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# JBUMDC

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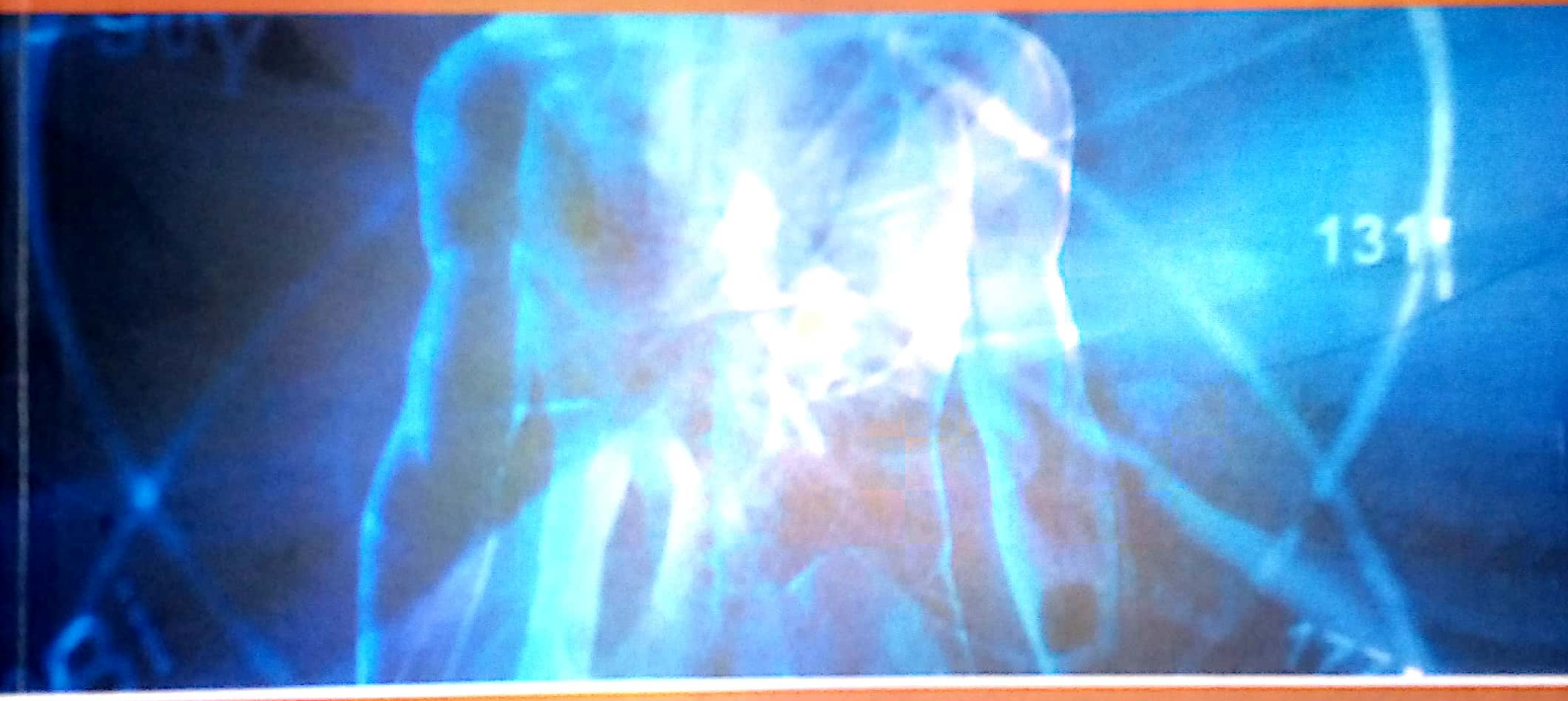

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**Biannual Journal**

# CONTENTS

# Tobacco Consumption and the Menace Of Oral Cancer in Karachi

Mohammad Mohiuddin Alamgir

Oral cancer is among the leading cancer type in South Central Asian men. In India, oral cancer is the leading cancer type among men and third most common cancer among women[1] Oral precancerous lesions (PCL5) such as leukoplakia and submucous fibrosis have a variably reported incidence from 0.4% to 24% from different parts of the world with a transformation rate of 2-12% to frank malignancies.[2] In Pakistan, cancer of the oral cavity and pharynx are amongst the commonest type of cancer. According to the reports published by Pakistan Medical Research Council (PMRC), it was the commonest cancer among males and second highest to breast cancer in females.[3,4,5] More recent data shows that oral cavity cancer in Karachi South ranks second in both genders with similar rates in both.[6]

An increase in the prevalence of oral cancer among young adults is a cause of special concern. There has been a 60% increase in the number of cases under 40 years of age with tongue cancer over the past 30 years. During the last 5-6 years it has been observed in one of the major hospitals in Karachi that the disease is appearing more in younger individuals, youngest being 12 years old. Major contributors in this increased incidence include various forms of chewable tobacco along with different additives that are used. These combinations are mostly in the form of Gutka, in particular Manpuri. In addition betal quid containing areca nuts with fungus Aspergillus, HPV infection, familial predisposition and mutations of tumor suppressor genes have also been implicated.[7] A survey in Karachi indicated that 36% of the males and 44% females chew pan or pan with tobacco. The age specific rates show a gradual rise to a maximum in the 7th decade in both sexes.[8] Tobacco is a conventional agricultural product. As soon as the crop of tobacco is ready, leaves are separated to be dried in sunlight. Special protective measures are taken to protect these tobacco leaves from rain, humidity, and water. When the leaves are dried out, they are heated in a particular furnace and are then used for making various consumable products, such as, cigarettes, niswar, gutka, and betel quid etc. Certain products are also made by dipping these in tobacco juice. China, Cuba, America and Pakistan are top producers of tobacco. Pakistan is also included in the list of high quality tobacco producers.

Use of tobacco is as old as human civilization. The mode of its usage has been changing from one era to another. Until the 18th century, in this part of the world the use of tobacco had been restricted to chewable niswar form. During 19th century, tobacco in the form of cigar and in 20th century as cigarette became common. Today the use of tobacco is in the form of cigar, cigarette, niswar and in so many other forms also. In modern times, there are two basic modes of tobacco consumption that is smoked and chewable tobacco. Smoking is through cigarette, cigar, shisha, chillum, huqqa and birri. Similarly, tobacco is consumed through mouth or nose without burning it. Chewable tobacco is used by chewing, by sucking, by applying its paste on teeth, stuffing tobacco between teeth and cheek, and finally by snuffing via nose. In recent times, there is a remarkable increase of consumption of these tobacco products in our population.

Dried niswar, humid niswar, common niswar, sutwali niswar, green niswar, black niswar, bannu niswar, swabi niswar, chaman niswar and also niswar and gutka from hawalian, kheni, narampatta, chemon, mishri, maras, plag, shama, tobacco tikkya, and tambak are included in the category of sucking tobacco addictions. Chewable tobacco is usually consumed by mixing additives like betel leave, betel nut, ikk-muk, qiwam , mawa, yung, narumpatta, tobacco chewing gum and zarda. Grounded tobacco with the addition of fragrance and flavor is used for sniffing. This includes dried and liquid niswar. Special tobacco tooth pastes are

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prepared for cleansing of teeth and treating toothache, e.g., red toothpaste, cream-wali niswar and gharhako. In Pakistan more than 50 types of niswar are prepared from tobacco leaves. Amongst these, F- 16 prepared at Mansehra and Lajawab, prepared at Haripur are very popular. The one prepared at Hawalian is also exported outside Pakistan. In addition to these, the niswar prepared at Bannu, Swabi and Chaman are also liked by niswar users. For preparing Kali niswar: Chai-2.5kg, tobacco-4 kg, water 2.5 kg, and gum powder 250 gms are mixed together. Then all these ingredients are grinded for 20 to 25 minutes followed by one hour more mixing, until they are homogenized. To prevent niswar from drying, Noushadar is added. This procedure requires two machines and three persons to complete this whole process of niswar making. Approximately 300 tablets of niswar are made per hour by this method. Black niswar is famous because of its place of origin and flavor, like, Bannu niswar, Saddi niswar, Satt-wali niswar and cardamom-containing niswar. During the past two decades several studies have contributed to a growing awareness of the importance of relatively common genetic and acquired susceptibility factors in modulating risks associated with exposure to various carcinogens. These studies provide substantial evidence that inherited differences exist which is related to the individual capacity of enhancing or detoxifying carcinogens by existing enzyme systems. Polycyclic aromatic hydrocarbons (PAHs), nitrosamines, aldehydes and ketones form the major carcinogens present in tobacco. Tobacco smoke contains pyrolysis products, which are generated due to high temperatures at the burning tip, whereas smokeless tobacco is rich in nitrosamines.[9] The concomitant use of betel quid leads to a 50-fold increase in reactive oxygen species generated.[2] Most of the carcinogenic moieties in tobacco are metabolically processed by xenobiotic-metabolizing enzymes in two broad steps: phase I mediated by cytochrome p450 (CYPs) and phase II catalyzed by glutathione S-transferases (GSTs), N-acetyltransferases, etc. Phase I reactions expose functional groups of the substrates and therefore yield highly reactive intermediates. These intermediates form the substrates for phase II reactions that involve their conjugation with endogenous molecules such as glutathione (GSH) and thus facilitate their elimination.[1]

The coordinated expression and regulation of these xenobiotic-metabolizing enzymes (XMEs) determines the outcome of carcinogen exposure. Understanding this phenomenon in the Pakistani context where oral cancers are most predominant not only becomes significant but also particularly difficult as the consumption of tobacco occurs in several forms (use of smokeless tobacco with or without additives and smoking of cigarettes and/or bidis) and most often, as mixed habits. Sequence variation in genes coding for tobacco metabolizing/detoxifying enzymes, such as members of the cytochrome P450 (CYP) and glutathione S-transferase (GST) families may potentially alter individual susceptibility to oral cancer. However, isolated sequence variants in carcinogen-metabolizing genes may be modest to moderate risk factors, explaining the inconsistent results. On the other hand, combinations of genotypes each conferring a small relative risk may add up to a relative risk large enough to be observed in epidemiological studies.[10]

The three xenobiotic-metabolizing enzymes reported in studies, i.e. CYP1A1, GSTM1 and GSTT1, significantly alter oral cancer risk singly and in combination. Further, specific tobacco exposures appear to modulate this risk. Thus there is a complexity of the interplay between genetic and environmental factors as determinants of oral cancer risk.

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**REVIEW ARTICLE:**

# Dens Invaginatus: Literature Review

Shama Asghar

**Abstract:**
Dens invaginatus is a developmental malformation of the tooth germ which originates as a result of the infolding of the enamel organ. It has been expressed as a 'tooth within a tooth' or 'dens in dent' or as an invagination of an enamel-lined tract extending into the root at a various depth, with or without involvement of the dental pulp. Search engines as Pak-Medinet, Pub Med, Medline and Google scholar were used to search literature about this abnormality. Dens invaginatus has complicated root canal morphology and the etiology of this developmental abnormality is still ambiguous. Possible causes include trauma, infection, development retardation of specific cells, interruption in factors regulating the development of enamel organ, and associations to genetic factors. Clinical features, radiological findings (periapical, occlusal radiograph, 3-dimensional imaging system CBCT) and surgical operating microscope help the clinician in classifying the morphology of the dens so that correct treatment planning and management alternative can be chosen. The treatments choices consist of; preventive sealing, restoration of the invagination, endodontic management, apical curettage and surgical endodontic, planned replantation and removal of tooth.
**Keywords:** Dens invaginatus, Dens in dent, Developmental abnormality, Trauma, Infection, Radiographic features, Pulp necrosis.

## INTRODUCATION:

Dens invaginatus (DI) is a developmental dental abnormality resulting from an infolding of enamel organ into the dental papilla before calcification of the hard tissues occurs.[1'2'3] The beginning of this infolding can be different, it may extend only to the amelo-cemental junction, penetrate into the pulp cavity, to severe type in which the invagination extends into the root and occasionally reach to the root apex with a second opening.[2'4]

Ploquet first described this type of abnormality in a Whales' tooth in 1794.[5]Socrates described a case of Dens invaginatus in human tooth in 1856.[6]Tomes illustrated this kind of anomalous in his textbook in 1887.[7]Hallet used the word dens invaginatus for this malformation to explain enamel is present centrally and the dentine peripherally due to the invagination.[8] Salter first recommended the term "a tooth within a tooth" for this abnormality in 1855 and Busch first used of 'dens in dente' termin 1897.[9]Hunter in 1951 introduced the term 'dilated composite odontome' that concludes an anomalous dilatation of the dental papilla at the same time as Colby suggested the term or gestant abnormality' for dense invaginatus.[10] Of the different names 'dens invaginatus' would appear to be the more suitable because it revealed the invagination of the external part (enamel) into the internal part (dentin)with the development of a pouch and dead space.[11](Table 1) This review article highlights the etiology, incidence, classification, clinical and radiographic features along with various treatment alternatives.

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**Table 1**

**Other synonyms used to express Dens Invaginatus**

- Dense in dente
- Invaginate dodontome
- Dentoid in dente
- Tooth inclusion.
- Dilated gestant odontome
- Dilated composite odontome
- Dents telescopes
- Telescopic tooth

## METHODOLOGY:

Following keywords and phrases (dense in dent, tooth within the tooth, theories of dense invaginatus, clinical and radiographic features of DI, treatment modalities of DI) were used on different search engines such as Google Search, Pak-medinet, Pub Med and Medline to search literature regarding this mal-development during the period of Jan 2013 to Dec 2013.

## AETIOLOGY OF DENS INVAGINATUS:

1. Several theories have been presented over the last few decades to clarify the etiology of this malformation but it is still controversial.

2. During development of the teeth, growth pressure on the dental arches will result in 'buckling' of the enamel organ leading to the invagination.[5]
3. At a certain point, the internal enamel epithelium fails to grow[14]
4. Rushton described that rapid proliferation of the inner enamel epithelium invading the dental papilla.[15]
5. Oehlers proposed that modification of the enamel organ take place at some stage in growth with extension of part of the enamel resulting to an enamel-lined canal finishing at the cingulum or the incisal tip.[16]
6. The 'twin-theory' described a cause of invagination is a joining together of two tooth germs.[17]
7. Infection[18] and trauma.[4]
8. Hereditary factors.[19]
9. Ecto-mesenchymal signaling coordination between dental papilla and the inner enamel epithelium may influence tooth morphology and the folding of enamel organ.[20]
10. Now the most accepted theory, it may possibly arise from a deep invagination of foramen caecum during tooth formation which in some cases can extend to form a second opening at apex,[21]

**OCCURRENCE OF DENS INVAGINATUS:**

Hovland reported the prevalence of Dens invaginatus to be varied from 0.04 to lO%.[22]This anomaly usually involves permanent maxillary lateral incisors accounting for 42% of all cases, followed by maxillary central incisors, premolars, canines and less commonly in the molars.[12'13]

Cakici et al described that DI was noticed in maxillary lateral incisors with no sexvariation.[23] Mandibular teeth are also affected, although this is not as common as maxillary teeth.[2'23] Bilateral occurrences accounting for 43% of cases and multiple incidence of have also been observed. Swanson and McCarthy reported about bilateral occurrence of invagination.[24]Deciduous dentition with this malformation has also been described in various studies[13]in association with other dental abnormality, for example dentino- genesis imperfect and supernumerary teeth.[13-20] By applying Oehlers' classification, Ridell et al reported in 200 ithe prevalence of each kind of invagination, Type I was the most frequent (79%) while Type II (15%) and Type III (5%).[29]

**CLASSIFICATION:**

The first classification of dens invaginatus was documented by Hallet in 1953 who recommended the presence of four kinds of infolding depending on both clinical and radiographic features.[8]Others also classified[25] DI for example, Schulze and Brand in l972 suggested a classification depending on twelve possible difference in clinical and radiographic features of the infolding.[26]The classification illustrated by Oehlers in l957 shows to be the most commonly used, as it has simple nomenclature and easy to apply.[16]

Oehlers categorized dense invaginations (coronal invaginations (Figure 1) into three classes as depending on radiographic extension of enamel infolding inside the tooth.[11,16]

**TYPE I:** The invagination or infolding of enamel organ is minimal and is restricted to the coronal portion of the tooth, not extending further than the cemento-enamel interface.[5,6]

**TYPE II:** The invagination which invades the root extends beyond the cemento-enamel junction ends as a blind pouch. It confines within the root canal and may or may not communicate with the dental pulp.[16]

**TYPE III (A):** The infolding of enamel organ penetrates throughout the root and communicates with the periodontal ligament space through a pseudo-foramen. It has no contact with the dental pulp.[5,11]

**TYPE III (B):** The invagination passes through the course of the root canal and communicates at the apical foramen with the periodontal ligament, giving rise to two or additional foramina. It may or may not communicate with the dental pulp.[27]In type III, any contamination inside the invagination give rise to a 'peri-invagination periodontitis'[1] Oehlers in 1958, also explained the radicular type of infolding.[27]This kind is uncommon and occur secondary to a proliferation of Hertwig's root sheath and radio graphically the involved tooth revealed an enlargement of the root.[28]Schulze & Brand in 1972, proposed a comprehensive classification, comprising invaginations originating at the incisal edge of the tooth and also telling dysmorphic root configuration.[26]Bhaskar[30]classified Dens invaginatus into two kinds,(a) Coronal type and (b) Radicular type.(Table2)

**Figure 1**

**Oehler's classification of Dens invaginatus**

**Type I Type II Type III-A Type III-B**

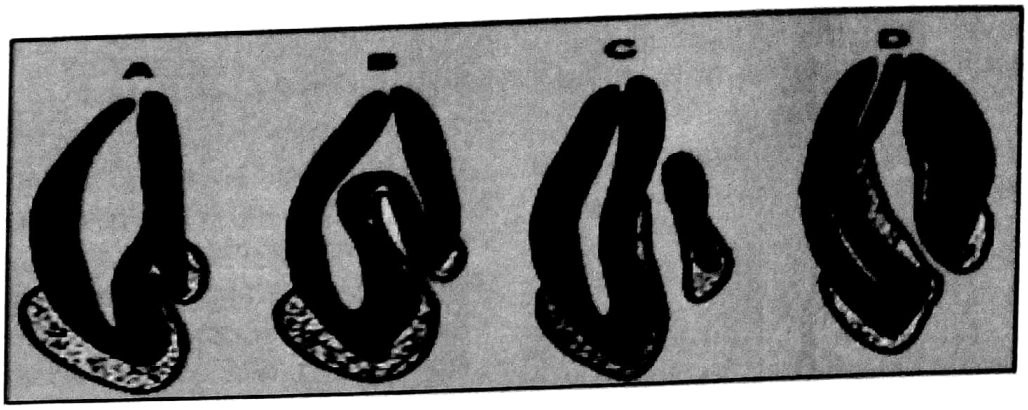


**Table 2**

**Bhaskar[30] classified Dens Invaginatus into two types**

| | |
|---|---|
| **Coronal type** | It is occurred by an invagination of all layers of the enamel organ into the dental papilla. The pulp is generally exposed, necrotic or inflamed. Not uncommonly, periapical lesions are related with this type, endodontic therapy is required. |
| **Radicular type** | In this type, folding of Hertwig's sheath into the developing root and pulpal necrosis and periapical apical lesions are frequently there. |

**HISTOLOGICAL FINDINGS:**

Histological examinations of this mal-developmental have showed contradictory results. Brabant and Klees[6] in 1956, Omnell et al in 196O[31], De Smitet al[32] in1984, Piatelli and Trisi[33]in 1993 described the infolded surface as being uniform and regular with no contact with the pulp. Kronfeld[14] and others [4,16] have observed disruption in the infolded surface which might provide gateway for irritants to the pulp.[27]

Atkinson[5] reported the structure of enamel was irregular while Baynon[2]described hypomineralized enamel at the bottom of the invagination. Morfis noticed phosphate and calcium eight times more in the enamel lining of dense invaginatus as compared with the outer enamel.[34]Bloca-Zupan et al found the internal enamel revealed more complicated rod appearances and its surface showed the distinctive honey comb prototype but no pen-kymata was seen on the external surface of tooth.[35]Kramer described irregularities in the composition of the enamel sheet of the infolding, with the safe and sound dentine. He explained that the deficiency of enamel in these parts allow direct entry of microbes into the dentine tubules and give rise pulpal infection.[36]The dentine beneath the invagination may be undamaged devoid of irregularities but Omnell et al[31] and others[2,5]also found irregular dentine surrounding the invagination.[5]

However, even though the limitations of various studies,[5,32] the widely accepted observation is that

teeth influenced with this abnormality has high threat of developing pulpal crisis.[15,17] This can take place without sign of any observable caries or history of trauma.[17]

**DIAGNOSIS:**

Often, teeth affected with Dens invaginatus do not exhibit any clinical signs of abnormality and hence cases may come to the dental surgeon as a consequence of the patient suffering from symptoms of pulpitis. In the majority cases, this abnormality is noticed accidentally on the radiograph. Clinical diagnosis, (1) the abnormal crown morphology (such as distended, hook or peg-shaped, barrel-shaped teeth) (2) a deep foramen caecum, can be significant clues.[10] While maxillary lateral incisors are more prone to coronal infoldings, so these teeth should be examined carefully clinically and radio graphically, especially in all cases in which a deep pit at the foramen caecum is present.[7,8,9] If one tooth is involved in a patient the contralateral tooth should also be examined. Pulpal contamination of teeth with this mal-development may occur immediately after tooth eruption, thus early identification is compulsory to initiate precautionary management.[2,6,31,34] Conventional radiograph cannot give comprehensive structural information regarding this abnormality. Newest radiographic technology (CBCT, spiral computed tomography) which are not only useful in identification of dens invaginatus but also provide three-dimensional picture of the root canal anatomy.[38]

**CLINICAL FEATURES:**

Clinical features of teeth with Dens invaginatus include incisal notching, peg-shaped development, pointed morphology, increased labio-lingual and mesio-distal width, and the occurrence of a distended palatal cingulum or cusp.[39]Clinical detection of the invagination entry can be difficult and be analogous to normal fissures. Methylene blue dye can be used to assist in the identification process.[11]Other diagnostic features are abscess and cyst development, dislocation of teeth, retention of neighboring teeth, internal resorption and cellulitis of face with undetected and untreated coronal invaginations.[11,29,39]

The infolding permits ingress of irritants into vicinity that is separated from dental pulp by a thin sheet of enamel and dentine and has a tendency for the progression of dental caries. In a few cases incomplete enamel-coating and connections might be present between the infolding and the dental pulp.[14] Hence, pulp necrosis frequently occurs in a short period after tooth eruption, occasionally before closure of root ending.[6,25]

**RADIOGRAPHIC EXAMINATION:**

Radiograph shows density of invaginations similar to that of enamel. The infolding of the enamel is generally more radio-opaque than the surrounding tooth structure and therefore can be recognized without problems.[14] when the infolding involves the coronal or radicular part of the tooth, the shape of the pulp space may modify resulting in 'rounding' of the horns of dental pulp.[20] The invagination may differ in size and shape from a loop like, pear shaped radiolucent formation to a severe appearance similar to 'tooth inside a tooth'.[16]

Type III (A) shows a deep fissuring of the tooth which egress on the one side of the root.[17]The root canal adjoining to the infolding may be anomalous. Microbes entranced onward the invagination can develop a peri-invagination periodontitis.[6,22] While connections between the invagination and the root canal can cause lose of vitality if the invagination is contaminated.[24,40] On the contrary, kind III (B)of Dense invaginatus is more hard to detect because it overlay on the root canal structure and in many cases presents with a well developed periapical infection.[5,32] The introduction of CBCT (cone-beam computed tomography) in clinical dentistry has aided not only in diagnosis but also provide support to the clinician in improved treatment planning of difficult cases requiring endodontic treatment.[46] Cone-beam computed tomography and surgical operating microscope not only help in the diagnosis, treatment-planning, endodontic treatment of a tooth with dens in dents and also improve the success rate.[47,55]Early diagnosis is essential as, if left untreated; the channel will permit gathering of microorganisms and irritants.

**MANAGEMENT OPTIONS:**

**PREVENTION:**

Clinically and radiographically, tooth with Dens invaginatus is vital and there is no indication of disease, a preventive approach should be acquired.[48]Composite resin and fissure sealant are used to seal the pit of invagination followed by preventive recommendation and regular follow-up. If the teeth develop infection, treatment will be compulsory.[42]The management modalities of alternatives will base on the following factors (Table 3).

The following treatment alternatives are offered for infected cases.[43]

**Table 3**

**Treatment modalities depend on following criteria[41,42]**

| | | |
|---|---|---|
| 1 | Function and aesthetics | Dens invaginatus commonly presents with anomalous crown shape which can have an effect on function, aesthetics or cause occlusal disturbances. |
| 2 | Configuration of root canal system | If the root canal morphology is complicated, access may not be easy and might result in entire crown destruction. |
| 3 | Stage of root development of tooth | Affected teeth with incomplete apices will need apexification before to completion of root canal therapy. Dens invaginatus has been reported in immature teeth. |
| 4 | Patient choice and co-operation | Due to the complexity of some treatments, co-operation is essential. Though, patients are often ready to keep the tooth, particularly an upper anterior tooth. |

**ROOT CANAL TREATMENT:**

If the apex has not closed; then

a). Apexification with the use of calcium hydroxide will be required.[49]

b). Mineral trioxide aggregate (MTA) can be utilized to make an apical barrier before the obturation of the canal. Obturation with warm gutta-percha techniques, (such as warm lateral condensation or thermoplastic methods) is usually the method of preference to ensure absolute filling of the canals.[50]

c). If the invagination has a separate apical foramen, and does not contact with the main pulp of the tooth, root canal treatment of the invagination can be done, thus maintaining the vitality of the pulp of the tooth.[51]

d). Revascularization technique was used by Narayana Pet al[54], in 2012 for the management of a complex dens invaginatus with immature root apex. They used CBCT scans in diagnosis and treatment planning and surgical operating microscope in a step-by-step clinical procedure. Yang J,[59] in 2013 described a case report for type II immature dens invaginatus with pen-apical infection. He suggested that endodontic therapy with pulp revascularization should be considered prior toperi-apical surgery, with adequate infection control, pulp revascularization can be a successful alternate technique.

**SURGICAL ENDODONTICS:**

If root canal therapy is not successful or if there is difficulty in gaining access to the canal, root end preparation and filling is the treatment of preference.[52]When the type III invagination is present and root canal treatment is done, but gutta-percha extruded into periapical tissues during obturation of the root canal system.[53] In these cases, apical curettage and surgical endodontics can be done instantly if needed. Though, if there are no severe problems, it can be left and monitored regularly. Teeth with complex root canal morphology, in which adequate instrumentation is difficult, a combination of root canal treatment and root end preparation should be selected.[49,53]

**EXTRACTION:**

In cases where adequate results cannot be attained with the above mentioned methods, extraction should be done.[52]

**MANAGEMENT OF TYPE I AND TYPE II DENS INVAGINATUS:**

When this anomaly has been recognized base-line vitality assessment should be done to find existing pulpal condition. When pathological infection is

not present the commencement of suitable prophylactic procedures must start. (1). It comprised the preparation of the invagination entry and restores it with amalgam or modern fissure sealant.(2) Microscope and ultrasonic instruments are used to open up and gain access to the invagination entry. When the infolding is entirely uncovered, MTA may be utilized to fill the invagination and entrance opening will be preserved with composite. The tooth vitality should be regularly checked. (3). Root canal treatment should be started, If tooth lost vitality. An intra-canal medicament (such as calcium hydroxide) is used but in recent times triple antibiotic paste (ciprofloxacin, minocycline, metronidazole) has been applied. (4) If apex is opened, this problem is solved by forming apical plug either using calcium hydroxide or by MTA (mineral trioxide aggregate) (5). When endodontic treatment is not succeeds then combination of nonsurgical and surgical treatment could be carried out.[56,58]

**TYPE III:**

Vital tooth related with pen-apical inflammation, this mal-development should be managed endodontically in the similar approach as a normal root canal to save the vitality of the pulp.[57,59]Intype III invagination, when pulp necrosis has occurred in a tooth is effectively handled by root canal treatment of the invagination alone, or with a collective endodontic and pen-apical surgery.[58]Ultrasonic can be applied for the entire elimination of invagination in a few cases to assist root canal treatment.[54]When the morphology of these teeth is compound, endodontic therapy is not achievable then extraction is generally suggested and prosthetic substitute is advised.[55]The option of planned re-implantation has also been discussed in very difficult class III dens invaginatus.[58,59]

**CONCLUSION:**

Dens invaginatus is a developmental abnormality of teeth. Involved teeth demonstrate a deep invagination of enamel and dentine originating from the foramen caecum or the incline of the cusps, which can penetrate deep into the root. Maxillary lateral incisors are most affected teeth. It is crucial that dens invaginatus cases are identified early, before the development of periapical infection, so that a precautionary measure of sealing the invagination is taken and the tooth is then monitored. If the teeth develop infection and become non-vital, the problems in root canal management should be kept in mind and explained to the patient mainly Type III cases, others options such as surgical intervention or extraction should be considered. The availability of 3- dimensional imaging system (CBCT) and use of a surgical microscope help in the removal of the dens part of a tooth without compromise the coronal tooth structure.

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ORIGINAL ARTICLE:

# Grip Strength Test: A Simple Functional Adjunct Tool for Rheumatoid Arthritis

Fuad Shaikh[1], Nasim Karim[2], Khalid Mahmood[3], Mohammed Ishaq Ghauri[4]

ABSTRACT:

**Objective:** To evaluate the usefulness of Grip Strength Test as an adjunctive tool for patients having rheumatoid arthritis.

**Materials And Methods:** A twenty four (24)-week, single-blind, interventional, prospective study was carried out from October, 2009 to March, 2011 in 126 patients of either sex, between 19-64 years of age. They were diagnosed to have rheumatoid arthritis according to the American College of Rheumatology Criteria. They were given tablet Methotrexate, 10 mg (4 tablets of 2.5 mg, orally) weekly for six months. Grip strength was measured by pneumatic method. Patients were made to compress a locked, aneuroid, sphygmomanometer cuff, inflated to 20 mm of Hg, in their palms. The level of pressure reached was recorded as a measure of grip strength.

**Results:** All patients had morning stiffness, symmetric arthritis, soft tissue swelling and arthritis of hand joints. Baseline values of Hb, TLC, ESR, PC, CRP, serum creatinine and SGPT were 10.76 ±1.12g/dl, 8572.06 ±1445.08 per cubic mm, 81.03 ±17.98 per cubic mm, 290,277.78 ± 68,813 per cubic mm, 2.33 ± 0.69 microgram/dl, 0.95± 0.16 mg/dl, and 31.67 ± 7.37 IU/L respectively. Grip Strength increased from a baseline of 71.10mm of Hg to 154.04mm ofHg in the right hand and from 70.58mm of Hg to 151.53mm ofHg in the left hand, both values being significant statistically [$p< 0.001$].

**Conclusion:** Grip strength test is a useful, simple, effective, functional, adjunct tool for assessing patients's response to therapy in rheumatoid arthritis.

**Keywords:** Grip Strength, Pneumatic Method, Adjunct Tool, Hand Joints, Rheumatoid arthritis.

## INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic, systemic, progressive, autoimmune disease in which joint destruction, with resultant loss of function, leads to deterioration in health-related quality of life[1]. It has 1% prevalence world wide, with the greatest incidence between 40 and 50 years and affects women three to five times as often as men[2]. Almost one-sixth of the world population lives in India and Pakistan with prevalence rates of 0.5% and 0.2-1% respectively[3].

In autoimmune diseases, affected individuals have a defect in the ability to distinguish foreign molecules from the body's own. Genetic association with (HLA-DR4)[4], cigarette smoking, use of decaffeinated coffee,[5] presence of Herpes virus, Epstein-Barr virus and Human Herpes Virus- 6 infections[6] are all risk factors and make a person susceptible to RA. In RA, monocytes are attracted to the joints where they differentiate into macrophages and become activated. They secrete tumor-necrosis factor (TNF), interleukin- 1, 6 and 8 (IL-i, IL6, IL-8). Growth factors such as granulocyte—macrophage colony-stimulating factor (GMCSF) and matrix metallo-proteinases (MMP5) contribute further to cartilage and bone destruction[7]. Patients present with joint inflammation and constitutional symptoms like fever, malaise, anorexia, weight loss, pain, local edema, synovial thickening and joint erosion[8]. They have painful, symmetrical joint involvement, initially of the hands, feet and cervical spine with shoulders and knees becoming involved later on. There is morning stiffness. Rheumatoid nodules are seen in 20-30% of patients and are indicative of a poor prognosis. Eventually, synovitis and resultant joint erosion leads to deformity and loss of function[9]. Extra-articular manifestations occur in about 15% of individuals[10].

There is no single test available to diagnose rheumatoid arthritis. Instead, the diagnosis is based upon the combination of American College of Rheumatology criteria [1987][11] (Table 1), physical examination, the results of laboratory tests and x-rays.

Rheumatoid arthritis is usually treated with Methotrexate, Leflunomide, Penicillamine and Cyclosporine etc. along with NSAIDs and Corticosteroids (where and when needed). In our clinical set-ups, the patients presenting with this disease are not too well-off. The repeated visits and laboratory tests, as well as the cost of drugs, proves to be a great financial burden, resulting in frequent drop-outs from therapy. Inadequate patient compliance thus leads to a subsequent increase in morbidity. Present study was designed to evaluate the usefulness of Grip Strength Test as an adjunctive tool in monitoring the patients' response to therapy.

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## MATERIALS AND METHODS:

This twenty four (24)-week, interventional, prospective, single-blind study was conducted from October, 2009 to March, 2011 as a part of requirements for the award of MPhil degree. The study was approved by the Institutional Review Board (IRB) and Board of Advanced Studies and Research (BASR), Dow University of Health Sciences (DUHS). It was carried out on patients visiting the out-patients department of a private consultant's clinic in Karachi. 170 patients fulfilling the American College of Rheumatology criteria were enrolled after a written, informed consent. They were given tablet Methotrexate, 10 mg weekly (4 tablets of 2.5 mg, orally) and were advised to return for follow up at 6, 14 and 24 weeks (3 times). Baseline values of hemoglobin (Hb), total leucocyte count (TLC), erythrocyte sedimentation (ESR), platelet count (PC), C-reactive protein (CRP), serum creatinine and serum glutamic pyruvic transaminase (SGPT) were carried out as the drugs used to treat RA can adversely affect them and changes in these parameters help guide the treating physician in tailoring the dose of the medications. They also helped in excluding patients with co-morbids. Financial aspects were mainly catered to by the researcher with minimal burden on the study participants.

### Grip Strength:

Disability in patients of rheumatoid arthritis has been associated with loss of hand grip strength and function[12]. Grip Strength Test is one of the methods used to assess and monitor patient response to therapy. It involves the measurement of the force or power exerted by a person while compressing a rolled-up, sphygmomanometer cuff. Results of grip strength testing have been used to determine a baseline measure of performance against which changes following therapy can be compared [13] The grip strength in normal subjects lies mostly between 300 and 600 mm. of Hg. In patients with rheumatoid arthritis the grip strength was seen to be less than 200 mm. of Hg, depending on the severity of the involvement of hand joints[14]. To assess grip strength a pneumatic type of apparatus was used in which an aneuroid, adult, sphygmomanometer cuff was evenly rolled to conform to a normal, functional, hand position for grip. A rubber band was placed around each end of the cuff to hold it in position. The cuff was then inflated to 20 mm of Hg, which was the starting position for measurement of each subject.

### Pre-requisites:

A standard testing position approved by the American Society of Hand Therapists (ASHT) is recommended[15]. This requires that the patient sit in a straight-backed chair with the feet flat on the floor, the shoulders adducted in a neutral position and the arms unsupported. The elbows should be flexed at 90 degrees with the forearm and wrist rotated in a neutral position and the fingers flexed, as needed for maximal contraction. The patient should breathe in through the nose and blow out through pursed lips as a maximum grip effort is made for 3 seconds[16]. A prior demonstration of how to perform the procedure should be given.

## STATISTICAL ANALYSIS:

The results are shown as mean ± SD. P-value of $< 0.05$ was considered to be statistically significant.

## RESULTS:

A total of 170 patients were enrolled out of which 126 completed the study, with the rest being lost to follow up due to their own reasons. Of the 126 patients 37 (29.4%) were males and 89 (70.6%) females. All of them had morning stiffness of more than 60 minutes duration, swelling of the involved joints along with symmetric arthritis and arthritis of the hand joints. Their mean age was 35.76 years ± 10.47 with a range of 19-64 years (Table 2). The mean baseline grip strength in the right hand was 71.10 ±16.49 mm of Hg while that in the left hand was 70.58 ± 16.81 mm of Hg (Table 2). The values of baseline laboratory investigations like Hb, TLC, ESR, PC, CRP, serum creatinine and SGPT (Table 3).

The grip strength in the right hand rose from the baseline value of 71.10 mm of Hg to 154.04 ±19.76 mm of Hg with $p<0.001$, while the grip strength in the left hand rose from the baseline value of 70.58 mm of Hg to 151.53 ± 16.15 mm of Hg with $p<0.001$. Both values were found to be significant statistically (Table 4).

**Table 1**

**The American College of Rheumatology Classification Criteria**

| S. No. | Parameter | Features |
|---|---|---|
| 1 | Morning stiffness | >1 hour most mornings |
| 2 | Arthritis and soft-tissue swelling | of > 3 of 14 joints/joint groups |
| 3 | Arthritis of hand joints | |
| 4 | Symmetric arthritis | |
| 5 | Subcutaneous nodules | |
| 6 | Rheumatoid factor | Present |
| 7 | Radiological changes | suggestive of joint erosion |

**Criteria 1-4 should have been present for at least 6 weeks.**

**At least 4 criteria have to be met for classification as Rheumatoid arthritis**

**Table 2**

**Demographic data & baseline Grip Strength**

**(N=126)**

| S.No. | Parameter | No (%) |
|---|---|---|
| 1 | Gender | |
| | Male | 37 (29.4) |
| | Female | 89 (70.6) |
| | | **Mean ± SD** |
| 2 | Age | 35.76 ± 10.47 |
| 3 | Grip strength (mm of Hg) Right hand | 71.10 ± 16.49 |
| 4 | Grip strength (mm of Hg) Left hand | 70.58 ± 16.81 |

**Table 3**
**Laboratory parameters (Baseline values)**
**(N=126)**

| S.No. | Parameter | Baseline values Mean ± SD |
|---|---|---|
| 1 | Hb (g/dl) | 10.76 ± 1.12 |
| 2 | TLC (per cubic mm) | 8,572.06 ± 1,445.08 |
| 3 | ESR (per cubic mm) | 81.03 ± 17.98 |
| 4 | PC (per cubic mm) | 290, 277.78 ± 68, 813 .68 |
| 5 | CRP (microgram/dl) | 2.33 ± 0.69 |
| 6 | Serum creatinine (mg/dl) | 0.95 ± 0.16 |
| 7 | Liver Enzyme (sgpt, IU/L) | 31.67 ± 7.37 |

**Table 4**
**Comparison of grip strength values at baseline and 24 weeks**
**(N=126)**

| Right hand Baseline values (Mean ± SD) | (mm of Hg) 24 weeks (Mean ± SD) | P value | Left hand Baseline values (Mean ± SD) | (mm of Hg) 24 weeks (Mean ± SD) | P value |
|---|---|---|---|---|---|
| 71.10 ± 16.49 | 154.04 ± 19.76 | < 0.001 | 70.58 ± 16.81 | 151.53 ± 16.15 | < 0.001 |

**DISCUSSION:**

It has been noted that people suffering from RA have demonstrated a 5-10 year reduction in their life span[17] along with a doubling of the risk for cardiac diseases[18]. Hence an early diagnosis with institution of immediate treatment with disease-modifying, anti-rheumatic drugs (DMARDs) is required to prevent the onset of deformities and morbidity in RA. Despite this a large number of patients exhibit evidence of impaired activities of daily living with almost 33% of sufferers disabled after 5 years of disease and almost half having substantial functional disability after 10 years[19]. Tilley et al conducted a 48-week, randomized, double-blind, multi-center trial to determine the efficacy and safety of Minocycline in rheumatoid arthritis. This MIRA trial was a placebo-controlled trial comparing Minocycline (mean age ± S.D. 55 ± 12.8 y, 76% women,

Eberhardt studied 183 patients with recent onset RA taking part in a longitudinal study initiated at Lund in 1985. There were 116 females (64%) with a mean age ± S.D. of 51.4 ± 12.4 years and grip strength was measured by a sphygmomanometer. They received either D-Penicillamine, antimalarial drugs or methotrexate. Grip strength values at the end of two years showed significant changes with p values of< 0.07[21].

Clark et al studied 126 patients with early rheumatoid arthritis in a double-blind, randomized trial over 24 weeks, who were randomly assigned to receive hydroxychloroquine, 400 mg/d, or placebo. Grip strength was assessed using a sphygmomanometer with a standard grip bag. The patients showed a 22% greater mean improvement with a p value of 0.01[22].

In a trial of the therapeutic effectiveness of flurbiprofen, contrasting different times of day and frequencies of administration grip strength was measured with an inflatable, grip bag, attached to an aneuroid sphygmomanometer. It was inflated to an initial pressure of 20 mm of Hg. The researchers found that grip strength was minimal in the morning when subjective pain and stiffness scores were highest and it consistently decreased with increasing pain and stiffness making it a valid measure of symptom severity[23]. Ferraz and colleagues evaluated the degree of morning variation in assessment of grip strength in patients with rheumatoid arthritis and their results also showed significant changes[24].

All the above mentioned studies were carried out on diagnosed patients of RA with the Grip Strength Test being a common denominator. The changes seen in the grip strength test in these studies are comparable to those seen in our study and indicate the usefulness of the grip strength test in monitoring the patients' response to therapy in RA. Wessel conducted a systematic review of related articles to evaluate the efficacy of hand exercises for persons with rheumatoid arthritis by searching the databases of Medline, Cumulative Index to Nursing and Allied Health Literature (C1NAHL), EMBASE, PEDro, and Cochrane. He concluded that grip strength should be used along with other parameters in patient assessment[25]. It is an easy-to-perform, reliable, reproducible, non-invasive test which does not cost the patient anything[26]. Appropriate key words and phrases were put into PubMed, Medline, Google Search etc. and the authors have not found any study against the grip strength test. This again emphasizes the effectiveness of this simple test.

In patients with RA follow-ups entail a financial burden. The patients have to undergo various blood tests repeatedly. In our study, where the patients are generally not well off, this frequently results in patients dropping out from therapy or wandering from one doctor to the other in search of rapid relief. A monitoring tool that is easy to perform, takes very little time of a busy consultant or physician, is reliable and, most importantly, is free of cost to the patient would go a long way in lowering the patient drop-out rate and subsequent morbidity and mortality. Grip strength is one such available tool which can be a part of the armamentarium of a physician or rheumatologist. It can be used for monitoring the response of patients to therapy and at the same time it can be used to minimize the costly laboratory investigations by ordering them only at times when they are actually required.

## CONCLUSION:

Grip strength test is a useful, simple, effective, functional, adjunct tool for assessing patients' response to therapy in rheumatoid arthritis. Furthermore it is a non-invasive and costeffective test suitable for use in clinical settings of a resource-poor country like Pakistan. Multi-center studies with large sample size are open horizons for future research.


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ORIGINAL ARTICLE:

# Effect and Toxicity of Methanolic Extract of Brassica Oleracea on Body Weight of Rabbits

Tahira Zamir[1], Rabia Arshad[2], Talea Hoor[3]

**ABSTRACT:**

**Objective:** To evaluate the effect and toxicity of methanolic extract of Brassica Oleracea var. capitata on body weight of rabbits.

**Materials And Methods:** This experimental study was conductedonl4 healthy white rabbits of either sex at department of pharmacology, faculty of pharmacy, university of Karachi in 2011. All animals were equally divided in two groups i.e. control and test group .Test group received methanolic extract of Brassica Oleracea in a concentration of 100 mg/kg of body weight for 30 days (4 weeks) through oral route once daily. While control group received normal saline lml/day equivalent to volume of dose given to test animals. Gross toxicity was observed during whole period in animals of both groups. Body weight of animals was recorded weekly on weighing machine.

**Results:** The animals who received methanolic extract of Brassica Oleracea in a dose of 100 mg/kg body weight showed significantdecrease in mean body weight of (1783±2.4)as compared to control animals (1957±4.92). Difference in mean body weight recorded on day 31 (at the end of 4 weeks) was 46gm as compared to animals of control group where decline was only 1 gm. While the percent decrease in mean body weight was found to be (3%) as compared to control animals (0%).Features of gross toxicity such as loss of hair, change in hair color, aggressiveness in behavior, diarrhea, and haematuria, were not found in animals of both groups during whole experimental period.

**Conclusion:** Methanolic extract of Brassica Oleracea exhibited weight reducing effect in rabbits without any gross toxicity.

**Keywords:** Brassica Oleracea, Methanolic extract, Body weight, Rabbits, Toxicity

## INTRODUCTION:

Plants based research is increasing worldwide revealing the immense potential of medicinal plants in the area of Pharmaco-therapeutics. Various medicinal plants have been studied using modern scientific approaches.[1,2]

Plants as medicinal agents were cited in history dating back many thousands of years.[3]Presently, these are reported to be used against a wide range of health problems.[4]Plant-derived remedies have been estimated by the World Health Organization (WHO) to be the most frequently used therapies worldwide[5]. Therapeutic agents derived from plants include pure chemical entities available as prescription drugs (e.g., digitoxin, morphine, and taxol) standardized extracts, herbal teas, and food plants; containing phytochemicals with potent pharmacological and toxicological properties[6].Screening for new drugs in plants implies the screening of their extracts for the presence of novel compounds and investigation of their biological activities.

Over 100, 000 secondary metabolites are known in nature, but only small percentage of all plant species have been studied to some extent for the presence of these secondary metabolites. It is currently estimated that approximately 4, 20, 000 plant species exist in nature but less than 5% of known plants only have been screened for one or more biological activities[7].

Brassica Oleracea L. var. capitata (Cruciferae) commonly called cabbage (figure 1) is a species of Brassica native to Coastal Southern and Western Europe, naturally occurring near to limestone sea cliffs, similar in composition to other Brassica vegetables.[8]It is available in various shades of green, red or purple. The most popular varieties are green, red, savoy and Chinese.[9]

**Figure 1**
**Brassica Oleracea[34]**

Bras□Oleracea is widely used as a vegetable and remedy for different diseases all around the world[10] It is found to have anticancer, antioxidant, antiplatelet and antihypercholesterolemic activities[11, 12]. It has been found to attenuate bronchoconstriction and inflammation by virtue of its anti anaphylactic activity[13].Compounds responsible for these activities of Brassica Oleracea include isothiocyanates and their cognate glucosinolates, phenolics including flavonoids and other non-nutrients.[14] Brassica Oleracea is a rich source of antioxidant nutrients, which regulate immune system and protect against various diseases such as heart disease and cancer. Furthermore, it contains 13 caroteine, lutein and zeaxanthine[15]. Increase in body weight leads to many complications in the form of chronic heart disease, diabetes, and stroke[16].Every year millions of people diet to reduce

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weight but the continuing response of this is poor as in reaction to food deprivation drive to eat increases and the metabolism slows down there by neutralizing the effects of dieting[17].Plants have achieved significant position in health care system all over the world not only in the diseased condition but also as promising agent for maintaining proper health[18] Many plants are documented in the literature for weight loss.[19]Studies have recommended that low-fat, plant-based diets decrease body weight, improve cardiovascular risk factors, provide glycemic control, and, in combination with other lifestyle modifications reverse atherosclerosis.[20] With this background, present study was specifically designed to evaluate the effect of Brassica Oleracea L. var. capitata on body weight of rabbits along with any gross toxicity.

## MATERIALS AND METHODS:

This experimental study was conducted in the Department of Pharmacology, Faculty of Pharmacy and University of Karachi after approval from Board of Advance Studies and Research (BASR) in 2011 as per fulfillment of requirement for M-Phil degree.

**Plant Material And Preparation Of Extract:**

Fresh cabbages were purchased from local market in Karachi and identified by Prof. Anjum Parveen, Director Centre for Plant Conservation Herbarium and Botanic Garden, University of Karachi, Karachi-75270.The voucher specimen (H.No.BO-09-12) was deposited in the Department of Pharmacognosy, University of Karachi. The crude extract was prepared through cold extraction process[21] After thorough washing, 5 kg of Brassica Oleracea leaves were chopped into small pieces and dried under shade for about a week. The dried material was ground to coarse powder. This powder was soaked in 80% methanol for 10 days with occasional shaking and stirring. The solvent was filtered through cotton and then through filter paper (Whatmann No.1). After filtration, the methanol extract was evaporated under reduced pressure in a rotary evaporator at 40°C - 45°C and then followed by freeze drying at -30°C, the extract so obtained was kept at-20°C until further use. The resultant yield of extract obtained was 325 g.

**Animals:**

The study was conducted on l4 healthy white rabbits of either sex (1500-2200g), housed at the animal house of Department of Pharmacology, University of Karachi, under controlled condition of temperature (22±2°C) and humidity (50to60%) in an alternating 12-h of light/dark cycle. The animals were kept in separate cages and were given standard diet and water regularly. The use of animals in this experiment was in accordance with the National Institute of Health (NIH) Guide for the Care and Use of Laboratory Animals[22].

**Preparation Of Dosage Of Plant Extract:**

Methanolic extract of Brassica Oleracea was given in sterilized water such that each 1 ml contained the 100 mg /kg body weight dose of the extract.

**Dosing:**

All the animals were equally divided in two groups i.e. control and test groups. Test group received methanolic extract of Brassica Oleracea in a concentration of 100mg/kg body weight. Extract was administered to animals of test group continuously for 30 days (4 weeks) through oral route once daily. While the animals of control group received normal saline per orally, imi/day equivalent to the volume of dose given to test animals.

**Body Weight Measurement:**

Initially base line body weight of all the animals of both groups was recorded. Thereafter, it was recorded daily and mean body weight was calculated at the end of each week till four weeks on weighing machine till the end of dosing. The difference in mean body weight of animals was calculated by subtracting the final mean body weight of animals from initial mean body weight of animals. Formula for calculating difference in mean body weight and percent decrease in mean body weight was adapted from the study of Hisham.[23]

**Gross Toxicity:**

During the whole experimental period, all the animals used were subjected to a detailed gross examination that included careful examination of the external surface of the body and all orifices. Features of gross toxicity like loss of hairs, change in hair color, behavioral changes and loss of activity, diarrhea, hematuria and sedation were also observed.

## STATISTICAL ANALYSIS:

All values were compared with the control by taking mean and standard error to the mean (Mean ±S.E.M) using one sample t-test. P- value $<0.05$ in comparison to the control were considered significant.

## RESULTS:

The animals who received methanolic extract of Brassica Oleracea in a dose of 100 mg/kg body weight showed significant decrease in mean body weight of (1783±2.4) in comparison to the control animals (1957±4.92).(Table 1) The difference in mean body weight from initial mean body weight of animals recorded on day 31 (at the end of four weeks) was 46gm in comparison to animals of control group where decline was only 1 gm.(Table 2) While the percent decrease in mean body weight was found to be (3%) in comparison to the control animals where it was (0%).(Table 3a, 3b). No gross toxicities were observed in any animal including control during the total period of experiment.

**Table 1**
**Baseline Body Weight of Animals**
**N=14**

| No.of Animals | Control group n=7 Body Weight (gm) | Test group n=7 Body Weight (gm) |
|---|---|---|
| 1 | 2000 | 2200 |
| 2 | 2100 | 2000 |
| 3 | 1800 | 1500 |
| 4 | 2000 | 1600 |
| 5 | 1700 | 1503 |
| 6 | 2100 | 2000 |
| 7 | 2000 | 2000 |

**Table 2**
**Mean Body Weight of Animals per Week**
**N=14**

| Number of Weeks | Control group n=7 Mean body weight (gm) | Test group n=7 Mean body weight (gm) |
|---|---|---|
| First week | 1958±3.2 | 1829±6.7 |
| Second week | 1958±2.9 | 1823±3.2 |
| Third week | 1957±0.1 | 1800±9.2 |
| Fourth week | 1957±4.92 | 1783±2.4 |

**Table 3a**
**Comparison of Mean Body Weigh**
**N=14**

| Mean body weight (gm) | Control gruup | Test group | P-value |
|---|---|---|---|
| Initial mean body weight | 1958±3.2 | 1829±6.7 | 2.37 |
| Final mean body weight | 1957±4.92 | 1783±2.4* | 0.04 |

n=7
Average value ± S.E.M
*P<0.05 as compared to control

**Table 3b**
**Difference in Mean Body Weigh**
**N=14**

| Mean body weight (gm) | Control gruup | Test group |
|---|---|---|
| Difference in gram (gm) | 1gm | 46 gm |
| Difference in percentage (%) | 0% | 3% |

**DISCUSSION:**

The World Health Organization describes the "escalating global epidemic" of obesity as "one of today's most blatantly visible yet most neglected public health problem". According to WHO, globally 1.5 billion people were reported to be overweight in the year 2008. Among which, over 200 million people were males and nearly 300 million were females. There have been two major reasons for increased body weight. Firstly, an increased intake of energy rich foods that are high in fat, salt and sugar content but low in vitamins, minerals and other micronutrients, and secondly, decrease in physical activity due to the increasingly sedentary life style, changing modes of transportation and increasing urbanization.[24] Obesity is the fifth risk factor for death worldwide Annually approximately 2.8 million people die due to obesity .Moreover, 44%cases of diabetes, 23 % cases of ischemic heart diseases and 7 to 41% cases of cancers are caused by increase in body weight. It is a major threat to human health. Increased body weight put stresses on almost every individual part of human body. It can lead to a variety of health problems like bone and joint disorders, gall stones, liver problems, coronary heart disease, congestive heart failure, stroke, increased blood pressure, increased blood lipid levels, increased blood sugar and sleep problems. Overall work efficiency of a human being is suffered due to being overweight.[25]

Worldwide change in dietary habits by taking more animal diet, partially hydrogenated fats, refined carbohydrates and less consumption of fibers has resulted in increased obesity and degenerative diseases.[26]On the contrary the populations that consume plant diet are reported to have less incidence of these diseases.[27]Several studies have confirmed the usefulness of plant based diet in the management of obesity and cardiovascular risk factors.[28,29]

Common treatment measures for weight loss include dietary changes, increase physical activity, behavioral changes, and anti-obesity medications. The preferred treatment modality for reducing weight is to change the dietary habits and increase the physical activity.[30]

Anti-obesity drugs are generally effective, but severe adverse toxicities limit their usefulness.[31]Herbal products are being extensively utilized because of their less side effects in comparison to chemically synthesized drugs. Many studies have documented that herbal products are less likely to cause toxicity, are effective in reducing appetite and promoting significant weight loss.[32]

In our study, administration of methanolic extract of Brassica Oleracea in a dose of 100 mg/kg body weight decreased the mean body weight in all the test animals in comparison to the control animals.The difference in mean body weight from initial mean body weight of animals recorded on day 31 (at the end of 4 weeks) was 46gm (3%) in comparison to animals of control group where decline was only 1 gm (1%). Decrease in body weight of animals indicates that Brassica Oleracea reduces body weight.

In literature, it is documented that Brassica Oleracea has hypolipidemic effect in animals. It can be assumed that the weight lowering potential of Brassica Oleracea might be due to its hypolipidemic effect[11].

As mentioned earlier, Brassica Oleracea is a rich source of protective phytochemicals. In one of the studies, it is stated that the weight lowering potential of plants is not merely due to their hypolipidemic effect but also due to the presence of phytochemicals in them. Therefore, weight lowering potential of Brassica Oleracea might also be contributed by the presence of phytochemicals[12].

Antioxidant compounds have the ability to decrease the levels of glucose, triglycerides and LDL, increase fat oxidation and lower body weight. They can also inhibit enzymes associated with fat metabolism.[33]It can be ascertained that the weight lowering potential of Brassica Oleracea might also be due to its antioxidant activity.

It has been documented that Brassica Oleracae also have hypoglycemic effect in animals.[35]The weight reducing ability of Brassica Oleracae might be due to its hypoglycemic effect .However, present study has not evaluated this effect.

Increasing awareness and consumption of plant derived products justify evaluation of their safety. We have found no gross toxic effect like loss of hairs, change in hair color, haematuria, aggressiveness in behavior, loss of activity and diarrhea in any animal during the whole experimental period. This indicates that Brassica Oleracea was completely safe at the administered dose and may be used as a nutritive alternative for weight management without any gross toxicity. Thus weight reducing effect of Brassica Oleracae can be attributed to combination of its phytochemical nature, hypolipidemic, antioxidant and hypoglycemic activities.

## CONCLUSION:

Methanolic extract of Brassica Oleracea exhibited weight reducing effect in rabbits without any gross toxicity. Studies with large sample size using different doses in normal, obese and diseased animals should be conducted.


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ORIGINAL ARTICLE:

# Ageing Ovaries and Endometrium in PCO

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ABSTRACT:

**Objective:** to measure the outcome of age on ovarian and uterine morphology in women with primary infertility due to polycystic ovarian syndrome (PCOS)

**Materials and Methods:** It was an observational cross sectional study. Two hundred primary infertile women with PCOs were subdivided into age groups (years) 20-30 (group I) and 31- 40 (group II). The ovarian volume (OV), follicles count (FC) and size (FS), uterine area (UA) and endometrial thickness (Endo) were determined by transabdominal (TAS) and trans -vaginal scan (TVS) using the ultrasound machine. Unpaired t-test was applied to evaluate the result

**Results:** Comparison between group I and group II was made to evaluate the outcome. A significant raise was noted in the uterine morphology of group II. The UA was 89.99±5.83cm$^2$ v/s 119.0±23.33cm$^2$ (0.001) and endometrial thickness was 0.48±0.11mm v/s 0.59±0.13mm (0.001). A significant decline was noted in the ovarian morphology of group II; the OV (TAS) was 15.36± 2.56cm$^2$ v/s 10.57±12cm$^2$ (0.001) and TVS showed 15.74±2.23mm v/s 10.37±1.08mm (0.001). The FC was 14.05± 1.56 v/s 12.47±0.89 (0.022) and FS was 9.45±7.98 v/s 4.33±5.88 (0.00).

**Conclusion:** The OV, FC and FS (ovarian morphology) variables decreases in the elder infertile group with PCOs but the uterine morphology variables showed an increase in area with thickening of endometrium in the elder group.

**Keywords:** Polycystic ovaries, Hyperandrogenism, Infertility, Ovarian volume, Follicle count, Follicle size, Uterine area, Endometrial thickness.

## INTRODUCTION:

The presence of 12 or more follicles measuring 2-9mm in diameter or increased ovarian volume (>10cm3) is known as polycystic ovarian syndrome (PCOS). It is associated with oligo-/ anovulation and raised serum levels of androgens, or evidence of hyperandrogenism after all known potential causes have been excluded. The ultrasound examination can play an important role in early diagnosis, and evaluating PCOS patients for endometrial hyperplasia.[1,2] Polycystic ovary syndrome (PCOS) is the most commonly encountered endocrine disorder in women of reproductive age; recent studies have shown that 5- 10% females of reproductive age group are affected. It has marked reproductive and non-reproductive consequences. Raised serum levels of luteinizing hormone (LH), testosterone and androstenedione, along with decreased or normal levels of follicle stimulating hormone (FSH) are believed to be present[1,2]. Many different definitions for PCO have thus been proposed. Twelve or sometimes more follicles measuring 9mm in diameter along the periphery like a string of pearls with an increased ovarian volume (>10cm$^3$) is known as PCO[2]. There are also deranged androgen levels and women tend to show increase levels of testosterone in the young age group which may be attributed to physical abnormalities like menstrual disturbances and hair growth in abnormal places[3].

The ratio of follicular androstenedione to estradiol is high in patients with PCO, suggesting defect in the enzyme causing aromatization of ovarian androgens produced by LH, estrogens by FSH in the ovary. A P450 aromatase gene mutation has been found to cause a form of this syndrome. The anovulatory cycles when last for a considerable period of time, the "polycystic ovary" results. As a consequence, affected women develop single or bilaterally enlarged ovaries, resulting in PCOs.[4] Infertility is defined as failure to conceive after one year of unprotected intercourse[5]. PCO is considered as one of the most common disease resulting in infertility. Lack of the ability to conceive due to PCO affects around 5-10% of women who are in their young reproductive age. The majority of these cases are associated with menstrual irregularities and is also linked to an increase in luteinizing hormone.[6,7,8] Such women have frequent failure during assisted reproductive techniques (ART) and show miscarriages after this technique.[9] Several studies have also linked PCO with other diseases one of which is cardiovascular diseases. Correlation of PCO with insulin resistance and obesity has also been reported since long. The symptoms resulting from infertility is a result of long term anovulation and menstrual irregularities, obesity, presence of adipose tissue in upper parts of the body, and skin changes such as hirsutism, acne, seborrhea etc [8] The presenting complaints in such women of reproductive age afflicted with this disease are

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chiefly hyperandrogenism and menstrual irregularities, examples of which are, oligomenorrhea or amenorrhea, where as infertility is the chief presentation in adult women with PCOS during the reproductive age[3].

There is enhanced evidence that the endocrine and metabolic abnormalities in PCOS have intricate effects on the endometrium, contributing to infertility and endometrial disorders [8,9] The hazards include unimpeded estrogen stimulation of the endometrium in anovulatory PCOS women, obesity, insulin resistance, insulin like growth factors, diabetes, nulliparity and progesterone resistance [2,10] association of BMI with PCOs and infertility has been very well- known and is documented in several studies [11,12] By relating BMI with the morphology of pelvic reproductive organs the underlying mechanism for sub fertility can be better understood especially in PCOs females who often suffer from obesity. The effect of BMI on endometrial thickness and uterine size can also help in predicting the risk factor for endometrial carcinoma and fibroids. A study [11] showed that PCOS is related to consumption of food. The authors have shown that certain type of food items like fried potatoes and white bread were taken in large amounts by the recruited subjects suffering from PCOS. Further investigation is needed with larger sample size on morphology of ovaries and uterus like organs to establish a strong relation with BMI so that preventive measures can be taken to control many associated diseases.[7]

The ultrasound examination can play a role in evaluating PCOS patients for endometrial hyperplasia, in accordance with menstrual history. Anthony et al found positive correlation between endometrial thickness and endometrial hyperplasia.[11] The long term effects of consistently high estrogen levels results in increased risk of endometrial hyperplasia and endometrial cancer. The risk is three times higher in women with polycystic ovaries as compared to normal women.[4]

## MATERIALS AND METHODS:

After obtaining ethical approval from the ethical review committee of Ziauddin University, this observational cross sectional study was conducted from January 2009 to March 2010, the subjects were sought from Ziauddin Hospital, Nazimabad Karachi. The sampling technique used was non probability simple random type. In this study women diagnosed with PCOs after ultrasound were included. Those included were diagnosed clinically and then ultrasound was performed to induct them in the study. The subjects were educated and belonged to the middle class who were determined by their monthly income according the set criteria by World Health Organization for developing countries. They were informed about the study and agreement was sought via a written informed consent and before the procedure signature of the subject along with two witnesses was sought.

The subjects were included in the study if they fulfilled the following criteria a) primary infertility b) females of ages between 20-40 years c) existence of 12 or more cystic follicles in one or both ovaries However the subject were excluded due to any one or more of the following reasons a) using ART for conception b) any pathology of pelvic reproductive organs other than PCOs c) a lab report showing that husband is infertile d) hypertension, diabetes, cancer etc or any other chronic illness e) secondary infertility f) The subject not using contraceptives for at least 2 months preceding the study Between 2nd to 7th day of the menstrual cycle scanning of the ovaries and uterus was performed [12] using Toshiba ultrasound machine. Transabdominal and transvaginal probes were used which were respectively of 3.75 MHz and 7.5 MHz frequency. Transabdominal scan (TAS) was performed on a full urinary bladder. This was carried out in order to eliminate abnormalities other then PCOs e.g. adhesions, tubal ligation, absence of ovaries (one or both), endrometriosis, fibroids, cancers etc. Transvaginal scan (TVS) was performed only in those patients who were diagnosed with PCO during TAS.

Following variables were measured and noted a) ovarian volume b) follicle count and size (2- 9mm) c) uterine area d) endometrial thickness. "Scanning of the two ovaries was done in the longitudinal (Dl), anteroposterior (D2) and transverse diameter (D3); the total volume was analysed by applying the ellipsoid equation which is D1XD2XD3XO.523cm$^3$ and the sum of the two ovaries was considered". [12]

Uterine length X anteroposterior diameter in cm the uterine area was calculated and applied

further analysis. From the top of the fundus to the cervix was the uterine length and by TVS the anteroposterior diameter was measured. [10, 11, 12] By TAS the endometrial thickness was measured in mm. [12]

For validation of the results all variables were measured twice and the mean of the two readings was taken as the final value. Clinically diagnosed 254 women with signs and symptoms of PCO during this period visited the ultrasound clinic. Out of the total women on scanning 14 had normal anatomy of the ovaries in spite of have clinical signs of hirsutism, 10 subjects out of 254 had adhesion bands and endometriosis, 11 were not suffering from primary infertility, 8 had undergone some assisted procedure, 4 were suffering from other associated problems and 7 did not give their consent. Therefore 54 women were excluded. The subjects were recruited till our desired number was achieved which was 200. These two hundred women were finally selected to be a part of the study group of which 100 belonged to the age group of 20-30 years and 100 of 31-40 years. The women finally selected were divided into two study groups; age range 20-30, Group I and with age range 31-40 were a part of Group II.

**STATISTICAL ANALYSIS:**

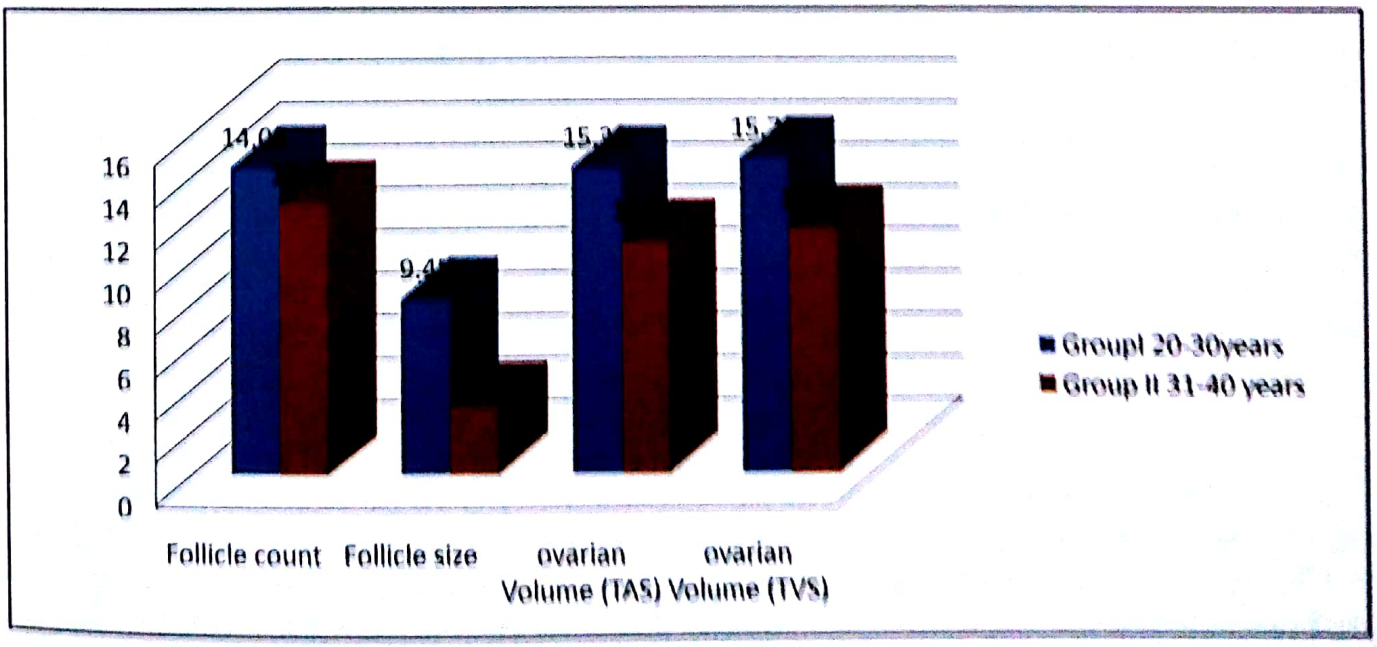
"SPSS version 12 for windows was used to enter and analyze the measurements"; unpaired t-test was applied. The results were demonstrated as mean± standard deviation (SD). "P-value of 0.05 or less was considered statistically significant. Comparison of ovarian morphology with PCOs was assessed by ovarian volume (OV), follicle count and follicle size. Effect of age on uterine area and endometrial thickness was also evaluated.

**RESULTS:**

Mean age in group I (n=100) was 26.46±3.55 and in group II (n=100) was 36.73±3.19 (Mean ± SD). (Figure 1) Trans abdominal and Trans vaginal scan showed a significant decrease in OV with the progression of age (p=0.001, p=0.001 at 95% CI. A decline in follicle count as well as follicle size in group II was noted; p=0.001 and p=0.001 at 95% CI respectively (Table 1).The association of age with uterine area between group I and group II was 89.99± 5.83 vs 119±23.33 The endometrial lining of PCO showed significant ascend in group II; 0.48±0.11 vs 0.59±0.13 (p=0.001 in both variables at 95%CI).

**Figure 1**

**Relation of age with ovarian morphology in primary infertile women with PCOs**




**Note: OV (TAS) = ovarian volume in cm$^3$ (TAS: Trans abdominal scan; TVS: transvaginal scan), follicle count in numbers, follicle size in mm, All Values expressed are mean ± SD; p-value is < 0.05 at 95% CI**

**Table 1**
**Relation of age with uterine morphology in primary infertile patients with PCO**

| Variable | Group I: (n=100) Age: 20-30(mean: 26.46±3.55) | Group II: (n=100) Age: 31-40(mean: 36.73±3.19) | P-value |
|---|---|---|---|
| UA | 89.99 ± 5.83 | 119.0 ± 23.33 | 0.001 |
| Endo | 0.48 ± 0.11 | 0.59 ± 0.13 | 0.001 |

**UA=uterine area in $cm^2$, ENDO= endometrial thickness in mm. Values expressed are mean ± SD; p-value< 0.05 are considered to be significant**

## DISCUSSION:

This study is an attempt to show a comparison between younger and elder primary infertile women affected with PCOs. An enormous increase in the incidence of PCO has been observed which can be credited to the technological development of ultrasonography. Polycystic ovary syndrome (PCOS) is the most common endocrine-metabolic disorder in women of reproductive age with 5-10% of prevalence [12,13]

With rising age the ovarian reserve (collection of primordial follicles) declines and ultimately results in menopause.[14, 15, 16] This depletion of the primordial follicles at the age of 45± 5 years results in the female being unable to conceive. PCOs and other pelvic disorders can however develop during regular ovarian functioning. Association of PCOs with endocrinopathies and certain genetic mutations is now evident and has been proved by several laboratories. [17, 18]

In this study morphological changes has been observed in pelvic reproductive organs in two groups of patients (group- I: 20-30 years & group II: 3 1-40 years) through ultrasound scanning. It was observed that the endometrial thickness was significantly increased in older age group (group I). Other studies also proved that the endocrine-metabolic abnormalities in PCOS may have complex effects on the endometrium due to the prolonged stimulatory effects of unopposed estrogen by chronic anovulation. [14, 15] Park JC et al proposed that the endometrial thickness and age were positively correlated with the presence of endometrial disease in women with PCOS. 12 Another study showed no such correlation and abnormal endometrial thickness has been associated with obesity, and diabetes mellitus along with PCO.[16,17]

In our study we observed that women with PCOs and primary infertility the ovarian volume, follicle count and follicular size was significantly raised in the younger group. Another study was proven to have similar results [18] , reason being due to hormonal imbalance in PCO patients, the luteinizing hormone causes the follicle reserve to increase in size and becomes cystic, the result of which is increase in the ovarian volume, and becomes >lOml. [19,20,21]

The reason for observed results is the fact that exhaustion of the primordial pool which is available at the time of birth is a physiological course which is present from menarche till menopause. The development continues in PCO, as an effect the follicle count decreases yet uterine size persists to be increased.[22,23]

Endometrial thickness undergoes changes according to different phases of menstrual cycle. At the time of menstruation the endometrium is about 1- 4 mm thick, becomes about 5- 7 mm during proliferative phase and reaches maximum thickness of 7-14 mm at the peak of secretary phase[21]. Significant agreement is present with regard to the relationship between BMI and endometrial thickness in multiple studies. Studies showed that the frequencies of thicker endometrium increased in relation to body mass index.[22,23,24,25]

Owing to the expansion in the field of ultrasonography and researches, PCOs are now being recognized at a much earlier stage. It has also been found that the changes in ovarian and uterine anatomy between fertile and infertile women show that the ovarian volume, follicular count and size decrease considerably in the infertile group of women. The authors have shown a decrease in

endometrial thickness in women afflicted with infertility resulting in a decrease in uterine size[8]. The PCOs women are often coupled with obesity, Type 2 diabetes, elevated cholesterol levels and insulin resistance. The relation of insulin resistance when develops the ovaries create oocyte with anomalous morphology. Due to the uncertain worth of the oocyte there is a shortage of fertilization potential of the ovum resulting in infertility.[7] The accurate cause of PCO is still under exploration but researchers have shown genetic connection to this condition. H Þ and LHR gene mutation have been reported to be associated to anovulatory PCOs. Amongst these, obesity and PCOs show cause-effect bond which is highly contentious since obesity has been acknowledged in 40-80% of PCOs women[9]. It has lately been reported that in PCOs patients the effect of the obesity-linked gene [24,25] is mediated all the way through the overload fat deposited due to unevenness in sex hormone. Insulin resistance, one of the imperative dysmetabolic factors of PCOs, is closely related to body weight.[24] At the identical time, obesity does aggravate many aspects of the phenotype, particularly cardiovascular threat factors such as glucose intolerance and dyslipidemia. The damaging synergic effects in PCOs with obesity thus [9] reduces chances of conception at the level of the ovary as well as on endometrial lining more than lean patients with PCOs. Due to the improvement in the field of ultrasonography, PCOs are now being diagnosed at an early age which is significant since early diagnosis leads to timely treatment which can avoid infertility due to this state and associated problems including genetic mutations.[24,25]

Further study is required to be carried out to evaluate the relationship between the endometrial diseases and endometrial thickness in patients with PCO.

## CONCLUSION:

Primary infertility may be an outcome of PCOS; this study measures the ovarian and uterine morphology in such women by using ultrasonography. In this study the ovarian volume, follicle count and follicle size are found to be significantly increased in the younger primary infertile women however the uterine area and endometrial thickness are found to be raised in the older primary infertile women with PCOs. A larger number of PCOs is being timely diagnosed by this simple radiographic technique. Due to this, diagnosis at an early age is possible. By using this diagnostic tool researchers have identified that the incidence of this disease is increasing in younger women of reproductive age. Therefore ultrasound can serve as an important tool in preventing primary infertility as evident by this study. There is limited research of the association of uterine morphology with PCOs and none in this region. In order to fulfill this gap, it is pertinent to understand this relationship to avoid misdiagnosis of endometrial cancer especially in the older age group.

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ORIGINAL ARTICLE:

# Placental Gross Morphology in Gestational Diabetes Mellitus

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ABSTRACT:

**Objective:** To examine the placental gross morphological features in patients having gestational diabetes mellitus.

**Materials and Methods:** One hundred patients were enrolled following written informed consent. At term the placentae were collected, preserved in formalin. Examination was done for size, shape, consistency, color, membrane completeness, detailed cord examination and for any gross pathology on cut section. The mean was taken out for numerical parameters and percentages were calculated for categorical data using SPSS version 16.

**Results:** Mean placental size was 15.98±2.75 cm and 13.58±2.54 cm. The mean placental width was 2.4±0.67 cm, mean weight of placentae was 630±137.4gm. Out of 100, 73 placentae were disc shaped,66 were soft, 85 had complete membrane covering ,59 were pale in color, 66 had central cord insertion and 30 had blue discoloration of the cord.23 had brown lesions, 29 had white lesions and 17 had both types of lesions whereas remaining 35 had no gross lesion.

**Conclusion:** Examination of the placental gross morphology in patients having gestational diabetes mellitus revealed features which necessitates that placenta should be examined in the labor rooms after delivery in GDM patients as it provides important information regarding prenatal life of the new born.

**Keywords:** Placenta, Placental examination, Placental size, Placental shape, Placental consistency, Cord examination.

## INTRODUCTION:

Placenta is an important organ of communication between the mother and the growing fetus.[1]It is essential for the survival of the fetus of all the mammals. The successful development, growth and maturity of placental vessels are important for normal fetal growth and continuation of pregnancy[2] Human placenta has a complex vascular system that allows exchange of different materials with fetal and maternal blood without actual mixing of the two. The maternal surface of placenta is divided in too many portions known as cotyledons. With the progressive development primary, secondary and tertiary villi are formed. Villi are the functional unit of the placenta[3]. On gross examination the placenta is a round disc like structure with multiple cotyledons on the maternal surface. The chorion and amnion are the membranes covering fetal part of placenta, with the large number of chorionic vessels converging towards the umbilical cord. At birth the umbilical cord may be 5 0-60 cm in length with 1.5- 2 cm in diameter. It has a tortuous structure forming spirals and false knots. Excessively long cord may entangle the fetal neck causing strangulation[4]Cotyledons receive blood from multiple spiral arteries. These 80-100 spiral arteries cross the maternal decidual plate and enter the intervillous space. There is development of pressure as spiral artery narrows in the end in inter villous space. The villous tree baths in the oxygenated blood. When the pressure is decreased, the blood flow back to the maternal circulation. Intervillous space contains approximately 150 ml of blood at one time and is replenished 3-4 times per minute. Placental circulation does not take place in all of the villi. Placental membrane separating maternal and fetal blood consists of endometrial lining, connective tissue in villous core, cytotrophoblast and finally syncytiotrophoblast[5].

During the 9 months period, placenta performs multiple functions. Nutrients and electrolytes are transferred to the growing fetus such as amino acids, free fatty acid, carbohydrates, folic acid and vitamins. Exchange of gases oxygen, carbon-di-oxide and carbon mono oxide occurs as simple diffusion.20-30ml of oxygen is diffused per minute through placenta. Placenta releases multiple hormones especially progesterone is the main hormone necessary for the continuation of pregnancy. Besides estrogen, placental lactogen (growth like hormone having strong diabetogenic effect), human chorionic gonadotrophin (used for detection of pregnancy in urine test) are the other important

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Placenta acts as a barrier and does not allow crossing of multiple infections and drugs from maternal circulation to the fetus At birth placenta is torn from maternal uterine cavity and is expelled out after approximately 30 minutes of delivery. Much of the decidua remains inside the uterine cavity and is expelled from the body with uterine bleed.[6]

Placenta is not being studied routinely unless and until a doctor wants to know the pathophysiology in certain bad obstetric outcome, as it can provides extensive information and facts regarding infants prenatal experiences.7 Present study was designed to examine the placental gross morphological features in patients having gestational diabetes mellitus.

## MATERIALS AND METHODS:

1. The study was approved by the IRB & ERB of Dow University of Health Sciences
2. After the written informed consent a total of 126 diagnosed GDM patients were enrolled from diabetic obstetric clinics of Mamji and Lyari General Hospital, in 6 months duration.
3. Placentae were collected from 100 diagnosed GDM patients who delivered at term per vaginally and through caesarean section at the above specified places ,after 3 0-40 minutes of delivery
4. GDM patients without any other co-morbidity were included in the study.
5. GDM patients with HBA1C within control limits were included in the study.
6. Placentae were preserved in 10% formalin labeled containers of adequate sizes
7. In gross examination of placenta8:
   - Shape and color was observed by placing the fetal side on the top of the cutting board.
   - Placental weight was measured by using a kitchen weighing machine.
   - Consistency was observed by finger tips.
   - Size was measured by using simple measuring tape in all three dimensions (x, y, z)
   - Examination of membranes was done for any obvious hemorrhages, color and transparency.
   - Cord examination was done for the site of insertion of the cord and color of the cord
   - Examination of fetal and maternal surfaces was done for any gross pathology in the placental tissue.
8. Placenta was cut with a sharp knife in pieces of 1.5 cm approximately to observe any other obvious deformity or lesion in placental tissues.
9. All the parameter findings were documented on a predesigned data form.

## STATISTICAL ANALYSIS:

Means were calculated for numerical values and percentages were carried out for categorical data, using SPSS 16.

## RESULTS:

Mean age of our study participants was 30.3 1±3.83 years. Mean placental size was 15.98±2.75 cm and in other dimension (placental size 2) wasl3.58±2.54 cm. The mean placental width was 2.4±0.67cm.The mean weight of placentae was 6.2±137.4kg.(Table 1)When placental shapes were evaluated, it was observed that out of 100 placentae 73 were disc like and 27 were of certain other shapes (oval and irregular).66placentae were soft whereas 34 were found hard in consistency. Out of 100, 85 placentae had complete membrane covering whereas 15 had incomplete membranes. When color of the membranes was evaluated it was noticed that 70 placentae were pale and 30 were reddish in color. On cord examination, 66 cords were inserted centrally and only 34 had peripheral insertion. 70 of the cords were pale whereas 30 of them had blue color. When placental pathology was done on cutting 1.5cm sections it was seen that 23 placentae had brown lesion, 29 placentae had prominent white lesions 17 placentae had both types of lesions whereas 35 had no lesions (Table 2)

**Table 1**
**Gross Examination of Placentae**
**N=100**

| Placental Variables | Mean ± SD |
|---|---|
| Placental size1(cm) | 15.98±2.75 |
| Placental size2(cm) | 13.58±2.54 |
| Placental width(cm) | 2.41±0.67 |
| Placental weight(gm) | 630±137.4 |
| Cord length(cm) | 43.1±7.45 |
| Cord width(cm) | 1.5±0.49 |

**Table 2**
**Gross Examination of Placentae**
**N=100**

| Placental Variables | Percentage (%) |
|---|---|
| **Placental shape** | |
| Disc-like | 73 |
| Non-disc like | 27 |
| **Placental consistency** | |
| Soft | 66 |
| Hard | 34 |
| **Cord color** | |
| Blue | 30 |
| Pale | 70 |
| **Cord insertion** | |
| Central | 66 |
| Peripheral | 34 |
| **Membranes** | |
| Complete | 85 |
| Incomplete | 15 |
| **Membrane Colour** | |
| Pale | 59 |
| Normal | 41 |
| **Gross deformity:** | |
| Present | 69 |
| Brown lesions (haemorrhage) | 23 |
| White lesions (infarction) | 29 |
| Both | 17 |
| Absent | 35 |

## DISCUSSION:

Mother - Placenta - baby act as a single unit with the placenta having the central position between the two. It is the main communicating factor between the growing fetus and the mother and any effect produced in the mother is transmitted to the fetus through the placenta[9] It has both maternal and fetal components. Due to pathological reason when maternal milieu is different from the normal, the placenta also exhibit changes. When the first two of the above mentioned triad (mother and placenta) are affected, impact is also produced on the third part that is the baby. Our results have shown that the mean size of placentae in two dimensions were 15.98cm and 13.58 cm with the width of 2.4 1cm. Then mean weight of our samples was 63Ogms.Mean length of the cord was 44 and cord width was 1 .5cms. Joseph stated that in humans, the normal placenta averages 22 cm (9 inch) in length in both the dimensions and 2—2.5 cm (0.8—1 inch) in thickness. It typically weighs approximately 500-600 grams. It has a pale, dark reddish or maroon color. It is connected to the fetus by an umbilical cord of approximately 5 0—60 cm (22— 24 inch) in length[10]Our results are not coinciding to those described by Joseph. Dombrowski has highlighted that thick placentae are associated with perinatal mortality, lower apgar score and adverse fetal outcomes.[11]

Normally placentae are discoid in shape, our results indicated that 73 placentae had normal disc shape and remaining 27 were either oval or irregular shape. Whole of the tissue is covered with membranes in 85 placentae. Jansson and Haffner have documented that reduced placental growth, reflected by its weight and volume, generally precedes diminished fetal growth.[12,13] As importantly, placental weight can be modified by maternal metabolic changes because placental weight at delivery is more when mothers receive high carbohydrate diet in the first trimester and high protein loads in end pregnancy [14]and it also correlates the weight of the infant[15,16] The placenta is typically described as round or oval in shape, but other shapes such as irregular, bilobate, or circumvallate can also be seen in clinical practice[17] Irregular placental shapes have been associated with lower infant birthweight,[18]suggesting that it might be associated with altered placental function. It has been proposed Kajinti that Women with preeclampsia have placentae with reduced surface area and the shape is more of oval than round [19]Salafia and Yampolsky conducted a detailed study to evaluate placental proportions and concluded that deviations in placental shape and relative thickness modify placental functional. [20,21]In our study 27 placentae had shapes other then discoid. This could have accounted for modified placental functions in the respective babies.

Our results indicate that on cord examination, 66 cords were inserted centrally while 34 had peripheral insertion. Insertions of the umbilical cord into the placental margin rather than into the main placental mass are well known to be associated with small placentae and subsequently smaller infants. However, Salafia and colleagues recently have applied mathematical analyses to the gross parameters of the placenta and had finally concluded that non marginal eccentric, cord insertion associates with reduced transport efficiency of the placental vasculature, and a reduced birth weight of the baby. Placentae which have a non-centrally inserted umbilical cord are usually heavier because of increased thickness due to developmental plasticity of the placenta to supply fetal demands for nutrients. This whole suggest that infants with eccentric insertions of the umbilical cord may be predisposed to effects of fetal programming that are not directly related to maternal nutrient deficiency or reductions in the maternal supply line to the placenta. It has also been indicated that the development of the gross appearance of the placenta can influence fetal outcomes and, in the process, predispose the fetus to programming.[22'23]

85 placentae had complete membranes and cotyledons in our results. Yatter has emphasized that maternal surface of the placenta should be inspected for the cotyledons and completeness of membranes. At times an entire placental lobe (e.g., succenturiate or accessory lobe) may be present and can be left inside the uterus. The color of maternal surface should also be assessed properly.

In our results 59 placentae were pale colored. Yatter documented that pallor of the maternal surface indicates the presence of fetal anemia and can be related to anaemia in mother. Anaemia in females is highly common in our population[24]Excessive thickening of the placenta can be related to increased calcification and it can also be a complication of storage of placentae in the formalin. Extra soft and spongy placenta can indicate excessive insulin release in the fetus due to gestational diabetes. In our results 66 placentae were soft.[25]

Benirschke has given in detail that firm areas in the placenta may represent fibrin deposition or infarction. These hemorrhages and infarcts affect the obstetrical outcome. Fresh infarcts are red, while older infarcts appear gray. Fibrin deposits are usually whitish gray and, if extensive, may be associated with intrauterine growth retardation and other poor fetal outcomes. Hemorrhages appear jelly like, dark red in color.[26]In our study brown lesions indicative of hemorrhages were 23%, white lesions indicative of infarctions were 29%and 17% GDM patients had both brown and white lesions both. This implicates that blood supply to these babies in utero was defective.

## CONCLUSION:

Examination of the placental gross morphology in patients having gestational diabetes mellitus revealed features which necessitates that placenta should be examined in the labor rooms after delivery in GDM patients as it provides important information regarding prenatal life of the new born.


## ACKNOWLEDGEMENTS:

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# Guide Lines for Item Writing by National Board of Medical Examiners Problem-Based Learning and Use of Case Clusters

Nighat Huda[1], Talea Hoor[2]

An increasing number of medical schools have adopted problem-based learning (PBL) as an instructional strategy for portions of the basic science curriculum. Although each school's approach to PBL is somewhat unique, all involve the use of written patient cases (problems) in basic science instruction. Problems are designed to stimulate learning of material from traditional basic science disciplines (e.g, anatomy, physiology, biochemistry) from a clinical perspective, and application of basic science principles to clinical situations is stressed. Material is typically covered through independent study and discussed in small groups with a faculty tutor.

Well-written multiple-choice tests can play a major role in assessment, as long as they stress application of basic science knowledge to patient care. Tests using "case clusters" — multiple- choice questions associated with the same patient presentation are particularly appropriate for PBL courses.

An example of a simple case cluster is shown below.

• It consists of a brief case presentation, followed by a series of three multiple choice questions.

• Each question addresses a somewhat different aspect of the case, looking at the clinical situation from a variety of perspectives.

• Like PBL more generally, use of test material like this emphasizes learning of basic science information so that it is organized to be useful in provision of patient care.

• First, it is desirable to avoid "cueing" providing hints at the answers to earlier questions in later questions. Students are very likely to "read ahead" for these clues, and item writers should avoid providing them. For example, in a cluster describing a patient with chest pain, if the first question addresses the most likely cause of the pain and the second requires selection of the most appropriate drug treatment, it is important that each of the diagnoses associated with the first question have a "matching" drug in the second (and vice versa); test-wise examinees can rule out diagnoses (and drugs) simply by comparing the option lists.

• Second, it is desirable to avoid "hinging" creating questions where students must know the answer to one question in order to answer other questions unless the topic to be tested is so important that the item writer is willing to have students receive either all of the points or none of the points associated with a cluster.

The cluster prepared by Drs. David Felten and Ralph Jozefowicz for the final examination in the University of Rochester first-year Neural Science course, illustrates one strategy to avoid hinging.

- It can be difficult for a single faculty member to prepare case clusters where the items draw on information from several basic science disciplines this requires substantial breadth of knowledge.
- One strategy for coping with this problem is to adopt a "team approach" to preparation of test material analogous to the method generally used for preparation of problems for use in PBL instruction. For example, a clinician member of a team can prepare the patient description with which the cluster begins, along with questions related to pathophysiology.

Accessed by Ms. Nighat Huda and Dr. Talea Hoor 30th May 2014

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A 34-year-old woman has had severe watery diarrhea for the past four days. Two months earlier she had infectious mononucleosis. She abuses drugs intravenously and has antibodies to HIV in her blood. Physical examination shows dehydration and marked muscle weakness.

1. Laboratory studies are most likely to show

A. decreased serum K+ concentration

B. decreased serum Ca2+ concentration

C. increased serum HCO3- concentration

*D increased serum Na+ concentration

E. increased serum pH

2. In evaluating the cause of the diarrhea, which of the following is most appropriate?

A. Colonic biopsy to identify Giardia lamblia

B. Culture of the oral cavity for Candida albicans

C. Duodenal biopsy to identify Entamoeba histolytica

D. Gastric aspirate to identify Mycobacterium avium-intracellulare

*E. Stool specimen to identify Cryptosporidium

3. Further studies to evaluate her HIV infection show the ratio of helper T lymphocytes to suppressor T lymphocytes to be 0.3. This occurs because HIV

A. induces proliferation of helper T lymphocytes

B. induces proliferation of suppressor T lymphocytes

*C infects cells with CD4 receptors

D. infects macrophages

E. stimulates the synthesis of leukotriene

An unresponsive 58-year-old woman is brought to the emergency department after collapsing at a local shopping mall. Her family reports that she felt well that morning but developed a headache that progressively worsened while she was shopping. She has had hypertension and atrial fibrillation and is taking an antihypertensive medication and an oral anticoagulant. Her blood pressure is 220/130 mm Hg and her respiratory pattern is one of apnea alternating with hyper apnea. She responds only to noxious stimuli with extensor posturing involving the right arm and leg. Fundoscopic examination reveals papilledema involving the left optic disc. Pupils are 3.0/7.0 (R!L) with no reaction to light on the left. There is a left gaze preference. There is diffuse hyper reflexia (R> L) and Babinski's sign is present bilaterally.

1. The dilated, unreactive left pupil is most consistent with injury to the left

A. optic nerve

B. optic tract

*C. oculomotor nerve

D. lateral geniculate nucleus

E. superior colliculus

2. The extensor posturing on the right is most consistent with injury to the left

A. telencephalon

B. diencephalon

*C. midbrain

D. pons

E. medulla

3. Her respiratory pattern is best described as

A. normal

*B. Cheyne-Stokes

C. central neurogenic hyperventilation

D. apneustic

E. ataxic

4. Which of the following herniation syndromes is most consistent with her clinical presentation?

A. Cingulate gyms beneath the falx

*B. Temporal lobe uncus across the tentorium

C. Diencephalon through the tentorial notch

D. Brain stem through the tentorial notch

E. Cerebellar tonsils through the foramen magnum

- Faculty members from relevant basic science disciplines can contribute items that address various aspects of the patient situation from the perspective of their discipline.
- Use of this kind of material is not, of course, restricted to curricula and courses taught using a PBL approach. It is completely appropriate any time it is desirable to stress clinical application of basic science information in teaching, learning and assessment.

Source: Constructing Written Test Questions For The Basic And Clinical Sciences-3' Edition http://www.nbme.org/PDF/ItemWriting2003/2003IWGwhole.pdf. Accessed 30th May 2014 (accessed by Ms. Nighat Huda and Dr. Talea Hoor)

**COMMENTARY:**

# Self Medication Practices in Pakistan

Tahira Zamir[1], Nasim Karim[2]

**ABSTRACT:**

Self medication is defined as consumption of medicinal products by a person to treat self recognized disorders, symptoms, recurrent disease or minor health problems. Globally, self-medication has been reported as being on the rise. According to WHO, self-medication must be correctly taught and controlled. To assess self medication practices in Pakistan various key words and phrases were used with search engines Google scholar and PakMedinet from the year 2010-2014. A total of five studies were found. Prevalence of self medication is found to be high in our country. Common reasons found for self medication were mild nature of the illness, high fee of private consultants and prior familiarity with the disease. Community based surveys and studies may be conducted to have exact figures of self medication prevalence of our country. Standard laws regarding the use of self medication should be made and implemented in true sense to promote rational use of drugs.

**Keywords:** Self medication Practices, Pakistan, Prevalence.

## INTRODUCTION:

Self-medication which is a major form of self care is widely practiced worldwide.[1] It is defined as the consumption of medicinal products by a person to treat self recognized disorders, symptoms, recurrent disease or minor health problems.[2] It also includes acquiring medicines without an authorized prescription, resubmitting old prescriptions to purchase medicines, sharing medicines with relatives or members of one's social circle or using leftover medicines stored at home.[3]

Globally, self-medication has been reported as being on the rise. In developing countries, people are not only using non-prescription drugs but also prescription drugs, as self-medication products, without supervision. The World Health Organization has emphasized that self medication must be correctly taught and controlled.[4]

Increased access to non-prescription medicines may encourage patients for misuse and abuse of such drug products. Misuse is defined as using an OTC product for a legitimate medical reason but in higher doses or for a longer period than recommended, e.g. taking more of a painkiller than recommended to treat headache. Abuse is the non medical use of OTC drugs, e.g. to use high dose of a drug to lose weight.[5] Studies have documented that increase in self-medication is due to a number of factors like socioeconomic factors, lifestyle, ready access to drugs, increased potential to manage certain illnesses through self care, educational level, age, gender, high cost of private doctor's consultations, prior familiarity and mild nature of the illness.[6] The negative outcomes as a consequence of self medication may include wastage of resources, increased resistance to pathogens, and generally entails serious health hazards such as adverse reactions, drug interactions and prolonged suffering. Although, OTC (over the counter) drugs are intended for self-medication and are of established efficacy and safety, their inappropriate use due to lack of knowledge of their side effects and interactions could have serious results, especially in children, elderly, pregnant and lactating mothers. Some OTC medicines may have severe interactions with prescribed medicines such as interaction of omeprazole and folic acid. Other hazards of self-medication may also include drug dependence and addiction like addiction of cough syrups, problems due to misdiagnosis as sinusitis is often misdiagnosed as allergy, over and under dosing like over dose hepatic toxicity with acetaminophen (paracetamol) and problems related to the side effect profile of specific drugs for example sedation with antihistamines. Use of NSAIDs and aspirin are associated with an increased risk of adverse drug events, hospitalization and death, with the elderly being particularly vulnerable. Patients taking non steroidal anti-inflammatory drugs or anti-platelet drugs (prescription medicines) for a long period of time without follow up of physicians frequently experience gastrointestinal toxicity. The use of antibiotics without prescriptions is a source of great

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concern. Antimicrobial resistance is a current problem worldwide particularly in developing countries where antibiotics are often available without a prescription.[7] Self medication whether it is of non-prescription medicines or prescription medicines can mask the signs and symptoms of malignant and potentially fatal diseases. Gender difference appears to be important factor in self medication patterns. Studies conducted in Spain showed that self-medication is more prevalent among women, persons who live alone, and persons who live in large cities.[8] FDA have strongly advocated that labeling of the OTC drugs should be easy to understand by the consumer and should contain the list of active ingredients, warnings, directions and inactive ingredients.[9]

Using the key words, Pakistan, Self medication, Population, and Prevalence on search engines Google scholar and Pak medinet from 2010-2014, a total of 40 studies were found related to self medication in Pakistan. Refining the search by using phrases, Self medication Pakistan and cities of Pakistan self medication curtailed the available number of articles to 5 that is 2010 (1), 2011(0), 2012(1), 2013(2), 2014(1).

In 2011, a randomized, cross-sectional, questionnaire-based, multicenter study of the prevalence of self-medication was performed in 4 large cities in Pakistan i.e. Rawalpindi, Islamabad, Abbotabad and Peshawar and their adjacent rural areas. The most commonly used drugs were antibiotics (20.5%), analgesics (18.0%), vitamins/ minerals (8.6%), NSAIDs (6.6%), cough syrups (6.1%) and ORS (4.1%). Self-medication was reported in 7.1% cases of rural population as compared to urban areas at 2.6%. Common reason found for increased tendency to self medicate was mild nature of the illness .[10]

In 2012, a study conducted on female students of two private sector institutes for higher education in Karachi revealed that the prevalence of self-medication practices was alarmingly high in the educated youth, despite majority being aware of its harmful effects.[11]

In 2013, a survey conducted in 4 areas of Karachi has documented self medication practice to be increasing in the youngsters of Karachi, mostly in males and undergraduate youngsters between 18-22 years of age. The reason was lack of time or not consulting to the doctor despite of the fact that majority of the respondents were aware that self medication can be hazardous.[12] Dania in 2013 on the basis of literature review reported that the prevalence of self medication in Pakistan is 51%.[13] In 2014, a study conducted on urban and rural population of Islamabad showed 61.2% prevalence of self-medication and it was more between 15- 30 years of age group. Analgesics were the most commonly used medicines (61 .1%) mainly acetaminophen (paracetamol) Common reasons for self medication were found to be prior familiarity with the disease and high fees of private consultants.[14]

A report published on 24th June, 2013 in daily Dawn newspaper had highlighted that an excessive and irrational drug use across the health sector in Pakistan is creating resistance to frontline antibiotics used to control infections .The report also pointed out low checks on registration and marketing of drugs in Pakistan that accounts to easy supply of drugs to the pharmacies and drug selling stores leading to easy acessability of drugs by the consumers. In nut shell, it is all business that is flourishing at the cost of patients health.[15]

Thus prevalence of self medication in Pakistan is increasing. Common reasons found for increasing prevalence of self medication in our country are documented to be mild nature of the illness, high fee of private consultants and prior familiarity with the disease. Standard laws regarding the use of self medication should be made and implemented in true sense to promote rational use of drugs. Furthermore drug authorities and health professionals need to educate people about the pros and cons of self-medication. At the same time community based surveys and studies may be conducted to have exact figures of prevalence regarding self medication in our country.

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# Awareness Regarding HIV-AIDS Among Non Medical University Students

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**ABSTRACT:**

**Objectives:** To assess the awareness regarding HIV-AIDS among non medical students.

**Materials and Methods:** This descriptive cross sectional Institute based study was conducted by the fourth year medical students of Bahria University Medical and Dental College, Karachi as their assigned project in the subject of Community Health Sciences. The study was carried out among non-medical students of NUST, NED and Bahria University, Karachi from Jan 2013 — June 2013. A five question, knowledge based questionnaire developed from Carey and Schroder was used to assess the awareness of the students regarding HIV-AIDS. Convenient sampling technique was used for selecting the participants. After verbal informed consent 105 students participated in the study. Five questionnaire forms were excluded due to incomplete filling.

**Results:** A total of 133 students were approached and 105 (79%) responded that they were aware of the term HIVAIDS. 100 students completely filled out the proforma and out of these only39% responded that they knew the relationship of HIV positive and having AIDS. 90% responded in favor of sexual contact as the main mode of transmission. Homosexuals were regarded to be the highest risk group (71%) for having HIV-AIDS by the students. Regarding preventive measures highest response (5 0%) came in favor of commercial sex control.

**Conclusions:** Assessment of awareness regarding HIV-AIDS among non medical students was found to be deficient in context to relationship of HIV positive and having AIDS, mode of transmission, high risk group, and preventive and control measures.

**Keywords:** HIV-AIDS, Awareness, University students, Non-medical.

## INTRODUCTION:

AIDS is an infectious disease of immune system caused by retroviruses Human Immunodeficiency virus I and II. In 1981 Pneumocystis carinii pneumonia (PCP) and kaposis sarcoma is identified in gay men in Los Angeles and New York. Initially the syndrome was named Gay Related Immune Deficiency (GRID).[1] In 1982 The syndrome is re-named Acquired Immunodeficiency Syndrome (AIDS) as it became clear that it did not just affect gay men.1983 Doctors at the Institute Pasteur in France isolated the virus and named it named lymphadenopathy-associated virus (LAV').[2] In 1984 The virus was named Human immunodeficiency virus (HIV) by the Americans and Western Blot test for HIV infection is introduced. In 1985 AIDS had been reported in 51 countries.[3]

The HIV- 1 pandemic is a complex mix of diverse epidemics within and between countries and regions of the world, and is undoubtedly the defining public-health crisis of our time. Research has deepened our understanding of how the virus replicates, manipulates, and hides in an infected person. Although our understanding of pathogenesis and transmission dynamics has become more pronounced and prevention options have expanded, a cure or protective vaccine remains elusive.[4]Antiretroviral treatment has transformed AIDS from an inevitably fatal condition to a chronic, manageable disease in some settings. This transformation has yet to be realized in those parts of the world that continue to bear a disproportionate burden of new HIV- 1 infections and are most affected by increasing morbidity and mortality. It was in June l98l that scientists in the United States reported the first clinical evidence of a disease that would become known as Acquired Immune Deficiency Syndrome or AIDS and within twenty years AIDS epidemic spread to every corner of the world.

According to WHO estimates by 2010, 35 million people died of AIDS and almost 70 million people were infected with the HIV virus. Globally an estimated 34 million people lived with HIV in 2011, including 3.3 million children and 2.5 million people being infected each year.[4]Sub-Saharan Africa remains the global epicenter of the AIDS pandemic (68% of all HIV positive people).Largest HIV positive population in South Africa followed by India and Nigeria. Life expectancy in some countries have dropped from 65 to 35 (Botswana 23% population HIV +ve).[7]

The pathophysiology of AIDS is complex. After the virus enters the body there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood. This response is accompanied by a marked drop in the numbers of circulating CD4T cells. This acute viremia is associated in virtually all people with the activation of CD8 T cells, which kill HI V-infected cells, and

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subsequently with antibody production, or sero conversion. The CD8 T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4 T cell counts rebound. A good CD8 T cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus. Ultimately, HIV causes AIDS by depleting CD4 T helper lymphocytes. This weakens the immune system and allows opportunistic infections. T lymphocytes are essential to the immune response and without them , the body cannot fight infections or kill cancerous cells. The mechanism of CD4T cell depletion differs in the acute and chronic phases.[10]

Thus an estimated 38 6 (33 4-46 0) million people are living with HIV infection worldwide, while about 25 million have died already[11]. In 2005 alone, there were 4 1 million new reported cases of HIV-1 infections and 2 8 million AIDS deaths. These estimates mask the dynamic nature of this evolving epidemic in relation to temporal changes, geographic distribution, magnitude, viral diversity, and mode of transmission. Today, there is no region of the world untouched by this pandemic [12] Present study was designed to assess the awareness regarding HIV-AIDS among non medical students of three institutes of Karachi.

## MATERIALS AND METHODS:

This descriptive cross sectional institute based study was conducted by the fourth year medical students of Bahria University Medical and Dental College, Karachi as their assigned project in the subject of Community Health Sciences. The study was carried out among non-medical students of NUST, NED and Bahria University, Karachi from Jan 2013 — June 2013. A 5 question knowledge based questionnaire developed from Corey and Schroder (HIV-QKQ18) [13]was used to assess the awareness of the students regarding HIV-AIDS. Convenient sampling technique was used for selecting the participants. The students whose parents were doctors and those who had done HSC (pre-medical) were excluded from the study. Permission was taken from the heads of the respective universities. We asked 133 students regarding awareness of the term HIV-AIDS, Out of 133 students 105 responded 'yes'. After verbal informed consent these 105 students participated in the study and were explained the study purpose. Their confidentiality was maintained. Five questionnaires were incompletely filled and were excluded from the study.

| Sr. No. | Question |
|---|---|
| Q1 | Have you heard the term HI V-AIDS? |
| Q2 | If someone is HIV positive, does it mean he/she has AIDS? |
| Q3 | What is the mode of transmission of HIV-AIDS? |
| Q4 | Which are the high risk people (group) to be affected by AIDS? |
| Q5 | What are the preventive measures for HIV-AIDS? |

The responses were tabulated as yes/no/don't know, Q3, Q4 & Q5 were provided with 7, 6 & 6 options respectively..

Results were expressed as percentage and frequency.

## RESULTS:

Out of 100 non medical students 55 respondents were from Bahria University 27 from NUST and 18 from NED University Karachi. Out of these 50 were males and 50 werefemale students. Their Mean age was 18-24 years(Tablel)

133 students were asked the question' Have you heard the term HIV —AIDS? 105 students responded yes accounting to 79%. Out of 100 students who completely filled out the performa, 39 reponded that HIV+ve means that the person has AIDS (Table 2) Regarding mode of transmission 90% responded in favour of sexual contact followed by blood transfusion 75% non sterile medical equipments use 71%, sharing razors/scissors and pregnancy 24% each, breast feeding 7%, coughing and sneezing 4% (Table 3a)

High risk groups in our study constituted the homosexuals 71% on the top of list followed by hetrosexuals 65%, intravenous drug users 56%, truck drivers and office workers 24% (Table 3b) Awareness regarding preventive measures of HIV-AIDS revealed control of commercial sex 50%, proper sanitation and quarantine 18%, sticking to religious practice 6%, screening of blood 7% , burning personal belongings of HIV —AIDS patients 1% (Table 4)

**Table 1**
**Gender, Mean age & Respondents**
**N=100**

| Gender | Number |
|---|---|
| Male | 50 |
| Female | 50 |
| Mean age | 18-24 years |
| Respondents | |
| NUST | 27 |
| NED | 18 |
| Bahria | 55 |

**Table 2**
**Awareness regarding the term HIV-AIDS and their relationship**
N=133

| Have you heard the term AIDS? | |
|---|---|
| Yes | 105 |
| No | 18 |
| Don't know | 10 |

If someone is HIV +ve, does this means he/ she has AIDS?

| Yes | No | Don't know | Total |
|---|---|---|---|
| 39 | 15 | 46 | 100 |

**Table 3a**
**Awareness regarding mode of transmission of HIV-AIDS**
**N=100**

| Sr.No | Mode of Transmission | Response |
|---|---|---|
| 1 | Coughing and sneezing | 4% |
| 2 | Breast feeding | 7% |
| 3 | Sharing razors /scissors | 24% |
| 4 | Non sterile medical equipments | 71% |
| 5 | Blood transfusion | 75% |
| 6 | Sexual contact | 90% |
| 7 | Pregnancy | 24% |

**Table 3b**
**Awareness regarding high risk groups that can be affected with AIDS**
**N=100**

| Sr. No | High risk group | Response |
|---|---|---|
| 1 | Homosexual | 71% |
| 2 | Heterosexual | 65% |
| 3 | Intravenous drug user | 56% |
| 4 | Truck drivers | 24% |
| 5 | Office workers | 24% |
| 6 | Students | 20% |

**Table 4**
**Awareness regarding preventive measures of AIDS**
**N=100**

| Sr. No | Preventive measure | Response |
|---|---|---|
| 1 | Religious practices | 6% |
| 2 | Screening of blood | 7% |
| 3 | Burn corps of HIV patient | 1% |
| 4 | Quarantine HIV-AIDS infected person | 18% |
| 5 | Proper sanitation | 18% |
| 6 | Control of commercial sex | 50% |

## DISCUSSION:

Human Immunodeficiency Virus (HIV) is a lentivirus that causes Acquired immunodeficiency syndrome (AIDS). It is believed to be a mutated form of SIV (Simian Immunodeficiency Virus), identified in chimpanzees found in west-central Africa. [14]AIDS is an infectious disease of immune system caused by retroviruses Human Immunodeficiency virus I and II. It cripples body's immune system making it susceptible to opportunistic infections and tumors. It affects T helper and CT cells, B cells, some endothelial cells, CNS cells (astrocytes, microglia, oligodendrocytes and Neurons). [15]Our study revealed that out of 133 students 105 students were aware of the term AIDS but only 39% knew the relationship between HIV +ve and having AIDS.

It is documented in the literature that groups worse affected are sex workers, truckers, Intravenous drug users and male! transgender sex workers. 71% students responded that sex workers are at higher risk of having AIDS followed by intravenous drug user group.Heterosexual transmission is the dominant mode of transmission and accounts for about 85% of all HIV-1 infections. Southern Africa remains the epicentre of the pandemic and continues to have high rates of new HIV- 1 infections. [16] Although overall HIV- 1 prevalence remains low in the emerging epidemics in China and India, the absolute numbers, which are fast approaching those seen in southern Africa, are of concern. [17] Outside of sub-Saharan Africa, a third of all HIV- 1 infections are acquired through injecting drug use, most (an estimated 8 8 million) of which are in eastern Europe and central and southeast Asia. [18] The rapid spread of HIV- 1 in these regions through injecting drug use is of importance, since it is a bridge for rapid establishment of more generalized epidemics. These results are in favor of our study however homosexuals in our study were the highest risk group instead of heterosexuals probably because our respondents were non medical undergraduates and were not aware of this. Regarding awareness about mode of transmission of HIV- AIDS our study revealed highest transmission mode according to respondents as sexual contact followed by blood transfusion and use of non sterile medical instruments.

Use of mass media for prevention, control,general awareness and behavioral change,avoidance of intravenous drug use and commercial sex, protected sex , use of sterile needles and instruments, use of tested blood and blood products,[19] targeting high risk groups such as sex workers, truckers and intravenous drug users [20] surveillance and research to compile data base of HIV, male circumcision that is said to reduce infection by 60% and cessation of breast feeding by HIV+ ye mothers are some means and measures to control HIV-AIDS infection [21]

Our study results showed that regarding prevention respondents were not aware of the importance of screening of blood. Only 7% students knew about the screening of blood and its role in the prevention of spread of AIDS. Our respondents were non medical students and they probably did not have exposure to blood donation campaigns being run in the medical colleges and universities. According to Sind AIDS control program (SACP) data presentation at a workshop recently it was highlighted that there has been almost a 300% increase in HIV-AIDS cases over past 5 years in the province of Sind alone. Out of 1,063 new cases of HIV-AIDS in 2013, 55% cases were related to injecting drug users while 33% to sex worker[22] Measures and recommendations at individual level could be that parents should develop friendship and close bonding with their children,one should get in touch with the religion, discourage myths and conspiracy theories about AIDS amongst peers. Parents, teachers and elder siblings should keep reinforcing moral values Mass media should be used to promote anti AIDS campaigns. Mandatory testing and screening of blood, HIV-AIDS awareness and testing centers should be established. Hospitals should be equipped with dealing with AIDS patients and provide palliative care. In rural areas campaigns giving general awareness and precaution should be a priority. Needle exchange program should be established in collaboration with NGOs that provide sterile needles in exchange for contaminated ones.[25]

## CONCLUSION:

The assessment of awareness regarding HIV-AIDS among non medical students was found to be deficient. Health education through TV, radio, advertisements, newspapers, community health workers etc. should be disseminated to improve

the awareness in our youth and community. Recommendations at government level and draft of HIV-AIDS prevention and control policy, to prevent it from becoming an epidemic in our country should be undertaken.

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CASE REPORT:

# A Rare Case of the Small Cell Neuroendocrine Carcinoma of Urinary Bladder

Anis Hussain Jafri[1], Aziz Abdullah[2], Saba Jamal[3]

ABSTRACT:

Small cell neuroendocrine carcinoma of urinary bladder (SCCB) is a rare, prevalent in males, highly aggressive carcinoma being diagnosed usually at advanced stages. The origin of the disease is unknown; however the multipotent stem cell theory applies best to this case. Histology and immune histochemistry shows a tumor which is indistinguishable from small cell lung carcinoma (SCLC). We report a case of SCCB in a 70 year old female who presented with history of recurrent urinary tract infections and hematuria for six months. CT scan showed a large mass in bladder, infiltrating muscle along the left lateral wall with no extra-vesical extension. Cystoscopy revealed a muscle invasive mass protruding into the bladder lumen, extending from 3-5 o`clock. Initial histopathology showed poorly differentiated urothelial neoplasm. She underwent an uneventful radical cystectomy with urinary diversion to ileal conduit. Final histopathology revealed SCCB. Patient is followed up in the oncology department.

**Keywords:** Urinary Bladder, Neuroendocrine Carcinoma, Small Cell Neuroendocrine Carcinoma.

## INTRODUCTION:

Small cell carcinoma of the bladder (SCCB) is a rare, poorly differentiated neuroendocrine epithelial tumor associated with a more aggressive behavior and poorer outcome than bladder transitional cell carcinoma (TCC). It is mostly diagnosed at advanced stage and generally believed to have a high metastatic potential. Current knowledge of this disease is limited and was based mainly on retrospective investigations. The disease was initially described in 1981by Cramer. Bladder small cell carcinoma (SCC) is frequently found combined with other histological forms of bladder cancer: TCC, adenocarcinoma and squamous cell carcinoma. The pathogenesis of primary SCCB is unknown. However, several hypotheses were proposed to explain the origin of SCC in the bladder.[1] Primary neuroendocrine carcinomas of Urinary Bladder account for <1% of bladder malignancies. Neuroendocrine tumors of urinary bladder comprise of carcinoid tumors, large cell neuroendocrine carcinomas, and small cell carcinomas. They are usually more prevalent in male patients in the ratio of 2:1-10:1.'However, this case report presents a case of small cell neuroendocrine carcinoma of the urinary bladder in a female.

## CASE REPORT:

A seventy year old female presented with a history of recurrent urinary tract infections and hematuria for last six months. The general physical examination was unremarkable except for mild pallor. The systemic examination revealed a third degree utero-vaginal prolapse. She was a known case of diabetes mellitus and was on oral hypoglycemic (Biguanide). The investigations revealed that her hemoglobin was 10 gm. /dl and she had good glycemic control. Her renal profile and serum electrolytes were normal. Ultrasound scan revealed a mass inthe urinary bladder along the left lateral wall. CT scan showed a large lobulated mass in bladder measuring 6.0 x 5.0 x 7.6 cm (AP x TS x CC) along the left lateral wall, infiltrating the muscles with no extra-vesical extension (Figure 1)

**Figure 1**
**CT-scan showing mass in the bladder**

On Cystoscopy, a muscle invasive mass was found protruding into the bladder lumen, extending from 3-5 o'clock, just above the bladder neck. As complete resection was not possible, multiple biopsies were obtained with a resectoscope. The Histopathology showed poorly differentiated urothelial neoplasm. She underwent an uneventful radical cystectomy with urinary diversion to ileal conduit. Final histopathology revealed small cell neuroendocrine tumor of urinary bladder with sensitivity to synaptophysin, chromogranin, (Figures 2 and 3) thyroid transcription factor-i (TTF-1) and CD 56. On microscopic examination it was revealed that the tumor had poorly differentiated papillary and nodular growth pattern. Her chemotherapy was planned.

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Figure 2a
Histopathology of specimen shows sensitivity to Chromogranin

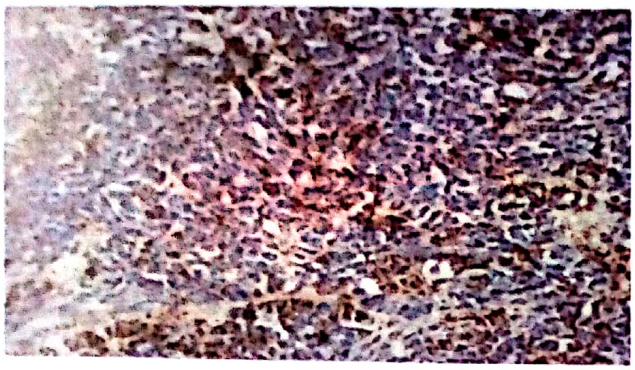
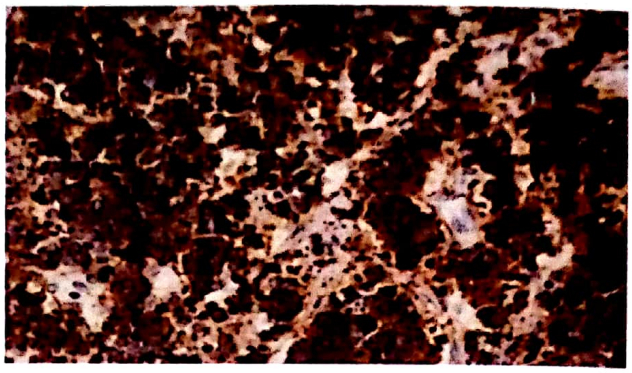


Figure 2b
Histopathology of specimen shows sensitivity to Synaptophsin



**DISCUSSION:**

Neuroendocrine tumors occur in the epithelium lined organs, especially of the gastro-intestinal and respiratory tracts. They can arise in the urinary bladder as well, but very rarely. They are classified as "Small Cell Carcinomas" (the most common, with over 100 cases reported), atypical and typical Carcinoid"(less common) and large cell neuroendocrine carcinomas" (very rare).[2,3] Small cell cancer of the urinary bladder is documented to have a mean frequency of 0.7% and a range between 0.35% and 1.8% . Searching done up till 2011 showed that the reported incidence is less than 1-9/1,000,000 habitant. Since 1980, less than 1000 cases of SCCB have been diagnosed and reported in the literature up to July 2011. The demographic characteristics of SCCB are similar to those seen in patients with transitional cell carcinoma (TCC). The majority of patients are male, with a mean sex ratio of 5:1, and a range between 1:1 tol6:1. Most patients are in the sixth to seventh decade. Mean age at the time of first diagnosis is 67 years; ranging between 32 to 91 years Like TCC, SCCB is often associated with a smoking history (in 65 to 79% of the cases) . White patients represent the vast majority of cases (74% to 97%).

The first small cell carcinoma of neuroendocrine origin was reported by Cramer in 1981 .[4]Pure small cell neuroendocrine tumor of the bladder is infrequent and is usually mixed with another histological subtype most commonly urothelial carcinoma. The tumor presents late, behaves more aggressively than urothelial carcinoma and carries a poor prognosis.[5]

Pathogenesis of SCCB is not well defined. However, several hypotheses were proposed to explain the origin of SCC in the bladder. Researchers have postulated the origin of this unique and rare neoplasm to be differentiation of the multi-potent stem cells, or sub-mucous neuroendocrinecells.[6]One hypothesis states urachal epithelium, a remnant of the fetal excretory canal: allantoismay be its origin.[7] It usually presents as an advanced cancer (70% in T3 and 16.3 % in T4 stage) at the time of diagnosis.[8]The 5-year survival rate has been reported to be 8. 1-19%, yielding a poor prognosis.[9] Diagnosis is made ontrans-urethralresection for tissue sampling. Neuroendocrine tumors are sensitive to Neuron-Specific Enolase (NSE), Keratin Cam 5.2, Synaptophysin, Chromogranin Q, Positive in one half of small cell and 5% of urothelial carcinoma), Polypeptide Glycoprotein 9.5, Thyroid Transcription factor-i (positive in 40%), p53 and Ki67.[10]

There is no established protocol to treat the disorder as yet. A combination of therapies:surgical, adjuvant/neo-adjuvant chemotherapy and radiation are being used depending upon patient's state of health and the stage of tumor at the time of presentation. There is a consensus that TURBT (Transurethral Resection of Bladder Tumor) may have better prognosis than chemotherapy. Thus primary SCCB is a rare and aggressive tumor. In more than 50% of the cases, the diagnosis is performed at advanced stages III/IV. Demographic and clinical features are comparable to those of bladder TCC. The origin of disease is not clearly defined; but the multi potent theory is the most accepted. Criteria of pathological diagnosis and

logical work-up are similar to those of SCLC. xistence of SCCB with other types of carcinoma ommon. Immunochemistry plays a major role e diagnosis using the markers of neuroendocrine ors. The staging system mostly used is the M-staging system of bladder TCC. The best eatment for this tumor is not established for certain; nly one prospective study has been published up ll now. The strategy of therapy was extrapolated from SCLC. In surgically resectable disease, the management should include multimodal therapy with chemotherapy first followed by radical resection or radical radiotherapy. In advanced disease, chemotherapy using platinum agent (cisplatin in fit patients) is the mainstay treatment. The prognosis of SCCB is poor. Pure small cell histology have worse prognosis than the mixed small cell histology. Further investigations are needed to improve our knowledge in the diagnosis and treatment of this rare disease.

**CONCLUSION:**

The reported patient is alive and is being followed up in the oncology department. Small cell carcinoma of the bladder (SCCB) is a rare, poorly differentiated neuroendocrine epithelial tumor associated with a more aggressive behavior and poor outcome. It is mostly diagnosed at advanced stage and generally believed to have a high metastatic potential. Current knowledge of this disease is limited and is based mainly on retrospective investigations.

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# Dengue Fever-Cause for Concern

Shakeel Ahmed

To Editor, Dengue virus is an endemic disease which has great public health significance in terms of morbidity and mortality. The disease has recently had major epidemics in most tropical and sub tropical areas with an estimated 50 to 100 million cases of Dengue fever and about half a million cases of Dengue hemorrhagic /Dengue shock syndrome worldwide every year, Dengue is now recognized as one of the major public health concerns globally.

Today, dengue is prevalent in more than 100 countries across Asia, Africa, America, Eastern Mediterranean, and West Pacific. Central to this is the enlarging habitat of its vectors, Aedes Aegypti and Aedes Albopictus. Particularly Aedes Aaegypti has taken advantage of increased urbanization rates and crowding to transmit the virus. The causes are multiple and include increases in the numbers of infected and susceptible human hosts, strains of dengue virus, and size of mosquito population. Also involved are changes in feeding habits, time from infection to infective state, and the likelihood of virus transmission from human to mosquito to human. Temperature also affects vector distribution, size, feeding habits, and extrinsic incubation period. Aedes Aegypti in particular, is highly adaptive in crowded areas; hence epidemics have been seen in cities with un-planned urbanization and overcrowding.

Dengue fever is the most prevalent arthropod borne illness in humans produced by the genus flavi-virus and consists of four distinct serotypes, namely DENy-i, DENV-2, DENV-3 and DENV-4. The virus can produce clinical symptoms that vary from a mild, self limited fever, rash and joint pain (Dengue Fever)[1] which can be undiagnosed or misdiagnosed, to severe illness recognized as hemorrhagic dengue and dengue shock syndrome.[2] Age is an important variable in the outcome of secondary dengue infection. Exposure of the virus occurs in the infantile to juvenile period and the prevalence of Dengue virus specific IgG increases with age and reaches its peak before adolescence Case fatality and hospitalization rates are higher in young infants and the elderly. Infection induces life long protective immunity to the homologous serotype but confers transient protection against other three serotypes.[3] Pakistan had dengue outbreaks in recent years owing to rapid urbanization,population growth and poor health planning. Epidemics have been reported especially in urban areas of Karachi and Lahore; the situation worsening especially after monsoon rains and floods. In October 2010, a total of 1,809 cases were suspected out of which 881 cases were confirmed of Dengue infection.[4]In 2011, the worst outbreak occurred in the country when more than 14 000 people were affected with dengue with over 300 deaths[5].

Until now there have been no studies to investigate the prevalence of dengue virus antibodies in the population in Pakistan; In a recently conducted study to estimate the prevalence of Dengue virus specific IgG among the asymptomatic children (from 1-15 years),conducted in an urban slum of Karachi, it was found that 46% of the population less than 15 years are positive for IgG in their serum indicating previous infection making these children more prone to develop severe haemmorhagic fever if re-infected with different dengue serotype. Considering the current situation of Dengue virus epidemics and limited data in Pakistan, urgent stringent measures and oversight is required to ensure the development of an effective preventive and curative program.

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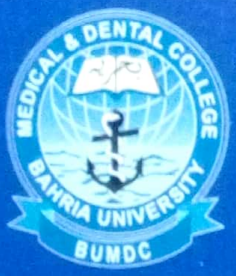


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