TSA levels were mutually compared in our study between the WDSCC and MDSCC it showed significantly increased levels of mean serum TSA in MDSCC but when mean serum TSA levels were compared between MDSCC and PDSCC, again we found significantly the increased levels of mean serum TSA in PDSCC as compared to the MDSCC which were statistically significant with p value < 0.01. Yet not any previous study has given such correlation. The possible reason could be subjective variation between histopathologic grading and only one case of PDSCC which was studied. Tumor burden might be the cause of higher values of serum TSA level in MDSCC and PDSCC when compared with WDSCC. This statement is in agreement with Joshi[19] but it is against the Vora.[5] The present study also suggests strong correlation between habits of tobacco chewing/betel nut chewing/ smoking[32,33,34]with increased levels of mean serum total sialic acid. This finding was inconsistent with Greenberg.[4]Kadam[21] and Kurtul.[25]

CONCLUSION:

Estimation of serum total Sialic acid (TSA) level in oral squamous cellcarcinoma, is suggestive of a positive relation between TSA level and stage of malignancy, specifically with the tumor burden. Serum total Sialic acid level can be used as an adjunctive diagnostic marker as well as an early indicator of oral cancer. Future studies with larger sample size on this aspect of Sialic acid should be explored by the researchers.

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ORIGINAL ARTICLE

Evaluation of Retinoblastoma According to Histological Grading, TNM Staging and Age at Presentation

Syed Muhammad Ishaq[1], Shahnaz Imdad Kehar[2], Noshaba Rahat[3], Abdullah Jan[4]

ABSTRACT

Objective: To evaluate retinoblastoma, according to histological grades, TNM staging and age at presentation.

Materials and Methods: This cross sectional study was conducted in Department of Pathology BMSI- JPMC Karachi from 1st January 2009 to 31st December 2013 during which a total of 80 cases of retinoblastoma were received. Out of which 68 were reviewed and morphological diagnosis was done on H&E staining. Histological grades and TNM staging were categorized. The data was analyzed by using SPSS version 22.

Results: In 80 cases of retinoblastoma the mean age of patients was 3.64 years with 3-4 years (53.75%) of age being the commonest. Amongst 68 cases, well differentiated retinoblastoma were seen in 7.35%, moderately differentiated 11.76%, poorly differentiated 26.47% and undifferentiated 51.41% cases. Varied pattern of TNM staging were observed. Majority (60.29%) in stage IV followed by 19.11% in stage I and 10.29% each in TNM stage II and III. Regional lymph node metastasis was seen in 4/68 cases (5.88%) while 3/68 (4.41%) showed distant (CNS) metastasis. All these cases (7/7) were in TNM stage IV with majority showing grade 4 (75%) and grade 3 (25%) histology.

Conclusion: Evaluation of retinoblastoma showed that commonest age group was 3-4 years. Majority of retinoblastoma cases were undifferentiated (G4) followed by poorly differentiated (G3). While in TNM staging system varied pattern was observed, majority were in stage IV followed by Stage I. Majority of lymph node and distant metastasis were seen in grade 4 histology and all of them were in TNM stage IV.

Keywords: Retinoblastoma, Histological grading, TNM staging, Age, Optic nerve, Rb1 gene

INTRODUCTION:

The commonest primary intraocular cancer in younger age is retinoblastoma[1,2,3] generally affects children, early diagnosis is curable while untreated cases lead to complications and even death[4]. Retinoblastoma arises as mutation in both alleles of Rb1 gene which occurs pre-zygotically or post-zygotically in germ cells[5]. Rb1 gene is situated in long arm of chromosome 13q14 [4,6,7,8] Hereditary form consists of 30-40% and non hereditary form 60-70%. Former had bilateral retinoblastoma, diagnosed in < 1 year of age and have more risk of secondary neoplasm that is bone and soft tissue sarcoma, melanoma and brain cancer. Latter have unilateral retinoblastoma, diagnosed at 2-5 years of age and is not prone to secondary neoplasm. [9,10,11,12]

Globally one case of retinoblastoma is recorded in up to 20,000 live births. Incidence is generally equal in North America, Europe, Australia and Asia whereas higher in Africa and other developing countries.[13,14,15,16,17] When retinoblastoma spread to the optic nerve, choroid and extra ocular tissue the mortality is high and prognosis is poor[18,19,20,21] Grossly retinoblastoma are presented as endophytic, exophytic, mixed endophytic and exophytic, diffuse infiltrating and complete spontaneous regression.[3,7,8,22]

On the basis of Flexner-Winter Steiner rosette (Lined by tall cuboidal cells that circumscribed an apical lumen and basal ends of the cells contain nuclei), Homer-Wright rossettes (cells are not arranged about a lumen but sends out cytoplasmic processes and form a tangle within the center) and pseudo rosette, retinoblastoma are divided into well differentiated, moderately differentiated, poorly differentiated and undifferentiated variant.[7,9,22,,23,24] On involvement of optic nerve, choroid, extraocular tissue and secondary metastasis to lymph node and distant tissue, TNM staging system of retinoblastoma developed, T is primary tumor, N is lymph node and M is distant metastasis.[7,22,23,24,25] This study was designed to evaluate retinoblastoma cases according to different histological grades, TNM staging and age at presentation in our local population.

MATERIALS AND METHODS:

The study was performed after approval from BASR, Karachi University at department of Pathology Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center (BMSI-JPMC) Karachi from 1st January 2009 to 31st December 2013. A total of 80 cases of retinoblas-

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toma were received and 12 cases were excluded due to inadequate material. In remaining 68 cases histological grading and TNM staging was done. These patients were operated at ophthalmology department of JPMC, Karachi. All enucleated eye specimens were included, while poorly fixed and inadequate tissue, ocular tumor other than retinoblastoma and metastatic tumors were excluded. Formalin fixed, paraffin embedded blocks, surgical pathology, clinical records and hematoxyline and eosin slides were used. Sections were taken and stained with H&E. all slides were studied under light microscope using scanner (4X), low power (10X) followed by high power (40X). The data was analyzed by using statistical package for social sciences (SPSS) version 22.

RESULTS:

Distribution of retinoblastoma according to age amongst 80 cases was, majority that is 53.75% cases were between ages 3-4 years followed by 20% cases in 5-6 years. The mean ± SD were 3.64 years (43.68 months) ±1.74, median age was 48 months. The minimum age was 02 months while maximum age noted was 09 years (Table 1)

Table: 1
Distribution of retinoblastoma according to age
(n=80)

Age (years)	No of cases	Percentage %	Cumulative index
<1 year	04	05	05
1-2 years	11	13.75	18.75
3-4 years	43	53.75	72.5
5-6 years	16	20	92.5
7-8 years	02	02.50	95
9-10 years	01	01.25	96.25
Unknown	03	03.75	100
Total	80	100	

Out of 68 cases, 7.35% were well differentiated (G1), 11.76% were moderately differentiated (G2), 26.47% were poorly differentiated (G3) and 54.41% were undifferentiated (G4) respectively. Out of 68 cases 5.88% cases showed regional lymph node and 4.41% showed distant metastasis, majority i.e. 75% of them were in G4 histology and 25% showed G3 histology (Table 2).

Table: 2
Distribution of retinoblastoma according to histological grades
(n=68)

Grades	No of cases	Percentage %	95% CI
G1	05	07.35	2.74-15.54
G2	08	11.76	5.61-21.11
G3	18	26.47	17.0-37.9
G4	37	54.41	42.51-65.94
Total	68	100	

CI: Conbidence interval

Distribution of retinoblastoma according to TNM staging system showed that out of 68 cases majority that is 60.29% were in TNM stage IV followed by 19.11% were stage I and 10.29% each were in TNM stage II and stage III. All the cases that showed regional lymph node and CNS metastasis, were in TNM stage IV (Table 3)

Table: 3
Cases of retinoblastoma according to TNM staging
(n=68)

Stage	No of cases	% of total cases	95% CI
Stage I	13	19.11	11.06-29.75
Stage II	07	10.29	4.61-19.3
Stage III	07	10.29	4.61-19.3
Stage IV	41	60.29	48.34-71.4
Total:	68	100	

CI: Confidence interval

Comparison and correlation of retinoblastoma according to TNM staging and histological grading showed that out of 68 cases majority that is 60.29% were in TNM stage IV. Out of these 2.43% were in histological grade I, 7.13% in G2, 29.26% in G3 and 60.29% in G4. TNM stage III showed 10.29% out of these 0% were in grade I, 14.28% in G2, 28.57% in G3 and 57.14% in G4. TNM stage II showed 10.29% out of these 28.57% each were in grade I, grade 2 and grade 4 histology While 14.28% in G3. TNM stage I showed 19.11% out of these 15.38% each were in histological grade 1 and grade 2, 23.07% in G3 and 46.15% in G4 (Table 4).

Table: 4
Retinoblastoma according to histopathological grading and TNM staging
(n= 68)

TNM Stage	Histopathological Grades				Total
	G1	G2	G3	G4	
Stage I	02 15.38%	02 15.38%	03 23.07%	06 46.15	13 19.11%
Stage II	02 28.57%	02 28.57%	01 14.28%	02 28.57%	07 10.29%
Stage III	00 00	01 14.28%	02 28.57%	04 57.14%	07 10.29%
Stage IV	01 2.43%	03 7.13%	12 29.26%	25 60.29%	41 60.29%
Total	05 7.35%	08 11.76%	18 26.47%	37 54.41%	68 100%

P value = 0.22; Chi Square = 11.77

DISCUSSION

In present study the most common age group was 3-4 years that is 53.75% cases followed by 20% cases in 5-6 years age group. These findings are comparable to the studies in Mumbai, India, Tata Memorial Hospital by Yeole[13] and Akhiwu[6] have reported 76.5% and 78% cases in under 4 years of age and 3-3.5 years of age groups respectively. Studies by Chintagumpala[1] and Rodrigues [20] have reported 80% cases under 3 years and

53% cases under 2 years of age respectively. In this study the mean age was 43.68 months. This finding was comparable with the work by Akhiwu [6] who has reported mean age 24 to 48 months, but dissimilar to Antoneli [21] and Arif [2] who have documented 28.7 and 32 months respectively. Dissimilarity with present study may be due to lack of awareness, lack of education and poverty leading to late presentation for medical consultation. In the present study varied histopathological grades were seen. Majority that is 54.41% were in grade 4 histology followed by 26.47% in G3, 11.76% in G2 and 7.35% in grade 1 histology. A Nigerian study conducted by Owoeys[9] have reported 82% and 17.4% cases in G3 and G1 and none of case in grade 1 and grade 4 histology. While Chinese study performed by Jia[19] has reported 24%, 14% and 62% cases in histopathological grade 1, G2 and G3 respectively. No case was reported in histological grade 4 while present study found majority of cases in grade 4 histology. This variation could be due to late presentation or genetic and environmental factors.

Similarly an interesting observation in this series was that TNM staging had variable pattern of presentation and majority were in stage IV followed by stage I and equal number of cases were in TNM stage II and stage III. The reason for patient being in high TNM stage at the time of clinical presentation as mentioned earlier may be due to lack of awareness and inaccessibility of proper medical services. Moreover, people prefer alternative medical therapy such as Hakeems before consulting doctors.

CONCLUSION:

Maximum number of retinoblastoma cases was seen in the age group of 3-4 years and majority of them had grade-4 histology. Most of these cases were seen in Stage IV. All cases of lymph node and distant metastasis were also seen in TNM stage IV.

In view of a high stage and grade at the time of presentation wide scale awareness through education to parents, community and counseling programs is needed. This will help to ensure early presentation of such cases that is in the initial stages and grades of the disease. This in turn could improve the clinical outcomes, morbidity and mortality in such cases.

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ORIGINAL ARTICLE

Are we Caring those who Deserve Special Care? Frequency of Depression among Older Population Residing in a Nursing Home at Karachi

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ABSTRACT:
Objective: To find out the frequency of depression and factors related to it among elderly admitted in a nursing home of Karachi
Materials and Methods: This cross-sectional study was carried out at DarulSukun, Karachi, for a period of four months. Official permission was obtained and 80 citizens (30 females and 50 males), 60 years of age or above, willing to participate, able to speak, express their views and understand Urdu language properly were included in this study.Data collection tool included a questionnaire consisting of two sections. The first had basic demographic information while the second had fifteen items Geriatric Depression Scale (GDS-15). Demographic data of each subject was obtained by direct interview. Age, gender, marital status, education,financial dependency and exercise were also recorded.
Results: Mean age was 67 years.Out of total 80 subjects, 62.5% (n=50) were males while 37.5% (n=30) were females.27.5% (n=22) had depression majority being females.Only 7.5% (n=6) were married and were living as couples. None of them had depression. 66.2% (n=53) participants were educated from Grade-5 till Grade-9.72.5% (n=58) were dependent on their families.Depression was more common in those subjects who were admitted in a period of 3 months or less.22 male subjects performed morning walk on routine basis. Only 3 of them had depression.
Conclusion: The frequency of depression among elderly admitted in a nursing home of Karachi was 27.5%. Gender, marital status, education, financial dependency,recent admission and exercise were found to be related with depression.
Keywords: Nursing homes, Old citizens, Depression, Frequency, Related factors

INTRODUCTION:

Depression is a serious matter of concern especially in the under-developed countries.[1] Among elderly population, depression is regarded to be the most common disorder of psychiatry which usually manifests as minor depression or major depression usually characterized by a group of common depressive symptoms.[2] According to the results of study related to Global Burden of Illness, it was revealed that by 2020, depression will be the leading cause of Disability Adjusted Life Years (DALY's) in under-developed world.[3]Different studies have reported under-treatment and under-estimation of depression among the elderly population not only in under-developed countries but also in developed-countries.[4,5,6] From the year 2000 to 2050, the proportion of elderly population all over the world having age of more than 65 years is expected to be doubled and thus exceeding the current percentage of 6.9% to more than 16%.[7] With the improvement in the health care facilities and the life expectancy, the elderly population is increasing accordingly both in underdeveloped and developed countries.This demographic drift has been noticed not only in developed countries but also in under-developed countries.[8]According to one study, it has been revealed that about 60% of the total world elderly population resides in under-developed countries and the percentage is estimated to be increasing up to 70% till 2020.[9] Pakistan is a developing state in South Asia and is regarded to be the 6th populous state in the world.The life expectancy on average here in Pakistan is 62.[10] Total 6.1 % of elderly population was estimated in the year 2009 and it is expected to further increase to 15% by 2050.[11]Therefore, there is a dire need to assess and evaluate appropriate measure that needs to be taken for elderly population in Pakistan where there is lack of appropriate social care and health facilities.[12] A considerable prevalence of depression in Pakistani community has been observed in different studies conducted in various regions of Pakistan.The study conducted by Mirza has depicted that mean prevalence of depressive and anxiety disorders in Pakistani community was more than 30%.In an underdeveloped state like Pakistan, the large chunk of elderly population financially and socially depends upon their children and off-springs.[12] This sort of support most importantly the physical and psychological support is quite practical in joint families.[13] Mason and Lyness in their studies have mentioned that the current trend of urbanization is most likely to erode the natural family trend to care and support the elderly population physically, morally and financially and thus eventually decreasing the co-

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residence of elderly parents with their adult children.[14,15] In order to determine the nature and magnitude of depression, it is essential to perform assessment of depression in homecare elderly personnels.[16,17] Previously, a Geriatric Depression Scale (GDS) containing 30 items was developed to rule out positive cases of depression among elderly population.[18] The introduction of shorter version of Geriatric Depression Scale has resulted in consuming comparatively less time along with other benefits.[19] It has been validated after its thorough evaluation in different elderly nursing homes, outpatient, inpatient and primary care settings. However, it has been reported in two different studies that the results of GDS are not that much reliable when interviewed from a person having little or no education at all.[16,20] Keeping in mind this point we developed our exclusion criteria. In another study by Tang, no obvious differential item functioning was observed in connection to the education in elderly population.[21]

Karachi is regarded to be the largest city of Pakistan. It accounts nearly for 10% of the total population of Pakistan.[22] While couple of studies have already been conducted in Karachi reporting the frequency of depression among the elderly population but not even a single recent published study is available to describe the frequency of depression among elderly living in nursing homes. It might be due to the reason that in Pakistan the trend of sending elderly to the nursing homes in not that much common. However, with the advancement of time, a trend has been developed in couple of bigger cities of the country. So there was a need to conduct an exclusive study in different elderly nursing homes to find the frequency of depression among the older population residing in nursing homes. We hypothesized that an appreciable number of elderly population admitted in the elderly nursing homes is suffering from depression. We aimed to find out the frequency of depression among elderly admitted in one of the prominent nursing homes of Karachi and to find association of depression with gender, marital status, educational qualification and financial dependency.

MATERIALS AND METHODS:

A cross-sectional study was carried out at one of the most prominent old age nursing homes in Karachi namely DarulSukun. Official permission was obtained from the administration of the said organization. A total of 80 old citizens (30 females and 50 males) were included in this study out of 85 (32 females and 53 males).

All those patients who were 60 years of age or above, willing to participate in this study, able to speak and express their views and were able to understand Urdu language properly were included in this study while those who were below 60 years of age or didn't provide consent to be a part of this study or were unable to understand Urdu were not included.

Data collection tool included a questionnaire consisting of two sections. The first section was meant to record the basic demographic information while the second section was Fifteen Item Geriatric Depression Scale (GDS-15) to measure the depression among the study participants. The demographic data of every subject was obtained by direct interview and the age, gender, origin, nationality, marital status, number of off-springs and occupation was duly noted.

As the national language of the country is Urdu so there was a need to translate the scale into Urdu language. In order to ensure a quality translated pre-tested version of manuscript, a pre-prepared version was obtained on request from the corresponding author of study titled, "Depression in the elderly: Does family system play a role? A cross-sectional study" published in 2007[1](Figure 1). The team of aforementioned study developed an Urdu version of questionnaire. Three separate translations of scale into Urdu language were performed and then back-translation was done and then finally the best final script was selected (Figure 2). The scale was thoroughly discussed by the interviewers to decrease the interviewer bias.

All the participants of study were interviewed by a panel of 2 medical students. Each interview lasted for not more than 16 minutes. The interviewers were first trained by a psychiatrist of DarulSukun regarding skills of taking a proper interview and interpreting the views of interviewee.

The ethical consideration was taken in account and confidentiality of subjects was secured. All the subjects were informed regarding the objectives of the study. It was decided and informed to the subjects that the names and personal identity of the subjects will not be disclosed to the third party without their prior written consent. The data was analyzed in SPSS version 19 while the graphs were designed in MS. Excel 2013. The entire study duration was about 4 months.

Figure: 1
15 Item Geriatric Depression Scale[17]

Geriatric Depression Scale (Short Form)

Patient's Name: _____ Date: _____

Instructions: Choose the best answer for how you felt over the past week. Note: when asking the patient to complete the form, provide the self-rated form (included on the following page).

No.	Question	Answer	Score
1.	Are you basically satisfied with your life?	Yes / No	
2.	Have you dropped many of your activities and interests?	Yes / No	
3.	Do you feel that your life is empty?	Yes / No	
4.	Do you often get bored?	Yes / No	
5.	Are you in good spirits most of the time?	Yes / No	
6.	Are you afraid that something bad is going to happen to you?	Yes / No	
7.	Do you feel happy most of the time?	Yes / No	
8.	Do you often feel helpless?	Yes / No	
9.	Do you prefer to stay at home, rather than going out and doing new things?	Yes / No	
10.	Do you feel you have more problems with memory than most people?	Yes / No	
11.	Do you think it is wonderful to be alive?	Yes / No	
12.	Do you feel pretty worthless the way you are now?	Yes / No	
13.	Do you feel full of energy?	Yes / No	
14.	Do you feel that your situation is hopeless?	Yes / No	
15.	Do you think that most people are better off than you are?	Yes / No	
		TOTAL	

Figure:2
Urdu translated version of GDS-15

	سوال	ہاں	نہیں
۱۔	کیا آپ بنیادی طور پر اپنی زندگی سے خوش ہیں؟	☐	☐
۲۔	کیا آپ نے اپنے کئی مشاغل اور کام ترک کر دیے ہیں؟	☐	☐
۳۔	کیا آپ زیادہ تر وقت خوش رہتے ہیں؟	☐	☐
۴۔	کیا آپ باہر جا کر نئے کام کرنے کی نسبت گھر پر رہنا پسند کرتے ہیں؟	☐	☐
۵۔	کیا آپ اکثر وقت اچھی امنگ میں رہتے ہیں؟	☐	☐
۶۔	کیا آپ سمجھتے ہیں کہ آپ کی زندگی بہترین ہے؟	☐	☐
۷۔	کیا آپ توانائی سے بھرپور محسوس کرتے ہیں؟	☐	☐
۸۔	کیا آپ اپنی زندگی کو ایک خلا سمجھتے ہیں؟	☐	☐
۹۔	کیا آپ اکثر بور ہوتے ہیں؟	☐	☐
۱۰۔	کیا آپ کو اپنے ساتھ کچھ برا ہونے کا خدشہ ہوتا ہے؟	☐	☐
۱۱۔	کیا آپ اکثر لاچار محسوس کرتے ہیں؟	☐	☐
۱۲۔	کیا آپ سمجھتے ہیں کہ آپ کو یادداشت کے ساتھ مسئلہ باقی لوگوں سے زیادہ ہے؟	☐	☐
۱۳۔	کیا آپ سمجھتے ہیں کہ آپ کو موجودہ حالت میں امید نہیں؟	☐	☐
۱۴۔	کیا آپ سمجھتے ہیں کہ زیادہ تر لوگوں کی زندگی آپ سے بہتر ہے؟	☐	☐
۱۵۔	کیا آپ اپنی موجودہ حالت میں اپنے آپ کو بے قدر سمجھتے ہیں؟	☐	☐

نوٹل اسکور۔

۰-۴ [ ]

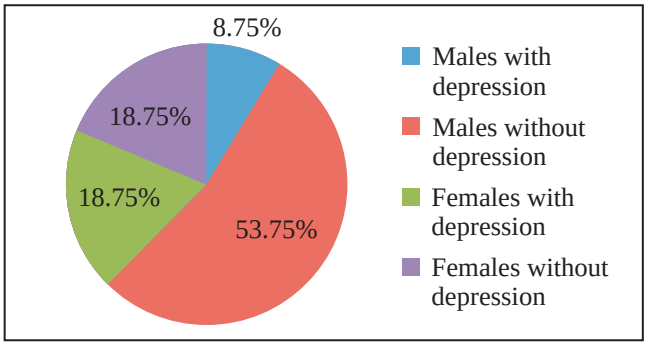
۵-۱۵ [ ]

RESULTS:

82subjects(30 females and 52 males) fulfilled the inclusion criteria and were requested to participate in the current study. Out of 82 subjects, 80 (30 females and 50 males) agreed to participate in the study making the response rate of 97.5%.

The mean calculated age was 67 years. Majority (86.8%) of the subjects fell in the age range of 65–74 years. Out of total 80 subjects, 62.5% (n=50) were male while 37.5% (n=30) were females. Out of the total 80 subjects, 27.5% (n=22) were diagnosed with depression using GDS-15. Majority of those who were found positive for depression by using GDS-15 were females. Out of 27.5% of subjects who were diagnosed with depression, 15 were females and 7 were males. Figure 3 depicts the detailed description of positive and negative cases of depression and its association with gender.

Figure: 3
Frequency of depression and gender



While focusing on the marital status, 92.5% (n=74) were unmarried. Those who were separated, divorced or widowed were also included in this category. Only 7.5% (n=6) were married and were living as couples. Among the married personnel, none of them were having depression according to GDS-15. Table 1 depicts the association of marital status with depression.

Table: 1
Association of depression with marital status
(n=80)

Marital Status	Total Number Subjects	Positive for depression according to GDS-15
Unmarried	74	22 (27.5%)
Married	6	0 (0%)

Total 66.2% (n=53) of the study participants were educated from Grade-5 till Grade-9, while 31.2% (n=25) had passed their matriculation examination (Grade-10). Remaining 2 (2.5%) study participants were having education of less than Grade-4. The educational status was also found to be related with depression. Table 2 portrays the detailed picture of relation of depression with the educational status.

Table: 2
Association of depression with educational status
(n=80)

Educational Status	Total Number Subjects	Positive for depression according to GDS-15
Grade 4 or below	2	2 (100%)
Grade 5 – Grade 9	53	16 (30.1%)
Grade 10 or above	25	4 (16%)

All the subjects were either unemployed or retired from their jobs. 23.75% (n=19) were financially dependent on their monthly pensions while 72.5% (n=58) were dependent on their families and rest of the 3.75% (n=3) were financially supported by the organization in every means. While associating depression with financial situation it was revealed that those who were financially dependent on their families were found to be comparatively more depressed as compared to those who were financially dependent on their pensions or organization itself (Table 3)

Table: 3
Association of depression with financial dependency
(n=80)

Financial Dependency	Depressed	Non-depressed	Total
Monthly pension	4 (21.05%)	15	19
Family / Relatives	18 (31.03%)	40	58
Organization	0 (0%)	3	3

Depression was more common in those subjects who were admitted in the elderly nursing care homes in a period of 3 months or less whereas the frequency of depression was comparatively less in those who were living there for more than 3 months duration. Among those who were admitted in a period of 3 months or less, 42.8% were found to be depressed while among those who were living for a period of more than 3 months, 26.5% were found to be depressed (Table 4).

Table: 4
Association of depression with duration of admission in nursing home
(n=80)

Admission duration	Depressed	Non-depressed	Total
3 months or less	9 (42.8%)	12 (57.1%)	21
More than 3 months	13 (26.5%)	36 (73.4%)	49

Involvement in different healthy activities including morning walk and exercise was found to have an important role in preventing depression. Majority of those who were involved in such healthy activities were mostly not having depression. Out of total 80 subjects, 22 reported to be performing exercise or morning walk on routine basis. All these 22 subjects were males. Out of these 22 subjects only 3 (13.63%) were having depression according to GDS-15.

DISCUSSION:

The current study helped us in finding the frequency of depression among elderly population residing in nursing home. Although previously, an appreciable number of studies have already been conducted to find the frequency of depression among elderly population living in different regions of Pakistan but according to our best available knowledge, not even a single study has been reported in Karachi depicting exclusively the frequency of depression among elderly admitted in nursing homes and old age houses.

Our study revealed that frequency of depression among elderly population residing in nursing homes is 27.5%. This percentage is slightly less than the prevalence of depression reported in another study that was conducted in Rawalpindi by using GDS-30.[23]The variation in findings could be due the difference in study settings as we conducted our study in a nursing home while the aforementioned study was conducted in an open community setting.

While correlating the findings of our study with similar studies conducted in neighboring countries of Pakistan, it was found that the prevalence of depression among elderly residing in an Indian community was ranging from 11.6% to 31.1%.[24] However, while analyzing the results reported by studies conducted in western countries, it was found that the prevalence of depression among elderly population was actually ranging from 14% to 42% in elderly residing in different institutions and 0.9% to 9.4% in elderly residing n private settings.[25] However, one of the studies conducted in United Kingdom reported prevalence of depression among 40% of elderly population[26].The prevalence of depression among elderly has been reported different in various studies and the variation has been attributed to different parameters including the diversity in population, culture, and different modalities that were used to assess depression.[27]

A strong evidence exists depicting higher prevalence of depression among elderly residing in nursing homes as compared to elderly living in their personal homes.[4,5,6] But on the other hand, a Korean study has revealed that the inhabitants of nursing homes are comparatively less depressed as compared to those who reside in their private homes. They have correlated this finding with the perception of safe environment, support and companionship as depicted by the residents of nursing homes.[20] Another study conducted in a local setting of Pakistan, in Rawalpindi revealed that people residing in nursing homes are at a high risk of developing depression as compared to those who reside in their personal homes. Pakistan has to face huge number of challenges while dealing with elderly population that is estimated to rise from 14.8% by the year 2050 from just 6.5% in the year 2013.[23]

CONCLUSION:

By using GDS-15, almost quarter of the subjects (27.5%) were found to have depression having comparatively more propensity in female subjects. Marital status, education, financial dependency on their families,recent admission in the nursing home and involvement in different healthy and recreational activities among the elderly admitted in one of the prominent nursing homes of Karachi were also found to be associated with depression.

Keeping in mind the current situation, it is the duty of the government to develop the health sector of Pakistan to meet the challenges of modern era. No doubt that the elderly population is the backbone of every society. They are the torch-bearers and blessed with visionary view of thinking. A nation cannot succeed without providing a contented platform to the entire elderly population.

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ORIGINAL ARTICLE

A Modified and Cost-Effective HPLC Method for Determination of Plasma Concentrations of Rifampicin in Pulmonary TB Patients

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ABSTRACT

Objective: To evaluate the pharmacokinetics of standard doses of rifampicin (RMP) in fixed dose combination in pulmonary tuberculosis patients by a modified high performance liquid chromatography (HPLC) method

Materials and Methods: This descriptive study was conducted after approval from Ethical Committee, Army Medical College Rawalpindi and was funded in part by National University of Sciences and Technology (NUST), Islamabad. Twenty adult patients with newly diagnosed pulmonary TB consented to participate in the study. RMP plasma concentrations were assayed by a simple and sensitive HPLC method in the initial phase of pulmonary tuberculosis treatment. The method was modified to use naproxen as an internal standard and validated according to International Conference on Hormonization (ICH) guidelines.

Results: The calibration curve of rifampicin was linear within the range of 0.781–50 µg/ml. Both intra-day and inter-day variability and accuracy demonstrated good reproducibility at all quality control levels. The developed method was found to be simple, precise and accurate for estimation of rifampicin in plasma. The pharmacokinetic parameters of RMP showed marked inter-individual differences and sub-therapeutic levels.

Conclusion: Evaluation of pharmacokinetics of standard doses of rifampicin in fixed dose combination in pulmonary tuberculosis patients by a modified high performance liquid chromatography (HPLC) method is precise, accurate and cost-effective. It may be used for monitoring plasma RMP levels in TB patients who are slow to respond or are non-responders and have less availability of resources.

Keywords: Tuberculosis, Rifampicin, Pharmacokinetics, High performance liquid chromatography, Accuracy, Precision, Cost effectiveness

INTRODUCTION:

The menace of tuberculosis (TB) with 9.2 million new cases and 1.5 million deaths annually, is a major public health issue. Pakistan, one of the highest burden countries contributes about 44% of the total TB burden in WHO Eastern Mediterranean region.[1] Despite TB declaration as national emergency since 2001 and expansion of directly observed treatment, short course (DOTS) throughout the health services, emergence of multidrug resistance is a matter of great concern and major public health challenge in Pakistan.

Poor bioavailability of rifampicin, in fixed dose combination (FDC) formulations with other anti-TB drugs such as isoniazid, pyrazinamide and ethambutol has raised serious concerns and impediment in wide-spread use of FDCs despite several advantages over separate formulations. This drop in bioavailability of rifampicin may lead to serious consequences such as increased treatment failure rates and selection of both isoniazid and rifampicin resistant strains of M. tuberculosis in the context of its high sterilizing activity, relapse preventing properties and prevention of emergence of resistance to its companion drugs.[2] A number of HPLC methods have been described in literature for pharmacokinetic (PK) analysis of rifampicin. However most of these methods used sophisticated instruments, expensive chemicals and internal standards. A simple, reliable and sensitive method is also been documented in the literature[3] but rifampicin used in this method as internal standard is quite expensive and is not available in our setup locally. The specified HPLC method for monitoring of rifampicin plasma levels in patients could be modified to make it more economical and applicable with the use of easily available and cost-effective internal standard, while maintaining the specificity, sensitivity and precision of original method, according to ICH guidelines.[4]

In this respect modification should be carried out by keeping in mind that after its incorporation the modified method should become easily reproduce-able for therapeutic drug monitoring of rifampicin. Especially in FDCs in TB patients whom response to treatment is very slow. With this background, present study was designed to evaluate the pharmacokinetics of standard doses of rifampicin (RMP) in fixed dose combinations (FDCs) in pulmonary tuberculosis patients by a modified high performance liquid chromatography (HPLC) method in our local setup.

MATERIALS AND METHODS:

This descriptive study was carried out in Pharmacology

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and Therapeutics department, Centre for Research in Experimental and Applied Medicine, Army Medical College, Rawalpindi, according to guidelines of Helsinki Declaration of 1975 and its amendments.[5] The study was funded in part by National University of Sciences and Technology (NUST), Islamabad Pakistan. After approval from Ethical Committee, Army Medical College, Rawalpindi twenty patients with newly diagnosed, active pulmonary tuberculosis were included in the study following informed consent. They were between 18 to 65 years of age and details about their phase of treatment and product details (FDC products or single drug products) were recorded on a proforma. Patients with deranged liver or kidney function tests, GIT diseases, diabetes mellitus, hepatitis B and C infection, history of drug addiction or alcohol intake, anti-HIV therapy, MDR-TB, pregnancy or lactation were excluded from the study. The patients were started on the standard anti-tuberculosis chemotherapy that is FDC Rifinah containing isoniazid (300mg) and rifampicin (600 or 450 mg), single drug products of pyrazinamide (maximum dose 1500 mg), ethambutol (maximum dose 850 mg) in accordance with DOTS, Pakistan National Tuberculosis Program guidelines based on the WHO DOTS TB control strategy. Eight patients weighing less than 50 kg received 450 mg of RMP/day orally and twelve patients more than 50 kg took 600 mg of RMP/day orally.

Analytical Procedure (Bioanalysis)

1. Instrumentation and Materials:

The HPLC system by Perkin Elmer Series 200 with autosampler and ultraviolet (UV) detector was used. Chromatographic separation was accomplished using a Schimadzu reverse phase-$C_{18,}$ stainless steel column (250 x 4.6 mm, 5 µm particle size) with a guard precolumn of the same packing material provided by Schimadzu Corporation, Kyoto Japan. The chromatograms were recorded on connected computer. The chemicals and solvents used in this study were of analytical and HPLC grade. Methanol and Sodium phosphate were purchased from Merck, Germany (C/O MS Traders, Pakistan). Phosphoric acid was purchased from Sigma Aldrich, Germany (C/O MS Traders, Pakistan). Naproxen (Internal standard) was provided by Ind-Swift Pharmaceuticals (C/O Guddia International, Pakistan) and Rifampicin by Schazoo Zaka Pvt Ltd.

2. Chromatographic Conditions and Preparation of Standards:

The UV detector was set at a wavelength of 254 nm. The final mobile phase composition optimized was methanol and 0.01 M phosphate buffer of pH 5.2, adjusted with 2% *o*- phosphoric acid (65:35 v/v). The mixture was filtered through 0.45 µm filter (Millipore, Sartorius, Goettingen, Germany) under vacuum and then sonicated. The mobile phase was pumped isocratically at a flow rate of 1.5 ml/min during analysis, at ambient temperature. The volume of injection was fixed at 50 µl. The chromatograms were recorded and integrated on connected computer. Rifampicin stock solution was prepared by dissolving it in methanol to make a 1 mg/ml solution containing 0.5 mg/ml of ascorbic acid to prevent oxidation of RMP. Calibration stock of RMP was suitably diluted to give working stock solution of 100 µg/ml and from this, calibration standards were prepared to contain concentration of 0.781, 1.562, 3.125,6.25, 12.5, 25, 50 µg/ml of rifampicin. Standard solutions were prepared fresh daily. Rifampicin used in this method as internal standard was quite expensive and not available locally, so it was modified to use naproxen as internal standard and validated according to requirements of International Conference on Hormonization (ICH) for validation of analytical procedures A stock solution of Naproxen was prepared by dissolving it in 65: 35 methanol: sodium phosphate buffer with a target concentration of 1mg/ml. From this stock solution dilutions were prepared to make 10, 50, 100, 200µg/ml working internal standard solutions. The solutions of internal standard were stored at -20°C between use and they were stable for, at least, two weeks.

3. Calibration Curve and Plasma Sample Processing:

Solutions of rifampicin and naproxen were made. The curve covered the concentration range of 0.781 to 50µg/ml for rifampicin using seven standard concentrations. Each concentration of standards was run in triplicate to make the calibration curve. The calibration curve was generated by plotting the ratio of the peak area of rifampicin and naproxen against the rifampicin concentration in standard solutions. The curve was based on simple linear model relating the rifampicin concentration to the HPLC response. Plasma samples were processed by adding 200 µl of calibration standards of different concentrations and 200 µl of naproxen (200 µg/ml) into 1.5 ml eppendorf tubes from working stock solutions. These mixtures were dried and mixed with 5 µl of methanol, then 95 µl of plasma was added and vortexed for 60 seconds. Spiked plasma was then extracted with 500 µl of methanol by vortexing for 3 min. The samples were centrifuged at 10,000 revolutions per minute for 15 minutes, and 300 µl of supernatant was taken into another micro centrifuge tube and vacuum dried in eppendorf concentrator. The residue thus obtained was reconstituted in 200 µl of mobile phase and finally aliquots were loaded on the autosampler tray and volumes of 50 ìl were injected onto the HPLC. The drug and internal standard were detected at 254 nm.[3]

4. Method Validation Procedures:

Pooled quality control samples were prepared to determine the precision and accuracy of the method, and to evaluate the stability of samples. All control samples were aliquoted into polypropylene vials and stored at approximately -80°C. Quality control samples were run as replicates of blank plasma spiked with a low concentration (3.125µg/ml), a middle concentration (12.5µg/ml) and a high concentration (25 µg/ml) of rifampicin along with a fixed concentration (200 µg/ml) of internal standard. The identification of rifampicin was made on the basis of retention time on chromatograms obtained from plasma samples spiked with standard solutions of rifampicin and comparing with blank plasma samples. The solution was considered

stable if in the described storage conditions variation in the concentration is inferior to 2 percent. The retention time for rifampicin was 8.5 minutes and it was 10.5 minutes for naproxen. The solution is considered stable if in the described storage conditions variation in the concentration is inferior to 2%. The limit of detection (LOD) is defined as the lowest concentration of the analyte in a sample which can be detected but not necessarily quantitated with precision. Linearity was assessed by calibration curve constructed using 7 standard solution concentrations covering the range of 0.781–50 µg/ml. Standard curves were analyzed in triplicate. The lower limit of quantitation (LLOQ) for rifampicin was selected as the lowest concentration of the standard curve at which the rifampicin peak was identifiable and discrete with suitable precision (coefficient of variation (CV) of less than 20 percent) and accuracy (determined concentration being within 20 percent variation of the nominal concentration). The acceptance criterion for precision of analytical method recommended by Food and Drug Administration for each calculated standard concentration is a 15 percent coefficient of variation from added concentration value except at the LLOQ, where it should not deviate by more than 20 %. In accordance with ICH recommendations, precision is determined at two levels, i.e., repeatability and intermediate precision. The acceptance criterion for accuracy of the method is that the mean measured concentration should be within 80–120 of the actual concentration. The precision and accuracy of the plasma assay for rifampicin was evaluated by analysis of 5 replicates of quality control samples at three different concentrations (within the calibration range), for 3 days.

5. Application of Analytical Method:

After validation, this method was applied to determine the pharmacokinetics of rifampicin in 20 pulmonary tuberculosis patients. On the scheduled day of pharmacokinetic assessment, patients abstained from the intake of any eatable or drugs from 11 p.m. on the day before the sampling until 1 hour after the intake of anti-TB drugs. Blood sampling was done before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after witnessed drug ingestion. Each sample was transferred to lithium-heparinized tubes placed in ice, and was immediately centrifuged at 4000 rpm for 10 min. Plasma was harvested into labeled eppendorf tubes containing ascorbic acid (0.5 mg/ml), and stored at -80°C within 1 hour of collection, until analysis. Plasma samples of the patients were processed in the similar manner as calibration standards along with internal standard.

6. Pharmacokinetic Data Analysis:

Data of drug plasma concentration versus time for rifampicin was tabulated using Microsoft Excel 2007 computer program. The data was used to calculate pharmacokinetic parameters i.e., elimination half life, area under plasma concentration time curve, volume of distribution and plasma clearance, by computer program, APO, MWPHARM version 3.60, a MEDIWARE product Holland.

The non-compartmental pharmacokinetic model was used to compute the pharmacokinetic parameters of rifampicin. The pharmacokinetic parameters for RMP were derived individually for each subject from the plasma concentration versus time data. Concentration-time curves were plotted for each series of drug assays. From these plots, the maximum concentration of drug in plasma was defined as the Cmax, and the time to reach this maximum concentration as Tmax. The area under the plasma concentration-time curve until 12 hours (AUC_{0-12} hr.mg/l) for rifampicin was determined by the (linear/logarithmic) trapezoidal rule up to the last data point. The AUC extrapolated to infinity (AUC_{0-8} hr.mg/l) was calculated using the relation AUC_{0-12} + *Cm*/kel, where *Cm* is the last measured concentration of rifampicin and kel is the slope of the least squares linear regression of the log concentration-time curve. The computer program, APO, MWPHARM version 3.60, a product of MEDIWARE, Holland, was used to calculate pharmacokinetic parameters. The non-compartmental pharmacokinetic model was used to compute the pharmacokinetic parameters of rifampicin derived individually for each subject from the plasma concentration versus time data.

RESULTS:

Method Validation:

The calibration curve of rifampicin in plasma using least square regression equation was linear within the range of 0.781–50 µg/ml (Figure 1). The correlation coefficient and intercept were, $y = (33366)\ x + (32760)$, $r^2 = 0.998$. The retention time for rifampicin was 8.5 minutes and it was 10.5 minutes for naproxen (IS) (Figure 2a & 3a). The LOD was determined by diluting solutions of known concentrations of RMP until the response was three times the noise. The LOD of rifampicin in plasma samples was 0.5µg/ml. For rifampicin analysis in plasma by this method LLOQ was 0.781µg/ml. The coefficient of variation was found to be 6.8%. The accuracy was found to be 92.73%. The stability of samples was demonstrated by subjecting the three different concentrations of rifampicin to three freeze-thaw cycles and storage for 24 hours at room temperature. The freeze-thaw cycles showed little effect on the stability of the samples as the percent accuracy was in the range of 96.40-101.12 % and variability ranged between 1.16 to 1.90 %. Rifampicin was stable in plasma, enriched with 1 mg/ml of ascorbic acid at -80°C, for at least 5 months.

The CV for intra-day variability ranged between 5.5–7.89% while the inter-day CV ranged between 7.35 to 9.93%. The percent accuracy was in the range of 89-102% for intra-day assays and 91-104% for inter-day assay (Table 1). The derived pharmacokinetic parameters for rifampicin in TB patients are given (Table 2). Representative HPLC chromatograms of rifampicin with blank plasma spiked with internal standard at 6.25 µg/ml, 12.5 µg/ml, LLOQ (0.781 µg/ml) and patient samples are provided in figures 2a, 2b, 2c and 3a, 3b, respectively.

Behaviour of mean values of pharmacokinetic profile of Rifampicin 450 and 600 mg are shown in Figure 3c.

Figure: 1
Calibration curve of rifampicin

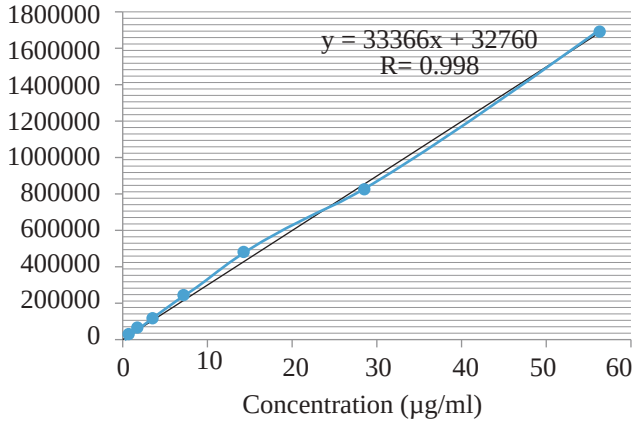

Figure: 2a
Chromatogram obtained from blank plasma spiked with internal standard and external standard of 6.25 µg/ml of rifampicin

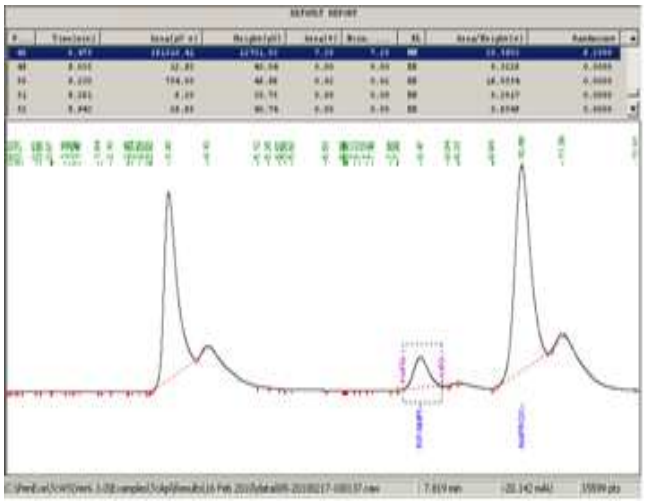

Figure: 2b
Chromatogram obtained from blank plasma spiked with internal standard and external standard of 12.5 µg/ml of rifampicin

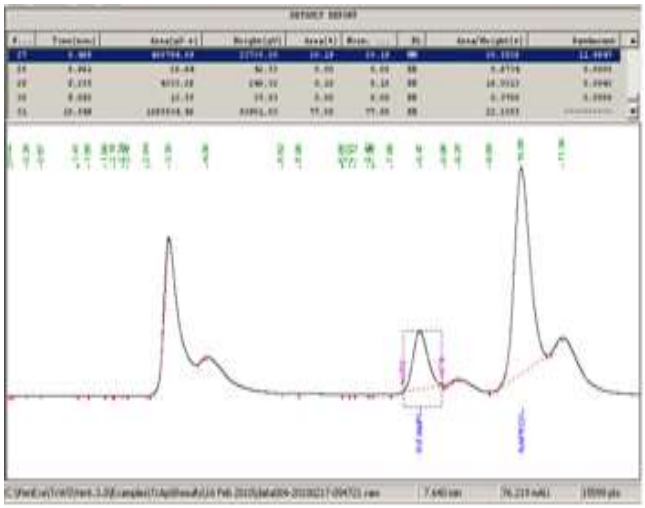

Figure: 2c
Representative HPLC chromatogram of rifampicin at LLOQ (0.781 µg/ml)

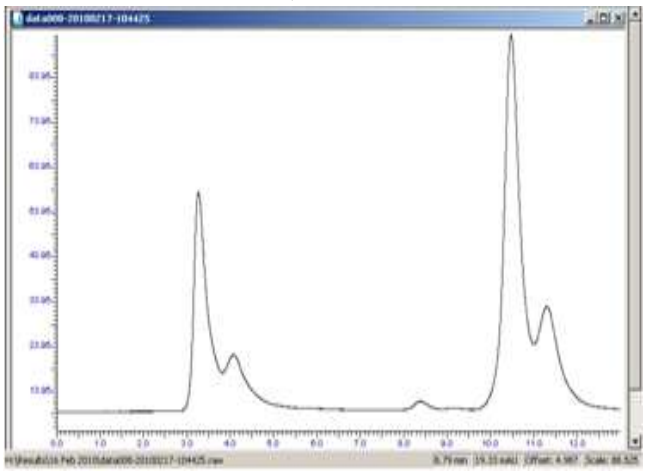

Figure: 3a
Chromatogram obtained from a TB patient plasma spiked with internal standard

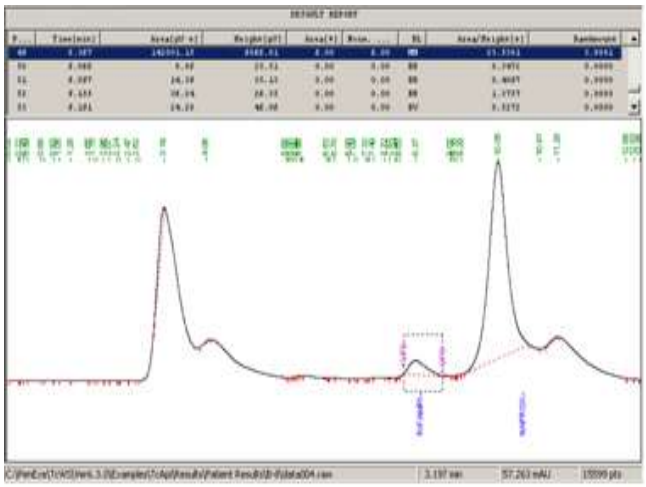

Figure: 3b
Chromatogram obtained from a TB patient plasma spiked with internal stand

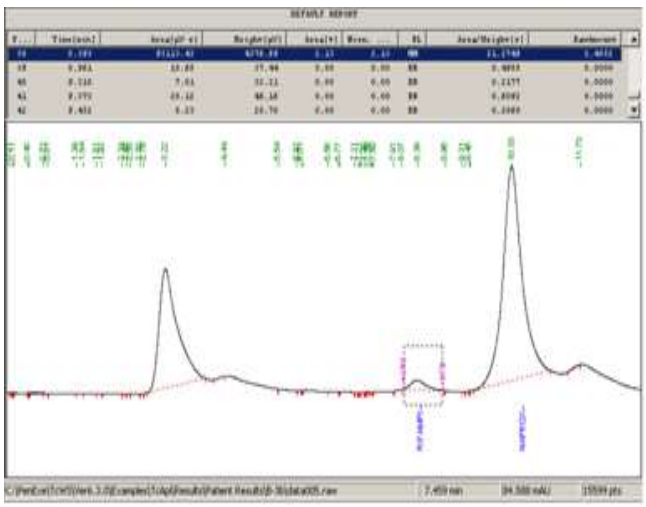

Figure: 3c
Behaviour of mean values of pharmacokinetic profile of Rifampicin 450 and 600 mg

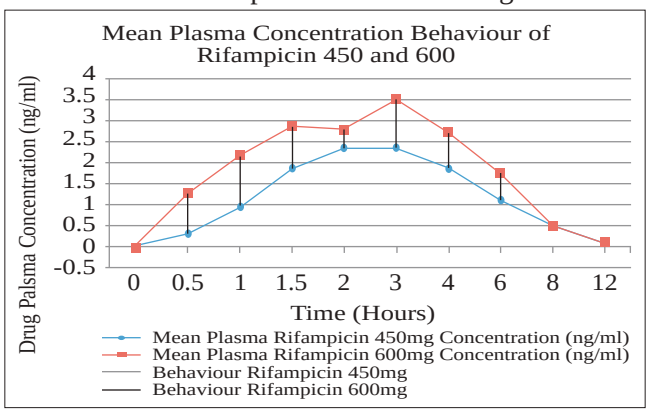

Table: 1
Intra and inter-day precision and accuracy of rifampicin assay

Assay Validation Procedures	Conc Added (µg/ml)	Conc Found (µg/ml) Mean ± SD	Coefficient of Variation (CV %)	Accuracy %
LLOQ	0.781	0.724 ± 0.050	6.80	92.73
	3.125	3.194 ± 0.252	7.89	102.21
Intra-assay	12.5	11.12 ± 0.722	6.49	88.96
Reproducibility	25	24.93 ± 1.370	5.5	99.74
	3.125	3.28 ± 0.326	9.93	104.96
Inter-assay	12	11.38 ± 0.860	7.56	91.04
Reproducibility	25	25.06 ± 1.841	7.35	100.23

Table: 2
Pharmacokinetic Parameters of Rifampicin in 20 TB patients after standard doses of rifampicin

Pharmacokinetic Parameters	Mean	± SD	Min	Max
AUC0-8 [h.mg/l]	17.43	± 6.97	6.08	34.17
AUC0-12 [h.mg/l]	16.83	± 6.63	6.01	31.53
CL [l/h]	35.93	± 14.81	17.56	74.04
Vd [l]	72.29	± 39.43	15.73	145.2
k [/h]	0.647	± 0.392	0.171	1.591
t ½ [h]	1.54	± 0.97	0.44	4.06
Tmax [h]	2.2	± 0.66	1	3
Cmax [µg/ml]	3.77	± 1.23	1.79	6.62

Min = Minimum; Max = Maximum
*Adapted from previous published work by the same author 14.

DISCUSSION:

A number of analytical methods have been reported in literature for determination of rifampicin in plasma. However this modified analytical method showed reasonable specificity, sensitivity, linearity, precision and accuracy in the entire range of clinically significant concentrations in the plasma. This modification and validation of method may be beneficial for therapeutic monitoring of RMP in TB patients with less expenses and easy reproducibility as internal standard naproxen used was cost-effective and easily available. In fact, there are many compounds selected for internal standard in different validated analytical methods reported in literature e.g, papaverine chloride, acetonitrile, acetanilide, carbamazepine[6,7,8.] However the associated solvents and chromatographic conditions requirement is very expensive in all these methods[9,10,11,12,13.] Some of these reported methods require LC-MS setup which is not even available at most research centers in Pakistan. So in a country with high TB prevalence the use of a validated and reliable method with use of internal standard naproxen instead of very expensive rifapentine may even improve the value of this chromatographic method and therapeutic drug monitoring in slow responders or non-responders and in quality evaluation of widely available FDCs and single dose formulations. The pharmacokinetic profile of our study patients has been published previously, according to which the mean maximum plasma concentration (Cmax) of rifampicin was 3.77 ± 1.23 µg/ml at standard doses. Our previous study also reported a widespread inter individual variability in plasma levels of rifampicin at two hours with a coefficient of variation 32.63%. Among 20 patients, seven patients exhibited peak plasma concentration of rifampicin between 4 and 8 µg/ml. whereas 13 patients had peak plasma levels below 4 µg/ml [14] The peak therapeutic range of rifampicin at 2 hours for optimum anti-mycobacterial effect is 8–24 µg/ml. Rifampicin concentration below 4ìg/ml is sub-therapeutic and associated with a risk of emergence of drug resistance.[11] A number of studies with tuberculosis patients, treated with 10 mg/kg RMP daily have revealed suboptimal peak plasma levels most probably due to lack of compliance, auto-induction of its own metabolism, dosage formulation and interaction with other drugs, mal-absorption syndromes, low albumin levels.[16,17,18,19] The compliance of patients to treatment was ensured in this study using DOTS in hospitalized patients and drug interactions were also ruled out when recruiting the patients for study.

In pharmacokinetic profile of our patients, the more noticeable decrease in the area under curve might be due to reduced bioavailability of rifampicin from the FDC. Our study patients were receiving a FDC product of RMP and INH in addition to pyrazinamide and ethambutol. Rifampicin in fixed dose combinations shows considerable variation in rate and extent of absorption as compared to single dose formulations. Dissolution and disintegration properties of oral formulations of rifampicin, delayed absorption of formulations of infer this significant drop in bioavailability of rifampicin.[20,21,22,23,24,25]

CONCLUSION:

In conclusion, this study has demonstrated modification and validation of a HPLC method, which can be effectively used for therapeutic monitoring of RMP in TB patients. Further studies are desperately needed to evaluate the bioavailability of RMP from local FDC preparations used in TB patients in context of its highest sterilizing potential and alarming increase in the incidence

of MDR-TB in Pakistan. The quality control problems are needed to be seriously addressed in local drug preparations especially FDCs, widely used among TB patients in Pakistan.

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ORIGINAL ARTICLE

Analysis of BMD and Serum Calcium Level in Patients with or without Bony Metastatic Breast Cancer

Hoor Fatima[1], Hafiz Rafiq Tagar[2], Afshan Chodhry[3], Shafqat Qamar[4]

ABSTRACT:

Objective: To analyze bone mineral density (BMD) and serum calcium in patients with and without bony metastatic breast cancer.

Materials and Methods: This descriptive study was conducted in KIRAN Hospital Karachi and Department of Biochemistry, BMSI-JPMC Karachi from March 2011 to March 2012 .After approval by BASR of Karachi University 200 diagnosed cases of breast cancer, reproductive and postmenopausal age group females, passing through any stage of cancer, married or unmarried, lactating or non-lactating, having different body mass index, passing through any cycle of chemotherapy and radiotherapy were selected. Consent of patients was taken on a form. Bone scan was done on Siemen E Cam scanner. Intravenous dye 20/mci technetium 99 MDP has been used, to check the bone metastasis in breast cancer patients. Test for Bone Mineral Density was done on Hologic software version 12. Serum calcium levels were checked on Selectra-E- semi auto biochemical analyzer.

Results: 40-49 years group showed highest number of cases of osteoporosis (24%). Bone scan positive patients showed osteopenia (11%) in 40-49 years group. Distribution of subjects with osteopenia (15%) was more common in bone scan negative patients especially in age group of 40-49 years. Serum calcium level was found to be comparatively increased in bone scan positive patients than in bone scan negative patients again in age group 40-49.

Conclusion: In bone scan positive patients osteoporosis and serum calcium were high in comparison to bone scan negative patients with most vulnerable age group being 40-49 years, in diagnosed cases of breast cancer.

Keywords: Breast cancer, Bony metastasis , Bone scan, Bone mineral density, Osteoporosis, Osteopenia, Serum calcium.

INTRODUCTION:

Breast cancer is a big challenge for health in females. It is still growing problem but strenuous efforts for early catch of disease and best treatment as a combine therapy has greatly decreased the associated mortality in metastatic cases. But 5 years survival rate is 25% only[1]. Short survival reasons may be the complex and heterogenous mechanism of metastasis influenced by various biological features and site of metastasis. Visceral metastasis has appeared as one of the main cause of short survival[2].

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A retrospective analysis of circulating cell tumor, there deposition and progress of disease has been done for the assessment of survival and as technique to monitor the disease. It has found that circulating tumor cells before treatment strongly correlate with visceral disease and direction of their spread (circulating tumor cells as early predictors of metastatic spread in breast cancer patients with limited metastatic dissemination)[3]. Bone scintigraphy is proved as a common procedure to extract the knowledge of tumor metastasis, extent of burden and associated survival.[4,5,6] Bone scan is a prognostic indicator and used as imaging biomarker in cancers, showing bony metastatic tendency[7,8,9]. The relationship between localized bone scan measurement with age and survival have found no correlation and localized bone scan imaging value was ($P= 0.1$), however result of regional bone scanning was significant ($P<0.05$)[10]. George have found direct relationship of higher BMD of total body to high lean mass and FM (Fat mass) of body[11]

Victims of breast cancer often suffer in skeletal weakening. As research has proved, non- pathological hip fractures are more common and at early on set in postmenopausal women. The risk of fall is 15% and 55% for fracture of hip.[12,13,14] Bone is the most common site of distant metastases from breast cancer and is the first affected site in a substantial proportion of women with advanced breast cancer.[15]In advance stages of cancer showing tendency to spread to bones are associated with severe skeletal illness and complications until they received Bis- phosphonates.[16]Hypercalcemia was commonly found in patients with squamous cell lung cancer, breast cancer, kidney cancers and some blood cancers. The main cause of this hypercalcemia was found to be bone destruction in almost 80% of cases. Hypercalcemia was also found in cancer metastasis

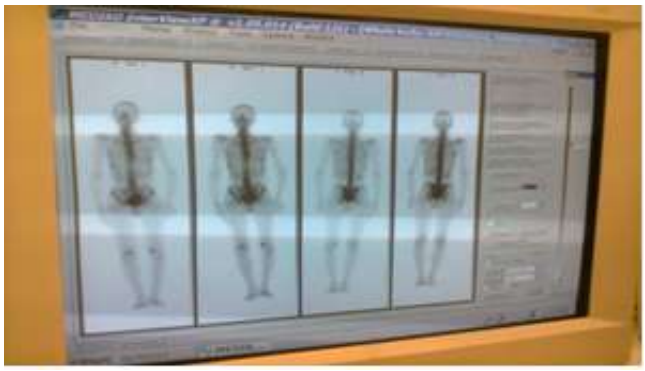
but the main cause might be reduced parathyroid and related hormones[17].Baker has documented resorptive changes and osteoporosis in relation to RANKL gene, ostoproteogen and AMG 162 and have found decreased calcium and phosphorous levels in patients with cancers resting AMG 162 as antiresorptive factor (Ant Rank L monoclonal antibody).[18]Present study was designed to find out the frequency of bone mineral density (BMD) and serum calcium in patients with and without bony metastatic breast cancer

MATERIALS AND METHODS:

Selection of patients: After approval by BASR of Karachi University 200 diagnosed cases of breast cancer were selected for this descriptive study. The study was conducted in the KIRAN Hospital Karachi, Biochemistry Department of BMSI-JPMC Karachi from March 2011 to March 2012.Reproductive and postmenopausal age group females, passing through any stage of cancer, married or unmarried, lactating or non-lactating, having different body mass index, passing through any cycle of chemotherapy and radiotherapy were included in the study. A memorandum of under standing (MOR) was signed by authorized persons of University of Karachi and KIRAN hospital. Willingness (signature) of every patient was taken on patients form.

Bone scan: Bone scan was done on Siemen E Cam scanner with accessories. Intravenous dye technicium 99 MDP was used. This test helps to see if a cancer has metastasized to bones and is useful because it provides a picture of the entire skeleton. For this purpose, 20/mci (dose) of radioactive material (technetium 99) was injected into a vein (intravenously or IV). The substance settles in areas of damaged bone throughout the entire skeleton over the course of a couple of hours. (Six hours to twenty four hours). Patient was made to lie down on a table for about 30 minutes while a special camera detected the radioactivity and created a picture of the skeleton (Figure 1).

Figure: 1
Bone scan film



Skeleton after dispersion of radioactive dye, affected areas appeared as dark spots. (With the permission of Kiran Hospital Karachi.)

Biophysical parameters BMD: was performed with DEXA technique using discovery-w (HOLOGIC), P/A spines and left hip images were acquired , the data was analyzed by HOLOGIC Soft ware version 12. Result of BMD (computerized software) was interpreted by calculating the area of image in square centimeter, bone mineral content, bone mineral density, T and Z score. T score is used for patients between 40- 65 age group and Z score is used for patients < 40 years and above 65 years age group. T score is < -1, BMD is normal. T score is in between 1.1- 2.4, patient is ostopenic. T score is > 2.5, patient is osteoporotic. Z score is< -2.0, BMD is normal. Z score is >2.0, patient is osteoporotic.

Biochemical parameter serum calcium: Serum Calcium was determined by in vitro test for the quantitative determination of calcium in human serum and plasma on Roche automated clinical chemistry analyzer. Kit Cat. No. 14862 Ecoline.[20] Sample collection: samples, 3ml, were collected in heparinized syringe. Reagents: were Reagent 1 composed of Imidazole buffer 100mmol/L PH 6.5. 1,8-dihydroxy-3,6-2-7- and Reagent 2 composed of naphthalene-bis dibenzenearsonic acid (Aesenazo 111) 120mmo/L.

All (except CA15-3) were done on Selectra–E, XL semi auto biochemical analyzer. Vital Scientific and diagnostic Machine, Netherland, Holand latest model by ROCH (Figure 2).

Figure: 2
Selectra-E XL semi auto- biochemical analyzer

RESULTS:

In patients with positive bone scan, bone mineral density was measured. Age group of 40-49 years showed highest number of cases of osteoporosis. Higher frequency of osteoporosis showed in age group of 60-69 years. Age group 50-59 years and above 70 showed the same frequency of osteoporosis but comparatively less as compared to age group 40-49 and 60-69 years (Table 1) Bone scan positive patients showed osteopenia in age group 40-49 years at same frequency. Distribution of subjects with osteopenia was more common in bone scan negative patients especially in age group of 40-49 years as compared to osteoporosis.24% cases had osteoporosis on BMD in five bone scan were significantly high as compared to 9% negative BS ($P<0.01$) (Table 2). Serum calcium level was found to be comparatively increased in bone scan positive patients than in bone scan negative patients, especially in age group 40-49 and above. Comparison of serum calcium levels among different age groups of positive and negative bone scan was found to be insignificant except in age group 40-49 years where serum calcium level was less in subjects

with negative bone scan as compared to positive bone scan (Table 3 & Figure 3)

Table: 1
Comparison of age with bone scanning

	Bone scanning		
Age in years	Positive (n=100)	Negative (n=100)	P-value
Under 30	8	5	
30-39	20	21	
40-49	32	35	
50-59	22	27	
60-69	12	9	0.732
70 & above	6	3	

** Statistically Significant p<0.01

Table: 2
Biophysical parameters in bone scanning positive and negative cases

	Bone scanning		
Bone Mineral Density	Positive (n=100)	Negative (n=100)	P-value
Normal	65	76	0.088
Osteoporosis	24**	9	0.004
Osteopenia	11	15	0.400

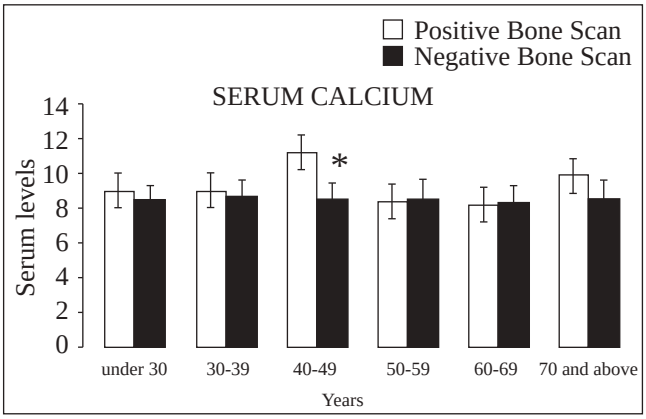
** Statistically Significant p<0.01

Table: 3
Biochemical parameter in bone scanning positive and negative cases

	Bone scanning (Positive) (n=100)			Bone scanning (Negative) (n=100)			P-
	Mean	S.D	SEM	Mean	S.D	SEM	value
Serum Calcium	11.3	21.09	2.13	8.5	0.67	0.07	0.191

** Statistically significant p<0.01

Figure: 3
Serum calcium levels in subjects with positive and negative bone scan



Values represented as means ± SD. Statistically significant difference from patients with positive bone scan following student t- test were not found

DISCUSSION:

The most frequent cancer all around the world is the breast cancer. Breast cancer in Asian population causes nearly 40,000 deaths per year. Every 1 in 9 of Pakistani women will suffer from breast cancer at some stage in their lives[20]. Pakistan faces a high burden of breast cancer disease with late presentation. In this study 81% patients were diagnosed in late stage. Another study also showed the late presentation in advanced stages III and IV, in 71% patients[21].The causes of late presentation were social, self-neglect, fear of surgery, and financial constraints etc.[22]

Previous research has established the percentage of breast cancer metastasis to bones approximately 80% or more especially in cases with advance stages of carcinoma and the destructive osteolysis. Many other bone related complications are associated with metastasis and osteolysis. Inspite of this patients with breast cancer and bone metastasis may survive for many years.[23,24,25] Houssani has proved that PET scan, MRI and CT scan may enhanced the accuracy of diagnosis of bone metastasis of cancer but the accuracy was only some degree greater than bone scan (BS), cost is very high of above mentioned tests as compared to bone scan and little evidence support application of these tests for diagnosis of bone metastasis. Still BS is preferred as first line of imaging.[26]

Our study showed significant relationship of bone scan, breast cancer and bone mineral density (P<0.04) in cases of breast cancer with bone metastasis for osteoporosis. That is evident of high risk of osteoporosis and morbidity in number of cases with positive bone scan of breast cancer. Ostopenia was seen more commonly in patients of breast cancer with negative bone scan. George has compared skeletal weakening and no pathological fractures in postmenopausal women without cancer and found increase incidence of non pathological hip fractures and osteoporosis at early age onset in patients with breast cancer .Disentangling the body weight bone mineral density association among breast cancer survivors. An examination of the independent roles of lean mass and fat mass.[11]

Fraenkel has provided the additional information based on research to find out the association of BMD and risk of breast cancer and found a significant risk of breast cancer development and low survival rate in cases with low BMD and high BMI as compared to women with low BMI and high BMD.[27]

Serum calcium level in patients with bony metastatic breast cancer and related osteopenia was non-significant in our study. Serum calcium levels were almost normal in most of cases in positive bone scan but levels were found to be decreased in negative bone scan in perimenopausal women. Rowan has found out the relation between breast cancer in postmenopausal women and $VitD_3$ level but result was significant.[28]In another study of 718 patients with bony metastatic breast cancer, hypercalcemia is indicated as a skeletal complication. Medium time for spread to skeletal areas and first relapse was determined to be 11 months. Survival was longer

in cases with the diagnosis of bony metastasis as compared to other site of metastasis.[17]

CONCLUSION:

In bone scan positive patients osteoporosis and serum calcium were high in comparison to bone scan negative patients with most vulnerable age group being 40-49 years There is a strong relationship seen between breast cancer, bone scan and bone mineral density. In Patients with bony metastatic breast cancer, osteoporosis is more common as a skeletal complication. Perimenopausal age group of breast cancer is more prone to osteopenia even without bone metastasis. Serum calcium level is independent of bone metastasis and was found comparatively less in negative bone scan patients.

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ORIGINAL ARTICLE

Pattern of Missing Teeth among Patients Visiting Hamdard University Dental Hospital Karachi

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ABSTRACT

Objective: To evaluate the pattern of edentulism in partially dentate patients according to Kennedy's system of classifying edentulous arches.

Materials and Methods: This cross-sectional study was carried out in the department of Prosthodontics of a tertiary care hospital.A total of 600(336 males and 264 females) patients were enrolled for the study. They were evaluated on a prescribed form.All patients visiting for replacement of missing teeth were included in the study. Completely edentulous and the patients with facial defects were excluded from the study.Collected data was analyzed on Statistical Package for Social Sciences version-16.

Results: Kennedy's Class I comprising patients were 49% while Kennedy's Class II, III & IV comprisingpatients were 15, 21 & 15%, respectively. More male patients reported for their teeth replacement as compared to females.

Conclusion: Evaluation of pattern of edentulism in partially dentate patients according to Kennedy's system of classifying edentulous arches showed Kennedy's class I to be the most common class. More mandibular teeth were found missing as compared to maxillary ones.

Keywords: Partial Edentulism, Kennedy's Classification, Missing teeth

INTRODUCTION:

Partial Prosthodontics has always been a versatile, affordable, easy to deliver and manageable method of treatment for partially dentate patients of any age group. Even though, recent reports have shown a consistent decline in the prevalence of partial edentulism during last few decades, they remain significant variation in tooth loss distribution[1].The primary purpose for categorizing and classifying the partially dentate arches is to identify potential combinations and relations of teeth to edentulous spans in order to facilitate communications among dental professionals, for the sake of better diagnosis and treatment planning. Teeth are integral components of the stomatognathic system. Their significant loss may affect the normal life and personality of the patients and their different functions like: speech, chewing abilities. These factors may further lead to poor aesthetics and other health issues like malnutrition and indigestion due to improper chewing. A definitive replacement of this partial edentulism is usually required to overcome these functions and aesthetic requirements of the patients, through proper diagnosis and treatment planning.[2]The designing and planning of the partial prosthesisalways depends upon the pattern of partial edentulism. In the absence of a reputable and reliable classification system, the numbers of possible combinations of the teeth present, from absence of a single tooth in mandible or maxilla, to the loss of all but one tooth in both jaws, is almost impossible to comprehend. A universally acceptable classification of partially dentate jaws would not only help to diagnose the potential combinations of teeth to edentatejaws but would help in facilitating communication, discussion, and understanding of the prescribed prosthetic treatment among dental professionals, students and laboratory personnels.[2] Not only this, but it will also facilitate the recording and simplification of exchange of information between dentists and their other supporting staff.[3,4,5]

Tooth loss an age related and almost an inevitable major clinical dental problem. This relation between age and natural tooth loss has been documented in the literature.[6,7]However, this may vary from one person to another on the basis of level of education and socioeconomic position of that individual, which in turn, may even affect the treatment plan.[8,9]Current changes in dietary trends and the life style of people are also among the factors that would affect and alter the oral condition and influence the pattern of loss and teeth and

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their supporting structures.[8]

Different literatures has shown that the ratio of tooth loss is more in males, as compared to the females reporting for partial prosthesis.[6,8,10]Dental caries is considered to be the major etiological factor behind the tooth loss followed by periodontitis and other oral problems as indicated in various publications world-wide.[6,9]

Documentation of the occurrence and configuration of partial edentulism is an indispensible diagnostic step in the treatment planning in all patients in general and in removable partial prosthodontics, in particular.[11]A clear understanding of the pattern of missing teeth in either arch enables clinicians and laboratory professionals to understand the needs and requirements for oral rehabilitation and prosthetic replacement and materials to be utilized in that course of treatment[12]. Also, it is regarded as one of the important measures for assessment of standard, availability and utilization of curative and preventive oral health care system.[7]Only a few studies have evaluated the occurrence of partial edentulism among dental patients in Pakistan so the purpose of this study is to determine the prevalence and pattern of missing teeth in relation to Kennedy's classificationa-mong patients visiting the department of Prosthodontics in a tertiary care hospital.

MATERIALS AND METHODS:

This cross sectional study was carried out from June 2008 to May 2009, at the Department of Prosthodontics of Hamdard University Dental Hospital Karachi, Pakistan. Convenient sampling technique was utilized for sample collection. The total sample size incorporated was 600 patients. Ethical approval was sought from the Ethical Review Committee of the University and written consent was taken from the patients. Patients of either gender, age above the fifteen years, having partially edentulous areas in one or both jaws were included in the study. Completely edentulous patients and mentally retarded patients were excluded from the study. A complete clinical examination of both the dental arches of each patient was carried out by using dental mirror on the dental unit. Patterns of partial edentulism were recorded by using the Kennedy Classification and collected data was recorded on a specially designed proforma.

Data was analyzed by using Statistical Package for Social Sciences version-16. Mean and Standard Deviation were calculated for continuous variables like age. Frequencies and percentages were calculated for categorical variables like gender, missing teeth in arch and type of Kennedy Classification. Cross tabulation was done to calculate different modifications of Kennedy classification. P- Value less than 0.05 was taken as significant.

RESULTS:

Male and female patients were 56% and 44%(336 males and 264 females) respectively. Male female ratio was 5.6:4.4. The mean age was 41.15, while the minimum age was 16 years and maximum age was 78 years with age range of 62 years (Table 1), 58.2% and 20.3% teeth were missing in lower jaw and upper jaw respectively while 21.5% teeth were missing in both jaws (Table 2).According to Kennedy classification 49% patients fall in Class-I, 15% in Class-II, 21% in Class-III and 15% in Class-IV (Figure 1). According to Modification of Kennedy classification, in class-I the modification-1, modification-2 and modification-3 was seen in 27%, 7.5% and 0.7% patients respectively, in class-II the most common modification was modification-1 and least common was modification-3 and in Class-III the common modification was modification-1 followed by modification 2 and 3 (Table 3)

Table:1
Frequency of gender

Gender	Freqency	Present(%)
Male	334	55.7
Female	266	44.3
Total	600	100.0

Table:2
Frequency of missing teeth according to arch

Type of Arch	Frequency	Present(%)
Mandible	349	58.2
Maxilla	122	20.3
Both	129	21.5
Total	600	100.0

Figure:1
Frequency of Kennedy classification

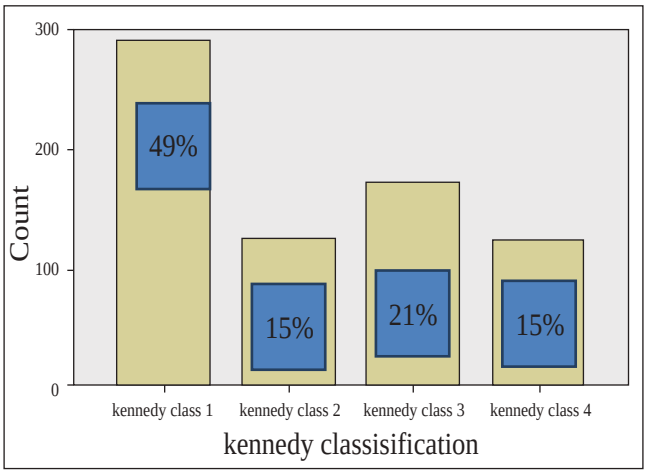

Table: 3
Frequency of modification of Kennedy classification

	Modification of Kennedy classification				
Kennedy Classification	Modification-1	Modification- 2	Modification- 3	No-Modification	Total
Kennedy Class-I	80 27.1%	22 7.5%	2 .7%	191 64.7%	295 100.0%
Kennedy Class –II	16 17.4%	6 6.5%	1 1.1%	69 75.0%	92 100.0%
Kennedy Class –III	30 24.2%	18 14.5%	10 8.1%	66 53.2%	124 100.0%
Kennedy Class –IV	0 .0%	0 .0%	0 .0%	89 100.0%	89 100.0%
Total	126 21.0%	46 7.7%	13 2.2%	415 69.2%	600 100.0%

DISCUSSION:

The primary purpose in using a classification for removable partial edentulous cases is to simplify the description of potential combinations of teeth to ridges. In this study, Kennedy's system of classification was preferred to fulfill this purpose[13] as it remains the most widely acceptable system for the purpose.

The results of the present study showed that more number of patients belonged to male gender which resembles the results of similar study by Butt[14]in contrary to the results of study by Zaigham[15]which reported for majority of female patients in their results. This contrast for more males presenting in our study with partial edentulism may be due to the local tradition and cultural values and difference in eating habbits of local population. In less developed countries like ours, females seek treatment less frequently; like dental restorations, especially if these are to be provided by male dentists. Poor socio-economic position and lack of awareness in local population may also be counted as an additional factor to this difference[16]. This contradiction may be due to the different socio-economic background and mal-habits like smoking and consumption of high sugar containing diets.

One of the principle advantages of the Kennedy classification is that it permits the immediate visualization of the partially edentulous arch, and enables a logical approach to the problems of design, and is therefore termed as a logical method of classification.[1,17,18,19,20,21,22]

It is also among the most widely accepted classification of partially edentulous arches. When evaluated clinically for Kennedy classification the results of our study showed that the most common class was Class-I while Class-II & IV were least common among reported patients.[23]This result is in agreement with the study results of Judy.[18]This attribution may be the result ofpaying less attention and care to the posterior teeth, making them more vulnerable and susceptible to dental decay and resulting the loss of these teeth by extraction, while at same time the patients paid more hygienic attention to their anterior teeth, resulting in their integrity and retention in the oral cavity.[24,25]During clinical examination for the missing teeth in both arches,it was revealed that the frequency of missing teeth was more in lower arch as compared to upper arch which is in concordance with the research results of Butt[14] and Curtis [19]. This again may be the result of poor oral hygiene and inaccessibility for proper cleaning, which ultimately leads to tooth decay and requirement for tooth extraction.

CONCLUSION:

Evaluation of pattern of edentulism in partially dentate patients according to Kennedy's system of classifying edentulous arches showed Kennedy's class I to be the most common class. Mandibular partial edentulism seemed to be more common than maxillary ones and male patients were affected more than females. Prevalence of class I is indicative of patients lack of care for their posterior teeth and they needed to be convinced for proper oral care for all teeth on equal levels. Though there has been considerable decline in tooth loss but still public awareness regarding over all oral health care needs to be lifted up, to guide the local population in saving their teeth.

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ORIGINAL ARTICLE

Relationship of Body Mass Index, Bone Turnover Marker and Bone Mineral Density in Postmenopausal Women

Shehla Shaheen[1], Syed Shahid Noor[2],Zahida Memon[3]

ABSTRACT:
Objective: To observe the correlation of body mass index (BMI) with bone mineral density(BMD) and bone turnover marker (NTX) in postmenopausal women
Materials and Methods: This observational cross sectional study was carried outfrom January 2014 to December 2014. In this study 85 postmenopausal women were included from Orthopedics and Gynecology outpatient departments of a tertiary care hospital of Karachi.Their BMI in Kg/m^2 and BMD by DEXA scan (femur and lumbar spine) were measured.Seruml evels of bone turn over marker, N-telopeptide of type I collagen (NTX) was assayed by ELISA.To evaluate the relationship between BMI, bone mass and NTX, Pearson Correlation co-efficient was computed (P-value significancewas <0.05).
Results: The correlation between BMI and BMD at both femur(r = 0.060, P = 0.586) and lumbar spine(r =0.093, P=.0.398)was weak and found to be non-significant. The correlation between serum NTX & BMI was negative but also found to be non-significant(r = -0.14, P=0.203).
Conclusion: Both bone mass and bone turnover marker (NTX) are not correlated to an index of obesity, BMI in postmenopausal women in our clinical set up.
Keywords: Bone mass, Body mass index, Obesity, Postmenopausal women, Bone turnover marker.

INTRODUCTION:

Osteoporosis and obesity,both diseases are highly rampant in the global scenario and even more prevalent among women of postmenopausal age group.[1,2]Globally according to an estimate about more than 200 million women have been suffering from osteoporosis. Furthermore, it has been predicted that yearly incidence rate of hip fractures, which is currently 1.66 million would increase to 6.26 million at the end of year 2050.[3]In 2014 WHO reported that worldwide about 1.9 billion of adult population was overweight, out of which more than 600 million were obese. Gender categorization revealed that about 11% of men and 15% of women were obese while 38% of men and 40% of women were overweight, which is clearly showing female predominance in both groups. Across the world, obesity claims 2.8 million lives every year due to its related co-morbidities[4].

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In Pakistan obesity and osteoporosis/ osteopenia (low bone mass) are quite prevalent among postmenopausal populationas documented by multiple studies**.**Qureshi in 2011 reported 63.64% and 30.30% postmenopausal women had osteopenia and osteoporosis respectively, based on BMD measurements by DEXA scan[5]. A study has documented that majority (64.3%) of the women 55 years or older had osteoporosis, which was even more (55.7%) prevalent in obese women[6.] Another study conducted in a tertiary hospital of Karachi showed 89% of postmenopausal women to be obese on the basis of BMI calculation[7]. To measure the extent of obesity, body mass index (BMI) is frequently used, whichis a ratio of weight in kilograms (Kg.) and height expressed in meters square (m^2). For Asians the appropriate BMI values based on WHO proposed cut-offs are from 18.5 to 22.9(kg/m^2).[8]According to WHO criteria the diagnosis of osteoporosis is based on the bone mineral density (BMD), expressed in T-score with a cut off value of -2.5 or more standard deviation (SD) lower than normal reference values[9].

The pathogenesis of osteoporosis and obesityrevolve around avariety of genetic and environmental factors; some of which are common to both of the diseases.Previously it was reported that obesity is positively correlated with increased bone mass[10,11],while some recent researches have regarded obesity as a risk factor forlow bone mass and osteoporosis[12,13,14].Due to theseconflicting results from the previous studiesthemechanisms involved in the common pathogenesis of obesity and bone mass are still not very clear.BMD measured by DEXA scan is the gold standard for the estimation of bone mass but it fails to elicit the changes in bone mass at a particular point of time. While bone markers although considered as surrogate markers for BMD but being dynamic represent the metabolic status of bone mass at any point of time[15].

It has been mentioned that about 90% of organic matrix of bone comprises of type 1 collagen, which being a

helical protein is cross-linked at its two poles,amide(N-terminal) and Carboxyl (C-terminal).Several studies have mentioned that the measurementof level of N-terminal of cross link Telopeptide of type 1 collagen (NTX) is proved to be a useful marker to exhibit elevated bone resorption in clinical conditions associated with increased bone turnover such as osteoporosis and bone metastasis[16,17].Furthermore, NTX is also employed to monitor the treatment response of anti-resorptives in osteoporosis[18]. Keeping in view the significance ofNTX as a marker of bone resorption,we included aforementioned in our current study to further know the exact status of bone at that time.The rationale of our study was to elaborate the correlation between two metabolic conditions,obesity and low bone mass(osteopenia and osteoporosis) by correlating BMD,bone turnover marker NTX and an index of obesity BMI in postmenopausal women in our clinical setup, which was previously not explained only by bone mass or BMD.

MATERIALS AND METHODS:

In this observational cross sectional study 85 postmenopausal women (menopause for six or more than six months) were included in our study by purposive convenient sampling techniquefrom the Orthopedics and Gynaecology OPDs of a tertiary care hospital of Karachi from January 2014 to December 2014. Before inclusion, the patients were explained about the study and their written informed consents were taken for their participation. Patients currently using medications that could affect bone or lipid metabolism were excluded from the study.Their bone densities were measured by DEXA scan (Hologic instrumentation) at lumbar spine and femoral neck. Reference levels were taken according to WHO criteria(T-scores at lumbar spine and femoral neck +1 or more than +1 is normal while -2 to -2.5 is osteopenic and <-2.5osteoporotic)The weight and height of all of the patients were measured in Kg and m^2respectively and after taking their ratios, BMI were calculated.About 4ml of blood was taken from each patient by standard venipuncture technique. Serum was separated after centrifugation, stored at -70$^?$C and assessed collectively at the end of total sample collection.Estimation of the serum levels of N-telopeptide of type I collagen (NTx)(Osteomark, Ostex International, Seattle, WA, USA,LOT no.10049115,REF. no.9021)was done by ELISA at Ziauddin Hospital North Nazimabad. Reference ranges were taken according to the manufacturer's kit (normal cutoffs = 6.2-19 nmol BCE/L(Bone Collagen Equivalent per liter).

Statistical Analysis:

Data was analyzed by Statistical Package for Social Sciences (SPSS) version 17.Quantitative data that is T-score femur neck, T-score lumbar spine,BMI, Serum NTX, duration of menopause(years)and Age (years) were presented in term of Mean SD.To evaluate the relationship between T-score femur neck, T-score lumbar spine,BMI, and Serum NTX, Pearson Correlation coefficient was computed (at level of significance = 0.05). Scatter Plots were used to represent the relationships between variables graphically.

RESULTS:

Table 1 shows the mean SD of the different variables of our study sample.Most of the women were in 51-60 year of ages and their mean duration of menopause was 13.987.39 years. Table 2 shows the frequencyof different classes of BMI, according to WHOin our study subjects.The correlationsof BMI with T-scores of femurneck(r = 0.060, P=0.586) & T-scoresof lumbar spine(r =0.093, P=0.398), both were weak and non-significant.A negative correlation (-0.14, P=0.203) was observed between serum NTX & BMI as shown in Table 3. Figure Ia and Ib shows the pattern of slightly increasing values of BMI corresponding to increasing values of T-score of lumbar spine and femur neck respectively in a linear fashion. In figure I c, all points are quite far from each other but also showing that as the BMI increases, serum NTX decreases which points towards a weak negative association between BMI & serum NTX as shown in Table 3.

Table: 1
Descriptive statistics

Variables	N	Minimum	Maximum	Mean	STD. Deviation
Age (years)	85	40	75	59.88	± 7.867
years since menopause	85	2	30	13.988	± 7.390
BMI	85	17	39	27.55	± 3.944
BMD lumbar spine (T-score)	85	-4	3	-2.47	± 0.733
BMD femur neck (T-score)	85	-4	3	-2.50	± 0.677
Serum NTX nm/BCE	85	21	48	31.70	± 6.818

Table: 2
Classes of BMI and their frequencies (n=85)

CLASSES OF BMI (According to WHO cut off values for Asians)	BMI FREQUENCY Total n=85
Underweight<18	1(1.17 %)
Normal BMI(18-22.9)	10(11.76%)
Over weight(23-24.9)	11(12.94%)
obese>25	63(74.11%)

Table: 3
Correlation between variables

Variables		Correlation (r)	P-Value
BMD femur neck (T-score)	BMI	0.060	0.586
BMD lumbar spine (T-score)	BMI	0.093	0.398
Serum NTX	BMI	-0.140	0.203

P-value significant<0.05

Figure: 1a
Scatter Plot between BMI & T- score Lumbar Spine

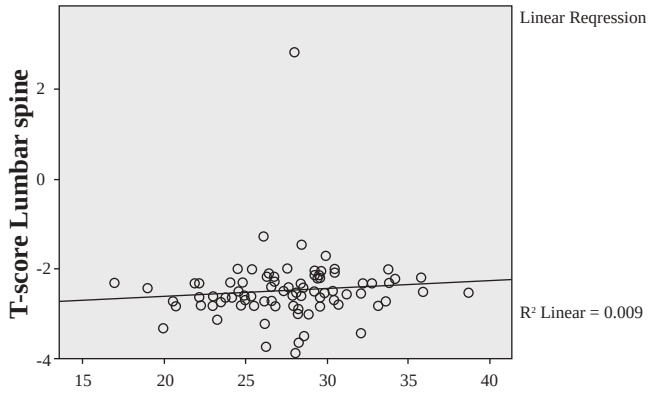


Figure: 1b
Scatter Plot between BMI & T-score Lumbar Spine

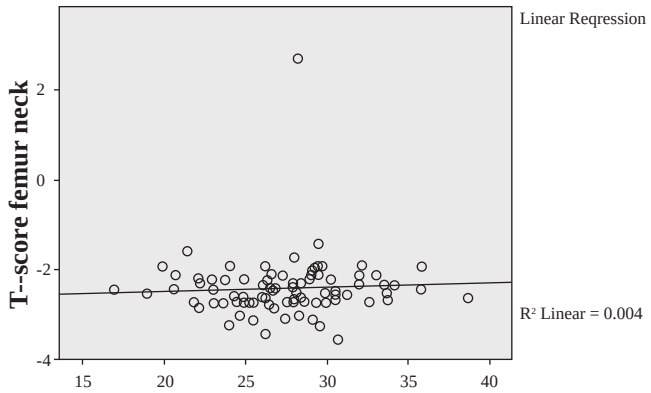
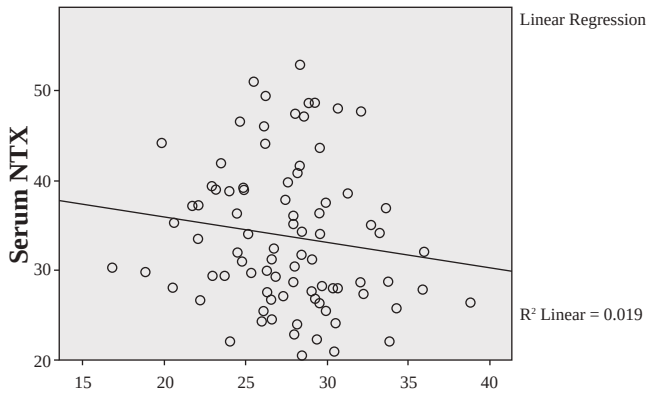


Figure 1c
Scatter Plot between BMI & Serum NTX



DISCUSSION:

In our study, majority of the patients were either obese or over weight (Table 2)which suggests that in our population obesity and its risk factors are highly prevalent in postmenopausal age group. These results are consistent with Khokhar[19]and Begum.[20]The mean BMD of femur neck and lumbar spine in T-scores were found to be lower than cut-offs (Table 1)which showed that the majority of our patients had either osteopenia or osteoporosis.This is strongly supported by previous studies showing osteoporosis and osteopenia most prevalent in postmenopausal women.[21,22.] The mean Serum NTX (nmol BCE/L)of our study group was 31.70 ± 6.818, displaying high bone turnover.This result is also consistent with I wamoto and Sambrook etal.[23, 24] It was reported by a number of studies that greater BMI is related to greater bone mass and weight reduction may cause reduction in bone mass.[11,25]On the other hand some studies have illustrated a converse relation between these two as reported by Hsu et al.that the greater amount of adipose tissue did not reduce the risk of fractures.[26]On the basis of these conflicting results from previous studies, as well as the complexity and involvement of multiple underlying mechanisms the exact correlation between obesity and bone mass is still not convincing. As mentioned earlier,obesity and osteopenia/osteoporosi-shas been detected simultaneously in the postmenopausal women.[1,2]In the current research beside bone density,serum levels of bone turnover marker NTX was also employed to observe their correlation with marker of obesity, BMI in postmenopausal women. Our study results showed that the correlation between BMI and BMD in T-score at both femur(r = 0.060, P = 0.586) and lumbar spine(r =0.093, P=.0.398) were non-significant.These results are in contrast to previous studies which mentioned BMI had positive correlations with BMD.[27, 28]On the other hand Blum et al. documented a negative correlation between proportion of fat and bone mass in 153 premenopausal women.[29] Although a negative correlation (-0.14) was observed between serum NTX & BMI but that was non-significant, P=0.203. It is important to note that all three variables namely,BMD at both femur neck and lumbar spine and serum NTX were not statistically significant when they were correlated with BMI, P=0.586,P=0.398,P=0.203 respectively. Parallel results were displayed by Shaarawy has documented another biomarker of obesity; serum leptin levels to have no correlation with bone turnover markers[30].Contrary to our results, Reid related obesity with BMD, bone markers and increased probability of fractures and in his previous study had already displayed a direct link between BMD and fat mass (P <0.0001)[31]. Our results also differ from Zhao who has displayed a significant negative correlation between BMDand fat mass[14].

In the light of above, it is obvious that high body mass index may not be a risk factor for low bone mass in postmenopausal age group in our community.

CONCLUSION:

Both bone mass and bone turnover marker (NTX) are not correlated to an index of obesity, BMI in postmenopausal women in our clinical set up. However, as learnt from the past studies certain common factors are involved in the development of obesity and low bone mass but a valid pathogenic link is missing between these two metabolic conditions. Further studies with other markers of obesity and bone metabolism in a larger sample size are vital to detect the exact common link between obesity and low bone mass.

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ORIGINAL ARTICLE

Frequencyof Medical Conditions in Patients of Low Socioeconomic Status Seeking Dental Treatment

Maaz Asad[1], Kashif Ikram[2], Asaad Javaid Mirza[3], Marwah Berkathullah[4]

ABSTRACT:

Objective: To determine the frequency of medical conditions prevalent in an area of inhabitants with low socioeconomic status seeking dental treatment

Materials and Methods:A cross-sectional study was performed employing medical histories of 341 patients reporting for dental treatment from June 2011- December 2011 at Baqai Dental College Hospital (BDCH).A questionnaire was designed consisting of demographic data and various common systemic diseases. The doctors on duty in the Department of Oral Diagnosis and Radiology were briefed about filling out the questionnaire and requested to fill one for each patient coming to BDCH for dental treatment. The collected data was analyzed using Statistical Package for Social Sciences (SPSS) version 17.

Results: The data was compiled keeping in view the most common prevailing disease in dental patients and relationship between gender and occurrence of systemic diseases.The results revealed that among the subjects of this study, the most prevailing medical problem was Hypertension 37(8.4%). Hepatitis 19(4.3%) and joint pains 16(3.60%) respectively were the 2nd and 3rd place common diseases.Regarding association between gender and occurrence of systemic diseases, hypertension (12.50%) and thyroid ailments (4.50%) were found to be more prevalent in females than males. Diabetes and hepatitis were more frequent in males while joint pain was found to be almost evenly distributed among both genders.

Conclusion: The frequency of medical conditions prevalent in an area of inhabitants with low socioeconomic status seeking dental treatment was 8.2% hypertension, 4.3%hepatitis and 3.60% joint pains.

Keywords: Medical emergencies, Dental education, Medically compromised dental patients.

INTRODUCTION:

The progress and advancement in medical technology, easier and greater access to medical facilities and awareness about maintaining health has increased life expectancy of a person in many parts of the world.[1,2].These improvements are exhibited by better oral health in a number of patients since they retain their natural teeth for longer ages than in the past. As a consequence, dentists are expected to encounter a greater number of patients, [2,3] especially the elderly. As the proportion of the elderly in the population continues to increase, there will be more patients with medically compromised conditions. When dentists have a chance to treat dental ailments of such patients, there are concerns that they should be aware of the effect of medical problems and their treatments on dental treatment plans, the dental or oral soft tissue problems that can arise in these patients and the effect of dental treatments on their medical conditions.[4,6]

Karachi is a metropolitan city of Pakistan with a population of around 24 million which makes it the 2nd most populous city of the world.[7]Air pollution, lack of proper waste management, absence of sufficient health facilities, poverty and growing industrialization are the major issues of this city. All these factors adversely affect environment which leave harmful effects on human health.These factors make it a city of unique health problems but surprisingly, there is lack of data concerning prevalence of medical conditions in patients who seek dental treatment in Karachi, especially patients from undeveloped areas and of low socioeconomic status. This study was done to determine the frequency of systemic medical conditions in dental patients attending dental OPD at Baqai Dental College Hospital (BDCH) so that appropriate dental treatment could be instituted keeping in view the systemic problem the patient is suffering from.

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MATERIALS AND METHODS:

This cross-sectional study was conducted at Baqai Dental College Hospital after approval from June to December 2011. A face and content validated self-administered questionnaire in English language was distributed among doctors who consented to participate in the study. The doctors were briefed about careful filling out of one questionnaire for each patient seeking dental treatment. The study included simple randomly selected 341 patients more than 18 years of age. The sample size was calculated using Raosoft - a sample size calculating software with

5% margin of error, 70% response rate and 95% confidence interval.

The questionnaire besides demographic data consisted of the medical conditions the patient might be suffering from. The medical conditions were classified into 10 categories as; Endocrine disorders,Cardiovascular diseases, Central nervous system diseases, Respiratory diseases, Hematological disorders, Eye and ENT problems, Gastrointestinal tract, Genitourinary, Gynecological and Musculoskeletal disorders.

The data was analyzed using the Statistical Package for Social Sciences (SPSS) software version 17. Descriptive analysis was obtained and frequency of distribution was calculated in percentages.

RESULTS:

The results were compiled according to the most common occurrence of the diseases in dental patients and effect of gender of the patients on prevalence of the systemic diseases (Table 1).

The results revealed that among the subjects of this study, the most prevailing medical problem in dental patients reporting BDCH was Hypertension (8.4%). Hepatitis was the 2nd most common systemic disease (4.3%) and joint pains took the 3rdplace (3.60%)(Table1). History of 213 male patients was reviewed which showed that 15(5.70%) patients were suffering from Hypertension but out of 128 females, 22(12.50%) had hypertension. This is evident here that female patients needing dental treatment suffered from hypertension more than male. Similarly, thyroid diseases were more common in female 8 (4.50%). However, Diabetes 7 (2.60%) and Hepatitis 11 (4.20%) were more prevalent in males as compared to the females. Joint pain was almost evenly distributed among male and female dental patients (Table 1).

Table: 1
Frequency of medical conditions among patients attending dental clinics of BDCH

Medical Condition		Total cases	No of Male cases	No of Female cases
Endocrine disorders	Diabetes mellitus	12 (2.7)	7 (2.60)	5 (2.80)
	Hyper/hypothyroidism	10 (2.3)	2 (0.80)	8(4.50)
Cardiovascular diseases	Myocardial infarction	1(0.2%)	1 (0.40)	0
	Hypertension	37 (8.4)	15 (5.70)	22(12.50)
Central nervous system	Seizures	1 (0.2)	1 (0.40)	0
	Stroke	1 (0.2)	1 (0.40)	0
Respiratory diseases	Asthma	3 (0.7)	2 (0.80)	1(0.60)
	COPD	1 (0.2)	1 (0.40)	1(0.60)
	Tuberculosis	1 (0.2)	0	1(0.60)
	Penumonia	1 (0.2)	0	1(0.60)
Hematological disorders		7 (1.6)	0	7 (4.0)
Eye and ENT disorders		1 (0.2)	0	1(0.60)
Gastrointestinal tract diseases	Peptic ulcer	7 (1.6)	4 (1.50)	3 (1.70)
	GERD	3 (0.7)	2 (0.80)	1(0.60)
	Hepatitis	19 (4.3)	11(4.20)	8 (4.50)
Genitourinary diseases		1 (0.2)	0	1(0.60)
Gynecological disorders		1 (0.2)	0	1(0.60)
Musculoskeletal disorders	Joint pain	16 (3.60)	8(3.0)	8 (4.50)
	Arthritis	12 (2.70)	6 (2.30	6 (3.40)
	Osteoporosis	2 (0.5)	0	2 (1.10)

COPD: Chronic Obstructive Pulmonary Disease, GERD Gastroesophageal Reflex Disease

DISCUSSION:

This study was done to determine the frequency of systemic medical conditions in dental patients attending dental clinics of low socioeconomic status so that appropriate dental treatment could be instituted keeping in view the systemic problem the patient might be suffering from. Awareness of attending dentist about the systemic disease of a patient could preventpotential

problems that may occur in a dental operatory. Although some emergencies are unexpected, many that occur in a dental clinic may be predicted by gathering adequate information and analyzing it in terms of risk assessment. Certain patients suffering from cardiovascular diseases, rheumatic heart diseases etc. may require further evaluation by their physicians.

Hypertension is one of the most prevailing medical conditions in Pakistani population[8]. Males suffer from Hypertension more than females[9], whereas a study done in Europe has reported that elderly females are more effected by hypertension[10].A study reported in Karachi, on prevalence of hypertension also have demonstrated that males suffer from hypertension more than females. However the results of our study showed that the females coming for dental treatment suffer more from hypertension than males. In this respect our results are in accordance with the studies done earlier[10]. On the contrary, our results do not match with the results of Costanzo et al., 2008 [9] and Safdar. 2004[8]. More research is required to determine whether hypertensive females need dental treatment more frequently or they become hypertensive at the time when they need dental treatment.

Hepatitis is another devastating infectious disease effecting around 10 million Pakistani people[11].Results of our study also showed that after hypertension, hepatitis was found common in the patients requiring dental treatment. In another study reported in Karachi regarding prevalence of Hepatitis, it revealed that 10% of 160 million Pakistani individuals suffered from this disease [12].Moreover, 13.1 % Patients attending Dental clinics of BDCH were suffering from one or the other type of hepatitis.

Joint pain is also a prevalent chronic health problem in elderly population which is also confirmed by the results of this study which showed that 16(3.60%) of the subjects are suffering from this form of disease. Medications prescribed in joint pain may prolong bleeding tendency, immune suppression and increase susceptibility for oral bacterial, fungal and viral infections[13].

Moreover, according to survey report published in Daily Dawn, diabetes is highly prevalent in Pakistani population and nearly 10% of the population suffers from this disease[14]. The results of present study contradict the mentioned results as only 2.6% of the dental patients were victims of this disease. This could be due to the reason that diabetes might be the problem of high socio economic income group subjects while this study enrolled subjects with low socio economic status. Another survey reported in Sindh province revealed that females are more prone to diabetes than males[15]whereas in our study it was found that males had slightly higher ratio of diabetes than females. Similarly, cardiovascular disease is reported to be the most commonly occurring disease, especially in elderly population[1]. However, this study doesn't support the findings of previous studies[16]. The reason for this could be the non-sedentary life style of the individuals enrolled in the study, whereas it has been observed that patients with sedentary life style are more prone to diabetes, cardiovascular diseases, obesity, osteoporosis, anxiety[17,18]Due to poverty malnutrition is a common occurrence in the individual of low socioeconomic group and malnutrition may be the cause of infectious diseases such as tuberculosis, malaria and pneumonia[19]. In this study patients with tuberculosis were also present.

Another reason for the disagreement in our findings could be due to the limitations of the study and therefore the results should be interpreted in context of these limitations; one of which is information bias due to self-reported nature of the study and small sample size. However studies with larger sample size will be required to emphasize more on the prevalence of medical conditions in Karachi, Pakistan.

As the numbers of medically compromised patients are increasing, this kind of study will help in estimating and then establishing proper guidelines prior to dental treatment. First and foremost is to record proper meaningful history so that medical conditions are not missed out.[20,21] Secondly, training of undergraduates and continuing dental professionals in the management of these medical conditions should be given more emphasis in dental curriculum as the data showed concerns about the ability of dentist to treat these medical conditions.[23,24,25]

CONCLUSION:

Due to marked decline in mortality and increased life expectancy in Pakistan, dentists will cater more medically compromised patients in their clinics. It necessitates emphasizing in the dental curriculums taught in Pakistan to recognize and manage commonly prevailing medical conditions.

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COMMENTARY

Vitamin D - Not Just a Simple Vitamin

Nasim Karim[1], Talea Hoor[2]

ABSTRACT:
Vitamin D refers to a group of fat-soluble secosteroids responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. In humans, the most important compounds in this group are vitamin D3 and vitamin D2.Very few foods contain vitamin D. Synthesis of vitamin D (specifically cholecalciferol) in the skin is the major natural source of the vitamin. Dermal synthesis of vitamin D from cholesterol is dependent on sun exposure. Vitamin D deficiency is said to be associated with osteoporosis, type 2 diabetes, rickets, psoriasis, depression, schizophrenia, cancers, obesity etc. Vitamin D deficiency is wide spread in South Asian especially in Pakistani population and is contributing to burden of disease in this region. It is suggested that vitamin D supplementation program may be undertaken by the government on mandatory basis.
Keywords: Vitamin D, Fact, Deficiency, Diseases.

INTRODUCTION:
Vitamin D refers to a group of fat-soluble secosteroids responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. In humans, the most important compounds in this group are vitamin D_3 (also known as cholecalciferol) and vitamin D_2(ergocalciferol).[1]They are known collectively as calciferol.[2] Vitamin D_2 the chemical structure of vitamin D_3 was established and proven to result from the ultraviolet irradiation of 7-dehydrocholesterol. Chemically, the various forms of vitamin D are secosteroids, that is steroids in which one of the bonds in the steroid rings is broken. The structural difference between vitamin D_2 and vitamin D_3 is the side chain of D_2that contains a double bond between carbons 22 and 23, and a methyl group on carbon 24.[3]
Cholecalciferol and ergocalciferol can be ingested from the diet and from supplements.[1,4,5] Very few foods contain vitamin D; synthesis of vitamin D (specifically cholecalciferol) in the skin is the major natural source of the vitamin. Dermal synthesis of vitamin D from cholesterol is dependent on sun exposure (specifically UVB radiation).
American researchers Elmer McCollum and Marguerite Davis in 1914[6] discovered a substance in cod liver oil which later was called "vitamin A". British doctor Edward Mellanby noticed dogs that were fed cod liver oil did not develop rickets and concluded vitamin A, or a closely associated factor, that could prevent the disease. In 1922, Elmer McCollum tested modified cod liver oil in which the vitamin A had been destroyed. The modified oil cured the sick dogs, so McCollum concluded the factor in cod liver oil which cured rickets was distinct from vitamin A. He called it vitamin D because it was the fourth vitamin to be named. It was not initially realized that, unlike other vitamins, vitamin D can be synthesized by humans through exposure to UV light. In 1925, it was established that when 7-dehydrocholesterol is irradiated with light, a form of a fat-soluble vitamin is produced (now known as D_3).Alfred Fabian Hess stated, "light equals vitamin D." [7]
Prevalence of Vitamin D Deficiency (VDD) of 92% and 81% in ambulatory patients has also been reported from centers in Karachi and Lahore recently.[8,9] Reports previously have also demonstrated Vitamin D Deficiency(VDD) from various regions of Pakistan. Unlike many Western countries that have a vitamin D food fortification policy, Pakistan does not have a mandatory Vitamin D fortification policy in place. In this situation the major source of vitamin D is exposure to Ultra Violet B (UVB) rays in sunlight. Vitamin D is perhaps the single most underrated nutrient in the world of nutrition. That's probably because it's free: our body makes it when sunlight touches our skin.[10,11,12,13]

Vitamin D - Fifteen Facts:

1. Vitamin D is produced by our skin in response to exposure to ultraviolet radiation from natural sunlight.
2. The healing rays of natural sunlight (that generate vitamin D in our skin) cannot penetrate glass. So we don't generate vitamin D when we are sitting in our car or home.
3. It is nearly impossible to get adequate amounts of vitamin D from our diet. Sunlight exposure is the only reliable way to generate vitamin D in our own body.
4. A person would have to drink ten tall glasses of vitamin D fortified milk each day just to get minimum levels of vitamin D into their diet.
5. The further we live from the equator, the longer exposure we need to the sun in order to generate vitamin D. Canada, UK and most US States are far from the equator.
6. People with dark skin pigmentation may need 20 -30 times as much exposure to sunlight as fair-skinned people to generate the same amount of vitamin D. That's why prostate cancer is epidemic among

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black men -- it's a simple, but widespread, sunlight deficiency.

7. Sufficient levels of vitamin D are crucial for calcium absorption in our intestines. Without sufficient vitamin D, our body cannot absorb calcium, rendering calcium supplementsuseless.
8. Chronic vitamin D deficiency cannot be reversed overnight: it takes months of vitamin D supplementation and sunlight exposure to rebuild the body's bones and nervous system.
9. Even weak sunscreens (SPF=8) block our body's ability to generate vitamin D by 95%. This is how sunscreen products actually cause disease by creating a critical vitamin deficiency in the body.
10. It is impossible to generate too much vitamin D in our body from sunlight exposure: our body will self-regulate and only generate what it needs.
11. If it hurts to press firmly on our sternum, we may be suffering from chronic vitamin D deficiency right now.
12. Vitamin D is "activated" in our body by the kidneys and liver before it can be used.
13. Having kidney disease or liver damage can greatly impair our body's ability to activate circulating vitamin D.
14. The sunscreen industry doesn't want us to know that our body actually needs sunlight exposure because that realization would mean lower sales of sunscreen products.
15. Even though vitamin D is one of the most powerful healing chemicals in our body, our body makes it absolutely free. No prescription is required.[14]

Diseases and conditions caused by vitamin D deficiency:

a. Osteoporosis is commonly caused by a lack of vitamin D, which greatly impairs calcium absorption.
b. Sufficient vitamin D prevents prostate cancer, breast cancer, ovarian cancer, depression, colon cancer and schizophrenia.
c. “Rickets” is the name of a bone-wasting disease caused by vitamin D deficiency.
d. Vitamin D deficiency may exacerbate type 2 diabetes and impair insulin production in the pancreas.
e. Obesity impairs vitamin D utilization in the body, meaning obese people need twice as much vitamin D.
f. Vitamin D is used around the world to treat Psoriasis.
g. Vitamin D deficiency can cause schizophrenia.
h. Seasonal Affective Disorder is caused by a melatonin imbalance initiated by lack of exposure to sunlight.
i. Chronic vitamin D deficiency is often misdiagnosed as fibromyalgia because its symptoms are so similar: muscle weakness, aches and pains.
j. Your risk of developing serious diseases like diabetes and cancer is reduced 50% - 80% through simple, sensible exposure to natural sunlight 2-3 times each week.
k. Infants who receive vitamin D supplementation (2000 units daily) have an 80% reduced risk of developing type 1 diabetes over the next twenty years.[15]

Sources of vitamin D:

Food: Very few foods in nature contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources. Small amounts of vitamin D are found in beef liver, cheese, and egg yolks. Vitamin D in these foods is primarily in the form of vitamin $D_3$and its metabolite 25(OH) D_3. Some mushrooms provide vitamin D_2 in variable amounts. Mushrooms with enhanced levels of vitamin D_2 from being exposed to ultraviolet light under controlled conditions are also available. Fortified foods provide most of the vitamin D in the American diet. For example, almost all of the U.S. milk supply is voluntarily fortified with 100 IU/cup.

Table: 1
Recommended Dietary Allowances (RDAs) for Vitamin D

Age	Male	Female	Pregnancy	Lactation
0–12 months*	400 IU (10 mcg)	400 IU (10 mcg)		
1–13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14–18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19–50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51–70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

* Adequate Intake (AI)

Sunlight: It has been suggested by some vitamin D researchers, for example, that approximately 5–30 minutes of sun exposure between 10 AM and 3 PM at least twice a week to the face, arms, legs, or back without sunscreen usually lead to sufficient vitamin D synthesis. Individuals with limited sun exposure need to include good sources of vitamin D in their diet or take a supplement to achieve recommended levels of intake.[16]

Interactions with Medications:

Vitamin D supplements have the potential to interact with several types of medications.Corticosteroid medications such as prednisone, often prescribed to reduce inflammation, can reduce calcium absorption and impair vitamin D metabolism.[17] These effects can further contribute to the loss of bone and the development of osteoporosis associated with their long-term use .*Other medications* like weight-loss drug orlistatand the cholesterol-lowering drug cholestyraminecan reduce absorption of vitamin D and other fat-soluble vitamins.[18,19] Both phenobarbital and phenytoin , used to prevent and control epileptic seizures, increase the hepatic metabolism

of vitamin D to inactive compounds and reduce calcium absorption.[20]

It is surprising to see so much of vitamin D deficiency in a country like Pakistan, with ample sunshine where one would assume it to be non-existent. Increased pigmentation due to which more prolonged exposure to sun is required, use of sun block, purdah observation and possibly the reason that women in general do not go outside the home may be responsible for Vitamin D Deficiency(VDD). However, to note even this cannot explain the existence of vitamin D deficiency in many sun-drenched areas such as South America, where clothing style is such that sunlight activity may not be hindered, vitamin D deficiency is still becoming a major public health problem.[8]

Thus Vitamin D deficiency is wide spread in South Asian especially in Pakistani population and is contributing to burden of disease in this region. It is suggested that a national program on the supplementation of vitamin D and public awareness through electronic and print media should be undertaken by the government.

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STUDENTS CORNER

Pharmacology Students Competition 2015

Post Competition report

Mehtab Munir[1], Arsalan Ahmed[2]

Pharmacology Department of Bahria University Medical & Dental College (BUMDC) carrying forward their tradition of conducting student`s centered activity each year, organized "Pharmacology Students Competition 2015" on Tuesday 15th September 2015 from 12:30PM -4:00 PM in the Ibn-e-Sina Auditorium of BUMDC. The chief guest of the ceremony was Vice Admiral (Retd.) Tahseenullah Khan HI (M), Director General BUMDC. Brig.(Retd.) Prof. Dr.Shaheen Moin, Dean Health Sciences and Principal BUMDC and Prof. Dr. Zubair Ahmed Abbasi , Principal Dental Section BUMDC embraced the occasion. Respectable Heads of Medical and Dental Departments with their faculty provided moral support to the young nurturing future doctors by their presence. Students of 3rd year MBBS and 2nd year BDS participated and attended the competition while final year MBBS students were invited to refresh their Pharmacology knowledge and to support their younger colleagues.

In her welcome address, Prof. Dr. Nasim Karim, HOD-Pharmacology besides welcoming the invitees and the students provided: (A) Time-line of student activity specifying little touch of innovation every year, 2012-- Poster Competition on Drugs,2013-- Poster Competition and presentation competition with newer aspect of older drugs,2014-- "Drug Updates" Power point presentations in National Pharmacology Conference, 2015-- Mnemonics and presentations (Power point plus video incorporations) (B) Justification of activity as a, part of teaching institute, need to work for system built up, gesture to contribute share andcoherent team work.(C) Objectives (i)for students as to arouse subject interest,facilitate subject learning, utilize current medical educational tools,update subject knowledge,gain marks in academics, development of communication skills and supplement CV for future carrier buildup (ii)for faculty an opportunity to groom and develop (iii) for institute to take leads, impact on visiting teams (PMDC etc.) and increment in the profile of BUMDC and Bahria University.

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All students (136) of 3rd year MBBS (93) and 2nd year BDS (43) participated in the competition. The competition had two parts (1) Mnemonics (2) Presentations (Power point plus video incorporations). A competition guideline was given and explained by the assigned departmental mentors to all students. 117 mnemonics were selected while 14 presenters (12 MBBS and 2 BDS, after several rounds) reached the finale. The judges for mnemonics competition were Prof Iqbal Hussain (HOD-ENT), Prof Ambreen Usmani (HOD-Anatomy), Prof Sajid Abbas Jafri (Medicine) and Dr. Irfan Ali Mirza (Microbiology-Pathology). Mehvish Sohail, (MBBS), Rabia Ramzan (MBBS) and Zunaira Shabbir (BDS) bagged 1st, 2nd and 3rd positions. The judges for presentation competition were Prof Asadullah Khan (HOD- Surgery), Prof Khalida Nasreen (HOD-OBS & GYN) Prof Shakeel Ahmed (HOD-Pediatrics). Zunaira Shabbir (BDS), Hira Jahangir and Rutab Mehtab (MBBS) and Kanwal Ali (MBBS) bagged 1st, 2nd and 3rd positions respectively.

Vice Admiral (Retd.) Tahseenullah Khan HI (M), Director General BUMDC handed over the shields to the honorable judges. Brig.(Retd.) Prof. Dr.ShaheenMoin, Dean Health Sciences and Principal BUMDC distributed the certificates to the winners. The third part of the competition that was kept as secret till the end, was related to the faculty (lecturers-the backbone of the department) who supervised their assigned students. Prof. Dr.Shaheen Moin gave the certificate of appreciation to Dr Ayesha Khan whose student bagged 1st position in mnemonic competition and to Dr. Afsheen Nazar whose student bagged 1st position in presentation competition. A certificate of appreciation was also given to Dr. Tauseef Sayyar as 05/14 contestants who reached the finale of presentations were supervised by her. Zunaira Shabbir (2nd year BDS) student was given certificate of appreciation for submitting maximum number (22) of mnemonics in the competition. The chief guest of the ceremony,Vice Admiral (Retd.)Tahseenullah Khan HI (M), Director General BUMDC in his remarks appreciated the students for their high level of creativity, applauded the faculty of Pharmacology department and emphasized the need of such curricular activities as a part of academics. Brig.(Retd.) Prof. Dr. Shaheen Moin, Dean Health Sciences and Principal BUMDC in her remarks strongly extended her encouragement and support for student competitions. She appreciated the entire team of Pharmacology Department and applauded the lecturers for completing their assigned task with dedication. She highlighted that these events are steps towards provision of positive learning environment and opportunity for students to gain confidence and must be undertaken on regular basis by the departments.

Prof. Nasim Karim thanked all the worthy guests, teaching and non-teaching staff members of Pharmacology Department with special thanks to lecturers who took this task assigned by her with great responsibility. A special vote of thanks was extended by her to 3rd year MBBS and 2nd year BDS students without whom participation the event would not have been possible.

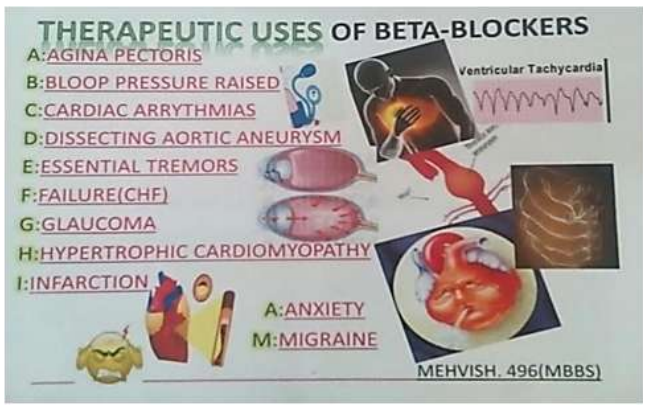
VIDEO PRESENTATION WINNERS:

1st Position
Zuneera Shabbir (BDS)

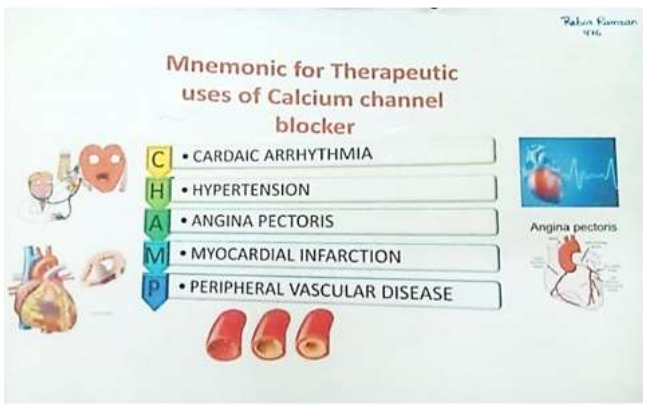
2nd Positions
Hira Jahangir & Rutab Mehtab (MBBS)

3rd Position
Kanwal Ali (MBBS)

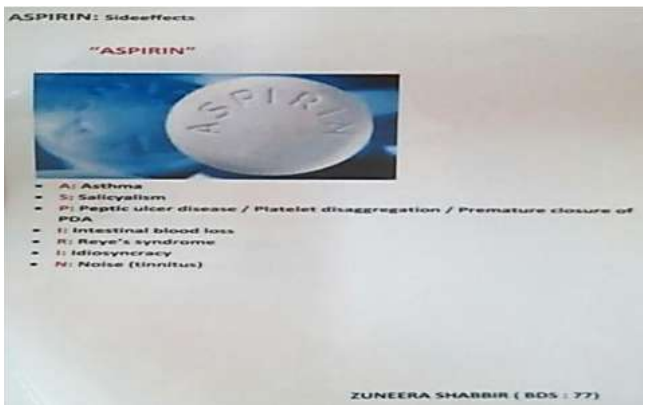
MNEMONICS PRESENTATION WINNERS:



1st Position
Mehvish Sohail (MBBS)



2nd Position
Rabia Ramzan (MBBS)



3rd Position
Zuneera Shabbir(BDS)

CASE REPORT

A Large Extra-Osseous Solitary Neurofibroma of the Hard Palate

Amer Sabih Hydri[1], Syed Shaukat Hussain[2], Iqbal Hussain Udaipurwala[3], Fatima Siddiqui[4]

ABSTRACT:
Solitary and isolated extra osseous neurofibroma of the hard palate is a rare clinical entity and literature search showed that only three cases have been published so far. The diagnosis is often arrived onimmuno-histochemistry after surgical excision of the tumour. We are reporting a case report of a large and solitary extra-osseous neurofibroma of the hard palate, which was not associated with generalized neurofibromatosis in a 30 years old lady. She presented with a painless and gradually progressive swelling on the hard palate which was interfering with the swallowing and speech. On examination there was a large pedunculated mass arising from the hard palate near its alveolar margin.Surgical excision of the swelling was done and histopathology showed the diagnosis of neurofibroma. There is no recurrence after a follow-up of 18 months till so far.
Keywords: Neurofibroma, Hard palate, Oral tumours,Von Recklinghausen's disease.

INTRODUCTION:

Neurofibroma is defined as a well-demarcated intraneural or diffusely infiltrative extraneural tumour arising from Schwann cells and perineurial fibroblasts.Neurofibroma of the oral cavity often presents as a sub-mucosal, non-tender, discrete mass. The head and neck region is commonly involved by neurofibroma because of the rich innervation of this area. The lip,tongue, buccal mucosa, and vestibular area are the common extra-osseous sites. Hard and soft palates are rarely affected by these lesions.

Neurofibroma may occur as solitary lesion or as part of a generalized syndrome of neurofibromatosis (von Recklinghausen's disease) or very rarely as multiple neurofibroma without any association with neurofibro-matosis syndrome. Generalized neurofibro-matosis is divided into two clinical forms NF1 (peripheral) and NF2 (central).Both of these types are clinically and genetically different. The predominant type is NF1 which occurs in almost 90% of the cases.It is imperative to ensure that there is no confusion between the diagnosis of isolated neurofibroma and those associated with NF1 since both have divergent clinical behavior, treatment, and prognosis.

An extensive review of the internet and medical literature revealed only three published reports of extraosseous solitary neurofibroma of the hard palate not associated with type 1 neurofibromatosis. We are reporting this case of a large and solitary extra-osseous neurofibroma of the hard palate.

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CASE REPORT:

A 30 year-old-female reported to the ENT OPD with the history of a lump on her palate. She had noticed this lump about a year back and it had grown steadily to its present size (Figure 1a). The lump was painless but had now started interfering with her speech and deglutition, especially solid food. On examination, the patient had full, healthy dentition with a solitary, smooth, firm, non-tender, elongated mass of about 4.5 x 2.5 x 2.5cms on the hard palate and extending on the soft palate. It appeared sessile at first but detailed examination revealed a small pedicle, which was arising from the left mid hard palate near the alveolar border. This mass was extending across the midline to the right side as well (Figure 1a). Apart from this growth, the intra-oral examination was unremarkable. Both the nasal cavities were normal on anterior rhinoscopy and x-ray PNS (Water'sviewand Sub mento-vertical view) were also normal. There was no extension of the mass in the nose or sinuses.

Excisional biopsy was planned for obtaining a histological diagnosis. After counseling the patient, informed consent was obtained and the patient was operated under general anesthesia. After inserting a mouth gag, the pedicle was identified as being attached to the greater palatine nerve (Figure 1b). The pedicle was meticulously removed by electrocautery, while preserving the nerve and the unblemished growth removed completely (Figure 2a). There was no bleeding after excision of the mass (Figure 2b).

Post-operatively there was immediate improvement in the patient's speech and deglutition and she was discharged the following day. Histopathology report

revealed the mass to be a neurofibroma.On her follow-up visit the patient was re-evaluated for type I neurofibromatosis in mind but no additional evidence could be elicited. At the 18 months follow-up the patient is asymptomatic and free from any recurrence.

Figure: 1a
Swelling seen on the palate

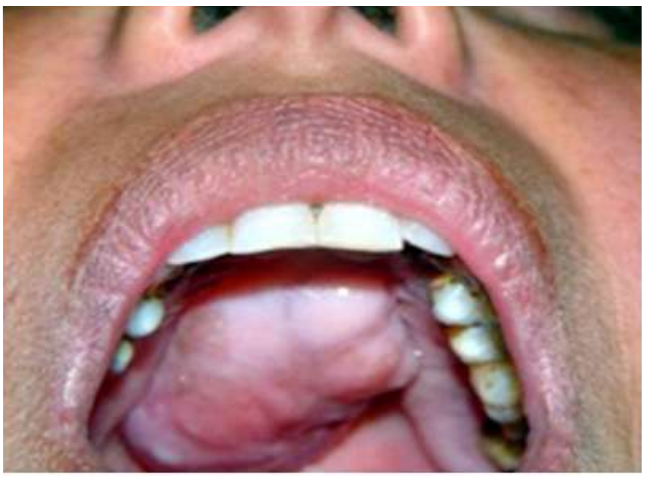


Figure: 1b
After inserting mouth gag, pedicle of the swelling was identified

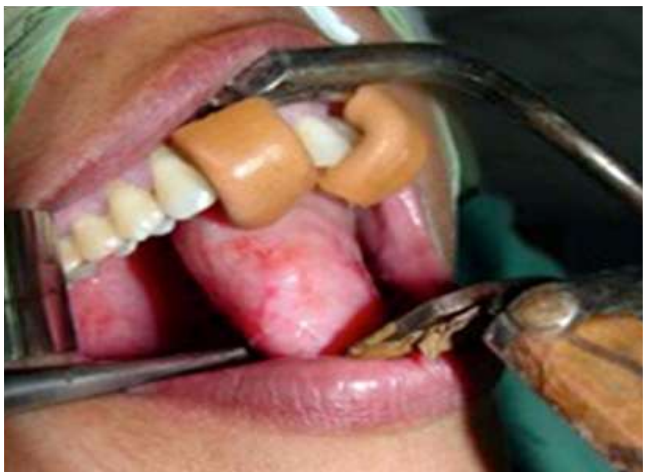


Figure: 2a
Complete mass after excision

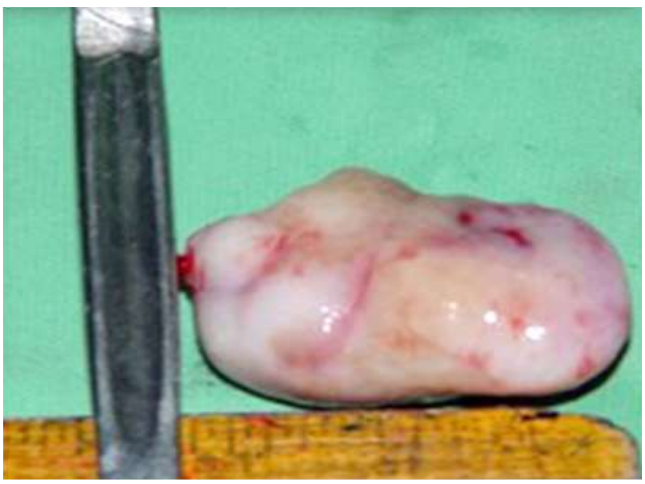
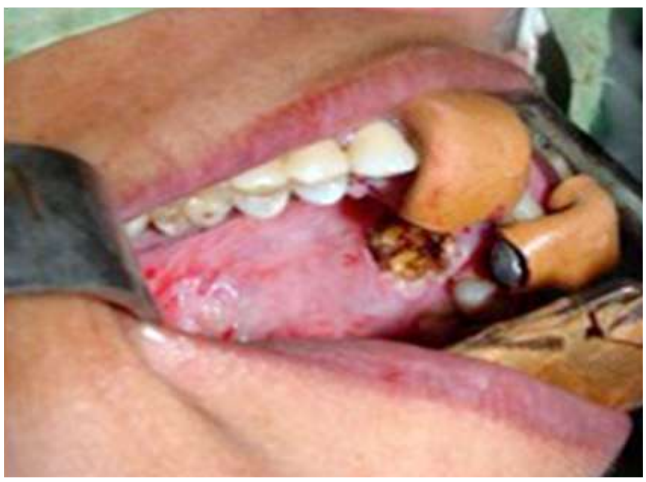


Figure: 2b
Surgical site after excision of the mass



DISCUSSION:

Palatal tumours of the neural origin are very uncommon. Clinically, oral neurofibroma usually appears as pedunculated or sessile mass, with a very slow growth rate. Malignant transformation of solitary neurofibroma takes place very rarely. Recurrence is also rare although some authors suggest higher rate of recurrence in head and neck regionin case of solitary neurofibroma.

Of the three cases reported earlier,[6,7,8]all were small and sessile growths. Our case is the first where the solitary neurofibroma was pedunculated and was also very large in size (4.5 x 2.5 x 2.5cms). Due to the slow growth of neurofibroma patients are usually asymptomatic, but depending on the location (e.g., tongue, palate), it may be traumatized and give rise to symptoms.

Regarding the soft tissue manifestation of neurofibromatosis, palate is affected in 8% of the patients, while the solitary extra osseous lesions are rare. Despite the large size of the palatal mass our patient remained asymptomatic for almost a year and only reported after it altered her speech. Although Sheejith[9]and Bongiornoin[10] their separate studies claim no predilection to gender or race yet Cherrick[11] reported a preference for females. Our patient was incidentally a female patient. Treatment for solitary neurofibroma is surgical excision, while preserving the nerve from which it originates and recurrence is rare as is evident from the follow up of all reported cases including our case. Confirmation of diagnosis is by histopathology and immuno-histochemistry.[12]Neurofibroma is immuno-positive for S-100 protein in 85 to 100% of the cases.

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LETTER TO EDITOR

Dengue: Beat Dengue Bite by Prevention

Sajid Abbas Jaffri

To,
The editor,

It is once again in news that dengue is roaming about in our surroundings. Dengue is a mosquito-borne viral disease that is transmitted by female mosquitoes belonging to the species Aedes aegypti followed by Aedes albopictus. The disease is widespread throughout the tropics, with local variations in risk influenced by rainfall, temperature and unplanned rapid urbanization. There are 4 distinct, but closely related, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4).ÊBefore 1970, only 9 countries had experienced severe dengue epidemics. The disease is now endemic in more than 100 countries. America, South-East Asia and Western Pacific regions are the most seriously affected ones. This viral infection causes flu-like illness, and occasionally develops into a potentially lethal complication called severe dengue. As mentioned earlier,dengue is found specifically in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas.Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries.[1]Dengue is endemic in Pakistan with its usual peak incidence in the post monsoon period.[2] In children under 16 years of age it was reported for the first time in Pakistan as an undifferentiated fever in year 1985.[3]Clinical presentation, laboratory diagnosis and management of dengue in Pakistan has been quite complex due to concurrent or super infection with malaria, typhoid and hepatitis. Thrombocytopenia, leukopenia with raised ALT and AST is the common laboratory presentation in patients presenting with high grade fever along with generalized body pain specially headache and backache. Highly variable mortality during various outbreaks may also be attributed to co-morbid conditions, lack of proper management guidelines and training of health care professionals.[4]There is no specific treatment for dengue, but early detection and access to proper medical care lowers fatality rates below 1%. Therefore due attention should be given to dengue prevention and control which solely depends on effective vector control measures. These include preventing mosquitoes from accessing egg-laying habitats by environmental management and modification, disposing solid waste properly, removing artificial man-made habitats,covering, emptying and cleaning of domestic water storage containers on a weekly basis,applying appropriate insecticides to water storage outdoor containers,use of personal household protection such as window screens, long-sleeved clothes, insecticide treated materials, coils and vaporizers, improving community participation and mobilization for sustained vector control,applying insecticides as space spraying during outbreaks as one of the emergency vector-control measures.[5]Being health professionals each one of us must disseminate this basic knowledge regarding dengue and its prevention in the community so as to share our responsibilities hand in hand with the governmental departments and agencies.

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The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164: 282-4.

c) No author given

Cancer in South Africa [editorial]. S Afr Med J 1994;84:15.

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Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

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