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Welcome to the Middle-East Journal of Internal Medicine.

We welcome you to the second issue of The Middle East Journal of Internal Medicine (ME-JIM). Since we launched the journal in March of 2008, we have received enormous support and enthusiasm from our colleagues in the Middle East. We are confident that ME-JIM will develop to your satisfaction.

In this issue, Ahmed et al examined the biochemical characteristics of serum acid phosphatases in breast cancer patients and compared them to controls and to patients with benign masses. The study concluded that breast cancer patients demonstrated a significant increase in acid phosphatases activity and affinity to tissue substrates when compared to normal controls.

A troubling report came from Jordan. The study noted persistent and unacceptable high rates of infant mortality in Irbid, Jordan. Regrettably, most of the causes of deaths are mostly preventable by improvements in prenatal and neonatal care.

A team from the medical school of the Universiti Sains in Malaysia examined the concept of small group discussion and teaching (SGD) and found that 80% of the respondents were in favor of the concept. 86% stated that SGD helped them better understand didactic lectures and complicated topics.

Sadoon et al studied 338 patients with chronic liver disease in Baghdad and discovered that viral hepatitis was etiology in more than 40 % of patients. Increasing scores of fibrosis and worsening liver failure correlated with age and male gender.

Finally, Mahmoud et al noted a significant increase in fasting serum total cholesterol, triglycerides, and lipoprotein levels VLDL and LDL and a significant decrease in the level of fasting serum HDL-C in patients with acute myocardial infarction. This study is certainly an ‘eye opener” as further research into this area may be warranted.

Biochemical Studies on Serum Acid Phosphatases in Patients With Breast Mass in Erbil City

ABSTRACT

Background and objectives: Acid phosphatases (APs) catalyse the hydrolysis of Pi from a broad range of phosphate monoesters and anhydrides in acidic medium. Unusually high or low enzyme expression is seen as part of the certain pathophysiological process like cancer.

No study was observed on serum enzyme kinetics in this disease, so we attempted to study the serum acid phosphatase activity. For this reason we studied acid phosphatase in healthy volunteers, and patients with benign breast masses and breast cancer.

Material and method: A prospective study was carried out during the period: from March to November 2007 in College of Medicine-Hawler Medical University on twenty patients with breast cancer, fifteen benign breast masses and the results obtained were compared with thirty normal subjects.

Results: A significant increase in level of serum ACP activity was observed in patients with breast cancer in comparison to normal healthy subjects and patients with benign breast masses.

The Km values were decreased in the presence of breast cancer by 63% and benign breast masses by 54% in comparison with healthy controls, while the Vmax (maximal velocity of reaction) values were (20.44, 21.18 and 26.52 IU/L) in controls, benign breast masses and breast cancer respectively. The results of thermodynamic parameters also show that the ΔH* and ΔG* values were positive in all groups while S* is negative, the Ea*, ΔH*, ΔS* were decreased in patients with breast cancer and benign breast masses compared with the control subjects.

Conclusion: Based on the findings of the present study it can be concluded that breast cancer causes significantly increased acid phosphatase activity, also affinities of the acid phosphatase for substrate and the active site numbers affected by breast cancer and benign breast masses.

However the thermodynamic studies of transition state (Ea*, ΔH*, ΔS* and ΔG* values) predicted that there may be a change in the mechanism of the ES* - complex formation in patients with breast masses.

Keywords: Acid phosphatase, kinetic study, benign breast masses, breast cancer , thermodynamic.

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Introduction

Human acid phosphatases (APs; EC 3.1.3.2) are a diverse group of enzymes that hydrolyze a variety of natural and synthetic phosphoesters at an optimal pH of 5-6. There are seven types of acid phosphatases in hematopoietic tissues that can be separated electrophoretically and identified by histochemical staining[1,2]. Their heterogeneity is reflected in the presence of several tissue-specific fractions distinguishable by many characteristics, including their electrophoretic mobility, susceptibility to various inhibitors, relative substrate specificity, and probably their immunogenicity[5].

However, pronounced changes in their synthesis occur in particular diseases, where unusually high or low enzyme expression is seen as part of the pathophysiological process. This observation suggests that APs could be diagnostically useful as serological and histological markers of disease, and could also be of use in the investigation of the pathophysiology of the associated disease[3].

Elevation of serum acid phosphatase enzyme has also been observed in the course of breast cancer and it has been suggested that its determination may also be useful to monitor the activity of breast carcinoma[4,5].

Breast cancer is a cancer of the glandular breast tissue , is the most common malignant tumor of females in the western world. It is also the fifth most common cause of cancer death (after lung cancer, stomach cancer, liver cancer, and colon cancer). The incidence of breast cancer remains high, and its clinical courses are highly variable[6]. Generally, cancer is the term applied to a group of diseases in which cells are not responsive to the normal restraints on growth[7]. Once a cell becomes a tumor cell, many biochemical changes are often found in the cells and at the surface of malignant cells, like alteration of surface charge, loss of certain antigen, alteration of o glycoprotein and glycolipid constituents, alteration of

permeability, inappropriate manufacturing of growth factors and hormones, increased rate of aerobic and anaerobic glycolysis and increased terminal transferase activity[8-12].

No study has been observed on serum enzyme kinetic in this disease, so we attempted to study the serum acid phosphatase activity. For this reason we studied acid phosphatase in healthy volunteers, benign breast masses and breast cancer patients.

Methods

1- Subjects

This study was performed at the College of Medicine Hawler Medical University Erbil, Iraq during the period between March to December 2007. Serum samples for this study were obtained from three groups of females as follows:

A -Group I (Control group):

Thirty age and sex matched healthy volunteers in the age group between (22) and (55) years with no clinical evidence of any type of diseases were used as control subjects. Data on family history, diet, medication and lifestyle was obtained using a questionnaire.

B- Group II (Patients with benign breast masses):

Fifteen patients with benign breast masses visited the breast center in the breast cancer center, Rizgary Teaching Hospital and Hawler Private Hospital ranging from (24) and (57) years of age, were enrolled in this study.

C-Group III (Patients with breast cancer):

Twenty patients with breast cancer ranging from 22-57 years of age participated in the study. Samples were collected before anti cancer therapy on the day of surgical removal of the tumors in the breast cancer center, Rizgary Teaching Hospital and Hawler private hospital. The diagnosis of disease was hematologically and histologically confirmed for both groups of benign breast masses and breast cancer.

2- Instruments and apparatus:

· Spectrophotometer (Spectronic 21)

· Centrifuge type Labofuge 200

· Water bath type Y14

3- Collection of Samples:

Blood samples (5 ml) were taken by venepuncture from (65) individuals. The blood was allowed to clot, and the serum was recovered by centrifugation at 3000 r.p.m for 15 minutes, for removal of any suspended cells. Biochemical analysis was performed on serum samples for estimation of acid phosphatase activity and kinetic studies.

4- Methods:

Ready made kits from Biomerieux Sa. (France) were used for determination of Serum acid phosphatase activity by an enzymatic colorimetry method according to the (…)[13].

Km (Michaels-Menton constant) and Vmax (Maximum Velocity) values of serum ACP for normal, benign breast masses and breast cancer were determined using Lineweaver-Burk plots(14 -16), the Hill coefficient (n) values were determined using Hill equation and plots as per the following[16 -18]

$$\text{Log}[V/(V_{max}-V)]=n\text{Log}[S]-\text{Log}K_1$$

Where V is the activity of ACP enzyme at a substrate concentration,

Where K1 is the rate constant of the forward enzyme reaction,

Diagrams were plotted between Log [V/(Vmax-V)] and Log[S]. Straight lines were obtained. Slope of this line is n-values.

The activation energy (Ea*) of the enzymes reaction were determined by the same protocols of ACP activity determination using different temperatures of incubation (5, 15, 25, 37 C°). Arrhenius plots were used to identify the Ea* values which calculate from the slopes of the line (16-18).

The thermodynamic parameters of the transition state; ΔH^* (Enthalpy change of transition state of enzyme-substrate complex), ΔG^* (free energy change of transition state of enzyme substrate complex), and ΔS^* (Entropy change of the transition state of the enzyme substrate complex) were calculated from the following equations[19,20].

$\Delta H^*=Ea^*-RT$ Where R=Gas constant , T =Temperature

$\Delta G^*=-RT\ln Vmax+RT\ln(K-T/h)$ Where K-=Boltzman constant , H=Planck's constant

$\Delta S^*=(\Delta S^*-\Delta G^*)/T$

5- Statistical analysis:

Statistical analysis of the results was done using SPSS software (release 6.0; SPSS Inc., Chicago, IL, USA). Data were expressed as mean±SEM. The data so obtained was analyzed to obtain appropriate conclusions. Student 'T' test was employed to find out the statistical significance. The levels of serum acid phosphatase activity of normal healthy subjects were compared with that of patients of breast cancer and benign breast masses concerning P value. Statistical significance was set at $P < 0.05$.

Results

Serum acid phosphatase level:

The mean±S.E levels for serum acid phosphatase activity were (15.3±0.3 , 16.8±0.7 and 21.5±0.9) IU/L with a range of variation (12.5-21.1, 13-27.3 and 13.8-32.9)IU/L in healthy volunteers, patients with breast masses and breast cancer respectively, Table (1)

A significant increased level of serum ACP activity was observed in women with breast cancer in comparison with normal healthy subjects and patients with benign breast masses.

But in comparison between healthy individuals and patients with benign breast masses, it was shown that there is an increase in S.ACP activity in benign breast masses, but the differences were not significant Table (1).

Kinetic studies:

a-The Km & Vmax values

The Km & Vmax values for serum acid phosphatase were determined by using Lineweaver-Burk plots and Michaelis Menten plots, Figures (1 & 2). All kinetic parameters are the means of five separate experiments (which included 5 healthy females, 5 patients with benign breast masses and 5 with breast cancer), however each point of each line or curve includes the statistical means of 5 individuals.

The Km values for S.ACP were (3.09, 1.43 and 1.15 mM) in control, benign breast masses and breast cancer respectively. The Km values were decreased in the presence of breast cancer by 63% and benign breast masses by 54% in comparison with healthy control.

The Vmax values were (20.44, 21.18 and 26.52 IU/L) in control, benign breast masses and breast cancer respectively - Table 2.

b-Serum acid phosphatase reaction rate parameter:

The Hill coefficient (n) values of the serum acid phosphatase binding to their substrate were estimated (Table 3) from hill plots Figure (3), for all groups.

Thermodynamic studies of transition states:

Figure (4) represents the Arrhenius plots for the serum ACP in normal, benign breast masses and breast cancer, From this figure the energy of activation (Ea*) of the enzyme substrate reaction were estimated - Table 4

The results show that the Ea* for serum ACP decreases in patients with breast cancer and benign breast masses

The results of ΔH*, ΔS* and ΔG* of the transition state for acid phosphatase enzyme-substrate reaction, indicate that (Table 4):

1. The ΔH* and ΔG* values were positive in all groups
2. There was a decrease in ΔH* values for breast cancer and benign breast disease
3. The ΔS* values were negative in all groups
4. The ΔS* values for the ACP enzyme reaction were lower in the case of breast cancer and benign breast masses compared with the control group.

Discussion

In an attempt to provide kinetic studies of acid phosphatase activity, we assayed a series of serum samples from patients with clinically defined breast cancer, benign breast masses and healthy controls.

I-Serum acid phosphatase activity:

Measurement of acid phosphatase activity demonstrated that patients with breast cancer had significant higher ACP activity than benign breast masses ($P<0.05$)and normal individuals ($P<0.01$), whereas ACP activity in benign breast masses was higher compared with controls but not significant. These results are similar to those obtained by other investigators[21, 22, 23, 24, 25].

Increased level of AP activity in breast tumors may be correlated to the amount of apoptosis which regulates TNF that is going on in the cells(26), Acid phosphatase is a lysosomal enzyme found in most, if not all lysosome. Lysosomal enzymes are activated during apoptosis in response to hormonal and other cellular triggers (acidic pH, lysomotropic agents, etc). These enzymes have the capability of degrading all macromolecules and ultimately destroying the entire cell[25 - 32].

II-Kinetic studies

Our results show the Km value for the serum acid phosphatase activity decreased in patients with breast cancer (63%), benign breast masses (54%) compared to the normal group. This means that the affinity of the enzyme for their substrate (ionic state) of the active sites become more suitable for the substrate for binding[20, 24, 26, 35, 36].

While the Vmax values for the acid phosphatase enzyme reaction increased in breast cancer (26.52 IU/L), and benign breast masses (21.18 IU/L) as compared to normal subjects (20.44 IU/L) this means that there is a change in active site conformation or number in the serum enzyme in breast cancer and benign breast masses which lead to increased enzyme activity and it's affinity (enzyme reactions velocity)[20, 33, 35, 37].

The values of Hill coefficient revealed that there was no incorporation and there were no significant changes in n-value in breast cancer and benign breast masses in compared to that of the control group, so our result suggested that no allosteric conformational changes

occurred in the enzyme molecule in all cases[20, 33, 35, 37].

III-Thermodynamic studies of transition states

We found in this study also that the Ea* for ACP decreases in breast cancer and benign breast masses and this result indicates that the breast cancer and benign breast masses may affect the mechanism of ACP reaction[20, 33, 35, 37, 38].

The positive values of ΔH* for ACP in all groups indicated that ACP reaction was endothermic and the heat content of the activated complex (ES*) were greater than that of the isolated species (E&S)[24,28,38].

Also the results show that the ΔH* values in breast cancer and benign breast masses decrease. This emphasized that the heat content of ES*-complex in breast cancer is smaller than benign breast masses and control subjects[20, 30].

A positive charged value for ΔG* for enzyme-substrate reaction in all groups indicated that the active complex ES* formation required input of energy[37].

The negative values of ΔS* reflects a change to a more ordered structure. The study revealed that the S* values for ACP reaction decrease in breast cancer and benign breast masses. This means that the transition complex ES* had more ordered structure in the patient group especially breast cancer for ACP enzyme[20, 33, 35, 37].

Conclusion

1. Breast cancer causes elevation of serum acid phosphatase activity.
2. Kinetic study showed that Km values for the serum enzyme-substrate binding were decreased in breast cancer and benign breast masses, while the V max values were increased. This result indicated that the affinities of the enzyme for substrate and the active site numbers, may be affected by breast cancer and benign breast masses.
3. The thermodynamic studies of transition state (Ea*, ΔH*,ΔS* and ΔG*) values predicted that there may be a change in the mechanism of the ES*-complex formation.

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Table 1. The host information of healthy volunteers and patient groups

Parameter	**Control**		**Breast cancer**		**Statistical evaluation**
	Range	**Mean±S.E**	**Range**	**Mean±S.E**	
ACP(IU/L)	12.5-21.1	15.3±0.3	13.8-32.9	21.5±0.9	P<0.01
ACP(IU/L)	Control		Benign breast masses		
	Range	Mean±S.E	Range	Mean±S.E	
	12.5-21.1	15.3±0.3	13-27.3	16.8±0.7	N.S
ACP(IU/L)	Breast cancer		Benign breast masses		
	Range	Range	Range	Mean±S.E	
	13.8-32.9	13-27.3	13-27.3	16.8±0.7	P<0.05

Table (2): Km and V max Values for serum ACP in control, patients with benign breast masses and breast cancer

Groups	**Km(Mm) ACP**	**Vmax(IU/L) ACP**
Control	3.09	20.44
Benign breast masses	1.43	21.18
Breast cancer	1.157	26.52

Table 3: Hill coefficient (n) values for ACP in control, patients with benign breast masses and breast cancer

Groups	**Hill coefficient (n)**
Control	1.19
Benign breast masses	1.22
Breast cancer	1.19

Table 4: Thermodynamic parameters of transition state for S.ACP in controls, patients with benign breast masses and breast cancer

Groups	**Ea*(Cal/mol)**	**ΔH*(Cal/mol)**	**ΔG*(Cal/mol)**	**ΔS*(Cal/mol/deg)**
Control	3795.066	3181.266	11725.12	-27.5608
Benign breast masses	3707.352	3093.552	11703.29	-27.7733
Breast cancer	2381.148	1767.348	11565.28	-31.6062

Figure 1: S.ACP in controls, patients with benign breast masses and breast cancer

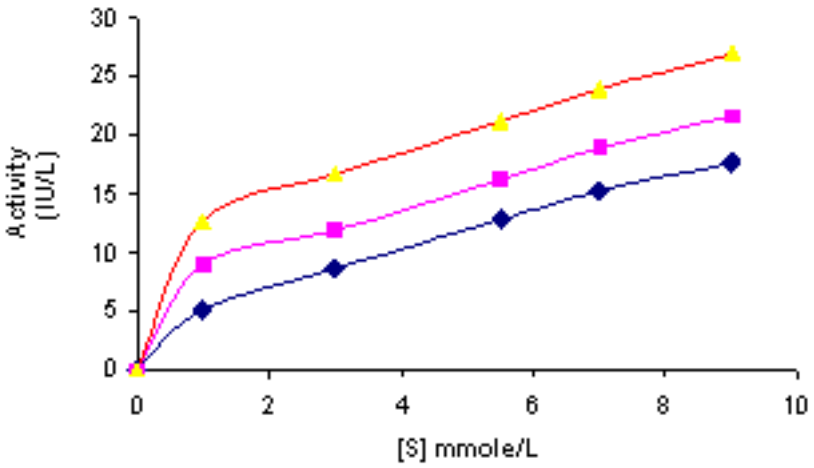


Figure 2: Lineweaver-Burk plot for S.ACP in control, patients with benign breast masses and breast cancer

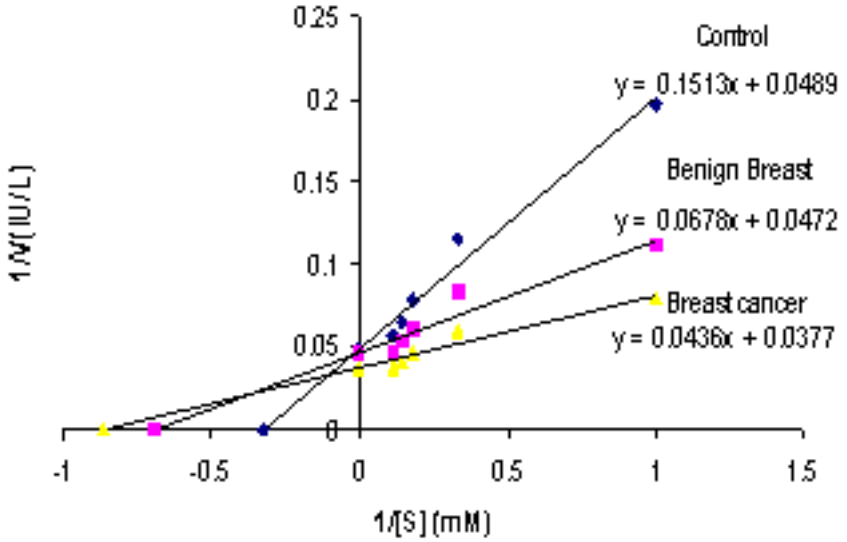
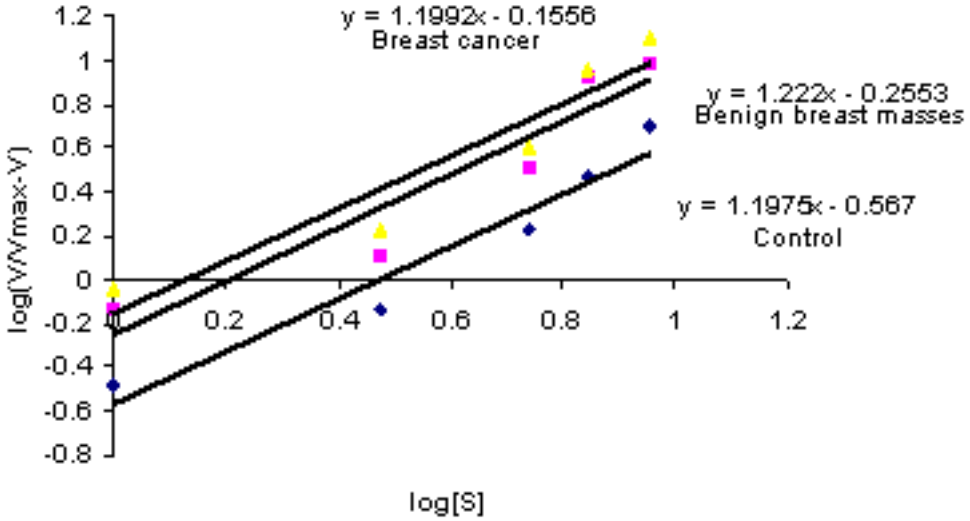


Figure 3: Hill plots for S.ACP in control, patients with benign breast masses and breast cancer



The Infant Mortality Rate in Irbid, Jordan

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ABSTRACT

Objective: To determine the cause-specific infant mortality rate (IMR) and to assess its major causes in Irbid city.

Material and methods: A retrospective study using information obtained from the birth and death registers and birth and death certificates for infants at PRH in the period from January 2005-2006.

Results: There were 6,078 live births in PRH in the study period.128 infants died in the same period.IMR was found to be 21.1/1000 live births.Major causes were premature delivery in 50 (39.1%), infections in 32 (25%), birth defects in 24 (18.8%), sudden infant death syndrome (SIDS) in 8 (6.3%) and difficult delivery in 6 (4.7%) cases. There were 90 cases in the neonatal period. The neonatal mortality was 14.8/1000.

Conclusion: IMR is still high in PRH, and most of the causes of deaths are preventable mostly by improving the neonatal settings. Improvements in prenatal care, neonatal care and adverse environmental factors will prevent many of the cases.

Keywords: IMR, cause-specific.

Introduction

Infant mortality rate (IMR) is a sensitive index of the general health and welfare of the population of a nation1-3. It is an indicator of the effectiveness of health services3.

Cause-specific mortality rate data are useful in the planning and the evaluation of strategies designed to address high IMR2. This is because the starting point of a sequence of events leading to death is known and death can be avoided or postponed by preventing the initiating cause1.

In many countries, IMR is declining rapidly1-6 and with time, factors associated with infant death will change. Moreover, continued monitoring of these data in the population will serve to assess the benefits of intervention and point to new areas for future preventive measures2.

It is by identifying major causes of death that an intelligent plan of action can be taken to reduce the impact of various causes of infant death on the IMR. The main objectives of the present study were to:

1) determine the IMR

2) determine major specific causes of infant death.

Data Collection and Methodology

Data Collection

The data was collected according to a field survey from May 20 to July 15 in 2005 from 500 respondents of Nawabganj Paurashava. For the method of data collection the household heads were directly interviewed and the desired information was collected by the predesigned questionnaire. The data was collected using stratified random sampling technique. Nawabganj Paurashava is constituted of 15 wards. Each ward is considered as a stratum. There are 15 strata. Next, data was collected from each ward by using stratified random sampling without replacement method with proportional allocation. The total household size of Nawabganj paurashava is 25,083 and our desired sample size is 500.

Methodology

Data analytic method envisaged in this paper is a percentage distribution and Stepwise regression analysis. Multiple regression analysis is performed in order to see how much variation is explained by all explanatory variables of the phenomenon under study and step wise regression analysis is used to assess the contribution of the influential variables and adequacy of the models with the limited number of variables.

Conceptual Framework

The conceptual framework of the present study is presented in Figure 1 and 2. When the people are not using healthy sanitary latrines or use open land as a lavatory how does the stool pose environmental problems? We can see by Figure-1. The human excreta

of a sick person or a carrier of disease is the main focus of infection. It contains the disease agent which is transmitted to a new host through various channels: (1) water, (2) fingers, (3) flies, (4) soil and (5) food. These events are shown in Figure 1.

Community medicine aims at breaking the disease cycle at vulnerable points. The disease cycle (Figure 1) may be broken at various levels: segregation of faeces, protection of water supplies, protection of foods, personal hygiene and control of flies. Of these, the most effective step would be to segregate the faeces and arrange for its proper disposal so that the disease agent cannot be reached by the new host. Figure 2 shows the segregation of the excreta by imposing a barrier called the "sanitation barrier".

Results

The data covered a total of 6,078 live births. These consisted of 3080 males and 2998 females, giving a male: female ratio of 1.03:1. There were 128 infant deaths, giving an IMR of 21.1 /1000.

Of the 128 deaths, 90 (70.3%) and 38 (29.7%) were neonatal and post-neonatal deaths respectively. Neonatal mortality rate was 14.81/1000 and post-neonatal mortality rate was 6.35/1000 ($P<0.01$).

Major causes of death are shown in Table 1. The IMR for various causes of infant death is also shown in Table 1. Major causes of neonatal deaths were prematurity in 40 (44.4%), congenital anomalies in 24 (26.7%), bacterial infections 20 (22.2%) and difficult labor in 6 (6.7%).

The two sexes were also equally affected. Of the 32 neonatal deaths caused by infection infections, 28 (87.5%) were due to septicemia and meningitis and 4 (12.5%) were due to pneumonia.

Discussion

TThe IMR in Irbid, PRH in this study was 21.1/1000; see Table 2 from WHO reports7. The main focus of the present study was on the IMR and the major causes of infant death. The major causes of infant deaths were prematurity, birth defects, infections, SIDS and difficult deliveries. About 75% of the deaths were due to preventable causes.

Improvements in prenatal coverage will reduce the impact of premature and difficult deliveries on IMR.9-12 Programs designed to prevent preterm births through prenatal care are required to reduce deaths due to prematurity1.

About 70% of the deaths occurred in the neonatal period. Al-Faraidy ET al.13 showed that neonatal care facilities were inadequate. With improvements in neonatal care facilities, the IMR will fall. Most of the decline recently in IMR in the USA and other developed countries has been associated with a fall in the neonatal mortality rate4, 5, 9. This is due mainly to recent advances in neonatal intensive care technology; in particular, the surfactant therapy in the very low birth weight infants4-6, 14. Improvement in sanitary conditions will reduce infant deaths due to infections. This will indirectly follow improvements in levels of education of parents9.

As improvements in prenatal and intrapartum care, care of the preterm infant, and NICU technology lead to reduction in IMR, birth defects will become more prominent as a cause of infant morbidity and mortality15. Efforts must also be directed at reducing the contribution of birth defects to IMR.

This should be a two-prong approach - prevention and early diagnosis and treatment. Preventive measures need more epidemiological data. Consanguineous marriage has been implicated as a contributing factor16. This needs further evaluation. In many of the hospitals, facilities are available for the management of gastrointestinal, central nervous system, and respiratory system anomalies. Infants with CVS anomalies, on the other hand, are not as fortunate. Some of the babies inevitably die while waiting to be transferred to the only center with facilities for managing infants with CVS anomalies. This will probably explain the relatively high percentage (41.6%) of deaths due to CVS anomalies since more of the babies with other system anomalies were saved.

Not enough is known about SIDS to suggest appropriate preventive measures. The proportion of deaths due to SIDS was 6.3%. This was less than the 12.0% reported from the USA8. In the USA, 1.6 to 2.3/1000 infants die of SIDS17. This is more than the 1.3/1000 reported here.

The present data show that about 75% of the deaths were due to preventable causes - preterm deliveries, infections, difficult deliveries and possibly SIDS. Improvements in prenatal care, neonatal care and adverse environmental factors will prevent many of the cases.

Conclusions

Prevention of premature delivery through improved prenatal care coverage and improvements in neonatal intensive care facilities will reduce deaths due to prematurity and difficult delivery.

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Table 1. The distribution of main causes of infant deaths

Causes.of deaths	Number	Percentage Infant Total deaths	Mortality rate/1000
Infections	32	25.0	5.4
Prematurity	50	39.0	8.3
Congenital anomalies	24	18.7	3.9
Difficult labor	6	4.7	1.0
SIDS	8	6.2	1.3
Drowning	2	1.6	0.3
Road traffic accident	2	1.6	0.3
Burns	2	1.6	0.3
Status epilepticus	2	1.6	0.3
Total	128	100	21.1

SIDS=sudden infant death syndrome.

Table 2. Infant mortality rates (IMR) and the percentage decline from 1978 to 1998 in 16 Arab countries of the Eastern Mediterranean[7]

Country	IMR	IMR	Decline in
	1978	1998	rate 1978–99
	‰	‰	%
Bahrain	43	17	60.5
Egypt	131	51	61.1
Iraq	84	95	–13.1
Jordan	65	26	60.0
Kuwait	34	12	64.7
Lebanon	48	29	39.6
Libyan Arab Jamahiriya	63	28	55.6
Morocco	110	51	53.6
Oman	95	25	73.7
Qatar	46	17	63.0
Saudi Arabia	75	23	69.3
Sudan	97	71	26.8
Syrian Arab Republic	67	33	50.7
Tunisia	88	30	65.9
United Arab Emirates	38	16	57.9
Republic of Yemen	158	80	49.4

The Frequency of HBV and HCVInfections in Chronic Liver Disease in Baghdad, Iraq

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ABSTRACT

Background: Viral hepatitis is still one of the most common causes of acute and chronic liver disease worldwide, specifically in developing countries.
Objectives: Clarify the correlation between HBV and HCV infection and chronic liver diseases using a new staging method.
Patients and Methods: The study included 338 patients with chronic liver diseases who attended the Gastroenterology and Hepatology Center, in Medical City in Baghdad during the period from the beginning of March 2004 until end of September 200.
Results: The study revealed that viral hepatitis caused by HBV, HCV or both of was found in 41.7 % of patients with liver disease. HBsAg was found in 35.5 %, anti-HCV in 58.9 % and co-infection in 5.7 % of patients. Liver biopsy revealed different grades of necro-inflammation and stages of fibrosis. Only 8% of patients with HBV had hepatocellular carcinoma (HCC). In general, the grade of necro-inflammation increased with stage of fibrosis The score of fibrosis increased with increasing age. Similarly, male gender was associated with an increasing score of fibrosis.
Steatosis was found in 18% of patients with HBsAg and 20.5% of patients with anti-HCV. In HBsAg positive cases, all patients were >30 years but the rate of steatosis decreased with increasing age. While in anti-HCV positive cases, all patients were >20 years and the rate of steatosis increased with increasing age. On the other hand steatosis was associated with fibrosis score decreased in cirrhotic patients with anti-HCV.
Conclusion: Viral hepatitis caused by HBV, HCV or both was found in 41.7 % of patients with liver disease and their frequencies were 35.5 %, 58.9 % and 5.7% respectively. The patients had different grades of necro-inflammation and stages of fibrosis as detected by liver biopsy and only 8% of patients with HBV had HCC. The grade of necro-inflammation increased with increasing the stage of fibrosis. The increasing score of fibrosis correlated with increasing age and male gender. Steatosis was associated with increasing fibrosis scores and decreased in cirrhotic patients with HCV infection.
Keywords: HBV, HCV, IRAQ

Introduction

Viral hepatitis is still one of the most common causes of acute and chronic liver disease worldwide. Five hepatotropic viruses A to E are now recognized and all are important health issues, although moreso in some countries than others[1]. Three additional viruses, hepatitis G, TT virus, and SEN-V have been discovered recently[2, 3]. The prevalence of each virus differs from one country to another and, within one country; the pattern of disease may change over time reflecting change in the social, economic and hygienic variables[4].

Chronic viral hepatitis B and C are the most common causes of liver fibrosis. During the chronic hepatitis course, fibrosis is a part of the inflammation activities[5]. It is generally accepted that the hepatitis B virus does not directly cause the pathological effects of acute and chronic necrotizing inflammatory liver disease. It is evident that an immune response mediated by cytotoxic T lymphocytes (CTLs) is primarily responsible for the associated liver disease[6]. However, 5-10 % of adults and up to 90 % of infants will become chronically infected[7].

The HCV is an enveloped, positive stranded RNA virus. Probably the most remarkable feature of HCV infection is its tendency to become chronic. Importantly, the large majority of chronically HCV infected patients, develop histological evidence of liver disease, ultimately leading to cirrhosis, hepatocellular carcinoma (HCC) and liver failure requiring liver transplantation. The outcome of the infection is determined to a large extent by the host's immune response[8].

The HBsAg assays are highly sensitive immunoassays that indicate the presence of HBV[9]. Antibody to HCV (anti-HCV) is a widely accepted method for the diagnosis of HCV infection[10].

Despite recent advances in the ability to diagnose liver diseases by the laboratory and radiological tests, assessing the liver tissue itself after obtaining a liver biopsy continues to be an integral part in the diagnosis of the majority of liver diseases. In patients with viral hepatitis, liver biopsy helps to exclude other forms of liver diseases, provide baseline

histology for further reference, and predict responsiveness to antiviral therapy. More importantly, liver biopsy helps prognosticate the patient and hence reach more reasonable decisions regarding their need for antiviral therapy[3].

Objectives: Clarify the correlation between HBV and HCV infection and chronic liver diseases using a new staging method.

Materials and Methods

Study Population

The study included 338 patients with chronic liver disease who attended the Gastroenterology and Hepatology Center, Medical City in Baghdad, during the period from the beginning of March 2004 until the end of September 2005. All patients were asked for name, age, gender, date of illness, and other chronic diseases if present. Blood sample of 5 ml was drawn from each patient for detection of HBsAg and anti-HCV. The patients were assured to be compatible for liver biopsy by prothrombin time and serum protein, that showed normal levels in all patients involved in the study. Liver biopsy was taken from patients who have HBsAg or anti-HCV or both. At the time of liver biopsy, a blood sample was drawn to check for biochemical tests. The study was approved by the ethical committee of the centre and written informed consent was taken from patients.

Detection of HBsAg

Hepanostika HBsAg Uni- Form II (bioMerieux Bv/ Boseind 15,5281 RM Boxtel, The Netherlands) was used for detection of HBsAg. Hepanostika HBsAgUni-Form II is an enzyme-linked immunosorbent assay (ELISA) based on a one-step "sandwich" principle. Antibody to HBsAg (anti-HBs) coupled to horseradish peroxidase (HRP) serves as the conjugate with tetramethylbenzidine (TMB) and peroxide as the substrate. Upon completion of the assay, the development of color indicates the presence of HBsAg, while no or low color development suggests the absence of HBsAg.

Specifically, microelisa wells are coated with anti-HBs (murine monoclonal). Each microelisa well contains an HRP-labeled anti-HBs (ovine) conjugate sphere. The test sample or appropriate control containing HBsAg is incubated in the microelisa wells. The conjugate sphere dissolves in the sample and a solid phase antibody/HBsAg/ enzyme-labeled antibody complex is formed. Following wash and incubation with TMB (tetramethylbenzidine) substrate a blue color is produced. The enzyme reaction is stopped by the addition of a sulfuric acid solution, which changes the color to yellow. When HBsAg is present in the sample, an intense color develops. However, if the sample is free of HBsAg, no or little color forms after the addition of substrate. Within limits, the amount of HBsAg in the sample is proportional to the degree of color development.

Detection of anti- HCV

The anti- HCV was detected using Bioelisa HCV kit (Biokit, S.A. Spain), which is an immunoenzymatic method .

The wells of a microplate are coated with recombinant antigens representing epitopes of HCV. Serum or plasma samples are added to the wells. If antibodies specific for HCV are present in the sample, they will form stable complexes with the HCV antigen on the well. After washing to remove the unbound material a rabbit anti-human IgG labeled with horse-radish peroxidase is added and, if the antigen/ antibody complex is present, the conjugate will bind to the complex. After a second wash, an enzyme substrate solution containing a chromogen is added. This solution will develop a blue color if the sample is positive. The blue color changes to yellow after blocking the reaction with sulfuric acid. The intensity of the color is proportional to anti-HCV antibody concentration in the sample. Wells containing negative samples remain colorless.

Liver Biopsy

Liver biopsy was performed percutaneously (through the skin). During a percutaneous biopsy, the patient will be lying on his or her back near the right edge of bed. The right arm of the patient will be under his or her head. A local anesthetic will be injected into the skin. A tiny incision will be made into the skin. The biopsy itself takes one second, during which the biopsy needle is passed quickly in and out of the liver, suctioning a small cylindrical sample of the liver tissue. The patient will be asked to lie on his or her right side for two hours to place pressure against the biopsy site to decrease the possibility of bleeding.

The liver biopsies were processed in usual steps in paraffin embedding technique. Slices of 5mm-thick were prepared from blocks of liver biopsy by using microtome. Slices were put on slides and allowed to dry. The slides were stained by hematoxylin and eosin.

Microscopic Examination

Microscopic examination was done by a pathologist to assess the grade of necro-inflammation and stage of fibrosis according to Knodell Histology Activity Index (HAI). The HAI classify fibrosis into 4 stages of increasing severity; stage 4 represents cirrhosis. Other findings including fatty changes and iron deposition were reported. This index was used for the first time in Iraq for evaluating the association between HBV & HCV and chronic liver diseases.

Statistical Analysis

The results were statistically analyzed using Chi-square test.

Results

Viral infection in patients with liver diseases.

The current study revealed that viral infection caused by HBV, HCV or both was found in 141 out of 338 (41.7 %) of patients with liver diseases (Figure 1).

Types of viral infection

The current study revealed that out of 141 patients with viral infection, the HBsAg alone (as indicator of hepatitis B infection) was detected in 50 patients (35.5 %), while anti-HCV was found in 83 patients (58.9 %). Co-infection with both HBsAg and anti-HCV represented only 5.7 % (8 out of 141 patients) (Figure 2).

Stages of liver disease in patients with different viral infections

Patients with HBsAg revealed stage I fibrosis in 24%. This rate declined to 22% with stage III, then 20% with stage II and 18% in stage IV fibrosis. Only 8% of the patients infected with HBsAg had no fibrosis on liver biopsy. Cases with HCC were only found in patients with HBsAg and comprised 8% of the patients (4 out of 50 patients), which was significant ($X2 = 11.53$, $p<0.05$).

Patients with anti-HCV had stage III in 41% of patients (34 out of 83 patients). Stage II fibrosis was found in 31.3%. Patients who had no fibrosis represented 9.6% of cases. The same rate of patients was found to have stage IV fibrosis, while patients with stage I fibrosis represented only 8.4%, which was significant ($X2 = 73.41$, $p< 0.05$).

Patients with co-infection with HBsAg and anti-HCV exhibited stage III and stage IV fibrosis with the same rate (37.5%). Stage I and Stage II fibrosis were found with equal rates (12.5%), which was significant ($X2 = 4.56$, $p< 0.15$)…(Table 1) and (Fig 3, 4, 5, 6 and 7).

Stages of liver disease and grades of necro-inflammation

Patients with HBsAg

In the absence of fibrosis, all patients had a minimal grade of necro-inflammation. In stage I fibrosis, 41.7% of patients had minimal grade and 58.3% had mild grade. In Stage II fibrosis, 40% and 60% of patients had minimal and mild grade. In Stage III fibrosis, mild and moderate grades were found in 36.3% and 63.6% of patients respectively. In Stage IV fibrosis, most patients (88.9%) had moderate grade while only 11.1% of patients had mild grade, which was significant ($X2 = 40.29$, $p< 0.05$) (Table 2).

Patients with anti-HCV

In the absence of fibrosis, 75% and 25% of patients had minimal and mild grade of necro-inflammation respectively. The minimal and mild grade was found in 28.6% and 71.4% of patients with Stage I fibrosis. No patients with Stage II fibrosis had minimal grade and 84.6% and 15.4% had mild and moderate grade respectively. In Stage III fibrosis, minimal, mild and moderate grade was found in 5.9%, 35.3% and 58.8% of patients respectively. However, half the number of cirrhotic patients had mild grade and the other half had moderate grade, which was significant ($X2 = 56.17$, $p< 0.05$) (Table 3).

Stages of liver disease according to age groups

Patients with HBsAg

Patients who showed no fibrosis on liver biopsy (Stage 0 fibrosis) were of the age group 30-39 years and 40-49 years; the total cases were 4, 2 for each age group (50%). Highest rate of patients with stage I fibrosis (41.6%) was of the age group 20-29 years. Patients with Stage I fibrosis and within the age group 10-19 years and those within the age group 40-49 years represented 8.3% of cases and patients who were aged <10 years comprised 16.6%. While in Stage II fibrosis, 50% of patients were of the age group 30-39 years, 30% of patients were of the age group 20-29 years and only one patient (10%) was within the age group 10-19 years. In Stage III fibrosis 45.4% of patients were of the age group 50-59 years, 27.2% were of the age group 40-49 years, 18.1% were of the age group 30-39 years and only one patient (9%) was within the age group 20-29 years.

In cases with Stage IV fibrosis: the highest rate of patients was aged ³ 60 years, followed by those within the age group 50-59 years. One patient within the age group 30-39 years and another patient within the age group 40-49 years were found to have Stage IV fibrosis. In HCC cases 75% of patients were of the age group ³ 60 years and only 25% were of the age group 40-49 years, it was significant ($X2 = 58.47$, $P < 0.05$) (Table 4).

Patients with anti-HCV

In cases with Stage 0 fibrosis: the highest rate (37.5%) was in the age group 30-39 years. Patients within the age groups: 10-19 years, 20-29 years, 40-49 years, 50-59 years and ³ 60yr showed no fibrosis with equal rates (12.5% for each age group). No patients under ten years showed no fibrosis. The age groups 20-29 years, 30-39 years and 40-49 years showed Stage I fibrosis with equal rates (28.5%). One patient under ten years revealed Stage I fibrosis. Patients within the age groups 20-29 years, 40-49 years and the age group 50-59 years showed Stage II fibrosis with equal rates (19.2 %). Patients within the age group 10-19 years and Stage II fibrosis represented 15.3%, while each of the patients within the age group <10 years and ³ 60 years represented 7.6 % of cases.

In patients with Stage III fibrosis 29.4% were of the age group 10-19 years, 20.5% were of the age group 50-59 years. Patients within the age groups: <10 years, 20-29 years and 30-39 years represented 17.6%, 8.8% and 11. % respectively. Each of the age groups 40-49 and ³ 60 years represented 5.8%. In Stage IV fibrosis, 37.5% were

of the age group 10-19 years. While the age group 50-59 years and age group ³ 60 years represented only 25%, and only one patient (12.5%) within the age group 40-49 years showed Stage IV fibrosis on liver biopsy, which was significant (X2 = 25.29, P > 0.05) (Table 5).

Stages of liver disease according to sex

Patients with HBsAg

Male patients with HBsAg represented 66%. In most stages of liver disease the rate of males was higher than that of females, which was significant (X2 = 6.756, P < 0.15) (Table 6).

Patients with anti-HCV

Male patients with anti-HCV represented 56.6%. In most stages of liver disease the rate of males was higher than that of females; it was significant (X2 = 3.112, P< 0.15) (Table 7).

Discussion

Hepatitis is a very general term for an inflammation of liver due to variety of causes that may be metabolic disease, drugs, alcohol, toxins and viruses. Viral hepatitis is one of the most important global health problems, infecting hundreds of millions of individuals and responsible for more than a million deaths per year[11]. The HBV and HCV are much alike in that they both cause a spectrum of clinical conditions ranging from the symptom-free carrier state through to chronic hepatitis and liver cirrhosis to eventual HCC. Despite a close similarity, infections with HBV and HCV are very different in many aspects, from early to end stage[12].

Results obtained by this study indicated that viral infection caused by HBV, HCV or both was found in 41.7% of patients with liver disease. The HBsAg was found in 35.5%, anti-HCV was found in 58.9% and both HBsAg and anti-HCV in 5.7% of patients with viral hepatitis. Al- Kassir and Al- Rawi[13] reported that chronic viral hepatitis due to HBV, HCV and combined infection was the commonest cause in 36.9% of patients with chronic liver disease. The HBV was found in 69.5%, HCV in 25.4% and combined HBV/HCV in 5.1%. A similar study was performed in the Republic of Yemen to evaluate patients with various classes of liver disease and revealed a prevalence rate of 37.1% of anti-HCV markers in the patients. The HBsAg was detected in 33.6% of cases. Anti-HCV and HBsAg were detected in 7.7% of cases[14].

Liver disease, including that caused by HCV, progresses in stages. It can range from inflammation, to fibrosis, to cirrhosis, to end-stage liver disease or liver cancer. The harmful outcome of chronic inflammation is fibrosis[3]. Fibrosis is the scar tissue that forms when the liver cells are destroyed by the virus. Cirrhosis is the result of continuous liver damage through chronic inflammation and development of areas of fibrosis throughout the liver.

This research demonstrated that necro-inflammation was found in the absence of fibrosis but in minimal grades in most cases, then the grade of necro-inflammation increased to mild and moderate grades as stage of fibrosis increased.

Generally speaking, inflammation is the precursor to fibrosis. Activity grade, which represents the necrosis feature, is not a good predictor of fibrosis progression[15]. In fact fibrosis alone is the best marker of ongoing fibrogenesis. Fibrosis stage and inflammatory grade are correlated but for one third of patients, there is discordance[16]. It has been confirmed that liver fibrosis does not develop at the same rate in all patients[17]. Individual differences in genes that are involved in the process of inflammation may also affect progression[18]. Fontaine et al[19] reported that fibrosis progression is significantly associated with the necro-inflammatory activity. It has been demonstrated that patients with moderate or severe necro-inflammatory activity have more rapid fibrosis progression than patients with no or minimal activity when infected by HBV or HCV[20].

A novel viral hepatitis B spliced protein (HBSP) has been identified in HBV-infected patients, which is encoded by spliced HBV RNA and is also expressed during the course of chronic HBV infection[21]. Spliced HBV transcripts are also encapsided, reverse transcripted and secreted as defective viral particles. The HBSP expression and the ratio of defective/ wild type viral particles is significantly higher in patients with severe fibrosis compared to patients with moderate fibrosis. In vitro, the expression of HBSP induces a moderate activation of the transforming growth factor-alpha (TGF-a) pathway. This suggests that HBSP protein and defective viral particles play a role in HBV pathogenesis and in particular hepatic fibrosis[22, 23].

In this study, Stage III fibrosis was found in 22% of patients with HBsAg and 41% of patients with anti-HCV. Stage IV fibrosis (cirrhosis) was found in 18% of patients with HBsAg and 9.6% of patients with anti-HCV.

Advanced hepatic fibrosis is an independent risk factor for development of HCC[24]. The rate of development of liver fibrosis in hepatitis C virus (HCV) infection varies between individuals. This accounts for the variation in duration of progression to cirrhosis[25]. Studies evaluating the natural history of HCV have reported rates of progression to cirrhosis from 2% to 20% over 20 years[26]. Some patients develop cirrhosis within a decade of infection: others are free of complications after 30 years[27]. According to HBV, between one third and one quarter of people infected chronically are expected to develop progressive liver disease (included cirrhosis and HCC)[28].

On a global basis, longitudinal studies indicate that cirrhosis related to either HBV infection or HCV infection represents the major risk factor for HCC and hence can be considered a premalignant condition[29]. The consumption of alcohol in any form, including such things as mouthwashes and cough medicines, must be completely avoided by people with cirrhosis[30].

Hepatocellular carcinoma is among the most prevalent and deadly cancers worldwide. Worldwide, chronic HBV infection is among the most common cause of liver cancer. Hepatitis B virus infection is the primary risk factor for HCC among Asian populations[31]. Results of liver biopsy in the current investigation indicated that cases of HCC were detected in 8% of HBV-infected patients and no one of HCV-infected patients had HCC on liver biopsy.

In Turkey, HBV infection is the leading cause of HCC, followed by hepatitis C infection and alcoholic liver disease[32]. In Southern Iran, the predominant etiology of HCC was hepatitis B, hepatitis C, but alcohol and metabolic diseases were only found in rare cases[33].

Egypt is a heavily populated country, with a strikingly high HCV infection prevalence of 26%. This high prevalence of chronic liver disease in Egypt has lead to increasing numbers of Egyptian patients suffering from end stage liver disease, necessitating liver transplantation[34]. In Egypt, the high prevalence of HCVAb positivity renders its contribution to the development of HCC over seven-fold higher than HBsAg positivity[35].

Several factors have been reported to be associated with increased risk for HCC among HBsAg carriers: male gender, older age (or longer duration of infection), Asian or African race, cirrhosis, family history of HCC, exposure to aflatoxin, alcohol and tobacco, and co-infection with HCV[36]. Chang et al[37] reported that HCC has a male predominance and is closely related to HBV infection. The HCC is increasing in many countries as a result of an increase in HCV infection[38]. Hepatitis C virus is another risk factor for HCC in the United States; however, this virus is believed to play a relatively minor role in the development of HCC in Asia and Africa[39].

The hepatitis B virus-encoded X antigen (HBxAg) may contribute to the development of liver cancer, in part, by stimulating the survival of infected cells in the face of ongoing immune responses[40]. The sustained hepatocellular proliferation may render chronic HBV carriers more susceptible to the effects of environmental carcinogens[41]. Aflatoxins together with chronic HBV infection contributed to the high incidence of HCC in developing countries[42]. Mutant p53 gene has lost its tumor suppression function and is considered to be a very important step in HCC development[43]. In hepatitis B virus, mutation in the p53 gene seems more related to exposure to aflatoxin than to hepatocarcinogenesis itself[31]. Kirk et al[44] confirmed that mutation in the p53 occurred in populations that were exposed to aflatoxins and have a high prevalence of HBV carriers.

Chronic HBV infection has been shown to cause HCC by inducing a long-term process of liver-cell necrosis, inflammation, and regeneration that is closely linked to the serum HBV load. Beyond clinical outcomes, serum HBV loads have been associated with the response to antiviral treatment. In addition, HBV carriers with HBV DNA level >105 copies/ ml have at least a 2-fold excess risk of developing HCC[45].

Though most people with hepatitis C never develop liver cancer, it is a risk associated with hepatitis C[30]. The mechanism of hepatocarcinogenesis in HCV infection is still undefined. One possibility is the involvement of oxidative stress, which can produce genetic mutations as well as gross chromosomal alterations and contribute to cancer development. It has been shown that after a long period; the core protein of HCV induces HCC in transgenic mice with marked hepatic steatosis but without inflammation, indicating a direct involvement of HCV in hepatocarcinogenesis[45]. Although more severe in the cirrhotic group, there was clear evidence of oxidant stress in non-cirrhotic patients with HCV infection[47].

The HCV core protein binds to and represses transcription from the p53 promoter, thus blocking p53 synthesis. This may play a role in survival of hepatocarcinoma cells transformed by HCV. Transgenic mice expressing the core protein develop HCC due to formation of intracellular reactive oxygen species caused by mitochondrial injury[48].

Gelatti[49] reported that coffee drinking was inversely associated with HCC regardless of its etiology. The inverse relation with coffee, in fact, was of similar magnitude in subjects negative or positive for HBV or HCV serum markers, as well as in non-or moderate drinkers and in heavy drinkers. Various components of coffee have been related to such a favorable effect, including caffeine, coffee oils kahweol or cafestol, and antioxidant substances from coffee beans, but no definite evidence is available for any of these components.

The current study revealed that the score of fibrosis increased with increasing age. This relationship was significant for patients with HBsAg but non-significant for patients with anti-HCV. In the Lebanese population, HBV prevalence increased with age and was higher among males (21.4 %) than females (16.9 %) while anti-HCV prevalence showed no significant age or sex differences[50]. Another study reported that patient age at time of liver biopsy was associated with stage of fibrosis[51]. Another study found an acceleration of fibrosis progression with aging[52]. Adverse effects of age on fibrosis progression were confirmed by Angelucci et al[53].

Another study suggested that HCV might somehow become more fibrogenic with advancing host age. There was no relationship between genotype and risk of development of fibrosis. The mechanism(s) behind the deleterious effect of aging may be related to environmental factors, especially oxidative stress, to reduction in blood flow, or to limited mitochondrial or immune capacities[20].

According to patients under ten years, they represented 6% and 10.8% of patients with HBsAg and anti-HCV respectively included in the current research. Chronic hepatitis C is often a mild disease in children, but whether this is related to younger age or shorter duration of infection is unclear. Histologic severity has been shown to correlate with duration of infection regardless of age[54].

In this study, male gender was associated with an increasing score of fibrosis. Rates of fibrosis progression differ markedly between the predominant causes of chronic liver disease and according to age and gender[20]. Wright et al[25] concluded that fibrosis process is shown to be progressive and faster for males and those who acquire the infection later in life.

In males, progression of liver fibrosis seems to accelerate with decades for HBV and HCV. Fibrosis progression was lower in females compared with males for HBV and HCV. It may be that estrogens have a direct anti-fibrosing effect[20]. On the other hand, one researcher found no correlation between the gender and age of patient and the risk factors for HCV infection[26].

The present findings indicated that 75% of HCC patients were aged ³ 60 years. Older age is an independent factor affecting progression to HCC in patients with HBV-related cirrhosis. Older age and male sex have been reported to be associated with an increased risk of HCC of different etiologies. Older age may reflect a longer duration of cirrhosis. The high risk of HCC among male cirrhotic patients could be explained by a tumorigenic effect of androgens. It has been suggested that independent of duration of disease, hepatitis C more rapidly leads to cirrhosis and HCC in older patients[29].

Among individuals with chronic hepatitis C 20% to 30% develop cirrhosis within two decades of onset of infection, and among those with cirrhosis, HCC develops in 1% to 4% per year [54]. Mohsen and Group[55] confirmed that anti- HCV positive patients showed fibrosis to be associated with age over 40, evidence of hepatitis B virus infection, and higher grade of necro-inflammatory grade but not with sex and viral genotype.

The well-known feature of concomitant infection by multiple hepatotropic viruses such as HBV and HCV is supported by the results obtained in the present study, in addition; presence of both HBsAg and anti- HCV associated with increasing fibrosis score.

Individuals with HCV are at risk for acquiring HBV because of shared risk factors. As no cross-immunity exists between HBV and HCV, double infections do occur[56]. Hepatitis B virus co-infection with HCV causes more severe hepatic injury than HCV alone[57]. Co-infection of HBsAg and HCV is associated with advanced hepatic fibrosis. Co-infection with HBV has an additive effect on the rate of progression in persons with hepatitis C[58]. Another study confirmed that HBsAg carriage alone may enhance fibrosis in HCV positive patient[59]. Dual infection with HBV and HCV in cirrhotic patients has been linked to an increased risk of HCC[29].

The current investigation revealed that steatosis was found in 18% of patients with HBsAg and 20.5% of patients with anti-HCV. In HBsAg- positive cases, all patients were ³ 30 years but the rate of steatosis decreased with increasing age. While in anti-HCV cases, all patients were ³ 20 years and the rate of steatosis increased with increasing age. On the other hand steatosis was associated with fibrosis score and decrease in cirrhotic patients with HCV infection.

Steatosis in chronic hepatitis B appears to be a result of metabolic factors of the host rather than the effect of the virus. Steatosis is unrelated to the degree of fibrosis which is considered as the histological indicator of liver damage. The effect of steatosis on histopathological damage in chronic hepatitis B is unknown. It has been reported that chronic hepatitis B has occurred concurrently with steatosis in 27% of patients[60].

Liver steatosis has been reported to be present in about 30-70% of individuals with chronic HCV infection[61]. In chronic hepatitis C (CHC), steatosis is associated with hepatic fibrosis[62]. Hepatic steatosis is a frequent histological finding in patients with chronic HCV infection. The virus has a direct steatogenic effect, as evidenced by the accumulation of intracellular lipids in some transgenic cell lines and animal models expressing HCV proteins. Steatosis may be a co-factor for tumorigenesis in subjects with chronic hepatitis C[63].

Steatosis was associated with increasing patient age and remained significantly associated with fibrosis. Steatosis is associated with fibrosis independently of necro-inflammation but declines in cirrhosis. It may represent a pathogenic pathway distinct from necro-inflammatory activity in the generation of liver fibrosis, and should be included in the assessment of biopsies for clinical and research purposes[64].

The mechanisms leading to a reduction in steatosis in the liver with cirrhosis remain uncertain but may be associated with portal-systemic shunting resulting in decreased hepatic exposure to insulin[65].

Conclusions

Viral hepatitis caused by HBV, HCV or both was found in 41.7% of patients with liver disease and their frequencies were 35.5%, 58.9% and 5.7% respectively. The patients had different grades of necro-inflammation and stages of fibrosis as detected by liver biopsy and only 8% of patients with HBV had HCC. The grade of necro-inflammation increased with increasing the stage of fibrosis. The increasing score of fibrosis correlated with increasing age and male gender. Steatosis was associated with increasing fibrosis scores and decreased in cirrhotic patients with HCV infection.

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Table 1. Stages of liver disease in patients with different viral infections

Stage of liver disease		Viral infection					
		HBsAg		anti-HCV		HBsAg/anti-HCV	
		No.	%	No.	%	No.	%
Fibrosis	0	4	8	8	9.6	0	0
	I	12	24	7	8.4	1	12.5
	II	10	20	26	31.3	1	12.5
	III	11	22	34	41	3	37.5
	IV	9	18	8	9.6	3	37.5
HCC*		4	8	0	0	0	0
Total		50	35.5	83	58.9	8	5.7
X2		11.53		73.41		4.56	
P		< 0.05		<0.05		<0.15	

Table 2. Stages of liver disease and grades of necro-inflammation in patients with HBsAg

Stage of liver disease (fibrosis)	No. of patients	Grade of necro-inflammation					
		Minimal		Mild		Moderate	
		No.	%	No.	%	No.	%
O	4	4	100	0	0	0	0
I	12	5	41.7	7	58.3	0	0
II	10	4	40	6	60	0	0
III	11	0	0	4	36.3	7	63.6
IV	9	0	0	1	11.1	8	88.9
Total	46	13	28.3	18	39.1	15	32.6

X2 =40.29, P< 0.05

Table.3. Stages of liver disease and grades of necro-inflammation in patients with anti-HCV

Stage of liver disease (fibrosis)	No. of patients	Grade of necro-inflammation					
		Minimal		Mild		Moderate	
		No.	%	No.	%	No.	%
O	8	6	75	2	25	0	0
I	7	2	28.6	5	71.4	0	0
II	26	0	0	22	84.6	4	15.4
III	34	2	5.9	12	35.3	20	58.8
IV	8	0	0	4	50	4	50
Total	83	10	12.1	45	54.2	28	33.7

X2 = 56.17, P< 0.05

Table 4. Association between stages of liver disease and age groups in patients with HBsAg

Stage of liver disease		No. of patients	Age Group (yr)													
			<10		10-19		20-29		30-39		40-49		50-59		≥ 60	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Fibrosis	0	4	0	0	0	0	0	0	2	50	2	50	0	0	0	0
	I	12	2	16.6	1	8.3	5	41.6	3	25	1	8.3	0	0	0	0
	II	10	0	0	1	10	3	30	5	50	1	10	0	0	0	0
	III	11	0	0	0	0	1	9	2	18.1	3	27.2	5	45.4	0	0
	IV	9	1	11.1	0	0	0	0	1	11.1	1	11.1	2	22.2	4	44.4
HCC*		4	0	0	0	0	0	0	0	0	1	25	0	0	3	75
Total		50	3	6	2	4	9	18	13	26	9	18	7	14	7	14

X2 = 58.47, P < 0.05, *Hepatocellular carcinoma

Table 5. Ecology of dermatophytes in hospital and community based studies.

Stage of liver disease (fibrosis)	No. of patients	Age Group (yr)													
		<10		10-19		20-29		30-39		40-49		50-59		> 60	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0	8	0	0	1	12.5	1	12.5	3	37.5	1	12.5	1	12.5	1	12.5
I	7	1	14	0	0	2	28.5	2	28.5	2	28.5	0	0	0	0
II	26	2	7.6	4	15.3	5	19.2	3	11.5	5	19.2	5	19.2	2	7.2
III	34	6	17.6	10	29.4	3	8.8	4	11.7	2	5.8	7	20.5	2	5.8
IV	8	0	0	3	37.5	0	0	0	0	1	12.5	2	25	2	25
Total	83	9	10.8	18	21.7	11	13.3	12	14.5	11	13.3	15	18.1	7	8.4

X2 = 58.47, P < 0.05, *Hepatocellular carcinoma

Table 6. Association between stages of liver disease and sex in patients with HBsAg

Stage of liver disease		No. of patients	Male		Female	
			No.	%	No.	%
Fibrosis	0	4	3	75	1	25
	I	12	7	58.3	5	41.6
	II	10	4	40	6	60
	III	11	9	81.1	2	18.1
	IV	9	6	66.6	3	33.3
HCC*		4	4	100	0	0
Total		50	33	66	17	34

X2 = 6.756, P < 0.15, * Hepatocellular carcinoma

Table 7. Infection type frequency in hospital and community based studies.

Stage of liver disease (fibrosis)	No. of patients	Male		Female	
		No.	%	No.	%
0	8	5	62.5	3	37.5
I	7	5	71.4	2	28.5
II	26	15	57.6	11	42.3
III	34	16	47.05	18	52.9
IV	8	6	75	2	25
Total	83	47	56.6	36	43.4

X2 = 3.112, P< 0.15

X2 = 25.29, P > 0.05

Serum Lipid and Lipoprotein Profiles in Patients with Acute Myocadial Infarction

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ABSTRACT

Background and objectives:
Acute myocardial infarction (AMI or MI), more commonly known as a heart attack, is a medical condition that occurs when the blood supply to a part of the heart is interrupted, most commonly due to rupture of a vulnerable plaque. The resulting ischemia or oxygen shortage causes damage and potential death of heart tissue. It is a medical emergency, and the leading cause of death for both men and women all over the world.
The present study was undertaken to examine the changes in fasting serum lipid and lipoprotein levels total cholesterol (TC), triacylglycerol (TAG), and lipoproteins: very low density lipoprotein- cholesterol (VLDL-C), low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C) in AMI patients.
Materials and methods: A prospective study was carried out during the period from April to September 2007 in collaboration between the department of Clinical biochemistry and internal medicine/ College of Medicine/Hawler Medical University, on fifty patients with myocardial infarction (MI) and the results obtained were compared with fifty normal subjects.
Results: The results showed that there was a significant increase ($P< 0.01$) in the levels of fasting serum TC, TAG, and lipoprotein levels VLDL-C and LDL-C and a significant decrease ($p< 0.05$) in the level of fasting serum HDL-C.
Conclusion: Based on the findings of the present study it can be concluded that myocardial infarction causes multiple abnormalities in the levels of lipid and lipoprotein.
Keywords: Acute myocardial infarction, serum lipid and lipoprotein profiles.

Introduction

Myocardial infarction (MI) generally occurs when there is a sudden cessation of coronary blood flow following a thrombotic occlusion of a coronary artery previously narrowed by atherosclerosis[1]. Slowly developing, high-grade coronary artery stenosis usually does not precipitate acute infarction because of the development of a rich collateral network over time. Infarction occurs when a coronary artery thrombus develops rapidly at a site of vascular injury (when the atherosclerotic plaque fissures, ruptures, or ulcerates). It usually occurs in persons with risk factors for atherosclerosi[2].

The frequent risk factors are smoking, hypertension, hyperlipidaemia, diabetes mellitus, aging, male sex, and others. In rare cases, infarction may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and vasculitis. Acute myocardial infarction presents with sudden onset severe central chest pain, dyspnea, sweating, pallor and syncope. Diagnosis of acute myocardial infarction depends on the presence of two out of three criteria which are: presence of chest pain, ECG changes (hyperacute T wave, ST segment elevation, and Q wave), and elevated cardiac markers (CPK, Troponin I & T). Early management includes admission to coronary care unit, relief of chest pain, Aspirin, ECG monitoring, coronary artery reperfusion therapy within the first six hours from the onset of chest pain by primary PCI (percutaneous coronary intervention) or thrombolysis (tissue plasminogen activator or streptokinase), and detection and treatment of acute complications[3].

Late management of MI includes risk factor stratification, drugs for secondary prevention (Aspirin, Beta-blocker, ACE inhibitors, Statins) and rehabilitation. Hypercholesterolaemia refers to a blood TC level above 200 mg/dl. A cholesterol level of 200 to 239 mg/dl is considered borderline high, and a level of 240 mg/dl is considered to be a high TC level. Risk factors for hypercholesterolaemia are dietary intake, genetic predisposition, sedentary lifestyle and associated secondary causes. Hypercholesterolaemia usually has no clinical findings, but occasionally may cause tendon xanthomas, xanthelasma, corneal arcus, and arterial bruits. Elevated levels of LDL and IDL, and chylomicron

contribute to the development of atherosclerosis. But high plasma HDL level is protective against atherosclerosis[4].

The aim of the present study is to investigate the link between AMI and the levels of fasting serum lipid and lipoprotein.

Subjects and Methods

1-Subjects

This study was conducted on one hundred individuals of both sexes, who were divided into two groups:

Group I (Control group): Included fifty healthy subjects. Their mean age was (58) years and the range of ages were 42-69 years. None of this group had clinical or biochemical evidence of cardiac, hepatic, renal or endocrine diseases, and none were taking medications and, informed consent was obtained from each individual.

Group II (AMI patients group): Included fifty AMI patients. Their mean age was 59 years and the range of age was 47-67 years. These patients were all admitted to the coronary care unit (CCU)/Erbil teaching hospital in order to receive treatment. The diagnosis of MI was established by clinical, ECG, and serum cardiac enzyme estimation.

The details concerning both groups are elucidated in Table 1.

2-Samples

Three ml of peripheral venous blood was drawn in the morning, after over night fasting from each subject, using a disposable syringe . The samples were transferred into glass tubes, leaving for 30 minutes for clotting, centrifuged for 30 minutes at 3000 r.p.m, and the separated serum was used for measurements of TC, TAG,VLDL-C, LDL-C, and HDL-C.

3-Methods

Ready made kits Biomerieux Sa. (France) were employed for estimation of fasting serum TC, and HDL-C according to the method of Trinder[5]. Fasting serum TAG was determined by a method described by Young and Destany[6], while serum fasting LDL-C and VLDL were calculated according to Friedewald equation[7].

VLDL = (TA G / 5)

LDL-C=TC - {HDL-C+(TAG / 5)}

4-Statistical analysis

Statistical analysis of the results was done using SPSS software (release 6.0; SPSS Inc., Chicago, IL, USA). Data were expressed as mean±SEM. The data so obtained was analyzed to obtain appropriate conclusions. Student 't' test was employed to find out the statistical significance. The levels of fasting serum lipid and lipoprotein of normal healthy subjects were compared with those of AMI patients. Concerning P value, statistical significance was set at $P < 0.01$.

Results

Group I (Control group)

The mean for fasting serum TC gives a value of 195 mg/dl and a range of (140-246 mg/dl). The mean level for fasting serum TAG was 137mg/dl and the range was 55-219 mg/dl. The mean values for fasting serum VLDL-C, LDL-C and HDL-C were 26, 111 and 63 mg/dl respectively, and their ranges were 11-43, 36-196 and 24-87 mg/dl respectively as shown in Table 2.

Group II (Patients with AMI):

The mean level for fasting serum TC was 272 mg/dl and the range was (185-305 mg/dl). The mean value for fasting serum TAG was 225 mg/dl and the range was (155-265)mg/dl. The mean values for VLDL-C, LDL-C and HDL-C were 48, 190 and 35 mg/dl respectively, whereas their ranges were 31-59, 130-214 and 23-61 mg/dl respectively as shown in Table 2.

Pb statistics obtained by student t-test. N.S. Non Significant differences. S.E. Standard Error

Discussion

The data obtained for Group I (control group) for the studied biochemical parameters (TC, TAG, VLDL-C, LDL-C and HDL-C) are similar to general accepted values.

The mean values obtained for Group II (AMI patients) for fasting serum TC, TAG, VLDL-C and LDL-C were significantly higher than those of group 1 ($p < 0.01$), whereas the mean value obtained for fasting serum HDL-C was significantly lower that of Group I . These results are in agreement with those obtained by other investigators[9, 10, 11, 12, 13, 14].

The mechanism responsible for an increase in TAG serum fasting level in AMI patients may be due to an elevated flux of fatty acids and impaired removal of VLDL-C from the plasma[15]. Another factor is an increase in serum C-reactive protein level, which may increase to a level that is several hundred-fold higher than baseline after an MI. The C-reactive protein binds selectively with LDL-C and interferes with its catabolism, thereby increasing the serum TAG concentration[16]. Nutritional habits may increase serum levels of TAG, as high consumption of saturated fats and/or sucrose[17,18]. Moreover, inherited or acquired abnormalities of lipoproteins especially VLDL-C, cause alterations in TAG level. Furthermore, high concentration of apoprotein B in survivors of AMI may lead to accumulation of chylomicron remnants, VLDL-C and IDL-C[19].

Since most of cholesterol in the plasma is carried by

LDL-C, an increase in LDL-C level directly may lead to an increase in TC levels[20]. LDL-C is probably the most atherogenic of all lipoproteins and when its plasma concentration is elevated; there will be accumulation of cholesterol, resulting in the formation of atherosclerotic lesions in the wall of the vessels. Elevated plasma LDL-C level may be due to either a decrease in its clearance or over production of this lipoprotein[14,21]. LDL-C is cleared from the circulation partly by cellular uptake via specific LDL-receptors located on the cell surface. Coronary heart disease modifies these receptors by blocking some of them and as a result serum LDL-C uptake is reduced[22]. A high production rate of LDL-C consequently might be due to either overproduction of VLDL-C (precursor of LDL-C) or to a decrease in fractional removal of VLDL remnants. The latter may result from a decrease in LDL-C receptors activity. Moreover, apoprotein B plays an important role in elevating LDL-C level, since an increase of its concentration may merely increase the concentration of LDL-C[23].

On the other hand the data obtained in this study indicates a significant decrease in the mean level of fasting serum HDL-C in AMI patients. Similar results were obtained by other researchers[9,10,11,12,13,14]. The mechanisms responsible for this change may reside in the decreased synthesis and secretion of HDL-C from the liver or intestine and/or accelerated elimination from the blood stream by extravasations. Increased permeability of the capillary membranes during the acute inflammation after AMI lead also to an extravasation of HDL-C. Furthermore, decreased level of apoprotein A affects directly the HDL-C level[14,24].

Conclusion

The most important conclusions and recommendations obtained can be summarized as follows:

1. The results obtained in the present study indicate a significant increase in the levels of fasting serum TC, TAG, VLDL-C, and LDL-C and a significant decrease in the level of fasting serum HDL-C in AMI patients.
2. The significant increase in the levels of fasting serum TC, TAG, VLDL-C and LDL-C and a significant decrease in the level of HDL-C in AMI patients and indicates a major link between hyperlipidaemia in general and the pathogenesis of MI.
3. In front of these results and other complications of hyperlipidaemia, we recommend first the dietary measures by replacement of the saturated fats by unsaturated fats and increasing the amount of dietary fiber intake.
4. We recommend also regular physical activity for healthy normal subjects as well as those which are at risk of ischemic heart diseases.
5. Further studies are necessary at the genetic level to evaluate the hormonal effects which are attributed to hyperlipidaemia.
6. Further studies are necessary to examine the effects of other biochemical and histopathological parameters which participate in the pathogenesis of ischemic heart diseases.

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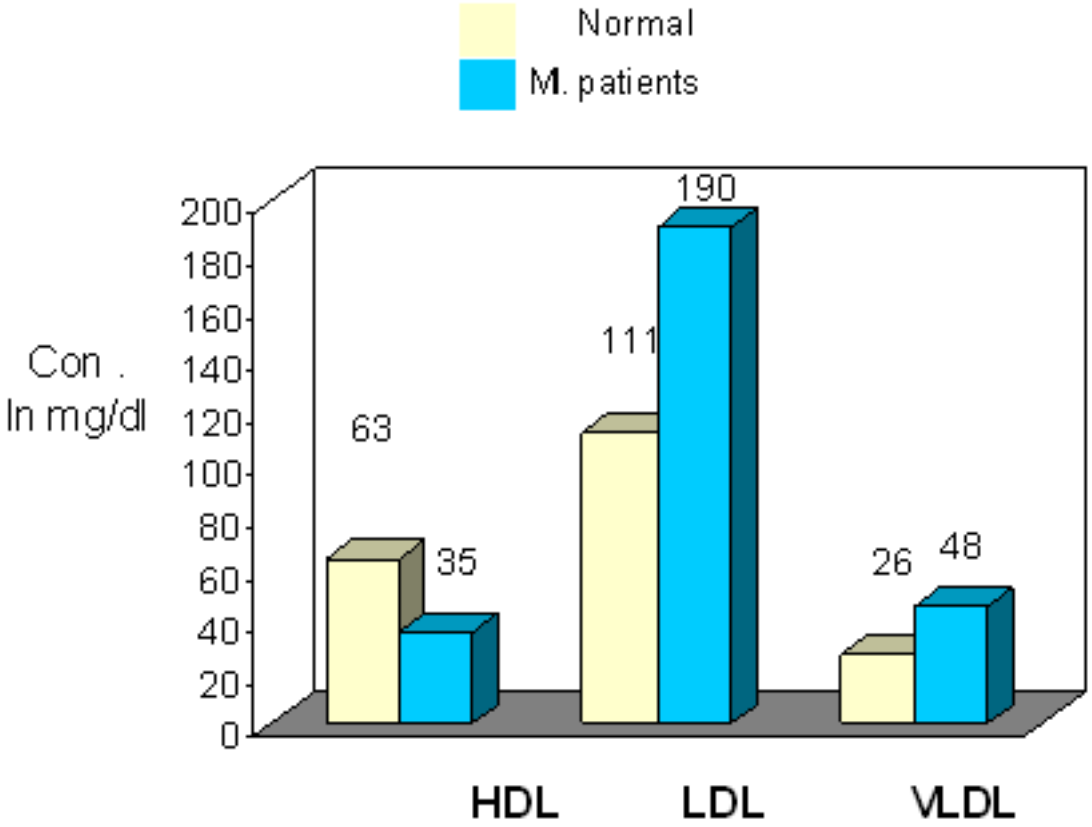

Figure (1): Serum Lipoprotein profile in normal and myocardial patients

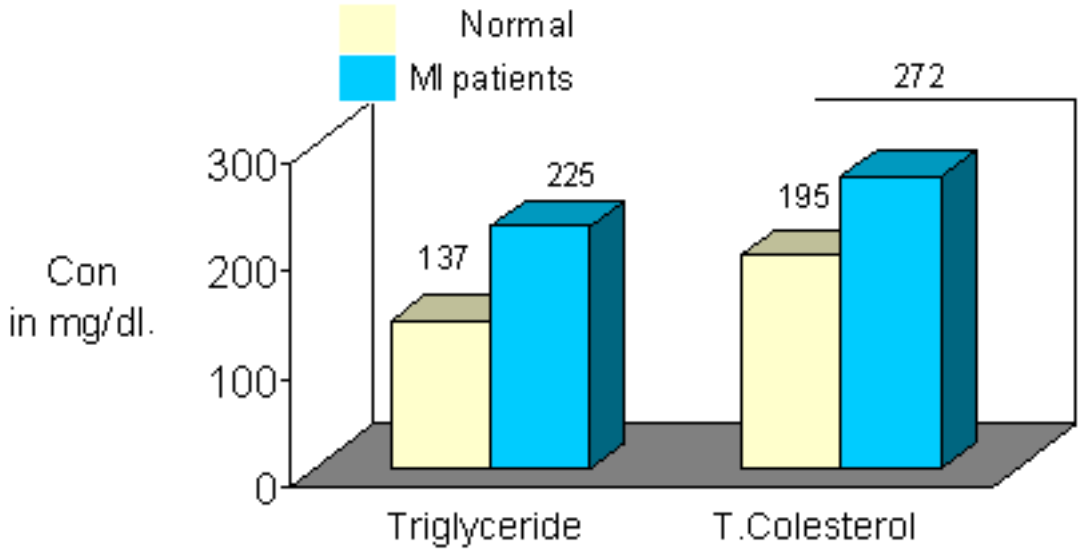

Figure (2): Serum TC and TAG in normal and myocardial infarction patients

Table 1: Basic characteristics of the studied groups.

Groups	Males	Females	Total	Age (Years)	
				Mean	Range
I control	35	15	50	58	42-69
II patients	38	12	50	59	47-67

Table 2: Details of biochemical parameters of the studied groups.

Parameters	Group I		Group II		Statistical Value(Pb)
	Range	Mean±S.E	Range	Mean±S.E	
TAG	55-219	137± 8	155-265	225± 9	P<0.01
TC	140-246	195± 5	185-305	272± 4	P<0.01
HDL-C	24-87	63± 4	23-61	35± 1	P<0.01
LDL-C	36-196	111± 7	130-214	190± 3	P<0.01
VLDL-C	11-43	26± 1	31-59	48± 0.9	P<0.01
Age	42-69	58± 1	47-67	59± 0.9	N.S

Students Perception of Small Group Teaching: A Cross Sectional Study

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ABSTRACT

Background and Objectives: Small group teaching is an important component of undergraduate medical education. Central to the effectiveness of small group discussion (SGD) is the ability of the tutor and students to guide and discuss together to understand a topic or to solve a problem. The objective of this study was to identify students' perceptions about SGD aimed at continuous educational development.

Methods: It was a cross sectional study carried out among 100 Phase-I (Year-1) undergraduate students of Medical School of Universiti Sains Malaysia (USM) of session 2003-2004. Study was done at the end of their preclinical training in the musculoskeletal block. Data was collected through a structured questionnaire containing questions on students' preparedness, participation in and understanding of the topic. The response rate was 85%.

Results: According to 81% of the respondents, they were well prepared for SGD, 81% were of the opinion that they participated actively, and 86% stated that SGD helped them to understand the topic very well.

Conclusion: Characteristics of an effective small group discussion in USM are maintained. For a successful small group discussion, all the participants must mentally prepare to take part in active discussion; share knowledge and skills for in-depth understanding of the topic.

Keywords: Students perception, Small group teaching.

Background and Objective

There are many different teaching styles and formats[1] ranging from the delivery of large group didactic lectures to facilitation of open small group teaching. Small group teaching has a long history; its great promoter is Socrates, who valued the development of attitudes as much as critical thinking. A small group is a collection of several learners, which varies in numbers, and who interact and work together to achieve common learning goals[2]. Subtle questioning was the core of Socrates' method[3].

Small group teaching method helps in the development of higher level intellectual skills such as reasoning and problem solving, the development of attitudes and the acquisition of interpersonal skills such as listening, speaking, arguing and group leadership4. These skills are important to medical students who will eventually become involved professionally with patients, other health care professionals, community groups, learned societies and the like[4].

Many medical schools have incorporated a significant number of small group teaching sessions in their undergraduate medical programs[5]. Medical school of USM is the pioneer school, which introduced problem-based learning (PBL) in undergraduate medical curriculum in the region6-7 that relies almost entirely on small group teaching methods, where a problem is posed by a tutor and then discussed together. The undergraduate medical curriculum of USM consists of three phases comprising Phase-1 (year-1), Phase II (year-2 and 3) and phase III (year-4 and 5). Phase-I students are taught through 15 blocks. Musculoskeletal block is one which is studied. There were in total ten SGD sessions held during six weeks of musculoskeletal block. The objective of this study was

to assess student perceptions of small group discussions of musculoskeletal block during their preclinical training, aimed at continuous educational development.

Methods

It was a questionnaire survey carried out among Phase-I (Year-1) students of School of Medical Sciences, USM of session 2003-2004. One hundred questionnaires containing attributes of SGD were distributed to the students at the end of six weeks teaching on musculoskeletal block. 85 questionnaires were received, hence the response rate was 85%. The rating scale in the questionnaire ranged as: agrees, undecided and disagrees. A mean score against variables was identified and analyzed as a percentage distribution.

Results

This study revealed that among 85 respondents, 81% were well prepared for SGD while 7% were not well prepared and 8% could not decide and 4% did not respond (Table-1).

Regarding level of discussion held during SGD session in musculoskeletal block, 81% of students were of the opinion that they had a good level of discussion in SGD session while 5% did not, and 12% students could not decide and 2% did not respond (Table-2).

According to 86% of students, SGD helped them to understand the topics of discussion very well whereas according to 8% students SGD did not help them to understand the topics. 5% students could not decide about it and 1% did not respond (Table-3).

Discussion

An important consideration in a teaching learning session is arousal that implies a state of readiness of the brain of the learner to accept new information[4]. This study revealed that 81% of the respondents were aroused and well prepared for SGD (Table-1), meaning that they were interested for SGD.

Motivation is a key factor for learning which implies a willingness to direct its activity to a specific task[4]. Like arousal and preparedness, exactly the same percentage of students (81%) opined that SGD of musculoskeletal block offered them an opportunity for good level of discussion (Table-2). It showed that all 81% of respondents who prepared well for SGD also actively participated in the SGD sessions, meaning that a good level of discussion was held. One study in UK confirmed that undergraduate medical students prefer interactive discussion sessions, which facilitate better knowledge retention[8]. Our study findings have similarity with that UK study as most of our respondents took part in interactive discussions that facilitated the better understanding of the topic.

The effectiveness of SGD increases if the level of discussion is high or optimal. Understanding cannot be achieved unless the students are attending and discussing to a class, a state of affairs which will be determined by his / her level of arousal and degree of motivation[4]. This type of teaching provides opportunities to ask questions, to work as a team and to learn to solve the problems and thereby enhancing critical thinking ability[9]. Mutual discussion in the form of small groups is very effective to clarify and understand the topic under discussion. Participants can share their knowledge gained from different learning resources like books, films, slides, charts and internet etc in SGD. This study revealed, 86% of the respondents were able to understand the topics of discussion (Table-3), which means the SGD was effective for understanding of the topics.

The successfulness of small group teaching and learning depends upon the strategies and skills of the tutor and students[3]. The tutor has to play a vital role as an influence on medical students in small groups, particularly with respect to tutor verbal behavior encouraging or discouraging students[10]. From the students' point of view, the main characteristics of a good tutorial as far as tutors are concerned consist of allowing enough time for discussion, accepting students as partners, regaining from interference and having expertise[11].

There were ten SGD sessions tutored by different tutors during the musculoskeletal block rotation. But the study examined the SGD sessions collectively rather than individual groups, which meant we were unable to compare the individual group activities. This study also has the limitations of being confined within three variables and did not examine the students' perception about facilitation skills of the tutor. However, the results of examination of these three variables were in favor of drawing the assumption that collectively the facilitation skills were effective.

Conclusion

The effectiveness of the small group discussion depends upon the strategies and skills of the tutor and students. Characteristics of an effective small group discussion in USM are maintained. For a successful small group discussion, all the participants must mentally prepare to take part in active discussion; share knowledge and skill for in-depth understanding of the topic.

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Table 1. Distribution of respondents on the basis of their preparedness for small group discussion

Preparedness for small group discussion	Number	Percentage
Well prepared	69	81.20
Not well prepared	6	7
Undecided	7	8.20
Not responded	3	3.60
Total	85	100.00

Table 2. Distribution of respondents on the basis of whether good discussion was held during small group teaching

Level of discussion	Number	Percentage
Discussion was good	69	81.20
Discussion was not good	4	4.70
Undecided	10	11.80
Not responded	2	2.30
Total	85	100.00

Table 3. Distribution of respondents on the basis of understanding of the topic of small group discussion

Understand the topic of discussion	Number	Percentage
Topic understood	73	85.90
Topic not understood	7	8.20
Undecided	4	4.70
Not responded	1	1.20
Total	85	100.00

Esophageal Structure Post Repair of Esophageal Atresia and Distal Tracheoesophageal Fistula

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ABSTRACT

We report a case of esophageal stricture which occurred after a straightforward short gap esophageal atresia and distal tracheoesophageal fistula (OA&DTOF) within the first weeks of life.

Case presentation and intervention: A three day old male patient product of normal vaginal delivery, full term; body weight 3750gm was born in Abu Obaidah Hospital. Referred on 25/3/07 to King Hussein Medical center. The main complaint is drooling of saliva on 22/3/07. He was been diagnosed as a case of OA&DTOF; ligation of the distal tracheoesophageal fistula using prolene5/0, and end to end anastomosis single layer using PDS (polydiaxanon) 5/0 interrupted stitches over a feeding tube size 8F.

Ten days later he developed vomiting, dysphagea, choking and shortness of breath. He was diagnosed as having stricture at the site of anastomosis; the decision was taken to start balloon dilatation.

Dilatation done 4 times failed; then excision of the stricture site done, followed by end to end anastomosis and antireflux procedure.

Barium meal can not exclude the presence of gastro-esophageal reflux especially when a well formed stricture is present in the esophagus. Early formation of persistent esophageal stricture with poor response to dilatation; is a strong indication for early surgical intervention.

Introduction

There are many different teaching styles and formats[1] ran Anastomatic stricture occurs in 18% to50% of patients who have undergone repair of esophageal atresia with or without tracheoesophageal fistula. Stricture resulting from surgical repairs are often short; surrounded by postoperative fibrotic tissue[1].

During the past two decades, balloon dilatation has been used to treat esophageal strictures. Studies have suggested that this technique is especially effective for treating congenital rather than acquired esophageal strictures and preferable to bougienage dilatation in children with esophageal atresia because of lower complications rate[2].

Case Report

Three day old male patient product of normal vaginal delivery, full term; body weight 3750gm born in Abu Obaidah Hospital on 22/3/07. Antenatal follow up does not reveal any abnormality. Referred on 25/3/07 to King Hussein Medical center. The main complaint is drooling of saliva.

Clinically no other congenital anomalies and review of other systems was normal. He was diagnosed as a case of OA&DTOF; routinely upon admission we do echocardiogram and renal ultrasonography for all patients with OA&DTOF; they were normal. ABG: normal; PCV, Electrolytes: Normal.

Surgery done in the same day; ligation of the distal tracheoesophageal fistula using prolene5/0, and end to end anastomosis single layer using PDS (polydiaxanon) 5/0 interrupted stitches over a feeding tube size 8F. The gap was short. Patient sent to pediatric ICU on ventilator with full sedation. On 28/3/2007 self extubation at 11PM.

He was maintaining good ventilation and oxygenation and did not need re-intubation. On 1/4/2007 the feeding tube slipped out at night. On 2/4/2007 oral feeding started. No leak through the chest tube. On 3/4/2007(the 7th day), the chest tube was removed, Patient was discharged from the ICU to the ward. On 5/4/2007 the patient discharged home; he was well.

On fifteenth of April the patient developed vomiting, dysphagea, choking and shortness of breath. Upon

admission Chest X-Ray was normal. Barium Swallow showed constant stricture at the site of anastomosis with proximal dilatation- no reflux [Fig 1 and 2]. He was diagnosed to have stricture at the site of anastomosis; the decision was taken to start balloon dilatation.

Dramatic improvement post dilatation; patient discharged home next day in good general condition.

On the thirtieth of April; readmission again with same clinical picture described above. Balloon dilatation done next day; he improved and was discharged home next day.

On twenty second of May readmission again with same clinical picture described above. Balloon dilatation done; improved and discharged next day. His age was 57days.

On sixteenth of June readmission again with same clinical picture described above. Balloon dilatation done on 18/6/07(the 4th time) improved and discharged home.

On first of July patient admitted for re-evaluation, decision was made to go for surgical treatment.

On 4th of July, thoracotomy was done, release of adhesions between the lung tissue and anterior chest wall followed by identification the site of the stricture; it was about 1cm in length; dissection around it was performed, followed by excision with end to end anastomosis; single layer using PDS 4/0 over a feeding tube size 10F. Postoperative period was uneventful.

Barium swallow and meal: showed Normal passage of barium through the esophagus. Gastro-esophageal reflux present. [Fig: 3]

Biopsy result: hypertrophic fibrosed muscularis with epithelial ulceration, tissue emphysema, granulomatous reaction, chronic and acute inflammatory cells.

Final diagnosis: Esophageal stricture with ulceration of the mucosa. Two weeks later anti reflux surgery done; patient asymptomatic.

Discussion

Esophageal stricture is a common complication of esophageal atresia repair. It occurs in 18-50% of repaired esophageal atresia[3].

Tension at the site of anastomosis, leakage of anastomosis; gab length and silk sutures can all predispose esophageal stricture formation. Mehran et al and others in his study showed that the use of polydiaxanone sodium was associated with less incidence of anastomatic stricture[3, 4,5].

Gastro esophageal reflux is common in patients with OA& TOF occurring up to 35 to58% of children and it is a common cause of anastomotic stricture[7, 8,5].

K. Aksgl et al in a study of gastro-esophageal reflux demonstrated by radiography in infants less than one year of age in comparison with PH monitoring; said that the radiological method proved to be a poor indicator of gastro-esophageal reflux, resulting in both false negative results and false positive results as compared to PH monitoring; but the definition of significant clinical reflux in infants as seen on PH monitoring is not well standardized[6].

In our case barium swallow after the first surgery failed to demonstrate the presence of Gastro esophageal reflux; the stricture was so severe and does not permit the barium to reach the stomach to demonstrate the presence of the reflux.

The best results in anastomatic stricture following esophageal atresia repair are related to early detection of esophageal stricture and rapid initiation of balloon dilatation sessions before scar tissue and fibrosis occur, reducing the chance of stretching the stricture[9].

Even though the dilatation was started within a few weeks post surgery the response was poor, the symptom free intervals shortened after each dilatation; so the decision was taken to go for surgical treatment. Patient has no symptoms since surgery.

Barium meal can not exclude the presence of gastro esophageal reflux especially when a well formed stricture is present in the esophagus. Early formation of persistent esophageal stricture with poor response to dilatation; is a strong indication for early surgical intervention.

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Fig 1: Barium swallow showing severe stricture at the site of repair.

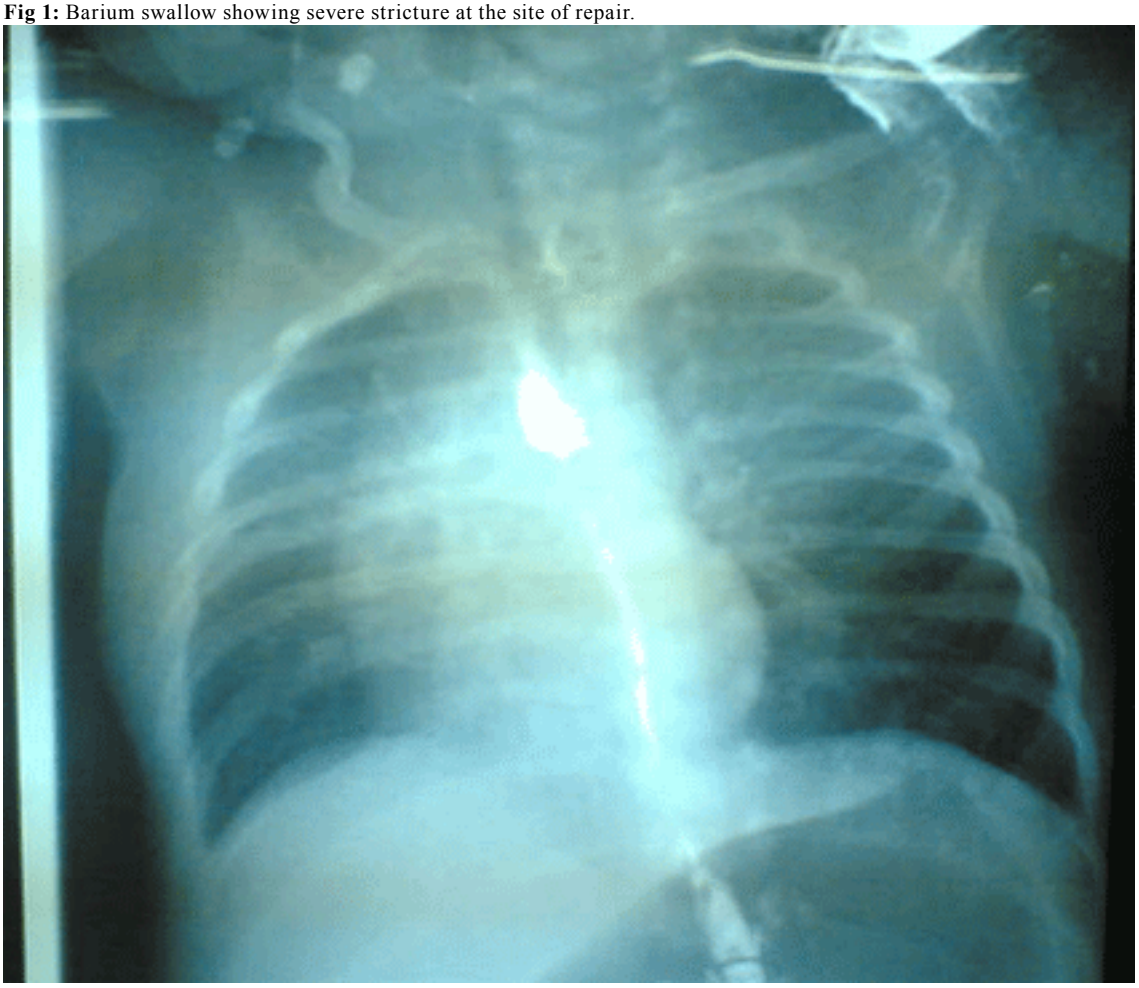


Fig 2: Barium swallow showing severe stricture at the site of repair.

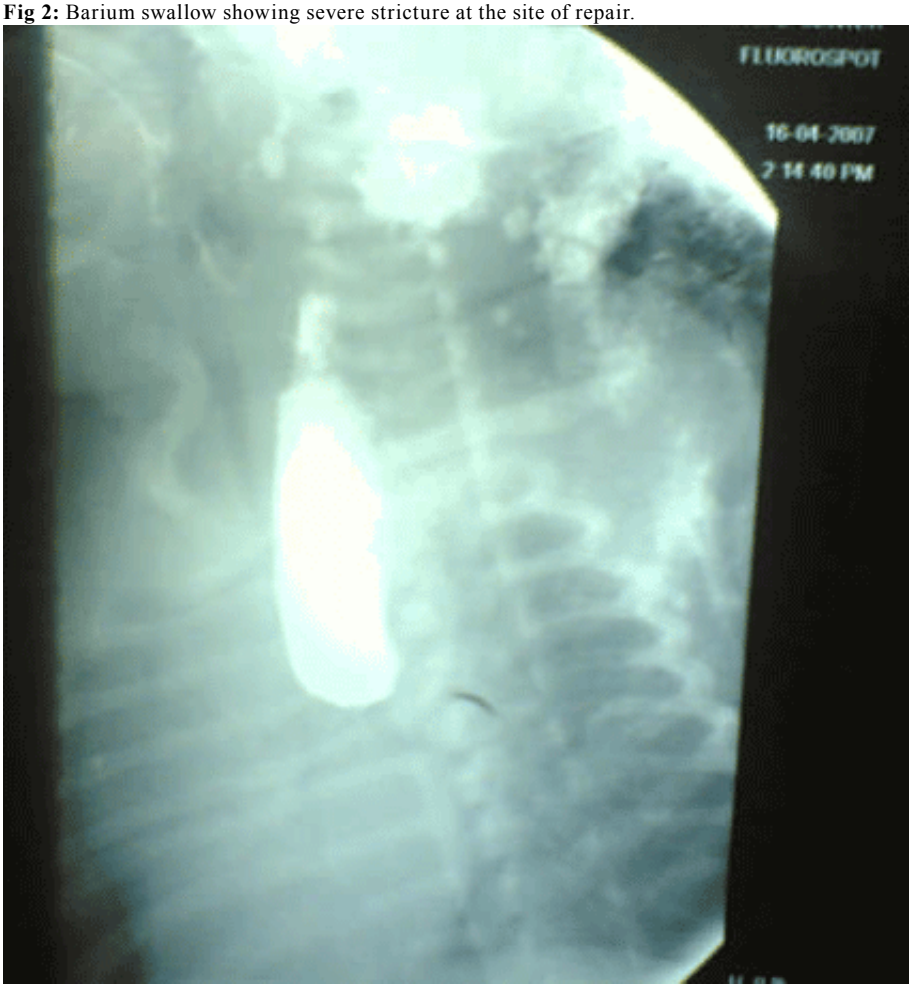
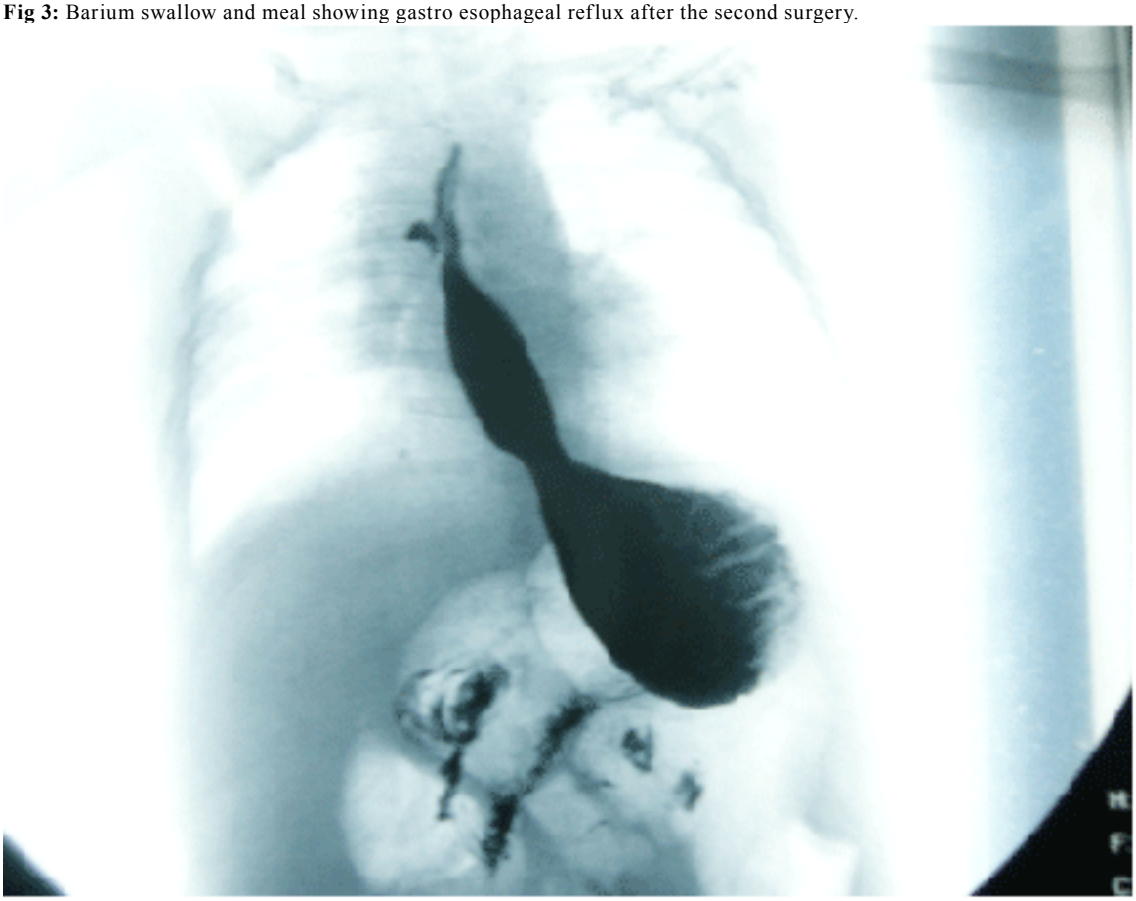


Fig 3: Barium swallow and meal showing gastro esophageal reflux after the second surgery.



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