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Content Page

SERUM HIGH SENSITIVE C REACTIVE PROTEIN (HS-CRP), AN ACUTE INFLAMMATORY MARKER

Shamima Jahan

Serum hs-CRP, the main acute phase protein in humans, is a sensitive marker for systemic inflammation. It is produced mainly by the liver and to some extent by the adipose tissue in response to pro inflammatory cytokine induced by inflammatory stimuli.[1]

Among apparently healthy men and women, the currently recommended serum hs-CRP cut-off points are <1.0 mg/L for low risk, 1-3 mg/L for average risk and >3.0 mg/L for high risk of future CVD.[2]

An inflammatory response produces increase number of polymorphonuclear neutrophil from bone marrow, as a result total white blood cell count increases in smokers.[3] Neutrophils secrete proinflammatory cytokine IL-1b, IL-6 and (TNF)-α. These proinflammatory cytokines bind to hepatocyte cell surface receptors and cause an intracellular signaling cascade. There are transcription of CRP-mRNA that is mediated by IL-1b, IL-6, transcription factors C/EBPβ and C/EBPδ.[4] All of these lead to release of serum hs-CRP in to the blood stream.[5]

This marker is used to detect and predict the outcome of various infections, inflammatory and necrotic processes and to assess the efficacy of treatment for those processes. Physiologic variables known to affect CRP level include age, sex, race, biological variation and lifestyle that include exercise, smoking, obesity, alcohol, anti inflammatory drugs and hormone therapy. It is also associated with other pathological factors including diabetes mellitus, hypertension, heart disease, renal insufficiency, insulin resistance and metabolic syndrome. However CRP has statistically remained as a statistically significant independent predictor of risk of CVD.[6]

Increase concentration of hs-CRP may suggest its direct involvement in the pathophysiology of atherosclerosis. In atherosclerosis, the serum hs-CRP level signals the low-grade inflammation that presents in the vessel wall and indicates greater cardiovascular risk in future.[4]

So, we can assess the acute inflammatory condition by this simple test serum hs-CRP.

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A STUDY ON CYTOMORPHOLOGICAL PATTERN OF CERVICAL PAPANICOLAOU SMEAR ABNORMALITIES BASED ON 2014 BETHESDA SYSTEM IN A TERTIARY CARE HOSPITAL LOCATED ON GAZIPUR

Kajol Akter[1], Mehdi Ashik Chowdhury[2], Saifeen Parvin[3], Afroze Shirin[4], Urmilata Biswas[5], Sonia Mahmuda Hauqe[6], Sampurna Sen[7]

ABSTRACT

Background: Cervical cancer is one of the leading causes of death of the female in developing countries. By screening test cancer of the cervix can be readily diagnosed even in its pre invasive stage. If treatment is provided the earlier stages the patient can often be cured of the disease. Carcinoma of the cervix is the fourth most common form of cancer in female worldwide. The use of cervical smear (Papanicolaou/Pap) as a screening method has significantly reduced the incidence of carcinoma of the cervix. Cervical Pap smear is a type of exfoliative cytology and has been widely accepted as a screening method for cervical carcinoma. Among the various devices used for collecting the samples from cervix, Ayre spatula (wooden) are used frequently. **Objectives:** To utilize cervical Pap smear examination in categorizing lesions according to the 2014 Bethesda System for cervical cytology, to analyse the spectrum of lesions and to evaluate its effectiveness as a screening procedure for detection of epithelial abnormalities in a teaching hospital in gazipur. **Methods:** A descriptive cross sectional study was carried on all conventional Pap smears received in the Department of pathology, International Medical College and Hospital. Reporting was done in accordance with the 2014 Bethesda System for reporting cervical cytology. Results: A total of 100 cases were included in the study. The most frequent presenting complaint was vaginal discharge. Pap smears were categorized as 'Negative for intraepithelial Lesion or Malignancy'/NIML. Specific infections were seen in 12%, Inflammation found in 79 cases in mild, moderate and.

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severe ranges, squamous metaplasia in 13%. Epithelial cell abnormalities such as Atypical Squamous Cells of Undetermined Significance (ASCUS) was 5%, Low grade Squamous Intraepithelial Lesion (LSIL) was 2%, High grade Squamous Intraepithelial Lesion (HSIL) was 1%, Squamous Cell Carcinoma (SCC) was 5% and Atypical Glandular Cells (AGC) was 1% **Conclusion:** The overall prevalence of epithelial cell abnormalities complied with these studies done in Gazipur by screening 100 Paps smear. NIML with inflammatory changes, ASCUS and Squamous Cell Carcinoma being the most common lesion.

Keywords: PAP smear, Screening test, Bethesda, Epithelial abnormalities.

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Introduction:

The Pap smear or Papanicolaou test, is a form of exfoliative cytology where in microscopic examination of cells taken from the cervix is performed. It was designed by Dr George Nicholas Papanicolaou (1883-1962), an American anatomist of Greek origin during the year of 1920s. It is a simple, non-invasive and quick method which has almost revolutionized the early detection of cancer as a screening for carcinoma of cervix. Pap smears are taken from the junction between ectocervix and the endocervical canal which is also known as the transformation zone (TZ) of the cervix, can be used for early detection of cervical epithelial cell abnormalities in the stage of intra-epithelial neoplasm itself.[1]

Cervical cancer is one of the leading causes of mortality as well as morbidity in women worldwide in developing countries like our bangladesh.[2] This can be prevented if it is diagnosed at early stage. According to Global cancer statistics 2018, Cancer cervix is the fourth most frequent cancer in women with an estimated 570,000 new cases representing 6.6% of all female cancers. Approximately 90% of deaths from cervical cancer occurred in low- and middle-income countries. Cervical cancer ranks fourth for both incidence (6.6%) and mortality (7.5%).[2] The aim of this study was to detect the cytomorphological findings of cervical papanicolaou (pap) smear.

Cervical carcinoma does not develop suddenly from normal epithelium but is presented by a spectrum of intraepithelial neoplastic changes that are precancerous lesion and were termed as cervical intraepithelial neoplasia (CIN). Cervical cytological screening is designed to detect over 90% of cytological abnormalities. This has also been established that most of the cervical cancers can be diagnosed at their preinvasive stage with an adequate and repetitive cytological screening. Keeping in view of the importance of carcinoma and the precancerous lesion (CIN) of cervix, study of different methods for the early detection of abnormalities in cervix, correlation with the clinical findings and comparison between the techniques was carried out.[3]

In developing countries like Bangladesh, the higher prevalence of cervical cancer is because of ineffective screening programmes. Pap smear is a simple, convenient, cost effective and reliable test for easy screening of cervical lesions. Since its introduction there has been a dramatic reduction in the incidence and mortality of invasive cervical cancer worldwide.[4]

Methods

This is a descriptive cross sectional study was carried on all conventional Pap smears received in the Department of pathology, International Medical College and Hospital from april, 2020 to march 2021 over a period of one year with the 2014 Bethesda System for reporting cervical cytology.

The study population was defined as all consecutive Pap smear samples received in the cytopathology section of department of pathology, during the study period, for which two conventional Pap smears slides were collected; both with Ayre spatula from the ectocervix and endocervical mucosa. They were placed in a Coplin jar containing 95% ethanol in fixative. They were labelled and sent to the cytopathology laboratory. All the smears received during the study period were stained as per the standard operating procedure of the laboratory for Papanicolaou stain. Reagents used in Pap stain were Harris haematoxylin for nuclear staining, orange G-6 (OG-6) for cytoplasmic counterstain and eosin azure (EA) which is a polychromatic stain made of 3 dyes, eosin Y for mature squamous cells, light green SF for metabolically active cells and Bismarck brown Y. Various concentrations of alcohol (ranging from 70 to 95%) were used for hydration and dehydration. The smears were reviewed blinded by cytopathologists, according to the standard system of the 2014 Bethesda system for reporting cervical cytology.

The cellular composition was studied in 4x, 10, and 40x power fields and the overall most predominant cell type was identified. Inflammation was graded as mild (25-50%;), moderate (50-75%,) and severe (>75;). This was estimated after compiling both the pap smears slide. Analysis of cytomorphologic data was performed to check the quality of technical parameters in the evaluation of Pap smears by two independent pathologists. All the statistical analysis was carried out using SPSS.

Specimen adequacy:

- Satisfactory for evaluation *(describe presence or absence of endocervical/transformation zone component and any 0ther quality indicators. e.g.,*
- *partially)' obscuring blood, inflammation. etc.)*
- Unsatisfactory for evaluation…(specif)' reason)
  Specirnen rejected/not processed (specif)'
- reason)
  Specimen processed and cxamined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

General Categorization (optional)

- Negative for Intraepithelial Lesion or Malignancy
  Other: Sec Interpretation/Result *(e.g., endometrial cells in a woman > 45 years of age)*
- Epithelial Cell Abnormality: See Interpretation/ Result (specify `squamous' or 'glandular' as appropriate)

Interpretation/Result

Negative for Intraepithelial Lesion or Malignancy

(*When there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report- whether or not there are organisms or other non-neoplastic findings)*

Non-Neoplastic Findings (optional to report)

- Non-neoplastic cellular variations
  Squamous metaplasia
  Keratotic changes
  Tubal metaplasia Atrophy
  Pregnancy-associated changes

Reactive cellular changes associated with:

Inflammation (includes typical repair)
Lymphocytic (follicular) cervicitis

Radiation

Intrauterine contraceptive device (IUD)

Glandular cells status post hysterectomy

Organisms

Trichomonas vaginalis

Fungal organisms morphologically consistent with Candida spp.

Shift in flora suggestive of bacterial vaginosis

Bacteria morphologically consistent with Actinomyces spp.

Cellular changes consistent with herpes simplex virus

Cellular changes consistent with cytomegalovirus

Other

Endometrial cells (in a woman ≥45 years of age) *(Specify if "negative for squamous intraepithelial lesion")*

Epithelial cells abnormality

- Squamous Cell
  - Atypical squamous cells of Undetermined Significance(ASCUS)
  - cannot exclude HSIL (ASC-H)
  - Low Grade Squamous Intraepithelial lesion (LSIL)
  - High Grade Squamous Intraepithelial lesion (HSIL)
  - Squamous Cell Carcinoma
- Glandular Cell
  - Atypical Glandular cells (AGC)
  - Endocervical adenocarcinoma In Situ (AIS)
  - Adenocarcinoma

Box 1: 2014 Bethesda System for Reporting Cervical Cytologic Diagnosis.

Results

During the study period a total of 100 pap smears were studied. Overall age range of all participants was from 15 to 60 years. Majority of the smears were satisfactory in material. The fixation was found to be optimal in all smears.

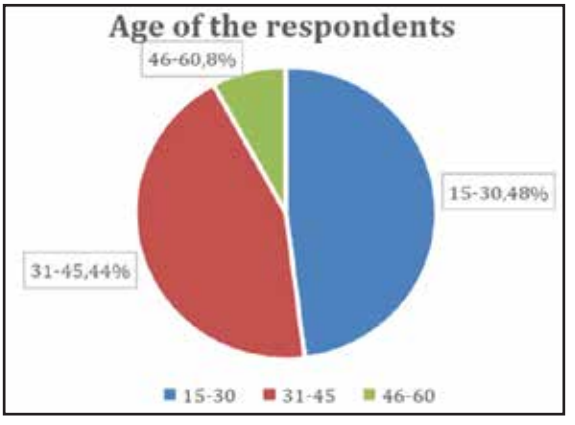

Figure 1. Pie chart showing age of the respondents

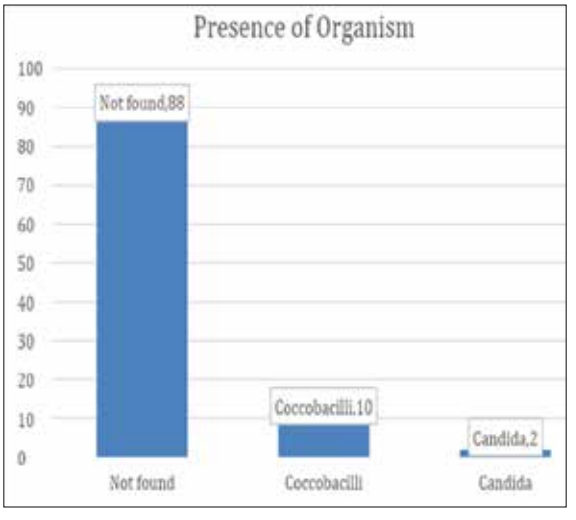

Figure 2. Bar diagram showing presence of organism

Table 1. Cytomorphological pattern of respondents by pap's smear

Cytopathology pattern	Frequency	Percent
NIML		
Present (No cancer),reactive change	86	86.0
Epithelial cell abnormality	14	14.0
Inflammation		
Mild	26	26.o
Moderate	40	40.0
Severe	13	13.0
No	21	21.0
Squamous metaplasia		
Yes	13	13.0
No	87	87.0
Epithelial cell abnormality		
LSIL		
Yes	2	2.0
No	98	98,0
HSIL		
Yes	1	1.0
No	99	99.0
ASCUS		
Yes	5	5.0
No	95	95.0
AGC		
Yes	1	1.0
No	99	99.0
Carcinoma cervix		
Yes	5	5.0
No	96	96.0
Total	100	100.0

Discussion

Cancer is one of the leading causes of death in this world. About 14 million new cancer cases are detected, and about 8 million people die from cancer every year.[5] Other studies show that cervical cancer will occur in approximately 1 in 53 Indian Women compared with 1 in 100 women in more developed countries.[6]

Exfoliative cytology is the study of cells that are shed off or scraped from mucosal surfaces. Pap smear is a form of exfoliative cytology wherein cervical cells are scraped and examined for cellular changes, often starting at the transformation zone. It is named after Dr. George Nicholas Papanicolaou, an American anatomist of Greek origin who collected and studied cells from vagina of guinea pigs.[7] Pap smear is strongly suggested as a screening tool for cervical cancers. There are different equipments for collection of Pap smears. These include cotton tip applicator, wooden spatula, plastic spatula and endocervical brush. According to TBS, 2014 Pap smear sampling is considered to be adequate if there are 8000 to 12000 well-preserved and well- visualised squamous epithelial cells in the smear.[8] Therefore, the ultimate aim of sample collection should be to fulfil both the adequacy criteria and the quality indicator. In our setting, Ayre spatula, a type of wooden spatula is being used.

In our experience the endocervical smears showed extensive mucoid background which often distorts the cellular morphology. This causes cell distortion and entrapment due to which clumped cells with poor spreading occurs leading to poor stain penetration is seen. Many studies have shown that smears with no endocervical cells are more likely to carry false negative results for cervical cancer.[9] Therefore, in order to minimize the number of false negative results, slides should contain adequate number of squamous cells and endocervical cells.[10] The age of the patient ranged from 15 to 60 years in our study and the predominant population in the present study was between 30-45 years (92%). This finding was similar to studies done by Hirachand et al, Ranabhat et al, Bukhar et al and Bamanikar et al.[11] However in studies done in mid western part of Nepal and Bangladesh there were no cases below 20 years. Contrast to this and our study the number of cases of pap smear below 20 years was quite high (48%).

There were 100% cases of smear in our study shows inflammation ranges mild, moderate and severe. Lots of variation was seen in several studies. The studies ranges from satisfactory to unsatisfactory. Studies done in Kathmandu, Pakistan and India revealed 0.3%, 1.8% and 1.2% cases of unsatisfactory smear respectively.[12] Negative for Intraepithelal Lesion or Malignancy was seen in 87% cases which correlates well with study done by Bamanikar et al in a tertiary hospital (88.93%.[13] Epithelial cell abnormalities represented 13% cases in our study which includes LSIL, HSIL, ASCUS, AGC and carcinoma cervix. Studies had shown that the prevalence of epithelial abnormalities were different in different places (1.7%,).[12] In a study done in the same hospital in 2010, epithelial cell abnormalities were seen in 1.1% cases. LSIL (2%) seen in our study was similar to other studies (0.15%).[12] HSIL was seen in 1% cases in our study. Studies done in Nepal and India showed findings (0.29%,) similar to our study.[12] Cases of ASCUS (5%) was also quite comparable to other studies (0.51%).[12] However in one study done in Gujarat India, the incidence of ASCUS (40.74%) was quite high.[14]

Bacterial vaginosis (10%) was common among the organism associated lesion in our study. Other studies revealed 5,4%, cases of bacterial vaginosis respectively.[15] Reactive cellular changes (86%) seen in our study was associated with inflammation. A studies done in India revealed 3.2% cases of reactive cellular changes.[16] This shows that interpretation of reactive cellular changes is very subjective and hence the results are variable.

Pap smear examination should be started as soon as the female are sexually active irrespective of the age and this should be practiced as a routine gynaecological screening program. Implementation of pap screening program is necessary for early detection of cervical premalignant lesion. nce of ASCUS (40.74%) was quite high.[14]

Conclusion

Pap smear is a very effective screening method for early detection of premalignant and malignant lesions of the cervix. The 2014 Bethesda system used for cervical cytology is a standard method and gives descriptive diagnosis that helps the gynaecologist in individual patient management. Awareness regarding the importance of pap smear screening test should be created among all the women worldwide. At least one Pap screening test of the cervix of all women between the ages of 40-50 years is recommended.

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DIFFERENT TECNIQUES OF AESTHETIC MASTOPEXY–OUR EARLY EXPERIENCE IN BANGLADESH PERSPECTIVE

Munny Momotaz[1], Tamanna Tithi Ahmed[2], Kh. Kaniz Fatima Katha[3], Rebeka sultana[4]

ABSTRACT

Background: Breast ptosis can occur with aging, and after weight loss and breastfeeding. Mastopexy is a procedure used to modify the size, contour and elevation of sagging breasts. The most important target for the techniques of mastopexy is try to achieve a good symmetry with a natural shape, a fullness of the upper pole and a long-lasting result. **Material and Methods:** A prospective study was conducted between July 2018 to June 2021, 11 patients with different degree of breast ptosis were treated with different technique of mastopexy at private hospital, Dhaka, Bangladesh. **Results:** Age range was 20 to 45 years. Preoperatively, among 11 cases, 6 patients presented with grade-3 ptosis, 3 cases presented with grade-2 ptosis & 2 cases with grade-1 ptosis. The traditional wise (inverted-T) pattern was performed in 6 cases (54.54%) whereas vertical mastopexy was completed in 2 cases (18.18%). >90% of patients reported satisfaction with their aesthetic outcomes, including absence of ptosis. No major complications occurred. **Conclusions:** Mastopexy is safe and effective procedure for correction of breast ptosis with no major complications rate.

Keywords: Breast ptosis/Mastopexy/Breast lift/Reduction mastopexy/Augmentation mastopexy

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Background:

Breast ptosis can occur with aging, and after weight loss and breastfeeding. Mastopexy is a procedure used to modify the size, contour and elevation of sagging breasts. The most important target for the techniques of mastopexy is try to achieve a good symmetry with a natural shape, a fullness of the upper pole and a long-lasting result. There is a variety of different morphologic features among the patients, such as skin condition, degree of ptosis and presence of asymmetry, which can compromise the outcome of the mastopexy procedure. The surgeon should assess the skin's elasticity during the preoperative examination. This is necessary to choose the right procedure to perform and predict the final result.

Actually the skin without ability to retract will be significantly detrimental to the success of the operation. The degree of ptosis and the presence of asymmetry are also important characteristics to keep in mind before performing the mastopexy techniques and must be measured.[1]

Material and Methods:

A prospective study was conducted between July 2018 to June 2021, 11 patients with different degree of breast ptosis were treated with different technique of mastopexy at private hospital, Dhaka, Bangladesh after fulfilling the inclusion and exclusion criterias. In this study we followed the Modified Vancouver technique to assess the level of satisfaction.

Selection criteria

Inclusion criteria:

- Patients with different degree of breast ptosis.
- Patients aged 18 years or above.

Exclusion criteria:

- Pregnant or lactating women.
- Any disease condition of the breast- abscess, mastitis and giant fibroadenoma.
- Carcinoma of the breast.
- Patients with major endocrine abnormalities.
- Pre malignant condition of the breast.

Surgical Technique:

Inverted –T (wise pattern)

We applied this technique for those women with moderate to severe ptosis with large skin excess. Moderate amount of glandular tissue also removed. Wise pattern verticle scar with long horizontal scar is found after closure.

Figure 1: Pre operative marking of Inverted-T (wise pattern)

Figure 2: Post operative view of Inverted-T (wise pattern)

Figure 3: Post operative view of Inverted-T (wise pattern)

Verticle pillar Mastopexy technique:

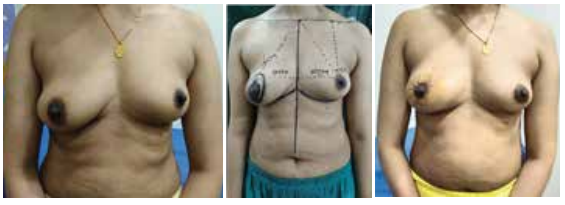


Figure 6: Pre & post operative view of Unilateral periareolar mastopexy

Peri-areolar mastopexy with fat graft technique:

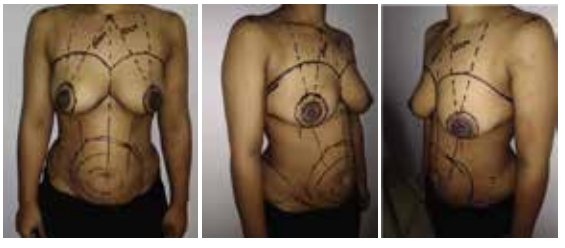


Figure 7: Pre operative marking Peri-areolar mastopexy with fat graft

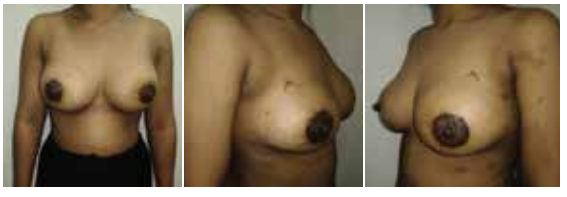


Figure 8: Post operative view of Peri-areolar mastopexy with fat graft

Augmentation mastopexy with fat graft technique:

Figure 9: Pre operative marking of Augmentation mastopexy with fat graft

Figure 10: Post operative view of Augmentation mastopexy with fat graft

Result:

Table 1 : Pre-operative presentation of study population, N=11

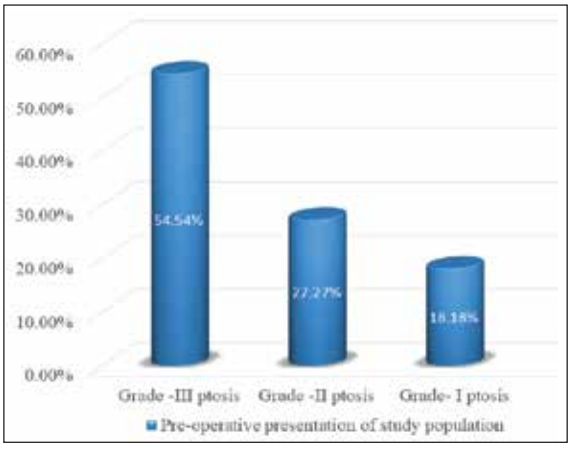


Table 2: Different technique of mastopexy applied in study population, N=11

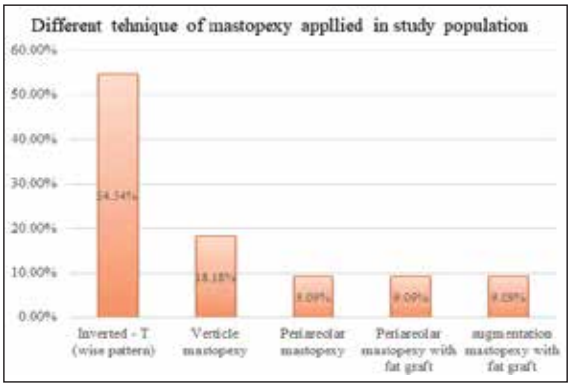


Table 3: Patient's satisfaction level of study population, N=11

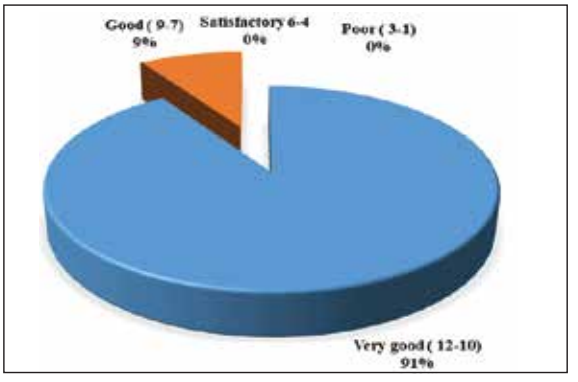


Table 4: Overall scoring of outcome by the observer, N=11

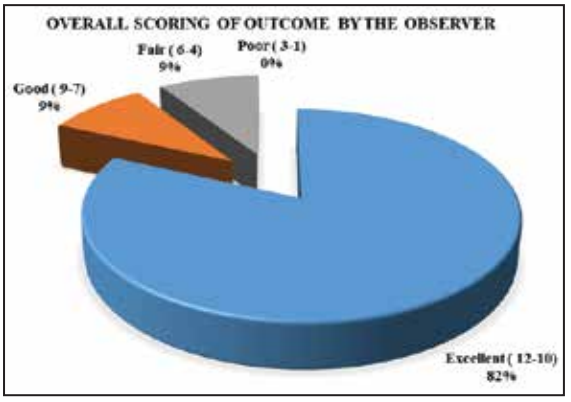
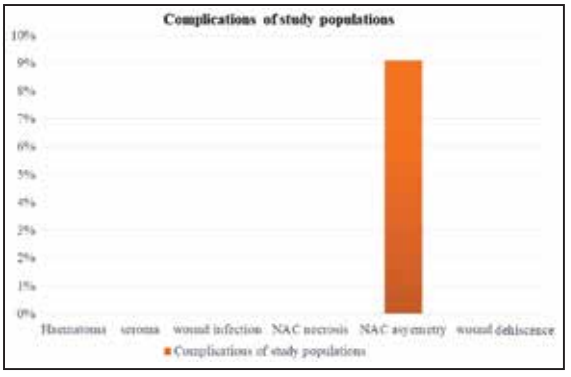


Table 5: Distribution of patients by complications, N=11



Discussion:

Various mastopexy pedicle techniques including inferior pedicle, superior pedicle, and superomedial pedicle have been reported for breast ptosis in various literatures. Different mastopexy types depending on skin pattern including peri areolar, vertical, Wise pattern were also summarized in previous literatures.[2-6]

Single-stage augmentation-mastopexy can be performed using any combination of implant insertion technique, fat grafting technique and skin reduction technique. The most appropriate technique, however, varies depending on the degree of breast (ie, glandular and nipple) ptosis and the desired amount of volume enhancement.[7-9]

Age range of the patients in our study were 20 to 45 years. In the present study peri-areolar mastopexy was done in 9.09% cases, peri-areolar mastopexy along with fat graft and augmentation mastopexy using fat graft was carried out in 9.09% and 9.09% cases respectively. Peri-areolar augmentation-mastopexy, is one such technique based on the concept of reducing the breast skin envelope by resecting an annular segment of peri-areolar skin and gathering the breast skin around the nipple-areolar complex (NAC). This technique has been demonstrated to effectively correct mild glandular ptosis and mild to moderate nipple ptosis while limiting scarring on the breast to an isolated peri-areolar incision. Some commonly cited problems of this mastopexy technique include scar widening, areolar distortion, and flattening of breast projection.[10-15]

The vertical pattern mastopexy, along with reducing the scar burden gives more flexibility for intraoperative adjustments but is used with a superior or superior medial pedicle, which can create vascular issues. All grades of breast ptosis have been addressed with vertical mastopexies. Care must be taken when performing this procedure in women who have a large amount of glandular tissue, as because the pedicle tends to be bulky, it can be compressed when the medial and lateral pillars are closed. It may be necessary to trim the pedicle or remove some of the glandular tissue so that the pedicle is not overly compressed. Additionally, in the same type of patient, the plication should be performed conservatively or avoided. Because of the compression of the pedicle by large amounts of glandular tissue, a tight plication can restrict nipple-areolar complex vertical movement and cause tethering.[16-19]

Wise pattern or inverted T mastopexy This technique has the greatest amount of scar relative to the breast vs other techniques. When associated with an inferior pedicle, it can also have the greatest frequency of bottoming out. This is most likely secondary to the inferior pedicle rather than the skin resection pattern. Additionally, one of the problems with the inverted-T mastopexy is healing at the T-junction, especially when an implant is added.[20-22]

In the mastopexy patient, whether an auto-augmentation is used or not, lipo-filling can be very effective in improving the upper pole volume without the use of an implant. Fat can reliably improve breast fullness, coverage, and cleavage, but is limited in the ability to appreciably enhance core projection of the breast. The combination seems to have an additive benefit in improving upper pole volume without the use of an implant. We performed uniform deposition of adipose tissue in several layers (subpectoral, intramuscular, subfascial, subcutaneous). This increases the graft take because it minimizes the accumulation of huge volumes of adipose tissue in a limited space and maximizes the interface with the recipient site and the vascularization of the graft.[23-29]

Complications such as scarring, wound healing issue, breast asymmetry, loss of nipple sensation, capsular contracture (Baker II, III, IV) were frequently observed in the various studies. In our study NAC asymmetry and hypertrophic scarring were noted in 2 cases only. Minimum follow up period in the present study was 6 months. More than 90% patients in the present study were satisfied with symmetry of breast and NAC, upper pole fullness, NAC sensation and relatively scar less appearance. NAC asymmetry and hypertrophic scars were noted in 1 and 1 cases respectively.

Conclusion:

Mastopexy is safe and effective procedure for correction of breast ptosis. It has fewer complications and good aesthetic outcome. Patient satisfaction has been very good. Results of these 11 patients have been excellent, showing significant improvement in aesthetic outcomes with a high degree of patient & observer satisfaction.

Limitations of the study:

- Sample size was not sufficiently enough.
- A longer period of follow up is required to prove sustainable aesthetic outcome

Conflict of interest: None

Ethical issues: Preserved

Source of fund: None.

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E-LEARNING: EXPLORING THE PROS, CONS, CHALLENGES AND SATISFACTION FOR UNDERGRADUATE MEDICAL STUDENTS

Sharmistha Roy[1], Riti Yusuf[2], Arunangshu Raha[3], Mohammad Ifta Khiarul Hasan[4]

ABSTRACT

Background: With the tide of change, societal structure has evolved, and the reins of human progress now lie in the hands of digitalization. In this era of digitalization, it is imperative for medical education to align itself with these changes. Online or E-learning stands out as a significant medium in adapting to this transformed landscape. Our medical students have to be prepared for this new educational paradigm. **Objective:** To study students' attitude, acquaintance, benefit, drawbacks, challenges and satisfactory level to e-learning. **Method:** Two batches from undergraduate 4th year medical students of Pharmacology and Therapeutics Department. Each batch containing 22 students A structured questionnaire was delivered among all 44 students, after conducting an online Zoom class. Their responses were analysed. **Result:** Among 44 students 100% use electronic devices. Among them 61.4% are using smartphone for academicpurpose. 50% prefer video for learning. 86.4% are comfortable to use electronic devices. 61.4% spend more than 90 minutes on screen. 68.2% understand their class effortlessly but 31.8% face difficulty. 90.9% agree e- learning to be helpful for exam preparation. 77.3%, 90.9%, 68.2%, 59.1% express that this is time saving, better interaction with instructors and this better learning, improve interaction with classmates respectively. 31.8%, 40.9%, 81.8%, 77.3% and 68.9% complain about problem on following instruction and less interaction with instructors, poor communication with classmates, poor internet coverage, limited internet data package respectively . Only few had no suitable devices. 50% are satisfied, 18.2% are neutral and 31.8% are not satisfied. **Conclusion:** The education system has embarked on a new horizon with online or e-learning. To propel medical education forward, students and facilitators must embrace and integrate with this innovative mode of education.

Key words: E-learning, Challenges, Satisfaction of medical students

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Introduction:

Learning is a process of achieving knowledge, skill and performance. Thus, learning is ultimately considered one of the fundamental pillars of society changes.[1,2] In the 21st century, technology is playing a crucial role in our daily lives and it calls professionals, educators, and learners reflect again over their basic beliefs in order to use technology for the re-design of education and training system. In addition, these technological devices play a significant role to help learners and teachers to get more advantages from it.[3]

E-learning is "the learning supported by digital electronic tools and media".[4] It is an umbrella term that refers to training, education, and instruction that occurs on a digital medium, such as computers or mobile devices.[5] Online learning can provide students with "easier and more effective access to a wider variety and greater quantity of information".[6] Sharma and Kitchens[7] stated that e-learning includes learning with the help of web-based training facilities such as virtual universities and classrooms that allows digital collaboration and technology assisted distance learning. According to Ally, e-learning plays a significant role in any nations in the educational growth and it offers opportunities to develop nations in order to enhance their educational development. Furthermore, it also helps for the new generation of teachers to upgrade their skills for pedagogies of learning of the existing teaching force to the 21st century tools.[8] Cognitive perspective focuses on the cognitive processes that involves in the learning and how does brain works.[9] In order to apply the cognitive pedagogical models in an e-learning environment, the smart learning system and adaptive learning technology can be used to optimize learner's progress; virtual worlds and other structured learning environments that can also help learners in the content. The support system can be guided and be used quickly to teach learners to communicate; and social and other collaborative tools can be used to promote dialogue, interaction and vicarious learning. Emotional perspective focuses on motivation, engagement as well as other emotional aspect of learning.[10] Kim points out various emotions, namely, pride, frustration, relief, resistance, fear, expectation, hopelessness, anxiety, confidence, complex and the envy confirms that these functions are strongly associated with the integration of cognition, motivation, and action.[11] Behavioural perspective focuses on the skills and behavioural outcomes of the learning process[9] and it focuses on the role-playing and application to on-the-job settings.[12] Contextual perspective focuses on the environmental and social aspects that can stimulate learning[9,12] and it focuses on the interaction with people, discovery of collaboration as well as the importance of peer support and pressure.[12] Medical education has many long established pedagogical approaches to learning including face to face lectures in classrooms - via a teacher-centred model.[13] This particular approach to educational practices can manifest within a teaching culture[14], becoming pervasive within an organisation or discipline, leading to a reluctance to adopt new and emerging practices and technologies. Over the last number of decades there has been a shift in medical education practice from traditional forms of teaching to other media which employ online, distance or electronic learning.[15]

In this study students' real time persuasion towards e- learning was evaluated. The study results can be lightened us about the benefits and drawbacks of this learning method. This will be helpful to overcome the gaps of total learning process of medical students.

Material and methods:

This is a cross-sectional study. This study was conducted in the department of Pharmacology, Dhaka Medical College on September to October, 2021. Two batches from 4th year were selected randomly. An online Zoom class was conducted. A structured questionnaire was delivered among 44 students conveniently. At first, student's understanding towards e-learning and then their experience towards the class was recorded. Responses were analysed meticulously and managed into tables for further calculation.

Data Analysis:

All 44 responses were analysed using activity theory as an analytical basis, it allows the analysis of changing systems and the learning associated with them.[16]

Result:

Table – I: Student's understanding towards e – learning

Question Keys		In number n = 44	Percentage (%)
1. Using electronic device for academic learning	Yes	44	100%
	No	0	0%
2. Preferred device for academic learning	Desktop	2	4.5%
	Laptop	10	22.7%
	Tablet	5	11.4%
	Smart phone	27	61.4%
3. Preferred content for e - learning	Video	22	50%
	PDF	10	22.7%
	PPT	9	20.5%
	Others	3	6.8%

Table I shows that 100% of students use electronic device for academic learning purpose. Among them 61.4%, 22.7%, 11.4% and 4.5% are using smartphone, laptop, tablet and desktop respectively. 50% of students prefer video as their learning content. 22.7%, 20.5% and 6.8% prefer PDF, PPT and others respectively.

Table – II: Student's acquaintance with e - learning

Question Keys		In number n = 44	Percentage (%)
1. Ease to use electronic devices:	Yes	38	86.4%
	No	6	13.6 %
2. Screen time:	(10 – 30) min	2	4.5 %
	(30 – 60) min	5	11.4%
	(60 – 90) min	10	22.7%
	>90 min	27	61.4%
1. Ease to understand the class:	Yes	30	68.2%
	No	14	31.8 %
3. Helpful in exam preparation:	Yes	40	90.9%
	No	4	9.1 %

Table – II reveals that 86.4% of students are feeling comfortable to use electronic devices. 13.6% are uncomfortable to use. 61.4% spend more than 90 minutes on devices. 22.7%, 11.4% and 4.5% spend 60 to 90 minutes, 30 to 60 minutes and 10 to 30 minutes respectively. 68.2% understand their class effortlessly but 31.8% face difficulty to understand. 90.9% of students agree that this method is helpful for exam preparation but 9.1% deny this.

Table III: Student's perspective towards e – learning (benefits, drawbacks and challenges)

Question Keys		In number n = 44	Percentage (%)
Benefits	Time saving –	34	77.3%
	Improved learning –	30	68.2 %
	Better interaction with instructor –	30	68.2 %
	Better interaction with classmates –	26	59.1%
	No benefits –	2	4.5%
Drawbacks	Couldn't follow full instruction –	14	31.8%
	Poor interaction with instructor –	14	31.8%
	Poor interaction with classmates –	18	40.9%
	No drawbacks –	0	0%
Challenges	Poor internet coverage –	36	81.8%
	Limitation in internet data package –	34	77.3%
	Lacking suitable devices –	30	68.9%
	No challenges –	0	0%

Table III shows 77.3% of student express that this learning method is time saving. 90.9% utter that this is flexible. 68.2% acknowledge that their interaction with their instructors is improved and this helps to improve their learning. 59.1% improve engagement with classmates and 4.5% find no benefit. 31.8% complain about poor instruction and poor interaction with instructors. 40.9% complain of poor communication with classmates. 81.8%, 77.3% and 68.9% of students complain about poor internet coverage, limited internet data package and scarcity of suitable devices respectively.

Table IV: Level of student's satisfaction for e-learning

Level of satisfaction	In number n = 44	Percentage (%)
Satisfied	22	50%
Neutral	8	18.2%
Not satisfied	14	31.8%

Table IV shows that 50% of students' response satisfied, 31.8% are not satisfied and 18.2% are neutral.

Discussion:

This study aimed to evaluate experience of undergraduate medical students in e-learning. E-learning is considered as nearly a new method of learning process in our undergraduate medical system. In this study, students' opinions for understanding, benefits, drawbacks, challenges and satisfactory level in this innovative learning technique were explored.

In the current time, face to face learning is increasingly encountering challenges due to rising demand and time constraints.[18] So, this traditional way of learning method is gradually deviating to online or e- learning to keep abreast of the time.[15] In this study, saving time was being reported 77.3%. Some authors also revealed the same scenario in their studies.[19,20]

In this study, 86.36% and 68.2% were reported for effortless online access and understanding classes respectively. Prasetyo et al., reported same in their study.[17] The usage of electronic gadgets is increasing day by day. Majority of students spend their considerable time on gadgets.[17,24] This study also revealed that 100% students used electronic devices and among them 61.4% spent more than 90 minutes on devices.

The scarcity of infrastructure, technology, internet access and poor quality of internet services are examples of barriers that impact the learners and faculty members.[22] This study also revealed the same. As it is a new technology and teaching material, some instructors have failed to adapt to this new approach.[23] 31.8% students complained about unable to follow full instruction and poor interaction with instructors in this study. This study found that 50% students were satisfied about this learning method. Satisfactory levels of students were fluctuating in many studies. Some study showed low[21] and some study revealed better.[24] 50% learners were satisfied, 18.2% were neutral and 31.8% were unsatisfied in this study.

In the context of all discussion, it can be said that e-learning will be able to take a revolutionary step in our medical educational system.

Conclusion

E-learning embodies a modernized approach to education. The adoption of e-learning is steadily rising across diverse educational framework,

encompassing medical education and beyond. Technical, infrastructural resources and underdeveloped skill of instructors to this new technology are the major challenges of this new approach of learning. Improving these barriers and overcoming the challenges will bring in a new era for the medical education system.

Recommendation:

The improvement of an extremely strong technical infrastructure, online network and fast internet speed is essential to overcome the situation. There should be a need for constructive training for the instructors, so they can improve their skills in this new approach to learning. Student's ease to use devices, specially mobile device can be utilised from the higher level of administration could be a good initiative.

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ROLE OF LIRAGLUTIDE IN ADULT PATIENTS WITH DIABETIC NEPHROPATHY

Shammin Haque[1], Badar U Umar[2]

ABSTRACT

Diabetes is a growing global concern, affecting more than 463 million people in 2019 and predicted to reach 700 million by 2045. More than 95% of diabetics have type-2 diabetes (T2DM). One of the major complications of uncontrolled diabetes is diabetic kidney disease (DKD). Almost 40% of people with T2DM develop DKD, which is the most common cause of chronic kidney disease and renal failure worldwide. For over two decades, the standard of care for DKD has been the use of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). With the advent of new therapeutics like-sodium-glucose cotransport 2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) there are some hopes to avert the progression of DKD in those patients. As these two novel therapeutics got approval and were widely used in obese T2DM patients with different stages of kidney involvement, concern for safety came up. Several clinical trials, including post-marketing safety trials have tried to establish the safety of SGLT-2 inhibitors and GLP-1RAs. We reviewed the available literature to gather some evidence in favor of the effectiveness and safety of GLP-1RA, especially liraglutide, in terms of safety of use in DKD patients and prevention of renal complications. This may help clinicians make informed choices for their patients.

Keywords: Chronic kidney disease, type 2 diabetes mellitus, end stage renal disease, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors.

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Introduction

In 2010, the prevalence of diabetes (DM) among the world's adult population (age 20-79 years) was 6.4% and was estimated to reach 7.7% by 2030.[1] In the year 2017, an estimated 462 million individuals were impacted by type 2 DM, which accounted for around 6.28% of the global population, and it ranked up from eighteenth to ninth leading cause of death world-wide.[2] Diabetes Mellitus is one of the most common forms of chronic kidney disease (CKD) and it is linked with hypertension.[3] The mortality and morbidity ratios are increasing in greater proportion; the consequences are expected to be at higher risk in the near future.[4] Moreover, diet and exercise alone doing not provide adequate glycemic control. Patients suffer from great financial burden during the management of chronic diseases, including investigations, consulting fees for medical services, travel, and unplanned hospitalizations.[5] 40% of people with diabetes will develop chronic kidney disease, according to UK and US based research. It's alarming that, as data from 54 countries shows, more than 80% of cases of end-stage renal disease (ESRD) are due to diabetes, hypertension, or a combination of both.[3] Kaur H. et al., (2021) cited that patients with diabetic nephropathy developed proteinuria or albuminuria or drop-off in glomerular filtration rate (GFR) or both for the extended period of time without interruption.[6] Limiting the risk of kidney disease requires control of blood glucose and blood pressure.[3] The diabetes-related disease was assumed to be one of the risk factors for treatment failure, as cited by Perwitasari DA et al.(2019).[7] The most appropriate strategies to curtail the impact of kidney disease in diabetes are to prevent type 2 diabetes mellitus (T2DM) and to diagnose and treat kidney disease early and effectively in people already living with diabetes.[3] An estimated 700 million adults worldwide will have diabetes by 2045.[8] The prevalence of kidney disease in the United States is about 15%, yet awareness of kidney disease is very low. Early diagnosis of kidney disease can slow the progression of the disease. Among people with diabetes, kidney disease doubles the risk for cardiovascular disease.[9] According to the US National Health and Nutrition Examination Survey (NHANES) data of 2007-2012, the age-adjusted prevalence of chronic kidney disease (CKD) in T2DM patients was 38.3% with almost 60% prevalence among seniors (≥65 years). More than 18% of them had normal renal function or mild renal impairment, 16.7% had moderate renal impairment, and 3.1% had severe renal impairment or end-stage renal disease (ESRD).[10] In most countries, diabetic kidney disease is the leading cause of dialysis-dependent CKD. Efforts to blunt the global increase in the prevalence of end-stage renal disease therefore include the prevention of new-onset diabetic nephropathy and the progression of established diabetic nephropathy.[11] The clinical practice guideline in 2020 for the management of patients with diabetes and chronic kidney disease (CKD) focused on comprehensive care needs, glycemic monitoring, lifestyle interventions, anti-hyperglycemic therapies, and educational and integrated care approaches.[12] Many conventional glucose-lowering agents are unsuitable for use in patients with advanced CKD because they can cause safety issues such as increased risk of lactic acidosis (with metformin) and hypoglycemia (primarily with sulfonylureas, glinides, and insulin), thus requiring dose modifications or withdrawals, as cited by Mann et al., (2020).[11]

Recent research efforts have increasingly focused on the renal effects of glucose lowering therapies, with the greatest benefits for renal outcomes reported for sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs).[13] In patients with type 2 diabetes and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications, a long-acting GLP-1 RA was recommended.[14] Ji Hyun Chun (2020) and Das U. et al., (2020) cited that GLP-1RAs also be classified based on the duration of GLP-1 receptor activation at recommended doses as being short-acting (exenatide, lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide extended-release [ER], liraglutide, semaglutide).[15-16] Górriz et al., (2020) cited that among the numerous beneficial effects mediated by GLP-1RA are blood glucose regulation, body weight reduction due to reduced food intake and gastric motility, stimulation of cell proliferation, reduction of inflammation, and apoptosis, and enhanced cardiovascular function, with protection of nervous and renal systems. In 2020, the American Diabetes Association stated that some GLP-1RA, including liraglutide, semaglutide, and dulaglutide, have also shown renal benefits, and, contrary to SGLT2i, can currently be administered up to an eGFR of 15mL/min/1.73m2.[17] The study also mentioned the incretin effect in healthy individuals, where glucose given orally exhibits higher insulin secretory responses than intravenous glucose, despite producing similar levels of glycemia. The gut-derived incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), mainly secreted from L cells located throughout the intestine, are responsible for this effect.

GLP-1 increases insulin secretion in response to nutrients, particularly glucose and suppresses glucagon secretion from pancreatic islet cells, with a reduction in postprandial glucose levels as the net result.[18] ADA guidelines suggested for patients with established atherosclerotic CVD (ASCVD), consideration of GLP-RAs with demonstrated CV benefits. It now recommends this practice independent of baseline HbA1c or an individualized HbA1c target.[19] Varghese L.(2020) cited that to produce an effective glycemic control and to avoid unwanted effects, drugs with different mode of action can be combined to provide additional effects on risk factors of cardiovascular system.[18] GLP-1RAs are used as second line drug after metformin, if ASCVD is absent, when HbA1c is still above target, particularly if there is a “compelling need to minimize hypoglycemia,” or a “compelling need to minimize weight gain or promote weight loss.” GLP-1 agonists should be considered for people with kidney disease, particularly if an SGLT-2I is not tolerated.20 Liraglutide, one of the long acting GLP-1RAs have been studied by researchers who revealed the drug showed greater reductions in AC1 level compared to other similar agonists.[21-22]

This review aims to present an outline of Liraglutide in the management of patients with T2DM with kidney disease. A summarised clinical update of the drug may aid the clinicians to hinder the progression of fatal complications among diabetic patients with renal impairment.

Review Method:

This review includes articles published between 2012-2021, mainly selected from Google, PubMed, Crossref and references "need to minimize hypoglycemia,” or a “compelling need

to minimize weight gain or promote weight loss." GLP-1 agonists should be considered for people with kidney disease, particularly if an SGL risk factors of cardiovascular system.[20] GLP-1RAs are used as second line drug after metformin, if ASCVD is absent, when HbA1c is still above target, particularly if there is a "compelling T-2I is not tolerated.[21] Liraglutide, one of the relevant publications that described the status of management of diabetes mellitus globally. Other data sources included recent updates from the International Diabetes Federation and American Diabetes Association. The search was made using various keywords for GLP-1 RA, Liraglutide, Type 2 Diabetes Mellitus, Chronic kidney disease, to filter research regarding the assessment of drug efficacy and safety. Review articles, randomized controlled trials, and ongoing clinical trials were also included.

History and Pharmacology of Liraglutide: Liraglutide was the first long-acting GLP-1RA to become available for the treatment of T2DM, receiving market authorization in 2009 in the EU. In January 2010, the FDA approved Victoza for the treatment of T2DM in adults. Victoza® is the approved brand name for liraglutide in Europe. Novo Nordisk launched Victoza® into the UK, Germany, and Denmark markets after receiving authorization. The drug has been approved as an auxiliary treatment to diet and exercise to enhance glycemic control in adults suffering from T2DM. The approval enables the drug to be used as a monotherapy, as a second-line treatment and also in combination with other oral medications prescribed for diabetes.[23-24] Short-acting GLP-1RAs are administered in empty stomach, this shows greater effect on gastric emptying and postprandial glucose, especially after meal, whereas long acting GLP-1RAs have less effect on gastric emptying and postprandial glucose excursions, but a more pronounced effect on fasting blood glucose and weight loss.[25]

Pharmacokinetics:

Liraglutide, is among the few anti-diabetic agents that can be used in patients with CKD stages 1-4, without any dose adjustment, as its pharmacokinetic parameters are not dependent upon the kidneys.[11] The half-life of liraglutide is 11-15 hrs approximately and hence administration once daily is needed. Recommended initial dose is 0.6mg/dose for one week, and if well tolerated, it is doubled to 1.2 mg/dose. The dosage can further be increased to 1.8 mg/dose if required.[26-27] It is metabolized locally in the target tissues by the common route of large proteins, without a specific organ identified as the main route of elimination. They are protected from renal clearance by their large molecular size or by their non-covalent binding to albumin.[28] These are injectable peptides which are resistant to DPP-4 degradation, providing supra-physiological stimulation of the GLP-1 receptor. Slow gastric emptying and increased satiety due to an effect on the brain by GLP-1RAs, may lead to weight loss in a significant proportion of patients. Compared to DPP-4 inhibitors, this group is less tolerant, as nausea, vomiting and diarrhoea are common, which however diminish later in most patients.[29]

Clinical status of liraglutide:

Liraglutide is reported to lower glucose levels, promote weight loss and reduce cardiovascular risk. Comparison of liraglutide with once weekly exenatide ER uncovered liraglutide's superiority over exenatide ER ($p < 0.05$) in terms of

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Clinical status of liraglutide:

Liraglutide is reported to lower glucose levels, promote weight loss and reduce cardiovascular risk. Comparison of liraglutide with once weekly exenatide ER uncovered liraglutide's superiority over exenatide ER ($p<0.05$) in terms of of reducing HbA1c value. Similarly, both HbA1c and body weight were reduced when compared with Albiglutide 50 mg weekly dose as summarized in Table 1.20,[29] In a multicenter, parallel-group, clinical trial conducted from July 2013 to August 2017 compared efficacy of four FDA approved medications namely- insulin glargine U-100, glimepiride, liraglutide, and sitagliptin. Seventy-one percent of the participants had primary metabolic outcome events, and these were lowest for insulin glargine and liraglutide. Though all four drugs reduced HbA1c levels glargine and liraglutide were more efficacious in achieving the targets.[30]

Table 1: Change in HbA1c and body weight after treatment

Title of study	Study design	Mean reduction in HbA1c (%)	Mean change in body weight (kg)
DURATION 6[20]	Exenatide ER 2 mg weekly Liraglutide 1.8mg daily	- 1.28 - 1.48	- 2.68(0.18) - 3.57(0.18)
HARMONY 7[29]	Albiglutide 50 mg weekly Liraglutide 1.8mg daily	- 0.78 - 0.98	- 0.6(3.12) - 2.2(4.15)

Sloan LA (2019) reviewed preclinical studies which examined the glycemic effects of liraglutide in patients with T2DM and renal impairment where improvements in glomerular hyperfiltration, albuminuria, oxidative stress, and histologic features indicative of DKD, suggesting a role for liraglutide in protecting renal function was demonstrated (Table 2).[31-32]

In a randomized controlled crossover clinical trial ($N=32$), treatment with liraglutide for 12 weeks significantly reduced the urinary albumin excretion rate compared to placebo (-32%; $P=0.017$) in patients with persistent albuminuria (UACR ≥ 30 mg/g) and eGFR ≥ 30 mL/ min/1.73 m2 who were receiving stable renin-angiotensin system-blockers, further suggesting a renoprotective role for liraglutide.[33-34] The effects of liraglutide on renal measurements have also been examined in patients with T2DM and impaired renal function. In a 12-month longitudinal study of liraglutide ($N=84$), eGFR reached normal range (≥ 90

mL/min) in 7 of 41 patients with baseline eGFR <90 mL/min.[35] In another study, 3 of 5 patients with baseline microalbuminuria returned to normal albuminuria. Among 23 patients with DKD who received renin-angiotensin system blockers, 12-month treatment with liraglutide significantly decreased proteinuria from 2.53 to 1.47 g/g creatinine and reduced the rate of eGFR decline from 6.6 to 0.3 mL/min/1.73 m2 per year (Table 2).[36]

Jaiswal A.(2022) mentioned in a review that various clinical and preclinical studies reported that GLP-1RA effectively decreased the level of albumin in urea by inhibiting the reabsorption of sodium ion.[37] Sloan LA (2019) also cited the work of Desai et al., where an observational study examined renal outcomes with glucose-lowering treatments among 466 patients studied for 3 years, 275 of whom were treated with a GLP-1RA (exenatide or liraglutide). GLP-1RA-treated patients had a mean decrease in albuminuria (-39.6 mg/g; P<0.0001) compared with a mean increase in albuminuria (+5.6 mg/g) in patients treated with unspecified glucose lowering drugs. Among those with macroalbuminuria at baseline, greater proportions of GLP-1RA-treated patients developed microalbuminuria (UACR 30-300 mg/g; 23%) or normoalbuminuria (UACR <30 mg/g; 2.8%) compared with those receiving unspecified glucose-lowering therapies (microalbuminuria, 12.3%; normoalbuminuria, 0%; P=0.0005). SBP was also lower among patients receiving GLP-1RAs (by 3 mmHg).[31]

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (N=9340), included ~23% of patients with moderate or severe renal impairment, studied cardiovascular outcomes during treatment with liraglutide vs placebo. A pre-specified subgroup analysis comparing the primary outcome of MACE in patients with moderate or severe renal impairment (eGFR <60 mL/min/1.73 m2) vs patients with eGFR ≥60 mL/min/1.73 m2 showed a greater benefit of liraglutide in moderate or severe renal impairment group (P=0.01). It also showed a beneficial effect of GLP-1RAs on some renal outcomes. The incidence of nephropathy (defined as new onset macroalbuminuria or a doubling of serum creatinine level and eGFR ≤45 mL/min/1.73 m2, the need for continuous renal replacement therapy, or death from renal disease) was lower with liraglutide vs placebo (5.7% vs 7.2%; HR, 0.78 [95% CI, 0.67-0.92]; P=0.003). This result was driven by a 26% reduction of new-onset persistent macroalbuminuria. It was also observed that placebo-subtracted reductions in cardiorenal risk factors, which included SBP (-1.2 mmHg) and body weight (-2.3 kg) at 36 months. Liraglutide reduced major cardiovascular and kidney outcomes and all-cause mortality, compared with placebo, in patients with type 2diabetes. The benefits were evident in those with CKD, in addition to those without CKD, at baseline. Liraglutide resulted in lower rates of the development and progression of diabetic kidney disease than placebo (Table 2).[38] Another 26-week RCT investigated liraglutide 1.8mg (n=140) vs placebo (n=139) in patients with moderate renal impairment (eGFR 30-59 mL/min/1.73 m2) demonstrated significant HbA1c reductions with liraglutide (-1.05% vs -0.38% with placebo [-11.5 vs -4.2 mmol/mol]; P<0.0001), with no effect on renal function as measured by UACR or eGFR.[39]

Table 2: Effects of Liraglutide on renal parameters in pre-clinical and clinical studies

Principal investigator	Study design	Experimental inferences
Hendarto et al.,[32]	Liraglutide 0.3 mg/kg/12 hr, for 4 weeks in a streptozotocin induced rat model of diabetes	Reduced oxidative stress markers, TGF-β1, fibronectin in renal tissues, and albuminuria
Zhao et al.,[34]	Liraglutide applied to HK-2 cells and liraglutide 0.3 mg/kg/12 h for 5 weeks in a streptozotocin-induced rat model of diabetes	Attenuated high glucose-induced toxicity in HK-2 cells; inhibited glomerular hypertrophy and attenuated high glucose-induced autophagy in diabetic rats
vonScholten et al.,[33] (NCT02545738)	12-week, randomized, placebo-controlled, crossover trial of liraglutide 1.8 mg qd in patients with T2DM and persistent albuminuria who were receiving RAS blockers	Liraglutide reduced UAER vs placebo (-32%; P = 0.017)
Zavattaro et al.,[35]	12-month observational study of liraglutide 0.6-1.8 mg qd in patients with T2DM	eGFR reached the normal range for 7 of 41 patients with baseline eGFR <90 mL/min/1.73 m^2
Imamura, Hirai and Hirai[36]	12-month observational study of liraglutide 0.3-0.9 mg qd in patients with T2DM and diabetic kidney disease	Liraglutide reduced proteinuria from 2.53 to 1.47 g/g creatinine and reduced rate of eGFR decline from 6.6 to 0.3 mL/min/1.73 m^2 per year
Marso et al.,[38] (LEADER; NCT01179048) Mann et al.,[11]	Randomized, placebo-controlled, event driven study (median 3.8years) of liraglutide 1.8 mg qd in patients with T2DM and established CV disease or CV risk factors	Nephropathy was lower with liraglutide vs placebo (5.7% vs 7.2%; HR, 0.78 [95% CI, 0.67-0.92]; P=0.003). Results driven by 26% decrease in new onset macroalbuminuria

HR: hazard ratio; CKD: chronic kidney disease; RAS: renin-angiotensin system.

TGF-β1: transforming growth factor β1; UACR: urinary albumin-to-creatinine ratio.

UAER: urinary albumin excretion rate.

Effect of GLP-1RA, liraglutide, on DKD (NCT01847313) is an ongoing study of Liraglutide in primary kidney outcomes currently under investigation. There is still limited research among DKD patients with stage 5 CKD in dialysis programs or kidney transplantation. Hence, more studies related to safety of this drug in this target group are essential.

Safety profile of liraglutide:

Liraglutide shows a similar safety profile in type 2 diabetes patients, both with and without CKD including stage 4. In fact, patients with CKD experienced serious adverse events and severe hypoglycemia episodes compared with those without CKD. The risk was similar among those treated with both liraglutide and placebo. In the LEADER trial population, treatment with liraglutide led to significantly fewer severe hypoglycemia events, but more acute gallbladder disease and more GI events (nausea, vomiting, and diarrhea) that led to discontinuation compared with placebo. Those differences between liraglutide and placebo were independent of eGFR or urine albumin. Also, no unexpected increase of acute kidney injury (AKI) was observed among liraglutide versus placebo users. Nausea and vomiting are common symptoms in advanced stages of CKD patients, but results of LEADER trial revealed no increased risk of nausea which caused any cessation of treatment in patients with CKD or albuminuria, compared with those without. Despite the gastrointestinal adverse effects being more significant in patients receiving liraglutide compared to placebo, the latter difference was not more in CKD patients compared with those without CKD or albuminuria. In patients with or without CKD or albuminuria, AKI is a common adverse event. But drug studies with liraglutide versus placebo showed there was no high risk of AKI in such a population. GLP1-RA therapy with liraglutide was safe and well tolerated by patients with CKD compared with patients without CKD. There were also no reports of differences in amputations or skin gangrene with liraglutide in patients with or without CKD, concerns that were recently raised for other glucose-lowering drugs.[40-41]

A researcher found that the safety profile of liraglutide versus placebo is analogous to type 2 diabetes patients, and subjects suffering from CKD or albuminuria, as compared with patients without CKD or albuminuria. Moreover, administration of liraglutide was of great benefit for severe hypoglycemia in patients with CKD or albuminuria. Results of this safety profile investigation, along with the significant benefit upon vital body systems especially in patients with CKD, enhance the risk/benefit ratio of liraglutide.9 In clinical practice, up-titration of GLP-1 RA agents should occur approximately every 4 weeks to reduce gastrointestinal side effects. In addition, in patients taking other agents that can induce hypoglycemia, such as insulin or sulfonylureas with appropriate glycemic control (HbA1c～7%), these background therapies may be down titrated.[42]

Conclusion:

GLP-1RAs are a breakthrough in diabetes therapy as they are free from the increased cardiovascular risks associated with certain other newer therapies like- glitazones and DPP-IV inhibitors. GLP-1RA liraglutide is a suitable alternative reflecting a significant advance in GLP-1-based therapies. Improvements in glycemic control and body weight reduction are major beneficial effects for type 2 diabetic patients. Besides, improved neuro protection, improvement in insulin resistance, prevention of macro albuminuria, reduction in declining eGFR and enhanced reno protection are certain beneficial effects. In addition, it also reduces the cardiovascular risk in this population. Reduction in body weight contributes in many ways towards amelioration of cardiovascular complication of diabetes. The drug shows a ray of hope for cardiovascular reduction which

happens to be a prime risk factor for type 2 diabetic patients. The once daily dosing is another convenience for the patient. If optimally chosen and used this drug will enable the clinicians to have better glycaemic control for their patients.

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Conflict of Interest:

The authors have no conflicts of interest regarding this investigation.

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SUCCESSFUL SURGICAL OUTCOME OF EXTENSIVE SCROTAL CALCINOSIS- A CASE REPORT

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ABSTRACT

Multiple sebaceous cysts over scrotum is one of the rare conditions encountered by surgeons worldwide. Although they are painless but cosmetically unacceptable. They pose a high risk for complications such as Fournier's gangrene or septicaemia. Surgical intervention by complete excision proves to be cosmetically good and holds minimal morbid results. Here we report a case of 33 year old male patient with symptoms of multiple sebaceous cysts over scrotum affecting 50% of overlying scrotal skin for last 18 years. In this case we did complete excision of affected scrotal wall with multiple sebaceous cysts followed by reconstruction of scrotal wall. Histopathological report reviewed scrotal calcinosis which is a rare condition .

Keywords: Multiple extensive scrotal calcinosis , surgical outcome, laser therapy

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Introduction

Sebaceous cysts, also coined as epidermoid cysts, are the most common benign epithelial cystic growths containing fluid or semisolid material. Histologically, an epidermoid cyst is lined by an epithelial cell wall of stratified squamous epithelium resembling epidermis and includes a granular layer and keratin lamellae in the lumen. These cysts are usually found in hair follicles bearing areas of body such as scalp, back, scrotum. They are often asymptomatic and painless but may become painful and red if infected. Long standing untreated epidermoid cyst may develop scrotal calcinosis via dystrophic calcification. While single cysts are common , multiple cysts in scrotum are rare and it is even rarer for them to cover such a large area (as in this case). Gold standard treatment of multiple epidermoid cyst involve complete excision of cyst with its content with minimum morbidity and good cosmetic result.

Case presentation

A 33year old married man driver by profession, hailing from Gazipur, reported to the surgery department of TMMCH, Gazipur with complaint of multiple swellings over the scrotum that started around 18 years ago, beginning as a few small nodules. Over the years, they increased in size and number, prompting him to seek a medical consultation .The patient had no co-morbidities and had tried various homeopathic treatments over the years without success. He reported foul-smelling swellings but denied any pain, discharge, or bleeding. Multiple swellings were found, ranging from 0.5 cm to 2.5 cm in size. The cysts coalesced into a mass covering two-thirds of the scrotum.The cysts were firm, non-tender, and not attached to the underlying structures or testes. Inguinal lymph nodes were not palpable, indicating no lymph node involvement. The examination confirmed multiple sebaceous cysts, covering a significant portion of the scrotum.The patient's lack of pain and absence of lymph node involvement suggest that these cysts are benign. However, the foul smell and cosmetic concerns likely impact his quality of life, making surgical intervention necessary(surgical excision was performed under spinal anaesthesia) .

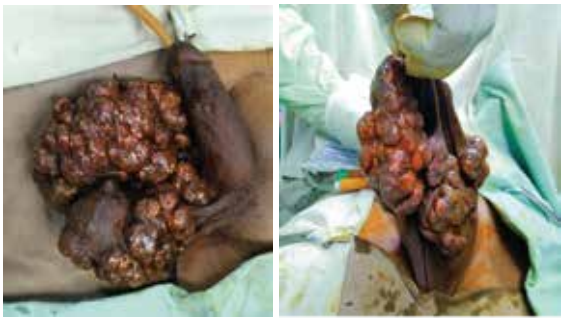

Figure 1: shows preoperative picture of multiple sebaceous cysts over the scrotum.

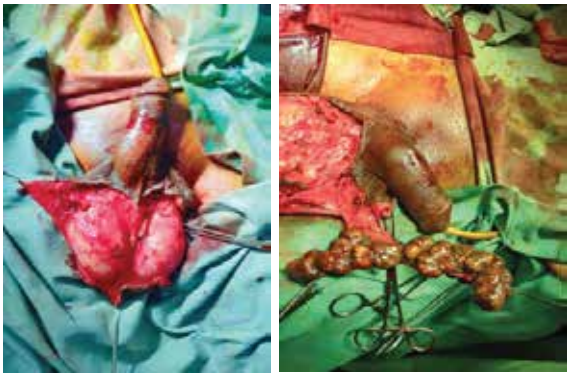

Figure 2: Intra-operative picture of multiple scrotal sebaceous cysts.

The minimal excision technique was employed, and the cysts were removed by making an elliptical incision all around the cysts which were involving 50% of the overlying scrotal skin. Multiple cysts were excised total and sent for histopathological examination. Scrotal wall was reconstructed by local advancement flaps and hemostasis was achieved. Two drains were

placed on each side of scrotum for 48 hours. The patient was catheterised and after operation condition of patient was uneventful.

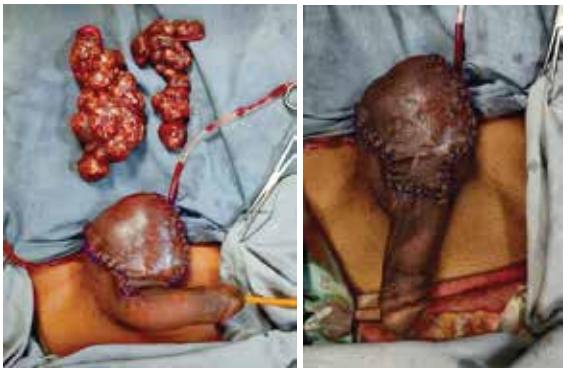

Figure : (A) Post-operative specimen of resected multiple scrotal sebaceous cyst. **(B)** immediately after operation.

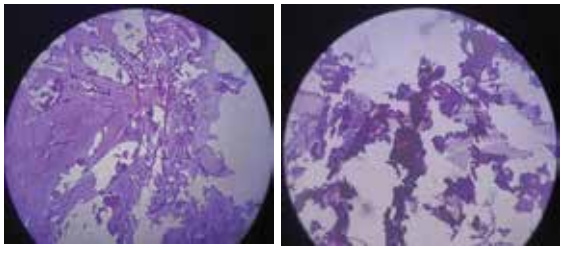

Figure : Histopathological of scrotal calcinosis (section shows- skin with multiple varying sized, granular, fractured calcium deposits within the dermis and subcutis)

Histopathological examination of the cysts revealed scrotal calcinosis ruling out malignancy. The following medications were administered to the patient during the postoperative period-Inj. Ceftriaxone (1gm) three days followed by oral cefixime for 7days.

Discussion

As described prior it is rare disease and aetiology is unknown. Most of the cases are benign but slowly progressive disease and condition first described by Lewinski in 1883. It appears mainly in men aged 20 to 40 years.

Khallouk A et al. reported that scrotal calcinosis consists of hard, yellowish nodules- vary in size (from 1 mm to several centimeters) and number (solitary or multiple) at scrotal skin. The nodules are usually asymptomatic. The delay between the occurrence of the disease and therapy is often several years because of the benign course and negligible symptoms encountered by the patient. The only treatment recommended is surgical. In our case, scrotal calcinosis consists of firm reddish nodules , size from 0.5cm to 2.5 cm and multiple in number at scrotum. Due to negligible symptoms and delayed course of the disease , the presented to surgeon later in the course of the condition.

From Deheng Cui et al. it was concluded that the disease is slowly progressing and benign. For smaller lesions, laser therapy may be considered; however surgical resection is the preferred treatment approach and is associated with a good prognosis. In our patient's following cyst excision, compliance was satisfactory, subsequent laser therapy was deemed unnecessary.

From Ali Al-Gonaim et al. idiopathic calcinosis of scrotum first reported case published in Saudi Arabia and excision was the choice of treatment that was done in case of our case .

According to D. Reddy et al case report , benign idiopathic scrotal calcinosis with unknown aetiology was well managed by simple surgical excision with patient counselling. Histopathological analysis is essential to confirm the diagnosis and exclude other more serious conditions. In our case, aetiology was not conclusive and after counselling the patient , excision was done then confirmatory diagnosis was done by histopathology.

Conclusion

Multiple sebaceous cyst or benign scrotal calcinosis is rare disease and the aetiology is still not completely understood. Surgical management remains the gold standard treatment for this condition, with patient counseling serving as a critical component of comprehensive care in patient management. Histopathological analysis is essential for confirming the diagnosis and excluding other, potentially more serious conditions.

Patient consent

Informed written consent was obtained from patient for publication of this case report and all imaging studies. consent form on record .

Conflicts of interest : No

Funding : Self

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