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# Editorial

Prof. Dr. K. Rajeshwar Reddy

## Medical Education

Education is a process, the chief goal of which is to bring about desirable changes in the behavior of the learner in the form of acquisition of knowledge, proficiency in skills and development of attitudes.

The goal of medical education is to produce the physician we would like to see if we are sick. Medical education technology has contributed a lot towards improving medical education. The medical councils, in its regulations for the undergraduate medical education, have specifically indicated that every medical college should have a Medical Education Unit. There is a felt need that teachers in medical colleges require training in medical education technology and keep himself/herself abreast of the emerging trends in medical education. This will help medical students, to put them in the effective path of learning, since they are adult learners.

Medical college is a functional entity with a system-goal of educating students to produce qualified health professionals. It consists of many departments which are interdependent and inter-related sub-systems. It is apparent that medical colleges should have institutional goals. It is also apparent that socio-political and economic realities constitute system environment of the college. These may result in a conducive or nonconducive milieu that helps or hinders its functioning.

The medical student enters a profession with established values and traditions of ethical conduct and responsibilities. The greatest responsibility in medical education is to foster compassion, a complete transformation of behavior and attitudes towards people/patients within the students of medicine. During medical school, students are taught the knowledge, skills and attitudes required to become competent doctors.

Most medical students enter the clinical years with certain anxieties clustered around the following questions:

How can I cope with the uncertainties of clinical medicine?

What are the boundaries of clinical medicine?

How much and what am I supposed to learn?

How will I function in my interactions with patients?

How will I measure up to the expectations of my colleagues?

How will I be able to maintain my own identity as an individual in a profession that so obsessively dominates my time and energy?

The medical educators have dual ethical obligation: firstly to the society at large which expects to produce competent health professionals and secondly to the medical students.

At the end of the MBBS course, the student would be able to provide preventive and curative cure to the individual and the community in health and sickness.

Thus, education is chiefly concerned with developing and modifying patterns of behavior in human beings in the realms of thinking, feeling and acting, i.e., attitude towards the course, subjects, field, learning, reading, discussion, inquiry, school, profession or career, society, classmates and self.

The biggest challenge in medical education today is to develop proper outcome measures of what it means to be a good doctor so that we can better understand whether our innovations are working.

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# An Alternative Technique of Sputum Concentration by Hypertonic Saline-Sodium Hydroxide Method for Increased Sensitivity of Sputum Smear Microscopy

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**Key words**:
Direct smear microscopy,
Concentration of sputum,
HS-SH concentration method,
Pulmonary tuberculsis (PTB).

## ABSTRACT

**Objectives:** Present scenario of tuberculosis (TB) demands a reliable method for rapid diagnosis of TB. In low-income countries, there is a special need for cheap and simple diagnostic techniques. Sputum concentration increases the sensitivity of smear microscopy for the diagnosis of tuberculosis. Hypertonic saline-sodium hydroxide concentration method found to be better for detection of acid fast bacilli (AFB) in sputum. Comparison of grading of direct AFB smears against concentrated AFB smears by hypertonic saline-sodium hydroxide and modified Petroff"s method, is the aim of the present study.

**Methods:** A total of 100 consecutive sputum samples - Ziehl-Neelsen (Z-N) stained smear positive from pulmonary tuberculosis (PTB) patients at St. John's Medical College and Hospital, Bangalore, India during March 2009 - August 2010, were collected and direct smears were prepared from all 100 sputum samples, followed by smearing after concentrating by Hypertonic Saline-Sodium Hydroxide (HS-SH) method and modified Petroff's Method. All the smears were heat fixed and stained by Z-N staining technique as per the guide lines of Revised National Tuberculosis Control Programme, India.

**Results:** Smears with a 3+ grading were more in HS-SH method (52/100, i.e. 52%), followed by modified Petroff's and direct smear methods as 46/100 and 18/100 respectively. The difference in number of smears with 3+ grading is highly significant with p-value <0.01, when HS-SH smears were compared with direct smears. Occurrence of pulmonary tuberculosis in males was 70% and in females was 30% with a male to female ratio 2.5:1. Most of the PTB cases (62%) were of age group 21-50 years.

**Conclusions:** The use of HS-SH method for the concentration of AFB in sputum, being better than direct smear method is recommended for use in routine laboratory diagnosis of PTB in developing countries.

## INTRODUCTION

Overall one third of the world's population (above 2 billion) is infected with tubercle bacilli, according to a WHO fact sheet on tuberculosis dated March 2010[1]. Direct microscopy of Ziehl-Neelsen (Z-N) stained sputum smear is a basis to diagnose tuberculosis (TB) worldwide[2]. In under developed countries, it is still a routinely used method for diagnosis of TB, because of its simple procedure, less turnaround time, cost effectiveness, high specificity and its capability to identify majority of infectious cases of TB as well[3,4,5,6,7]. But this technique has a low sensitivity (22 – 43%) for single smear[5] and up to 60% under optimal conditions[6], when compared with cultures[6,8]. The threshold for detection of acid fast bacilli in sputum

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samples under optimal conditions is between 104 and 105 bacilli/ml[9], which can be obtained by concentration techniques even though a sputum sample have very low bacillary load. Modified Petroff's method is a simple, inexpensive method for decontamination and concentration of sputum while in hypertonic saline sodium hydroxide (HS-SH) method, hypertonic saline acts as a mucolytic agent[10] and provides better digestion of thick sputum samples[11].

Hence, there is a need to assess the efficiency of HS-SH method for sputum concentration technique in pulmonary tuberculosis.

## METHODS

A comparative study was carried out in the Microbiology Laboratory at St. John's Medical College and Hospital, Bangalore, India during March 2009 - April 2010. Total of 100 consecutive sputum samples collected from pulmonary tuberculosis patients showing Ziehl–Neelsen stained smear positive as well as not falling under exclusion criteria with inappropriate sample without purulent material (saliva only) were collected after a verbal consent from the patients who had visited our hospital for diagnosis and treatment. Direct smears were prepared from all 100 sputum samples, followed by smearing after treated with hypertonic saline-sodium hydroxide method (2 ml of sputum sample mixed with 2 ml of 7% NaCl and 2 ml of 4% NaOH, followed by homogenization, incubation, neutralization and centrifugation)[11] and modified Petroff's method[12]. All the smears were heat fixed and stained by Z-N staining technique as per the guide lines of Revised National Tuberculosis Control Programme (RNTCP), India[13].

The data was anlysed by using paired t-test, to observe the significant difference between direct sputum smear microscopy and the microscopic finding after HS-SH concentration method. Similarly to assess the significant differences between direct smear microscopy and modified Petroff's method.

## RESULTS

Out of 100 samples received from pulmonary tuberculosis, 70% were males and remaining 30% of females, with a male: female distribution ratio 2.3:1. Majority of the patients with pulmonary tuberculosis belonged to the age group between 21 to 50 years (62%). Tuberculosis was found to be low among the children and adolescents.

Table 1: Gender and age wise distribution of the cases

| SN | Characteristics | No. of patients ( n=100) | Percentage |
|---|---|---|---|
| 1. | Sex | | |
| | Male | 70 | 70% |
| | Female | 30 | 30% |
| 2. | Age ( years) | | |
| | 10-20 | 20 | 20% |
| | 21-30 | 28 | 28% |
| | 31-40 | 16 | 16% |
| | 41-50 | 18 | 18% |
| | >50 | 18 | 18% |

Sputum samples of AFB positive result were smeared, Z-N stained and re-examined by using direct microscopy and after adoption of concentration techniques - modified Petroff's and HS-SH concentration methods. All the smears were observed under oil immersion lens and graded as per RNTCP guide lines. Smears with a 3+ grading were more in HS-SH method (52/100, i.e. 52%), followed by modified Petroff's and direct smear methods as 46/100 and 18/100 respectively. The difference in number of smears with 3+ grading is highly significant with p-value <0.01, when HS-SH smears were compared with direct smears. A significant difference has also been seen while the smears with 3+ grading after modified Petroff's method were compared those after direct smears. The results were similar when the smears were graded as 2+ by all three aforementioned techniques - direct smear, modified Petroff's and HS-SH methods with the incidence of 25%, 24% and 24% respectively. Only 2 cases were of scanty grade after HS-SH method whereas, direct smears were found more in number (26/100) with scanty grading.

Hence, the grading of sputum smears had a significant alteration after concentration of sputum compared to direct smears; the number of smears with 3+ grading being increased and those with a scanty grading decreased, of the two concentration techniques. HS-SH method had a better impact on the grading of Z-N smears.

Table 2: Comparison of grading of direct Z-N smear with modified Petroff's method and HS-SH method

| S.N. | Grading of Z-N smears | Direct Smear | After modified Petroff's method | After HS-SH Method |
|---|---|---|---|---|
| 1. | 3+ | 18 | 46 | 52 |
| 2. | 2+ | 25 | 24 | 24 |
| 3. | 1+ | 31 | 24 | 22 |
| 4. | Scanty | 26 | 6 | 2 |
| | Total | 100 | 100 | 100 |

## DISCUSSION

Tuberculosis is the second leading cause of death among the infectious diseases[14]. It is essential to provide early and accurate diagnosis of cases, to ensure the proper treatment and limit its transmission[15].

In this study a total of 100 AFB positive sputum sample were analysed. Of these 70% were males and 30% were females with male to female ratio 2.3:1. Higher prevalence of TB in male patients have also been reported in other studies[16,17,18,19].

Of all patients, those aged 21-50 years were more likely to be sputum positive for AFB (62%) compared with other age groups. In a study at Lucknow, showed the age group of 11-30 years with incidence of 66.5% of the total positive cases[18]. Contrary to present study, Ipuge YA *et al*[19] reported less number of cases in the age group 25-54 years.

AFB microscopy is believed to be the most practical and fastest technique to diagnose TB, especially in developing countries[15]. Though AFB microscopy is simple, inexpensive and provides rapid result, it has some limitations[3,4,5]. The threshold for

detection of AFB in sputum samples under optimal conditions is between 104 and 105 bacilli per m[19]. Direct microscopy clearly has many advantages when it comes to speed and feasibility, and if sensitivity could be improved it has the potential to become an even more valuable tool for National Tuberculosis Control Programmes (NTPs) around the world. Many researchers have suggested that the performance of sputum smear microscopy can be significantly improved if sputum is liquefied with chemical reagents and then concentrated by centrifugation prior to acid-fast staining[12,20].

In this study the AFB positive direct sputum smears were compared with smears prepared after HS-SH and modified Petroff's method of concentration. Highly significant differences were found, when direct smears with 3+ grading (18/100) were compared with those smears after HS-SH (52/100) and modified Petroff's method (46/100) of concentration. Ganoza *et al*[11] reported higher (71.4%) sensitivity result of AFB microscopy after HS-SH method of concentration, followed by N-acetyl-L-cysteine (NALC) with 2% sodium hydroxide (NaOH) method and direct smear with sensitivity of 66.7% and 28.6% respectively. Improved results of sputum microscopy and culture after implication of HS-SH concentration method has also been reported in other study[21].

The difference in number of smears with 3+ grading is not significant when the result of modified Petroff's method compared with the result of HS-SH method. But during course of study we noticed that HS-SH method has better liquefying activity than those of 4% NaOH, used in modified Petroff's method. This could be due to presence of hypertonic saline - a chemcal component used in HS-SH method, as a mucolytic agent[10].

## CONCLUSIONS

The grading of sputum smears had a significant alteration after concentration of sputum compared to direct smears - the number of smears with 3+ grading being increased and those with a scanty grading decreased, of the two concentration techniques. HS-SH method had a better impact on the grading of Z-N smears. To assess the exact sensitivity of sputum microscopy by HS-SH concentration method as well as to evaluate the merits of HS-SH concentration method over the conventional modified Petroff's method, a large scale field study with more number of samples (with unknown sputum smear finding) is required.

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## REFERENCES

1. Geneva: WHO [Last cited on 2010 Oct 15]. World Health Organization. Fact Sheet. 2010; No.104: Tuberculosis.
2. World Health Organization: Global tuberculosis control 2008: surveillance, planning, financing. Geneva: WHO; 2008.
3. Albert H: Economic analysis of the diagnosis of smear-negative pulmonary tuberculosis in South Africa: incorporation of a new rapid test, FAST PlaqueTB, into the diagnostic algorithm. *Int J Tuberc Lung Dis.* 2004; 8: 240-247.
4. Van Cleeff M, Kivihya-Ndugga L, Githui W, Ng'ang'a L, Kibuga D, Odhiambo J, *et al*. Cost-effectiveness of polymerase chain reaction versus Ziehl-Neelsen smear microscopy for diagnosis of tuberculosis. *Int J Tuberc Lung Dis*. 2005; 9: 877-883.
5. Keeler E, Perkins MD, Small P, Hanson C, Reed S, Cunningham J, *et al*. Reducing the global burden of tuberculosis: the contribution of improved diagnostics. *Nature*. 2006; 444: 49-57
6. Toman's tuberculosis. Case detection, treatment, and monitoring. 2nd edition. Geneva: World Health Organization; 2004.
7. Behr MA, Warren SA, Salamon H, Hopewell PC, Ponce DL, Daley CL, *et al*. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet*. 1999; 353: 444-449.
8. Asper L, Mutsvangwa J, Magwenzi J,Chigara N, Butterworth A, Maso NP.and Van der Stuyft P. A comparison of direct microscopy, the concentration method and the Mycobacteria Growth Indicator Tube for the examination of sputum for acid fast bacilli. *Int J Tuberc Lung Dis*. 2003; 7: 376-381.
9. IUAT. Tuberculosis bacteriology-priorities and indications in high prevalence countries: position of the technical staff of the Tuberculosis Division of the International Union Against Tuberculosis and Lung Disease. *Int J Tuber Lung Dis*. 2005; 9: 355-361.
10. Donaldson SH, Bennett WD, Zeman KL, *et al*. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med*. 2006; 354: 241–250.
11. Ganoza CA, Ricaldi JN, Chauca J, *et al*. Novel hypertonic saline - sodium hydroxide (HS-SH) method for decontamination and concentration of sputum samples for *Mycobacterium tuberculosis* microscopy and culture. *J Med Microbiol*. 2008; 57: 1094-1098.
12. Kent PT, Kubica GP. Public Health Mycobacteriology a guide for the level III laboratory. Centre for Disease Control Manual. 1985; 21-44.
13. Revised National Tuberculosis Control Programme. Module for laboratory technician: 4th ed 2002; 14-30.

14. World Health Organization: Global Tuberculosis Control: WHO Report. 2011.

15. Huebner RE, Good RC, Tokars JI: Current practices in mycobacteriology: results of a survey of state public health laboratories. *J Clin Microbiol*. 1993; 31(4): 771–775.

16. Borgdorff MW, Nagelkerke NJD, Dye C, *et al*. Gender and tuberculosis: comparison of prevalence surveys with notification data to explore sex differences in case detection. *Int J Tuberc Lung Dis*. 2000; 4: 123-132.

17. Kumaresan. IA, Raviglione MC. Munay CIL. Tuberculosis. The global burden of disease and risk factors in 1990: World Health Organization Press.1996.

18. Verma SK, Verma SK, Surya K, Santosh K and Prasad R. A Five-Year Follow-up Study of Revised National Tuberculosis Control Programme of India at Lucknow. *Ind J Chest Dis Allied Sci*. 2008; 50: 195-197.

19. Ipuge YA, Rieder HL, Becx-Bleumink M, Kimerling ME. Evaluation and planning in national tuberculosis control programmes: the usefulness of the standardised patient treatment card. *East Afr Med J*. 1997 Dec; 74(12): 816-8.

20. Heifets LB, Good RC. Current laboratory methods for the diagnosis of tuberculosis. Washington DC: Tuberculosis: pathogenesis, protection, and control. *American Society for Microbiology*. 1994: 85–110.

21. Ricaldi JN, Guerra H. A simple and improved method for diagnosis of tubercuosis using hypertonic saline and sodium hydroxide to concentrate and decontaminate sputum. *Trop Doct*. April 2008; 38(2): 97-99.

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# Pregnancy Outcome in Different Types of Placenta Praevia

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**Key words**:
Antepartum hemorrhage,
Cesarean section,
Placenta praevia,
Obstetric hemorrhage.

## ABSTRACT

**Objectives:** To compare risk factors and pregnancy outcome between different types of placenta praevia (PP).

**Methods:** We conducted a retrospective study of 50 women presenting with PP over a 3-year period from November 01, 2009 to October 31, 2012. Differences in incidence regarding age, parity, cesarean section, antepartum hemorrhage, preterm deliveries, operative complications, and neonatal outcome in women with major and minor PP (placenta praevia) were recorded and analyzed.

**Results:** The overall proportion of PP was 0.55%. Major PP (Complete or partial PP) occurred in 32 women (64%) and minor PP (marginal PP or low-lying placenta) in 18 women (36%). There were no differences between women with major and minor PP regarding age and parity. Women with major PP showed a significantly higher incidence of antepartum hemorrhage (90.6%) than minor PP (55.5%). Antepartum hemorrhage was associated with premature delivery more commonly in women with major PP (87.5%). The only significant difference between women with major and minor PP regarding neonatal outcome was that major PP was associated with a higher incidence of admission to the neonatal intensive care unit (87.5%).

**Conclusions:** Complete or partial placenta praevia is associated with higher morbidity than marginal placenta praevia or low-lying placenta.

## INTRODUCTION

Placenta praevia is a localization of placenta in the lower segment of the uterus over or near the internal cervical os[1]. Traditionally, PP is classified as "complete" when the placenta completely covers the internal cervical os, "partial" when the placenta partially covers the os, "marginal" when the lower edge of the placenta just reaches the os, and "low-lying" when the placenta is in the lower segment but does not reach the internal os[2].

Complete and partial PP are considered "major placenta praevia", while marginal PP and low lying placenta are considered "minor placenta previa"[3,4].

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The frequency of this condition is about 3 to 6 per 1000 deliveries. Its incidence is higher among Asian women as compared to White women[5]. Etiology of placenta praevia is unknown but it is thought to be caused by repeated trauma to the endometrial tissue which leads to endometrial scarring resulting in requirement of greater area and abnormal position for placentation[6].

A trend of increasing placenta praevia was observed in past decade, mainly because of increasing c-section and advancing maternal age at conception[7]. Massive obstetric hemorrhage is a major cause of maternal death and morbidity and placenta praevia represents a true obstetric emergency that is still significantly associated with increased perinatal and maternal

morbidity and mortality in developing countries[8]. Because of the speed with which obstetric hemorrhage at delivery can become life threatening the cesarean hysterectomy, internal iliac artery ligation or embolization may be necessary. These procedures require not only the advanced surgical or radiological skills but also the ability and experience to decide quickly when these procedures are necessary to save the maternal life and serious maternal morbidities that may arise from severe blood loss including hypovolemic shock, DIC, renal failure, liver failure and adult respiratory distress[9].

## METHODS

This was a hospital based retrospective study. The study was conducted at Gandaki Medical College Teaching Hospital, Pokhara, Nepal, which has about 1000 deliveries annually and a total annual obstetrics admission is about 3000 cases. Period of data collection was three years. We conducted a retrospective study of cases admitted from November 01, 2009 to October 31, 2012.

During this period 50 cases presenting with PP were enrolled. Differences between women with major and minor PP regarding age, parity, cesarean section, antepartum hemorrhage, preterm deliveries, operative complications, and neonatal outcome were detected.

All pregnant women who fulfilled the inclusion criteria were enrolled for the study. Data were collected from the case notes of women who were found to have PP on trans-abdominal or trans-vaginal ultrasound scanning and in whom the diagnosis was confirmed during cesarean section. Pregnancies beyond 28 weeks' gestation were included. When there was any discrepancy between the ultrasound findings and the findings at surgery, the case was excluded from the study. When a woman had more than one ultrasound examination, the result of the most recent ultrasound examination was used in the study. The classification of the degree of PP was based on ultrasound findings. Placenta praevia was classified as major when the placenta completely or partially covered the internal os. When the placenta just reached the internal os or the margin was less than 3 cm above the internal os, it was classified as minor. Demographic characteristics of women included in the study, together with details of surgical findings and procedures, the volume of blood transfusions, and complications were extracted from the medical records. The neonatal outcomes were extracted from the neonatal case.

## RESULTS

Table 1: Obstetric outcome in major and minor placenta praevia

| | Major (no-32) | | Minor (no-18) | |
|---|---|---|---|---|
| | No. | % | N0. | % |
| APH | 29 | 90.6 | 10 | 55.5 |
| Preterm labor | 28 | 87.5 | 6 | 33.3 |
| Cesarean section | 32 | 100 | 8 | 44.4 |
| B.T. | 24 | 75 | 2 | 11.1 |
| PPH | 6 | 18.7 | 1 | 5.5 |

Table 2: The neonatal outcome in women with major and minor PP (placenta praevia)

| | Major ( no-32) | | Minor (no-18) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Premature | 27 | 84.3 | 6 | 33.3 |
| Still birth | 2 | 6.2 | 1 | 5.5 |
| Live birth | 30 | 97.2 | 18 | 100 |
| NICU admission | 28 | 87.5 | 8 | 44.4 |
| NND | 5 | 15.6 | 0 | 0 |
| IUGR | 6 | 18.7 | 2 | 11.1 |

## DISCUSSION

Factors such as old age, multiparity, previous abortion, previous cesarean section is frequently associated with placenta praevia. They are accounted as risk factors of major and minor placenta praevia. Similar incidence of these risk factors has been found both in major and minor placenta praevia cases. Faiz *et al* claimed that age, parity, history of cesarean section and history of abortion should be adjusted when demographic investigation on placenta praevia is pursued[10]. The present study revealed a higher incidence of major PP (64%) than of minor PP (36%). This is in agreement with most other recent studies[11,12,13].

Placenta praevia is a leading cause of antepartum hemorrhage with associated increased maternal and perinatal morbidity and mortality even at the best equipped obstetric unit. In our study, women with major PP had a significantly higher incidence of antepartum hemorrhage. This agrees with the studies of Gourab[14] and Dola *et al*[8].

The incidence of preterm delivery (before 37 weeks) was significantly higher in women with major PP (87.5%), than minor PP (33.3%). This may be because the premature deliveries were mainly due to the higher incidence of antepartum hemorrhage. Bhat *et al*[11] reported that the presence of antepartum hemorrhage significantly predicted preterm outcome[11].

Regarding neonatal outcome, the difference according to degree of PP found in this study was that babies born to women with major PP showed a higher incidence of admissions to the NICU. The increased rate of admissions was due to the increased incidence of preterm babies in women with major PP. Dola *et al*[8] reported women with complete PP having infants with lower birthweight[8]. The rate of admission of neonates to NICU and duration of stay in hospital were increased in pregnancies complicated with placenta praevia[15].

The amount of blood transfused was significantly more in women with major PP. The increased incidence of operative interference also led to an increased incidence of intraoperative and postoperative complications in major PP than minor placenta praevia.

The present study revealed a higher frequency of intrauterine growth restriction among women with major placenta praevia (18.7%) than minor placenta praevia (11.1%). Scarring at placental bed also increases the risk for developing fetal growth

restriction in pregnancies complicated by placenta praevia[16]. Bahar *et al* in their study concluded that major placenta praevia imposes a greater risk of fetal and neonatal losses than minor placenta previa[17]. This is similar to our study.

## CONCLUSIONS

Women with major PP are at an increased risk of antepartum bleeding, premature labor and to have postoperative complications than women with minor degrees of PP. To reduce morbidity, the delivery of these women should be planned in an institution with optimum facilities and with preset precautions.

## RECOMMENDATIONS

We strongly recommend antenatal care for every pregnant women and delivery of women having major and minor placenta praevia should be conducted at the hospitals having facilities of cesarean section, blood transfusion, maternal Intensive Care Unit and Neonatal Intensive Care unit.

## REFERENCES


1. Philip N. Baker, Obstetrics Ten Teachers, Publi Book Power, ed 18th, Antenatal Obstetrical Complication, 2006; chap 11, 125-45.
2. Oyelese Y, Smulian JC. Placenta previa, placenta accreta, and vasa previa. *Obstet Gynecol*. 2006; 107: 927–41.
3. Love CD, Fernando KJ, Sargent L, Hughes RG. Major placenta praevia should not preclude out-patient management. *Eur J Obstet Gynecol Reprod Biol*. 2004; 117: 24–9.
4. Royal College of Obstetricians and Gynaecologists. Guidelines No.27. Placenta praevia and placenta accreta: diagnosis and management. January 27 Edn. 2005.
5. Yang Q, Wu Wen S, Caughey S, Krewski D, Sun L, Walker MC. Placenta previa: its relationship with race and the country of origin among Asian Women. *Acta Obstet Gynecol Scand*. 2008; 87(6): 612.
6. Scott JR. Placenta previa and placental abruption. In: Scott JR, Disaia PJ, Hammond CB, *et al*. eds. Danforth's obstetrics and gynecology. Philadelphia: JB Lippincott Company, 1994: 489-500.
7. Frederiksen M, Glassenberg R, Stika C. Placenta previa: A 22-year analysis. *Am. J. Obstet. Gynecol*. 1999; 180: 1432-1437.
8. Dola CP, Garite TJ, Dowling DD, Friend D, Ahdoot D, Asrat T. Placenta previa: does its type affect pregnancy outcome. *J Gynaecol Obstet*. 2006; 93: 110-7.
9. Olive EC, Roberts CL, Algert CS, Morris JM. Placenta praevia: maternal morbidity and place of birth. *Aust N Z J Obstet Gynaecol*. 2005; 45: 499-504.
10. Faiz AS, Ananth CV. Etiology and risk factors for placenta previa: an overview and meta-analysis of observational studies. *J Matern Fetal Neonatal Med*. 2003; 13: 175-90.
11. Bhat SM, Hamdi IM, Bhat SK. Placenta previa in a referral hospital in Oman. *Saud Med J*. 2004; 25: 728–31.
12. Love CD, Fernando KJ, Sargent L, Hughes RG. Major placenta praevia should not preclude out-patient management. *Eur J Obstet Gynecol Reprod Biol*. 2004; 117: 24–9.
13. Dola CP, Garite TJ, Dowling DD, Friend D, Ahdoot D, Asrat T. Placenta previa: does its type affect pregnancy outcome? *Am J Perinat*. 2003; 20: 353–60.
14. Ghourab S. Third-trimester transvaginal ultrasonography in placenta previa: does the shape of the lower placental edge predict clinical outcome? *Ultrasound Obstet Gynecol*. 2001; 18: 103–8.
15. Joan M, Crane G, Michiel C, Van Denhof, Linda Dodds, Anthony Armson B, Robert Liston. Neonatal Outcomes with Placenta Previa. *Obstet Gynecol*. 1999; 93: 541–4 .
16. Varma TR. Fetal growth and placental function in patients with placenta praevia. *Br J Obstet Gynaecol*. 2005; 80(4): 311-5.
17. Bahar A, Abusham A, Eskandar M. *et al*. Risk factors and pregnancy outcome in different types of placenta previa. *J Obstet Gynaecol Can*. 2009; 31: 126-31.

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# Review of Pediatrics In-Patient at Gandaki Medical College

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**Key words**:
Pediatric Inpatients,
Morbidity,
Mortality,
IMCI.

## ABSTRACT

**Objectives:** This study was undertaken to describe the morbidity pattern in the pediatric ward at Gandaki Medical College and Teaching Hospital with the aim that the results obtained will help in planning and implementing preventive and curative health care activities of the children in resource poor community.

**Methods:** This study was carried out retrospectively for one year from January 2011 - December 2011 on the basis of age and sex and the frequency of disease according to the system involved.

**Results:** A total number of 1091 patients were admitted during the study period. There were 686 (63%) male and 405 (37%) female children. Less than five years age group accounted for 712 (65.26%). In the study period, respiratory tract infections were the commonest cause of admission in all age groups 371(34%), gastrointestinal 272 (25%) including diarrheal diseases were 148 (13.56%), enteric fever comprised of 99 (9.07%), and other diseases comprised of about 25 (2.5%) of the total admissions. CNS diseases comprised of 114 (11%) of which, febrile convulsion 54 (47.37%), neurocysticercosis 19 (16.67%), seizure disorder 39 (34.21%), meningitis 2 (1.75%). Renal and urinary tract diseases and cardiovascular diseases were 8.5% and 1.5% respectively.

**Conclusions:** Children under five years age being the most common age group amongst all, with infection being the most predominant cause of pediatric morbidity, community level interventions including IMCI should be strengthened for reducing hospital admissions. Further study should be done for the high prevalence of neurocysticercosis in Kaski and neighboring districts.

## INTRODUCTION

Worldwide, children younger than fifteen years of age account for 28% of the total population[1]. A large proportion of the Nepalese population (37%) is under age fifteen years. Eleven percent of the population is under five years[2].

Childhood illnesses comprise major portion of hospital admissions in the world with significant mortality. About 7.6 million under-five children died in 2010, three-quarters of which are mainly due to preventable causes: neonatal conditions, pneumonia, diarrhea, malaria, and measles[3]. Pneumonia and diarrheal diseases are the two biggest killers of children under five years old, accounting for 18% and 15% of all deaths respectively in 2008[4]. Pneumonia is the largest single cause of death in children less than five years of age, and is responsible for nearly 1.4 million deaths every year. Diarrheal diseases account for 840,000 deaths among under-five children in the world[3]. As major population of our country is comprised of children; knowledge of morbidity and mortality pattern of children in different parts of the country is essential for planning, programming and implementing preventive and curative healthcare activities. Few studies on childhood admission profile in pediatric wards have been done in Nepal[5,6,7].

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Morbidity pattern can vary in different seasons and regions. As such type of study was not performed in this region of the country; this study was conducted with an objective to determine the disease pattern of children prevalent in this region of Nepal.

## METHODS

This retrospective study was conducted in pediatric patients admitted and treated at Gandaki Medical College and Teaching Hospital, Prithivi Chowk, Pokhara. Patients come to this hospital from various parts of Kaski district and neighboring districts Syangja, Tanahun, Lamjung, Gorkha, Parbat, Baglung, Myagdi and from Palpa as well. The data was collected from the records of patients admitted in pediatric ward of the hospital over one year (January 2011 - December 2011). The patients were admitted through emergency and outpatient departments of the hospital. The details of each case were taken from patients' case records. Name, age, sex, address, date of admission, hospital stay and diagnosis were recorded from the record sheet. Diagnosis was made as per International classification of diseases. Pediatric patients up to age fourteen years were included in the study. Admitted neonates up to twenty eight days of life were not included in the study. The data was entered in a computer database and analyzed using excel.

## RESULTS

A total no of 1091 patients were admitted during the study period. Males were 686 (63%) and females were 405 (37%) as shown in figure 1.

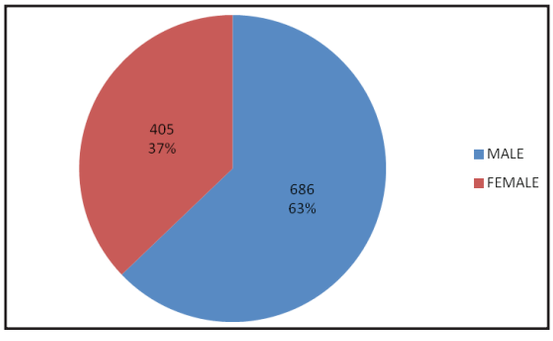


Fig 1: Gender distribution of patients

Less than five years age group accounted for 712 (65.26%) excluding the neonates (Fig 2).

As shown in Figure 3, respiratory tract infections were the commonest cause of admissions in hospital followed by gastrointestinal diseases in all age groups. Respiratory infections were 371 (34%), gastrointestinal including diarrheal diseases were 272 (25%). Acute gastroenteritis comprised of 148 (13.56%), enteric fever 99 (9.07%), and other gastrointestinal diseases about 25 (2.5%) of the total admissions. Around 59% of admissions were due to gastrointestinal and respiratory causes. Diseases other than respiratory and gastrointestinal diseases comprised 448 (41%) amongst the total admissions.

Among other diseases, renal and urinary tract disease were 121 (11.09%), out of which 103 (9.44% of total admission and around 85% of renal and urinary tract diseases) were urinary tract infections (UTI), 16 (13.22%) were acute glomerulonephritis (AGN) and 2 (1.65%) were nephrotic syndrome (NS). Central nervous system (CNS) cases were 114 (10.45%) of total admissions out of which 2 (1.75%) were meningitis. 54 (47.37%), 39 (34.21%), 19 (16.67) of total CNS cases were febrile convulsions, seizure disorder and neurocysticercosis respectively. There were 8 cases of cardiovascular system (CVS) (0.7% of total admissions), 6 (75%) of the CVS cases were rheumatic heart diseases. Other cases were 205 (18.79%) of total admissions.

Highest number of admissions was in the months of August and September and lowest admissions were in the months of November 40 (3.67%) and December 50 (4.58%) as seen in Figure 4.

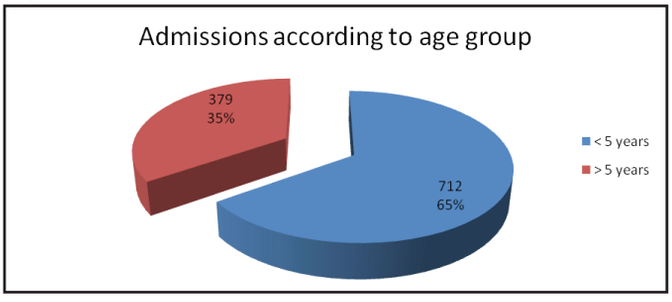


Fig 2: Total number of admissions according to age group

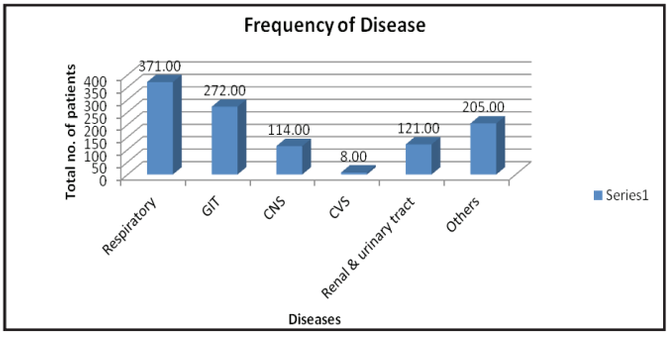


Fig 3: Showing System wise Frequency of Diseases

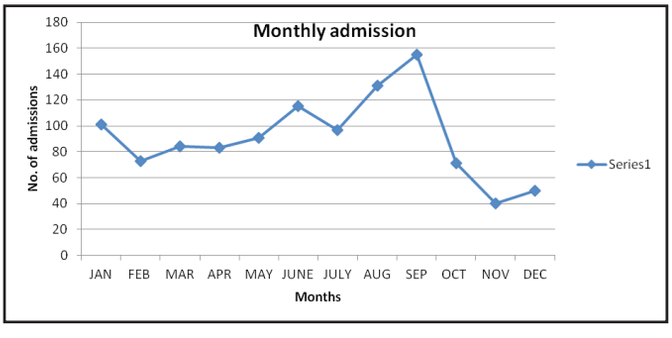

Fig 4: Line diagram showing seasonal trend in admissions (Total)

The highest number 92 (24.8%) of respiratory diseases were admitted in September as shown in figure 5 below.

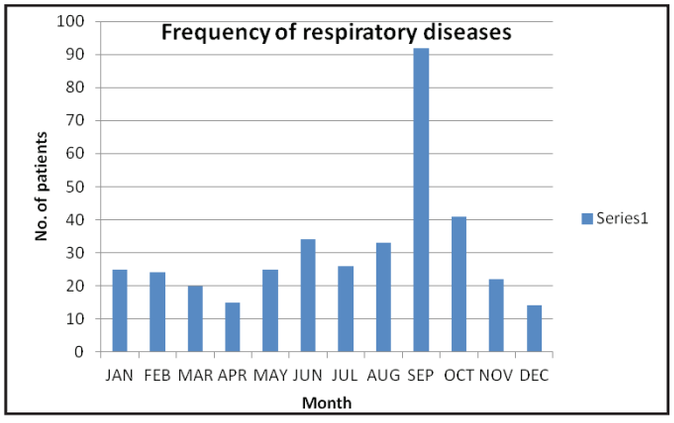


Fig 5: Graph showing frequency of respiratory diseases

More than 55% cases of total diarrheal diseases were admitted in the months January to April. Minimum hospital stay of the patient was one day and maximum was 15 days with mean 4.5 days. As depicted in Table 1, majority patients stayed in hospital for 5 days followed by 1-3 days.

Geographically maximum number of patients came from Kaski district 516 (47.3%) followed by Syangja, Tanahun, Parbat and others. Pokhara, being a tourist place, few foreigners and patients from Kathmandu were also admitted with respiratory and diarrheal problems.

Table 1: Showing days of stay in Hospital .

| Duration of hospital stay (days) | No. of patients |
|---|---|
| 1-3 | 326 |
| 4 | 139 |
| 5 | 353 |
| 6+ | 273 |

## DISCUSSION

### Age and sex distribution

In the study period, among 1091 admitted children, 686 (63%) were males and 405 (37%) were females. The male and female ratio was 1.69, higher than 1.455 and 1.436 that was obtained in the study conducted among 977 and 453 patients in Lumbini Zonal Hospital and Nepal Medical College and Teaching Hospital respectively. The male and female ratio was comparable to 1.677 and 1.788 that was obtained in the study conducted among 761 and 312 patients in Kathmandu Medical College Teaching hospital (KMCTH) and Dhulikhel Hospital (Kathmandu University Teaching Hospital) respectively; lower than (2.6)[9] that was obtained in the study conducted on 9205 patients in pediatric emergency unit in Chandigarh hospital, India. Whatever may be the male and female ratio observed in different hospitals in different places, it was found that less number of female children was admitted in the hospital. This may be due to the parents' preferences to bring them to hospital on boys over girls.

Less than five years age patients admitted in the pediatric ward were 712 (65.26%) of the total number of admissions which is comparable to study done in Kathmandu Medical College[7] and Lumbini Zonal Hospital[5] but is more than the number in a study done in Nepal Medical College[6]. The least number of admitted patients were with the age of more than 12 years.

### Pattern of Disease

In this study, 371 (34%) diseases comprised of respiratory tract infections including pneumonia, acute bronchiolitis and asthma. Acute gastroenteritis comprised of 148 (13.56%). Few other studies[5-7,9-13] showed similar findings with respiratory and diarrheal diseases on top of the morbidity list.

Tuberculosis comprised of 7 (0.64%) of the admitted cases that was significantly less than (4.5%)[5], (4.1%)[6], (2.4%)[7] and (3.2%)[8] in the studies done in Lumbini Zonal Hospital, Nepal Medical College, Kathmandu Medical College, and in Dhulikhel Hospital respectively. These figures were statistically low in all studies in our country as compared to the study done by Murray CJ[14] which vary between 15% in developing countries and below 5% in the United States and European Countries. The low incidence in our studies could be due to difficulty in estimating the TB burden in children. Challenges for doing so include difficulties in establishing a definitive diagnosis, the increased presence of extra pulmonary disease in young children, the lack of standard definition, and the low priority on the public health agenda compared to adult TB[15]. Lack of education, poor socioeconomic status, lack of health awareness and the belief in traditional healers were the reasons for late presentation contributing to the morbidity and mortality due to the diseases. Particularly very low incidence of tuberculosis in our hospital might be due to patients attending to Western Regional Hospital nearby our hospital where DOTS facility is available.

Febrile convulsions were seen in 4.94% of total cases and 54 (47.37%) of the CNS diseases which was comparable to the study conducted in Lumbini Zonal Hospital (52%)[5], KMCTH (50%)[7] and Dhulikhel Hospital (48.27%)[8] but less than in Nepal Medical College (60%)[6]. Worldwide cumulative incidence of febrile convulsions among children ranges from about 1% in China to more than 8% in Japan[16]. Of the total CNS cases 39 (34.21%) and 19 (16.67%) cases were seizure disorder and neurocysticercosis respectively. Cases of neurocysticercosis were comparatively high in our study than studies done in other parts of Nepal[5-8]. More than 50% of the neurocysticercosis cases were from different parts of Kaski and Tanahun district. Further study should be done for the high incidence of

neurocysticercosis in Kaski and neighboring districts. Only 2 cases of meningitis were seen.

Out of 121 (11.09%) renal and urinary tract diseases, 103 (85.12%) cases were UTI and 18 (14.88%) cases were renal diseases, out of which 16 (88.89%) of renal diseases were nephritic syndrome and 2 (11.11%) were nephrotic syndrome. The low incidence of childhood renal diseases in our study could be because renal diseases in children are commonly associated with few or no symptoms[24].

Out of 8 (0.73%) cardiac patients, 2 (25%) cases were VSD and 6 (75%) cases of acute rheumatic fever were also admitted out of which 1 case presented with only chorea as the sole manifestation of acute rheumatic fever. Majority of the cardiac patients were of rheumatic origin and this is attributed to the poor socioeconomic status leading to unhygienic living conditions and overcrowded households that predisposes to the spread of streptococcal infections and poor and under-nutrition of our patients that alter the immunological response in increasing the susceptibility to infections.

Other cases included poisoning (OP, kerosene, CO and some unknown), 2 cases of ITP, 3 cases of HSP, 2 cases of congenital hypothyroidism, 3 cases of wasp bite etc. unlike Lumbini zonal hospital cases of regional diseases like snake bite, malaria and dengue were not seen in our study period[5].

Among the respiratory cases, most were pneumonia followed by acute bronchiolitis. Acute bronchiolitis were admitted mainly during the winter season, this might have been due to seasonal outbreak of respiratory viral infection particularly respiratory syncytial virus and influenza viruses[18]. Diarrheal diseases were mostly seen during rainy season as found in other study in Varanasi, India[13].

**Days of Stay in Hospital**

In the study period, it was seen that maximum number of patients, 353 (32.35%) stayed for 5 days followed by 326 (29.89%) stayed for less than 4 days. 139 (12.74%) patients stayed for 4 days and 272 (25.02%) patients stayed for 6 days and more (Table 1). Patients with complications of pneumonia, meningitis, and nephritic syndrome were found to have longer duration of stay.

**Geographic Distribution of In-Patient Admissions**

In the study period, the maximum number of patients came from Kaski district 516 (47.29%) followed by neighboring districts namely Syangja, Tanahun, Parbat, Baglung and others.

**Monthly Admissions**

In the study period, the highest number of admissions was in the months of June to September. This may be because of increased number of diarrheal and respiratory diseases during this hot and rainy season. The number of admissions was lowest in November/December corresponding to cold season. The highest number of admissions during hot and rainy seasons was seen in the study done in Lumbini zonal hospital[5], Nepal Medical College[6], Kathmandu medical college[7] and Dhulikhel hospital[8].

World Health Organization (WHO) had started Integrated Management of Childhood Illnesses (IMCI) strategy to address diagnosis, management and preventive aspects of major killer diseases in under five children in 1992[20] which helped reducing under-five mortality worldwide, including diarrhea and pneumonia related deaths. The number of under-five deaths worldwide has declined from more than 12 million in 1990 to 7.6 million in 2010[21] due to community level interventions including IMCI.

Nepal Government began National Control of Diarrheal Diseases (CDD) program in 1983 and National Control of Acute Respiratory Illnesses (ARI) program in 1987 which were later merged with IMCI strategy from 1995 and gradually expanded throughout the country[22].

Although pneumonia and diarrhea related deaths have been decreased significantly over the last few years causing decrease in under- five mortality from 87 in 1996 to 54 in 2011 in Nepal[2], it is still high as compared to developed countries like Sweden and Finland who have three per thousand under five mortality[1].

Acute respiratory illnesses are high in developed countries as well but pneumonia needing admissions is less there as compared to ours. This could be due to overcrowding in our families, use of firewood in cooking and poor hygienic conditions of the rural families causing secondary bacterial infections. High number of diarrhea morbidity and admissions in hospitals could be due to contaminated water, as only 46% of households in urban areas and 13% in rural areas treat drinking water[2]; unhygienic practices in food preparations and poor excreta disposal causing water and food material contamination, as only two in five households (38%) have an improved (not shared) toilet facility and 36% of households still use a bush or open field for defecation[2].

In cities, contamination of water supply system with water carriage system could be the cause for more incidences. Similarly hepatitis and enteric fever cases are due to poor hygiene, food and water contamination.

## CONCLUSIONS

Children under five being the most common age group amongst all, with infection being the most predominant cause of pediatric morbidity related to poor hygiene, contaminated foods and water, overcrowding and poor health education of the people and community health interventions including IMCI should be strengthened further to reduce hospital admissions and mortality. Further study should be done for the high prevalence

of neurocysticercosis in Kaski and neighboring districts.

## REFERENCES


1. Bonita F, Stanton, Richard E, Behrman. Overview of Pediatrics: In Kliegman RM, Behrman RE, Schor NF, St. Geme III JW and Stanton BF. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: W.B. Saunders Company, 2011; 1-13.
2. Ministry of Health and Population (MOHP) [Nepal], New ERA, and ICF International Inc. 2012. Nepal Demographic and Health Survey 2011. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland.
3. WHO. Child health epidemiology. [Homepage on the internet]. c2012 [updated 2012; cited 2012 May 5]. Available from http://www.who.int/maternal_child_adolescent/epidemiology/ child/en/index.html. Accessed 12th September 2012.
4. WHO. World Health Statistics. 2011; 14-19.
5. Paudel KM, Sharma S. Review of Pediatrics Inpatient at a Zonal Hospital. *J Nepal Paedtr Soc*. 2012; 32 (3): 239-244.
6. Upadhyay S, Sharma A, Rijal P, Shrestha S. Review of Pediatrics In-Patient at Nepal Medical College and Teaching Hospital. *J Nepal Paedtr Soc*. 2011; 31(1): 25-29.
7. Bajracharya BL, Joshi P, Manandhar DS, Baral MR. Review of Pediatrics Inpatient at Kathmandu Medical College. *J Kathmandu Med Col*. 2002; 4: 43-49.
8. Nepali N, Ghimire R, Shrestha RPBS. Review of Pediatrics Inpatient at Dulikhel Hospital, Kathmandu University Teaching Hospital. *J Nepal Paedtr Soc*. 2007; 26: 16-19.
9. Salaria M, Singhi S. Profile of patients attending pediatric Emergency service at Chandigarh. *Indian J Pediatr*. 2003; 70 (8): 621-24.
10. Singhi S, Jain V, Gupta G. Pediatric emergencies at a tertiary care hospital in India. *J Trop Pediatr*. 2003; 49(4): 207-11.
11. Garg P. Pediatric Hospitalizations at two different setting Community Hospitals in North India: Implications for Regionalization of Care. *Indian J Pediatr*. 2009; 76(7): 711-16.
12. Abdullah HB, Rahman M, Zaman K, *et al*. A Population-based Study of hospital admission incidence rate and bacterial etiology of acute lower respiratory infections in children aged less than five years in Bangladesh. *J Health Popul Nutr*. 2007; 25(2): 179-188.
13. Mohapatra SC, Mohapatra P, Singh IJ, Gaur SD. Epidemiology of gastrointestinal and respiratory tract disease in rural areas of Varanasi (India). *Eur J of Epid*. 1989; 5(1): 117-22.
14. Murray CJ, Styblo K, Rouillon A. TB in developing countries: burden, intervention and cost. *Bull Int Union Tuberc Lung Dis*. 1990; 65(1): 6-24.
15. Cooreman E. Global epidemiology of Pediatric Tuberculosis. In: Seth V, Kabra SK. Essentials of Tuberculosis in children, 3rd Ed. Jaypee, 2006; 11.
16. Hauser WA, The prevalence and incidence of convulsive disorder in children. Available on http://www.ncbi.nlm.nih.gov/ pubmed/8275976. Accessed on 27th September 2012.
17. Tandon R. Rheumatic Heart Disease. In: Ghai O.P, Gupta P, Paul V.K, Essential Pediatrics, 6th Ed, New Delhi, CBS publishers, 2004; 375.
18. Chew FT, Doraisingham S, Ling AE, Kumarrasingha G, Lee BW. Seasonal trends of viral respiratory tract Infection in the tropics. *Epidemiol Infect*. 1998; 121: 121-28.
19. Sheikh A, Khan A, Malik T, Fisher-Hoch SP. Cholera In Developing Megacity, Karachi, Pakistan. *Epidemiol Infect*. 1997; 119(3): 287-92.
20. WHO. WHO/UNICEF Strategy of integrated management of childhood illnesses (IMCI) [homepage on the internet]. c2012 [updated 2007; cited 2012 May 5]. Available from http://www.icatt-training.org/IMCI/About IMCI/tabid/84/Default.aspx. Accessed 15th Sept 2012.
21. UNICEF. Levels and trends in child mortality, Report. 2011; 1.
22. Child Health Division, Department of Health Services, Ministry of Health. Diarrheal diseases; Acute respiratory infections and Integrated management of childhood illnesses. In: The Child Health Profile of Nepal. Kathmandu 2003; 54: 35-42.
23. Annual Report. Department of Health Services, Ministry of Health and population, Government of Nepal 1995/1996, 2010/2011.
24. Michael IO, Ofi li AN. Childhood renal diseases in Benin-City: Assessment of knowledge and practices among general medical practitioners. *Tropical J Health Sci*. 2005; 12(1): 31-35.

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# Nature of Domestic Violence in Female Patients Attending Emergency Care at Gandaki Medical College

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**Key words**:
Domestic violence,
Injuries,
Bruises,
Punches.

## ABSTRACT

**Objectives:** To describe the nature of domestic violence in female patients attending emergency department at Gandaki Medical College.

**Methods:** A hospital based cross-sectional descriptive study conducted by extracting data from register of the emergency department of Gandaki Medical College (Charak) hospital, Pokhara, Nepal in one year period from April 2011 to March 2012.

**Results:** Total female patients in one year period attending emergency department was 5236. Of the total sample, female trauma patients in emergency were 938 and assaulted patients in emergency were 46. Husband was mostly responsible for violence in majority of cases and some women reported the involvement of in-laws.

**Conclusions:** Injuries from physical assaults occurred in all age groups but most commonly affecting the young females and majority of them were in the productive age group. This underlies the importance of problem and need to address it. Health services organizations should establish measures to improve quality of care for victims.

## INTRODUCTION

Crimes of violence are becoming more prevalent in Nepal.

Domestic violence is a serious public health issue affecting untold numbers of women worldwide. Domestic violence also known as intimate partner violence (IPV) is one of the leading causes of serious injury among women of childbearing age[1].

In this paper, domestic violence (DV) is defined as illness or injury resulting not only from the deliberate actions of an intimate partner but also from others members of family.

Universal screening for intimate partner violence in the emergency department has been advocated by many medical institutions. Policies implemented for IPV screening have met with numerous obstacles. One such obstacle is the perception by emergency personnel that patients might be offended by such screening if they presented to emergency department (ED) for problems unrelated to trauma[2] like sexual and psychological abuse.

An audit of assault victims attending the emergency department of Gandaki Medical College was conducted to assess the prevalence and nature of assault and other related issues of various forms of domestic violence against women of this region.

Given the high prevalence of domestic violence and its associated health sequelae, it is not surprising that governmental organizations and medical governing bodies and colleges have repeatedly called for the development of domestic violence related policies and protocols and additional training and

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education for healthcare professionals. As a result, a number of education and training initiatives for medical students, residents and practitioners have been developed[3-5].

## METHODS

In our study, we included all the domestic violence patients attending the emergency department of Gandaki Medical College (Charak) Hospital, Pokhara, Nepal in one year period from April 2011 to March 2012.

Doctors were involved in interviewing and examining the assault victims. Each doctor incorporated the interview into the routine of taking a history and clinical examination. The doctors then recorded the findings on a proforma. Every patient was informed about the study. Women were asked whether their husband or any other family members committed violence against them. Exclusionary criteria were life threatening injury or inability to understand language or inability to give oral informed consent or to be questioned without family members.

## RESULTS

Total number of patients was 5236 in one year study period from April 2011 to March 2012. Of the total sample, trauma patients in emergency was 938 and assaulted patients was 46 (Fig 1). The most commonly involved age group in females was 20-30 years (Fig 2).

In our study, in females, assaults were inflicted mostly by husbands (59%) under the influence of alcohol then followed by relatives (in-laws) (Fig 3). Others include strangers and boy friends in cases of females. A victim was most likely to have been assaulted between 7 PM to 12 AM midnight (Fig 4).

Women were more likely to be attacked in their homes (Table 1). One elderly mother has chopped off her chin by her own son under the influence of marijuana.

Physical assaults without weapon (fists and feet) were used in 40% of attacks, sticks in 33%, knives and other sharp blades in 20%, miscellaneous objects were used in 7% (Fig 5).

Most victims, the nature of the injuries was accurately recorded had only a single injury, 28% a double injury. Soft tissue injury was the most (55%) frequently recorded injury, bruise, hematoma, abrasion was second (30%) most frequently recorded injury, laceration accounted for 12% of injuries, fracture in 3% of cases (Fig 6).

In females, head injuries were present in 17 cases, 10 cases of back, 4 injuries to the pelvis, 4 injuries to the abdomen, 4 injuries to the upper limbs, 3 injuries to the chest, 2 injuries to lower limbs, 1 injury to the nose, 1 injury to the orbit (Fig 7).

In females, 21 patients discharged on the same day, 15 patients were admitted to the hospital and 10 cases were referred to other hospital (Fig 8).

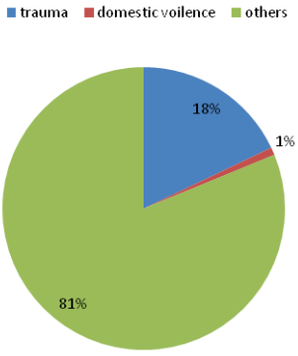


Fig 1: Total female patients attending Emergency department

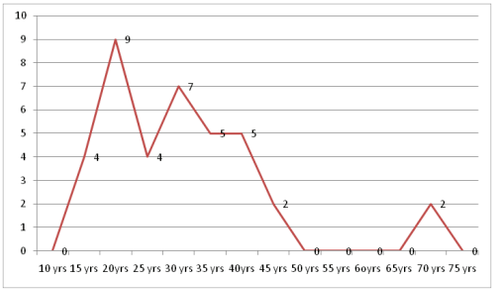


Fig 2: Age group of assailants

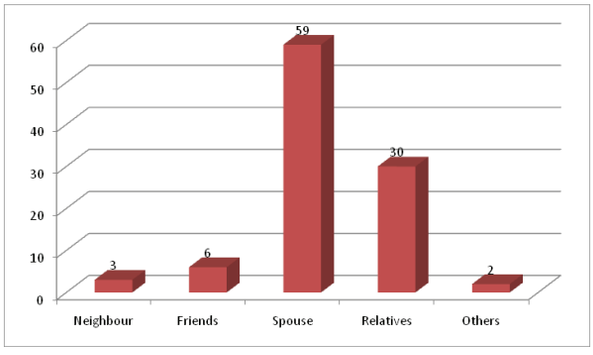


Fig 3: Type of assailants (in %)

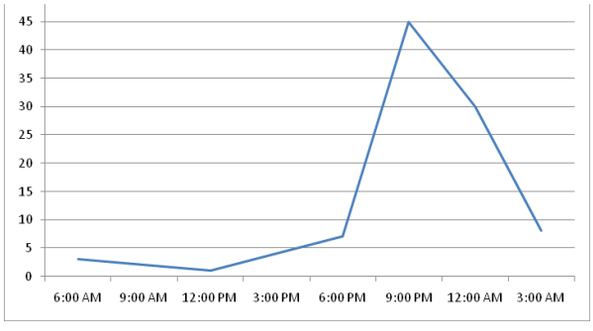


Fig 4: Time of physical assault

Table 1: Location of physical assaults

| Location of Assault | Female |
|---|---|
| Street (Public Place) | 5% |
| Home | 80% |
| Work | 4% |
| Other (park, club) | 11% |

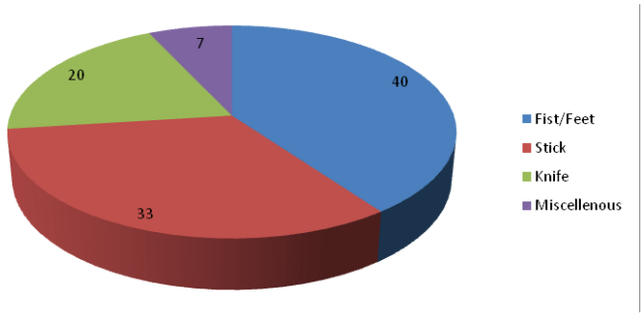


Fig 5: Weapons used in assault (in %)

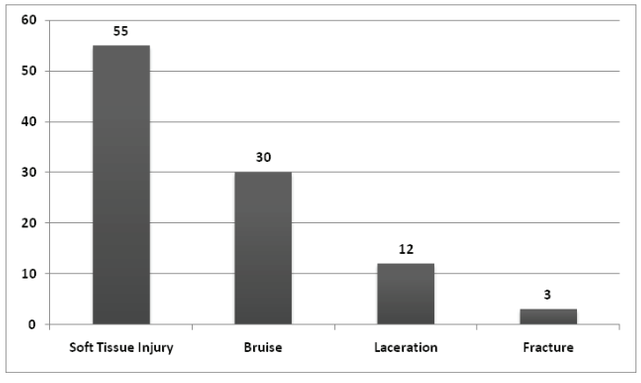


Fig 6: Type of injuries (in %)

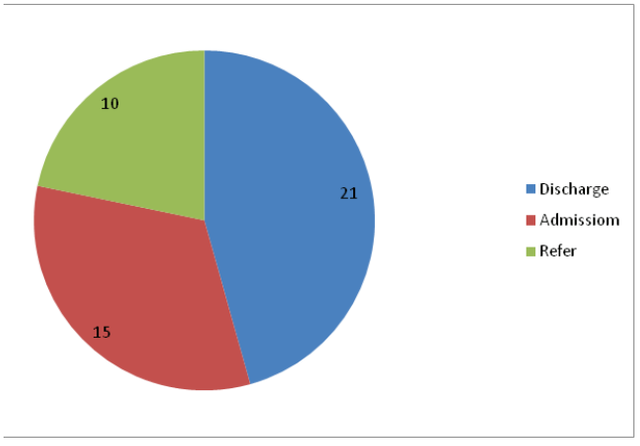


Fig 7: treatment given to victims

## DISCUSSION

The study was intended to obtain an impression of the circumstances that Pokhara has seen recently in crimes involving physical assaults to female patients.

Domestic violence is increasingly being recognized as a public health problem that has long term human and economic costs[6].

An increasing amount of research is beginning to offer a global picture of the extent of violence. The magnitude, nature and health impact of violence differ greatly for men and women. Men and women's respective experiences of violence are characterized by widely differing power and gender relations, inherent in the different settings, contexts, mechanisms and perpetrators of violence[7,8].

Most violence experienced by women is perpetrated by men and primarily occurs in public places. Violence usually occurs as isolated incidents, rather than repeated ongoing abuse[9,10].

Violence against women has been distinguished from other forms of violence as 'gender based violence' rooted in gender inequality and the perpetuation of male power and control[11]. WHO estimates that at least one in five women has been physically assaulted by a man at sometime in their life[8]. Interpersonal violence against women is primarily perpetrated by a male intimate partner and occurs within the confines of the home[7,13]. The violence is hidden from public view and when it becomes visible, it is often dismissed as a private, family affair[14]. Intimate partner violence is often repeated, continuous and used as a means to control the woman's actions and behavior. The physical abuse coupled with social and economic inequalities often render the woman "powerless" and dependent and the male abuser powerful. Women in violent relationships may also have responsibility for children, which may further prevent them from leaving their abuser[15].

Alcohol is a major contributor to assault. The public are well aware of the rise in violence within our society although they often have incorrect perception regarding the etiology of violence.

All risk groups need to be targeted for education, most of the victims of assault are young people. If a program of education was established in secondary schools this would give health professionals the opportunity to get some very important message across to young people regarding alcohol, drugs, violence.

If we are concerned about a friend and their explanation do not fit the injury or if a pattern of injury is evident, you should expect physical abuse might be a possibility.

Warning signs and symptoms of physical marks are pushing, pulling, slapping, and striking with an object. Excessive pinching on the body, tripping, kneeing, strangling, head butting, drowning sleep deprivation, exposure to cold, freezing, exposure to heat or radiation, burning, exposure to electric shock, placing in stress positions (tied or otherwise forced) cutting or otherwise exposing somebody to something sharp, exposure to a dangerous animal throwing or shooting a projectile, causing impairment of sight biting, exposure to stinking body odors, releasing bodily fluids spitting, vomiting,

urinating, bleeding etc.,[17,18].

Other well documented majority of injuries by fists and feet. Howe A, Crilly M[9] had documented time of assaults was at weekend and night[19].

Sometimes adults who are abused feel like committing suicide, have abnormal eating behaviors, and feel anger and rage, avoid social contact. Physical abuse has many effects, lack of empathy for others, poor performance, low self esteem, depression, aggressiveness, high level of anxiety[20].

There are many factors that contribute to domestic violence. Common factors that are likely to cause domestic violence are social isolation, family pressure, and alcohol and drug abuse.

It is so important to realize that this is NOT your fault; It is NOT ok that this is not happening to you or someone you know. Abusing is illegal. Do NOT blame yourself and do NOT let it go unnoticed[20].

## CONCLUSIONS

Injuries from physical assaults occurred in all age groups but most commonly affecting the young females and majority of them were in the productive age group. This underlies the importance of problem and need to address it. Health services organizations should establish measures to improve quality of care for victims. There are well developed guidelines for the identification, screening, treatment and prevention of domestic violence. It is possible for domestic violence questionnaires to be implemented in emergency department of teaching hospital.

## REFERENCES


1. Mason R, Schwartz B, Burges R, Irwin E. A resource for victims of domestic violence. *Emerg Med*. 2010; 27: 561-564.
2. Hurley K F, Brown-Maher T, Campbell SG, Wallace T, Venugopal R. Emergency department patients' opinions of screening for intimate partner violence among women. *Emerg Med J*. 2005; 22(2): 97-98.
3. Hendricks MM. A survey of family-violence curricula in Virginia medical schools and residencies at university medical centers. *Acad Med*. 1997; 72: 54–6.
4. Kripke EN, Steele G, O'Biren MK, *et al*. Domestic violence training program for residents. *J Gen Intern Med*. 1998; 13: 839–41.
5. Alpert EJ, Albright C, Webb S. Massachusetts medical society seminar series on domestic violence. *Acad Med*. 1999; 74: 589–90.
6. Watts C, Zimmermann C. Violence against women: global scope and magnitude. *Lancet.* 2002; 359: 1232–7.
7. Dobash RE, Dobash R. Violence against wives: a case against the patriarchy. London: Open Books, 1980.
8. Buss DM, Malamuth NM. Sex, power, conflict: evolutionary and feminist perspectives. Oxford: Oxford University Press, 1996.
9. Jewkes R. Violence against women: an emerging health problem. *Int Clin Psychopharmacol*. 2000; 15: S37–45.
10. Christensen E, Koch-Nielsen I. Vold ude og hjemme. [Violence in public and at home]. Copenhagen: Reproset, Oct 1992.
11. United Nations Female Population Fund (UNFPA). Promoting gender equality. http://www.unfpa.org/gender/violence.htm (accessed 1 May 2003).
12. World Health Organization. Violence against women. Geneva: WHO/FRD/WHD, 1998.
13. Jewkes R. Intimate partner violence: causes and prevention. *Lancet*. 2002; 359: 1423–9.
14. Bograd M. Feminist perspectives on wife abuse. An introduction. In: Yllö K, Borgrad M, eds. Feminist perspectives on wife abuse. Newbury Park: Sage, 1980.
15. Lees S. Carnal knowledge: rape on trial. London: H Hamilton, 1996.
16. Wright J, Kariya A. Assault patients attending a Scottish accident and Emergency department. *J R Soc Med*. 1997; 90: 322–6.
17. Norway: Treatment Program for Men Who Batter (Haugan, Grethemor Skagseth and Nøttestad, Jim Aage. Norwegian University of Science and Technology. Trondheim, Norway).
18. Child Abuse & Neglect: Physical Abuse (Giardino, Angelo P., Eileen R Giardino. 12 December 2008. eMedicine. WebMD).
19. John Wright MRCP FRCS, Ash Kariya MRCGP DRCOG, Assault patients attending a Scottish accident and emergency department, *J R SOC Med.* 1997; 90: 322-326.
20. Shepherd J. Violent crime in Bristol: an accident and emergency department perspective. *Br J Criminol*. 1990; 30: 289–305.
21. Howe A, Crilly M, Identification and characteristics of victim of violence identified by emergency physician triage nurses and the police. *Injury Prevent*. 2002; 8: 321-323.

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# The Relationship Between Hypertension, Dyslipidemia and Salt Sensivity Test in Hypertensive and Diabetic Type-2 Patients.

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**Key words**:
Hypertension,
Diabetic type-2,
Dyslipidemia.

## ABSTRACT

**Objectives:** To study the relationship between hypertension and dyslipidemia and salt sensivity test in hypertensive and diabetic type-2 patients.

**Methods:** This was a hospital based study that involved 200 subjects with hypertension and diabetic type-2 patients. The duration of the study was of 3 months from December 2011-February 2012. The detail biochemical blood investigations was carried out at Gandaki Medical College.

**Results:** Patients suffering from hypertension and diabetic type-2 showed increased the level of LDL-cholesterol, triglyceride and total cholesterol as well as decreased the salt sensitivity compaired with normotensive individuals.

**Conclusions:** Long standing hypertensive and diabetic type-2 patients relatively higher prevalence of dyslipidemia and decreased the salt sensitivity which influences on the progression the risk of stroke and cardiovascular diseases.

## INTRODUCTION

Hypertension and diabetic type-2 is a condition that affects many people in Nepal and is an important risk factor for cardiovascular disease[1]. Although several risk factors for the development of hypertension and diabetic type-2 has been identified, its etiology is still not fully understood. Hypertension and diabetic type-2 is commonly associated with other cardiovascular risk factors, such as obesity, sedantary life style, 1st degree CAD, smoking and dyslipidemia. The presence of these cardiovascular risk factors and the resulting endothelial dysfunction may play a role in the pathophysiology of hypertension[3].

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Dyslipidemia, a strong predictor of cardiovascular disease, cause endothelial damage may became manifested as increased blood pressure[6]. Therefore factors like dyslipidemia[7] that cause endothelial dysfunction may lead to hypertension. A few studies have prospectively showed that the relationship between plasma lipids and hypertension, finding that there is an association between plasma lipids and development of hypertension. Small trials have looked at the effect of lipid lowering on blood pressure. Additional prospective data on the association of lipids with hypertension will help us clarify the relationship. Whether for, prospectively examined whether total cholesterol (TC), triglyceride, HDL and LDL cholesterol are associated with the risk of developing hypertension as well as decrease the salt sensitivity in long standing diabetes type-2[7].

## METHODS

This was a cross-sectional study carried out in the OPD, in the Department of Medicine, Gandaki Medical College and Research Center, Pokhara. This study was done from December 2011 to April 2012. The study consisted of 200 hypertensive and

diabetic type-2 patients (221 males and 79 females) between the age of 30 to 80. All the participants were asked baseline blood samples for the lipid profile measurements (fasting).

We collected potential baseline risk factors that may be confunders, such as age (years), body mass index (kg/m$^2$), smoking status, alcohol consumption, exercise, hypertension and diabetes. Among the 200 hypertensive and diabetic type-2 patients with available TC, HDL and LDL cholesterol, systolic blood pressure >140mm of Hg and diastolic blood pressure of >90mm of Hg.

For a subject to develop hypertension and diabetic type-2 during OPD, subject must have initiated treatment for hypertension, diabetes had a SBP >140mm of Hg or had a DBP >90mm of Hg. The diagnosis of incident hypertension and diabetes was based on self reported treatment and some are newly diagnosed provided by subjects.

To examine the role of baseline blood pressure on the association between lipids and hypertension, we used according to the JNC-7 definition of hypertension[2].

Fig1: Relationship between dyslipidemia and hypertension

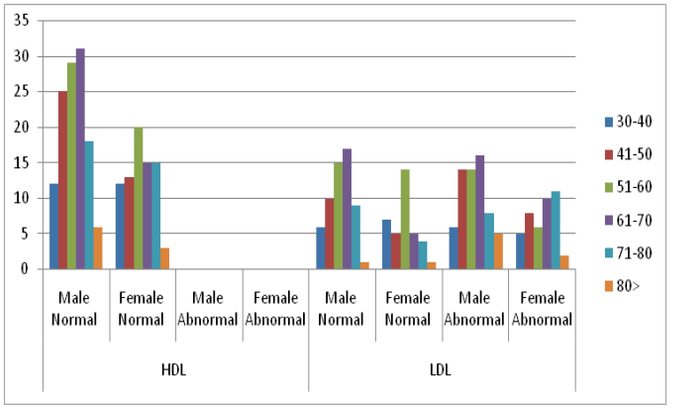


Table 1: Age group and duration of hypertension and type-2 diabetes

| age group/ time period | <1 month | | 1mth- 1 year | | 1 year – 5 year | | 6-10 year | | 11-15 year | | 16-20 year | | >20 yera | | total | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | m | f | m | f | m | f | m | f | m | f | m | f | m | f | | |
| 30-40 | 5 | 3 | 2 | 6 | 3 | 2 | 0 | 1 | 1 | - | - | - | - | - | 23 | 11.5 |
| 41-50 | 3 | 1 | 6 | 4 | 8 | 6 | 5 | 1 | 1 | 1 | 2 | - | - | - | 38 | 19 |
| 51-60 | 5 | 2 | 7 | 10 | 13 | 8 | 2 | 5 | 3 | 1 | 1 | - | - | - | 57 | 28.5 |
| 61-70 | 2 | 1 | 6 | 4 | 16 | 9 | 3 | - | 1 | 1 | - | - | - | - | 43 | 21.5 |
| (71-80 | - | 1 | 6 | 3 | 5 | 3 | 6 | 2 | 2 | 2 | - | 1 | 1 | - | 32 | 16 |
| >80 | - | - | 1 | 1 | 1 | 1 | 1 | - | 3 | - | - | - | - | - | 8 | 4 |

Table 2: Salt sensitivity concentration tests

| | 0.08 | | 0.16 | | 0.32 | | 0.64 | | 1.28 | | total | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | male | female | male | female | male | female | male | female | male | female | | |
| 30-40 | | | 1 | | 3 | 7 | 9 | 3 | | 1 | 24 | 12 |
| 41-50 | | | 1 | | 9 | 2 | 15 | 8 | 4 | 1 | 40 | 20 |
| 51-60 | | | | | 6 | 5 | 22 | 10 | 1 | 4 | 49 | 24.5 |
| 61-70 | | | | | 5 | 5 | 17 | 11 | 7 | | 45 | 22.5 |
| 71-80 | | | | | | 2 | 12 | 11 | 5 | 3 | 33 | 16.5 |
| 80> | | | | | 1 | 1 | 1 | 1 | 4 | 1 | 9 | 4.5 |

## RESULTS

Patients with hypertension and diabetes type-2 showed increased levels of LDL-cholesterol 53% (32% in males and 21% in females), triglycerides-21% (15% males and 6% females) and total cholesterol 1% as well as decreased the salt sensitivity. Adjusting for all of the other variable dyslipidemia[2], our study showed that incidence of hypertension and diabetes increased with men than women. In the age adjusted hypertensive patients, compared with having an increased serum LDL-cholesterol have highest incidence of uncontrolled hypertension (53%) than hyper-triglyceridemia (21%) and decreased the salt sensitivity response[7].

Our study showed that there was increase trend of hypertension and diabetes patients in dyslipidemic patients more in LDL-cholesterol compared with hyper-triglyceridemia. We then categorized the stratification by baseline SBP and DBP, including the JNC-7 definitions prehypertension of 120-139 mm of SBP and 80-89mm of Hg DBP, hypertension stage-I of 140-159mm of Hg and 90-99mm of Hg DBP and hypertension stage-II of >160mm of Hg SBP and 100mm of Hg DBP.

## DISCUSSION

This prospective study demonstrates that hypertensive and diabetic type-2 patients with higher levels of plasma LDL-cholesterol as well as triglyceride are independently associated with a subsequent increased risk of incidence of cardiovascular disease[4] in males as well as female patients. The relationship between dyslipidemia and hypertension and diabetes is preserved even after the exclusion of patients with diabetes and obesity.

Dyslipidemia and hypertension and diabetic type-2 have been associated in several studies. Castell and Anderson found that BP and serum dyslipidemia were strongly correlated among the hypertension and diabetic type-2 patients, which led to early recommendation to treat elevated cholesterol in patients with hypertension and diabetes. Gaziano also noted a potential interaction between dyslipidemia and hypertension and diabetes in the development of myocardial infarction[4,5] that suggested a direct relationship rather than the effect of two independent predictors.

A few smaller studies have looked prospectively at the relationship between serum lipids and hyprtension. San Antonio

Heart Study suggested that risk factors for the development of atherosclerosis, including triglycerides, also predicted hypertension.

We would expect that if dyslipidemia played a role in the development of uncontrolled hypertension, then treating dyslipidemia would have more effect on controlling BP. The investigators demonstrated a significant decrease in BP treated with lipid lowering medication and greatest for those treated a Statin.

The biological mechanisms by which lipids may play a role in the development of hypertension remain poorly understood[6]. Atherogenic lipid abnormalities clearly cause endothelial dysfunction. A dysfunctional indothekkium, possibly though impair nitric oxide production and activity as well as alterations in indothelin-1 and endothelin-A and B receptors expression, cannot respond to changes in inter vascular stimuli and eventually to increase BP. Because atherosclerosis can be a diffuse process, it is possible that hypertension is manifestation of diffuse atherosclerotic process in large conduct arteries, as well as similar resistance vessels. It has been suggested that hypertension and dyslipidemia are associated because they are two components of metabolic syndrome.

Hypertension, which often occurs after other components of the metabolic syndrome, may instead be a late stage manifestation, rising secondary tool derangements of other components of the metabolic syndrome such as dyslipidemia or prospective study finds independent relationships between increase lipid levels and incident hypertension that predates the development of uncontrolled hypertension. This leads support to that hypertension represents in early manifestation of the atherosclerotic process alternatively more research needed to understand the role of hypertension in the development of dyslipidemia. This relationship between a common risk factor arthrosclerosis[4,5], dyslipidemia and hypertension suggest that hypertension may be a manifestation of atherosclerotic process. Currently not enough is known about the cause of hypertension, despite its high prevalence, and more studies are needed to determine whether dyslipidemia actually cause of hypertension. By identifying potential risk factor amenable to intervention, we may eventually be able to reduce the burden of hypertension and subsequent cardiovascular disease.

## REFERENCES


1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA*. 2003; 289: 2560–2571.
2. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA*. 2002; 288: 1882–1888.
3. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities: the role of insulin resistance and the sympathoadrenal system. *N Engl J Med*. 1996; 334: 374–381.
4. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. *Ann Intern Med*. 2003; 139: 761–776.
5. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. *JAMA*. 1987; 257: 2176–2180.
6. Nickenig G, Harrison DG. The AT(1)-type angiotensin receptor in oxidative stress and atherogenesis: Part II: AT(1) receptor regulation. *Circulation*. 2002; 105: 530–536.
7. Giner V, Poch E, Brangulat E, Oriolat J, Gonzales D, Coca A et al. Renin-angiotensin system genetic polymorphisms and salt sensitivity in essential hypertention. *Hypertension*. 2000; 35(2); 515-517.
8. Hiraga H, Oshima T, Watanabe M, Ishida T, Shingu T, et al. Angiotensin I converting gene polymorphism and salt sensitivity in essential hypertention. *Hypertension*. 1996; 27: 569-572.
9. Raij l, Azar S, Keanew F. Role of hypertension in progressive glomrular injury. *Hypertension*. 1985; 7: 398-404.

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# Seroprevalence of Hepatitis B in Bheri Zonal Hospital and Nepalgunj Medical College Teaching Hospital, Nepalgunj

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**Key words**:
Hepatitis B virus (HBV),
Hepatitis B surface antigen (HBsAg),
Nepal.

## ABSTRACT

**Objectives:** To study the number of cases of hepatitis B in different months of the year and their distribution with respect to age and gender among patients visiting Nepalgunj Medical College Teaching Hospital (NGMCTH) and Bheri Zonal Hospital (BZH), the two major hospitals of Mid-western and Far-western regions of Nepal.

**Methods:** 5268 and 2586 blood samples were collected in NGMCTH and BZH respectively during 2009/2010.

**Results:** Of the 5268 samples tested in NGMCTH, 142 samples were found positive for hepatitis B surface antigen (HBsAg); overall prevalence rate being 2.70%. In BZH, of 2586 samples tested, 130 samples were found positive for HBsAg with overall prevalence rate of 5.03%. No seasonal differences were observed in the distribution of HBsAg in both hospitals. Male to female ratio was found to be 238:100 for NGMCTH and 225:100 for BZH suggesting that there was male predominance among cases in both hospitals and the same was maintained in all age groups. Most of the cases were of the age group 21-40 years in both NGMCTH and BZH (64.79% and 61.54% respectively). The average age of cases in NGMCTH was 24.58 years ± 13.00 years while in BZH, average age of cases was found to be 25.81 years ± 13.41 years. On the average, female cases were older than their male counterparts in both NGMCTH (26.84 years ± 12.31 years against 23.58 years ± 13.16 years) and BZH (27.61 years ± 13.64 years against 25.08 years ± 13.25 years).

**Conclusions:** The study shows that prevalence of hepatitis B was found to be high and most commonly observed in young and productive age group males.

## INTRODUCTION

Hepatitis is inflammation of the liver. Viral infection is one of the causes of hepatitis. Hepatitis B Virus (HBV), which is a deoxyribonucleic Acid (DNA) virus, is the cause of hepatitis B. The hepatitis B virus (HBV) lives in blood and other body fluids. HBV is transmitted from person to person through unprotected sexual intercourse with an infected person, or through the sharing of infected needles or other sharp instruments that break the skin. Mother to child transmission during perinatal period has also been reported and preventive measures are recommended during this period. Hepatitis B virus infection can cause several disease conditions including acute hepatitis, chronic hepatitis B, inactive HBsAg carrier state, resolved hepatitis B, acute exacerbation or flare of hepatitis B, reactivation of hepatitis B, cirrhosis of liver and hepatocellular carcinoma.

The burden of Hepatitis B virus (HBV) infection varies widely among different countries with its prevalence ranging from 1 to 20 percent in different parts of the world[1]. HBV presently infects over 2 billion people and there are over 350 million chronic

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carriers worldwide, and is the ninth leading cause of mortality with an estimated over one million deaths per year[2,3,4,5,6]. The prevalence of HBsAg chronic carriers is found to be lowest or decreasing in countries or areas with high standards of living[7]. It is less than 2% in Western Europe, North America and parts of South America and intermediate (2-7%) in Southern and Eastern Europe[8]. The prevalence of chronic HBsAg carriers in countries with lower socio-economic level or developing nations of Asia and Africa is high (more than 8%)[8,9]. This leads to consumption of ample portion of health resources in developing countries being directed towards this particular disease[10]. In the South East Asian Region (SEAR), annually, approximately 14-16 million people are infected with HBV. It is estimated that there are 98 million HBV carriers which is almost 6% of the total population of this region[4,5]. In China, the prevalence of HBV is 20%[11]. In Thailand, it was 10%; in Korea and Bangladesh, it was 9%; in Maldives, Indonesia and Bhutan, it was 6%; in India, it was 5% and in Sri Lanka, it was 1% for the year 2004[11].

In Nepal, the total morbidity due to acute hepatitis by HBV for the year 2004-2005 was 30,071 out of 9,699,858 hospital visits[12]. HBV is a major cause of jaundice in Nepal[13]. A study among the Sherpa community revealed prevalence of HBsAg, anti-HBs (antibody to HBsAg) and anti-HBc (antibody to HBcAg) to be 1.9%, 22.3%, and 24.3%, respectively[14]. HBsAg positivity was found to be 0.45% in a study among voluntary blood donors conducted in the Department of Microbiology, Universal College of Medical Sciences, Bhairahawa, Nepal[15]. In a study of the Nepalese male population inhabiting various districts, HBsAg was found to be positive in 4% of the individuals. The percent positivity of HBsAg was found to increase steadily from the Eastern (2%) to the Far Western (6.2%) development regions. The Kailali district showed a characteristically high prevalence, followed by Rukum and Kaski. Other districts having a high prevalence of HBsAg were Sankhuwasabha, Jhapa, Ramechhap, Sarlahi, Dhanusa, Baglung, Gulmi, Palpa and Dang[16].

HBV infection is common in Nepal but the HBsAg carrier rate is much lower than reported from other Asian countries. HBV infections are not active in Eastern Nepal[17]. Sero-epidemiological studies of Hepatitis B in Nepal have shown HBsAg in 0.9 percent of the population (1.5 per cent in male and 0.5 per cent in female)[18]. In a recent ten year serological survey of hepatitis B virus infections in Nepal showed 1.1% HBsAg positivity[19]. The results showed that Nepal fell in WHO category of intermediate endemicity zone for hepatitis B infection (WHO).

## METHODS

This study involves comparison of frequency and distribution of HBV cases between Nepalgunj Medical College Teaching Hospital (NGMCTH) and Bheri Zonal Hospital (BZH) in Nepalgunj for the fiscal year 2066/67 B.S. (July 16 2009/ July 16, 2010). Diagnosis of chronic HBV infection was made by presence of the hepatitis-B surface antigen (HBsAg). Information on baseline characteristics- age and sex, of all positive cases was tracked and recorded from outpatients and inpatients records of the hospitals for use in the final analysis. Numeric variable in the study was summarized using its mean and is expressed in the format (Mean ± Standard Deviation). For independence of categorical variables Pearson's Chi-square test of independence was performed and confidence intervals were determined by using Student's 't' distribution for numeric variables and by using normal approximation with Wilson calculation method for categorical variables.The statistical analysis of the obtained data was done with IBM SPSS 20 for Microsoft Windows and Microsoft Office Excel 2010 for Windows.

## RESULTS

In NGMCTH, a total of 5268 patients underwent blood test for serological detection of hepatitis B surface antigen (HBsAg) during the study period, among them, 142 subjects were positive. In BZH, HBsAg was found positive in 130 subjects out of 2586 sample tested. The distribution of positive cases in different months of the study period for both the hospitals is shown in Table 1.

Table 1: Monthly distribution of hepatitis B (HBV) in NGMCTH Teaching Hospital and Bheri Zonal Hospital (2009/2010)

| Months | NGMCTH | | | | | BZH | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Samples examined | Positive cases | Prevalence Rate (%) | 95% CI | | Samples examined | Positive cases | Prevalence Rate (%) | 95% CI | |
| | | | | Upper Limit | Lower Limit | | | | Upper Limit | Lower Limit |
| July/August | 446 | 14 | 3.14 | 1.52 | 4.76 | 224 | 15 | 6.70 | 3.42 | 9.97 |
| August/September | 414 | 9 | 2.17 | 0.77 | 3.58 | 179 | 8 | 4.47 | 1.44 | 7.50 |
| September/October | 474 | 11 | 2.32 | 0.97 | 3.68 | 262 | 10 | 3.82 | 1.50 | 6.14 |
| October/November | 337 | 10 | 2.97 | 1.16 | 4.78 | 179 | 9 | 5.03 | 1.83 | 8.23 |
| November/December | 414 | 11 | 2.66 | 1.11 | 4.21 | 189 | 9 | 4.76 | 1.73 | 7.80 |
| December/January | 356 | 6 | 1.69 | 0.35 | 3.02 | 143 | 5 | 3.50 | 0.49 | 6.51 |
| January/February | 414 | 17 | 4.11 | 2.19 | 6.02 | 209 | 15 | 7.18 | 3.68 | 10.68 |
| February/March | 524 | 13 | 2.48 | 1.15 | 3.81 | 255 | 12 | 4.71 | 2.11 | 7.31 |
| March/April | 527 | 13 | 2.47 | 1.14 | 3.79 | 287 | 12 | 4.18 | 1.87 | 6.50 |
| April/May | 442 | 10 | 2.26 | 0.88 | 3.65 | 221 | 9 | 4.07 | 1.47 | 6.68 |
| May/June | 458 | 15 | 3.28 | 1.65 | 4.91 | 233 | 13 | 5.58 | 2.63 | 8.53 |
| June/July | 462 | 13 | 2.81 | 1.31 | 4.32 | 205 | 13 | 6.34 | 3.01 | 9.68 |
| **Total** | **5268** | **142** | **2.70** | **2.26** | **3.13** | **2586** | **130** | **5.03** | **4.18** | **5.87** |

The overall prevalence rate of HBsAg was found to be 2.70% (95% CI: 2.26% - 3.13%) and 5.03% (95% CI: 4.18% - 5.87%) respectively for NGMCTH and BZH. Month-specific prevalence rate of HBsAg, along with 95% confidence interval estimate for both hospitals is also summarized in Table 1 above. Differences in month-specific prevalence rates of HBsAg among different months of the study period was not statistically significant (with p-values > 0.50 for both hospitals) for both the hospitals.

Table 2 summarizes age and gender distribution of HBsAg cases for both hospitals. The overall male to female ratio was 238:100 for NGMCTH and 225:100 for BZH. In both NGMCTH and BZH, for all age-groups, male to female sex ratio was found in favor of males. 74.65% and 75.38% cases of HBsAg were under 40 years of age in NGMCTH and BZH respectively with 64.79% cases and 61.54% cases belonging to 21-40 years age group alone, respectively. Mean age of HBsAg cases was 34.72 years ± 3.89 years for NGMCTH, while for BZH it was 33.73 years ± 4.11 years. This gave 95% confidence interval estimate of 34.07 years to 35.37 years for NGMCTH and 33.02 years

to 34.44 years for BZH (Table 2). Sex specific mean age of HBsAg cases were also determined and are shown in this table along with their 95% CI's.

Table 2: Age and Sex distribution and age-specific mean age of Hepatitis B (HBV) for NGMCTH and BZH (2009/2010)

| Age (years) | NGMCTH | | | | | | BZH | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male | % | Female | % | Total | % | Male | % | Female | % | Total | % |
| 0 to 20 | 9 | 64.29 | 5 | 35.71 | 14 | 9.86 | 12 | 66.67 | 6 | 33.33 | 18 | 13.85 |
| 21 to 40 | 67 | 72.83 | 25 | 27.17 | 92 | 64.79 | 57 | 71.25 | 23 | 28.75 | 80 | 61.54 |
| 41 to 60 | 19 | 67.86 | 9 | 32.14 | 28 | 19.72 | 17 | 68.00 | 8 | 32.00 | 25 | 19.23 |
| 61 to 80 | 5 | 62.50 | 3 | 37.50 | 8 | 5.63 | 4 | 57.14 | 3 | 42.86 | 7 | 5.38 |
| Total | 100 | 70.42 | 42 | 29.58 | 142 | 100 | 90 | 69.23 | 40 | 30.77 | 130 | 100 |

| Statistics | Male | Female | Total | Male | Female | Total |
|---|---|---|---|---|---|---|
| Mean ± Standard deviation | 34.50 ± 4.65 | 35.26 ± 7.17 | 34.72 ± 3.89 | 33.38 ± 4.97 | 34.50 ± 7.41 | 33.73 ± 4.11 |
| 95% Confidence interval of mean | 33.58 to 35.42 | 33.03 to 37.49 | 34.07 to 35.37 | 32.34 to 34.42 | 32.13 to 36.87 | 33.02 to 34.44 |

## DISCUSSION

Prevalence of hepatitis B varies from country to country and depends upon a complex mix of behavioral, environmental and host factors. In general, it is lowest in countries or areas with high standards of living (e.g., Australia, North America, North Europe) and highest in countries or areas where socio-economic level is lower (e.g., China, South-East Asia, South America)[20]. In this study, overall prevalence rate of HBsAg was found to be 2.70% and 5.03% respectively for NGMCTH and BZH. In Nepal, studies performed by different investigators have shown differences in prevalence of HBsAg. A study done by Chander *et al*[16] in 2003, among blood donors at the Universal College of Medical Sciences, Bhairahawa, showed the prevalence of HBsAg to be 0.45%. Another study done in 2002 by Shrestha B[21], in a Nepali population which required medical checkup for going abroad, detected the seroprevalence of HBsAg to be 0.93%. A study by Manandhar *et al*[17] on the seroprevalence of HBsAg in various districts of Nepal showed a prevalence of 4%. In 1996, Sawayama *et al*[20] studied the sero-prevalence of HBsAg in two rural Nepali villages, where the prevalence rate was found to be 1.1%. Usually, hospital based studies are found to provide higher prevalence of HBsAg. This also parallels with the results of this study. In a similar study conducted in BPKIHS, Dharan, HBsAg (Hepatitis B surface antigen) prevalence rate in hospital patients was found to be 5%[22]. In another study conducted in Surkhet valley, HBsAg prevalence rate was found to be 8.8% in the hospital patients[23]. In another study conducted in Kathmandu valley, prevalence of hepatitis B among commercial sex workers was found to be 10.9%, which is higher than this study because that study was conducted in higher risk groups[24]. This may be attributed to the fact that being a hospital based study; most of the people included in the study would be those with complaints of HBV infection (thus clinically suspected of being infected). Hence the study subjects would not sufficiently represent the general population.

In our study the male to female ratio among the HBV cases were 238:100 for NGMCTH (Percentage of males: 70.42%) and 225:100 for BZH (Percentage of males: 69.23%) suggesting that more than twice many cases of HBV are males. This same trend in the distribution of male and female cases was observed in all age groups, with this sex differential being statistically significant in both hospitals (p-value <0.0001 for both NGMCTH and BZH). This gender distribution was similar to that observed in a study done by Easow JM *et al*[25], in which, of the 36 positive samples, 30 (83.33%) were from males and 6 (16.66%) from females; and also in a study done by Chander and co-workers[16]. A study done by Shrestha SM[19] showed the prevalence of HBsAg to be higher in males than in females, which was in agreement with this study. Zali and coworkers in Iran found the prevalence in males and females to be 1.9% and 1.5%, respectively[11].

This study showed high proportion of cases belonging to the age group 21-40 years in both NGMCTH and BZH (64.79% and 61.54% respectively) indicating that most of the cases of HBV are of young and productive age group. This was also evident by the fact that mean age of HBV cases was 34.72 years ± 3.89 years for NGMCTH, while for BZH it was 33.73 years ± 4.11 years. This result is similar to the report of BPKIHS, Dharan and Surkhet valley study. This observation was also supported by the study done by Chander *et al*[16], where they found most seropositive cases of HBsAg belonged to the age group of 15-45 years. A study done by Gyawali *et al*[14] also detected a higher prevalence of HBsAg in the age group of 21-30 years, which is similar to the results of our study. In another population studies, the HBsAg carrier rate is observed to increase directly with age up to a peak and then to decline among the older age group[26]. Further, the mean age for females was found slightly exceed to that of males in both hospitals (NGMCTH: 35.26 years ± 7.17 years for females, 34.5 years ± 4.65 years for males; BZH: 34.50 years ± 7.41 years for females, 33.38 years ± 4.97 years for males), however, this difference in mean age between male and female cases was not statistically significant.

## CONCLUSIONS

The above study shows that prevalence of hepatitis B was found to be high and most commonly observed in young and productive age group males. Since there is no specific treatment, general preventive measures that include health education, improvement of personal hygiene and strict attention to asepsis and sterilization are important tools for its management. Other equally important preventive measures are screening of blood donors for HBsAg, which is now mandatory and immunization. Both pre-exposure and post-exposure administration of hepatitis B vaccine would result beneficial. Therefore ample importance must be directed towards them so as to cease its possible development as a public health problem in Nepal.

## REFERENCES

1. Jawetz E, Melnick JL, Adelberg EA. Medical Microbiology. 20th ed.: Norwalk, Connecticut: Appleton & Lange, 1995, pp. 403-4.
2. Viral Hepatitis. In. Dominant Communicable Diseases; Southeast Asia region. 1997; WHO.
3. Hallauer J, Kane M, McCloy F, Meheus A. Universal HB

immunization by 1997: where are we now? Belgium: Viral Hepatitis Prevention Board. Viral hepatitis fact sheet no. 2. 1998; 1.

4. McMahon BJ. Epidemiology and natural history of hepatitis B. *Semin Liver Dis*. 2005; 25 (Suppl 1): 3–8.
5. Health situations in the South-East Asia Region. New Delhi: WHO Regional office for South-East Asia. World Health Organization. 1998-2000; 90-2.
6. Hepatitis B. WHO Fact Sheet 204 (Revised August 2008). World Health Organization.
7. Lee WM. Hepatitis B virus infection. *N Engl J Med*. 1997; 337: 1733–45.
8. WHO. World Health Forum. 1983; 4(2): 135-141.
9. Maddrey WC. Hepatitis B – an important public health issue. *Clin Lab*. 2001; 47: 51-5.
10. Dunton N, Ueberberg A, Tibbs CJ, Smith HM. Epidemiology. Clinician's guide to viral hepatitis. London: Arnold group. 2001; 123-8.
11. Zali MR, Mohammad K, Farhadi A, Masjedi MR, Zargar A, Nowroozi A. Epidemiology of Hepatitis B in the Islamic Republic of Iran. *East Mediterr Health J*. 1996; 2: 290-8.
12. Safe blood and blood products. Screening for HIV and other infectious agents. World Health Organization. Geneva: WHO Module. 2002; 106-10.
13. Annual Report. 2005/2006. Morbidity sheet 1 of 3. His Majesty's Government of Nepal. Ministry of Health: Department of Health Services, Kathmandu; 432.
14. Gyawali K, Kumar BCR, Devkota B, Acharya B. A study on correlation between Hepatitis B surface antigen and liver function test and the possible factors responsible for Hepatitis B among the patients attending Tribhuvan University Teaching Hospital. National Health Research Council: Kathmandu, Nepal. August 2001;
15. Chiba H, Takezaki T, Neupani D, Kim J, Yoshida S, Mizoguchi E, *et al*. An epidemiological study of HBV, HCV and HTLV–1 in Sherpas of Nepal. *Asian Pac J Cancer Prev*. 2004; 5: 370-3.
16. Chander A, Pahwa VK. Status of infectious disease markers among blood donors in a teaching hospital, Bhairahawa, Western Nepal. *J Commun Dis*. 2003; 35: 188-97.
17. Manandhar K, Shrestha B. Prevalence of HBV infection among the healthy Nepalese males: a serological survey. *Journal of Epidemiology*. 2000; 10(6): 410-3.
18. Rai SK, Shibata H, Satoh M, Murakoso K, Sumi K, Kubo T, Matsuoka A. Seroprevalence of hepatitis B and C viruses in eastern Nepal. *Kansenshogaku Zasshi*. 1994; 68 (12): 1492-7.
19. Shrestha SM. Seroepidemiology of hepatitis B in Nepal. *Journal of Communicable Diseases*. 1990; 22 (1): 27-32.
20. Sawayama Y, Hayashi J, Ariyama I, Furusyo N, Kawasaki T, Kawasaki M, Itoh K, Acharya GP, Kashiwagi S. A ten-year serological survey of hepatitis A, B and C viruses infections in Nepal. *Journal of Epidemiology*. 1999; 9(5): 350-4.
21. Shrestha, B. HBsAg carriers among healthy Nepalese men: A serological survey. *J Health Popul Nutr*. 2002; 20: 235-8.
22. Bhatta CP. Prevalence of viral hepatitis B in BPKIHS Dharan Nepal. *Journal of Nepal Medical Association*. 39: 281-283.
23. Shrestha MS. Seroepidemiology of viral hepatitis in Surkhet, Nepal. *Journal of the Institute of Medicine*. 1989; 1-10.
24. Bhatta P, Neupane S, Baker J, Friedman M. Commercial Sex workers in kathmandu valley, profile & prevalence of sexually transmitted diseases. *Journal of Nepal Medical Association*. 1993; 348-351.
25. Easow JM, *et al*. Seroepidemiology of Hepatitis B Virus infection diagnosed at a teaching hospital in Western Nepal. *Journal of Clinical and Diagnostic Research*. 2010; (4): 3100-3105.
26. Da Villa G, Andjaparidze A, Cauletti M, Franco E, Roggendorf M, Sepe A, Zaratti L. Viral hepatitis in the Bhutanese population: preliminary results of a seroepidemiological investigation. *Researches in Virology*. 1997; 148(2): 115-7.

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# Proportion and Outcome of Pregnancies with Nuchal Cord at GMC Teaching Hospital

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**Key words**:
Nuchal cord,
Perinatal outcome,
Vaginal delivery,
Fetal heart rate,
Intrapartum complications.

## ABSTRACT

**Objectives:** To find out the proportion and outcome of pregnancies with nuchal cord at the time of delivery at GMC.

**Methods:** Prospective, comparative study of 200 cases at Department of Obstetrics & Gynaecology at Gandaki Medical College Teaching Hospital (GMCTH) in the period of six months.

**Results:** Out of a total 200 inclusive cases, 41 (20.5%) newborns had cord around the neck at the time of delivery, among which 33 (80.4%) had single loop and remaining 8 (19.6%) cases had 2 or more loops of cord. The incidence of intrapartum complication is relatively high in nuchal cord group comparing to control group. Similarly the rate of vaginal delivery is significantly high in nuchal cord group. Apgar score of newborns at 1 minute is relatively high in nuchal cord group, however in all of those newborns, Apgar score increased to >7 at 5 minutes.

**Conclusions:** Nuchal cord is not related to adverse perinatal outcome nor it is an indication for cesarean delivery.

## INTRODUCTION

An umbilical cord entanglement around the fetal neck (Nuchal cord) is a common finding at delivery. It affects 23% to 33% of all pregnancies and is generally assumed the cause for cord compression, low birth weight of the newborns and other intrapartum complications, sometimes leading to fetal death.

However, the actual significance that a nuchal cord has on the intrapartum events and perinatal outcome is still controversial. This study was conducted to find out the proportion of nuchal cord at delivery, intrapartum complications like fetal distress, meconium staining of liquor, mode of delivery, and perinatal outcome in the cases with nuchal cord.

## METHODS

The study includes all pregnancies and fetus delivered at Department of Obstetrics and Gynaecology, Gandaki Medical College Teaching Hospital in the period of six months from 1st May to 30th October, 2012. The data was collected from admission and perinatal sheets which were filled immediately after the admission of pregnant and after the birth of infants respectively. All the pregnant women who delivered after twenty eight weeks of gestational age were enrolled in the study. The variables recorded were maternal age, gestational age at delivery, parity, mode of delivery (MOD), the labor events like fetal distress (FD), meconium staining of liquor (MSL), abnormal fetal heart rate irregularities (AFHR), birth weight of fetus, Apgar score at the 1st and 5th minutes, transfer to the neonatal unit, the presence of nuchal cord at delivery, the number of loops and whether it was loose or tight. A nuchal cord was considered to be loose when it could be easily uncoiled before delivery of the fetal trunk. When it needed to be clamped and cut before delivery of the trunk, the nuchal cord was considered tight.

Fetal heart rate (FHR) monitoring was done with intermittent auscultation with stethoscope every 30 minute in first stage of labor and every 10 minute in second stage of labor during propulsive phase and after every contraction in expulsive phase of second stage of labor. In cases with FHR irregularities, fetal

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heart monitoring was done more frequently. Persistent FHR irregularities (<110/minute and >180/minute) for 10 minutes was considered as a sign of fetal distress. FHR irregularities lasting for less than 10 minutes was termed as transient FHR irregularities. All the deliveries were attended by a team from obstetrics and pediatric department. The cases with nuchal cord at the time of delivery were taken as study group and the cases which did not have nuchal cord were put in control group. Outcome variables between the study group and control group were compared.

Statistical analysis was done using SPSS software version 12.0. For statistical significance we used chi square (X2) test or Fisher's exact test for differences in qualitative variables and the Student's t-test for differences in continuous variables. A P-value <0.05 was considered to be statistically significant. Pregnancies complicated by prior cesarean section, intrauterine fetal death with severe congenital anomalies, and abnormal fetal lies were excluded.

## RESULTS

Out of a total 200 inclusive cases, 41 (20.5%) newborns had cord around the neck at the time of delivery, among which 33 (80.4%) had single loop and remaining 8 (19.6%) cases had 2 or more loops of cord. In 22 (53.7%) cases, the nuchal cord was found to be tight.

Table 1 compares the given variables between the study and control group. The rate of normal vaginal delivery was significantly high in study group (p <0.05). However the presence of FD, MSL or AFHR (p <0.05) and the rate of transfer of the fetus to neonatal unit were significantly low in control group (p <0.001). Concerning the neonatal outcome, rate of low Apgar score (<7) at 1 minute was found to be significantly high in study group (p <0.05).

Table 1: Comparision between the study (nuchal cord) group and control group

| Variables | study group (n=41) | control group (n= 159) | *p* value |
|---|---|---|---|
| Mean maternal age (years) | 23.65 ± 4.08 | 24.69 ± 4.58 | 0.18 |
| Mean gestational age (weeks) | 39.00 ± 1.34 | 38.86 ± 1.46 | 0.61 |
| Primipara | 22 (53.65%) | 88 (55.34%) | 0.49 |
| Vaginal delivery | 33 (80.48%) | 102 (64.15%) | 0.03 |
| Mean birth wt (kg) | 2.93 ±0.44 | 3.03 ± 0.45 | 0.21 |
| FD/MSL/AFHR | 14 (34.14%) | 22 (13.83%) | 0.04 |
| Apgar score <7 in 1 min | 12 (29.26%) | 21 (13.20%) | 0.02 |
| Apgar score <7 in 5 min | 0 | 3 (1.88%) | --- |
| Transfer to neonatal unit | 12 (29.26%) | 6 (3.77%) | <0.001 |

## DISCUSSION

One of the largest published studies with nuchal cord has quoted that nuchal cord is not associated with adverse perinatal outcome and neither is an indication for induction[7]. Larso *et al*[8] reported that the occurrence of nuchal cord increases linearly from 5.8% at 20 weeks of gestation to 29% at 42 weeks. The incidence of nuchal cord in this study was 20.5% of all the deliveries at twenty eight weeks of gestation and above. Our incidence rate is comparable to 14.7% to 22.8% reported in some studies[7,9-11,16]. It is, however, lower than 33.7% reported by Schaffer *et al*[12]. The difference could be explained by the fact that study population was only the term pregnancies in the study conducted by Schaffer *et al*[12].

The overall incidence of multiple nuchal cords (two or more entanglement) was 4.0% in this study which is similar to a study done by Larson *et al*[8] (3.8 %) and Shrestha *et al*[11] (3.9%). Incidence of multiple nuchal cords was 5.8 % in term deliveries and 5.5% in post term deliveries in the study done by Schaffer *et al*[12]. Several studies have analyzed the effect of nuchal cord on intrapartum events and neonatal outcome with differing results[9,10,12].

This study found higher incidence of intrapartum complication like fetal distress, meconium staining of liquor or transient abnormal fetal heart irregularity in study group, comparing to control group (p <0.05). Bohem[13] observed cord entanglement in most cases of abnormal tracings, and concluded that cord compression was the mechanism of the decelerations. In another prospective study[14], 19% of the patients with abnormal monitors had nuchal cord, suggesting cord pathology as an important contributor, but not as a major cause of abnormal FHR tracings.

The rate of normal vaginal delivery however was significantly higher in study group (p = 0.03) indicating lower of cesarean delivery rate in such cases. Sheiner *et al*[7] and Mastrobattista *et al*[8] in their study also found significantly lower cesarean section rate in women whose fetuses had nuchal cord at the time of delivery. Similar to Sadan *et al*[15], our study shows lower mean birth weights in the nuchal cord group but the difference was not statistically significant (p = 0.21).

Apgar score <7 at 1 minute was slightly higher in study group (p = 0.02) may be because of birth asphyxia as a result of cord compression during labor. However all had good recovery and none of these cases had Apgar score <7 at 5 minute.

Rate of transfer of the newborns to neonatal unit was significantly higher in our study, contrary to other studies[8,10-12,16], probably because of low Apgar score at 1 minute and relatively small sample size.

## CONCLUSIONS

Even though the nuchal cord is related to increased rate of intrapartum complications like fetal distress or meconium stain liquor, it does not affect the perinatal outcome, however the rate of NICU transfer of such newborns are significantly high comparing to control group, Nuchal cord itself is not an indication for cesarean section.

## REFERENCES

1. Hankins GDV, Snyder RR, Hauth JC, Gilstrap LC, Hammond T. Nuchal cords and neonatal outcome. *Obstet*

*Gynecol*. 1987; 70: 687-91.

2. Paul RH, Krosnick G. Fetal heart rate in excessive cord encirclement. *Obstet Gynecol*. 1966; 28: 646-9.
3. Goldkrand JW, Speichninger JP. "Mixed cord compression", fetal heart rate pattern, and its relation to abnormal cord position. *Am J Obstet Gynecol*. 1975; 122: 144-50.
4. Stembera ZK, Horska S. The influence of coiling of the umbilical cord around the neck of the fetus on its metabolism and acid-base balance. *Biol Neonate*. 1971; 20: 214-25.
5. Bruce S, Stanley LF, Bowe E, Rey H, Shamsi H. Umbilical cord complication as a cause of perinatal morbidity and mortality. *J Perinat Med*. 1978; 6: 89-94.
6. Verdel JCM, Exaito N. Tight nuchal coiling of the umbilical cord causing fetal death. *J Clin Ultrasound*. 1994; 22, 64-6.
7. Sheiner E, Abramowicz JS, Levy A, Silberstein T, Mazor M, Hershkovitz R. Nuchal cord is not associated with adverse perinatal outcome. *Arch Gynecol Obstet*. 274 (2006); 81–83.
8. Larson JD, Rayburn, WF., Harlan, VL. Nuchal Cord entanglement and gestational age. *Am J Perinatol*. 1997; 14 (9): 555-557.
9. Peregrine E, O'Brien P, Jauniaux E. Ultrasound detection of nuchal cord prior to labor induction and the risk of cesarean section. *Ultrasound Obstet Gynecol*. 2005 Feb; 25 (2): 160-4.
10. Mastrobattista JM, Hollier LM, Yeomons ER, Ramin SM. Day MC, Sosa A, Gilstrap LC 3rd. Effects of nuchal cord on birthweight & immediate neonatal outcomes. *Am J Perinatol*. 2005 Feb; 22(2): 83-5.
11. Shrestha NS and Singh N. Nuchal cord and perinatal outcome. *Kathmandu Univ Med J (KUMJ)*, 5 (2007); 360–363.
12. Schaffer L, Burkhardt T, Zimmermann R, Kurmanavicious J. Nuchal Cords in Term and Post term deliveries- Do we need to know? *Obstetrics and Gynecology*. 2005; 106: 23-28.
13. Bohem FH. Prolonged end stage fetal heart rate decelerations. *Obstet Gynecol*. 1975; 45: 579–582.
14. Sheiner E, Hadar A, Hallak M, Katz M, Mazor M, Shoham-Vardi I. Clinical significance of fetal heart rate tracings during the second stage of labor. *Obstet Gynecol*. 2001; 97:747–752.
15. Sadan O, Fleischfarb Z, Everon S, Golan A, Lurie S. Cord around the neck: should it be severed at delivery? A randomized controlled study. *Amer J Perinatol*. 2007; 24: 61–64.
16. Kemfang Ngowa JD, Kasia JM, Nsangou L, Zedjom C, Domkan L, Morfaw F, Bossiko B. Nuchal Cord and Perinatal Outcome at the Yaounde General Hospital, Cameroon. *Clinics in Mother and Child Health*. 2011; Vol. 8.

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*Review Article*

# Locking Plates & Screws: A Boon for Problematic Fractures

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**Key words**:
Conventional plates,
Fixation,
Locking plates,
Strain,
Stability.

**Abbreviations:**
MIPPO= minimal invasive percutaneous plate osteosynthesis
ORIF= open reduction and internal fixation
DCP= Dynamic compression plating

## ABSTRACT

**Objectives:** To review the biomechanical principles that guide fracture fixation with plates and screws. It specifically compares and contrasts the function and usages of the conventional unlocked plates to locked plates and screws in different types of fracture fixation. We review different study works to find out the function of locking plate and screws and rationale of its usages.

**Study selection**: Papers selected for this review study were drawn from different orthopedic English journals. All selected papers discussed the biomechanical principles for the use of both conventional non locking plates and locking screw plates.

**Discussion:** The following topics are analyzed from those study works: 1) plate and screw function, 2) fracture stability- specifically how does it affect the gap strain and fracture union, 3) biomechanics of the conventional and locking plates.

**Conclusions:** Locking plates and conventional plates rely on completely different biomechanical principles for fracture fixation. The conventional non locking plates are still useful in most of the simple diphyseal long bone fractures in adults. But the locking plates have certainly proved boon for problematic periarticular, comminuted fractures and in osteoporotic bones. Conventional plates are still gold standard in those intra articular fractures where perfect anatomical reduction is needed and in certain nonunions which require compression and increased stability for union.

## INTRODUCTION

A"Necessity is the mother of invention". Invention of locking plates & screws is the result of the failure of conventional plates and screw constructs to meet the demands of minimally invasive and indirect bridging fixation. It is also the result of failure of compression plating techniques to provide an environment favorable to secondary bone healing. Locking plates are fracture fixation devices with threaded screw holes, which allow screws to thread to the plate and function as a fixed angle device. New generation plates usually have a mixture of holes that allow placement of both locking and traditional non locking screws; called "Combi plates"[1]. The first locking plates were introduced in early 1980s for the use in spinal and maxillo-facial surgery[2]. Their proper use in limb bones started in early years of 21st century by Orthopedic surgeons in North America, which became popular very fast in rest of the world[3].

The purpose of this article is to describe and compare the function, biomechanics, design rationale and indications for usages of conventional and locking plates.

### Plate and screw function

The function of standard plate and screw constructs depends upon the stability requirements of a particular fracture. Plate-screw-bone constructs can act as load-sharing or load bearing devices depending on fracture reduction and fragment interference. Neutralization plates function as load-sharing

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devices[4]. Plates are placed across a fracture, already reduced and compressed by lag screws to neutralize the effect of bending, rotational, and axial forces on the fracture site. But buttress plates are load–bearing devices that act to counter shear forces at a fracture site by converting them to compressive axial forces. These plates are placed at the tensile side of the fracture and act as load-bearing devices.

The concept of stability is crucial in fracture surgery. Stability determines the amount of strain at the fracture site, and strain determines the type of healing that can occur at the fracture site. Primary bone healing occurs when strain is kept to less than 2%; secondary bone healing occurs when strain is kept between 2-10%. But bone doesn't form when strain is greater than 10%[5].

Fracture gap strain determines the type of healing that occurs at the fracture site. Primary bone healing (endosteal healing) occurs when there is absolute stability at the fracture site. It requires that motion be kept to a minimum and strain must be less than 2%. Compression and neutralization plating provide rigid fixation, minimizing strain by decreasing gap motion and prohibiting increase in gap length. Hence, the fixation methods demand that plates be placed on the tension side of the fracture so that fracture compression is assured and excess gap motion is prevented[6].

Secondary bone healing (enchondral ossification) occurs when relative stability is provided and strain is kept between 2% - 10%. Splints, casts, external fixators, locked plates etc. provide this relative stability where callus is formed in the process of union. The callus is formed from initial hematoma formation after going through different stages. Each step in the healing cascade decreases the motion at the fracture gap, therefore the gap strain, ultimately creating an environment conducive to bone formation. Gap strain is reduced by parameters that increase the gap length or decrease the motion at the fracture site. Gap length can be increased by fracture comminution. Similarly, bone resorption at the fracture site can decrease strain by increasing gap length. Strain reduction then leads to relative stability.

Relative stability and secondary bone healing are the goals of the newer "biologic fixation techniques". Bridging fixation provided by splints, plaster casts, external fixators, I/m nails, locked plate constructs decrease gap strain by minimizing motion while tolerating an increased gap length.

**Conventional plate biomechanics**

Conventional plating techniques are designed to provide absolute stability. When employed properly as compression plates or neutralization plates, conventional plates have the ability to resist axial, torsional, and bending loads. This is particularly true when no fracture gap exists and the plate is placed on the tension side of the fracture. Conventional plates loaded axially in tension and/or compression convert the force applied to shear stress at the plate-bone interface. The axial forces are countered by frictional force between the plate & bone. Osteoporotic or comminuted bone may not be able to resist the shear forces generated by advancing screw threads. In this situation, it becomes impossible to develop sufficient screw torque to generate sufficient normal force to prevent plate and fracture motion. Compression plating demands sufficient screw torque to prevent motion, but also demands that screw torque not exceed the shear resistance of the bone that would lead to screw stripping and loss of fixation.

The weakest link in the plate-screw-bone construct is the shear interface between the screw and the bone. The necessary normal force between the plate and the bone to prevent plate motion generates compressive forces under the plate that prevent periosteal perfusion. Prevention of periosteal perfusion under the plate can result in periosteum and bone necrosis deep to the plate and adjacent to the fracture site[7]. Attempts to minimize this problem led to the advent of limited contact plate (LC-DCP)[8]. The LC-DCP reduces contact by 50% but still relies on the plate-bone interface for stability.

**Locking Plate Biomechanics**

Any plate that allows the insertion of fixed-angle/angular-stable screws can be used as a locking plate. The main biomechanical difference from conventional plates is the fact that the latter require compression of the plate to the bone and rely on friction at the bone-plate interface. With increasing axial loading cycles, the screws can begin to toggle, which decreases the friction force and lead to loosening of the plate. Premature loosening of the plate leads to fracture instability, resulting into implant failure and non union. The conventional non locked plates & screws are inadequate in achieving fixation in osteopenic or pathological bone. It leads to necrosis induced bone loss; which is potential nidus for infections. It results in stress shielding, which weakens bone and increases the potential for refracture after implant removal. It also creates an environment where lack of stability is conducive to delayed or non union. In contrast, the locked plates control the axial orientation of the screw to the plate, thereby enhancing the screw-plate-bone construct stability by creating a single-beam construct. Single-beam constructs are four times stronger than load-sharing beam constructs where motion occurs between the individual components of the beam construct[9]. Locked plates are single-beam constructs by design (Fig 1, 2). In contrast, the conventional plates can function as single-beam constructs only in ideal circumstances where there is no motion between the plate and the bone.

Functioning as a fixed-angle device, locked plates can enhance fracture fixation in circumstances where fracture configuration (Fig 1) or bone quality do not provide sufficient screw purchase to achieve the plate-bone compression necessary to minimize gap strain with unlocked plate screw constructs. Locking plates convert shear stress to compressive stress at the screw-bone interface. In locked plates, the strength of fixation equals the sum of all screw-bone interfaces rather than that of the single screw's axial stiffness or pullout resistance as seen in unlocked plates[10]. It follows the biomechanical principle of external fixators and do not require friction between bone and the plate.

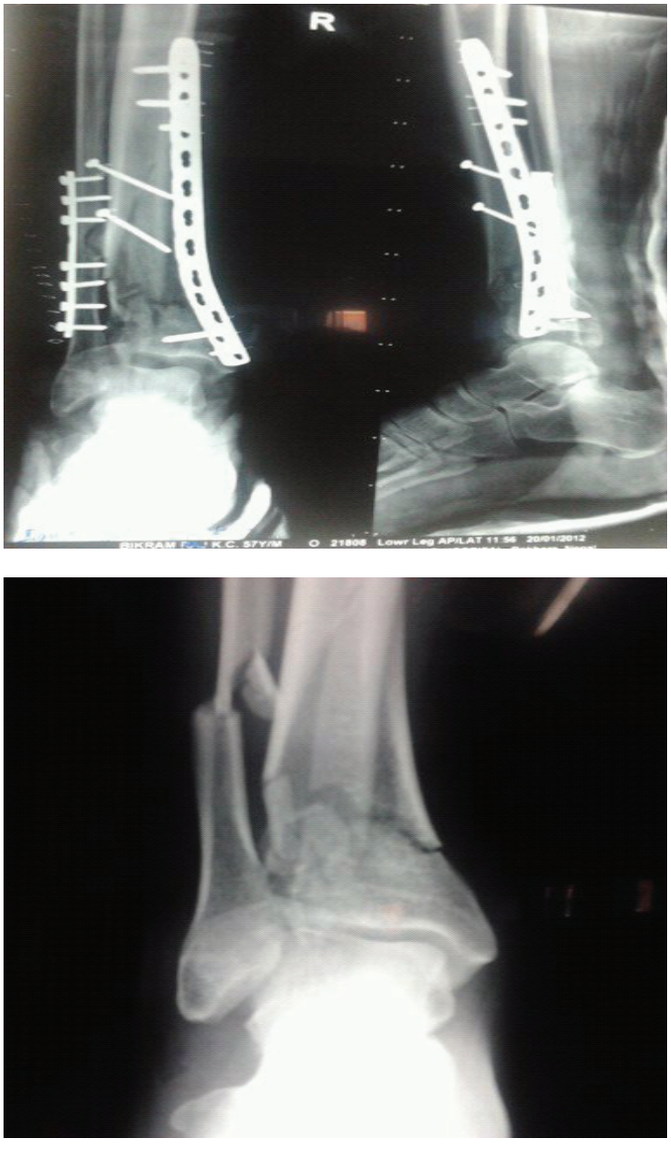


Fig 1: Comminuted distal tibial metaphyseal fracture and locking plate-screws fixation

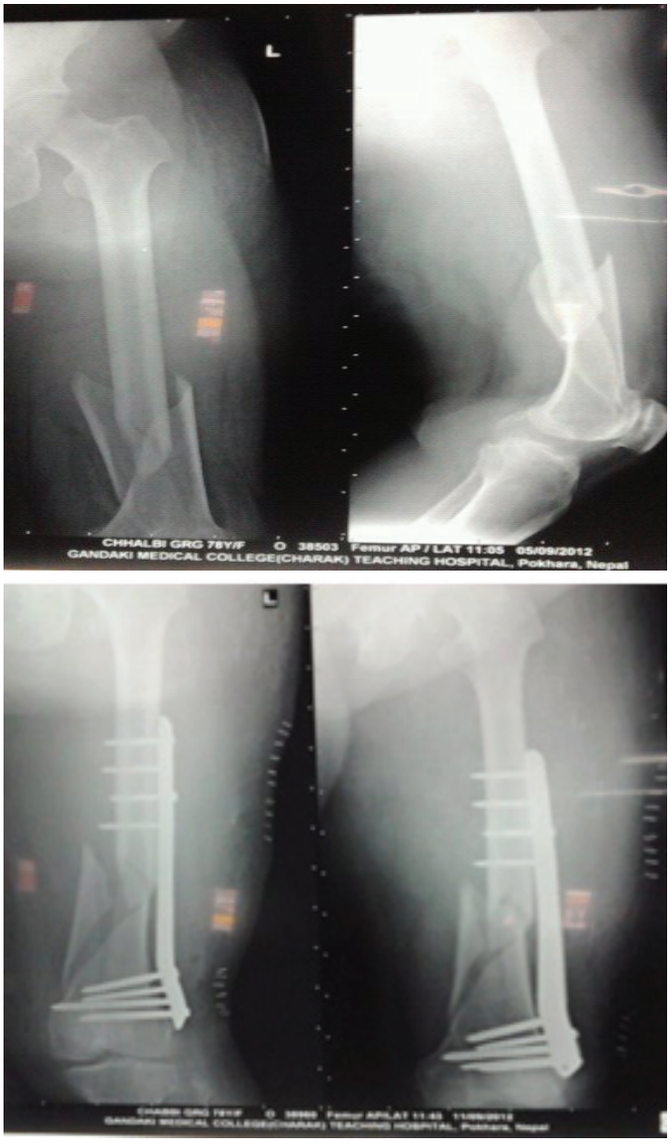


Fig 2: Distal femoral comminuted diaphyseal fracture and locking plate screws fixation

They are considered to be internal fixators from a biomechanical standpoint since the angular-stable interface between the screws and the plate allows placement of the plate without any contact to the bone[11]. However, the locking plates can be considered to be external fixators placed underneath the skin envelop, hence called "internal external fixators", being more stable as a result of the shorter distance between the plate and the bone.

Fixation rigidity is a function of the pin (screw) material, length, and diameter, and the dimensions of the fixator bar (plate). Screw lengths for the locked plates are 10 to 15 times shorter than for external fixators, thus greatly increasing fixation rigidity. Strain at the fracture site is optimized, so that secondary bone healing with callus formation is favored over fibrous non union or primary bone healing[12].

As internal fixators, locked plates no longer rely on frictional force between the plate and bone to achieve compression and absolute stability, thus allowing the preservation of local blood supply under the plate. The preserved periosteal blood supply allows for more rapid bone healing and decreased incidence of infection, bone resorption, delayed union, nonunion and secondary loss of reduction.

Varieties of locking plate and screws based on anatomy specific designs are available these days in the market. The most commonly available implants include anatomically pre-shaped plates for proximal & distal parts of femur, tibia, humerus, calcaneus, as well as locking compression plates for shaft of these long bones. Newer plating systems allow the surgeons to blend locked plating and compression plating together. But combining the two methods of fixation runs the risk of failing to achieve either absolute or relative stability and creating an environment where high gap strains prevent union[13].

## DISCUSSION

The decision-making regarding the use of a locking plate must include precise preoperative consideration of the exact principle by which the locking plate will be used. The main indications for the use of a locking plate include four different classic principles[14]. 1) The compression principle for osteoporotic diphyseal fractures. 2) The neutralization principle, also for osteoporotic diphyseal fractures. 3) The bridging principle ("locked internal fixator" principle) for comminuted diaphyseal or metaphyseal extra-articular fractures, and 4) The combination principle ("combi plate" principle) for comminuted metaphyseal intra-articular fractures.

The surgeon using a locking plate for fracture fixation must be well aware of the exact indication, according to these four different principles. For simple, non comminuted diphyseal fractures in osteoporotic bone requiring ORIF, locking plates offer the advantage of increased pull out resistance of the locking head screws compared with that of conventional screws, provided the screws are eccentrically placed in the dynamic compression unit of the "combi hole". On the basis of the same rationale, locking plates can also be used according to the neutralization principle to protect a lag screw in osteoporotic bone, with increased pull out resistance of the locking head screws. However, it is crucial to understand that locking head screws can never provide interfragmentary compression of its own. Classic and ideal indications for fracture fixation with locking plates are represented by the bridging principle and the combination principle. Both concepts apply to fixation of fractures with substantial comminution, which may either be high energy fractures in young patients or low energy osteoporotic fractures in elderly patients. The bridging principle is typically represented by the concept of minimally invasive percutaneous plate osteosynthesis ("MIPPO"). In contrast to the compression and neutralization principles, which provide absolute rigid stability leading to primary fracture healing; the bridging concept provides relative, elastic fixation that leads to secondary fracture healing by callus formation. The question about the number of screws to be placed proximally and distally is still under debate. Hertel *et al* advised at least 3 cortices on either side of the fracture secondary to clinical observation of radiolucencies at the bone-screw interface[15]. Sommer currently recommends at least two screws per main fragment with purchase of at least 3 cortices for simple fractures and purchase of at least 4 cortices for comminuted fractures[14]. For adequate bridge plate fixation, three or four holes of the plate should be left empty at the level of the fracture in order to achieve a larger area of stress distribution on the plate, otherwise the plate is bound to fail (Fig 3). Hence, adequate axial alignment, length and rotation of the extremity by reduction and manipulation without exposing the fracture site are mandatory for success of "MIPPO".

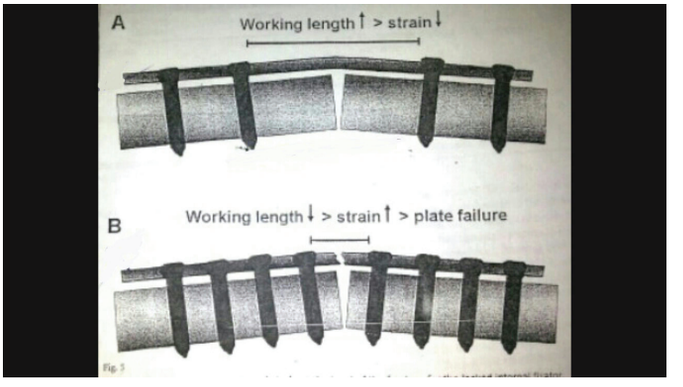


Fig 3: Courtesy: JBJS ORG: Locking Plates: Tips & Tricks

Although the invention of locking plate and screws has come as a boon for many of the difficult fractures, it does have some contraindications for its use where this system is bound to fail. So the surgeon should be judicious in its proper use. The two main contraindications to the use of a locking plate as a locked internal fixator are:

A) Simple fracture pattern that requires inter fragmentary compression e.g. simple diaphyseal fracture of the fore arm bones which heal more rapidly with the conventional method of ORIF with DCP. The use of MIPPO technique in such fractures violates the principle of the fracture gap width in relation to the strain and thus leads to nonunion[13].

B) Displaced intra-articular & periarticular fractures, which require anatomic open reduction and inter fragmentary compression.

Other fractures which can be easily dealt with simpler methods and cheaper implants are the relative contraindication for the use of locking plates because of their cost.

## CONCLUSIONS

### Tips & Tricks

Success of locking plates depends on the adherence to established principles of operative fracture care and learning the tricks of the specific technology. Gautier and Sommer have recently presented certain guidelines which may improve the individual learning curve of the surgeons who are less familiar with the newer technique.

In general, successful use begins with a formal preoperative drawing. The sequence of screw placement, the length and position of the plate, and the surgical approach are all critical to success. Correct positioning of the patient is equally vital, particularly for MIPPOs. Preoperative plan for fracture reduction is empirical because it is challenging task with minimal exposure procedures. Conventional screws can be used to pull the bone to the plate initially to secure fracture reduction; and to be replaced or supplemented later by locking screws. The length of the plate ideally should be more than two times the length of the fracture zone. Screws should be spread evenly, and ideally there should be at least one empty hole between each pair of holes filled with screws.

**Pitfallls**

More than 50 angulations between the screw and the locking hole can cause the screw to eventually fail. Mal aligned screw threads can lead to loose screws and loss of reduction. The weakest part of the combi locking plate is the dynamic compression unit, which breaks first when there is increased stress concentration and strain on the plate[16].

Locking plates allow the use of both bicortical and unicortical locking head screws. Two factors are essential for decision making with regard to the use of unicortical or bicortical locking head screws. These are the quality of the cortical bone and the extent of the rotational forces applied to the fractured bone. Bicortical fixation therefore, is recommended for all osteoporotic bones in general and metaphyseal fractures of bone of normal quality. Similarly, unicortical fixation is preferred in periarticular fractures. Mal reduction can result in failure regardless of whether the plate is conventional or locking. Hence, satisfactory reduction is mandatory before using the locking plates.

## REFERENCES:


1. Frigg R. development of the Locking compression plate. *Injury*. 2003; 34(Suppl 2): 63-6.
2. Arnold W. Initial clinical experience with cervical spine titanium locking plate. *Unfallchirurg. German*. 1990; 93: 559-61.
3. Sommer C, Gautier E, Muller M, *et al*. First Clinical results of the Locking Compression Plate. *Injury*. 2003; 34(Suppl 2): B43-54.
4. Gautier E, Parren SM, Ganz R. Principles of internal Fixation. *Curr Orthop*. 1992; 6: 220-32.
5. Kenneth A, Egol, Eric N Kubaik, *et al*. Biomechanics of Locked plates & Screws. *Orthop Trauma*. Sept 2004; 18 (8).
6. Perren SM. Evolution of the Internal Fixation of long bone fractures. The scientific basis of biological internal fixation: choosing a new balance between stability and biology. *Journal of Bone Joint Surg Br*. 2002; 84: 1093-1110.
7. Perren S. Point Contact Fixator: part I Scientific background , design and application. *Injury*. 1995; 22( Suppl 1): 1-10.
8. Frigg R. Locking compression Plate. An Osteosynthesis plate based on the dynamic compression plate and the Point contact fixator. *Injury*. 2001; 32( suppl 2): 63-66.
9. Gautier E, Perren SM, Cordey J. Effect of plate position relative to bending direction on the rigidity of a plate osteosynthesis. *Injury*. 2000; 31(suppl 3): C14-C20.
10. Cordey J, Borgeaud M, Perren SM. Force transfer between the plate and the bone: relative importance of the bending stiffness of the screws friction between plate & bone. *Injury*. 2000; 31(Suppl 3): C21-C28.
11. Sommer C, Gautier E, Muller M, *et al*. First Clinical results of the Locking Compression Plate (LCP). *Injury*. 2003; 34 (Suppl 2): b43-54.
12. Schutz M, Kaab MJ, Haas N. Stabilization of proximal tibial fractures with the LIS-system: early clinical experience in Berlin. *Injury*. 2003; 34(suppl 1): A30-A35.
13. Perren SM. Evolution and rationale of locked internal fixator trchnology. Introductary remarks. *Injury*. 2001; 32(suppl 2): B3-B9.
14. Gautier E, Sommer C. Guidelines for the clinical application of the LCP. *Injury.* 2003; 34 (Suppl 2): B63-76.
15. Hertel R, Eijere H, Meissser A, *et al*. Biomechanical and biological considerations relating to the clinical use of the Point Contact-Fixator: evaluation of the device handling test in the treatment of diaphyseal fractures of the radius and/or ulna. *Injury*. 2001; 32(suppl 2): SB10-SB14.
16. Sommer C, Babst R, Muller M, Hanson B. Locking Compression plate loosening and plate breakage: a report of four cases. *J Orthop Trauma*. 2004; 18: 571-7.

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*Review Article*

# Matrix Metalloproteinase

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**Key words**:
Matrix metalloproteinases (MMPs),
Transcriptional regulation,
Furin activation,
Extracellular matrix (ECM).

## INTRODUCTION

The extracellular matrix (ECM) plays a key role in maintaining tissue architecture and homeostasis. ECM constituting mainly of collagen provides the scaffold necessary for the organization of cells that constitute the tissue. Numerous other proteins contribute to specialized components of the ECM structure, such as the basement membrane, including laminin, entactin, collagen IV, and various growth factors and proteases. Another class of molecules that play an essential role in the composition of the ECM are secreted proteoglycans whose protein core is covalently bound to high-molecular-weight glycosaminoglycans, including chondroitin, heparan, and keratan sulphate[1].

Degradation of extracellular matrix (ECM) is an important feature of normal development, morphogenesis, tissue repair and remodelling[2]. Several families of enzymes (serine, cystein, aspartic and metalloproteinase) are responsible for the degradation of extracellular matrix (ECM) proteins during the remodeling of tissues. An important family of such enzymes is that of the matrix metalloproteinases (MMPs) also called as matrixin[2]. MMPs are a family of zinc-dependent endoproteases collectively referred to as metzincins. The metzincin superfamily is distinguished by a highly conserved motif containing three histidines that bind to zinc at the catalytic site and a conserved methionine that sits beneath the active site[2,3,4,5].

Under normal physiological condition, the activities of MMPs are precisely regulated at level of transcription, activation of precursor zymogen, interaction with specific ECM components, and inhibition by endogenous inhibitors and the loss of activity control may result in diseases such as arthritis, cancer invasion and metastasis, artherosclerosis, aneurysms, nephritis, tissue ulcers and fibrosis[2,5,6].

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## MATRIX METALLOPROTEINASE FAMILY

### Metzincin Superfamily

Proteolytic enzymes are classified as either exopeptidases or endopeptidases based on whether they cleave terminal or internal peptide bonds, respectively. Most endopeptidases are classified as serine, cysteine, aspartic or metalloproteinases based on their catalytic mechanism and inhibitor sensitivities, and the metalloproteinases are further separated into five superfamilies based on sequence considerations. Of these, the metzincin superfamily is distinguished by a highly conserved motif containing three histidines that bind zinc at the catalytic site and a conserved methionine turn that sits beneath the active site zinc[5].

Interstitial collagenase was the first member of MMP to be discovered in 1962 by Grass and Lapiere[7] while explaining collagen remodeling during the metamorphosis of tadpole into a frog. As many as 24 different MMPs have been identified

among vertebrates, of which 23 of them have been found in humans. MMPs are either secreted (MMPs 1–13 and 18–20) or anchored to the cell membrane by a transmembrane domain (MMPs 14–17), in which case they are also referred to as membrane type MMPs (MT-MMPs). MMPs have been subdivided into distinct categories based on its structural and functional criteria (Table 1)[2].

Among the many attributes of MMPs, they are proteinases that degrade at least one component of the extracellular matrix, contain a zinc ion and are inhibited by chelating agents, are secreted in a latent form, requiring activation for proteolytic activity, are inhibited by tissue inhibitors of metalloproteinases (TIMPs), function at neutral pH and share common amino acid sequences[8].

## STRUCTURE

The basic structure of MMPs is made up of the following homologous domains as shown in Figure 1. The predomain, signal peptide directs MMPs to the secretory or plasma membrane insertion pathway, Prodomain, confers latency to the enzymes by occupying the active site zinc, making the catalytic enzyme inaccessible to substrates; Zinc and Calcium ion containing catalytic domain; Hemopexin domain, mediates the interactions with substrates and confers specificity of the enzymes and Hinge region which links the catalytic and the hemopexin domain (Fig 1)[6,8,9,10].

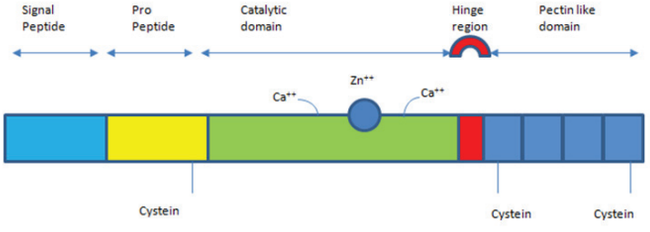


Figure 1. The domain structure of MMPs. MMP-7 lacks a hemopexin domain and the transmembrane domain is found only in the membrane-type MMPs. The MMPs are activated by cleavage of the N-terminal propeptide, (Curren S and Murray G I[9,10])

All MMPs contain a N-terminal of 17-29 amino acid signal peptide predomain, followed by a prodomain of about 77-87 amino acid residue that constitutes the $NH_2$-terminal domain of the secreted MMP. The propeptide domain has a conserved unique PRCGXPD sequence. The Cys within this sequence (the "cysteine switch") ligates the catalytic zinc to maintain the latency of pro-MMPs[5,9,10,11]. The prodomain is followed by a catalytic domain of about 170 amino acid residue. The catalytic center of MMPs contains a zinc-binding HEBXHXBGBXHS motif, where H is histidine, E is glutamic acid, B is a bulky hydrophobic amino acid, G is glycine, X is variable amino acid and S is serine.

Table 1. Vertebrate MMPs and some of their substrates (Visse & Nagase2 2003)

| MMP | Common name(s) | Some substrates | Chromosomal location |
|---|---|---|---|
| MMP-1 | Collagenase-1 | Collagen III>I>II, VII, VIII, X, XI, Gelatin, Entactin, Perlecan, Laminin, Casein, Pro-MMP-1, Prommp-2, Prommp-9 | 11q22-23 |
| MMP-2 | Gelatinase-A | Gelatin, Collagen I, III, IV, V, VII, X, XI, Elastin, Fibrinogen, Laminin, Aggregan, Vitronectin, Decorin, Plasminogen | 16q13 |
| MMP-3 | Stromelysin-1 | Aggregan, Laminin, Gelatin, Fibronectin, | 11q23 |
| | Transin-1 | Collagen III, IV, V, IX, X, Xi, XVIII` | |
| MMP-7 | Matrilysin | Fibronectin, Laminin, Gelatin, Aggregan, collagen I, IV, V, IX, X, XI, XVIII | 11q21 |
| MMP-8 | Collagenase-2 | Collagen I>II>III, VII, X, Gelatin, Entactin, Neutrophil Collagenase Aggregan, Tenascin, Pro-MMP-8 | 11q21-22 |
| MMP-9 | Gelatinase-B | Gelatin, Collagen I, IV, V, VII, X, XI, XVIII, Elastin, Laminin, Fibronectin, Vitronectin, proMMP-2, proMMP-9 | 20q11.2-13.1 |
| MMP-10 | Stromelysin-2 | Collagen I, III, IV, IV, Gelatin, Elastin, proMMP-1, 8 and 10 | 11q22.3-23 |
| | Transin-2 | | |
| MMP-11 | Stromelysin-3 | Fibronectin, Laminin. Aggregan, Gelatin | 22q11.2 |
| MMP-12 | Metalloelastase | Elastin, Collagen I, IV, Fibronectin, Laminin, Macrophage Elastase Proteoglycans, Fibrinogen | 11q22.2-22.3 |
| MMP-13 | Collagenase-3 | Collagen II>III>I, VII, X, XVIII, Gelatin, Entactin, Tenascin, Aggregan | 11q22.3 |
| MMP-14 | MT2-MMP | Collagen I, II, III, Gelatin, Laminin, Aggregan, ProMMP-2, -13 | 14q11-12 |
| MMP-15 | MT1-MMP | Proteoglycans, ProMMP-2 | 15q13-21 |
| MMP-16 | MT3-MMP | Collagen III, Fibronectin, ProMMP-2 | 8q21 |
| MMP-17 | MT4-MMP | Gelatin, Fibrinogen, ProMMP-2 | 12q24.3 |
| MMP-18 | Collagenase-4 | Collagen, I, II, III, Gelatin | Not found |
| Xenopus | Not found in human | | |
| MMP-19 | Stromelysin-4 | Collagen I, IV, Gelatin, Laminin, Tenascin | 12q14 |
| MMP-20 | Enamelysin | Amelogenin, Aggregan, Laminin | 11q22.3 |
| MMP-21 | XMMP(Xenopus) | Gelatin | |
| MMP-22 | CMMP(Chicken) | | |
| MMP-23 | (CA)MMP Cysteine array | Gelatin | 1p36.3 |
| MMP-24 | MT5-MMP | Fibronectin, Gelatin, ProMMP-2 | 20q11.2 |
| MMP-25 | MT6-MMP | Collagen IV, Gelatin, ProMMP-2, -9 | 16p13.3 |
| MMP26 | Matrilysin-2 | Collagen IV, Gelatin, ProMMP-9 | 11p15 |
| MMP27 | Epilysin | Casein | 11q24 |
| MMP28 | | | 17q21.1 |

Some MMPs, such as MMP-11 contains a threonine in place of this serine residue[5,11]. There is also a conserved methionine located close to the HEBXHXBGBXHS motif and the zinc ion forms a unique "Met-turn" structure which forms a base to support the structure around the catalytic zinc[11,12]. Three ligands of zinc binds to histidine in the catalytic domain and the fourth ligand site is occupied either by $H_2O$ (in the mature active enzyme) or by a single unpaired Cys residue in the propeptide (in the latent precursor). All MMPs contain a highly conserved Glu- and Asp-rich region between the $Zn^{2+}$-binding site and a hinge region that is likely to constitute a $Ca^{2+}$ binding site[11]. The zinc binding motif in the catalytic domain, and the ''cysteine switch'' motif PRCGXPD in the propeptide coordinate with each other and this Cys-Zn coordination keeps proMMPs inactive by preventing a water molecule which is essential for substrate catalysis, from binding to the zinc atom[2, 12].

All MMPs except MMP-7, MMP-23 and MMP-26 contain a hemopexin/vitronectin-like –COOH terminal domain of about 200 amino acids and is linked to the catalytic domain by a short 5-50 residue proline rich linker or a hinge region. The COOH-terminal domain consists of four tandem repeats that share some sequence homology with hemopexin/vitronectin. The four tandem repeats are held together by a single disulfide bond with Cys residues flanking the hemopexin-like domain. The hemopexin/vitronectin-like C-terminal domain is responsible for multiple protein-protein interactions. It binds tissue inhibitors of matrix metalloproteinases (TIMPs), certain MMP substrates and is involved in the MMP activation. In the others which lack the hemopexin-like domain completely, a cysteine-

and proline-rich interleukin-1 type II receptor- like domain is found instead[5,11,12].

Domains that are not common to all members of MMPs include the collagen-binding domain (CBD) of gelatinases and the transmembrane domains of MT-MMPs. The CBD domain is composed of three fibronectin type II like repeats and is involved in the binding of collagenous substrates, elastin, fatty acids and thrombospondins. MT-MMPs have a transmembrane domain and a short cytoplasmic domain (MMP-14, -15, -16 and -24) or a glycophosphatidyl inositol (GPI) insertion signal (MMP-17 and -25)[3,13]. Based on the domain organization and substrate preference, MMPs are grouped into six categories such as collagenases, gelatinases, stromelysins, matrilysins, membrane-type (MT)-MMPs and other MMPs[2, 3, 8, 12] (Table 2).

Table 2 : The following table describes the domain composition[12]

| Enzyme | MMP | Domain composition | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SS | Pro | CS | RX[R/K] R | Cat | FN2 | LK1 | HPx | LK2 | TM | GPI | Cyt | CysR-1 |
| Collagenase 1 | MMP-1 | + | + | + | - | + | + | + | + | | | | | |
| Collagenase 2 | MMP-8 | + | + | + | - | + | - | + | + | | | | | |
| Collagenase 3 | MMP-13 | + | + | + | - | + | - | + | + | | | | | |
| Collagenase 4 | MMP-18 | + | + | + | - | + | - | + | + | | | | | |
| Gelatinase A | MMP-2 | + | + | + | - | + | + | + | + | | | | | |
| Gelatinase B | MMP-9 | + | + | + | - | + | + | + | + | | | | | |
| Stromelysin 1 | MMP-3 | + | + | + | - | + | - | + | + | | | | | |
| Stromelysin 2 | MMP-10 | + | + | + | - | + | - | + | + | | | | | |
| Stromelysin 3 | MMP-11 | + | + | + | + | + | - | + | + | | | | | |
| Matrilysin 1 | MMP-7 | + | + | + | - | + | - | - | - | | | | | |
| Matrilysin 2 | MMP-26 | + | + | + | - | + | - | - | - | | | | | |
| MT1-MMP | MMP-14 | + | + | + | + | + | - | + | + | + | + | - | + | |
| MT2-MMP | MMP-15 | + | + | + | + | + | - | + | + | + | + | - | + | |
| MT3-MMP | MMP-16 | + | + | + | + | + | - | + | + | + | + | - | + | |
| MT4-MMP | MMP-17 | + | + | + | + | + | - | + | + | + | - | + | - | |
| MT5-MMP | MMP-24 | + | + | + | + | + | - | + | + | + | + | - | + | |
| MT6-MMP | MMP-25 | + | + | + | + | + | - | + | + | + | - | + | - | |
| Macrophage elastase | MMP12 | + | + | + | - | + | - | + | + | | | | | |
| | MMP-19 | + | + | + | - | + | - | + | + | | | | | |
| Enamelysin | MMP-20 | + | + | + | - | + | - | + | + | | | | | |
| | MMP-21 | + | + | + | + | + | - | + | + | | | | | |
| | MMP-23 | + | + | - | + | + | - | - | - | - | - | + | - | + |
| Epilysin | MMP-28 | + | + | + | + | + | - | + | + | | | | | |

Groups of MMPs - SS signal peptide, Pro pro-domain, CS cysteine switch motif, RX[R/K] proprotein convertase recognition sequence, FN2 fibronectin type II motif, LK Linker, GPI glycosylphosphatidylinositol anchoring sequence, Cyt cytoplasmic domain, CyR-Ig cystine rich and Ig domain.

**Three-dimensional (3D) structure MMPs**

To date, X-ray or NMR structures comprising at least the catalytic domains, isolated or in complexes with inhibitors, are available for MMP-1-to-MMP-3, MMP-7-to-MMP-14, MMP-16, and MMP-20,12,13.

## ZYMOGEN STRUCTURE

MMPs are kept under control through prodomains and, to date, structures of pro-MMP-1, -2, -3, and -9 have been reported[13]. The prodomain consists of three α-helices and connecting loops. The first loop between helix 1 and 2 is a protease-sensitive "bait region" but the structure of this region has not been resolved in the case of proMMP-1, proMMP-3 and proMMP-9 due to its flexible nature. After helix 3, the prodomain harbors a extended peptide region containing conserved 'cysteine switch' motif PRCGXPD in the substrate-binding cleft of the catalytic domain forming fourth ligand of the active-site zinc replacing catalytic solvent molecule essential for zymogen activation and thus keeping the zymogen inactive[2,3,12,13]. The orientation of this segment is opposite from that of a peptide substrate and the SH group of the cysteine interacts with the catalytic zinc ion. Upon activation the interaction of Cys-$Zn^{2+}$ is disrupted, which allows a water molecule to bind to the zinc atom[3].

The catalytic domain consists of a five-stranded βeta-sheet, three α-helices, and bridging loops. The catalytic domains have 2 zinc ions (one catalytic and the other structural) and 3 calcium ions, which are required for the stability and the expression of enzymic activity[12]. MT1-MMP (MMP-14), MT2-MMP (MMP-15), MT3-MMP (MMP-16) and MT5-MMP (MMP-24) have an additional 8 residues between β-strand II and III. This loop is critical for activation of proMMP[23,12].

The catalytic zinc ion lies at the bottom of cleft and is coordianted with 3 histidines and fourth ligand is water molecule, a catalytic solvent molecule which is substituted by other ligand cystein from the prodomain giving rise to tetrahedral metal coordination and below the zinc sit, the met-turn feature, having conserved methionine in position. The reason for the strict conservation of the Met-turn is not clear. Some mutation studies suggested its role in folding and stability of metzincins but others did not[14]. The glutamic acid which is essential for catalysis, lies adjacent to the first histidine[1,12].

At the active site of the catalytic domain there is a cleft, the bottom of which is closed by the specificity loop, which is responsible for a hydrophobic S-substrate binding site or specificity pocket (S1V) and displays variations in depth and nature. The catalytic zinc ion lies at the bottom of the cleft[13].

Upon activation, the carbonyl group of the peptide substrate bond to be cleaved coordinates with the catalytic zinc in the substrate binding domain. The substrate docking is dictated by the structure of the substrate binding site, including a pocket called the "S1V pocket", located to the right of the zinc atom. Binding of a substrate to the enzyme displaces the water molecule from the zinc.

The peptide bond hydrolysis is then facilitated by the carboxylate group of the glutamate in the active site which draws a proton from the displaced water and allows a nucleophilic attack of the polarized water on the carbonyl carbon of the peptide bond[2, 3, 12,13].

In catalytic domains of gelatinases, fibronectin type II (Fn II) domains are inserted in the loop between the fifth β-strand and the second helix. The Fn II domains in MMP-2 and MMP-9 have a similar conformation. They consist of two antiparallel β-sheets connected with a short α-helix and stabilized by two disulfide bonds. However, the placements of the Fn II

domains in the two gelatinases are significantly different. After superimposing the catalytic domains of proMMP-2 and proMMP-9, Fn II domain 1 and domain 3 fall roughly in the same places, but the position of domain 2 differs[3].

Domain 2 of proMMP-2 has an area that interacts with the catalytic domain, but the corresponding domain of proMMP-9 is rotated and twisted away from the catalytic domain without making contacts. Domain 3 in both progelatinases makes contact with the propeptide and with the catalytic domain[3].

The hemopexin domain has a 4-bladed β-propeller structure with a single disulfide bond between the first and the fourth blades. The center of the propeller generally contains one calcium ion and a chloride and a proline rich linker region connects the catalytic domain and the hemopexin domain[3,12].

**Regulation of MMP activity**

To accomplish the normal or pathologic functions, MMPs must be present in the right cell type and pericellular location, at the right time, and in the right amount, and they must be activated or inhibited appropriately. Thus MMPs are tightly regulated at the transcriptional and post-transcriptional levels and are also controlled at the protein level via their activators, their inhibitors, and their cell surface localization[5]. Most MMPs are expressed at low levels or not at all in resting-state adult tissues. However, numerous cytokines and growth factors as well as physical cellular interactions provide stimuli that can rapidly induce MMP expression[1].

**Transcriptional regulation of MMP genes**

Most MMPs are closely regulated at the level of transcription and is inducible[5]. Formerly, it was thought that MMP-2 could only be post-transcriptionally regulated, nowadays a number of well-known transcriptional elements have been identified in the MMP-2 promoter[15]. The two most important types of binding sites found within the promoter regions of MMP genes are the Activating Protein-1 (AP-1) site, AP-1 being a transcription factor composed of Jun and fos subunit and the Polymer Enhancer Activator (PEA3) site[16].

Several cytokines and growth factors, including interleukins, interferons, EGF, KGF, NGF, basic FGF, VEGF, PDGF, TNF-α, HGF and the extracellular matrix metalloproteinase inducer EMMPRIN induce the expression MMPs. Several growth factor and cytokine regulatory pathways converge at the AP-1 binding site, activator protein-1 (AP-1) sites[4].

Molecules such as transforming growth factor beta (TGF-β), retinoids, thyroid hormones, glucocorticoids, progesterone and androgens that inhibit the expression of inducible MMP genes also appear to act via the AP-1 site. Agents such as gluco corticoids, retinoids modulates the expression of MMPs by inducing transcription of the tissue inhibitors of metalloproteinases (TIMPs) and also require the AP-1 site to exert their influence[16].

TGF-β repress MMP production. However it has been observed that MMP-2 and 9 is turned on by TGF-β (Fig 4). IL-1, TGF-β, TNF-α, EGF increased gene expression of tissue inhibitor of MMP-1 and TGF-β repress gene expression of tissue inhibitor of MMP-2[17].

It had been shown that hepatocyte growth factor induces expression of the Ets-related E1AF transcription factor gene whose product in turn activates MMP genes and leads to oral cancer cell invasion[18].

**Post transcription regulation**

**Regulation of MMP secretion**

Although most MMPs are constitutively secreted once they become translated, secretory control do exist. For example MMP-8 (collagenase-2, neutrophil collagenase) and MMP-9 are synthesized by differentiating granulocytes in the bone marrow, stored in the specific and gelatinase (tertiary) granules of circulating neutrophils, respectively, and released following neutrophil activation by inflammatory mediators[5].

Post-transcripitionally, activity of secreted MMPs is restricted by the latency. ProMMPs are kept in a catalytically inactive state by the interaction between the thiol of the conserved prodomain cysteine residue and the zinc ion of the catalytic site, excluding water (Fig 2). MMPs need to be activated to initiate its function and are activated both extracellularly, at the cell surface and intracellularly by furin or related proprotein convertases[19,20]. Most of the secreted MMPs are activated extracellularly by the disruption of thilo$Zn^{2+}$ interaction and the replacement of thiol group by water molecule, which then targets the peptide bonds of MMP substrate [19, 20].

This mechanism which is a prerequisite for the activation of all proMMPs has been termed as cysteine switch[21].

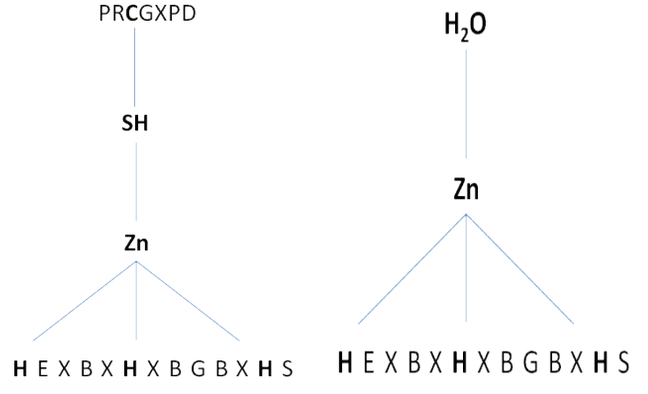


Fig 2 : Catalytic site of MMPs. The thiol group from the cysteine side chain in the conserved PRCGXPD sequence present in the prodomain coordinates with the catalytic zinc ion in the latent MMPs and during activation, a water molecule replaces the thiol group resulting in catalytically active enzyme[11].

The latent MMP can gain catalytic activity by three different mechanisms as described in Figure 3. There could be reduction of the free thiol by oxidants e.g. ROS or by nonphysiologic reagents such as alkylating agents, heavy metal ions,

organomercurials, and disulfides, or direct cleavage of the pro-domain by another proteinase or by allosteric activation. Thiol reduction and allosteric controls would lead to inter or intramolecular autolytic cleavage of the prodomain[22].

Chemical agents such as thiol-modifying agents (4-aminophenylmercuric acetate, $HgCl_2$, N-ethylmaleimide), oxidized glutathione, sodium dodecyl sulfate, or choatropic agents can unfold the structure breaking the cysteine zinc contact to expose zinc. These reagents will then react with sulfhydryl group resulting in inactivation of cysteine. This, in turn, enables the enzymes to undergo autocatalytic cleavage to completely remove the prodomain[2,22].

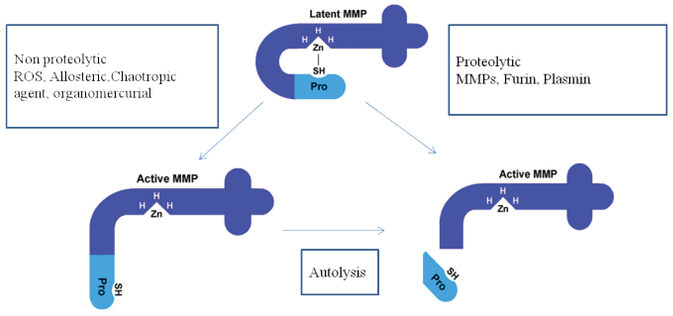


Fig 3 : Mechanisms of ProMMP activation.

Latency of MMPs (i.e., proMMPs) is maintained by an electrostatic interaction between the free thiol of a conserved cysteine in the prodomain with the His-ligated zinc atom in the catalytic pocket. In this state, the prodomain covers the catalytic cleft thereby barring an interaction with a protein substrate. Proteolytic cleavage of the prodomain by furin or other proteases removes the thiol constraint. The thiol-Zn interaction can also be disrupted by non-proteolytic means, and in the lab, this is easily achieved with organomercurials. In cells and tissues, proMMPs can be anchored to other macromolecules, such as integrins and proteoglycans, and these interactions can lead to allosteric disruption of the thiol-Zn bond. Even though the pro-domain may not be cleaved, the MMP will be active. However, final activation of MMP involves prodomain cleavage, which following a conformational change of cysteine switch, result in autolysis[22].

Alternatively, proteolytic enzymes such as MMPs of other type, trypsin and plasmin can cleave the propeptide ahead of cysteine so that cystein is no longer held in tight position to zinc atom. In a second step, these active forms can be autocatalytically cleaved by the activated metalloproteinase to remove the propeptide and confer permanent activity. Most likely MMP activation in vivo involves tissue and plasma proteinases and bacterial proteinases together with oxidative stress[14,21].

**Furin activation**

Pei and Weiss *et al*[20] first demonstrated that proMMP-11 (stromelysin 3) is activated intracellularly by furin. ProMMP-11 possesses a furin recognition sequence, KX(R/K)R, at the C-terminal end of the propeptide, between the pro and catalytic domains, which serves as a target sequence for proprotein convertases or furins[2, 20]. Several other MMPs, including the six MT-MMPs, MMP-23, and epilysin (MMP-28), have a similar basic motif in the propeptide and are activated intracellularly. Because these proteins are most likely secreted as active enzymes, their gene expression and inhibition by endogenous inhibitors would be critical for the regulation of activity[2].

**MT-MMPs as Zymogen activators /Cell surface activation of ProMMP-2**

Most secreted proMMPs are activated by tissue or plasma proteinases and opportunistic bacterial proteinases, but proMMP-2 is an exception. The activation of proMMP-2 is thought to take place on the cell surface which was initially shown with human fibroblasts treated with concanavalin A (Con A). This process is mediated by the MT-MMPs and the effective activation of proMMP-2 on the cell surface requires TIMP-2. Currently three of the MT-MMPs, i.e. MT1-MMP, MT2-MMP, and MT3-MMP have been shown to activate proMMP-2, but detailed activation studies have been conducted only with MT1-MMP (Figure 4)[2,23].

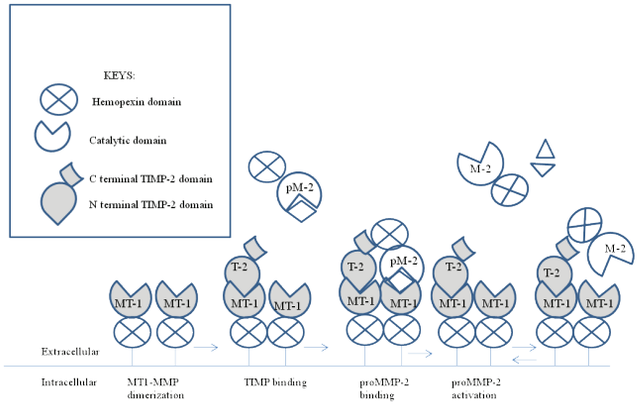


Fig 4 : Model of proMMP-2 activation by MT1-MMP and TIMP-2. Active MT1-MMP on the membrane binds a molecule of TIMP-2, inhibiting its activity. MT1-MMP can form dimers or multimers on the cell surface through interaction of the hemopexin domains. ProMMP-2 subsequently binds to the C-terminal domain of TIMP-2 through its hemopexin domain. The second, active, MT1-MMP then cleaves the bait region of proMMP-2, thereby partly activating it. The MMP-2 (M-2) dissociates from the membrane and is fully activated by intermolecular processing[2].

Strongin *et al*[24] first demonstrated that the activation of proMMP-2 by cell surface MT1-MMP was greatly enhanced in the presence of a small amount of TIMP-2. This was proposed to result from the formation of the ernary proMMP-2/TIMP-2/MT1-MMP complex on the cell surface, where the N-terminal inhibitory domain of TIMP-2 binds to the active site of MT1-MMP and its C-terminal domain tightly interacts with the C-terminal hemopexin domain of proMMP-230. By this model it could be demonstrated that when the molar ratio of MT1-MMP to TIMP-2 was in the range 3:1 to 3:2, activation of proMMP-2 was enhanced compared to the absence of exogenous TIMP-2 where no increase in proMMP-2 activation was noted. Also when the molar ratio was 7:6 and excess, TIMP-2 resulted in

inhibition of activation[20,23].

**Mechanism of MMP-2 activation by TIMP-2 and MT1-MMP**

ProMMP-2 forms a tight complex with TIMP-2 through their C-terminal domains, therefore permitting the N-terminal inhibitory domain of TIMP-2 in the complex to bind to MT1-MMP on the cell surface. Alternatively, MT1-MMP inhibited by TIMP-2 can act as a "receptor" of proMMP-2. This MT1-MMP/–TIMP-2/–proMMP-2 complex is then presented to an adjacent free MT1-MMP for activation. Clustering of MT1-MMP on the cell surface through interactions of the hemopexin domain facilitates the activation process[2, 25]. This process occurs only at low TIMP-2 concentrations relative to MT1-MMP to permit availability of enough inhibitor-free MT1-MMP to initiate pro-MMP-2 activation. On the other hand, high levels of TIMP-2 inhibit activation by blocking all free MT1-MMP molecules[25].

## REFERENCES:


1. Stamenkovic I. Extracellular matrix remodelling: the role of matrix metalloproteinases. *J Pathol*. 2003; 200: 448-64.
2. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res*. 2003; 92: 827-839.
3. Murphy G, Nagase H. progress in matrix metalloproteinase research. *Mol Aspects Med*. 2008; 29: 290-308
4. T Stoker W, Bode W. Structural features of a superfamily of zinc endopeptidases: the metzincins. *Curr Opin Str Biol*. 1995; 5: 383-390.
5. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. *Annu Rev Cell Dev Biol*. 2001; 17: 463-516.
6. Nagase H, Woessner J F. Matrix Metalloproteinases. *Journal Biol Chem*. 1999; 274: 21491-21494.
7. Gross J, Lapiere CM. Collagenolytic activity in amphibian tissues; a tissue culture assay. *Proc Natl Acad Sci USA*. 1962; 48: 1014-1022.
8. Parsons SL, Watson SA, Brown PD, Collins HM, Steele SJ. Matrix metalloproteinases. *Br J Surg.* 1997; 84: 160-166.
9. Curran S, Murray GI. Matrix Metalloproteinases In Tumour Invasion And Metastasis. *J Pathol.* 1999; 189: 300-308.
10. Birkedal-Hansen H, Moore WGI, Bodden MK, Windsor LJ, Birkedal-Hansen B, DeCarlo A, *et al.* Matrix metalloproteinases: a review. *Crit Rev Oral Biol Med*.1993; 4: 197-250.
11. AMikael Björklund, Erkki Koivunen. Gelatinase-mediated migration and invasion of cancer cells. *Biochim Biophys Acta*. 2005; 1755: 37- 69.
12. Nagase H, Visse R, Murphy G. Structure and function of MMP and TIMP. *Cardiovas Res*. 2006; 69: 562-573.
13. Tallant C, Marrero A, Gomis-Rüth FX. Matrix metalloproteinases: fold and function of their catalytic domains. *Biochim Biophys Acta*. 2010; 1803: 20-8.
14. Knäuper V, López-Otín C, Smith B, Knight G, Murphy. Biochemical characterization of human collagenase. *J Biol Chem*. 1996; 271: 1544-1550.
15. Klein G, Vellenga E, Fraaije MW, Kamps W A, Bont De. The possible role of matrix metalloproteinase (MMP)-2 and MMP-9 in cancer e.g., acute leukemia. *Crit Rev Oncol/Hematol*. 2004; 50: 87-100.
16. Curran S, Murray GI. Matrix metalloproteinases: molecular aspects of their roles in tumour invasion and metastasis. *Eur J Cancer*. 2000; 36:1621-30.
17. Munshi HG, Wu YI, Mukhopadhyay S, Ottaviano AJ, Sassano A, Koblinski JE. Differential regulation of membrane type 1-matrix metalloproteinase activity by ERK 1/2- and p38 MAPK-modulated tissue inhibitor of metalloproteinases 2 expression controls transforming growth factor-beta1-induced pericellular collagenolysis. *J Biol Chem*. 2004; 279: 39042-39050.
18. Hanzawa M, Shindoh M, Higashino F, Yasuda M, Inoue N, Hida K. Hepatocyte growth factor upregulates E1AF that induces oral squamous cell carcinoma cell invasion by activating matrix metalloproteinase genes. *Carcinogenesis*. 2000; 21: 1079-85.
19. Nagase H. Activation mechanisms of matrix metalloproteinases. *Biol Chem*. 1997; 378: 151-160.
20. Pei D, Weiss SJ. Furin-dependent intracellular activation of the human stromelysin-3 zymogen. *Nature*. 1995; 375:244-247.
21. Springman, EB, Angleton EL, Birkedal-Hansen, Van Wart HE. Multiple modes of activation of latent human fibroblast collagenase: evidence for the role of a Cys 73 active-site zinc complex in latency and a "cysteine switch" mechanism for activation. *Proc Natl Acad Sci USA*. 1990; 87: 364-368.
22. Jeong Ra H, Parks W. Control of matrix metalloproteinase catalytic activity. *Matrix Biol*. 2007; 26: 587-596.
23. Brew K, Dinakarpandian D, Nagase H. Tissue inhibitors of metalloproteinases: evolution, structure and function. *Biochim Biophys Acta*. 2000; 1477: 267-283.
24. Strongin AY, Collier I, Bannikov G, Marmer BL, Grant GA, Goldberg. Mechanism of cell-surface activation of 72-kDa type-IV Collagenase. Isolation of the activated form of the membrane metalloprotease. *J Biol Chem*. 1995; 270: 5331–5338.
25. Hernandez-Barrantes S, Bernardo M, Toth M, Fridman R. Regulation of membrane type-matrix metalloproteinases. *Semin Cancer Biol*. 2002; 12: 131-138.

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*Case Report*

# Case Report of a Giant Lithiasis in a Female Urethral Diverticulum

**Bhuju S**

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**Key words**:
Urethral diverticulum,
Urinary calculus,
Recurrent urinary tract infection.

## ABSTRACT

**Objectives:** We describe the successful repair of a large urethral diverticulum with giant calculus in a female by transvaginal approach and reviewed briefly about female urethral diverticula.

**Methods:** A 50-year-old woman with a history of postvoid dribbling, dyspareunia and recurrent urinary tract infections for 4 months came to our department. After investigation, a urethral diverticulum with calculus was diagnosed. Transvaginal diverticulectomy was performed and an anterior vaginal wall flap was placed. The published literature on female urethral diverticula was also analyzed.

**Results:** Post operative period was unremarkable. The patient regained normal voiding after surgery. In the published literature, there is no agreement seen in the diagnostic and surgical techniques for female urethral diverticula.

**Conclusions:** Urethral diverticula are diagnosed with increasing frequency. However, this entity continues to be overlooked because the symptoms may mimic other disorders. Cystourethroscopy, retrograde urethrograme using a double balloon catheter and recently magnetic resonance imaging may diagnose this disease. Complete excision through the anterior vaginal wall is the most successful treatment modality with minimum postoperative complications.

## INTRODUCTION

Urethral diverticulum is defined as a localized outpouching of the urethra into the anterior vaginal wall. Hey described the first female urethral diverticulum in 1805. Since this initial report, urethral diverticulum has been diagnosed with increasing frequency. Despite the increased awareness in recent years, this entity continues to be overlooked during routine evaluation of women with voiding problems[1].

Incidence of female urethral diverticulum ranges from 1.4 - 5% but may be higher. True incidence is unknown because many urethral diverticula are clinically asymptomatic[2]. Urethral diverticula occur most commonly in people aged 30-60 years. The mean age at diagnosis is 45 years. Occurrence in children is rare. The pathogenesis of this condition is poorly understood, and these lesions represent a spectrum of disorders ranging from isolated suburethral cysts to herniation of the urethral lining into the vaginal mucosa.

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## CASE REPORT

A 50 years lady presented in our hospital with difficulty and burning micturition from many months, red color urine for 10 days, urine R/E shows pus cells plenty, bacteria +++, so diagnosed as UTI and admitted at Medical Ward. Gynecology consultation was done for C/O swelling on vagina (Fig 1) for 2 years, pain on and off, no other complain. During per vaginal examination, hard mass was palpated on the anterior wall of vagina which was non tender. So suspected of bladder/ urethral mass/stone referred to urology department. On local examination, swelling of 4 cm X 3 cm in the anterior wall of vagina was found and was hard stone like feeling, and tender, no any discharge per urethra on pressing the swelling. So sent for KUB X-ray which shows right renal calculus, urinary bladder

calculus and ?urethral calculus. IVU was done which shows non excreting right kidney, urinary bladder calculus with huge ?urethral calculus (Fig 2). She underwent urethrocystoscopy which showed urethral diverticulum on proximal urethra, it's opening lies about 1 cm from bladder neck, even diverticular stone can seen from the scope and urinary bladder with single stone 3 X 2 cm size. So, she was diagnosed as non functioning right renal stone, urinary bladder stone and urethral diverticulum with stone. She underwent cystolithotomy and excision of diverticulum from anterior vaginal wall after removal of stone. Urethra was also repaired at same time. Post-operatively period was uneventful, planed for right nephrectomy after 3 months.

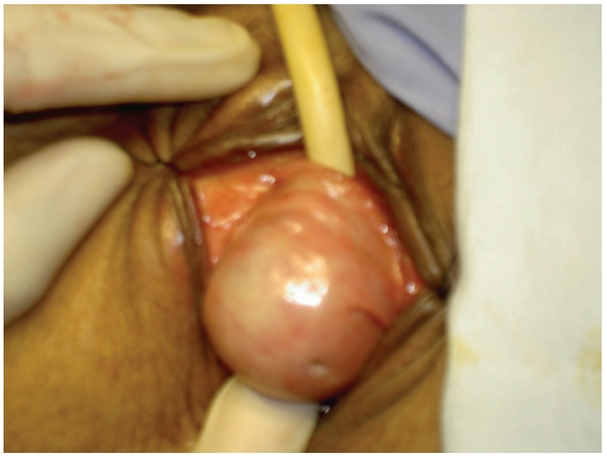
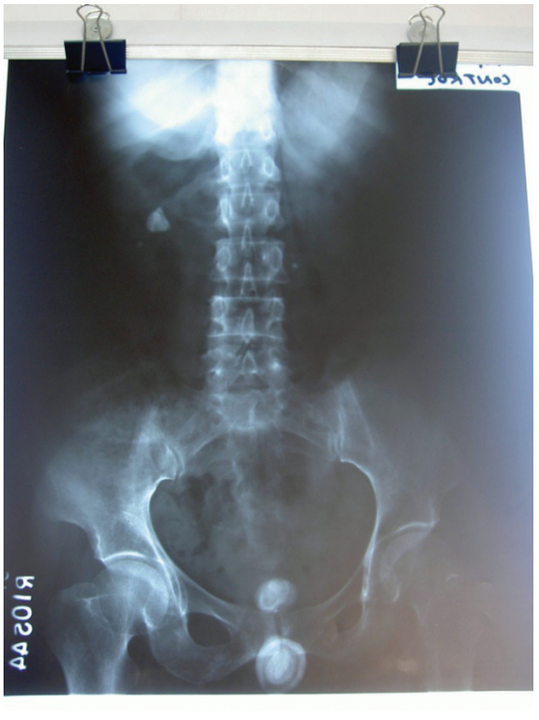


Fig 1: Swelling on vagina (hard mass on anterior wall of vagina)



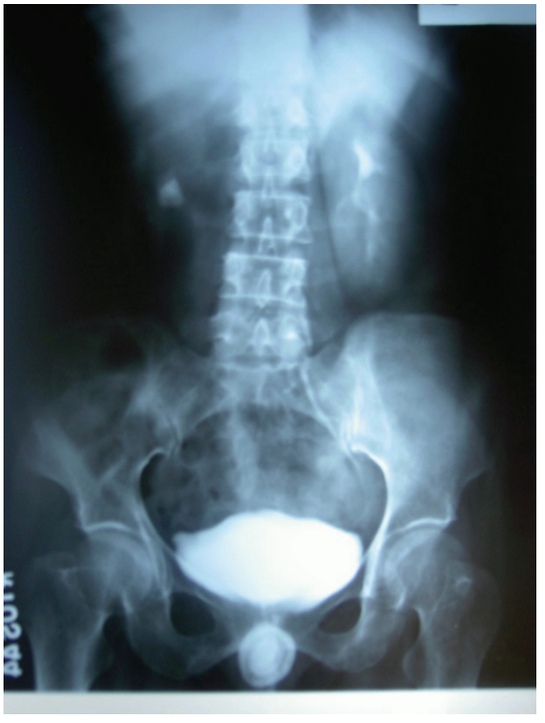
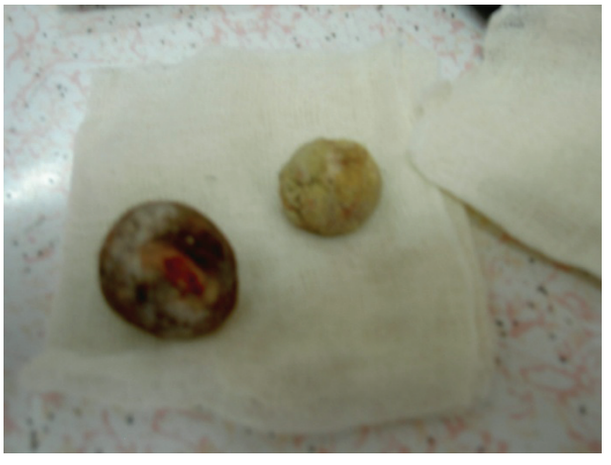


Fig 2: Urethral calculus (right)



## DISCUSSION

As early mentioned, urethral diverticulum incidence may be higher than what was written on books as most of them are asymptomatic. Presenting symptoms are classically described as the triad of post void dribbling, dysuria, and dyspareunia. However, the symptoms of urethral diverticula are quite variable. Irritative voiding symptoms, such as urinary frequency, urgency, and dysuria, are most common. Recurrent urinary tract infections occur in approximately 40% of patients, whereas approximately 25% report post void dribbling, and approximately 10% report dyspareunia. Other less frequent symptoms include hematuria and an anterior vaginal wall mass. Urethral diverticula have no classical presentation; they often present with many symptoms and it is important that the diagnosis is not overlooked[3].

A careful pelvic examination frequently reveals the suburethral mass on the anterior vaginal wall. Palpation of the anterior vaginal wall may reveal a soft spherical mass, which often is exquisitely tender. Compression of the mass may express urine or purulent material from the external meatus. Distinct firmness or hardness may reflect the presence of a stone or neoplasm within the diverticulum. Female urethral diverticula may be complicated by infection, stones, bladder outlet obstruction, and malignancy.

Stone formation within urethral diverticula is reported to occur in 1-10% of patients, when proximal urethral diverticula become very large.

The most helpful radiologic study is a properly performed voiding cystourethrography (VCUG). Retrograde urethrography using a double-balloon catheter may be useful if a suspected diverticulum cannot be observed on a VCUG. Cystourethroscopy is often performed using a short beaked female urethroscope with a 0-degree lens. Alternatively, flexible cystoscopy or an urethrotome sheath may be used. Constant water flow and bladder neck occlusion during urethroscopy allows the entire urethra to be distended to enhance visualization. High-resolution multiplanar US and MR imaging allow comprehensive evaluation of abnormalities of the female urethra[4].

Surgery is the current treatment of choice for urethral diverticula. Multiple open surgical and endoscopic approaches have been described for the treatment of urethral diverticula. They include transurethral cauterization of the diverticulum, marsupialization of the diverticular sac into the vagina, and excision of the diverticulum. Surgical treatment by transvaginal diverticulectomy with closure in several layers is the most frequent approach. Postoperative complications are rare[5].

## CONCLUSIONS

Urethral diverticula are diagnosed with increasing frequency. However, this entity continues to be overlooked because the symptoms may mimic other disorders. Cystourethroscopy, retrograde urethrograme using a double balloon catheter and recently magnetic resonance imaging may diagnose this disease. Complete excision through the anterior vaginal wall is the most successful treatment modality with minimum postoperative complications.

## REFERENCES

1. Gousse A, Lorenzo-Gomez MF, Lebouef L. Female urethral diverticulum. Report of a case. *Actas Urol Esp*. 2003 Nov-Dec; 27(10): 814-21.
2. Lee JW, Fynes MM. Female urethral diverticula. *Best Pract Res Clin Obstet Gynaecol*. 2005 Dec; 19(6): 875-93.
3. Rufford J, Cardozo L. Urethral diverticula: a diagnostic dilemma. *BJU Int*. 2004 Nov; 94(7): 1044-7.
4. Prasad SR, Menias CO, Narra VR, Middleton WD, Mukundan G, Samadi N, Heiken JP, Siegel CL.Cross-sectional imaging of the female urethra: technique and results. *Radiographics*. 2005 May-Jun; 25(3): 749-61.
5. Canovas Ivorra JA, Prieto Chaparro L, Rodriguez Fernandez E, Lopez Lopez C, Quilez Fenoll JM, Romero Maroto J. Surgical treatment of female urethral diverticula. Our experience. Bibliographic review. *Arch Esp Urol*. 2005 Jan-Feb; 58(1): 4-8.

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Use the decimal point, not a comma, for example 5.7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mm Hg).

**STATISTICS**

For detailed guidence on the handling of statistical material consult Br J Slug 1991; 78:782-4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

**DESIGN**

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (JAMA 1996; 276: 637-9).

**PRESENTATION**

Whenever possible use graphical presentation to illustrate the main fi ndings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

**ANALYSIS**

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistics, the number of degrees of freedom and the P value. Actual P values should be reported to two decimal places, especially when the result is not signifi cant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to P values.

## INTERPRETATION

Take great care in your interpretations. Do not place Undue emphasis on secondary analyses.

## REFERENCES

Type the references with double spacing in the Vancouver style (see preparation of manuscripts). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted. In the text, number references consecutively by superscript 1: or 1-3. References cited only in tables or figures should be numbered in sequence.

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