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Editorial

Dengue, a Global Scourge

It is estimated that each year about 50 million dengue infections occur, out of which about 500,000 (one percent) develop dengue hemorrhagic fever who need hospitalization. In India, Over 35000 dengue cases have been reported this year till 30th September with 64 deaths. Of course there must be a very large number of unreported cases in addition.

As is well known, dengue is caused by a virus (DENV) which has 5 serotypes. Four of these have been named as DENV-1, DENV-2, DENV-3 and DENV-4, fifth serotype was discovered in 2013. Virus is transmitted by Aedes mosquitoes, especially an aegypti, which thrives in fresh stagnant water, in close proximity of humans. Transmission through infected blood transfusion, organ transplants and mother-to-child (during pregnancy or delivery) has also been reported.

In 1997, WHO classified dengue fever into 3 groups, viz. undifferentiated fever, dengue fever and dengue hemorrhagic fever. Dengue hemorrhagic fever was further subdivided into Grades I, II, III, & IV, with Grade I referring to easy bruising and Grade IV to severe shock. In 2009, WHO revisited the classification to simplify it. According to this classification, dengue has been divided into only 2 groups: uncomplicated and severe. When dengue is associated with bleeding, organ dysfunction or severe plasma leakage, it is called severe. If not, it is called uncomplicated.

As there is no specific antiviral treatment available for dengue at present, WHO recommends an integrated vector control program to contain the disease. Most effective method of vector control is to eliminate habitats of Aedes mosquitoes by preventing open collections of water. This requires vigorous efforts by public health bodies and communities. Also mosquito bites can be prevented by using appropriate clothing, mosquito nets and mosquito repellent creams.

No vaccines are approved yet, but lot of efforts are under way all over the world for developing these. Four types of vaccines are being developed and studied: live attenuated vaccines, purified inactivated vaccines, subunit vaccines (using a portion of envelope protein of dengue virus) and plasmid DNA vaccine. One of these (CYD-TDV), being developed by Sanofi Pasteur, which is a live attenuated chimeric vaccine is already undergoing phase 3 clinical trials. Hopefully, an effective dengue vaccine may be available as early as 2016. Until, then we all have to redouble our efforts at preventing dengue by eliminating habitats of Aedes mosquitoes, and by protecting ourselves against mosquito bites.

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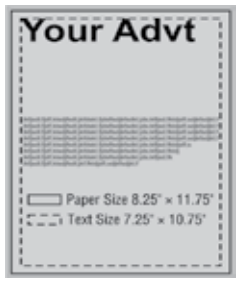

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ORIGINAL ARTICLE

Degree of Impairment of Liver Function in Dengue Fever Correlates to the Severity of its Complications

[1]Samir Uchadadia, [2]Babita Ghodke, [3]Kunal Bhuta, [4]Amrit Kejriwal, [5]Jaishree Ghanekar

ABSTRACT

Background: Dengue fever with its severe manifestations, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) has emerged as a major public health problem of international concern. Dengue, presenting as dengue fever (DF) or DHF or DSS, also has some effect on liver function. This study was conducted to find out the impact of dengue on liver function and correlation between clinical manifestation of dengue fever and degree of liver injury.

Materials and methods: This prospective randomized study was done on 200 outpatient department/inpatient department (OPD/IPD) patients in age group of 12 to 60 years including both sexes who confirm to the predetermined inclusion and exclusion criteria. Investigation included measurements of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), prothrombin time/international normalized ratio (PT/INR) and creatinine. Degree of liver involvement was classified in four groups.

Results: Out of 200 cases, 181 (90.5%) were diagnosed as dengue fever, nine (4.5%) as DHF, five (2.5%) as DSS, five (2.5%) as hepato-renal involvement; 24 (12.0%) had grade 0 liver injury, 126 (63.0%) had grade 1 liver injury, 34 (17%) had grade 2 liver injury, 10 (5.0%) had grade 3 liver injury and six (3.0%) had grade 4 liver injury.

Conclusion: Mild elevation of the liver enzymes is a common feature of dengue infection. There is high relation between the degree of liver damage and the appearance of the complications.

Keywords: Degree of liver injury, Dengue fever, Dengue hemorrhagic fever, Dengue shock syndrome, Prothrombin time.

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INTRODUCTION

Dengue virus is a member of the flaviviridae family, which includes west nile virus, yellow fever virus, Japanese encephalitis virus and tick-borne encephalitis virus, among others.[1] Dengue is caused by four antigenically distinct viruses, designated as dengue virus type 1 to 4 and is transmitted between vertebrate hosts by an insect vector—Aedes aegypti. The most serious manifestations of the infection are dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). No effective vaccine or antiviral drug therapy is currently available against dengue virus.[1] Dengue viral infection has been recognized as one of the world's biggest emerging epidemics. Throughout the tropics, this virus infection has an annual incidence of 100 million cases of dengue fever (DF), 250,000 cases of DHF and mortality rate of 24,000 to 25,000 per year.[2-4]

Typically, people infected with dengue virus are asymptomatic (80%) or only have mild symptoms, such as an uncomplicated fever.[5-6] Others have more severe illness (5%), and in a small proportion it is life-threatening.[5,6] The incubation period ranges from 3 to 14 days, but most often it is 4 to 7 days. The characteristic symptoms of dengue are: sudden-onset of fever, headache (typically behind the eyes), muscle and joint pains, and rash. The alternative name for dengue, 'break-bone fever', comes from the associated muscle and joint pains.[5,7]

This severe disease is marked by two problems: dysfunction of the endothelium and disordered blood clotting.[8] Endothelial dysfunction leads to the leakage of fluid from the blood vessels into the chest and abdominal cavities, while coagulation disorder is responsible for bleeding complications. Higher levels of virus in the blood and involvement of other organs (such as the liver) are associated with more severe disease.[9] Dengue may occasionally affect several other body systems.[10] This may be either in isolation or along with the classic dengue symptoms.[9] Hepatic dysfunction is common in dengue infection, and is attributed to a direct viral effect on liver cells or as a consequence of deregulated host immune responses against the virus. Other contributing factors include: race, diabetes, hemoglobinopathies, pre-existing liver damage and the use of hepatotoxic drugs.[10,11] Although there are isolated case reports of fulminant

hepatic failure, the derangements in the transaminases are usually mild and self-limiting.[10] Although the number of patients affected by the virus is increasing each year, little work has been done in the studied area (regarding the pathogenicity, changes in the liver and the complications of dengue infection). Therefore in this study, we aimed to evaluate the degree of liver injury by measuring the level of the liver enzymes, prothrombin time (PT) and creatinine. These parameters were compared with the clinical presentation of the patients; to see how was the degree of liver damage related to the complications of the disease. The first significance of this study is increasing the awareness of the local health staff about the degree of severity of liver damage in dengue infected patients. The second is the importance of measuring the liver enzymes like aspartate aminotransferase (AST) in the follow-up of dengue virus infection. Thirdly, this research forms a baseline for future studies in the region regarding the outcome, mortality, hospital stay and the prognosis of dengue infection according to the level of liver damage.

MATERIALS AND METHODS

It is a prospective randomized hospital based study. Two hundred OPD-IPD patients in age group of 12 to 60 years including both sexes, who confirmed to the pre-determined inclusion and exclusion criteria, were included in the study. The study was carried out between November 2012 and October 2014 in the MGM Hospital, Kamothe, Navi Mumbai, Maharashtra, India.

Inclusion Criteria

- Age ≥ 12 and ≤ 60 years.
- Diagnosed with dengue fever (immunoglobulin M/NS1 Ag).
- Willing to get investigated for serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum creatinine, prothrombin time/international normalized ratio (PT/INR).
- Willing and able to complete study information sheet and questionnaires.
- Willing and able to provide written informed consent prior to enrollment in the study.

Exclusion Criteria

- All the patients below the age of 12 years.
- All the patients above the age of 60 years.
- All the patients who refuse to participate in the study after informed consent.
- Positive for malaria, typhoid and leptospira.
- HbsAg positive.

Grading of Liver Injury

- Grade 0—Normal levels of liver enzymes;
- Grade 1—Mild elevation in the liver enzymes, more than two times of reference value;
- Grade 2—Elevated liver enzymes, with the levels of the enzymes increased to more than three times the reference values;
- Grade 3—Acute hepatitis, with liver enzymes' levels increased to at least 10 times their normal values;
- Grade 4—Evidence of hepatic failure (high PT) or hepato-renal involvement (high creatinine).

All liver function tests were done on fully automated AU480 biochemistry analyzer.

Serum bilirubin total and direct analysis were done by 2,5-dichlorophenyldiazonium (DPD) color test, and indirect bilirubin was calculated.

Serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase analyses were done by kinetic UV and alkaline phosphatase by kinetic color.

Prothrombin time—INR analysis was done by Thromborel S coagulation method.

Serum creatinine was analyzed by Jaffe's kinetic color test.

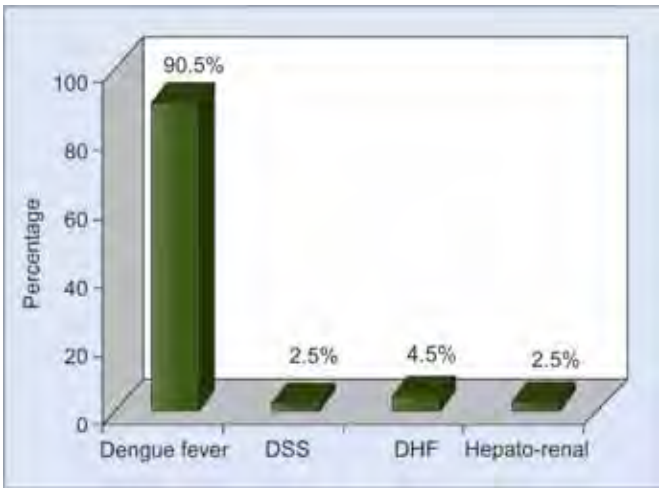
RESULTS

In the present study, 200 cases were enrolled; of which 104 cases (52%) were males and 96 cases (48%) were females. In the population studied, maximum cases were in 20 to 40 age group (115 cases—57.5%), and 79.5% in 20 to 50 age group. Among all the subjects studied, the eldest was 59 years old and the youngest was 16 years old. Out of the 200 cases, 181 (90.5%) were diagnosed as DF, 9 (4.5%) as DHF, 5 (2.5%) as DSS and 5 (2.5%) as hepato-renal involvement (Table 1 and Graph 1). Among the 200 cases, 24 (12.0%) had grade 0 liver injury, 126 (63.0%) had grade 1 liver injury, 34 (17%) had grade 2 liver injury, 10 (5.0%) had grade 3 liver injury and 6 (3.0%) had grade 4 liver injury (Table 2 and Graph 2).

- Grade 0 liver injury—100% had DF
- Grade 1 liver injury—98% had DF and 2% had DHF
- Grade 2 liver injury—85% had DF, 9% had DHF and 6% had DSS
- Grade 3 liver injury—40% had DF, 40% had DHF and 20% had DSS
- Grade 4 liver injury—83% had hepato-renal involvement and 17% had DSS

Table 1: Distribution of patients according to diagnosis

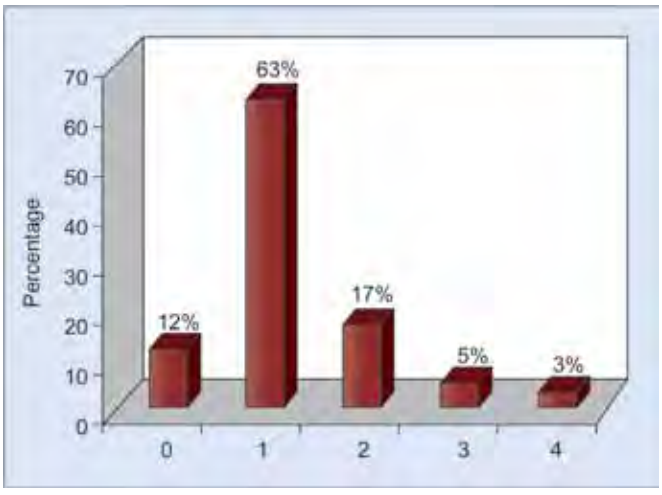
Diagnosis	*Frequency (patients)*	*Percent*
Dengue fever	181	90.5
DSS	5	2.5
DHF	9	4.5
Hepato-renal	5	2.5
Total	200	100



Graph 1: Distribution according to diagnosis

Table 2: Distribution of patients according to grade of liver injury

Grade of liver injury	*Frequency (patients)*	*Percent*
0	24	12.0
1	126	63.0
2	34	17.0
3	10	5.0
4	6	3.0
Total	200	100



Graph 2: Distribution according to grade liver injury

Thus, there is a high correlation between the degree of liver damage and the appearance of the complications (Table 3 and Graph 3).

The mean rise in SGOT levels was 171.27 ± 190.03 and that in SGPT levels was 144.71 ± 162.77. Therefore, SGPT (AST) levels (171.27 ± 190.03) tend to be greater than SGOT (alanine transaminase) levels (144.71 ± 162.77) (Table 4).

DISCUSSION

Dengue fever is one of the most important arboviral infections. It has become a major global public health problem. Classical dengue fever is an acute febrile illness, but in a small percentage of dengue infection, a more severe form of disease known as DHF occurs. Early recognition and meticulous management are very important to save precious lives from this killer disease.

Table 3: Grading of liver injury according to the diagnosis

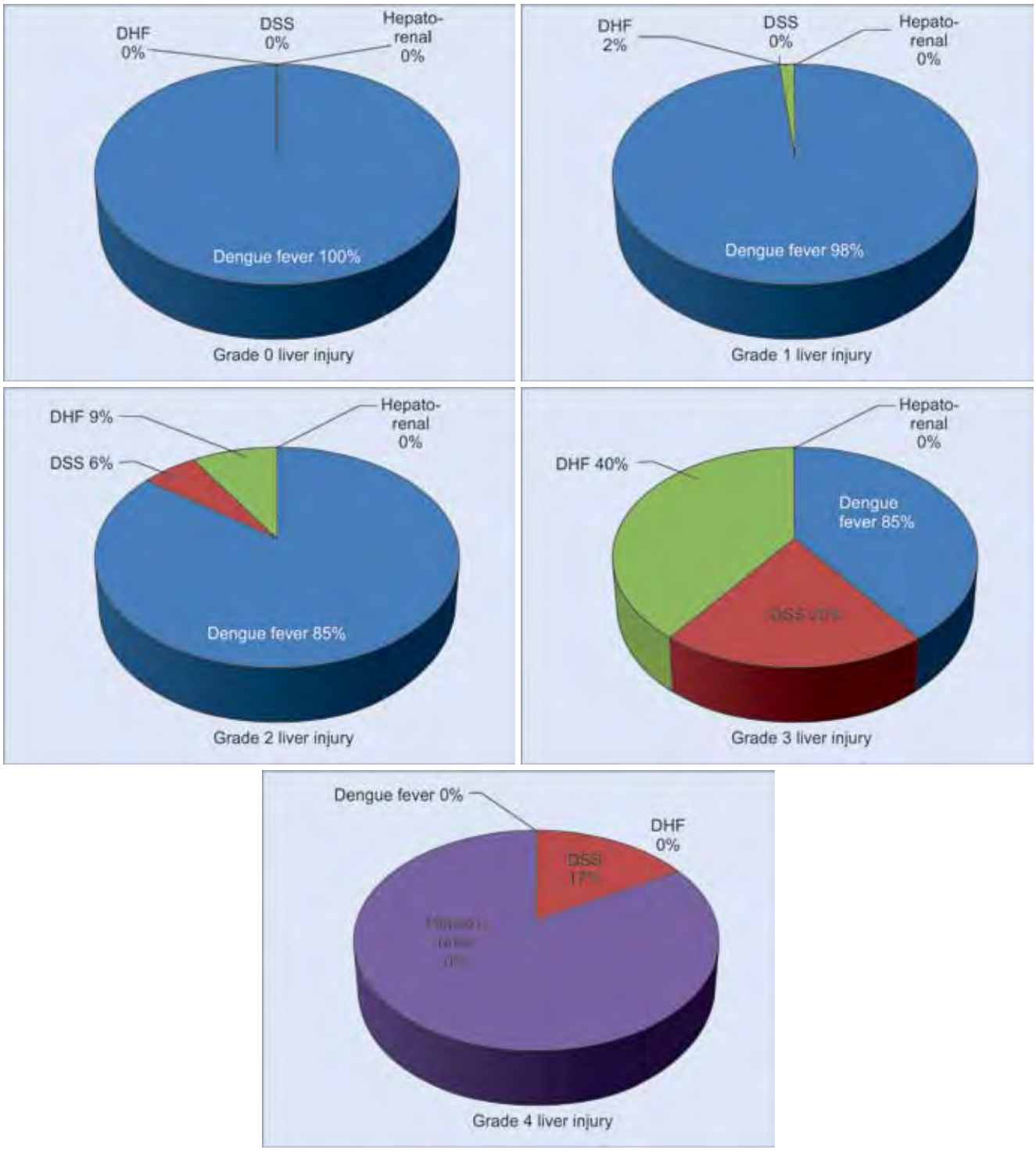
	Diagnosis				
Grade of liver injury	*Dengue fever*	*DSS*	*DHF*	*Hepato-renal*	*Total*
0	24	0	0	0	24
1	124	0	2	0	126
2	29	2	3	0	34
3	4	2	4	0	10
4	0	1	0	5	6
Total	181	5	9	5	200

Table 4: Descriptive statistics of investigation

Parameter	*N*	*Min.*	*Max.*	*Mean*	*SD*
SGOT	200	16.00	1100.00	171.27	190.03
SGPT	200	18.00	950.00	144.71	162.77
PT/INR	200	0.90	3.20	1.30	0.32
S. creatinine	200	0.60	3.90	0.97	0.36

The importance of this study lies in the severity of liver damage in dengue infection. In this research, we included dengue patients with mild symptoms seen in the outpatient department and severe cases who were admitted in the inpatient units. Therefore, this study covers both mild as well as severe cases of dengue virus infections.

Till date, there are two hypotheses that explain the damage of the liver in dengue patients. The first is immune enhancement hypothesis. In 2004, a strong correlation was found between T-cell activation and hepatic cellular infiltration in immune-competent mice infected with dengue virus.[12] It was noted that the kinetics of liver enzyme elevation was also correlated with that of T-cell activation, which suggested a relationship between T-cell infiltration and elevation of liver enzymes.[12] One of the studies detected the appearance of different helper cells and cytokines in human white blood cell cultures, infected *in vitro* with dengue virus type 2.[13] They reported that during dengue infection; monocytes, B-cells, T-cells and mast cells produce large amounts of cytokines. Despite all this, the role of host immunity in dengue infection is still very unclear. Unregulated host immune response may play some part in severity of dengue infection, therefore, by modifying the immune response, severe infection can be prevented.[10] The second hypothesis relates the damage in the liver to direct virulence of the virus.[10] According to these studies, we hypothesized the same mechanism responsible for the liver damage which occurred in our patients.



Graph 3: Grading of liver injury according to diagnosis

Liver damage with elevation of aminotransferases and reactive hepatitis was a common complication of dengue virus infection. Hence, measurement of AST and ALT is mandatory to see the liver involvement.[14]

The SGOT/AST levels in dengue infection tend to be greater than SGPT/ALT levels.[15,16] In our study too, aspartate aminotransferase levels (171.27 ± 190.03) tend to be greater than alanine aminotransferase levels (144.71 ± 162.77). This pattern is similar to that we see in alcoholic hepatitis but differs from that seen in other viral hepatitis. The exact cause of this is uncertain, but it has been suggested that it may be due to excessive release of AST from damaged myocytes during dengue infection.[17] This preferential elevation of liver enzymes, with AST being significantly higher than ALT was also noted in other study.[18] This abnormality may act as an early indicator of dengue infection.

In our study, we noticed high correlation between the degree of liver damage and presence of the complications. In 77% of the patients having dengue hemorrhage, severe

degree of liver damage occurs (Grades 2 and 3). We suggest a significant role of deranged liver functions in the causation of bleeding in addition to thrombocytopenia. Severe degree of liver injury (Grades 2 and 3) was also found in 80% of dengue shock syndrome cases. All the patients having encephalopathy had grade 4 liver damage. Encephalopathy in our patients may be due to fulminant hepatic failure or a high level of the virus that directly damages the brain. Involvement of the kidneys was also related to the severity of liver damage (Grade 4). Again, this may be a part of hepato-renal syndrome or direct virus virulence.

Similar results to our work were seen in other countries. In Saudi Arabia, Khan et al (2008) had made an association between high AST level and complications of dengue virus. In Taiwan,[17] has reported higher bleeding episodes in those who had high levels of AST, ALT and GGT. In Vietnam,[20] reported that DHF may cause mild to moderate liver dysfunction in most cases; only some patients may suffer from acute liver failure leading to encephalopathy and death. A report from India done by Shah (2008), pointed to high mortality in dengue patients with hepatitis and encephalopathy.[17,19-21]

CONCLUSION

Mild elevation of the liver enzymes is a common feature of dengue infection. On the other hand, this could be severe to a degree of acute hepatitis or even to fulminant hepatic failure. There is a high correlation between the degree of liver damage and the appearance of the complications. At least, the levels of SGOT/SGPT should be assessed in the first visit, and the follow-up of all dengue infected patients. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) can be a useful surrogate marker to predict disease severity, and bleeding outcome in dengue infection. The level of the other liver enzymes, PT, creatinine, and electrolytes should be assessed in all severe cases of dengue infection.

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ORIGINAL ARTICLE

Gender Difference in Acute Poisoning Cases in an Urban Area in Navi Mumbai, India

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ABSTRACT

Background: Poisoning is a global health problem and one of the major causes of hospitalization through emergency department. In several studies, preponderance of males in younger age group and pesticide consumption has been reported.

Method: The present study was undertaken at MGM Hospital and Research Centre, Central Business District (CBD) Belapur, Navi Mumbai, India to study the epidemiological profile of acute poisoning cases; following a chance observation of female preponderance among poisoning cases attending the hospital. Acute poisoning cases, who visited the hospital during the period of five years from 1st July 2007 to 30th June 2012, were included in the study. The data were pooled into pre-designed variable structure for the analysis.

Results: A total of 234 poisoning cases have been reported, majority of which, reside in neighboring areas of Belapur and Kharghar inhabited by middle to high income population group. Out of them, 172 (69.51%) patients were in the age group of 16 to 35 years and mean age was 26 years. The female to male ratio was 1.75:1 and contrary to other comparative studies, this reverse gender trend was found statistically significant ($p < 0.001$). A total of 137 (58.55%) poisoning cases were married. However, the proportion of married women–92/149 (61.74%), was statistically significant, placing young married women at higher risk of poisoning ($p < 0.0001$). In 32 (13.68%) cases, poisoning was accidental, while in remaining 202 (86.32%) deliberate self-harm (DSH) was the reason. Among the poisons consumed, psychotropic drugs (24.79%), insecticides (11.54%) and disinfectants (11.11%) constituted the bulk.

Conclusion: This is the first study, in Maharashtra and one among few in the country, which has reported high preponderance of young married women among poisoning cases. Adverse male to female ratio (1000:893) in Thane district where Navi Mumbai is located, coupled with findings of high incidence of acute poisoning in females, is a clear indication of social distress among women in this part of the country.

Keywords: Gender, Hospital information systems, Poisoning, Urban population.

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INTRODUCTION

The word 'poisoning' has been defined variously by the experts and dictionary. Random house dictionary (1969) defines poisoning as 'the condition produced by a poison or a toxic substance'. However, mere exposure to a poison or toxic substance may not be sufficient to produce the toxic effect of the poison. Poisoning has also been defined as 'any exposure to a toxic quantity of a poison'. Such a definition calls for setting of toxic dose, which is not defined/set for every poison.

In order to address above difficulties, Goulding[1] and Busik and Hindmarsh[2] have defined poisoning as 'any exposure to poison regardless of the dose and effect on the poisoned person'. However, each of these definitions, depending upon the one followed for estimation of the magnitude, may either over or underestimate the incidence.

World Health Organization (WHO), in first global estimate in 1990 based on extrapolation from limited data, estimated 3 million cases of pesticide poisonings and 2,20,000 deaths annually, majority of them being intentional.[3] The nature of poison used depends on the socioeconomic factors, cultural diversity and easy availability. Based on the above factors, the pattern of poisoning may vary in different parts of the world and even in different parts of same country.

The WHO estimates, based on 2001 data,[4] indicate that 8,49,000 people die globally from self-harm each year. However, poisoning is the commonest form of fatal self-harm in rural Asia, accounting for over 60% of all deaths, and is of far greater importance than hanging and other physical forms of self-harm.[5]

A national survey in Bangladesh showed that 14% of all deaths (3,971 out of 28,998) of women, between 10 and 50 years of age were due to self-poisoning, the majority with pesticides.[6] The problem is particularly severe in Sri Lanka,[7] where pesticide poisoning was the commonest cause of hospital death in six rural districts during 1995. With the progress in the industrial and agricultural field, and advances in medical sciences, a vast number of insecticides have become available, which on exposure may produce severe toxicity.

Information available in India is limited, with regard to acute poisoning in adults, including hospitalized patients.[8-12] In general, accidental poisoning is more common in children, whereas suicidal poisoning is more common in young adults.[8] It is important to know the nature and severity of poisoning in order to take appropriate preventive measures.

Primary objective of the present study was to examine gender difference, if any, among poisoning cases, and secondary objective was to study epidemiological profile of poisoning cases attending the emergency department following a chance observation of female preponderance among poisoning patients, contrary to male preponderance reported in majority of other Indian studies.

METHODS

The present study was undertaken at MGM Hospital and Research Centre, Central Business District (CBD), Belapur, Navi Mumbai. It was a retrospective hospital-records-based study, analyzing secondary data for the period of last 5 years, conducted after approval of authorities, and does have inherent limitations of records-based hospital studies.

In the present study, definition by Goulding and Busik[1,2] has been followed to define a case of poisoning. Poisoning can be classified variously based on the agendas mentioned by WHO in 1977,[13] host and environmental circumstances of poisoning,[14,15] and severity of symptoms.[16] Classification based on broad classes of environmental circumstances of poisoning as proposed by Proudfoot[14] has been adopted in this study, which includes[14]—accidental poisoning, deliberate poisoning, homicidal poisoning and non-accidental poisoning.

The records of 234 acute poisoning cases, excluding three deaths (about which the detailed data were not available), who visited hospital during the period of 5 years from 1st July 2007 to 30th June 2012 were included in the study. The data were pooled into pre-designed standardized variable structure for the analysis.

RESULTS

A total of 234 poisoning cases have been reported (2.72% of 8597 admissions through casualty and 1.64% of 14193 total hospital admissions during the study period), majority of which reside in dwelling units in neighboring areas of Belapur and Kharghar, which were either constructed and allocated by city and industrial development and construction organization (CIDCO) on the basis of income, i.e. low, middle and high income, or constructed by private builders and sold to the occupants. Majority of the cases pertain to residents residing in middle income and high income dwelling units. However, income information was not available in hospital records. Few cases were also reported from the adjacent slum areas that enjoy free or concessional services of the hospital.

Majority of the poisoning cases (91.88%) resided in CBD Belapur and adjoining Kharghar localities of Navi Mumbai. Geographical distribution of cases residing in Belapur and Kharghar areas of Navi Mumbai has been mapped in Figure 1. The sector eight of CBD Belapur urban area reported 27 cases of acute poisoning, which is the largest number from one particular sector.

The year and sex distribution of 234 cases of acute poisoning, which attended emergency department of the hospital during the period of study, has been shown in Graph 1. The number of cases seen over the period of 5 years suggests a sustained trend. The maximum number of cases were reported in the first quarter of the year ($n = 70$) and minimum in the last quarter ($n = 42$). Between 2007 and 2011, October was the only month to report minimum number of cases ($n = 7$).

As shown in Table 1, 172 (69.51%) patients were in the age group of 16 to 35 years and mean age of poisoning cases was 27.1 years. The youngest and the oldest victims of poisoning were 1 and 75 years old respectively. The proportion of females in the age group 16 to 35 years was higher and continued to remain high even among cases above 35 years. The female to male ratio was found to be 1.75:1 (females = 145, males = 85), and contrary to other comparative studies this reverse gender trend was found significant ($p < 0.001$). Female preponderance was noted, throughout the study period of 5 years.

Out of the 234 patients, 202 (86.32%) subjects took recourse to poisoning as a tool for deliberate self-harm as compared to the remaining 32 (13.68%), who were victims to accidental poisoning. The sex difference in selection of timing for poisoning was not observed. However, in majority of cases, poisoning took place in the afternoon and early night hours. A total of 137 (58.55%) cases were married individuals. Higher proportion of married individuals in acute poisoning was observed in both sexes as shown in Graph 2. However, proportion of young married females at the risk of acute poisoning was significantly higher ($p < 0.001$).

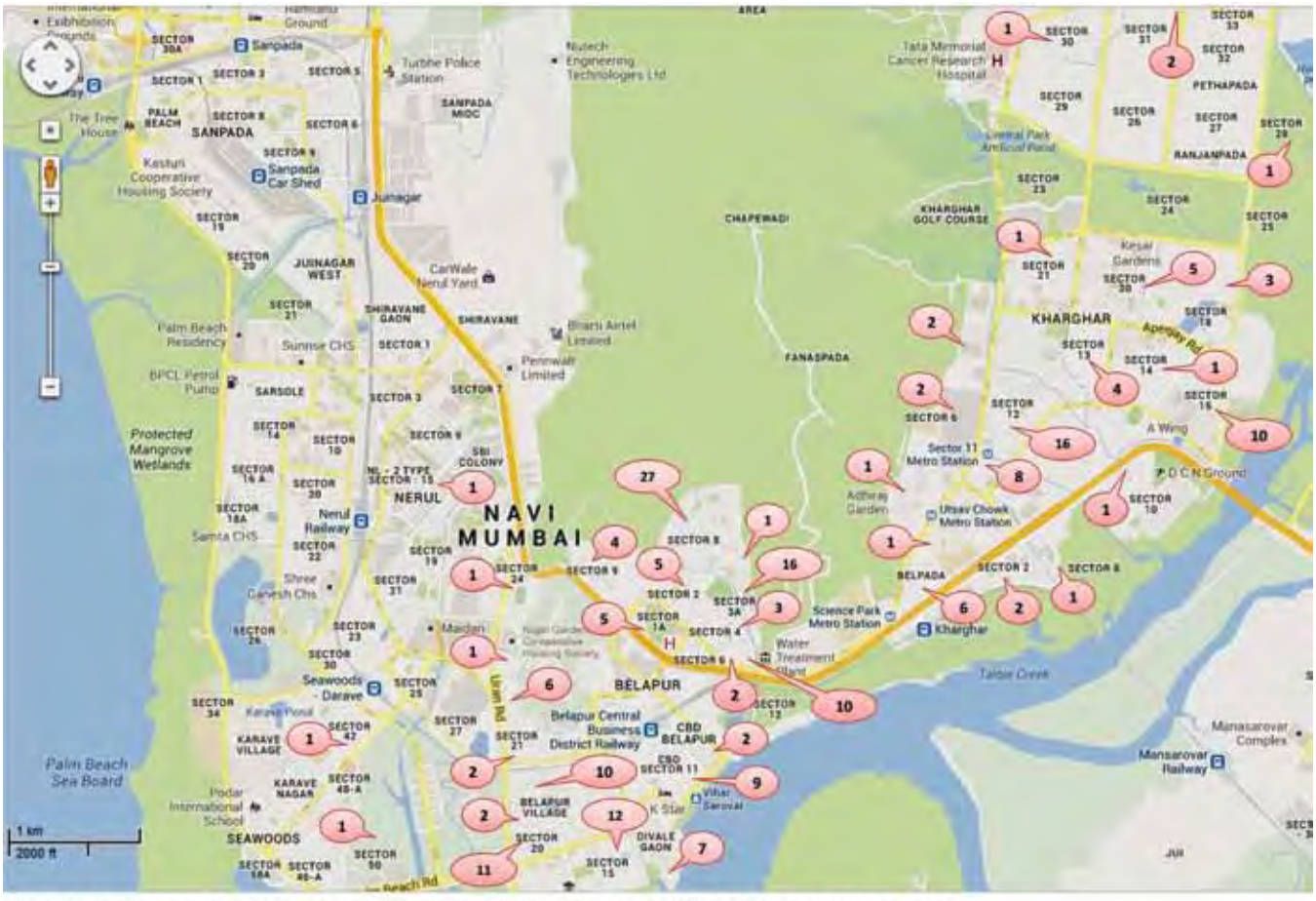
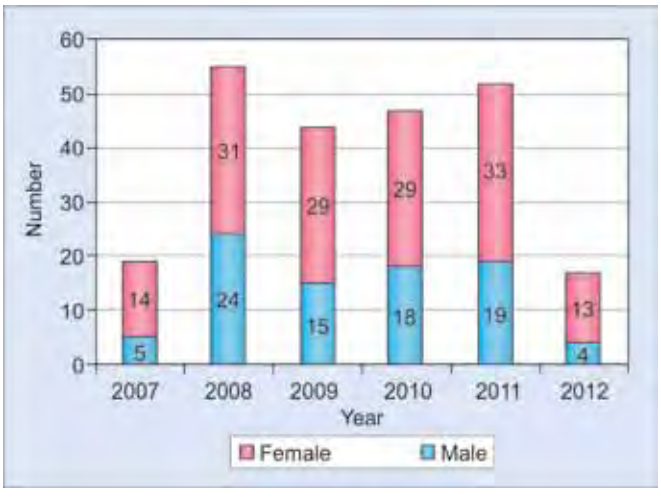


Fig. 1: Geographical distribution of cases residing in Belapur and Kharghar areas of Navi Mumbai



Graph 1: Year wise distribution of poisoning cases

As shown in Table 2, poisoning agents belonged to various groups including—household products, agricultural pesticides, industrial chemicals, drugs, plants, etc. The household poisons mainly comprised of pyrethroids, rodenticides, carbamates, phenyl, detergents, corrosives, etc. The drugs implicated included benzodiazepines, anticonvulsants, analgesics, antihistamines, tricyclic antidepressants, antihypertensive, etc. Among the agricultural pesticides, organophosphates and herbicides were also consumed. The psychotropic drugs (24.79%), insecticides (11.54%) and disinfectants (11.11%) constituted the bulk.

Table 1: Age and sex-wise distribution of poisoning cases

	Male		*Female*		*Total*	
Age group	*No.*	*%*	*No.*	*%*	*No.*	*%*
0–5	8	9.41	6	4.03	14	5.98
6–15	3	3.53	7	4.70	10	4.27
16–25	30	35.29	61	40.94	91	38.89
26–35	27	31.76	54	36.24	81	34.62
36–45	8	9.41	11	7.38	19	8.12
46–55	4	4.71	5	3.36	9	3.86
Above 55	5	5.88	5	3.36	10	4.27
Total	85	100	149	100	234	100

In this study, it was noticed that out of 237 (n = 234 and three excluded), only three patients died with a death rate of 1.27%.

DISCUSSION

The present study has reported female to male ratio of 1.75:1 (females–149, males–85), which is contrary to the male preponderance reported in comparative studies in India (referred later). This female preponderance is not only statistically significant ($p < 0.001$), but also has been persistent throughout the study period.

Graph 2: Marital status of poisoning cases

Table 2: Type of poisons consumed

	Male		*Female*		*Total*	
Poison	*No.*	*%*	*No.*	*%*	*No.*	*%*
Household poisons	37	43.53	53	35.58	90	38.47
Drugs	33	38.83	66	44.30	99	42.30
Agricultural pesticides	7	8.23	6	4.02	13	5.55
Not known	8	9.41	24	16.10	32	13.68
Total	85	100	149	100	234	100

The study further reported higher proportion of married individuals in acute poisoning in both sexes. However, proportion of young married females at the risk of acute poisoning was significantly higher ($p < 0.001$). Other Indian studies have shown married men to be at more risk, contrary to these findings.[9]

The findings of the present study are at variance from majority of studies in India, as it reports strong association of young females as major victims of acute poisoning. There are also few studies from South-east Asian countries, which have reported females as the major victims of acute poisoning like—Nepal,[17,18] Malaysia,[19] Thailand,[20] and West Bengal, India.[21] A few studies from Europe have also observed similar findings.[22,23] The present study area, Navi Mumbai, being an urban area has socio-demographic profile akin to urban areas worldwide including western societies, and thus presents poisoning profile more similar to the scenario in other urban areas.

A study from Vellore has shown an increasing trend of self-poisoning,[12] especially among young adults. Many studies have shown that deliberate poisoning has far higher morbidity and mortality than accidental-poisoning. Our findings are similar to those reported by number of other investigators in India and abroad.

The nature of poison consumed usually depends on easy accessibility, and similar observation has been made in the present study also. These study findings are comparable with similar studies undertaken in urban areas in India.[25,26] In contrast to majority of studies on acute poisoning among predominantly rural population, which have reported preponderance of organophosphorus compounds (OPCs) and other pesticides commonly used for agricultural purposes, a distinct pattern of poisoning was noted among male and female cases of poisoning. The females preferred drugs in general and psychotropic drugs in particular for poisoning, while males preferred alcohol mixed with psychotropic drugs, insecticides and rodenticides. The preponderance of young males and OPCs as the preferred poison have been reported uniformly in various studies undertaken in urban and rural areas in northern,[24,25] southern[9,27] and western[28,29] India. Many of such studies, though hospital based, had large number of victims from rural areas where OPCs are easily accessible.

It is interesting to note that researchers in India across the country, irrespective of rural or urban background, have reported preponderance of acute poisoning among young males. Studies conducted by Vaidya and Hulke,[28] and Zine and Mohanty[29] in Maharashtra; Unnikrishnan et al,[9] Kanchan and Menezes,[27] Bose et al,[30] and Ramesh et al[31] in Kerala; Kumar et al[32] in Andhra Pradesh; Jesslin et al,[33] and Jaiprakash et al[34] in Karnataka; Gargi et al,[24] and Singh et al[26] in North India, have reported young male preponderance among poisoning cases contrary to our findings.

The Navi Mumbai area belongs to Thane district of Maharashtra state. This district has one of the lowest sex ratio (893:1000—Census 2001) in the country. Hence, these findings send alarming signals to the public health authorities for critical examination of gender issues in the area.

A comparative data revealed that, in developed countries, the mortality rate due to poisoning is only 1 to 2%; but in developing countries like India,[35] it varies from 15 to 30%, and is the fourth most common cause of mortality, especially in rural India.[9,12]

CONCLUSION

The present study provides an insight into the epidemiological trend of poisoning in urban India. The study clearly establishes a significant association of young married women and acute poisoning in urban area. Male to female ratio in Navi Mumbai is one of the lowest in India, coupled with findings of high incidence of acute poisoning in females; it is a clear indication of social distress among women in this part of the country. There is a need of more research work for in-depth study of psychosocial factors contributing to acute poisoning among young population in general, and women in particular.

The large gender difference and young age suggests need for focused efforts to regulate the sale of commonly used poisons. Also, counseling services in schools and colleges to inculcate healthy attitudes and practices in younger generation, and promotion of self-help groups in community to help married women, are suggested. It would require the united efforts of multiple sectors to stop the beginning of the end, effectively.

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ORIGINAL ARTICLE

Level of Recovery after Stable and Unstable Intertrochanteric Hip Fractures

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ABSTRACT

Introduction: Hip fracture is a major public health problem because of its prevalence, economic costs, and health consequences. Intertrochanteric hip fractures account for approximately half of the hip fractures in the elderly; out of this more than 50% fractures are unstable. Displacement and stability of an intertrochanteric fracture are an important determinant of treatment.

Aims and objectives: To find out the level of recovery in different types of intertrochanteric hip fractures and to assess the functional capacity of patients who had an intertrochanteric hip fractures of different types.

Materials and methods: Fourteen subjects who underwent hip surgery for stable or unstable intertrochanteric fracture with internal fixation since 6 months to 1 year in the age group of 40 to 60 years were analyzed using the Harris hip score (HHS) to assess the level of recovery of the patient.

Results: Fourteen subjects with intertrochanteric fracture were recruited for the study. The pain component of HHS depicts that stable type of an intertrochanteric fracture displays a better mean pain score of 40.00 (SD = 0.00) compared to unstable type with a mean score of 36.29 (SD = 6.05) and the score for activity limitation concludes that there is less activity limitation in stable type compared to the unstable type of an intertrochanteric fracture with a mean score of 34.86 (SD = 6.69) and 23.86 (SD = 14.06) respectively. Deformity infers that stable type of intertrochanteric fracture shows less deformity at a score of 0.000 as compared to unstable type at 0.571 (SD = 1.51) and score for range of motion (ROM) is limited in stable type with a score of 3.86 (SD = 0.72) compared to 4.13 (SD = 0.55) scored by unstable type of intertrochanteric fracture group. The results for HHS shows stable type of intertrochanteric fracture displays a better HHS at 78.71 (SD = 6.18) compared to 64.85 (SD = 16.33) scored by unstable type group. A statistical comparison of HHS using Mann-Whitney U Statistic shows that there is no significant difference at 0.05 levels between stable and unstable type of intertrochanteric fracture groups.

Conclusion: This study concludes that a descriptive statistics of HHS mean scores falling in favor of stable type of intertrochanteric fracture, but a statistical comparison using Mann-Whitney U Statistic shows that there is no significant difference at 0.05 levels between stable and unstable type of intertrochanteric fracture groups.

Keywords: Intertrochanteric, Recovery, Stable, Unstable.

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INTRODUCTION

Hip fracture is a major public health problem because of its prevalence, economic costs, and health consequences.[1] Hip fracture rates for men and women combined in India is estimated to be <150/100,000.[2]

A hip fracture is generally a fracture of the proximal femur. Such injuries may be divided into three categories, according to the anatomical area in which they occur. Femoral neck and intertrochanteric fractures account for over 90% of hip fractures, occurring in approximately equal proportions and subtrochanteric fractures account for the remaining 5 to 10%.[3,4]

Intertrochanteric fractures are defined as fractures involving upper end of femur through and in between both trochanters with or without extension into the upper femoral shaft. There is an increasing incidence of intertrochanteric fractures with advancing age worldwide. They are the most frequently operated fracture type, have the highest postoperative mortality rate of surgically treated fractures and the complications associated with it have become a serious health resource issue because of the high cost of care required postoperatively.[5]

Although the treatment success of hip fractures using modern sliding implants has improved compared with rigid implants, considerable morbidity and mortality still exist especially in comminuted and unstable fractures. Excessive sliding of the femoral neck screw has been associated with suboptimal results.[6,7] The development

of the dynamic hip screw in the 1960's saw a revolution in the management of unstable fractures. However, the implant also failed to give good results in extremely unstable and the reverse oblique fracture apart from complications after surgical procedures.[5]

It is estimated that in the year after a hip fracture there was a decline in functional abilities, reduction in mobility and related functions and a reduction in tasks not related to hip function.[8] It was estimated that many sufferers were not able to achieve their pre fracture level of independent living a year after fracture together with a substantial decline in functioning.[1,9,10] Despite changes in functioning after hip fracture, the extent to which these changes can be attributed to the fracture remains uncertain; identifying this excess loss is important for understanding the level of recovery that can be expected following a fracture.[1]

Patients with hip fractures are not a homogeneous group. Intertrochanteric fractures can be defined as stable or unstable based on the involvement of the medial cortex.[11] Intertrochanteric hip fractures account for approximately half of the hip fractures in the elderly; out of this more than 50% fractures are unstable.[12] Displacement and stability of an intertrochanteric fracture is an important determinant of treatment.[13,14] There is a wealth of research to find the level of recovery after intertrochanteric fractures with mixed results with most of them showing less than 50% success rate[9, 10,15-19] and the predictors for recovery considered are pre injury general health and activity level, age and psychosocial factors.[20-27] Despite the wealth of outcomes research in patients with hip fractures, little is known about the outcomes of stable and unstable type of intertrochanteric fractures. Cornwall R et al in 2004 observed that patients with nondisplaced femoral neck fractures had higher overall, locomotion, transfer, and self-care functional independence measure (FIM) scores than did patients with unstable intertrochanteric fractures and patients with stable intertrochanteric fractures had better locomotion FIM scores at 2 months than did patients with unstable intertrochanteric fractures.[28]

The current study identified subjects with stable or unstable intertrochanteric fractures treated with dynamic or intramedullary hip screw. Information regarding pain, activity limitation, deformity and range of motion of affected hip were used as predictors for the recovery outcome.

MATERIALS AND METHODS

Fourteen subjects from rural areas of Raigad District, India, who underwent hip surgery for intertrochanteric fracture with internal fixation since 6 months to 1 year were recruited for the study after the ethical approval. The patients underwent surgery and further care in MGM Medical College Hospital, Kamothe, Navi Mumbai, India. Out of the recognized patients, only a few responded to the request for an appointment. They were called to Department of Physiotherapy, MGM Medical College Hospital, Navi Mumbai, or were visited at home for data collection. An informed consent was taken prior to data collection. The subjects were included on a convenient sampling method. The inclusion criteria were patients who had undergone surgery with internal fixation for intertrochanteric fracture. Those with bilateral hip fractures, pathologic fractures, previous ipsilateral hip fractures or surgery, fractures involving the pelvis, subtrochanteric region or femoral shaft, non-union and patients who underwent or undergoing physiotherapy rehabilitation[29-31] postsurgery were excluded from the study. Preoperative X-rays or photograph of X-rays were used to distinguish between stable and unstable types of fractures which were done by an orthopedic surgeon. Harris hip score (HHS) was used to assess the level of recovery of the patients. The multidimensional HHS was developed to evaluate outcome in orthopedic surgery of the hip joint.[32,33] Results are available on the responsiveness of the HHS in evaluating outcome of total hip replacement which shows higher responsiveness ratios than generic scales like the SF-36.[32-37] The SF-36 showed good responsiveness in trials on the effectiveness of various medical interventions such as total hip replacement, pharmacological therapy, and exercise program in osteoarthritis (OA).[34,35,37,38] Harris hip score is an observational assessment, which makes it less sensitive to a patient's subjective bias (such as socially desirable answers) than experienced recovery. Finally, functional disability (that is, the decrease of range of movement and hip function) can be more specifically considered with a multidimensional measure. Therefore, the HHS rather than a patient's global assessment is preferred.[39] Harris hip rating scale measures response to pain, limp, support, distance walked, sit, enter public transportation, stairs, put on shoes, absence of deformity, range of motion (ROM). Pain score with a total score of 44, activity limitation with a total score of 47, deformity with a total score of 4 and ROM of hip with a total score of 5 thus make total HHS of 100. Except for deformity, all other components perform better as the score goes higher.

The data thus collected by interviewing subjects using HHS were then entered in the website http://www.orthopaedicscore.com/scorepages/harris_hip_score.html and the final score was downloaded to Microsoft Excel software and further analyzed using SPSS software.

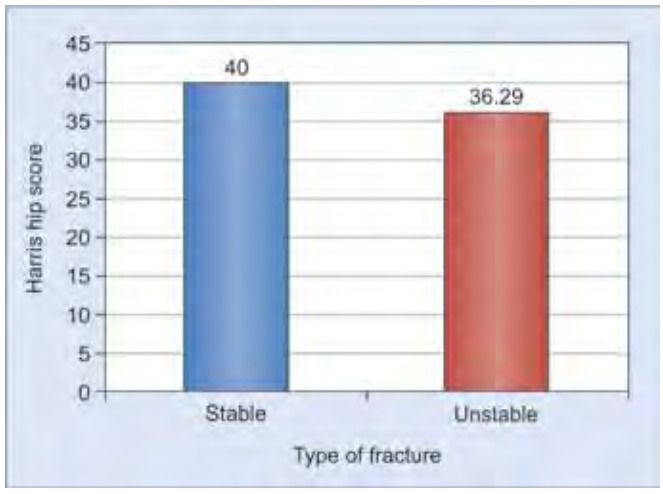
RESULTS

Fourteen subjects with intertrocahanteric fracture (7 stable and 7 unstable intertrochanteric fracture) who underwent surgery with internal fixation since 6 months to 1 year were recruited for the study. The subjects were in the age group of 40 to 60 years.

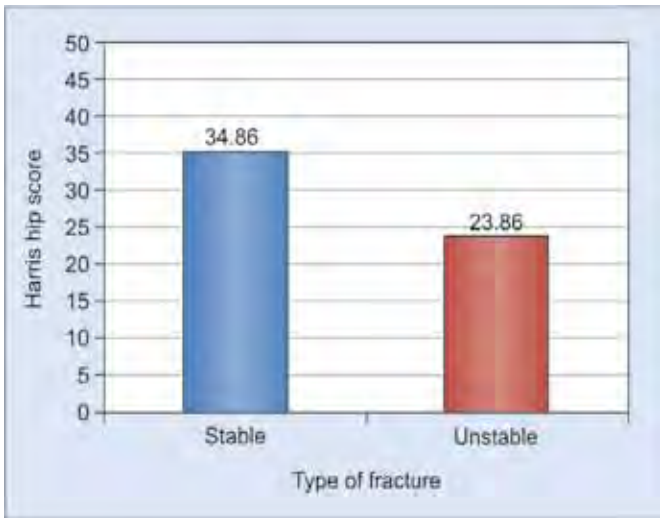
The mean and standard deviation (SD) of all the components of HHS, i.e. pain, activity limitation, deformity, ROM and of the total scoring of HHS are shown in Table 1. The pain component of the scale having a total HHS of 44 depicts that stable type of intertrochanteric fracture displays a better mean pain score at 40.00 (SD = 0.00) compared to unstable type with a mean score of 36.29 (SD = 6.05) (Graph 1) and the score for activity limitation concludes that there is less activity limitation in stable type compared to unstable type of intertrochanteric fracture with a mean score of 34.86 (SD = 6.62) and 23.86 (SD = 14.06) respectively against a total score of 47 (Graph 2). Deformity infers that stable type of intertrochanteric fracture shows less deformity at a score of 0.000 as compared to unstable type at 0.571 (SD = 1.51) against a total score of 4 (Graph 3) and score for ROM concludes that ROM having a total score of 5 is limited in stable type with a score of 3.86 (SD = 0.72) compared to 4.13 (SD = 0.55) scored by unstable type of intertrochanteric fracture group (Graph 4). Graph 5 shows overall scores of the HHS which is out of 100. The results for HHS shows stable type of intertrochanteric fracture displays a better HHS at 78.71 (SD = 6.18) compared to 64.85 (SD = 16.33) scored by unstable type group. Even though a descriptive comparison of mean scores of HHS falling in favor of stable type of intertrochanteric fracture, a statistical comparison using Mann-Whitney U Statistic shows that there is no significant difference at 0.05 levels between stable and unstable type of intertrochanteric fracture groups (Table 2).

Table 1: Group statistics shows mean and SD

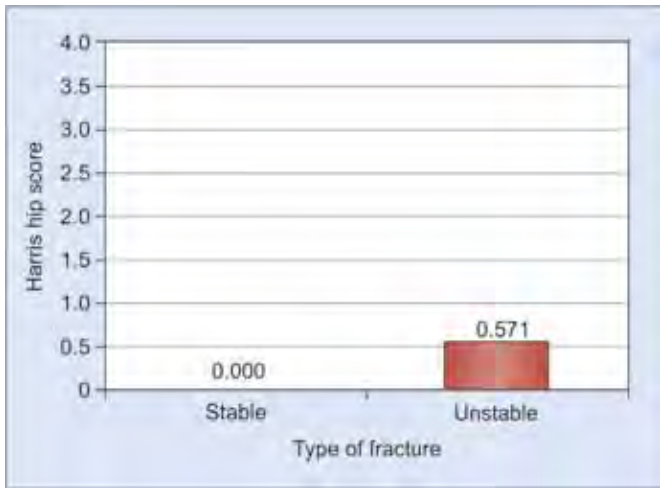
Group statistics					
Parameter	*Group*	*N*	*Mean*	*SD*	*SEM*
Pain score	Stable	7	40.000	0.000	0.000
	Unstable	7	36.286	6.047	2.286
	Total	14	38.14	4.54	1.213
Activity limitation	Stable	7	34.857	6.619	2.502
	Unstable	7	23.857	14.064	5.316
	Total	14	29.36	12.00	3.208
Deformity	Stable	7	0.000	0.000	0.000
	Unstable	7	0.571	1.512	0.571
	Total	14	0.29	1.07	0.286
ROM	Stable	7	3.857	0.723	0.273
	Unstable	7	4.132	0.551	0.208
	Total	14	3.99	0.63	0.169
HHS	Stable	7	78.714	6.177	2.335
	Unstable	7	64.846	16.331	6.172
	Total	14	71.78	13.87	3.708



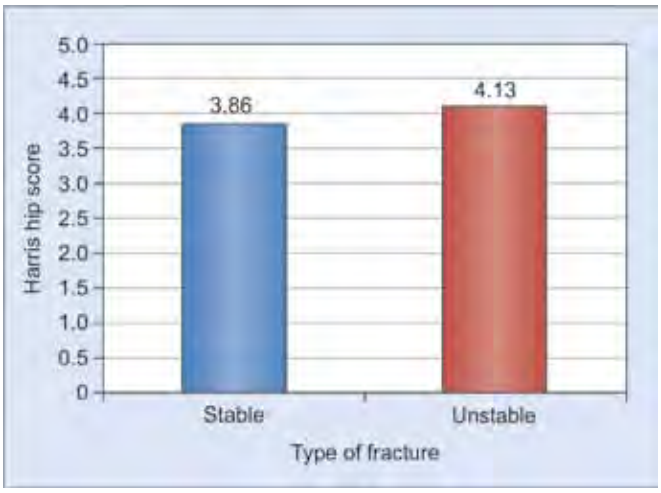
Graph 1: Stable type of intertrochanteric fracture displays a better pain score compared to unstable type



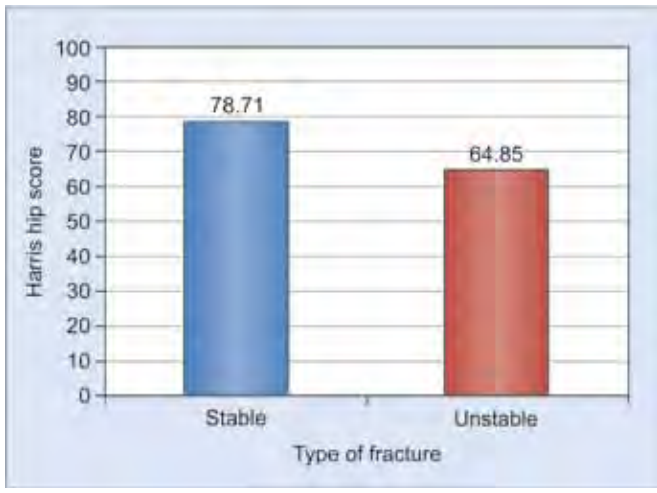
Graph 2: There is less activity limitation in stable type of intertrochanteric fracture compared to unstable type



Graph 3: There is less deformity in stable type of intertrochanteric fracture compared to unstable type. This is in advantage to the stable group



Graph 4: Range of motion is limited in stable type of intertrochanteric fracture compared to unstable type



Graph 5: Stable type of intertrochanteric fracture displays a better HHS compared to unstable type

Table 2: Comparison between stable and unstable type of intertrochanteric fracture (Using Mann-Whitney U test)

Comparison using Mann-Whitney U statistic						
Parameter	*Groups*	*N*	*Mean rank*	*Sum of ranks*	*Mann-Whitney U test*	*p-value*
Pain score	Stable	7	8.50	59.50	17.5	0.383
	Unstable	7	6.50	45.50		
Activity limitation	Stable	7	9.00	63.00	14	0.209
	Unstable	7	6.00	42.00		
Deformity	Stable	7	7.00	49.00	21	0.71
	Unstable	7	8.00	56.00		
ROM	Stable	7	6.71	47.00	19	0.535
	Unstable	7	8.29	58.00		
HHS	Stable	7	9.00	63.00	14	0.209
	Unstable	7	6.00	42.00		

DISCUSSION

The main result of this study is, there is a marginal inclination toward the results of subjects of HHS which measures response to pain and functions post surgery in the group of stable intertrochanteric fracture as compared with unstable intertrochanteric fracture. When a bone sustains enough force to be fractured, it is quite likely that ligaments and tendons are damaged as well. While bones generally heal quite well on their own with the help of a cast, ligaments and tendons usually do not heal completely. In addition, post-fracture pain may be due to the fact that the outside of the bone, or the periosteum, has not completely healed, something that would not show up on an X-ray. The inside of a bone does not contain nerve endings and, therefore, cannot feel pain, the outside of the bone does.[40] In the treatment of stable trochanteric fractures the problems involved in obtaining fracture union are minor, internal fixation is not a great mechanical problem because of an exact fracture reduction, which can usually be obtained, leads to a stable weight-transmission system in which load on the hip joint is transmitted to the femoral head through bone contact over the fracture line.[41] The internal fixation of unstable trochanteric fractures is primarily a mechanical problem.[1] So there is less pain and deformity in stable group as compared to unstable group.

In the present study, the levels of activity limitation attributable to the hip fracture were identified. Hip fracture takes its greatest toll on lower-body function. Also, stress falls on hip during standing and walking affects its recovery and due to the stability of fracture, stable group has less activity limitation as compared to unstable group.[42]

However, ROM shows marginally reverse attitude compared to the results of other study parameters. This fact is in contrast to the overall result between stable and unstable inter trochanteric hip fractures. There is no clinical explanation envisaged at this time but it should be noted that the difference is very minimal. Overall, there are no noteworthy differences found among stable and unstable intertrochanteric fracture groups. As the result shows there is a slight difference noted in favor of stable intertrochanteric group compared to unstable group but this is not statistically significant. This might be due to the small sample size. This makes the study necessary to continue on a larger population.

It is imperative that recovery from a hip fracture involves more than just repairing the fracture itself. Recovery involves rehabilitation to regain the ability to do tasks of daily living and to prevent further injuries. The orthopedic, medical, and rehabilitative teams must pay close attention to the type of hip fracture to generate appropriate prognostic goals and therapeutic strategies accordingly. This study should be continued on a larger population to establish the findings of this study.

CONCLUSION

This study concludes that a descriptive statistics of HHS mean scores falling in favor of stable type of intertrochanteric fracture but a statistical comparison using Mann-Whitney U statistic shows that there is no significant difference at 0.05 levels between stable and unstable type of intertrochanteric fracture groups.

This might be due to the small sample size. This makes the study necessary to continue on a larger population to establish this fact.

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ORIGINAL ARTICLE

Comparison of Different Methods for Diagnosis of Malarial Parasites

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ABSTRACT

The study aims to evaluate the sensitivity and specificity of different methods for diagnosis of malarial infection. Total 200 blood samples were collected in ethylenediaminetetraacetic acid (EDTA) Vacutainer tube from clinically suspected malaria patients. Each sample was processed as thick and thin smear stained with Leishman's stain for light microscopic examination, quantitative buffy coat test and rapid malarial antigen (HRP II and pLDH) test. The detection rate of malarial parasites by microscopic examination was 13.5%, quantitative buffy coat test was 18% and rapid malarial antigen (HRP II and pLDH) test was 20%. Thus, findings of microscopic examination must be compared with other more sensitive methods for confirmation of malaria. This will help early detection, proper diagnosis and treatment of malaria.

Keywords: Diagnosis, Malarial infection, Quantitative buffy coat, Rapid malarial antigen test.

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INTRODUCTION

Malaria is one of the highest killer diseases affecting most tropical countries. It affects over 500 million people worldwide and over one million children die annually from malaria.[1,2] According to the United Nations International Children's Emergency Fund (UNICEF), in every minute, malaria kills a child in the world.[3] Of all the human malaria parasites, *Plasmodium falciparum* (*P. falciparum*) is most pathogenic and frequently fatal if not treated in time.[3] In India, according to Nandwani et al[4] a total of 1.82 million cases of malaria and 0.89 million cases of *P. falciparum* cases were reported in the year 2002. According to National Vector Borne Disease Control Program[5] there were 10,66,981 malaria positive cases and 5,33,535 *P. falciparum* in the year 2012.

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The increasing incidence of *falciparum* malaria, the need to identify and treat the additional infective carriers (reservoirs) and to reduce the chances of transmission has given an impetus for development of simple and rapid methods for the diagnosis of *falciparum* malaria. Conventional Leishman's, Giemsa or Romanowsky's stained peripheral blood examination by light microscopy is the standard method for malaria diagnosis in malaria endemic countries. Conventional light microscopy has the advantages that it is relatively inexpensive, provides permanent record and can be shared with other disease control programs. However, it suffers from disadvantages, such as it is labor intensive and time consuming.[6]

The purpose of this study was to compare three methods of malaria diagnosis, i.e. microscopic examination of thick and thin blood smear stained with Leishman's stain, quantitative buffy coat (QBC) test and *malascan* rapid test for malaria (Pf/Pan Devices) to evaluate the sensitivity and specificity of these tests.

MATERIALS AND METHODS

This prospective study was carried out at Department of Microbiology, Mahatma Gandhi Mission Medical College and Hospital, Kamothe, Navi Mumbai, Maharashtra, India, over a period of 1 year from January 2013 to December 2013.

Study Design

It was a cross-sectional study.

Study Type

It was an prospective and analytical type of study.

Statistical Test

Chi-square test, Z-tests and statistical package for the social sciences (SPSS) (version 17) software was used for statistical analysis.

Inclusion Criteria

A total of 200 samples were collected from clinically suspected cases of malaria of all the age groups in both the sexes attending tertiary care hospital.

Exclusion Criteria

a. Patient already on antimalarial treatment.

b. In case of malarial parasite smear negative—patients with other positive lab test results—for typhoid fever and dengue fever.

Ethical Clearance

Ethical clearance was obtained from the Institutional Ethical Committee of Mahatma Gandhi Mission Institute of Health Sciences (Deemed University), Navi Mumbai, before starting the project.

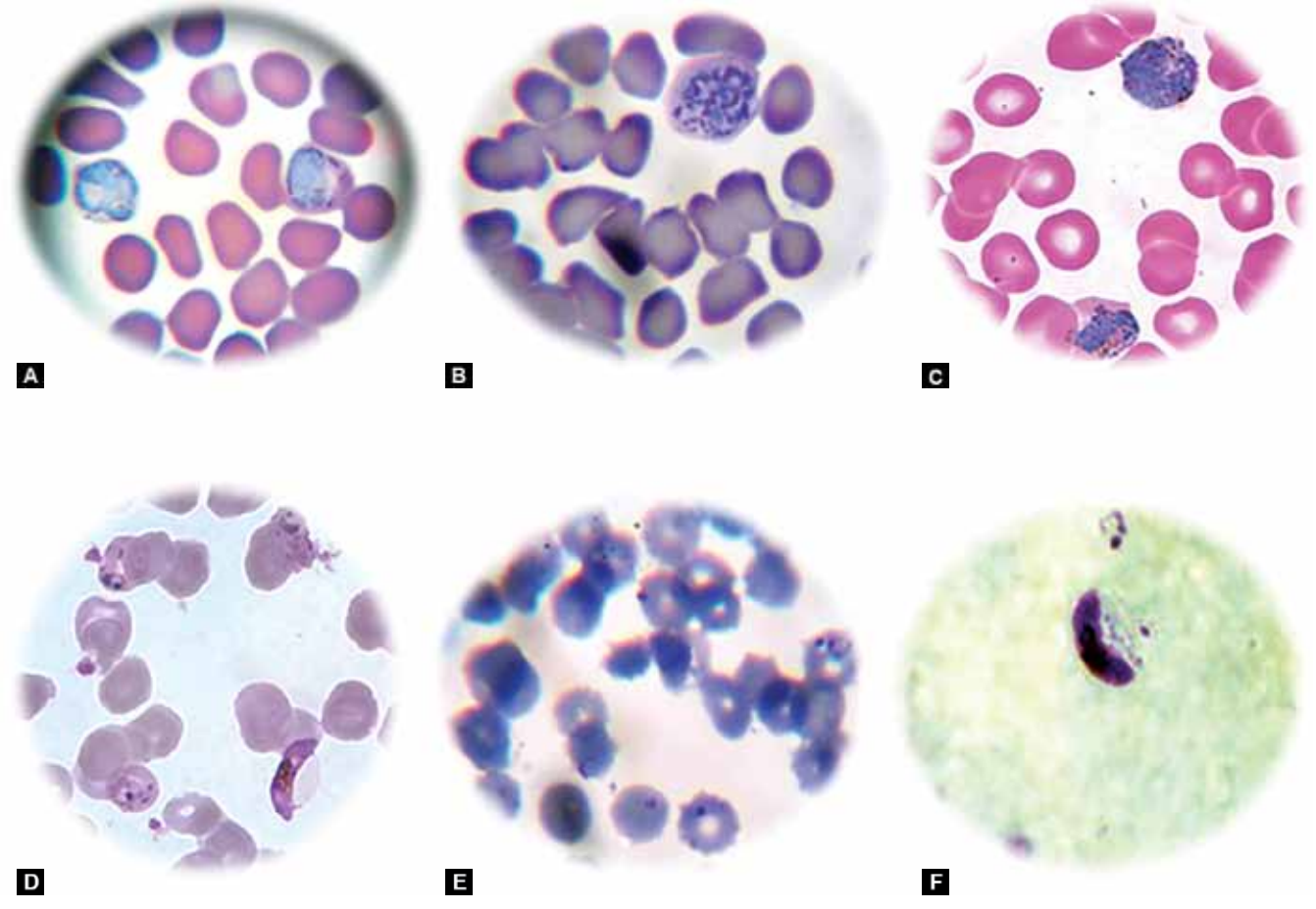
The detailed history, clinical signs and symptoms were recorded in the proforma. A total of 3 ml venous blood was collected into ethylenediaminetetraacetic acid (EDTA) tube (Becton Dickinson) under sterile precautions. Standard thick and thin smears were prepared. The smears were stained with Leishman's stain (Lot No. 0000168288-HiMedia Laboratories Pvt Ltd, India) and observed under 100x oil immersion objective lens (Figs 1A to F). The blood collected in EDTA was subjected to QBC test and rapid malarial antigen (RMA) test.

Quantitative buffy coat test was done using QBC kit (Diagnour RFCL Ltd, India). The QBC malaria tube was filled with venous blood upto black marking keeping tube nearly horizontal, rolled tube between fingers several times to mix blood and anticoagulants. Tube was rolled between fingers at least 10 times or for at least 5 seconds to mix blood with coating of acridine orange. Tube was sealed using tube plug and then tube suspender inserted into open end of QBC tube using clean forceps, provided with the kit. Quantitative buffy coat tube was centrifuged immediately. Quantitative buffy coat tube placed on rotor of microcentrifuge and centrifuged at 12000 revolutions per minute (rpm) for 5 minutes (Figs 2A to D).

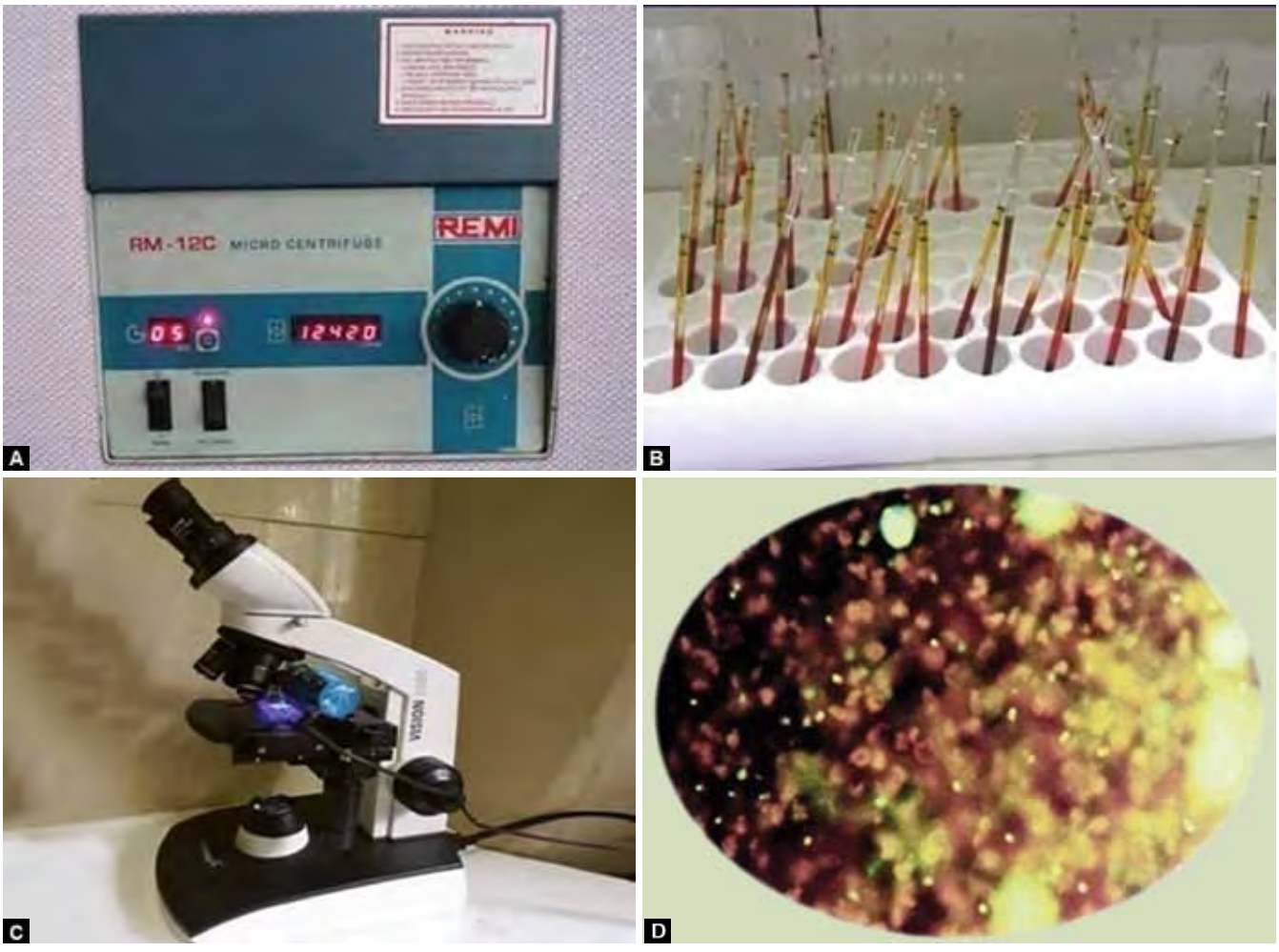
Malaria plasmodium lactate dehydrogenase (pLDH)/ histidine rich protein II (HRPII) was detected according to manufacturer's instruction using *malascan* rapid test for malaria (Pf/Pan Devices) (Lot No. V71103Z-Zephyr Biomedicals, India) (Fig. 3).

RESULTS

This prospective and analytical study was carried out at Department of Microbiology, Mahatma Gandhi Mission Medical College and Hospital, over a period of 1 year from January 2013 to December 2013. Total 200 blood samples were taken from malaria suspected patients after obtaining informed consent. All samples were tested by three different methods: (a) thick and thin smear made



Figs 1A to F: Different stages of malarial parasites: (A) Trophozoites of *P. vivax*, (B) schizont of *P. vivax*, (C) gametocytes of *P. vivax*, (D) gametocytes of *P. falciparum*, (E) ring stage trophozoites of *P. falciparum* and (F) gametocytes of *P. falciparum* in thick smear



Figs 2A to D: Detection of malarial parasites by QBC test: (A) Microcentrifuge machine for QBC test, (B) processed QBC tube, (C) para lens advanced w/60x objective attached microscope with para viewer and (D) trophozoite and schizonts of plasmodium vivax along with malarial pigment

Fig. 3: Detection of malarial parasites by RMA test

from all blood samples and stained with Leishman's stain and microscopic examination was done, 27 samples out of 200, were positive for malarial parasites i.e. 13.5%, (b) quantitative buffy coat test showed that 36 samples out of 200 were positive for malarial parasites, i.e. 18% and (c) rapid malarial antigen test showed positive result for 40 samples out of 200, i.e. 20% (Table 1 and Graph 1). Actual number of species detected by three methods is shown in Graph 2 and Table 2.

In our study, microscopic findings showed *P. vivax* 55.56%, *P. falciparum* 18.52% and mixed species 25.92% (Graph 3). The QBC test showed *P. vivax* 61.11%, *P. falciparum* 22.22% and mixed species 16.67% (Graph 4).

Rapid malarial antigen (HRP II and pLDH) test showed *P. vivax* 62.50%, *P. falciparum* 25% and mixed species 12.50% (Graph 5).

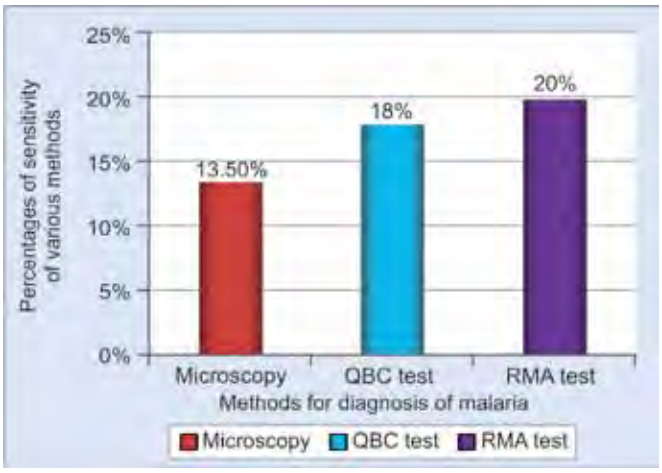
Statistical analysis of microscopy is Chi-square = 2.12, df=1,p-value=0.141nandofQBCtestChi-square=0.177,df=1, p-value = 0.674; p-value of microscopy and QBC test as compared to RMA test are 0.141 and 0.674 respectively nearer to significant p-value of 0.05.

In our study, the sensitivity and specificity of different methods was as follows:

1. Microscopy 67.50% (95% CI: 61.71 to 86.23%) and 100% (95% CI: 97.70 to 100%)

Table 1: Comparison of different methods for diagnosis of malarial parasite

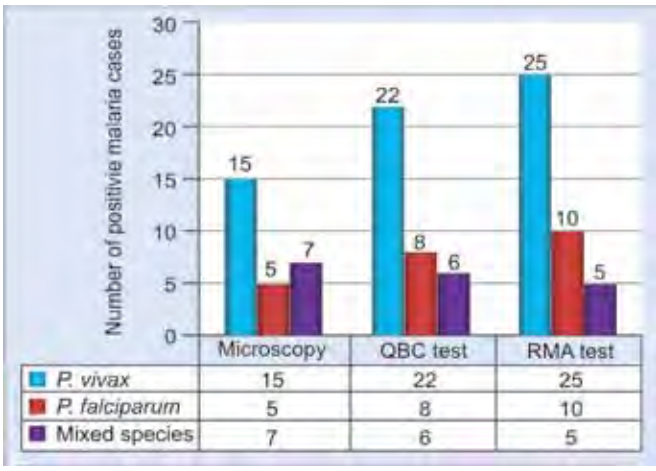
Methods	*Malaria positive*	*Percentages*
Microscopy	27/200	13.5
QBC test	36/200	18
RMA test	40/200	20



Graph 1: Sensitivity of various methods for detection of malarial parasites

Table 2: Comparison of diagnostic methods for detection of malarial parasites

Methods	*P. vivax*	*P. falciparum*	*Mixed species*	*Total samples*
Microscopy	15 (55.56%)	5 (18.52%)	7 (25.92%)	27 (100%)
QBC test	22 (61.11%)	8 (22.22%)	6 (16.67%)	36 (100%)
RMA test	25 (62.50%)	10 (25%)	5 (12.5%)	40 (100%)

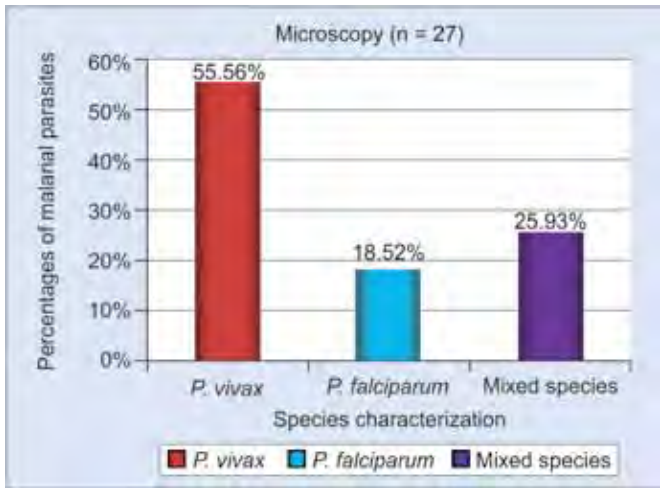


Graph 2: Specificity of various methods for detection of malarial parasites

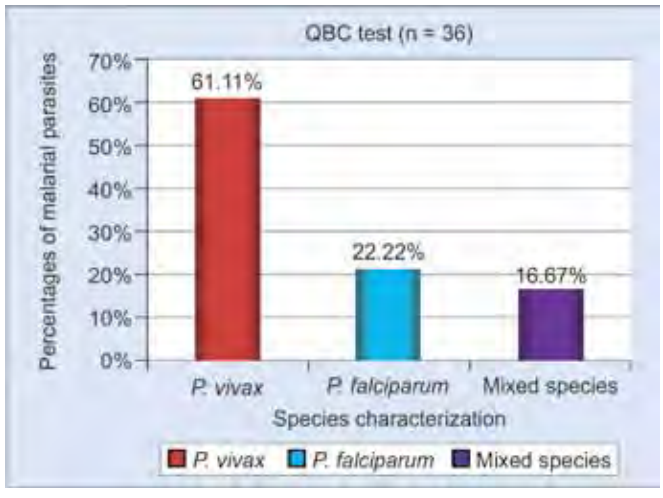
2. QBC test 90.91% (95% CI: 78.31 to 97.41%) and 100% (95% CI: 97.70 to 100%)
3. RMA test 100% (95% CI: 91.11 to 100%) and 100% (95% CI: 97.70 to 100%).

DISCUSSION

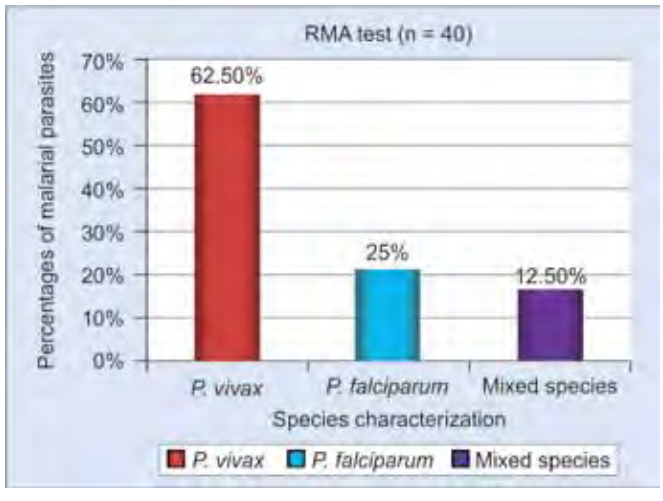
There are reports or studies on diagnosis of malaria by different methods from India and other countries. There



Graph 3: Species characterization of malarial parasites by microscopy



Graph 4: Species characterization of malarial parasites by QBC test



Graph 5: Species characterization of malarial parasites by RMA test

are some differences depending on geographic location, disease burden, endemicity and methods followed.

Total 200 blood samples of suspected malaria cases were studied by different methods. Microscopy, QBC test and RMA test showed positivity of malarial parasites as 13.5, 18 and 20% respectively in our study (Table 1).

Table 3: Comparison of work of different workers

Workers	*Place*	*No. of samples*	*Leishman's*	*Field's*	*Acridine*	*QBC test*	*RMA test*
Mendiratta DK et al[6]	Sevagram Maharashtra	443	18.28%	6.32%	18.28%		18.1%
Azikiwe CCA et al[7]	Nigeria	200	59%				64%
Aparna Y et al[8]	Karnataka India	137	13.87%			20.44%	15.33%
Ali-Akbar et al[9]	Kahnuj, Iran	124	77%				
Our study	Navi Mumbai India	200	13.5%			18%	20%

Our results of microscopy compared well with Mendiratta DK et al[6] (18.28%) and Aparna Y et al[8] (13.87%). Azikiwe CCA et al[7] from Nigeria reported microscopic finding of malaria as 59%, Ali-Akbar et al[9] from Kahnuj, Iran found sensitivity of 77% by microscopy sensitivity of 77% by microscopy (Table 3).

The reasons for low sensitivity of microscopy are:

1. It is affected by time of blood collection. Malarial parasites will be seen only when blood sample is collected at the time of febrile episode.
2. Lot of subjective variation. Many false positives and false negatives.
3. Prior treatment with antimalarial can lead to negative results in microscopy.

Reporting of malarial parasites by microscopy is subjective and many variations can occur in results from person to person. Some over or under reporting can occur. Similarly, the higher values are reported from highly endemic areas like Africa.

Our results of QBC test (18%) correlate well with Aparna Y et al[8] (20.44%). Other workers do not have data for QBC test. Quantitative buffy coat test is more sensitive than light microscopy as the blood sample is centrifuged at 12,000 rpm and RBCs are concentrated. Positivity of RMA test in our study (20%) is close to Mendiratta DK et al[6] (18.1%), Aparna Y et al[8] 15.33%. Azikiwe CCA et al[7] reported higher positivity of RMA test (64%) as compared to microscopy, which is similar to our findings. Sensitivity of RMA test was higher than light microscopy and QBC test. As mentioned in review, light microscopy and QBC test detect the parasites in red blood cells where as RMA test can detect the malarial antigen in plasma which is released by analysis of RBCs in blood, in patient (*in vivo*) and then in the test procedure (*in vitro*).

As regards, species wise detection of malarial parasites by different methods, in our study, microscopic findings were *P. vivax* 55.56%, *P. falciparum* 18.52% and mixed species 25.92% (Graph 3). In QBC test findings, positive results were *P. vivax* 61.11%, *P. falciparum* 22.22% and mixed species 16.67% (Graph 4). In RMA (HRP II and pLDH) test, findings out of 40 were *P. vivax* 62.50%, *P. falciparum* 25% and mixed species 12.50% (Graph 5).

The results show that with RMA test which is based on detection of malarial antigens (HRP II and pLDH), the results of mixed species by microscopy decreased from 7/27 (25.92) to 5/40 (12.5%). Microscopy is subjective and there is possibility of over reporting of mixed malarial parasitic infection.

Statistical analysis of microscopy is Chi-square = 2.12, df = 1, p-value = 0.141n and of QBC test Chi-square = 0.177, df = 1, p-value = 0.674.

p-value of microscopy and QBC test as compared to RMA test are 0.141 and 0.674 respectively nearer to significant p-value of 0.05.

CONCLUSION

Quantitative buffy coat test and RMA test are more sensitive than microscopy. Rapid malarial antigen being immunological method (detecting HRP II antigen and pLDH enzyme) has high sensitivity and specificity, easy to perform. Quantitative buffy coat test is less sensitive than RMA test requires specialized equipment and training. Light microscopy is least sensitive and subjective. Hence, when microscopic examination is negative, it is necessary to perform RMA test, which has high sensitivity and specificity. This will help early detection of malaria, proper diagnosis and treatment, reducing morbidity and mortality.

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ORIGINAL ARTICLE

Comparative Study of Serum Calcium and Magnesium in Pre-eclamptic Pregnancies in Third Trimester and its Comparison with Healthy Normotensive Nonpregnant and Pregnant Women and to Evaluate their role in Pregnancy-induced Hypertension

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ABSTRACT

Background: Despite numerous studies, the etiology of pre-eclampsia has not been fully elucidated. The study of serum calcium and serum magnesium is gaining ground in the pathophysiology of hypertension.

Objective: A comparative study of serum calcium and serum magnesium in women with pre-eclamptic pregnancy and its comparison with healthy normotensive nonpregnant women and healthy normotensive pregnant women in third trimester.

Materials and methods: Serum calcium and serum magnesium were measured in 52 women with pre-eclampsia in their trimester of pregnancy as patients group, and in 73 healthy normotensive nonpregnant women and 65 healthy normotensive pregnant women as control groups with similar maternal and gestational ages. Pre-eclamptic group was further divided into two subgroups mild (n = 36) and severe pre-eclampsia (n = 16). This is the case-control hospital based study carried in the Department of Biochemistry, MGM Medical College and associated MY Hospital, Indore, Madhya Pradesh.

Results: There were no significant differences among the three groups in age and body mass index (BMI) ($p > 0.05$) but significantly higher differences in gestational age, systolic and diastolic blood pressure was observed ($p < 0.001$). When comparison of serum calcium and serum magnesium between healthy normotensive nonpregnant women (9.87 ± 0.6 mg/dl, 2.60 ± 0.3 mg/dl) and healthy normotensive pregnant women was done, the levels were lower in the healthy normotensive pregnant women (9.34 ± 0.49 mg/dl, 2.36 ± 0.13 mg/dl) with statistically higher significant difference ($p < 0.001$). Lower mean values of serum calcium and serum magnesium were found in pre-eclamptic women (8.82 ± 0.93 mg/dl, 1.74 ± 0.24 mg/dl) than those of healthy normotensive nonpregnant women (9.87 ± 0.6 mg/dl, 2.60 ± 0.3 mg/dl) and healthy normotensive pregnant women (9.34 ± 0.49 mg/dl, 2.36 ± 0.13 mg/dl) in third trimester with statistically higher significant differences ($p < 0.001$). As compare to mild pre-eclamptic pregnant women (9.07 ± 0.8 mg/dl, 1.77 ± 0.24 mg/dl), the levels of serum calcium and serum magnesium in severe pre-eclamptic pregnant women (8.25 ± 0.97 mg/dl 1.65 ± 0.24 mg/dl) was lower and the difference was significantly higher ($p < 0.001$).

Conclusion: These findings support the hypothesis that hypocalcemia and hypomagnesemia are possible etiologies of pre-eclampsia and levels of calcium may be more important than magnesium.

Keywords: Calcitonin gene related peptide, Parathyroid hormone related peptide, Pre-eclampsia, Pregnancy-induced hypertension, Serum calcium, Serum magnesium.

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INTRODUCTION

Hypertension, defined by a blood pressure (BP) of 140/90 mm Hg or more, is a universal problem affecting at least 10% of all pregnancies.[1] Half of the pregnant women with hypertension have pre-eclampsia. Hypertensive disorders accounts for up to 40,000 maternal deaths annually.[2] Pre-eclampsia (hypertension in pregnancy in association with the excretion of >300 mg of urinary protein per day after 20th weeks of gestation) is an important cause of both maternal and perinatal morbidity and mortality.[3] It is a transient but potentially dangerous complication of pregnancy affecting 5 to 8% of pregnancies.[4] Because of multiple hypothesis, it has been dubbed as the 'disease of theories'. Although the etiology of pre-eclampsia has not been fully elucidated,[5] the contributing factors are obesity, diabetes, calcium deficiency, older maternal age. Environmental and nutritional factors may, therefore, play a role in the etiology of pre-eclampsia.[6]

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Calcium, one of the intracellular ions, is the most prevalent cation and the abundant mineral found in the body. These are needed for transmission of nerve impulses, muscle contraction, blood vessel contraction and expansion, secretion of hormones and enzymes, act as a cofactor in certain enzyme reactions, water balance in the cells, sending messages through the nervous system and in the coagulation of the blood as it is factor IV in blood coagulation.[7] It is known that the deficiency of calcium may lead to capillary hemorrhages, tetanic convulsions, tissue exudation, osteomalacia, etc.[8] Regulation of intracellular calcium plays a key role in hypertension.[9]

Magnesium is the 4th most abundant cation of intracellular fluids. It is present in more than 300 enzymatic systems where it is crucial for ATP metabolism. It also acts as a calcium channel antagonist.[10] The results of low magnesium may lead to a reduction in cerebral blood flow, cerebral vasospasm, and neuronal burst. Magnesium has a vasoprotective effect.[11] These features have gotten some resemblance to the clinical manifestations and pathological findings in pregnancy induced hypertension (PIH), particularly eclampsia.[8] Magnesium acts as a potent vasodilator and its depletion increases the vasoconstrictor effect of angiotensin II and nor-adrenaline thus increases blood pressure.[12] Since the serum calcium and serum magnesium contribute significantly in the functioning of the vascular smooth muscles, the present study was designed to evaluate the role of the serum calcium and serum magnesium in PIH.

MATERIALS AND METHODS

This case control study was conducted in the Department of Biochemistry, MGM Medical College and associated MY Hospital, Indore. The subjects were pregnant women clinically diagnosed as pre-eclampsia during third trimester (28–40 weeks) with the age 18 to 35 years (group-C) visiting obstetrics OPD and wards of MY Hospital. The study group was further divided into two subgroups. It comprised of 36 mild pre-eclamptic pregnant women (Subgroup C1) and 16 severe pre-eclamptic pregnant women (Subgroup C2) on the basis of blood pressure, (both systolic and diastolic) proteinuria and pathological edema, which is the diagnostic criteria of pre-eclampsia. As a control group-73 healthy normotensive nonpregnant women (Group A) and 65 healthy normotensive pregnant women (Group B) were taken. The healthy normotensive pregnant women were also in the third trimester (28–40 weeks) of their pregnancy with the age 18 to 35 years. Group A women were normotensive, nonproteinuric and in child bearing age of 20 to 40 years. Inclusion criteria for women included in the study were should not be using any kind of oral contraceptives, anticoagulant drugs, should be non-smokers and nonalcoholics and exclusion criteria were: past history of diabetes, systemic or endocrine disorder, chronic infection, chronic renal disease and hypertension (in groups A and B only), women in the labor pains, were excluded from the study. Institutional ethics committee's approval was obtained prior to start of the study.

Pre-eclampsia was diagnosed according to American College of Obstetrics and Gynecology (ACOG) criteria: a blood pressure higher than 140/90 mm Hg and proteinuria more than 300 mg/24 hr were observed on at least two occasions more than 6 hours apart after the 20th weeks of pregnancy. Pre-eclampsia were classified as severe if diastolic blood pressure increased to at least 110 mm Hg, proteinuria >5000 mg per day and the presence of headache, visual disturbances, epigastric pain, oliguria, elevated liver function test (LFT), elevated renal function test (RFT), thrombocytopenia.

Sample Collection

Blood samples were collected in the morning in a plain bulb with aseptic conditions. In the pre-eclampsia group, blood samples were collected when the patients presented for evaluation and before initiation of medical therapy. Serum calcium levels were measured by kits using an Arsenazo III method and serum magnesium levels were measured by kits using an calmagite method. The results were expressed as mean ± SD and groups were compared using analysis of variance (ANOVA).

Statistical Analysis

It was carried out by using statistical package for social sciences (SPSS) software, version 20. The level of significance was set at < 0.05.

RESULTS

The anthropometric factors of the study groups are summarized in Table 1. Maternal age and body mass index (BMI) were not significantly different between the groups ($p > 0.05$, Table 1). Gestational age, systolic and diastolic blood pressures were significantly higher in pre-eclamptic groups as compared to healthy normotensive nonpregnant and healthy normotensive pregnant women ($p < 0.001$, Table 1). The same when compared between mild and severe pre-eclamptic groups, it was found to be significantly higher in severe pre-eclamptic group ($p < 0.001$, Table 1).

Serum calcium and serum magnesium in healthy normotensive pregnant women (9.34 ± 0.49 mg/dl, 2.36 ± 0.13 mg/dl) was reduced when compared with healthy normotensive nonpregnant women (9.87 ± 0.6 mg/dl,

Table 1: Comparison of mean and standard deviation of anthropometric factors of control and pre-eclamptic groups

Anthropometric factors	*Group A healthy non-pregnant women (n = 73)*	*Group B healthy normotensive pregnant women (n = 65)*	*Group C Pre-eclamptic pregnant women (n = 52)*	*Subgroup C1 mild pre-eclamptic pregnant women (n = 36)*	*Subgroup C2 severe pre-eclamptic pregnant women (n = 16)*
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*
Age (years)	22.73 ± 3.65	22.67 ± 2.53	23.57 ± 3.73	23.52 ± 3.8	23.68 ± 3.7
BMI (kg/m^2)	24.21 ± 1.31	23.82 ± 1.61	24.19 ± 1.94	24.38 ± 1.95	23.78 ± 1.90
Gestational age (weeks)	—	38.81 ± 3	36.63 ± 1.68	36.94 ± 1.54	35.93 ± 1.8
Systolic blood pressure (mm Hg)	114.10 ± 7.68	114.0 ± 7.02	146.92 ± 16.27	138.61 ± 5.92	165.62 ± 16.72
Diastolic blood pressure (mm Hg)	73.84 ± 7.64	75.07 ± 5.33	98.65 ± 13.10	92.5 ± 7.22	112.5 ± 12.9

Table 2: Comparison of mean and standard deviation of clinical parameters of control and pre-eclamptic groups

Clinical parameters	*Group A healthy non-pregnant women (n = 73)*	*Group B healthy normotensive pregnant women (n = 65)*	*Group C preeclamptic pregnant women (n = 52)*	*Subgroup C1 mild pre-eclamptic pregnant women (n = 36)*	*Subgroup C2 severe pre-eclamptic pregnant women (n = 16)*
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*
Serum calcium (mg/dl)	9.87 ± 0.6	9.34 ± 0.49*	8.82 ± 0.93**	9.07 ± 0.8$^{@}$	8.25 ± 0.97$^{\#}$
Serum magnesium (mg/dl)	2.60 ± 0.3	2.36 ± 0.13*	1.74 ± 0.24**	1.77 ± 0.24$^{@}$	1.65 ± 0.24$^{\#}$

*$p < 0.001$—compared with healthy non-pregnant women, **$p < 0.001$—compared with healthy non-pregnant women and healthy normotensive pregnant women, $^{@}p < 0.001$—compared with healthy non-pregnant women and healthy normotensive pregnant women, $^{\#}p < 0.001$—compared with healthy non-pregnant women and healthy normotensive pregnant women and mild pre-eclamptic pregnant women

2.60 ± 0.3 mg/dl) with statistically higher significant difference ($p < 0.001$, Table 2) and was found to be lowest in pre-eclamptic pregnant women (8.82 ± 0.93 mg/dl, 1.74 ± 0.24 mg/dl) as compared to healthy normotensive nonpregnant women and healthy normotensive pregnant women with statistically higher significant difference ($p < 0.001$, Table 2). When serum calcium and serum magnesium in mild pre-eclamptic pregnant women (9.07 ± 0.8 mg/dl, 1.77 ± 0.24 mg/dl) was compared with severe pre-eclamptic pregnant women (8.25 ± 0.97 mg/dl 1.65 ± 0.24 mg/dl), it was found to be reduced in the latter group and the difference was significantly higher ($p < 0.001$, Table 2).

DISCUSSION

The estimation of serum calcium and serum magnesium in PIH provides a very useful index for the study of physiological and pathological changes during pregnancy. In many studies, decrease in serum calcium levels[13] and decrease in serum magnesium levels[14] has been considered as the cause of pathogenesis of pre-eclampsia. On the basis of some studies claim that serum calcium and serum magnesium have a relaxant effect on the blood vessels of pregnant women.[15] In the present study, a highly significant decrease in serum calcium was seen in the normal pregnant women as compared to the healthy nonpregnant women, with a further highly significant decrease in the pre-eclamptic pregnant women. This contention is amply supported by a few other studies.[13,16] Calcium metabolism is under strain during pregnancy. Expected mothers need to store about 30 to 50 gm of calcium during the course of pregnancy, of which 25 gm are needed by the fetus for fetal bone formation. Eighty percent of the total fetal calcium is deposited during the third trimester. The transport of ionized calcium from the mother to the fetus increases from about 50 mg/day at 20 weeks of gestation to a maximum of about 350 mg/day at 35 weeks of gestation.[17] As during pregnancy, there is a hemodilution and with the expansion of extracellular fluid volume, there is a dilution of the cation and also lead to normal hypercalciuria of pregnancy consequent to increased glomerular filtration.[18] Our study concluded that the serum calcium in normal pregnant women was reduced

when compared with healthy nonpregnant women with the statistically highly significant difference ($p < 0.001$) as supported by Olatunbosun et al[19] who earlier in their study observed a highly significant reduction in serum concentration of calcium during the third trimester of normal pregnancy.

According to one study, in normal pregnancy hemodilution effect of estrogen and increased demand of fetus decreases the serum magnesium level.[20] In the present study, serum magnesium levels in normal pregnant women as compared to healthy nonpregnant women was low in accordance with that of the study shown by Kesteloot H.[20] Our study reveals that serum calcium and serum magnesium levels in pre-eclamptic pregnant women as compared to normal pregnant women was lower and the difference was statistically higher ($p < 0.001$). When comparison between mild and severe pre-eclamptic groups was done, it was concluded that the levels of both the parameters were lower in the latter group with statistically highly significant difference ($p < 0.001$). These results match previous data which suggest that there was an inverse relationship between serum calcium and magnesium and incidence if pregnancy-induced hypertension.[13,16,21] Decreased serum calcium levels lead to an increase in the parathyroid hormone levels, thereby increasing the intracellular calcium levels, which leads to an increase in vascular smooth muscle contraction and thus, an increase in blood pressure.[8] Some researchers have also shown an increased intracellular ionized calcium concentration and an increased sensitivity of these cells to angiotensin II in women with pre-eclampsia.[22] Magnesium acts peripherally to produce peripheral vasodilatation by increasing the prostacyclin release from the endothelial cells which acts as a potent vasodilator and a fall in blood pressure. Thus, low level of magnesium predisposes to an increase in the arterial pressure by increasing the vasoconstrictor effects of angiotensin II and nor-adrenaline.[23]

According to another study, calcitonin gene-related peptide (CGRP) and parathyroid hormone-related peptide (PTHrP) is a potent vasodilatory peptide which increases in maternal circulation during pregnancy. Both peptides may have a role in blood pressure regulation because of their vasorelaxant properties,[24] CGRP and PTHrP is involved in uterine relaxation during pregnancy. Increased receptor number in pregnancy signifies its importance in the maintenance of normal systemic hemodynamics in that condition. It is suggested that the peptide is involved in maintaining the human myometrium in quiescence during pregnancy by antagonizing the actions of uterine stimulants like oxytocin, and a decrease in the CGRP receptors towards the end of pregnancy aids in the initiation of labor.[25] But in pre-eclampsia both the circulating peptides are imbalanced, and thus its low level was found to be responsible for the increase of peripheral resistance and BP, thus, it may be important in pathogenesis of pre-eclampsia.[26]

CONCLUSION

It is concluded from the study that low levels of serum calcium and serum magnesium were found in pre-eclamptic pregnant women as compared to healthy nonpregnant and healthy normotensive pregnant women. As compared with mild pre-eclamptic group, the level of serum calcium and serum magnesium was significantly lower in severe pre-eclamptic group. These results may support the hypothesis on the role of calcium and magnesium deficiency in pre-eclampsia pathophysiology and suggest the usefulness of its assessment in the early diagnosis of the disorder. Thus, hypocalcemia and hypomagnesemia leads to smooth muscle contraction and an elevation in blood pressure causing PIH.

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REVIEW ARTICLE

Predictive Perspectives of Disease—Transformed Protein Biomarkers

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ABSTRACT

With advancement in instrumentation, computation and understanding of disease etiology, proteomics has been expanded to harness the knowledge of change in protein folding and misfolding, protein-protein interaction, protein modification, etc. during progression of disease which is a source of discovery for various biomarkers including predictive biomarkers. Various methodologies for disease prediction are reported using 'omics' technology; however, advancement in proteomics with discovery of protein biomarker allows for the estimation of disease risk from years to decades before any disease even manifests internally. Specific proteins as disease biomarkers that appear in the body fluid/diseased tissues are generally measured. Recently, new proteomics technologies are also being developed in order to facilitate both the high-throughput and high-sensitivity requirements of disease-related applications of proteomics and possibly providing the framework for prediction of diseases. Therefore, there is a growing interest in proteomics technologies to discover processes that are involved in various diseases, to discover new biomarkers that correlates with the prediction and early detection of diseases. Now there is change in research thinking where already known biomarkers alone or in combination of others are under investigation for advanced application like in prediction and early detection of chronic diseases. In this review, we have emphasized the prediction perspective of some of the protein biomarkers like CA-125, Lp-PLA_2 and tau protein for diseases like cancers, cardiovascular diseases, and Alzheimer's respectively.

Keywords: CA-125, Lp-PLA_2, Predictive biomarker, Protein biomarker, Tau protein.

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INTRODUCTION

Presently, global disease burden is showing worrying trend which is a major concern of disease management. Unfortunately, the burden of chronic diseases is rapidly increasing worldwide. The burden of the proportion of noncommunicable diseases (NCDs) is expected to increase to 57% by 2020.[1] Recent projection on chronic diseases indicated that, by 2020 these diseases will account for almost three-quarters of all deaths worldwide. Projections on communicable diseases also indicate that these would also occupy critically important positions up to 2020[2] and 82% of 'premature' deaths would occur in low and middle income countries in the age group of 70 years and above. Certain diseases like cardiovascular diseases, malignancies, chronic respiratory diseases, neurological and mental disorders as well as musculoskeletal diseases shall be on the rise in those aged 60 years and above.[3,4]

Disease detection techniques has played very crucial role in disease management. Various techniques based on colorimetric, fluorescence and radiometric methods gave a baseline platform for disease detection, whereas enzyme-linked immunosorbent-assay (ELISA), Biorobotic, Biochip, Biosensor, Imaging techniques, microscopy and more recently nanotechnology have supported as add on for the disease detection and has revolutionized the detection methodology in favor of effective disease management. Recently, interdisciplinary scientific intervention and the basic understanding of etiology of diseases have been tried for identification of several disease specific biomarkers for better disease management. However, rationalization of detection techniques at the level of early detection and prediction is still a major challenge.

Proteins, which are the principle constituents of the protoplasm of all cells, undergo transformations under different conditions of stress. The study of all the proteins expressed by the genome under stressful conditions of ageing and others, provide insights into the health of the genome. In a herd of multiple thriving cells and tissues, the conditions of change/transformation get embedded and expressed within the dynamic change of nucleotide sequences of the cell population, the

surrounding ribonucleic acids (RNAs) and eventually within the transformations of the proteins expressed by the integrated genome pool. Not all the cells in the herd get transformed into diseased cells at a time. However, the gradual transformation of the healthy cells into the diseased ones leave several 'transformed metabolites' which can be identified over a period of time by use of sophisticated instruments and measurements. Great insight can be had from such studies about the health conditions of the tissues by studying such 'transformed metabolites' and especially the protein pools thus expressed.

Advancement in proteomics research and technology helps for discovery of various protein biomarkers including predictive biomarker. Besides traditional ways of identification and characterization of proteins, several new techniques like matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS)[5,6] and surface-assisted laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS)[7] have contributed significantly in protein profiling of various samples, and thereby the disease detecting technology. The techniques of protein-chip arrays have also been used to understand protein-protein interactions for a wide range of diseases, this made base platform for discovery of biomarkers.[8,9] The advancement in proteomics technologies have led into high-throughput and high-sensitivity assays. Nanotechnology has also offered some unique diagnostic capabilities for development of highly selective and sensitive assays[10] in favor of discovery of certain biomarkers. This advancement in proteomics opens up an innovative platform for discovery of various protein biomarkers which will allows for the identification and prediction of various diseases on the basis of protein structure and function. Using such studies many diseases can be predicted well in advance.

Research in biomedical instrumentation is also going in high pace for development of advanced version of instruments which can fulfill the requirement of very high detection efficiency and efficacy. Advancement in these instrumentations led to its application in discovery of various biomarkers and this is playing important role in effective disease management. It helps in prediction of disease, early diagnosis, disease prevention, drug target identification, drug response, etc. These biomarkers can be discovered using various OMICS platforms, such as genomics,[11] proteomics,[12,13] lipidomics,[14,15] etc.

Genomics platform using techniques, such as Northern blot, Gene expression, polyacrylamide gel electrophoresis (PAGE), deoxyribonucleic acid microarray (DNA microarray) etc. have played important role in discovery of biomarker, whereas in proteomics approach with advancement in instrumentation has opened fine gateway for discovery of biomarkers to diagnose disease. Secretomics, a subfield of proteomics has recently emerged as an important tool for the discovery of biomarkers[13] that is related to secretion of proteins and secretion pathways using proteomic approaches. Multiple modern techniques like MALDI-TOF-MS and SELDI-TOF-MS, Ab microarray have been explored for discovery of biomarkers which is boosting the disease detecting technology for protein profiling in various samples. Recently, matrix-assisted laser desorption/ionization (MALDI) have been employed widely for rapid determination of proteins in particular mixtures for proteomic study. Fluorescence two-dimensional differential gel electrophoresis (2-D DIGE) can be used to quantify variation in the 2-D DIGE process and establish statistically valid thresholds for assigning quantitative changes between samples.[16] The techniques of protein-chip arrays have been extensively used to understand protein-protein interactions for a wide range of diseases. Table 1 summarizes the main advanced techniques in proteomics that are used for the discovery of biomarkers for disease detection.

Computational predictive models are also boosting the discovery of various protein biomarkers.[17] Application of this have been demonstrated in which extensive and diverse feto-maternal protein trafficking occurs during pregnancy can be readily detected non-invasively in maternal whole blood.[18] The proteomic networks contain many biomarkers that are proxies for development. It extended into potential clinical application which can be used to monitor normal and abnormal fetal development.

Recently, nanobiotechnology application has been extended to improve the discovery of biomarkers. One such example being the sensitive detection of multiple protein biomarkers by nanobiosensors for the management of cancer made most important chapter of nanomedicine. Nanobiotechnology has refined and significantly implemented to molecular diagnosis of cancer through the use of gold nanoparticles and quantum dots. Therefore, it is an expectation and hope nanobiotechnology will facilitate the combination of

Table 1: Advanced techniques in proteomics for discovery of biomarkers

Techniques
• MALDI-TOF-MS
• SELDI-TOF-MS
• Protein-chip array
• Ab microarray
• 2D-PAGE
• Fluorescence two-dimensional differential gel electrophoresis (2D DIGE)
• Nanobiotechnology
• Computational predictive models

diagnostics with therapeutics which is an important feature of a personalized medicine approach to cancer. For diagnosis and targeted delivery of cancer therapy monoclonal antibody nanoparticle complexes are under extensive investigation.

Disease Prediction and Protein Biomarker

In coming year, disease detection aspect is going to be key factor in disease management. Although more basic research may be needed on some important aspects of the mechanisms of disease progression, biomarker of disease detection is going to be the focal point for future disease detection. However, rationalization of disease detection at the level of prediction is major challenges of disease detection. The future of medicine's focus may potentially shift for preventing disease rather than treating existing diseases, typically late in their progression. Therefore, a new philosophy in healthcare has emerged which will provide platform for personalized patient's treatment. Predictive diagnostics is considered as the basis for targeted preventive measures and consequent development of individualized treatment approaches. One of the best examples in this category is a paradigm shift toward personalized cancer medicine.[19] Therefore, there are several opportunities for discovery for new predictive biomarkers for predictive diagnostics which will strengthen the platform for joint venture for R&D, regulatory and increased market share of diagnostics. Now, there are opportunities in this direction for new global and national actions which includes strengthened interaction and partnerships, regulatory, legislative and fiscal approaches, etc.

There are various prediction methodologies which include genomics, proteomics, cytomics, etc. but the most commonly used method for prediction of disease is based on genetics. However, the presence of faulty genes of diseases does not necessarily mean that someone will get the disease.[20] It is considered that lifestyle and environment has significantly played role in development of common and complex diseases in the wider population but is not affected only by heredity. Therefore, genes are not perfect predictors of future disease development and progression. However, advancement in proteomics with discovery of predictive biomarker allows for the estimation of disease risks years to decades before any disease even manifests internally which can offer lifestyle advice or medication with the aim of preventing/delaying the predicted illness. A protein being the predictive biomarker has a number of advantages over others. Determining the body fluid's secretary proteins can be important for protein function annotation and disease biomarker discovery.[21] This approach indicates that the network-based prediction method is quite promising. It is anticipated that the method will benefit the relevant areas for both basic research and applied research. Knowledge on systematic configuration of protein structure may also help in discovery of biomarker and it may act as predictor of particular disease. In this direction three-dimensional (3D) structure elucidation of proteins may help improving the prediction of disease-related variants.[22] Protein interaction is a well-known phenomenon in biological system; therefore, protein interaction background could provide important clues to help better illustrate single aminoacid polymorphisms (SAPs) functional association which is responsible for the majority of human-heritated diseases. This research will facilitate the post genome-wide association studies. Network features are found to be most important for accurate prediction and can significantly improve the prediction performance.[23] Protein folding and misfolding have played important role in disease development and progression; therefore, harnessing the knowledge of misfolding and folding of protein during disease progression can be channelized into disease prediction. A number of diseases are mediated by mutation-induced protein misfolding.[24] Unfolded protein to misfolding disease is classical example of this category.[25] It is found that an unstructured protein possess destructive potential during progression of disease.[26] Many proteins also undergo wide variety of chemical modifications after translation. The post-translational modifications are very critical to the protein's function which is also recognized for its important role in disease development and progression.[27] One such classical example of modification of protein is phosphorylation which occurs to many enzymes and structural proteins in the process of cell signaling. In addition to phosphorylation, proteins can be subjected to other modification, such as ubiquitination, methylation, acetylation, glycosylation, oxidation and nitrosylation, which all can contribute to diseases. Therefore, degree of protein modification and their pattern can be explored as predictor of disease progression and development. Although in many diseases enzyme is considered as biomarker still there is need to understand the kinetics pattern of respective enzyme during disease progression which may help for discovery of predictive biomarker for disease prediction.

Prediction Perspective of CA-125 Biomarker in Cancer

There are enormous changes in diagnosis of cancer from turn-around-time to automation has become a major catalyst in this growth. Tremendous support of molecular techniques like fluorescent *in situ* hybridization (FISH),

polymerase chain reaction (PCR) and microarrays are recorded in cancer diagnosis. In recent years, biomarkers have gained importance by oncologists. The mix and match of molecular and protein markers has given platform for the whole new generation of tests. The integration of advanced proteomics with informatics for disease-related expression profiles can be used for identifying high-risk groups with much more reliability and it will allow us monitoring preventive strategies. In recent year, several proteins have been considered as biomarkers for early detection of certain types of cancer, still there is need of search for more predictive protein biomarker for various other types of cancers. During past decades several tumor markers have been enlisted that enable diagnosis, monitoring, and screening. Some biomarkers have found their way to clinical use. The most notable ones are alpha-fetoprotein (AFP) which appears in primary liver cancer and some rare forms of testicular cancer. Carcinoembryonic antigen (CEA) is another important biomarker which can help detect colorectal cancer. Cancer antigen 125, carcinoma antigen 125, or carbohydrate antigen 125 (CA-125) is also known as mucin 16. It is a well-established biomarker for ovarian cancer. Prostate-specific antigen (PSA) appears in prostate cancers. There is hope that advanced proteomics together with accelerated informatics platform can provide disease-related expression profiles in specific combination that could identify high-risk groups with much more reliability and will allow developing preventive strategies.

Now there is change in research thinking where already known cancer biomarker alone or in combination with others is under investigation for advanced application like its prediction and early detection of disease. Recently researchers found out that CA-125 protein may help detect ovarian cancer in its early stage.[28] Cancer antigen 125 is an important marker in cancer detection.[29] Schematic diagram of the structure of CA-125 is provided in Figure 1.

OVA1 test^{TM}—the first blood test cleared by the US food and drug administration (FDA) can indicate the probability of cancer in an ovarian mass disease. Ovarian cancer is a silent killer as its symptoms are very nondescript. Under normal circumstances, a physician is unable to know the ovarian mass is either caused by cancer or something else until operates and tests it. The test utilizes five well-established biomarkers in well define combinations and proprietary software to determine the likelihood of malignancy in women with ovarian mass for whom surgery is planned. This includes established blood tests known as tumor markers: Cancer antigen 125 (CA-125 II), Transthyretin (TT or prealbumin), apolipoprotein A-1 (Apo A-1), Beta2-microglobulin (Beta2M), and Transferrin (Tfr). The results of these blood tests are combined in an equation to produce a single numerical score. It is also found that elevated CA-125 is sufficient to detect 80 to 90% of recurrences of ovarian cancer.[30,31] It is surprising to know that menopausal females with an elevated CA-125 and without ovarian cancer are exposed to an increased risk of premature mortality.[32] Investigations tells us that high CA-125 levels (>150 U/ml) can rule in the presence of atrial fibrillation in patients with heart failure.[33] Recently, potential of serum CA-125 along with L-amino acid oxidase (LAAO) also highlighted in future predictor of cancer recurrence.[34]

There are several established markers of cancer, which have been validated over the years. Important among such biomarkers are tabulated in Table 2.

Prediction Perspective of Lp-PLA$_2$ in Cardiovascular Diseases

Several diagnostic tests have been used for detection and progression of heart disease including protein biomarkers. Of the lipid variables, the ratio of total cholesterol to high density lipoprotein (HDL) cholesterol and Apo lipoprotein B-100 were the most powerful predictors. In cardiovascular disease atherosclerosis is now recognized to be an inflammatory process. Four

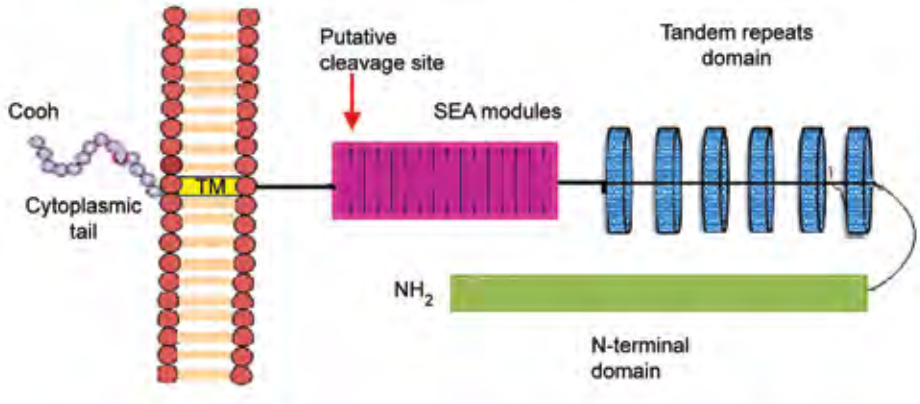

Fig. 1: Structure of CA-125 (Mucin 16) Adapted and derived from Wikipedia https://en.wikipedia.org/wiki/CA-125

Table 2: Some important biomarkers in cancer detection

Biomarkers
• Alpha-fetoprotein (AFP) of liver cancer and rare form of testicular cancer
• Carcino-embryonic antigen (CEA) in colorectal cancer
• CA-125 for ovarian cancer
• Prostate-specific antigen (PSA) in prostate cancer
Matrix metalloproteinases (MMPs) and
A disintegrin and metalloproteinases (ADAMs)

markers of inflammation were found to be significant predictors of the risk of future heart attacks—C-reactive protein (CRP) test, Serum amyloid A, interleukin 6, and soluble intercellular adhesion molecule-I (sICAM-I). However, C-reactive protein has been identified as one of the most significant risk factors for cardiovascular disease and heart attacks. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is also considered as risk factor for the development of atherosclerosis.[35] Lipoprotein-associated phospholipase A_2 is highly specific biomarker for vascular inflammation linked with increasing cardiovascular (CV) risk level. It is considered to be an independent risk marker, as well as an additive to the predictive value of high-sensitivity C-reactive protein in assessing myocardial infarction (MI) risk in moderate-risk populations. Increased Lp-PLA_2 level is independently associated with coronary artery disease (CAD) severity, and Lp-PLA_2 level may be used to discriminate those who are at increased risk of cardiovascular disease.[36]

A Lp-PLA_2 also known as platelet-activating factor acetylhydrolase (PAF-AH) is an enzyme that in humans is encoded by the phospholipase A2, group Homo sapiens VII (PLA2G7) gene. Lipoprotein-associated phospholipase A_2 is a 45-kilo Dalton (KDa) protein of 441 amino acids. It cleaves oxidized fatty acids from lipids in plasma mainly carried by low-density lipoprotein cholesterol (LDL-C). Elevated levels of Lp-PLA_2 (>200 ng/dl) predict a 40 to 400% (avg~100%) increased risk for MI and stroke (adjusted for cardiovascular disease risk factors). Further, a growing number of preclinical and genetic studies support a causal role of Lp-PLA_2 in atherosclerosis. The development of a novel therapeutic agent that directly inhibits the Lp-PLA_2 enzyme has provided a unique opportunity to directly test the hypothesis that inhibition of this inflammatory enzyme will translate into improved clinical outcomes.[37]

The vast majority of plasma Lp-PLA_2 mass binds to low-density lipoprotein (LDL) while a smaller amount is associated with high-density lipoprotein (HDL). Lipoprotein-associated phospholipase A_2 is also bound to lipoprotein (a) [Lp(a)], very low-density lipoprotein (VLDL) and remnant lipoproteins. Several lines of evidence suggest that the role of plasma Lp-PLA_2 in atherosclerosis may depend on the type of lipoprotein particle with which this enzyme is associated. Data from large caucasian population studies have supported plasma Lp-PLA_2 (primarily LDL-associated Lp-PLA_2) as a cardiovascular risk marker independent of, and additive to, traditional risk factors. On the contrary, the HDL-associated Lp-PLA_2 may express antiatherogenic activities and is also independently associated with lower risk for cardiac death.[38] A schematic diagram showing the role of Lp-PLA_2 in developing atherosclerosis is provided at Figure 2.

The PLAC™ test for Lp-PLA_2 is launched which is the blood test that helps identify hidden risk for heart attack and stroke. Early detection of Lp-PLA_2 by this test disease can be prevented by more aggressive treatment. The PLAC® Test for Lp-PLA_2 is a blood test cleared by the FDA to aid in assessing risk for both coronary heart diseases (CHD) and ischemic stroke associated with atherosclerosis.[40]

A number of protein biomarkers for detecting cardiovascular diseases are in Table 3.

Alzheimer's Disease: Prediction Perspective of Amyloid 'tau'

Diagnostic tools and criteria have been developed in recent years to make a clinical diagnosis of Alzheimer's disease (AD) with an accuracy rate of 85 to 90%. The factors used to complete a diagnosis include: medical history, mental status evaluation, physical examination, neurological examination, neuropsychological evaluation, brain scans, laboratory tests, biomarkers etc. Recently

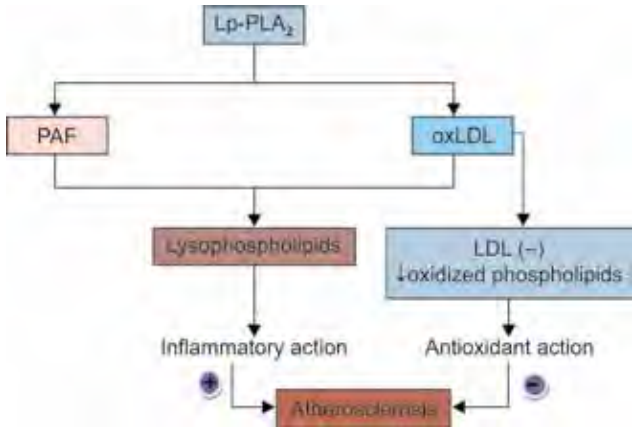

Fig. 2: Schematic diagram of role of Lp-PLA_2 (adapted and derived from reference number 39)

Table 3: Protein biomarkers in cardiovascular disease

Biomarkers
• C-reactive protein
• Serum amyloid A
• Interleukin-6
• sICAM-1
• Surfactant protein-D
• Apolipoprotein B-100
• Lp-PLA_2

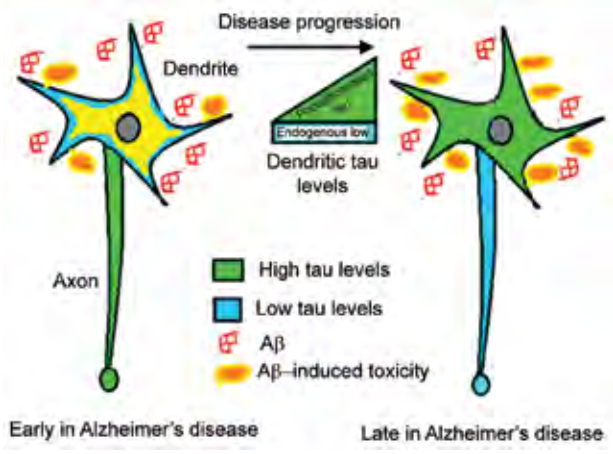

Fig. 3: Change in the content of phosphorilated *tau* after the onset of AD (Adapted and derived from the article by Jim Schnabel, Date 20 May, 2013. The DANA Foundation http://dana.org/News/Details.aspx?id=43549 Date 01/01/2015 time; 17.17 PM

protein based markers have been discovered which can be found few years before the onset of symptoms, creating a new preclinical stage.[41] The biomarkers include amyloids, which are abnormal proteins that accumulate in the brain of a person with AD which causes neuro-degeneration. This predictive biomarker called amyloid 'tau' accumulates inside brain cells, causing the cells to die. Biomarkers flagged in the new diagnostic criteria may be the key to predicting AD before a person exhibits any symptoms. The biomarkers include amyloid accumulation and neurodegeneration. Many scientists believe the great accumulation of amyloids plays a pivotal part in brain damage. In neurodegeneration, the biomarker called 'tau' accumulates inside brain cells, causing the cells to die.[42-44] Recently, it was demonstrated that 'tau' is extensively post-translationally modified by lysine acetylation, which impairs normal tau function and promotes pathological aggregation. The identification of 'tau' as an acetyltransferase provides a framework to further understand 'tau' pathogenesis and highlights 'tau' enzymatic activity as a potential therapeutic target.[45]

It has been suggested that exogenous human P301L 'tau' induces synaptosomal distribution of 'tau' protein with a certain amount of phosphorylation. Regulating the synaptosomal 'tau' level might be a potential target for a therapeutic intervention directed at preventing neurodegeneration.[46] Cerebrospinal fluid (CSF) levels assessment of Aβ1-42 and 'tau' proteins may be accurate diagnostic biomarkers for the differentiation of preclinical AD from age-associated memory impairment, depression and other forms of dementia in patients with mild cognitive impairment (MCI). The recent results confirm the key role of CSF biomarkers in predicting patient conversion from MCI to dementia. The study suggests that CSF biomarkers may also be reliable in a real world clinical setting.[47]

CONCLUSION

Disease detection techniques are perceived by researchers as one of the most important aspect of disease management. There are enormous challenges for scientists to overcome the issues at the level of early detection and prediction of disease. Advancement in proteomics allows for the identification and discovery of various protein biomarkers. Protein-3D structure, Protein misfolding, protein-protein interaction, protein modification and kinetics of catalytic protein can be explored for discovery and design of novel predictive biomarkers. Using such studies many diseases can be predicted well in advance. In this review, we have focused mainly on predictive perspective of protein-based biomarkers in some diseases like certain types of cancer, cardiovascular diseases and AD. These markers are for identification and prediction of these diseases on the basis of presence and functionality of certain identified specialized proteins. The review would provide useful lines and linkages for adopting further research in these areas.

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REVIEW ARTICLE

Biophysics and Surface Chemistry in Physiology

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ABSTRACT

Even though the physiology deals with the study of normal functions of the body the various physiological processes can be explained better with the help of underlying physical and chemical changes. The scientific progresses and advances in the subjects like physics, chemistry and biology gave us opportunity to apply principles of these sciences to understand the working of living organisms better. The underlying physical properties of lipids, water and their surface interaction led to the discovery of cell membrane.

The use of vegetable oil to calm the sea waves was known to mankind since 4000 BC since the time from Akkadian ruler Hammurabi, but the more scientific experiments in this area were done by Benjamin Franklin, Lord Rayleigh, Agnes Pockels and Irving Langmuir.

In this review we trace back the history of surface chemistry of lipids on water surface and their application in physiology.

Keywords: Lipid bilayers, Oil, Sea waves, Surface chemistry, Surface tension, Water.

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INTRODUCTION

Babylonian Lecanomancy

Mesopotamia is considered as the cradle of civilization. Mesopotamia in Greek means 'land between the rivers.' This is the land between the rivers 'Tigris' and 'Euphrates' located in the modern country of Iraq and Kuwait. The Sumerians were the first people to migrate to Mesopotamia.

Mesopotamia is the first region where people formed villages and farms. It is called the birth of civilization. The sumer people built temples to worship their gods and they built large cities. They used pictures for words and to write sentences. The stories on clay tablets date back to the earlier Sumerian civilization 4000 BC. They invented the oldest known written language. They wrote in clay with a suitable stylus and it was baked and the inscriptions were preserved. The Akkadians (2000 BC) dominated Sumerians and they adopted the Sumerian cuneiform to suit their own needs. The Akkadians established the Akkadian Empire. The ancient cuneiform clay tablet belonging to the Akkadian ruler Hammurabi's time (1758 BC) was discovered by David Tabor in Ashmolean Museum at Oxford. Tabor got it translated and wrote a paper on Babylonian Lecanomancy. It was probably the first scientific paper about the Sumerian manuscript dealing about the spreading of oil on the water. In Babylonian Lecanomancy a diviner made his prophecies based on the way oil spreads on water.[1,2]

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The Greeks' use of Oil to Smoothen the Sea Waves

Around 1000 years after the Hammurabi's period, Greeks started using oil to smoothen the sea waves. Plutarch attributed to Aristotle (385 BC–322 BC) that 'the oil produces calm by smoothing the water surface so that the wind can slip over it without making an impression'.[3]

Gaius Plinius Secundus better known as 'Pliny the Elder' (23-79AD)–A Roman philosopher and encyclopedist had first mentioned in his encyclopedic work 'Naturalis Historia' his observations about how oil smoothened rough sea waves. He also stated that divers added oil to water to make it smoother and easier to see the bottom.[4,5]

Benjamin Franklin's Scientific Experiments

Benjamin Franklin (1706–1790)—Founding father of the United States of America, statesman, philosopher, diplomat, inventor, and self trained scientist, was the first to perform more scientific research on spreading of oil on the water. Benjamin Franklin was born in Boston on January 17, 1706. In 1757, he was sent by the American House of Assembly of Philadelphia to Great Britain. During this journey, in the fleet of 96 ships which were encountered by windy weather he noticed that two of the ships were sailing much more smoothly than the rest. After the inquiry with the Captain for a reason, he came to know that the cooks were emptying their greasy vessels, which has greased the sides of those ships.

Almost after a decade he decided to revisit his questions on the water-calming effect of oil. In 1774, While staying in the Clapham Common area in south London he and his merchant friend Christopher Baldwin went to Lake Mount Pond, and did the experiment. One day when the pond was very rough with the wind, he dropped a spoonful of oil (probably olive oil) on the water. He saw it spread itself upon the surface, produced an instant calm over a space several yards square, which spread amazingly, and extended itself gradually till it reached the lee side, making all that quarter of the pond, perhaps half an acre, as smooth as a looking-glass and as much thinner as to be invisible, except in its effect of smoothing the waves at a much greater distance.[6,7] The oil film was thin and it produced the prismatic colors, for a considerable space, and beyond that so much thinner as to be invisible, Franklin also observed that when a drop of oil is put on a polished marble table, or on a looking-glass that lies horizontally, the drop remained in its place, and spreading of oil was very little.[6,7] In Franklin's contribution to surface chemistry, he assumed that the oil forms a monomolecular layer. Although Franklin's experiments were published, they were not noticed over a century.

Surface Tension and Spreading of Oil on Water

John Aitken—A Scottish meteorologist suggested that the calming effect of oil on water was not because of the reduction in the frictional force of the air on the surface but the surface tension on the water surface. Around 200 years after Franklin's experiments, Professor Charles Giles professor of chemistry at the University of Strathclyde identified the pond where Franklin did his experiments which still exists as 'Clapham Common'. He repeated Franklin's experiments and took photographs.[8-10]

Franklin's experiment was repeated by Lord Rayleigh. Lord Rayleigh, originally known as John William Strutt was born on November 12, 1842 at Langford Grove, Maldon, Essex. He was a grandson of Captain Richard Vicars, RE who was an outstanding scientist. He studied in Trinity College, Cambridge. In 1879, he was appointed as Professor of Experimental Physics and Head of the Cavendish Laboratory at Cambridge. In 1884, he left Cambridge to continue his experimental work at his country seat at Terling, Essex, and from 1887 to 1905 he was Professor of Natural Philosophy in the Royal Institution of Great Britain, being successor of Tyndall.

Lord Rayleigh's work ranged over almost the whole field of physics, covering sound, wave theory, color vision, electrodynamics, electromagnetism, light scattering, flow of liquids, hydrodynamics, and density of gases, viscosity, capillarity, elasticity and photography. He was awarded Nobel Prize in Physics 1904.

In 1890 Lord Raleigh conducted a series of quantitative experiments with oil and water. He was able to carefully measure the area to which a known volume of oil would expand over water and also calculated the thickness of the oil film. Foundation of modern surface chemistry was laid in 1890 by Lord Raleigh.[5,11,12]

A German woman named Agnes Luise Wilhelmine Pockels, was a German scientist. Agnes Pockels, was born in Venice, Italy, in 1862. She was a German pioneer in chemistry. Her work was fundamental in establishing surface science. She did not attend college. While taking care of her parents, she occupied her mind by reading material provided by her brother, a student at the University of Heidelburg. She conducted experiments in the kitchen sink, using kitchen bowls, string and buttons, and had developed on her own a device for carefully measuring the exact area of an oil film. Lord Raleigh assisted Agnes Pockels in publishing her work on surface tension and the results were published in the journal Nature in 1891. Her greatest contribution to science was the device that she invented, which is still used today by chemists and physicists studying surface phenomena. She invented a tin trough with a sliding barrier that was used to measure surface tension.[5,13,14]

The next important discovery was made by Sir William Bate Hardy (1864–1934) in 1912, when he found that oils without polar functional groups (Nonpolar oils-mineral oils, petrolatum,) did not spread on a water surface like oils with a polar group (polar oils- Olive oil, coconut oil, Avocado oil) and stated for the first time that polar molecules might have an orientation on the water surface, induced by long range cohesive forces between these molecules.[15]

Pinnacle of Surface Chemistry

Irving Langmuir (1881–1957) was born in Brooklyn, New York, on January 31, 1881. He graduated as a metallurgical engineer from Columbia University in 1903, and Postgraduate in Physical Chemistry under Nernst in Göttingen Germany in 1906. He was awarded Nobel Prize in Chemistry 1932.[16] Charles Tanford, a well known surface scientist states that 'scientifically Irving Langmuir represents the pinnacle of surface chemistry'.[17] Langmuir conducted research on the nature of oil films while working in the laboratories of General Electric USA. He was able to make careful measurements of surface areas occupied by known quantities of oil by using an improved version of the apparatus originally developed by Agnes Pockels known as a Langmuir

trough. Langmuir in his paper on molecular monolayer proposed that the fatty acid molecules form a monolayer by orienting themselves vertically with the hydrocarbon chains away from the water and the carboxyl groups in contact with the surface of the water.[18]

This was the key piece in understanding lipid bilayers and cell membranes.

Lipid Bilayers and Cell Membranes

Gorter and Grendel extracted the lipids from red blood cells. Using a modified trough, similar to Langmuir, they were able to demonstrate that lipid molecules could form a double layer or as a monolayer. They showed that the surface area of the lipids extracted from the red blood cells was about twice the surface area of the cells themselves.[19,20]

The first membrane model was proposed by Danielli and Davson in 1935. It was basically a 'sandwich' of lipids (arranged in a bilayers covered on both sides with proteins).[21] Later they included 'active patches' and protein lined pores.[22]

The unit membrane model was eventually replaced in the early 1970s by the current model of the membrane, known as the fluid mosaic model, was proposed by biochemists Singer and Nicolson.[23] This model retains the basic lipid bilayer structure proposed by Gorter and Grendel and modified by Danielli and Davson and Robertson. The entire membrane is fluid—the lipid molecules move within the layers of the bilayer while the proteins also freely move within the bilayer.

Fat Receptors in Oral Cavity and Gastrointestinal Tract

There are fat and water receptors present in the oral cavity and the gastrointestinal (GI) tract mainly in the small intestine.[24,25] There is evidence showing that free fatty acids are important stimuli used by taste receptors for the detection of fat. The proteins for the release and transport of lipophilic fatty acids are found in the oral cavity and also the taste cells have fatty-acid-sensitive ion channels and transport molecules for the uptake of fatty acids.[26] This membrane-bound long-chain fatty-acid transporter is specifically localized to the apical parts of taste-bud cells, in the circumvallate papillae identified as CD36.

CD36 works as a dietary fat sensor and signal is sent to the brain via the glossopharyngeal nerve.[27] CD36 is also present on apical enterocyte membranes of small intestine and it is a major mediator of fatty acid-induced release of CCK and secretin.[28] GPR40 and GPR120 are potential drug target for type 2 diabetes.[29-31]

The mean total surface area of the oral cavity is 215 cm^2. When saliva is spread evenly throughout as a thin film it forms 70 to 100 μm thick layer. The average unstimulated salivary flow rate is 0.3 to 0.4 ml per minute. During sleep, the salivary flow rate is negligible and its protective effect is lost.[32]

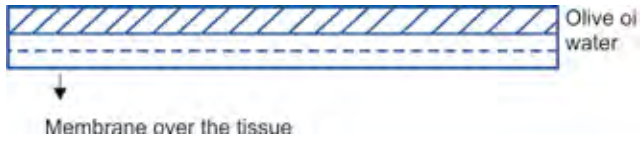

Fig. 1: Olive oil layer over water

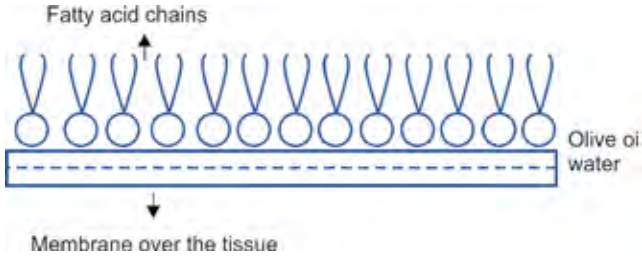

Fig. 2: Monolayer of olive oil

The olive oil significantly decreases bacterial growth and adhesion in the oral cavity.[33] Virgin olive oil decreases water evaporation.[34] Lipids add hydrophobic characteristics to the tooth surface thus hampering bacterial colonization and decreasing caries susceptibility. Also lipid-enriched pellicles are more resistant in case of acid exposure and therefore reduce the erosive mineral loss.[35] Swishing of 1 to 2 ml of olive oil is sufficient to form a thin film in the entire oral cavity thus helping to prevent bacterial adhesion and growth. Virgin olive oil forms a film over tissues in the oral cavity and this protects the tissues in the oral cavity at night when salivary secretion is reduced as it also decreases evaporation of water in the oral cavity. Virgin olive oil can be used as oral hygiene supplement in the oral cavity (Figs 1 and 2).[35]

Apart from CD36 many G-protein-coupled receptors-GPR 40, 41, 43, 84, 119 and 120 for free fatty acids in stomach, intestine, pancreas, adipocytes which are involved in modulation of many hormonal secretion like ghrelin, secretin, insulin and glucagon. Extravirgin olive oil improves postprandial glucose and LDL-Cholesterol, and this effect may account for the anti atherosclerotic effect of the mediterranean diet.[36]

CONCLUSION

Virgin olive oil can be used as oral hygiene supplement to prevent dental and periodontal infections and it has a role in reduction of cardiovascular diseases and blood glucose rise after meal.[35] As large number of people in developing countries are suffering from dental and periodontal infections a nutrient like vegetable oil (sesame oil, sunflower oil, coconut oil and olive oil) in small quantity (2 to 3 ml) can be used as oral hygiene supplement.

We are dedicating this article to the teachers and our former presidents Dr S Radhakrishnan and Dr APJ Abdul Kalam.

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REVIEW ARTICLE

Nanotechnology: Applications in Clinical Practice

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ABSTRACT

Changelings were raised regarding the feasibility of application envisioned by researchers in the field of molecular nanotechnology culminated into a development of new technique in research which rose in all the stream of biology and information technology. The paper depicts about the use of nanotechnology in multifunctional areas of clinical practices briefly. It has now become possible to overcome many biological, biophysical, and biomedical barriers in health sector. The paper has not only highlighted the importance of nanotechnology in diagnostic, imaging, therapeutic relationships but also focused on an interrelationship of nanotechnology with other chains of research fields such as; information technology, biotechnology, and medicine.

Keywords: Biotechnology, Diagnosis, Medicine, Nanotechnology, Treatment.

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INTRODUCTION

During the last 5000 years, unique cultures have come into existence as humans continuously attempted to have a better life for themselves and the society around them. Particularly in the last 200 years, the society got transformed from purely agriculture to industrial, and then to information with different manifestations. The Industrial Revolution in the 18th century paved way for economic development making the life better with new opportunities and a large-scale employment. Information Technology (IT) revolutionized our lifestyle further and became a major part of economy. In addition to the industrially developed countries, the economy grew faster in the developing countries also due to the information revolution. The IT revolution taking the advantage of large skilled human resource further added to the economic prosperity. Recent developments in bio- and nanotechnologies and their convergence with IT opened up greater opportunities for the future.

The IT and communication technology have already converged leading to Information and Communication Technology (ICT). Information technology, combined with biotechnology, has led to bioinformatics. Similarly, photonics has grown out from the labs to converge with classical electronics and microelectronics to bring in new high speed options in consumer products shown in Figure 1. Flexible and unbreakable displays using thin layer of film on transparent polymers have emerged as new symbols of entertainment and media tools. Nanotechnology is the field of the future that will replace microelectronics and many fields with tremendous application potential in the areas of medicine, electronics and material science. The confluence of these newly acquired capabilities, coupled with advances in imaging, bioinformatics, and systems biology, holds tremendous promise for answering some of biology's most challenging biochemical and genetic questions.

What is Nanotechnology?

Nanotechnology is a new area of science that involves working with materials and devices that are at the nanoscale dimensions, in various fields, such as electronics, computer technology, and cosmetics industry and

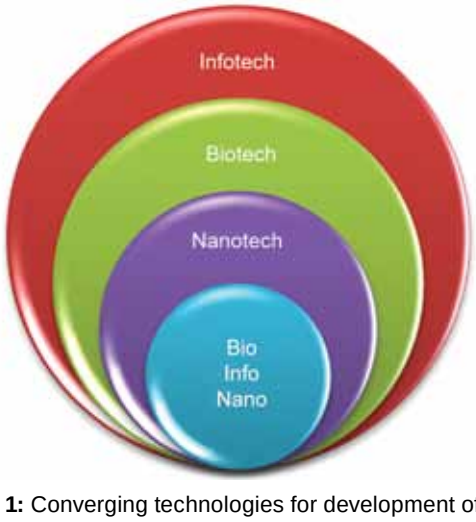

Fig. 1: Converging technologies for development of life

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in drug delivery or medical diagnostics. The birth of nanotechnology is usually associated with a talk entitled 'Plenty of room at the bottom' presented by Nobel-prize winner Richard P Feynman to the American Physical Society in Pasadena on December 1959, whose text has appeared in the book entitled 'The Great Explainer: The story of Richard Feynman'. Nanotechnology has the potential for major scientific and practical breakthroughs. A nanometer is billionth of a meter, that is, about 1/80,000 of the diameter of a human hair, or ten times the diameter of a hydrogen atom. Nanotechnology alters the way we think, it blurs the boundaries between physics, chemistry, and biology; the elimination of these boundaries will pose many challenges and new directions for the organization of education and research. It manipulates the chemical and physical properties of a substance at the molecular level. These practical applications explain why nanomaterials are gathering great interest in the scientific and economic spheres. Although much of nanotechnology is still in the research and development phase, nanomaterials are expected to be used in a wide variety of applications ranging from biomedical drug delivery to electronics, pollution remediation, and less toxic modes of manufacturing.[2] Many scientists and policy-makers see nanotechnology as the wave of the future, and, as a result, investment in nanotechnology has continued to increase. The role of nanobiotechnology in molecular diagnostics and personalized medicine is depicted in Figure 2.

Nanotechnology in Biology

Although nanomaterials are similar to components in biological system in respect to size and shape, the advanced applications possible through bionanotechnology distinguishes it from biophysics or structural biology or virology. This is the same distinction that separates biotechnology from molecular and cell biology or physics from electronics and chemical engineering from chemistry. Recognizing that nanotechnology and biology share common length scales at this level, we can see how the combination of the two creates the opportunity to produce and apply novel hybrid structures, materials, and devices that exploit the distinctive features of both. Exploitation spans the use of nanomaterials as tools in fundamental biological research, the development of novel approaches to diagnose, and treat disease as well as new ways to generate energy or clean up the environment.

This article focuses on developing nanotechnology to address healthcare-related applications in both therapeutic and diagnosis methods. Medical advancements are constantly being researched. Technologies, such as nanoparticles are being used to improve or replace today's therapies. Nanoparticles have advantages over today's therapies because they can be engineered to have certain properties or to behave in a certain way. These properties include size and shape, solubility and targeting.

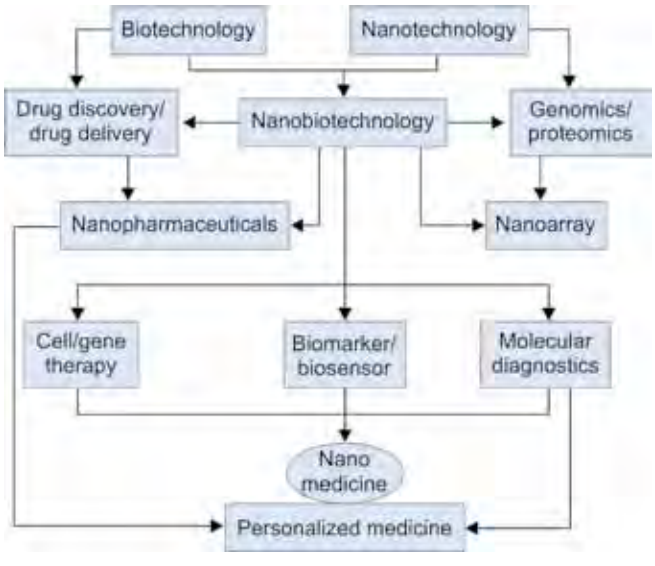

Fig. 2: Interrelationship of various technologies that contribute in diagnostic and therapeutic methods for human betterment

Advantages of Nanosize

The most important advantage of nanomaterials is our ability to synthesize them in required size, shape, and biocompatibility in relation to biological systems. Nanoscale devices and components are of the same basic size as biological entities (Fig. 3). Nanoscale constructs are smaller than human cells (10,000–20,000 nm in diameter) and organelles and similar in size to large biological macromolecules and enzymes, such as hemoglobin (~5 nm in diameter) and lipid bilayer (~6 nm thick). Nanoparticles smaller than 20 nm in diameter can transit through blood vessel walls and can also penetrate the blood-brain barrier, testis barrier, or the stomach epithelium.[4-9] Magnetic nanoparticles can be used in imaging metastatic lesions in lymph nodes because of their ability to exit the systemic circulation through the permeable vascular epithelium.[3]

To be suitable as a delivery platform, the size of nanoparticles must be small enough to avoid rapid filtration by the spleen, with filaments spaced at roughly 200 nm,[10] which serve as a meshwork for phagocytic cells.[11] Similarly, to traverse the liver, the particles must be small enough to pass through the organ's 150 to 200 nm sized fenestrae and avoid the Kupffer cell-lined sieve plates.[12] Drug carrying liposomes are believed to have increased life spans, related in part to their ability to extravasate through splenic and liver fenestrae.[13]

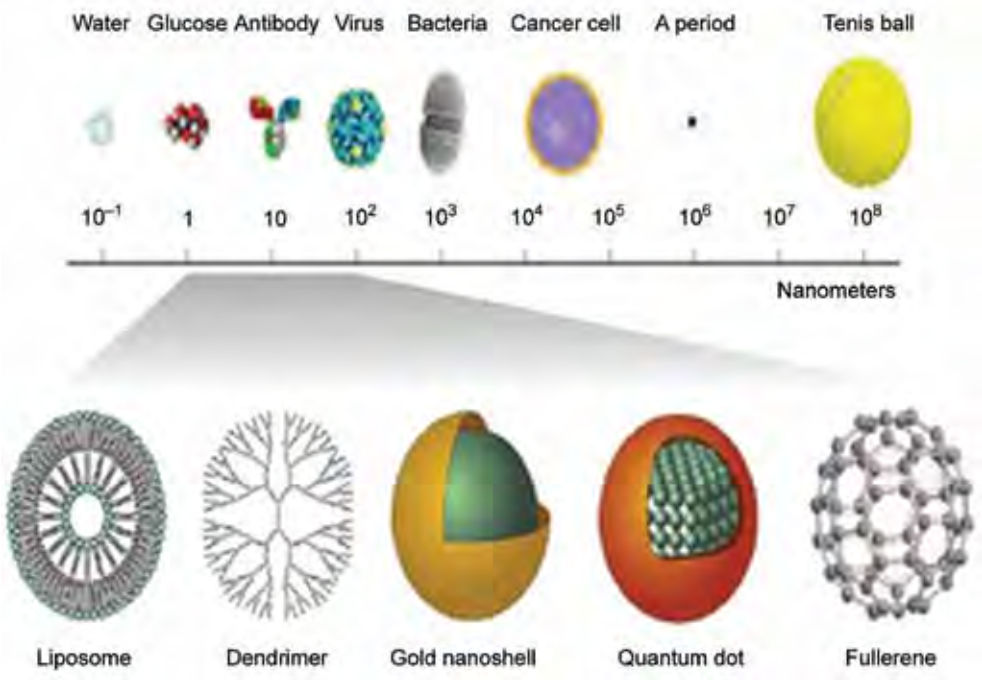

Fig. 3: Nanoscale components compared with size of biological entities

The size of nanoscale devices also allows them to interact readily with biomolecules on the cell surface and within the cell, often in ways that do not alter the behavior and biochemical properties of those molecules.[14]

Solubility Matters

Solubility of nanoparticles is as important as its size. Modification of the outer layer of nanoparticles permits the covalent binding of a large variety of chemical, molecular and biological entities. This alteration in the corona confers advantageous properties to the particle such as increased solubility and biocompatibility. Attaching hydrophilic polymers to the surface, such as polyethylene glycol (PEG), greatly increases the hydration (i.e. solubility) of the nanoparticles and can protect attached proteins from enzymatic degradation when used for *in vivo* applications.[15] This property of nanoparticles is perhaps most applicable in drug discovery and delivery.

Targeting Matters

One of the earliest examples of applying nanotechnology to solving problems in biology was the use of liposomes as drug delivery vehicles.[16] The liposomes of size 50 to 70 nm in diameter are taken up rapidly by macrophages, which then carry the liposome and drug to the site of fungal colonization. A liposomal formulation of the potent but toxic antifungal agent amphotericin B has revolutionized the treatment of life-threatening, systemic, fungal infections in immune compromised patients by allowing patients to receive normally lethal doses of amphotericin B with minimal risk of toxicity.[17]

Cancer therapy has benefited from the use of liposomal doxorubicin, a formulation that again increases the therapeutic index of the active agent through a combination of passive tumor targeting and reduced toxicity.[18] In this case, coating the liposome with PEG significantly decreases uptake by macrophages and allows the liposomes to concentrate in tumors by escaping from the leaky vasculature surrounding solid tumors[18] through a phenomenon known as the enhanced permeation and retention effect.[19-21]

DIAGNOSIS

Nanotechnology has been described as a general purpose technology. Development of nanotechnology will provide clinical medicine with a range of new diagnostic and therapeutic opportunities, such as drug delivery platforms.[22] Contrast enhanced image agents,[23] chip-based nanolabs capable of monitoring[24] and manipulating individual cells[25] and nanoscale probes that can track the movements of cells[26] and individual molecules[27] as they move about in their environment (Fig. 4). Such an unprecedented ability to observe and influence complex systems *in vivo* and in real-time provides detailed information about the fundamental mechanisms and signalling pathways involved in the progression of disease and greatly extends the existing toolset for drug delivery and noninvasive drug monitoring. Nanoparticles such as manganese, polystyrene, silica, titanium oxide,

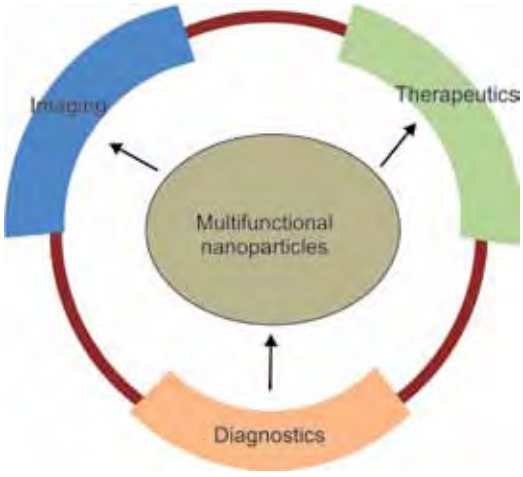

Fig. 4: Multiple applications of nanoparticles in health sector

gold, silver, carbon, quantum dots, and iron oxide have received enormous attention in the creation of new types of analytical tools for biotechnology and life sciences.[28]

Medical Imaging

Nanoparticles can provide significant improvements in traditional imaging of cells and tissues using fluorescence microscopy as well as in modern magnetic resonance imaging of various regions of the body.[29] Particle charge, size, shape, and hydrophilicity remain among the most important properties of nanoparticles for effective delivery to the desired target. Polyethylene glycol molecules have been investigated extensively as an effective means to provide hydrophilic 'stealth' properties, commonly yielding reduced nonspecific adsorption of serum proteins *in vivo*, thus producing longer circulation times.[30] Conversely, positively charged nanoparticles are being designed for enhancing endocytosis or phagocytosis for cell labelling.[31] Metallic nanoparticles possess immense potential as X-ray contrast imaging agents owing to their potent X-ray absorption and low toxicity profiles observed over short durations in animals.[32,33]

Medical Diagnosis

The accurate targeting and quantification of molecules indicative of cellular disorders at the single-molecule level is a demanding task for analysis systems. The combination of nanoparticles with other nanotechnology-based materials has the potential to address this emerging challenge and provide technologies that enable diagnosis at the level of single cells and single molecules.[34] Antibodies, peptides, proteins, and nucleic acids are biologic molecules which could be linked covalently to functionalized nanoparticles which have been developed as nanoprobes for molecular detection. These functionalized nanoparticles can provide a direct rapid method of detection of infectious diseases and viruses in particular with high sensitivity.[35,36]

Nanotechnology-based Medical Diagnosis Techniques under Development

- A method for detecting cancer cells in the bloodstream is being developed using nanoparticles called nano-flares. The nanoflares are designed to bind genetic targets in cancer cells, and generate light when that particular genetic target is found.
- A method for early diagnosis of brain cancer under development uses magnetic nanoparticles and nuclear magnetic resonance (NMR) technology. The magnetic nanoparticles attach to particles in the blood stream called microvesicles which originate in brain cancer cells. Nuclear magnetic resonance is then used to detect these microvesicles/magnetic nanoparticle clusters, allowing an early diagnosis.
- Carbon nanotubes and gold nanoparticles are being used in a sensor that detects proteins indicative of oral cancer.
- Silver nanorods in a diagnostic system are being used to separate viruses, bacteria, and other microscopic components of blood samples, allowing clearer Raman spectroscopy signals of the components. This method has been demonstrated to allow identification of viruses and bacteria in less than an hour.

Cytogenetic

Cytogenetics in a broader sense rather than the classical is used mainly to describe the chromosome structure and identify abnormalities related to disease. In the age of molecular biology, it is also referred to as molecular cytogenetic. The localization of specific gene probes by fluorescent *in situ* hybridization (FISH) combined with conventional fluorescence microscopy has reached its limit. Within the last 10 years or so, however, there has been a growing relationship between nanoscience and fluorescent biological imaging.[37] Applications of fluorescent imaging have generated a tremendous drive to develop new probes for tagging molecules, enabling changes in their localization, concentration and activities to be documented, for example quantum dot (QD) FISH.[38]

Fluorescent *in situ* hybridization techniques have thus continuously been adapted but, as with many fluorescence microscopy applications, phase limitations imposed by the use of organic fluorophores. These include the number of available fluorochromes and their broad emission spectra that make multicolor experiments difficult to resolve because of spectrum overlapping and photobleaching. Thus, QDs, are most suitable candidates for the study of chromosomes through adaptations of

FISH protocols, particularly as the conjugation of QDs and streptavidin is already widely reported. Indeed, QD-FISH has the potential to revolutionize. Fluorescent *in situ* hybridization by overcoming many of the inherent difficulties from the use of organic fluorochromes.[39,40]

TREATMENT

Drug Delivery

Medical therapies have become more tailored to both specific diseases and to patients on an individual basis in recent years. Most pharmaceutical agents have primary targets within cells and tissues; ideally, these agents should be preferentially delivered to their sites of action within the cell. Selective subcellular delivery is likely to have considerable therapeutic benefit.[41] Developed nanoscale particles or molecules improve the bioavailability of the drug delivery both at specific places in the body and over a longer period of time.[42] Drug delivery systems are based on nanoparticles which have a mesoscopic size range of 5 to 200 nm, allowing their unique interaction with biologic systems at the molecular level to produce multiple advantages, for example, reduced rate of drug clearance, alteration of the pharmacokinetics and biodistribution of the drug, passage of drugs through cell membranes and into the cell cytoplasm, and regulated drug release which can avoid the tissue damage caused by some drugs.[43]

Oncology

Cancer therapies are currently limited to surgery, radiation and chemotherapy. All three methods risk damage to normal tissues or incomplete eradication of the cancer. Nanotechnology provides researchers with the opportunity to study and manipulate macromolecules in real time and during the earliest stages of cancer progression. Nanotechnology can provide rapid and sensitive detection of cancer-related molecules, enabling scientists to detect molecular changes even when they occur only in a small percentage of cells. Nanotechnology also has the potential to generate entirely novel and highly effective therapeutic agents.

To produce minimal damage to normal tissue, therapeutic drugs have been conjugated with monoclonal antibodies that selectively bind to antigens or receptors which are usually abundantly or uniquely expressed on the tumor cell surface. Nanoparticles have been shown to overcome both cellular- and noncellular-based drug resistance and to increase selectivity of drugs toward cancer cells while reducing their toxicity toward normal tissues.[44] Several types of anticancer drugs, such as liposome-based formulations of several anticancer agents (stealth liposomal doxorubicin, liposomal doxorubicin, and liposomal daunorubicin), have been approved for the treatment of metastatic breast cancer.[45]

The study carried by Rasmussen JW et al showed destruction of tumor cells by using a zinc oxide nanoparticle. The study claimed that the nanoparticles of ZnO or any other metal oxide could be a choice of treatment. However, there are still many aspects to be cleared before using them in the form of treatment because over dosage may lead to toxicity.[46] The relevance of hyperthermia induced by magnetic nanoparticles in the treatment of gliomas has shown positive results in both preclinical and clinical assays. Magnetic hyperthermia consists of heat generation in the region of the tumors through the application of magnetic nanoparticles subjected to an alternating magnetic field, thus proving a beneficial treatment for malignant gliomas,[47] Georgios A Sotiriou et al used silica-coated Au/Fe_2O_3 nano aggregates to kill cancerous cell by applying the phenomena of photo thermal effect. The SiO_2 shell facilitates dispersion and prevents the reshaping or coalescence of Au particles during laser irradiation, thereby allowing their use in multiple treatments.[48] Green synthesis of silver nanoparticles capped with selective biomolecules was shown to have anticancer properties, It was found that both silver nanoparticles and its capping biomolecules have antiproliferative effects in colon cancer treatment.[49]

Application of Nanotechnology in Stem Cell

Nanotechnology and stem cells are two of the most promising research areas in recent times. The recent application of nanotechnology in stem cell research promises to open new avenues in regenerative medicine. Though stem cells hold a great potential for the treatment of many injuries and degenerative diseases, several obstacles need to be overcome before their therapeutic application can be served. These include development of advanced techniques to monitor micro environmental signals and also track and guide the transplanted stem cells. Thus, nanotechnology can be a valuable tool to track and image stem cells, to drive their differentiation into specific cell lineages, and ultimately to understand their biology.

Quantum dots (QDs) and a range of other nanomaterials have been used in stem cell research for *in vitro* and *in vivo* bioimaging. The labelling of human mesenchymal stem cells (hMSCs) with RGD-conjugated QDs during self-replication and multiline age differentiations into osteogenic, chondrogenic and adipogenic cells. Quantum dot labeled hMSCs remained viable as unlabeled hMSCs from the same subpopulation.[50] These findings suggest the use of

bioconjugated. Quantum dots as an effective probe for long-term labelling of stem cells. Few studies developed fluorescein isothiocyanate (FITC)—incorporated silica-coated core-shell SPIO nanoparticles, SPIO@SiO_2(FITC), with diameters of 50 nm, as a bifunctionally magnetic vector that can efficiently label hMSCs, via clathrin- and actin-dependent endocytosis with subsequent intracellular localization in late endosomes/lysosomes and also tested an *in vivo* osteochondral MSCs tracking system (IOMTS) to monitor the migration of bone marrow-derived MSCs.[51,52]

In particular, hybrid nanobiomaterials, which can be used to fabricate scaffolds and implantable substrates for the treatment of neurological disorders, such as Alzheimer's disease, Parkinson's disease, and spinal cord injuries, are now being intensively investigated in order to elicit specific behaviors from stem cells, including differentiation, migration and proliferation. Solanki et al in 2013 developed arrays of graphene-nanoparticle hybrid nanostructures for the differentiation and growth of human neural stem cells (hNSCs). More importantly, these graphene-hybrid nanostructures bring the formation of highly aligned axons from the differentiating hNSCs to fruition. This research result can provide an engineered microenvironment to the neural stem cells NSCs through novel nanomaterial construct. This new technology can specifically control the axonal alignment and growth of NSC-derived neurons for the development of more effective treatments for spinal cord injuries.[53]

OTHER APPLICATIONS

Application of Nanoparticles for Discovery of Biomarkers

There is an urgent need to discover novel biomarkers that provide sensitive and specific detection of early stage disease when it is highly treatable. Currently, available molecular diagnostic technologies have been used to detect biomarkers of various diseases. During the past few years, the potential of nanotechniques and nanomaterials in biomarker discovery has been extensively studied.[54,55] Such emerging approaches are advantageous due to their high sensitivity, minimum sample requirements, accuracy, real-time sensing, and simplicity of the instruments, low cost and potential diagnostic applications.

Among other nanomaterials, QDs, gold nanoparticles (AuNPs), carbon nanotubes (CNTs) and silicon nanowires are promising candidates for biomarker detection and discovery. In addition, there are other potential nanotechniques which include microcantilevers, microfluidics, gold nanowires, or silver nanomechanical resonators.[56]

Clinical applications of nanodiagnostics: Some of the clinical applications of nanodiagnostics are mentioned along with technologies elsewhere in report.[57] The report describes some examples of the use of nanodiagnostics in diagnosing cancers, infections and neurological disorders.

Nanobiosensors

Nanobiosensors are nanosensors used for detection of chemical or biological materials. Nanomaterials are exquisitely sensitive chemical and biological sensors.[20] These sensors can be electronically gated to respond to the binding of a single molecule. Prototype sensors have demonstrated the detection of nucleic acids, proteins and ions. These sensors can operate in the liquid or gas phase, opening up an enormous variety of downstream applications. The detections schemes use inexpensive low voltage measurements and detect binding events directly, so there is no need for costly, complicated, and time consuming labelling methods, such as fluorescent dyes or the use of bulky and expensive optical detection systems. As a result, these sensors are inexpensive to manufacture and are portable. It may even be possible to develop implantable detection and monitoring devices on the basis of these detectors.

CONCLUSION

The visions described in this article may sound unlikely, implausible, or even heretic. Yet, the theoretical and applied research to turn them into reality is progressing rapidly. Nanotechnology will change healthcare and human life more profoundly than many developments of the past. As with all technologies, nanotechnology carries a significant potential for misuse and abuse on a scale and scope never seen before. However, they also have potential to bring about significant benefits, such as improved health, better use of natural resources, and reduced environmental pollution. These truly are the days of miracle and wonder.

Once nanomechanics available, the ultimate dream of every healer, medicine man, and physician throughout recorded history will, at last become a reality. Programmable and controllable microscale robots, comprised of nanoscale parts fabricated to nanometer precision, will allow medical doctors to execute curative and reconstructive procedures in the human body at the cellular and molecular levels. Nanomedical physicians of the 21st century will still make good use of the body's natural healing powers and homeostatic mechanisms,

because, all else equal, those interventions are best that intervene least.

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CASE REPORT

Fabrication of Hollow Bulb Obturator with Maxillary Partial Denture for Congenital Cleft Palate Defect

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ABSTRACT

Rehabilitation of congenital cleft palate defect improves the quality of life for the patient as normal as possible. Obturator size depends on defect's size and volume. The prosthesis should be easy to handle, simple to maintain, biocompatible, light in weight and conventional for future adjustments. This case report describes a cleft palate patient, which was rehabilitated with a hollow bulb obturator.

Keywords: Cleft palate, Hollow bulb obturator, Maxillofacial defects, Rehabilitation.

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INTRODUCTION

Man's need for artificial replacement of missing body parts undoubtedly dates back as far as humanity itself. Over the centuries, people have used their creativity and adapted the available materials for use in prosthetic restoration. The earliest attempts at obturator construction are credited to Ambrose Pare who, around 1530, described button-shaped obturators made of metal and sponge.[1] As so often happens, Pare may not have been the first to perform these procedures, but he is one of the first to write about, describe and illustrate them. Prosthodontic rehabilitation for a congenital maxillary defect begins after full growth of patient. Alteration of physiologic functions, such as speech, mastication, deglutition and salivary control associated with ablative surgery requires timely prosthetic intervention.

Cleft palate is a condition in which the two plates of the skull that form the hard palate (roof of the mouth) are not completely joined. The soft palate defect also occurs in these cases cleft as well. In most cases, cleft lip is also present. Cleft palate occurs in about one in 700 live births worldwide. Cleft palate can occur as complete (soft and hard palates, possibly including a gap in the jaw) or incomplete (a 'hole' in the roof of the mouth, usually as a cleft soft palate). When cleft palate occurs, the uvula is usually split. It occurs due to the failure of fusion of the lateral palatine processes, the nasal septum and/or the median palatine processes (formation of the secondary palate).

The hole in the roof of the mouth caused by a cleft connects the mouth directly to the nasal cavity. According to GPT-8, obturator can be defined as a prosthesis to close a congenital or acquired tissue opening primarily of soft or hard palate.[2] The present article is a case report explaining the rehabilitation of a patient who had undergone rehabilitation with hollow bulb obturator for congenital cleft palate defect.

CASE REPORT

A 46-year-old man reported to Department of Prosthodontics, Career Post Graduate Institute of Dental Sciences and Hospital, Lucknow, Uttar Pradesh, India, with a main complaint of missing teeth and difficulty in speaking. He had complains of hypernasality of voice, regurgitation of food in the nasal cavity and difficulty in eating (Figs 1A to C). The patient gave history of congenital soft cleft palate defect.

After examining intraorally, it was revealed that a subtotal defect of soft palate was present with partial edentulism, with respect to both arches. Mandibular movements were in normal range and tongue function was normal.

Treatment Plan

Our treatment objective was to provide prosthesis to obturate the defect to improve speech, deglutition and mastication, to restore facial contour and to replace the lost teeth. Maxillary and mandibular removable partial denture with maxillary definitive closed hollow bulb obturator was planned for the patient.

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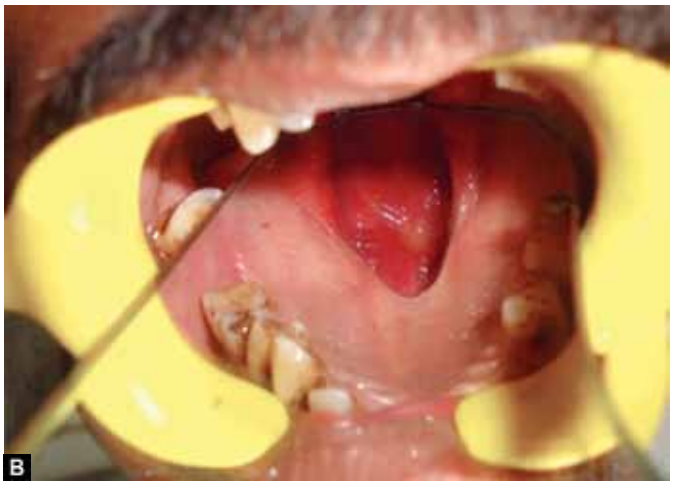

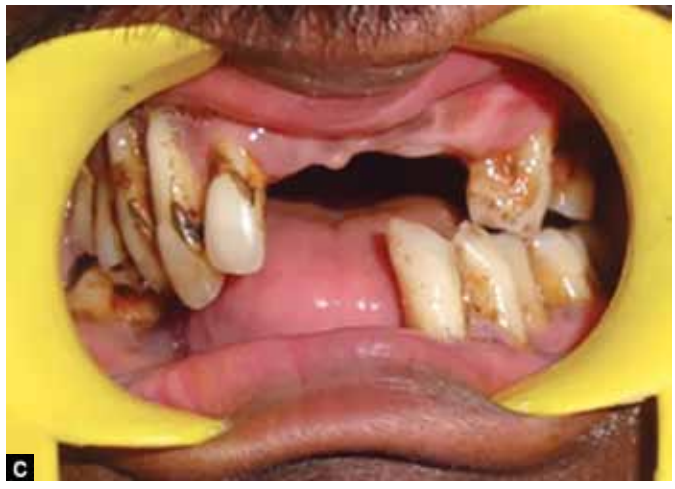

Figs 1A to C: Preoperative view

Procedure

In the present case, support was provided by remaining posterior teeth and palatal tissues. Retention was achieved by embrasure clasps and anatomical undercuts. A gauze piece was packed in the defect and floss was tied to it for its retrieval. A perforated stock tray was selected and impression was made with irreversible hydrocolloid (Zelgan, Mittal Private Ltd) (Figs 2 and 3).[3]

Primary cast obtained was used for fabricating custom tray for final impression using autopolymerizing resin. Border molding was done to record the soft tissue surrounding the defect using low fusing impression compound (Figs 4 and 5).

Details of the defect area were recorded using light body elastomeric impression material (3M ESPE Express STD, Germany) and the wash impression was completed using medium body addition silicone elastomer (Figs 6 and 7).

Master cast was obtained (Fig. 8). The cast was used to fabricate the bulb of the obturator. The defect area in the original cast was blocked out using plaster. On this cast, denture base and wax rims were prepared to record jaw relations, followed by try-in of wax-up denture. On the master cast, a double layer of modeling wax was adapted in the defect area (Fig. 9).

A hollow bulb obturator was fabricated along with the maxillary partial denture (Fig. 10). A lid for the bulb was prepared and attached to the open end of the bulb using autopolymerizing acrylic resin. The mandibular partial removable denture was fabricated using conventional technique (Fig. 11). Both the dentures were finished, polished and inserted in the patient's mouth.

Post insertion results showed improvement in speech, mastication, swallowing and facial esthetics. The patient was satisfied with the prosthesis in the recall check-ups. Hygiene maintenance of the prosthesis was emphasized by home protocol instituted by the patient.

DISCUSSION

Obturator prosthesis is commonly used in rehabilitating the patients with congenital and acquired maxillofacial defects. The delivery of care for patients who are in transitions and for those in need of assessment, planning and ongoing management can be quite challenging.[4] Congenital defects in maxilla results in communication between oral and nasal cavity affecting deglutition,

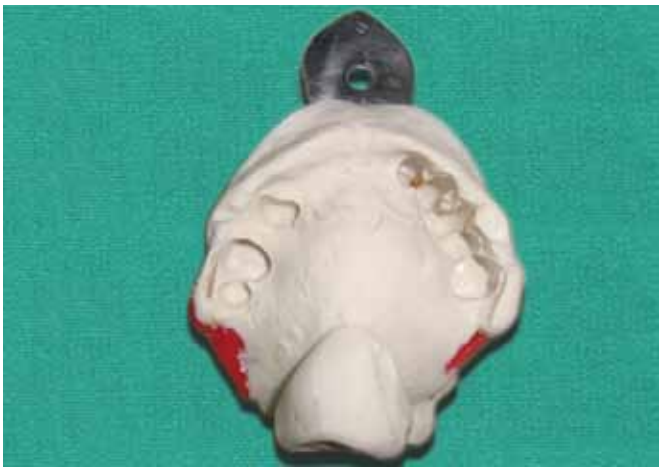

Fig. 2: Diagnostic maxillary impression

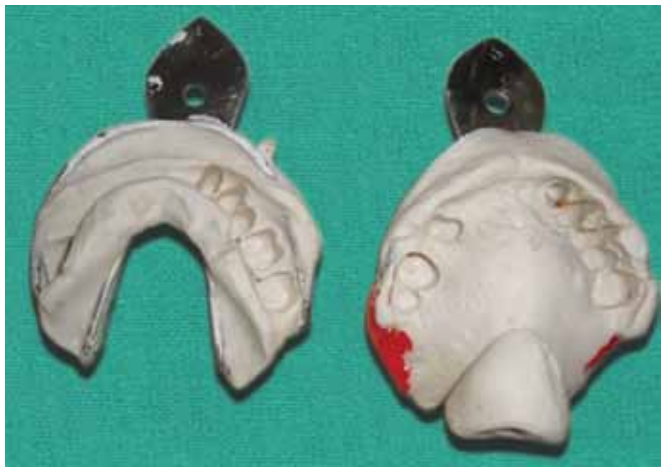

Fig. 3: Diagnostic maxillary and mandibular impressions

Fig. 4: Movements during border molding

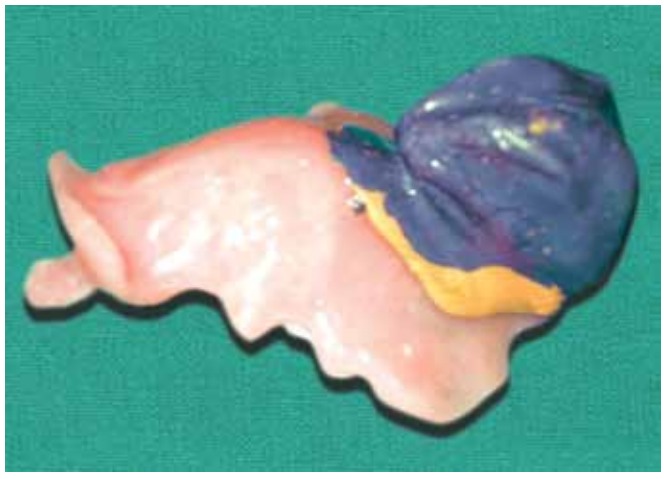

Fig. 5: Completed border molding

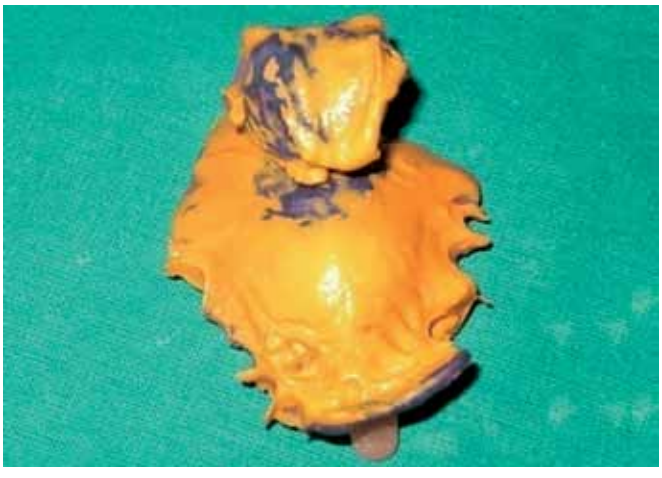

Fig. 6: Final impression of defect

Fig. 7: Final pick-up impression

speech and facial esthetics. Along with these functional impairments, it can also be psychologically debilitating to the patient. In the 18th century, a French surgeon, Ambroise Pare, described Button obturator made up of 'cuff link' or 'sponge'. In 1820, Delabarre used steel metal plate with wired metal bands clamped on teeth.[5] This was the first artificial velum designed. In 1953, Ackerman fabricated hollow obturator prosthesis. Recent investigations have confirmed the effect of obturator prosthesis in terms of speech, swallowing and appearance. In 1978, Dr Mohammed Aramany presented a system of classification based on the relationship of the defect to the remaining teeth and the frequency of occurrence. Since the defect was not so large, the retention and stability of the

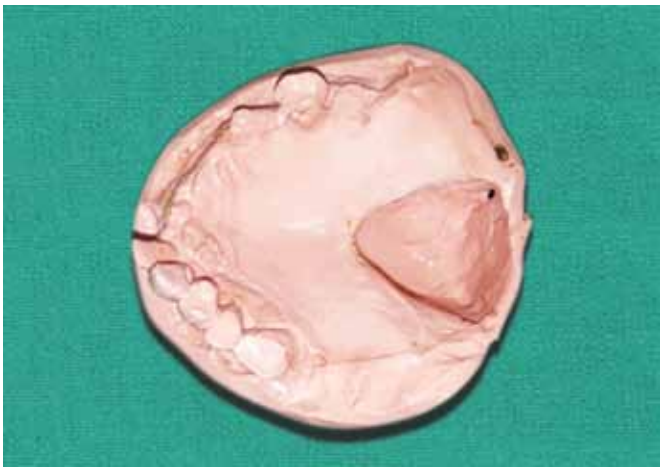

Fig. 8: Master cast

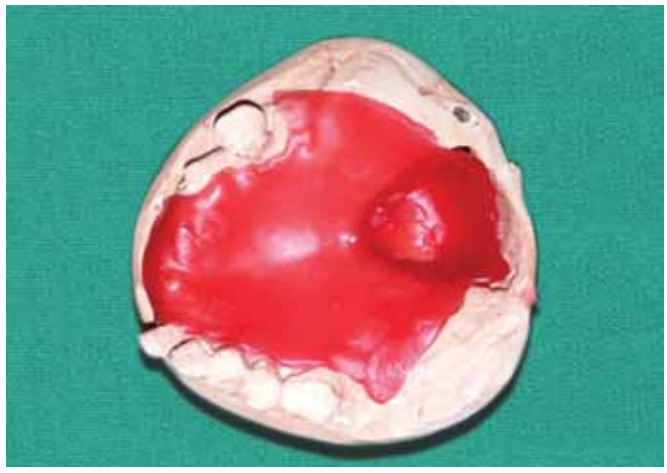

Fig. 9: Wax-up

Fig. 10: Finished and polished prosthesis

Fig. 11: Removable partial dentures with respect to lower anterior teeth

obturator was enhanced by making the obturator portion of the denture hollow. For improving stability, maximum extension of the prosthesis in all lateral directions was provided so that the defect itself would enhance stability of the prosthesis (Fig. 12).

CONCLUSION

The present case report describes the prosthodontic rehabilitation of a congenital maxillary defect in a patient, using definitive closed hollow bulb obturator, took care of the different domains of care, giving the patient an opportunity to live life as close to normal as possible. Teamwork enables the broader needs of patients and families to be addressed. The use of hollow bulb obturator design improves the patient comfort by decreasing the weight of prosthesis.

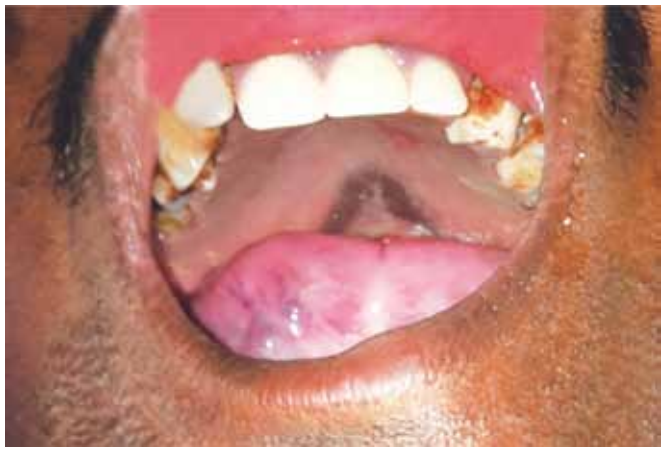

Fig. 12: Insertion

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CASE REPORT

Local Allergic Reaction to Contrast Material during Retrograde Urethrography

[1]Nandkishor Raut, [2]Piyush Singhania, [3]Sanish Shringarpure, [4]Nitin Joshi

ABSTRACT

Adverse reactions associated with parenteral use of contrast agents are widely recognized, but reactions to contrast agents following retrograde urethrography are much less common. A rare case of local allergic reaction to ionic contrast during retrograde urethrography in a 25-year-old male patient, who was treated conservatively, has been described.

Keywords: Ionic contrast medium, Local allergic reaction, Retrograde urethrography.

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INTRODUCTION

Local allergic reactions to contrast media used during retrograde urethrography or micturating cystourethrography procedure are rare, although absorption through intact bladder mucosa has been documented. A rare case of a 25-year-old male patient who developed a local allergic reaction to ionic contrast medium (meglumine diatrizoate) during retrograde urethrography and was treated conservatively has been described.

CASE REPORT

A 25-year-old male patient presented to the outpatient department with difficulty in micturition and poor flow of urine. On examination, meatal stenosis was diagnosed. Urine examination was normal. Ultrasound of abdomen and pelvis was normal. The patient was subjected to undergo a retrograde urethrography to rule out any associated urethral strictures. Retrograde urethrography was performed under strict aseptic precautions using ionic contrast medium (diatrizoate meglumine 18%). After injecting the contrast agent, the patient developed itching with flaccid bullae on the glans around the meatus. The procedure was immediately abandoned. The patient was given hydrocortisone and chlorpheniramine injections immediately. The bullae ruptured immediately forming an ulcer which extended on the ventral aspect of the glans with perimeatal edema and erythema (Fig. 1). Meatal dilatation was done. The patient was put on systemic antibiotics with local steroid application. The ulcer responded to this conservative treatment with complete healing without complications in 2 weeks.

DISCUSSION

The incidence of any reaction to ionic radiocontrast media is estimated to be between 0.6 and 12.66%.[1] For nonionic materials, the risk for any reaction ranges from 0.3 to 3%.[2] The risk for a severe hypersensitivity reaction is 0.16% with ionic contrast materials and 0.03% with nonionic contrast materials. Risk factors for contrast media reactions include (but are not limited to)—previous reactions to either ionic or nonionic contrast media (six fold increase), asthma (5–10 fold increase), history of multiple allergies (1.5–3 fold increase), female gender (29), drug allergy (30), and patients taking interleukin-2.[3]

Adverse reactions to contrast media are divided into two broad categories: chemotoxic reactions and hypersensitivity reactions. Chemotoxic reactions are

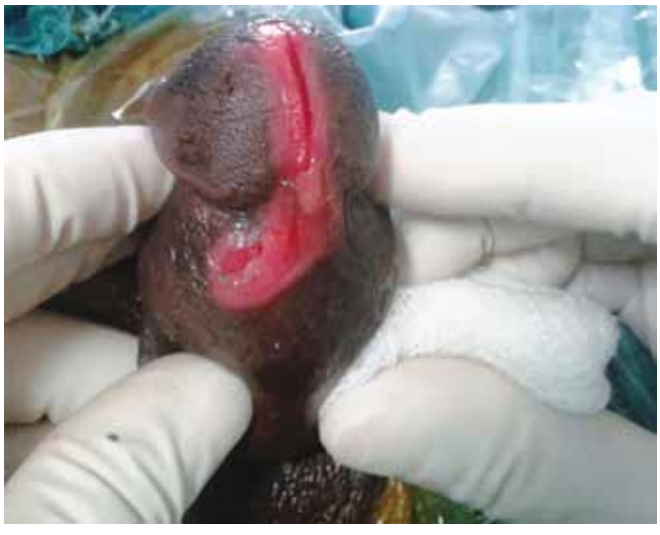

Fig. 1: The ulcer on the ventral aspect of the glans with perimeatal edema and erythema

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related to the chemical properties of radio-contrast agents, whereas hypersensitivity reactions are idiosyncratic and can be further subdivided into immediate and delayed.[4,5] The exact mechanisms of most adverse reactions to contrast material are unknown and are under active investigation. Most of them seem to employ direct mast cell and basophil activation and involve the release of a number of vasoactive mediators. The pathophysiology of immediate hypersensitivity reactions is believed to be nonimmunoglobulin E (IgE)-mediated in the majority of cases, although a small percentage of these reactions may involve IgE.

Wood et al[6] described similar local allergic reaction to ionic contrast medium during voiding cystourethrography. Two children were described to develop an apparent cutaneous contact reaction to contrast material in urine. Both the children had undergone uneventful voiding cystourethrography with diatrizoate meglumine injection 18%, followed by intravenous urography with diatrizoate meglumine injection 60%. Approximately 1 hour after urography, cutaneous bullae and surrounding erythema of the buttocks (one case) or foreskin (one case) were noted. This reaction resembled a superficial chemical burn. Weese et al[7] described two cases of anaphylactoid reaction during voiding cystourethrography and retrograde pyelography.

Bettany et al[8] also reported a case of systemic absorption of contrast material through the bladder mucosa, causing adverse effects, during micturating cystourethrography.

CONCLUSION

The case illustrates that significant reactions can occur during retrograde urethrography or micturating cystourethrogram and appropriate resuscitation facilities must be available.

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CASE REPORT

Concomitant Repair of Superficial Femoral Artery and Vein in a Case of Peripheral Vascular Trauma

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ABSTRACT

Vascular trauma results from penetrating, blunt or iatrogenic injuries. Young males are at highest risk and the leading causes of injury include motor vehicle crashes, falls, wounds from firearms, wounds from cutting or piercing instruments and burns. Peripheral vascular injuries account for 80% of all cases of vascular trauma. We report the case of a 21-year-old male patient with history of fall from 10 feet height on to a sharp metallic plate. Patient presented to emergency department with a lacerated wound of 15 x 10 cm on right mid thigh with active pulsatile bleed. After fluid resuscitation, patient was immediately shifted to operation room where examination revealed complete transaction of superficial femoral artery and vein with 10 cm tissue loss of both. Both vessels were reconstructed using saphenous venous graft from opposite thigh. Postoperatively, patient made a steady recovery with strong pedal pulsations and no edema or neurological deficit. Patients with hard signs of arterial trauma should be taken for surgical exploration without any diagnostic investigations. Traumatic muscular lacerations with gross contamination of wound precluded the use of any prosthetic graft and hence saphenous venous graft was most appropriate. Review of literature reveals that patients with concomitant peripheral arterial and venous injuries have a very high amputation rate and simultaneous reconstruction of both leads to improved chances of limb salvage. It is our recommendation that such patients should receive postoperative anticoagulation to avoid thrombosis of graft in venous position.

Keywords: Lower extremity, Saphenous vein graft, Vascular injury.

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Conflict of interest: None

INTRODUCTION

Vascular trauma results from penetrating, blunt or iatrogenic injuries. Young males are at highest risk and the leading causes of injury include motor vehicle crashes, falls, wounds from firearms, wounds from cutting or piercing instruments and burns. Peripheral vascular injuries account for 80% of all cases of vascular trauma. A minority of patients present with hard signs of an arterial disruption, such as pulsatile external bleeding, an enlarging hematoma, absent distal pulses or an ischemic limb in which case immediate surgical exploration in the operating room, without further diagnostic testing, is preferred.

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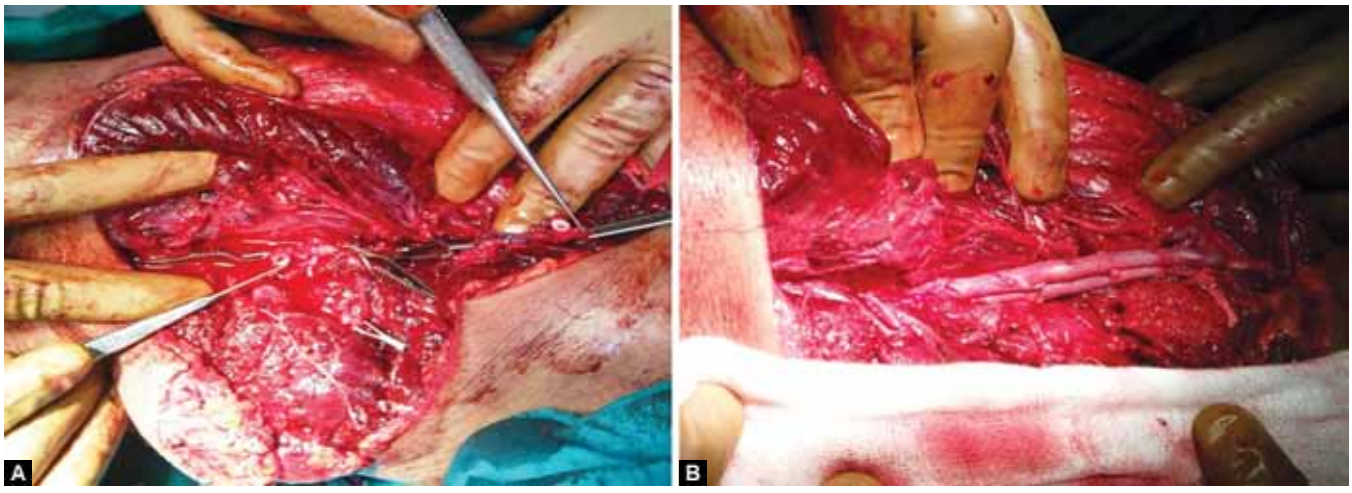
CASE REPORT

A 21-year-old male presented to emergency department with history of fall from 10 feet height onto a sharp metallic plate 2 hours back. On examination, the patient was conscious and alert with a heart rate of 130 bpm and a blood pressure of 80/40 mm Hg. There was a laceration of 15 × 10 cm on the anteromedial aspect of right mid thigh which was bone deep with evidence of gross muscular lacerations and a pulsatile bleeding. Peripheral pulses were absent distal to the site of injury. Compression bandage was applied and fluid resuscitation immediately begun. The patient was managed according to advanced trauma life support (ATLS) protocols with triple immobilization of spine, trauma series of X-rays and a focused assessment with sonography for trauma (FAST) scan of abdomen which revealed no other major injury. The patient was then immediately shifted to the operating room with cross-matched blood. Surgical exploration revealed complete transection of both superficial femoral artery and vein with a tissue loss of 10 cm of both. The long saphenous vein was also disrupted. Proximal and distal cut ends of the artery and vein were isolated after exploration of the proximal and distal parts of the wound. Both ends were freshened by excising the contused segments and both arterial ends were cleared with Fogarty embolectomy catheter. A saphenous vein graft of adequate length was harvested from contralateral unaffected thigh. The right superficial femoral artery was reconstructed using reversed saphenous vein graft and the right superficial femoral vein with unreversed saphenous vein graft (Figs 1A and B). Hemostasis was achieved. Devitalized muscle tissue was excised and muscles repaired. Vascular reconstruction was covered with viable muscle tissue and the wound was closed over drains. In the postoperative period,



Figs 1A and B: (A) Image on the left shows the cut ends of the right femoral artery and vein and (B) image on the right shows completed repair using reversed saphenous vein graft

patient was maintained on low molecular weight heparin, strict limb elevation and active and passive physiotherapy. Immediate postoperative examination revealed a strong distal pulsation with some pitting edema in foot and no neurological deficit. The edema subsided by day 4 postoperative and a computed tomography (CT) angiogram on day 10 revealed patent arterial graft and competent venous graft (Fig. 2). Patient was discharged on day 14 postoperative on oral anticoagulant maintaining international normalized ratio (INR) between 2 and 2.5 (Fig. 3).

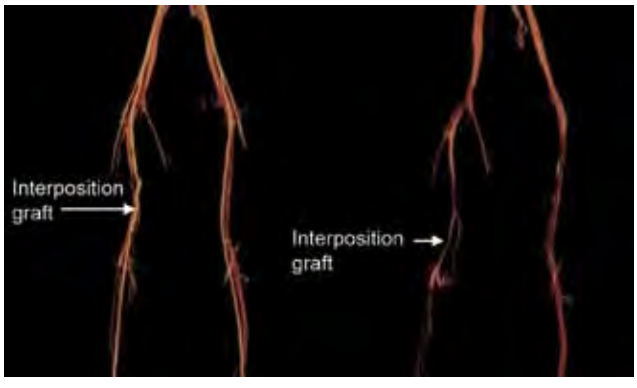


Fig. 2: Computed tomography angiography in the postoperative period showing patent arterial (left) and venous (right) grafts

Fig. 3: Postoperative image of the patient with healed wound

DISCUSSION

Following blunt trauma, tissue injury is produced by local compression or rapid deceleration. In penetrating trauma, the injury is produced by crushing and separation of tissues along the path of the penetrating object. The patient in this report had a combination of blunt and penetrating injury which created vascular disruption with tissue loss. The absence of any other major injury allowed us to proceed with reconstructive vascular procedure. Traumatic muscular avulsions along with gross contamination precluded the use of prosthetic grafts making autologous saphenous vein graft the graft of choice. The systematic review of literature by Klinkert et al[1] shows that the saphenous vein is superior to polytetrafluoroethylene (PTFE) with a primary patency at 5 years of 69% compared with 49%, respectively, and, has convincingly demonstrated that if the saphenous vein is available, a venous bypass should be chosen, even for patients with a short anticipated life expectancy (<2 years). The paper by Phifer et al[2] supports femoral venous reconstruction following traumatic injury in view of the acute morbidity after ligation of the deep femoral veins, particularly with concomitant major arterial injury with an amputation rate of 100% in this group. Specifically, ligation of the superficial femoral vein in association with a major superficial femoral artery injury requiring an interposition vein graft for repair is a highly significant risk factor for lower extremity amputation.[3,4] Previous proponents of femoral venous reconstruction stressed long-term morbidity with stasis changes following deep venous ligation.[5] Since venous reconstruction was performed, the patient was maintained on postoperative anticoagulation with INR target similar to that maintained in acute deep venous thrombosis.

CONCLUSION

Concomitant arterial and venous reconstruction in combined injury in vascular trauma should be performed to improve chances of limb salvage. Patients with venous reconstruction should be placed on postoperative anticoagulation to prevent venous thrombosis.

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CASE REPORT

Favre-Racouchot Syndrome with Predominant Nose Involvement

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ABSTRACT

Favre-Racouchot syndrome (FRS) is a dermatological condition predominantly affecting individuals with an excessive sun-exposure. We report a case seen in an elderly male with a predominant involvement of the nose.

Keywords: Comedones, Favre-Racouchot syndrome, Nose involvement.

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Source of support: Nil

Conflict of interest: None

INTRODUCTION

Favre-Racouchot syndrome (FRS) is a disorder occurring in individuals with history of prolonged sun exposure. Though it is mostly reported in Caucasian men mainly affecting periorbital and temporal areas, it is not uncommon in India. Here we report a case of FRS with a predominant nose involvement which is a rare site.

CASE REPORT

A 65-year-old male presented to us with a history of asymptomatic but progressive raised lesions on the face for 15 years. He also complained of generalized itching with aggrevation during winter months of 2 years duration.

He was a farmer till 10 years ago with an average of 8 hours of sun exposure per day. He denied excessive sun exposure at present time. There was no history of any drug intake or associated illness. He was a nonsmoker.

On examination, apart from generalized xerosis, there was diffuse thickening, yellowish discoloration, furrowing and wrinkling on the face especially in the periorbital region and nose with multiple open comedones, nodules and cysts (Fig. 1). Lateral madarosis was also present.

As there was no history of flushing and on examination, presence of multiple comedones and absence of telangiectasia, sebaceous hyperplasia on nose and absence of cheek involvement, ruled out Rosacea induced rhinophyma. A diagnosis of FRS with senile xerosis was made. The patient was not willing for a biopsy of the facial skin and did not want any treatment for his facial lesions though topical tretinoin was offered as a treatment option. He was treated with topical emollients for xerosis.

DISCUSSION

Favre-Racouchot syndrome also known as nodular cutaneous elastosis with cysts and comedones was originally described in 1932 by Favre[1] and reviewed in detail by Favre and Racouchot in 1951.[2] Though it is found predominantly in middle aged or elderly white men with extensive exposure to sun and weather,[3] it is not so uncommon in Indian patients suggested by a few case reports.[4,5]

The pathogenesis of FRS is uncertain. It has been postulated that damage from ultraviolet (UV) radiation, combined with an unknown host predisposition, leads to alteration of the dermal connective tissue and development of the syndrome.[6] Increased association of FRS in smokers have also been reported suggesting its possible pathogenic role.[7]

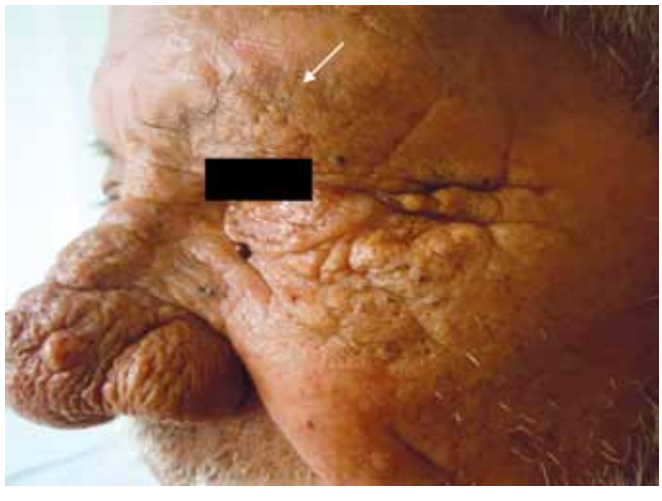

Fig. 1: Multiple comedones, wrinkles and irregular elastotic nodules on the nose and periorbital region with lateral madarosis

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The condition is characterized by open and closed comedones, nodules and cysts on the background of severely actinic damaged skin in the form of wrinkled, thickened yellowish skin on the periorbital and temporal areas often bilaterally and rarely on the lateral neck, postauricular area, forearm or nose. Our case had a predominant nose involvement which is an uncommon occurrence.

Histologically, there are dilated pilosebaceous openings and cyst like spaces filled with horny material.[8] Signs of dermal solar elastosis along with epidermal atrophy also are noted. The conditions which mimic FRS include: comedonal acne, colloid milia, milia, trichoepithelioma, and syringoma.

The treatment consists of avoidance of excessive sun exposure and the use of regular sunscreens to prevent progression of the disease and topical therapy with tretinoin, adapalene or tazarotene.

Various surgical treatment modalities like dermabrasion, curettage and plastic surgery have been tried with variable success and there has been little benefit with comedone extraction or peels used for acne.[9] Carbon dioxide laser has also been used with promising results.[10]

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