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Ahmad Husari

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Welcome to the Middle-East Journal of Internal Medicine

On behalf of the editorial team, I welcome you to the first issue of the Middle East Journal of Internal Medicine (MEJIM) for the year 2012. In this issue, Dr Arabiat examined the possible associations between disturbances of lipids and lipoproteins and the development of Coronary Arterial Diseases (CAD). The study examined 674 cases of patients with and without CAD. The study noted a stronger association between a total cholesterol/ HDL ratio and CAD in males as compared to females. Cholesterol/HDL ratio is an effective indicator of CAD and the risk for myocardial infarction.

Adiantum capillus is well known in herbal medicine with applications in patients with asthma, pleurisy and other medical conditions. In this issue of MEJIM, Sultan et al induced diabetes in an animal model and examined whether Adiantum capillus supplementation will attenuate the ill effects of Diabetes Mellitus (DM). The study concluded that supplementation of Adiantum capillus is a powerful reversal of the systemic effects of DM in an animal model. Further studies will have to be conducted before further extrapolation to humans.

In this issue we have accepted two papers in Ophthalmology. The first paper noted no significant association between the incidence of metabolic syndrome and cataract as compared to controls. The second study investigated the relationship between central corneal thickness and intraocular pressure in patients with glaucoma.

Once again, welcome to MEJIM. We are counting on your support and participation. MEJIM is your internal medicine journal for years to come.

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Histological, Immunocytochemical and Biochemical study of the effect of Adiantum capillus on alloxan induced diabetic rats

ABSTRACT

The present study was designed to investigate the hypoglycemic effect of aqueous extract of Adiantum capillus (100mg/kg) which was given once daily to rats. The animals were divided into diabetic and non-diabetic control groups. The duration of each experiment lasted from two weeks to one month, and the results were compared with that of the standard hypoglycemic drug Metformin (100mg/kg), which was given once daily. In this study biochemical, histochemical and immunohistochemical techniques were used in alloxan (single intraperitoneal injection 100 mg/kg) induced diabetic male rats.

The diabetic rats showed a significant (p<0.05) decrease in their body weight and serum amylase with marked elevation in blood glucose, serum cholesterol, triglycerides, urea, alkaline phosphatase (ALP), and serum transaminases (AST and ALT) after two weeks till one month of diabetic duration. Histological examination of the pancreas of diabetic rats revealed a significant increase in the thickness of basement membrane of the blood vessels in the islets of Langerhans, as well as decreased activity of Beta-cells and increase activity of (Alpha, Delta cells) using both Gomori Aldehyde Fucshin (GAF) and Immunohistochemistry (IHC) techniques.

The kidney results showed increased thickness of basement membrane of the glomerular capillaries tubule basement membrane and an increase in PAS +ve granules in cells of distal convoluted tubule. In the liver tissue a marked increase in the PAS +ve granules inside hepatocytes was observed.

Administration of aqueous extract of Adiantum capillus (100mg/kg) caused dramatic changes in all parameters measured in this study which include; an increase in the body weight and serum amylase, while lowering the level of blood glucose, serum cholesterol, triglycerides, urea, alkaline phosphates (ALP), and serum transaminases (AST and ALT) in comparison to the diabetic group. These results were compared to the results obtained from the use of the hypoglycemic drug Metformin in all parameters in this study.

Finally, it was concluded that administration of this plant extract reversed most blood and tissue changes caused by alloxan induced diabetes in rats.

Key words: Adiantum capillus, Metformin, Antihyperglycemic effect, Immunocytochemical and biochemical study

Introduction

Diabetes mellitus (DM) is a non-communicable disease, which is considered one of the five leading causes of death in the world (1). About 150 million people suffer from diabetes worldwide, which is almost five times more than the estimates ten years ago and this may be doubled by the year 2030 (2). There is emerging evidence that oxidative stress which refers to a serious imbalance between the production of free radical and antioxidant defense leading to potential tissue damage, and free reactive oxygen species (ROS) makes a significant contribution to the progression of diabetes and its complications (3). The metabolic dysregulation associated with DM caused secondary pathophysiological changes in multiple organ systems DM is the leading cause of end stage renal disease, non traumatic lower extremity amputation, and adult blindness. Microvascular complications are one of the most serious burdens of diabetes, with an increasing incidence worldwide DM will be a leading cause of morbidity and mortality for the foreseeable future (4). Horio et al (2002) observed that diabetes associated endothelial dysfunction plays an important role in progression of vascular complications, including diabetic retinopathy, while Emily et al (2003) showed that type I diabetes has been associated with deceased bone mineral density compared with non diabetic control subjects.

The management of diabetes with agents devoid of any side effects is still a challenge to the medical system. This has led to an increase in the demand for natural products with hypoglycemic activity having fewer side effects (7). A multitude of plants have been used for the treatment of diabetes throughout the world. In fact, in many parts of the world especially in poor countries, this may be the only form of therapy available for treating diabetic patients (8, 9). Plant extracts were tested under specific test conditions such as glucose loaded, alloxan, steptozotocin or naturally diabetic
subjects in various animal models such as rodents. The identification and isolation of compounds from medicinal plants with anti-diabetic activity may provide an opportunity to develop a new class of anti-diabetic agents. Recent data indicated that aqueous extract of Adiantum capillus has antihyperglycemic effects in rabbits (10). Adiantum capillus has long held a place in herbal medicine systems worldwide. It is a good remedy for asthma, pleurisy, etc., and being a gentle diuretic. This plant is also used widely throughout the world for dandruff, hair loss, and menstrual difficulties. The chemical analysis of adiantum capillus revealed an array of compounds including triterpenes, flavonoids, phenylpropanoids, and carotenoid. Interestingly, despite its ancient use, there has been no specific research on adiantum concerning its isolation and biological activity (10, 11).

Since there are no published studies on the effect of aqueous extract of Adiantum capillus on histopathology of pancreas, liver and kidney, therefore we suggested studying the hypoglycemic effect of aqueous extract of Adiantum capillus on biochemical tests and tissue structure of pancreas kidney, and liver of normal and alloxan-induced diabetic rats.

Materials and Methods

Animals and housing

Healthy, adult male albino rats of Wister strain weighing approximately (200-290) gm were used in the present study. The animals were housed under standard laboratory conditions (12 h light: 12 h dark photoperiod, 22 C °± 2 C°). The animals were given standard pellets and tap water ad libitum.

Preparation of the aqueous plant extracts

Fresh clean leaves of Adiantum capillus were collected from Shwan district in Kurdistan of Iraq. The leaves were dried within three days, and an aqueous extract was prepared by method of infusion 1000 mg of the plants material was macerated in 20 ml of boiling water in a conical flask for 60 minutes, and filtered (10).

Induction of experimental diabetes

Diabetes was induced by a single intraperitoneal injection of alloxan monohydrate (100mg/kg) (BDH Chemical Ltd. England) (12).

Experimental design

The animals were divided to nine groups of 6 animals each, to study the effect of aqueous extracts of Adiantum capillus for (14 and 30) days:

- Group I: normal control rats given D.W
- Group II: diabetic control rats given D.W for 14 days
- Group III: diabetic control rats given D.W for 30 days
- Group IV: normal rats given aqueous extract of Adiantum capillus (100 mg /kg)
- Group V: diabetic rats given aqueous extract of Adiantum capillus (100 mg /kg) for 14 days
- Group VI: diabetic rats given aqueous extract of Adiantum capillus (100 mg /kg) for 30 days
- Group VII: normal rats given aqueous solution of Metformin
- Group VIII: diabetic rats given aqueous solution of Metformin for 14 days
- Group IX: diabetic rats given aqueous solution of Metformin for 30 days

Sampling and biochemical analysis

After 14 days and 30 days of oral administration of extract, the animals were fasted overnight and anaesthetized with chloroform, blood was drawn by cardiac puncture into plastic syringe. The serum obtained was used for biochemical tests.

Preparation of tissue samples

At day 14 and 30 after oral administration of plant extract, samples of pancreas were removed from the scarified animals. All samples were fixed in Bouines solution for 24 hours (13), and then the samples were processed by light microscopy. Tissue blocks of pancreas, were cut at 5 microns by electronic microtome.

Sections were mounted on glass slides and stained by
1- special stain PAS (Periodic Acid Schiff) and then examined.
2- immunohistochemistry (IHC) (anti-insulin, anti-glucagon)

Method of IHC staining:- The Dako Cytomation EnVision®+Dual link system-HRP(DAB+) staining protocol was used for immunostaining to detect insulin and glucagon expression which was applied to Bouin’s-fixed, paraffin embedded tissues.

All system reagents were brought to room temperature (20-25o C) prior to performing the procedure. Likewise, all incubations were performed at room temperature. The sections were not allowed to dry during the staining procedure, by placing slides in a humid environment (humidified chamber).

Counting per unit length and Histological measurements

A calibration stage micrometer was used which formed of 100 lines each one representing 0.01 millimeter (10 micron). After calibration examination, measurement and calculation of the histological sections was done in PAS stain for pancreas, liver and kidney to measure the thickness of the basement membrane the unit of measurement is micrometer.

Scoring of immunostaining:

Positive expression of immunostaining gives clear cut cytoplasmic staining of brown color with DAB and orange colour with AEC. The cells were calculated by the special computerized method called grid cell count. Positive cells were determined by counting 1000 cells. All significantly
TND = Treated Non Diabetic Rats, DC = Diabetic Control, TD = Treated Diabetic Rats, C = Control, L.S.D: different letter mean statistically different (P<0.05)

Table 1: The effects of 100 mg/kg of Adiantum capillus (PO) on the biochemical tests in normal and alloxan induced diabetic rats

Stained cells were considered positive and divided by 10 to acquire the percentage (immunostaining index); at least 10 HPFs were measured for each case for the purpose of scoring (14).

The extent of immunostaining was assessed as follows:
- Negative: when index was <5%.
- Mild positive: when index was > 5% and <20%.
- Moderate positive: when index was > 20% and <50%.
- Strong positive: when index was > 50.

Statistical analysis:
All data are expressed as means± standard error means (M±SEM) and statistical analysis was carried out using statistically available software (SPSS Version 11.5). Data analysis was made using one-way analysis of variable (ANOVA). The comparison between groups was done using Duncan test. P<0.05 was considered as statistically significant.

Results
Compared to the control group the level of blood glucose, serum cholesterol, triglycerides, urea, alkaline phosphates (ALP), serum transaminases (AST and ALT) in alloxan-induced diabetic rats were significantly increased at 14th and 30th days. Whereas the level of serum amylase and the result in the body weight in alloxan-induced diabetic rats were significantly decreased at 14th and 30th days as compared to the control group, as shown in Tables 1 and 2.

After treatment of diabetic animals with Adiantum capillus extract for 14 and 30 days marked improvement was noticed and most of the biochemical tests were returned to normal level compared to normal controls i.e. the level of blood glucose, serum cholesterol, triglycerides, serum urea, serum alkaline phosphates (ALP), and serum transaminases (AST and ALT) were all decreased, while the level of serum amylase was increased. There was marked increase in the body weight too compared to normal control. No significant changes were recorded when Adiantum capillus extract or Metformin was used in healthy non diabetic controls. (Tables 1 and 2).

Histological changes in diabetic animals
The pancreas (Using PAS and H&E staining methods)
Compared to the control group the measurements of the thickness of basement membrane in blood vessels and capillaries in alloxan-induced diabetic rats were significantly increased at the 14th and 30th days, as shown in Table 3 and Figures (1 and 2).
The thickness of basement membrane of capillaries in the islets of Langerhans was significantly greater in diabetic animals at the 30th day.

**Adiantum capillus and it is effect on pancreas:**

Using PAS and H&E staining methods

A significant reduction in the thickness of basement membrane of pancreatic blood vessels as well as that of capillaries in islets of Langerhans were found in diabetic rats treated with both (Adiantum capillus extract and Metformin) at 14th and 30th days as compared to the diabetic controls, but it did not return to normal range as in the control group. (Tables 3, 4, Figure 3). No significant changes were found in treated non diabetic rats at 14th and 30th days in both (Adiantum capillus extract and Metformin) groups when compared to the control group Tables 3, 4.

Using immunohistochemical staining technique

Compared to the control group the results of insulin localization by immunohistochemistry in alloxan-induced diabetic rats indicate a significant reduction at 14th and 30th days, as shown in Tables 3, 4 and Figures 4 and 5, while the results of the immunohistochemistry of glucagon in alloxan -induced diabetic rats indicate significant increase in the activity at 14th and 30th days compared to normal controls, as shown in Tables 3 and 4.

**Discussion**

In the present study, a significant reduction in the blood glucose level was observed in diabetic rats treated with extract of Adiantum capillus at 14th and 30th days as compared to the untreated diabetic rats. This result is in agreement with a study on Adiantum capillus (Dizaye et al, (2011) (10) who observed
Figure 1: Arterioles from exocrine pancreas from normal animals showing normal architecture and basement membrane (B.M.) stained with (PAS) 1000x.

Figure 2: Arteriole in the exocrine part of pancreas from diabetic animals showing an increase in the thickness of basement membrane (B.M) stained with (PAS) 1000x.
Table 3: The effects of 100 mg/kg of Adiantum capillus (PO) on the histological changes of pancreas in normal and alloxan induced diabetic rats

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DC 14 days</th>
<th>DC 30 days</th>
<th>TND 14 days</th>
<th>TD 14 days</th>
<th>TND 30 days</th>
<th>TD 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV.BM (μm)</td>
<td>2.96 ±0.26</td>
<td>5.58 ±0.42</td>
<td>5.73 ±0.30</td>
<td>2.83 ±0.08</td>
<td>4.40 ±0.43</td>
<td>2.73 ±0.24</td>
<td>3.66 ±0.28</td>
</tr>
<tr>
<td>C.BM (μm)</td>
<td>0.27 ±0.01</td>
<td>0.68 ±0.07</td>
<td>0.87 ±0.10</td>
<td>0.25 ±0.01</td>
<td>0.40 ±0.02</td>
<td>0.24 ±0.01</td>
<td>0.35 ±0.01</td>
</tr>
<tr>
<td>B cell %</td>
<td>71.15 ±1.86</td>
<td>9.03 ±1.52</td>
<td>7.88 ±1.63</td>
<td>72.5 ±1.80</td>
<td>43.75 ±2.07</td>
<td>70.76 ±1.15</td>
<td>58.66 ±1.99</td>
</tr>
<tr>
<td>A cell %</td>
<td>26.61 ±1.59</td>
<td>86.33 ±1.89</td>
<td>87.53 ±1.64</td>
<td>25.33 ±2.02</td>
<td>53.78 ±2.31</td>
<td>26.86 ±1.37</td>
<td>38.35 ±1.98</td>
</tr>
<tr>
<td>D cell %</td>
<td>2.23 ±0.39</td>
<td>4.63 ±0.38</td>
<td>4.75 ±0.35</td>
<td>2.16 ±0.65</td>
<td>3.45 ±0.24</td>
<td>2.36 ±0.40</td>
<td>3.00 ±0.41</td>
</tr>
<tr>
<td>IHC-insulin</td>
<td>61.16 ±4.11</td>
<td>7.66 ±0.66</td>
<td>8.50 ±0.76</td>
<td>60.33 ±4.22</td>
<td>11.33 ±1.45</td>
<td>60.50 ±4.12</td>
<td>18.16 ±0.60</td>
</tr>
<tr>
<td>IHC-glucagon</td>
<td>10.16 ±1.24</td>
<td>58.33 ±4.11</td>
<td>65.00 ±4.39</td>
<td>11.16 ±1.93</td>
<td>36.50 ±4.24</td>
<td>11.00 ±1.06</td>
<td>25.00 ±1.65</td>
</tr>
</tbody>
</table>

TND = Treated Non Diabetic Rats, DC = Diabetic Control, TD = Treated Diabetic Rats, C = control, different letter mean statistically different (P<0.05).

Table 4: The effects of 100 mg/kg of Metformin on the histological changes of pancreas in normal and alloxan induced diabetic rats

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DC 14 days</th>
<th>DC 30 days</th>
<th>TND 14 days</th>
<th>TD 14 days</th>
<th>TND 30 days</th>
<th>TD 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV.BM (μm)</td>
<td>2.96 ±0.26</td>
<td>5.58 ±0.42</td>
<td>5.73 ±0.30</td>
<td>2.90 ±0.11</td>
<td>3.95 ±0.28</td>
<td>2.93 ±0.12</td>
<td>3.35 ±0.20</td>
</tr>
<tr>
<td>C.BM (μm)</td>
<td>0.27 ±0.01</td>
<td>0.68 ±0.07</td>
<td>0.87 ±0.10</td>
<td>0.25 ±0.01</td>
<td>0.39 ±0.02</td>
<td>0.23 ±0.01</td>
<td>0.30 ±0.01</td>
</tr>
<tr>
<td>B cell %</td>
<td>71.15 ±1.86</td>
<td>9.03 ±1.52</td>
<td>7.88 ±1.63</td>
<td>73.40 ±2.06</td>
<td>51.05 ±2.66</td>
<td>71.65 ±1.55</td>
<td>57.10 ±2.07</td>
</tr>
<tr>
<td>A cell %</td>
<td>26.61 ±1.59</td>
<td>86.33 ±1.89</td>
<td>87.53 ±1.64</td>
<td>24.66 ±1.69</td>
<td>46.06 ±2.52</td>
<td>27.61 ±1.13</td>
<td>39.91 ±2.03</td>
</tr>
<tr>
<td>D cell %</td>
<td>2.23 ±0.39</td>
<td>4.63 ±0.38</td>
<td>4.75 ±0.35</td>
<td>1.93 ±0.50</td>
<td>3.58 ±0.48</td>
<td>2.40 ±0.31</td>
<td>2.98 ±0.69</td>
</tr>
<tr>
<td>IHC-insulin</td>
<td>61.16 ±4.11</td>
<td>7.66 ±0.66</td>
<td>8.50 ±0.76</td>
<td>61.66 ±3.80</td>
<td>12.00 ±3.80</td>
<td>59.33 ±3.92</td>
<td>16.00 ±1.18</td>
</tr>
<tr>
<td>IHC-glucagon</td>
<td>10.16 ±1.24</td>
<td>58.33 ±4.11</td>
<td>65.00 ±4.39</td>
<td>11.13 ±1.64</td>
<td>34.00 ±3.84</td>
<td>12.16 ±1.42</td>
<td>33.83 ±3.23</td>
</tr>
</tbody>
</table>

TND = Treated Non Diabetic Rats, DC = Diabetic Control, TD = Treated Diabetic Rats, C = control, different letter mean statistically different (P<0.05).
that a decoction extract of these plants possesses a significant hypoglycemic effect and blood sugar lowering activity in alloxan-induced diabetic rabbits. In the present study, the hypoglycemic effect of the plant extract may be due to the presence of insulin-like substances in the plants like Flavonoids or other materials that stimulate regeneration and reactivation of Beta cells to produce more insulin and this improvement is shown in histological results on pancreatic tissue by increasing the number of Beta cells, which may permit recovery of partially destroyed Beta cells or may also have initiated cell proliferation, and observed a significant reduction in the number of Alpha and Delta cells as a result of regeneration of beta cells. By the histological measurement of the thickness of basement membrane in the blood vessels of pancreas and capillaries in islet of Langerhans, there is a significant reduction due to substances like flavonoids which are frequently implicated as having antidiabetic effects and may lead to prevent or delay progression of microvascular changes, but these improvements did not lead to 100% recovery and this may be due to the short duration of the
Like the plant extract, Metformin also produced significant reduction in blood glucose levels, and an increase in the number of Beta cells and a reduction in the number of both Alpha and Delta cells of alloxan diabetic rats. This result is in agreement with Deore et al (2008) who suggested that Metformin decreased gastrointestinal glucose absorption and indirectly improves pancreatic B-cell response to glucose by reducing glucose toxicity and free fatty acid levels (15).

In the present study, a significant increase was observed in the activity of serum amylase in diabetic rats at 14th and 30th days after treated with plant extracts (Adiantum capillus), as compared to the diabetic controls. These results may be due...
to presence of insulin like substances in plants which stimulate Beta-cells to produce more insulin and stimulate pancreatic exocrine function to secrete amylase. Histological finding of the pancreas by using immunohistochemical technique showed a significant increase in the activity of beta cells and a significant decrease in the activity of alpha cells, but did not return to normal, and this may be explained by the fact that these plants may contain insulin-like substances, that stimulate islet cells in the pancreas causing activation and regeneration of Beta cells. The surviving beta-cells regenerated and virtually regained their normal immunostaining and functional status for insulin. Mechanisms such as the stimulation or regeneration effects on beta cells or extra pancreatic effects are proposed for the hypoglycemic action of these plants (16).

Metformin as the plants extract produced significant increase in serum amylase levels of diabetic rats, but there was a non significant difference in activity of beta cells, and significant decrease in alpha cell activity was observed in diabetic rats treated with Metformin using IHC technique at 14th and 30th days as compared to diabetic controls. This result indicates that Metformin did not affect on regeneration of Beta cells, but they affected them indirectly.

In this study, the level of both serum cholesterol and triglycerides were significantly decreased in treated diabetic rats at 14th and 30th days after administration of Adiantum capillus extract, as compared to the diabetic controls. This finding is in agreement with Bopanna et al (1997) and Pari and Latha (2002), who indicated that these plant extracts may antagonize the metabolic aberration in alloxan diabetic rats and thereby restore the normal metabolism by tilting the balance from high lipids to high carbohydrate turnover (17, 18). In this study the reduction of cholesterol and triglyceride serum levels after treatment with plant extracts probably caused by decreasing the level of free fatty acids. Furthermore histological findings on the liver tissue showed a significant decrease in glycogen deposition after treatment with plant extracts due to insulin like substances as flavonoids which have a protective effect on liver tissues of diabetic rats and may lead to reduce enzyme abnormality. In the present study the improvement in biochemical and histological changes was not up to the normal level and this may be due to the short duration of treatment or may require a higher dose.

Metformin treatment produced a significant decrease in the serum cholesterol and triglycerides of alloxan-induced diabetic rats similar to that of plant extracts. This result agrees with Gin (1985) and Janssen et al (1991) who indicated that Metformin treatment was associated with a decrease in total serum cholesterol (19, 20). There is also a significant reduction in glycogen deposition when diabetic rats are treated with Metformin. In the diabetic state, increased rate of glycogenolysis was entirely responsible for the increased rate of glucose production, Metformin treatment led to a reduction in the rate of glucose production, and it was concluded that this occurred through a reduction in hepatic glycogenolysis, the latter is in coincides with the results of (21), (22).

A significant decrease in the level of blood urea was observed in treated diabetic rats at 14th and 30th days after administration of (Adiantum capillus) extracts, as compared to the diabetic controls In the present study, this reduction of blood urea seems to be due to its ability to reduce renal dysfunction. The stabilization of these renal parameters by the aqueous extract was a clear indication of the improvement of the functional status of the kidney.

Diabetic rats showed a significant decrease in the activity of serum (ALP, AST and ALT) at 14th and 30th days after treatment with a daily dose of Adiantum capillus extracts, as compared to the diabetic controls. In the present study the reduction in the activity of these enzymes after administration of aqueous extracts of these plants was a clear indication for the improvement of the functional status of the liver, and its ability to repair the damage produced in the structural integrity of liver after induction of diabetes. The histological findings of liver tissues showed that the number of granules inside hepatocytes(PAS +ve granule) were significantly reduced and this may be due to the plants content which have a protective effect on the liver tissues of diabetic rats preventing its damage and stopping the release of enzymes in large quantities (1). In this study the findings show marked improvement.

Metformin produced a significant decrease in serum ALP, AST, ALT levels, and a significant reduction in glycogen deposition in the hepatocytes of alloxan-induced diabetic rats. This result is in agreement with (17, 21, 22), in which they suggested that in the diabetic state increased rate of glycogenolysis was entirely responsible for the increased rate of glucose production, and Metformin treatment led to a reduction in the rate of glucose production, it was concluded that this occurred through a reduction of hepatic glycogenolysis.

In this study, treated diabetic animals showed significant increase in body weight at 30 days of treatment with (Adiantum capillus) compared with diabetic rats. The ability of the plant extracts to increase body weight seems to be due to its ability to repair slightly the hepato-renal damage, but there were no significant changes observed at 14 day as compared to the diabetic controls. The results indicated that in order to return to normal or to improve weight loss more exposure time and higher concentration of the plant extracts are required. Metformin as the plant extract, produced significant increase in the body weight of alloxan diabetic rats.

While no significant changes in biochemical and histological study were found in treated non diabetic rats at 14th and 30th days of administration in the groups (Adiantum capillus and Metformin) when compared to the control group, these results indicate that the administration of Adiantum capillus and Metformin have no affect on biochemical and histological changes of healthy animals.

**Conclusion**

The results of tissue structures and serum biochemical estimation indicated that this plant has regeneration, and repair effects as it could reverse most blood and tissue changes caused by alloxan induced diabetes in rats.
References
3- Barry, H. Food-derived antioxidants: how to evaluate their importance in food and in vivo. Taylor and Francis group, ILC.Singapore. (2002).
Fracture of Percutaneous Inserted Central Catheter - Unusual Complication: Case Report and review of the literature

ABSTRACT

Abstract: Central line or percutaneous long line is an intravascular catheter that terminates at, or close to the heart, or in one of the great vessels and which is used for infusion, parenteral nutrition, withdrawal of blood, or hemodynamic monitoring. A rare complication of removal of central line is fracture catheter.

Method: We report a female preterm infant (34+5) week's gestational age with duodenal Artesia, polyhydramnios, where central venous catheter was inserted in the left cubital vein on the second day of life.

Result: A silastic catheter rupture occurred during removal and was incidentally found to have a distal fragmented piece of central venous catheter on simple chest X-Ray films, at a time when the length of the catheter was checked correctly when removed. A chest roentgenogram confirmed the suspected diagnosis. The fragment of catheter was successfully removed via cardiac catheterization technique.

Conclusion: The most important step in identifying such a complication after removal of the catheter is to confirm the length of the catheter that was inserted to be able to measure it after removal. Fragmented CVC should be removed using cardiac catheterization.

Keywords: Silastic catheter, central venous catheter, complication removal.

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Introduction
Central venous access is of critical importance in sick neonates, and it has become an integral part of the management of children and newborn admitted to the critical care unit that require long term access for medication and nutrition. Patients in the Neonatal Intensive Care Units (NICUs) often require parenteral antibiotics for treatment of sepsis or other infections, total parenteral nutrition (TPN) and life support medications. In addition, neonates have large fluid losses because of their relatively large body surface area, which increases their need for a reliable access to deliver hydration. (1). There have been many reports on the complications that occur not only at the time of line insertion, like pneumothorax, infection, thrombosis hemothorax, chylethorax or malposition (2) but also complications during removal of the central venous catheter and one of the rare mechanical complications is fracture and catheter migration (3-6) with an estimated rate of 0.1% (7). However, there are rare reports of complications that occur at time of removal of the central line. In our report we review the complication that occurred at the time of removal of a central venous catheter. The aim of our study, is to recognize a rare complication of central venous catheter, during removal, and at the time of placement, to reduce the incidence of serious events.
Case Report
A 34+5 week gestational age baby girl was born by cesarean section due to polyhydramnios, with an Apgar score 8 at 1/5/10 minutes respectively. Her birth weight was 2440g and length 46 cm. The patient was diagnosed to have duodenal atresia and she required ventilatory support for respiratory distress syndrome. Placed on day two of life was a Silastic percutaneous central venous catheter (PCVC) 24G (2Fr) ((Epicucaneo-Cava-Catheter, Art. No. 2184.00, Vygon Medical Products, Germany) for parenteral nutritional support. The catheter was introduced percutaneously and advanced without difficulty through the left median cubital vein. Chest X-ray (CXR), which was performed to locate the tip of the catheter, revealed the tip was in the original location, a successful operative correction of duodenal atresia was performed at the 4th day of life. Catheters were removed when they were no longer required for patient care; at the time of line removal 29 days later, it was noted that about 12 cm of the catheter was missing. Chest X-ray demonstrated that the catheter fragment had migrated to the left pulmonary artery (Figure 1). After discussions with interventional radiology, and pediatric cardiology, it was decided that the catheter should be removed and therefore the patient was taken to the operation room in intensive care unit for attempted transcatheter removal. The embolized fragment, which was 12 cm in length, was retrieved using an endovascular retrieval snare through a 4 F sheath (Amplatz “Goose-Neck” microsnare, Microvena,), introduced via the right femoral vein. There was no cardiovascular compromise or other complications (e.g. femoral vein thrombosis, bleeding, and prolonged radiation exposure) during the procedure, and the right leg moved without limitation thereafter. The follow-up CXR and echocardiogram showed normal cardiac status after the procedure. The intervention time was 10 minutes and the fluoroscopy time was 74 s. Examination of the catheter did not reveal any plausible reason for the break.

Discussion
Central venous catheter or peripherally inserted central lines are being increasingly used for reliable intravascular access in preterm infants and newborn admitted to NICU. Central venous catheter fractures are rare, but constitute a serious complication of their use. These occur more commonly in catheters inserted peripherally. (8) Factors predisposing central line or percutaneous central lines to break are related to the characteristics of the catheter, the insertion, the removal technique, and the clinical problems for which they are used. Silastic catheters have advanced since their introduction in neonatology and are now widely found. They are comparatively easy and safe to create and assign themselves with a long waiting time at a low risk profile (9). Disadvantages are the long course of intravascular, low maximum flow rates and the limited ability of the catheter pressure measurements or to use blood samples. Silastic catheters are prone to fracture at or near the entrance site, where the calibre of the line narrows. Catheter damage may be caused by the introducer needle in peripherally inserted central catheters. The different mechanisms involved in the rupture of an intravascular catheter are: a manufacturing defect in the catheter, trauma during manipulation of the catheter during its installation, the damaging of the material by the injection of hypertonic or, and the use of hydrostatic pressure too high, especially when there are attempts at unblocking a catheter partially or completely blocked (10, 11).

In our case the central catheter was a silastic catheter inserted in left cubital vein easily and the position of the catheter was confirmed by X-ray. There was possibility of introducer needle-associated damage to the catheter which was not seen immediately following insertion of the line. There was a history of catheter blockage. The ruptured catheter was noted very soon after removal of the catheter. We therefore, had not recognized the time where the catheter fractures happened.

A pure literature search probably leads to an underestimation of the actual frequency of catheter outlines and embolisations. Also the literature on this subject consists mostly of small series and case reports. Appropriate review articles are missing. The probability that catheter fragments are discovered on later radiographs is relatively low. In any case one should be examined and the completeness of the catheter should be documented, when removing.

There are a few published studies on the complications resulting from removal of central venous catheter in the medical literature, and a rare reported study about fractured central venous catheter. It is difficult to estimate the incidence of these complications in the literature mainly because there are descriptions of individual cases. The authors of the various reports agree that this complication is very rare. In this report we describe a fracture of percutaneous central catheter and migration to the left pulmonary artery also, we summarized published cases on fractured catheter in premature and newborn in Table 1 - pages 15 and 16.

Seven out of 10 cases used interventional recovery. In three cases the interventional rescue attempt failed so the affected children were operated on.

In summary, we report the successful recovery of an embolized fragment of silastic catheter into the right ventricle and the right pulmonary artery. The most commonly used procedure is non-surgical method of removing the PICC fragment by snaring and pulling the catheter into the sheath that is then pulled out of the body. Before the use of snare-loop catheter, surgical removal was used as the first choice method. Most often this is done under direct visualization, by an interventional radiologist. Migration of a fragment embolization usually does not lead to hemodynamic instability, even when it enters the heart or lungs. In our case, there was no problem or complication during insertion of the catheter, which done by an experienced pediatric intensivist, and it was easily removed with snare catheter by percutaneous technique use.

When using a percutaneous inserted central venous catheter, firstly we should consider precautions to prevent any unnessarily problems caused by manipulation such as high pressure infusion(13) and catheter damage by introducer needle(12) which have been postulated to be the main cause of breakage of central catheter.
Figure 1: Chest X-ray showing the broken catheter in the left pulmonary artery. Below is the size of catheter after removal.
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Author name</th>
<th>Pub. year</th>
<th>Patient age</th>
<th>Description of Complication</th>
<th>Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Toce S, Khilnani P</td>
<td>1990</td>
<td>37 weeks GA</td>
<td>1.9 Fr. silastic catheter in Rt external jugular vein broken and migrated to Lt pulmonary artery</td>
<td>Failure removal by snare-Thoracotomy and pulmonary arteriotomy removed</td>
</tr>
<tr>
<td>13</td>
<td>Watkin and Stephenson</td>
<td>1994</td>
<td>35 Weeks Gestational age</td>
<td>Rt long saphenous vein broken due to high pressure flush Broken and migrated to bifurcation of pulmonary artery</td>
<td>Surgery after unsuccessful cardiac catheterization</td>
</tr>
<tr>
<td>14</td>
<td>Ruiz CE, Nystrom GA et al</td>
<td>1995</td>
<td>30 week GA 1,117 gm</td>
<td>Umbilical vein catheter inserted too far, upon attempting to withdraw that line, the catheter broke and lodged in the left superior pulmonary vein</td>
<td>A 4 Fr Amplatz snare was inserted through the pigtail catheter into the right atrium, crossing the foramen ovale into the left atrium and was successfully removed</td>
</tr>
<tr>
<td>15</td>
<td>Young T, Shaddy RE.</td>
<td>2003</td>
<td>28 week GA 800 gm</td>
<td>Right antecubital fossa. Because it could not be successfully advanced into the subclavian vein, the catheter was removed then successfully advanced in left antecubital fossa into the right atrium. At the first attempt the catheter was broken and migrated to right atrium into the mid superior vena cava</td>
<td>The catheter was encircled with the gooseneck snare and removed from the patient through the 4 French sheath</td>
</tr>
<tr>
<td>16</td>
<td>Chiang MC, Chou YH</td>
<td>2006</td>
<td>28 weeks GA 1120 gm</td>
<td>Silastic catheter in Rt antecubital vein, broken during withdrawn 2 cm and catheter lodged between Rt atrium and Rt ventricle</td>
<td>Removed by Grosse Neck snare no complication</td>
</tr>
<tr>
<td>17</td>
<td>Chen C-C, Liang C-D et al</td>
<td>2006</td>
<td>27 weeks GA 980 gm</td>
<td>Silastic catheter in Rt femoral vein while removed missed 5 cm inside remnant between Lt and right atria through a patent foramen ovale</td>
<td>Removed by 5 Fr Judkins catheter, A 3 Fr Busket device catheter was advanced through the Judkins catheter and hook the PICC</td>
</tr>
<tr>
<td>Case</td>
<td>Authors</td>
<td>Year</td>
<td>GA/Weight</td>
<td>Details</td>
<td>Comments</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
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<td>----------</td>
</tr>
<tr>
<td>18</td>
<td>Kohli V, Joshi R.</td>
<td>2007</td>
<td>32 weeks GA 2.1 Kg</td>
<td>Silastic PICC line was inserted from right brachiocephalic vein, the catheter was looped all around the pulmonary valve with some segments hanging in the right ventricle.</td>
<td>First attempts at snaring the catheter with 4F Right Judkins catheter were not successful. A Microvena snare (3 mm) was used and the PICC line snared and pulled into the microvena catheter. The retrieval after snaring was smooth.</td>
</tr>
<tr>
<td>19</td>
<td>Puvabanditsin S, Garrow E, Weerasetsithir R</td>
<td>2008</td>
<td>25 weeks GA 405 gm</td>
<td>Broviac 2.7-Fr CV catheter inserted via the right saphenous vein, the catheter was occluded multiple attempts to flush it with a heparinised solution using 3 ml syringes. The occlusion resolved after flushing Two days later, a chest X-ray showed a catheter fracture in the right iliac vein.</td>
<td>Through the left femoral vein inserted 4-French sheath with a 5-mm Microvena Amplatz gooseneck snare device and removed. There were no complications.</td>
</tr>
<tr>
<td>20</td>
<td>Wong AR, Suhaimi H, Ridzuan MAR et al</td>
<td>2009</td>
<td>One week old</td>
<td>Long venous catheter, inserted in the left saphenous vein at the ankle, fractured due to pinching of the catheter hub on the catheter line which migrated into the right ventricular outflow tract.</td>
<td>Successfully retrieved the line using a 4-mm 4F goose neck loop snare, from the left pulmonary artery.</td>
</tr>
<tr>
<td>21</td>
<td>Vesselin Dimov</td>
<td>2009</td>
<td>27 week GA</td>
<td>1,9 F PICC inserted in left antecubital site inflammation at site of insertion line during removal it broke and 7cm inside</td>
<td>Patient was sent to surgery for removal of catheter after failed attempt of catheterization removal.</td>
</tr>
</tbody>
</table>

Table 1: Published cases of broken silastic catheter in preterm and term newborn.
Secondly, during the removal process, there is a possibility that resistance may be present. The catheter must never be forcefully tugged as this could break it. The resistance could be caused by a venous spasm. Warmth often relieves the spasm and after a brief period of time it may easily be removed. Thirdly and the most important point, after central venous catheter is completely removed, the actual catheter length should be measured and compared with the documented insertion length. The documented and actual length must be equal as this is the only way to confirm that the catheter has not broken and has been removed intact. In addition, the catheter tip should also be examined to insure there is no breakage at the end.

Conclusion
Breakage or fracture of PICC is a rare complication of neonatal and preterm infant. Clinicians should be aware of this potential lethal complication and be prudent when removing the catheter. An embolized fragment can be retrieved using a percutaneous cardiac catheterization, even in a tiny premature infant.

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15: Young T, Shaddy RE. Successful percutaneous retrieval of an intracardiac catheter fragment in an 800 g premature infant. J Perinatol 2003; 23: 67-68
Evaluation of seminal plasma creatine kinase and its iso-enzymes of primary infertile males in Erbil city

ABSTRACT

Background and objectives: Approximately (15%) of couples attempting their first pregnancy meet with failure. Most authorities define these patients as being primary infertile if they have been unable to achieve a pregnancy after one year of unprotected intercourse.

The aim of this study was to evaluate the seminal plasma creatine kinase activity and its iso-enzymes of primary infertile males in Hawler city.

Subjects and methods: This study was carried out during the period from November 2006 to September 2009 on (500) married males, who were referring continuously to the infertility and I.V.F. center in Erbil city.

Three hundred and thirty one cases have been identified by consultants as having primary infertility and (200) cases of those were suffering from oligospermia and as a control group we had 50 normal volunteers.

The activity of (CK) and its iso-enzymes in the seminal fluid of both groups was estimated. The results obtained were compared with age matched (50) normal volunteers.

Results: The activity of seminal plasma Creatine Kinase in infertile oligospermic males was significantly higher than that of controls (P< 0.01). Ages between 20-29 years were found to be more exposed to oligospermic primary infertility than the ages between 30-39 and 40-49 years. Seminal plasma CK activity was significantly higher in low occupations than those of medium and high occupations.

Seminal plasma CK analysis resulted in two iso-enzymes.

Conclusions: The data obtained revealed that the activity of seminal plasma CK was significantly higher than that of normal subjects and this increase is due mainly to an increase in the activity of one of the two iso-enzymes.

Key words: Male primary infertility, Oligospermia, Creatine kinase, Creatine kinase iso-enzyme.

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Introduction

Conception normally is achieved within 12 months in 80-85% of couples who use no contraceptive measures. Persons presenting after this time should therefore be regarded as possibly infertile and should be evaluated. Data available over the past 20 years reveal that in approximately 30% of cases, pathology is found in the man alone, and in another 20% both the man and woman are abnormal. Therefore, the male factor is at least partly responsible in about 50% of infertile couples (1-2).

Male infertility can be due to a variety of conditions; some of these conditions are identifiable and reversible, such as ductal obstruction and hypo-gonadotropic hypo-gonadism. Other conditions are identifiable but not reversible, such as bilateral testicular atrophy secondary to viral orchitis (3).

If a male infertility factor is present, it is almost always defined by the finding of an abnormal semen analysis, although other male factors may play a role even when the semen analysis is normal (4).

When identification of the etiology of an abnormal semen analysis is not possible as is the case in many patients, the condition is termed idiopathic. Rarely patients with normal semen analysis have sperm that do not function in a manner necessary for fertility (5).

Semen analysis must include: ejaculate volume, liquefaction time, pH, sperm concentration, total numbers, morphology and motility, viability and mixed agglutination reaction (MAR) a test used to detect anti-sperm-antibodies (6).
The determination of enzyme activities and the screening of their regulators is a major risk in clinical chemistry. A broad variety of enzymatic reactions is associated with the consumption of Adenosine triphosphate (ATP), including in particular, phosphorylation reactions catalyzed by kinases, such as creatine kinase (CK) (7).

There are a significant correlation between semen volume, sperm concentration and many enzyme activities such as aspartate transaminase (AST) gamma glutamyl transferase (GGT), alkaline phosphatase, (ALP), acid phosphatase (ACP), lactate dehydrogenase (LDH), creatine kinase CK), glutathione peroxidase (GSH-Px), glutathione reductase and superoxide dismutase (SOD) (8).

The enzymatic equipment of spermatozoa is similar to that of seminal plasma and a close relationship exists between the enzymatic equipment of spermatozoa and their fertilizing capacity (9).

Creatine kinase (C, CPK) is an enzyme that belongs to a class of transferases with a classification number (EC 2-7-3-2), and plays a central role in energy transactions in cells, displaying high and variable rates of ATP turnover. CK is involved in energy storage in tissues, primarily muscles (10).

CK is predominantly found as a dimer of two catalytic subunits, each with a molecular weight of 40 KDa, the two subunits are termed M (muscle) and B (brain). The three resulting isoenzymes are CK1 (BB), CK2 (MB) and CK3 (MM). Another structurally different form of CK, with a molecular weight of 64 KDa, is present in mitochondria, although it is seldom released to the circulation and termed macro-CK2. CK is found in small amounts throughout the body, but it is in high concentration in muscle and brain (11).

A number of independent studies indicate that sperm function is frequently associated with elevated activities of certain key enzymes including CK and these enzymes act as biochemical markers for normal sperm differentiation and induction of peroxidative damage (12).

Cells requiring high energy such as spermatozoa are characterized by high activity of CK. It is generally accepted that there are two iso-enzymes of CK in human spermatozoa, designated as CK-MB and CK-MM (13).

CK is a marker of sperm maturity that correlates with the sperm fertilizing capacity; elevated levels are associated with an increased rate of functional abnormalities and increased cytoplasmic retention. (14)

The classical biological criteria of fertility are sometimes insufficient and might be overcome by some biochemical criteria, so the enzymatic profile of spermatozoa should constitute a good indication of functional metabolic activity. (15)

CK present in seminal fluid is shown to be derived from secretions of seminiferous tubules, spermatozoa, epididymis, seminal vesicles and prostate gland, thus the estimation of CK in semen permits one to obtain markers of seminal quality (16).

In the light of these data and to the best of our knowledge, no attempt has been made to study this important and unexplored field in the Iraqi-Kurdistan region. Therefore the present study was designed to investigate the serum activity of CK and its iso-enzymes in primary oligospermic infertile males and comparing the results obtained with those of age matched fertile volunteer males (Normospermics), in order to know whether CK activity can be used as a biomarker for male infertility or not.

**Subjects and Methods**

**Subjects**: This study was conducted during the period from November 2006 to September 2009 at the Department of Medical Biochemistry, College of Medicine, Hawler Medical University, Erbil, Iraq.

Informed consent was obtained verbally from the two groups. All participants were carefully screened to exclude evidence of congestive heart failure, hepatic and renal diseases, endocrinological disorders. Seminal plasma samples were collected at ifertile care and I.V.F. Center, Hawler city, after their diagnosis by consultants.

**Samples**: Oligospermic infertile and fertile males were provided with standard instructions for semen collection. These instructions included a defined period of abstinence of 2-3 days. Semen samples were collected by masturbation or by intercourse using special semen collection condoms that do not contain substances detrimental to sperm. The specimens were collected at home or at the laboratory and kept at room temperature or body temperature during transport and examined within one hour of collection. (17)

**Methods**: The seminal plasma (2.3) ml was obtained by centrifugation of the samples at maximum speed (preferably at 3000 rpm) for (15) minutes and the (50) µl was used for estimation of CK activity of both groups according to a method described by Tietz (18).

The seminal plasma CK iso-enzymes were partially purified using gel filtration chromatography in a cold room (4o C) and they were quantified according to a method described by Hershenson et al (19) and Gundogan (20).

**Statistical analysis**: The overall predictive value for the results in both studied groups were performed according to an office program windows XP 2002. Arithmetic mean and standard error of mean (S.E.M.) were calculated using statistical methods.

Concerning P-value, any value less than 0.01 (P < 0.01) was regarded to be significant.
**Results**

The data obtained indicates clearly that the activity of seminal plasma CK was significantly higher in oligospermic patients than that of controls (P < 0.01).

On the other hand there was also a significant difference between the oligospermic infertile males according to their age ranges and occupations (P < 0.01). Those of the age range between (20-29) years represented (45 %), (30-39) years represented (40%) and (40-49) years represented 15%, whereas those of low occupation represented (50%) than those of medium (40 %) and high (10%), Table (2).

Table 3 shows that the fractioning of seminal fluid CK iso-enzymes and the estimation of their activities resulted in the separation of two peaks of activity for both groups. The activities of both iso-enzymes were significantly higher (P <0.01) than those of controls. On the other hand the CK iso-enzyme in peak one is more than that in peak two in both groups.

**Discussion**

Male infertility may be either primary (refers to the biological inability of a man or a woman to contribute to conception) or secondary (describes couples who have been pregnant at least once, but have not been able to achieve a pregnancy again).

The simplest evaluation of a male infertility is the semen analysis. Semen volume (>2-3 ml), pH (7.2-7.8), sperm concentration (> 20 * 10^6 / ml), viability (> 75%), time to liquefy (5-25 min.), W.B.C (< 1*10^6), MAR test (negative), sperm motility (> 50%), morphology (> 30% normal), Zinc (> 2.4 mole / ejaculate and Fructose (120-145 mg / dl) serve as an integral screen of sperm fertilization potential (17).

Generally the clinicians depend on semen analysis for the assessment of male infertility and also for evaluating testing efficacy of male fertility regulating agents.

Apart from the routine semen analysis, specific investigations are also required to assess the functional status of sperm (21).

Severe infertility is diagnosed if severe oligospermia is found, whereas relative infertility is diagnosed if the sperm count is between 2,000,000-5,000,000 / ml (1).

Male factor infertility can be a problem of sperm production, sperm function, or sperm delivery. Sperm production may be completely absent (azoospermia) in for example, testicular failure. More commonly a patient may present with a reduced count of sperm of normal appearance (oligospermia).

Additionally, a high proportion of the sperm may be poorly motile, lacking the normal forward progressive movement (asthenospermia), or may appear morphologically defective (teratospermia) with abnormalities of the head, mid-piece or tail (22).

Infertile male patients are classified into six groups: Oligospermia, azospermia, asthenospermia, teratospermia, aspermia and normospermia. The oligospermic group provides the highest number of patients among all of these. The data obtained in this study indicate that among 331 primary infertile males 200 were oligospermic primary infertiles (60.42 %); similar results were obtained by Jalal (23), Razzak and Wais (24).

The results of the present study indicated also that there was a significant difference between the oligospermic infertile males according to the age and occupation. Those of the age range 20-29 years are more susceptible to oligospermia and represented 45%, 30-39 years represented 40% and 40-49
years represented 15%. These results are also in agreement with those of Jalal (23) who reported that male infertility was increased in age group of 18-29 years.

The data obtained also reveals that the low occupation represented 50%, medium 40% and high 10 % of the total oligospermic infertile males. Martin Du Pan and Sakkas (25) found similar results and reported that a number of occupational factors affect male fertility such as working for a long time often affects sperm count and heat exposure has an adverse effect on spermatogenesis. The mean seminal plasma Ck activity of oligospermic infertile males was (372.35± 14.10 IU / L ) (mean ± SE), which was significantly (P < 0.01) higher than that of the normal group (103.76 ± 6.33 IU / L ). This finding is similar to the results obtained by Hallakabed et al (14), who reported that elevated CK activity was associated with severe oligospermia, irrespective of the clinical diagnosis. The same authors suggested that CK activity estimation in seminal plasma may be a sensitive indicator of sperm quality and maturity in the follow up of patients treated for male infertility.

The inverse relationship between CK activity and sperm concentration and morphological forms suggest that CK activity can be a reliable marker for semen quality in infertile males (26). The measurement of CK activity in the seminal plasma of oligospermic infertile males is also of great value to select appropriate treatment for couples with male factor or unexplained infertility, particularly when considering the option of intruterine insemination, varicocelectomy, followed by a waiting period, or ovulation workup / induction in wives of men who are oligospermics, but may have fertile sperm. (27)

On the other hand Huzar and Vigue (12) reported that measurement of CK activity and similar biochemical markers will facilitate selection of men for various approaches in assisted reproduction.

Moreover, the origin of CK is fundamentally prostatic, so it could be a parameter of prostatic function in studies of male fertility (28).

The results obtained reveal two CK peaks which are corresponding to two iso-enzymes (CK-MM , CK-MB) , and their activities in oligospermics were significantly higher (P < 0.01) than those of normospermics.

Huszar and Vigue (12) conducted a study and obtained similar results. Moreover they reported that the relative concentration of sperm CK-MM isozyme is a biochemical marker of cellular differentiation that may also predict the functional infertility such as fertilization potential of spermatozoa.

Finally Gershbein and Thielen (29) found also that CK-MM comprised the main iso-enzyme of semen CK .

Conclusions
Conclusions can be summarized as follows :

1- Estimation of CK activity in seminal plasma of oligospermic primary infertile males is an easy, cheap, and reliable method.

2- The results obtained reveal a significant higher activity of CK and its iso-enzymes in oligospermic primary infertile males than those of normal subjects, so they can be used as biomarkers of male infertility.

3- Age range between (20-29) years was found to be more exposed to oligospermic primary infertility than the age ranges between 30-39) and (40-49) years.

4- The results also revealed that occupation also affects male infertility.

5- The data obtained revealed two iso-enzymes of CK in seminal plasma of oligospermics and controls designated as CK-MB and CK-MM .The activity of CK-MM was significantly higher than that of CK-MB in both groups.

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Lipid and lipoprotein changes in Chronic Heart Disease

ABSTRACT

Objective: The purpose of these studies is to identify criteria for evaluating people at high risk of coronary heart diseases (CHD).

Methods: During a period of six months (in 2009), the age span of MI and CHD patients was 20-75 years with 674 cases including patients with Coronary Arterial Diseases (CAD) and normal healthy subjects who were investigated at King Hussein Medical Center to determine the change in total cholesterol (TC), triglycerides (TRG), high density lipoprotein-cholesterol (HDL-C) and TC: HDL ratio that varies with age and sex due to association with an increased risk of CHD. The enzymatic method was used and analysis was done within 48 hours using Hitachi auto analyzer.

Result: Six hundred and seventy four subjects were studied at K.H.M.C for seven month. As expected, TC: HDL ratio was higher in the patient group than healthy group whereas the HDL-C was lower. Moreover, TC: HDL ratio in MI males was higher than female patients as seen in Table 1, in our study. We found that the TC: HDL ratio is an effective indicator of this risk.

Conclusion: The effect of disturbances of lipids and lipoproteins on the development of CHD patients may also depend on the presence of other non-lipid risk factors.

Keywords: Coronary heart disease (CHD), Cholesterol Lipoproteins, HDL cholesterol, Myocardial infarction, Triglycerides. King Hussein Medical Center (K.H.M.C)

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Introduction

Serum lipids are important determinants of cardiovascular disease and are related to morbidity. The high heritability of circulating lipid level is well established and earlier studies of individuals with extreme lipid value or families with mendelian forms of dyslipidemias have exposed the involvement of numerous genes and respective proteins in lipid metabolism. (1,2)

Heart disease is the number one cause of death in women, as it is in men; risk factors include high cholesterol, high triglyceride, low HDL-C, diabetes, hypertension and cigarette smoking.

The incidence of coronary heart disease (CHD) is much lower in younger women than in age-matched men and this had led to the popular misconception that cardiovascular disease is a disease of men, and is relatively rare in women. (3)

Hypercholesterolemia (> 350 mg/dl, > 9.0 mmol/l) is recognized as an important risk factor in the development of coronary heart disease (CHD). Other lipid-related risk factors, have also been implicated in the development of CHD and include raised serum triglycerides, LDL-cholesterol, cholesterol-HDL ratio and lowered HDL-cholesterol concentration.(4,5)

In this connection, one Finnish study revealed that more than half of Finnish adult male and female population have mild to moderate hypercholesterolemia and fall into the range of 192-288 mg/dl.(6)

Moreover, the Framingham study showed that cholesterol >350 mg/dl (>9.0 mmol/l) is a very good discriminator of risk in men, Most patients with CHD came from the middle range of cholesterol levels (192-288mg/dl) and there were many of those who did not.(7)

The total cholesterol to HDL ratio is a practical way to express its role in relation to CHD. The usefulness of cholesterol ratio was tested by the Prospective Cardiovascular Munster Trial (PROCAM) with more than 18,000 participants of both sexes aged between 17-65 years,
which was found to be good predictor of the incidence of MI.(6,8)

In the UK, like other European and US populations, about 4-5% of people have serum HDL-cholesterol level of < 35 mg/dl which is often recommended as indicating a significant increase in CHD risk.(9)

Although there is no national programme for risk assessment for CHD in Jordan, our study was planned to determine age and sex-wise changes in TC, TRG, HDL-C and ratio of TC, HDL in CHD patients and normal healthy subjects. The risk of CAD is markedly increased in hypercholesterolemic patients who have other concurrent risk factors. However, if cholesterol levels are very low, CAD is uncommon even if other risk factors are present. To determine the lipid profile of patients with proven CAD by angiogram we conducted a prospective study to assess the lipid profile in these patients, to evaluate the prevalence of dyslipidemia in both diabetics and non-diabetics and to stratify the risk factors in this cohort (12).

**Patients and Methods**

This study was conducted on 374 patients of CHD or MI and 300 healthy individuals at King Hussein Medical Center, Jordan, for seven months (2009-2010).

In all 374 patients included for study had either CHD (n=225, 177 males, 48 females), or MI (n=149, 114 males, c35 females) and were admitted to the Queen Alia Heart Center at King Hussein Medical Center, Jordan, with some clinical evidence of CHD while others were admitted to the CCU with MI. Patient files were studied for age, sex, blood pressure, smoking habit and diabetes status. All the patients had a history of hypertension and their systolic blood pressure range was 150-170 mmHg (prior to treatment). However, individuals with pre-existing CHD were excluded from the original study.

Healthy individuals were included from blood donors at King Hussein Medical Center (n=300, 200 males, 100 females). They were already examined for blood pressure and other vital signs. Thorough medical history of each subject was recorded. Blood donor taking lipid lowering drugs or anti-hypertensive drugs were excluded and usually they were a non smoker.

**Laboratory Investigations**

Blood specimens were collected from these individuals; serum was separated and stored at 2-8 C. Analysis was done within 48 hours after collection. Serum total cholesterol triglyceride was done by enzymatic method using Hitachi 704 auto analyzer.(11) HDL-cholesterol was measured by using the precipitation technique.

**Results**

Tables 1 (next page) to 2 show the results and data obtained for the patients of CHD, MI, hypercholesterolemic, healthy individuals and the percentage of CHD-risk according to the age and sexes.

As can be seen, the value of cholesterol, T cholesterol : HDL-C ratio CHD/MI group and hypercholesterolemic group was greater than that of the healthy individuals.

The Total cholesterol : HDL-C in hypercholesterolemic patients was greater than that of CHD patients but the value of HDL-C in CHD and MI patients was less than the control group but in hypercholesterolemic patients had a similar average.

The TC: HDL-C ratio for females was greater than that at CHD males but vice versa in MI and hypercholesterolemia.

### Table 2: Hypercholesterolemia patients age (30-70)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Age</td>
<td>40 (22-55)</td>
<td>43 (20-60)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Smoking</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cholesterol(mg/dl)</td>
<td>233 (136-343)</td>
<td>226 (106-301)</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>50 (30-70)</td>
<td>45 (27-69)</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>5.0 (3.2-11.4)</td>
<td>5.4 (3.4-8.6)</td>
</tr>
<tr>
<td>CHD-Risk</td>
<td>&lt;15%</td>
<td>&lt;15%</td>
</tr>
</tbody>
</table>

Table 2: Hypercholesterolemia patients age (30-70)
Discussion

The strong independent, continuous and graded positive association between total cholesterol level or LDL cholesterol level and risk of coronary artery disease events has been clearly demonstrated both in men and women of all age groups (15).

The increased levels of cholesterol, and decreased HDL-C and TC: HDL ratio has been associated with increased risk of CHD. There was a significant difference in the value of these risk factors, found in either men or women, with established CHD, MI or hypercholesterolemic patients and the values found in samples from healthy controls. This indicates the importance of lipid risk factors in the development of CHD, MI and hypercholesterolemic patients. The European atherosclerosis society suggests a target cholesterol level of 200 mg/dl to reduce the incidence of CHD.(11,13)

In the UK, serum cholesterol level of 192-288 mg/dl was found in 4-5% people; some 4% of the Manchester population had HDL-cholesterol value < 35 mg/dl. The limitation of cholesterol level and the relative advantages of cholesterol to HDL ratio were shown by Assman and his colleagues in the PROCAM study. In this large population study the cholesterol cut-off from the National Institute of Health recommendation, i.e, >250mg/dl, was used. It was found only to identify 44% of men who developed myocardial infarction and yet it had taken in about 33% of the German population, the majority of whom had only a small risk of dying prematurely from heart disease. If the cut-off level was raised to 300 mg/dl, the risk rate does rise, but even a smaller percentage of people (13.3%) who will have coronary heart disease, will be identified. Clearly, cholesterol level alone is not a good way of identifying a substantial population at risk of CHD. Moreover, the TC: HDL ratio can be used to determine the percentage risk from the Sheffield table or the modified Sheffield tables.(12,16)

The concentration of TC:HDL ratio found in apparently healthy controls is approximately not variable while concentrations of HDL, cholesterol are variable and differ from other studies depending on the genetic inheritance, region and habits of the population studied. According to the recommendations of the European Atherosclerosis Society, there is no lipid disorder in given individuals if the concentration of cholesterol is < 200mg/dl and HDL-cholesterol is > 35mg/dl, but the range of normal value in our study was 150-250mg/dl and HDL-cholesterol > 35mg/dl.(11)

Increased rates of coronary heart disease (CHD) occur with advancing age in both sexes, although the CHD rate in women lags behind those of men by about ten years. There is a sharp increase in CHD rate among women after approximately fifty years of age and the reasons for this are not completely understood and are undoubtedly multifactorial(3).

Serum cholesterol and HDL-cholesterol concentration increases with age, as shown in this study as does the concentration of cholesterol,(13,14). HDL-cholesterol in elderly patients with CHD, and MI in males or females was greater than the normal range in the younger generation group.
CHD patients showed more than the normal range of cholesterol in 7.6% of males and 20% of females while MI patients showed > normal range of cholesterol in 23.3% of males and 25% of females. Taking cholesterol alone as a risk factor in CHD is well established by the Framingham Heart study, but it is clear that the larger number of people who are healthy will be included among the risk group(7), so we have to use other parameters in addition to the cholesterol to identify patients at higher risk of CHD(5,9,13).

In contrast, Assman found that the ratio of total serum cholesterol to HDL-cholesterol of about 6.0 will identify nearly 70% of the people at risk of CHD or destined to have CHD.(6,9,10)

As shown in this study, the mean value of TC:HDL ratio of 6.0 will identify the people at risk of CHD, and MI, but in hypercholesterolemic patients, the ratio will be of 5.0.

CHD, MI and hypercholesterolema patients were found to have higher cholesterol, lower HDL-cholesterol and higher TC:HDL ratio but some (37.5%) have normal values compared to younger subjects of healthy individuals; further investigation for this group are indicated. For this particular percentage, we found a high CHD risk i.e. >15% for ten years by using the modified Sheffield table. (12,16,18).

There is clear evidence that treating hypercholesterolemia reduces cardiovascular risk in women, as well as in men. Also hypertension is one of the major risk factors for the development of CHD. The incidence of hypertension increases with age and is higher in men than in women up to the age of about 50. Beyond middle age however, blood pressure in women exceeds that in men.(3) The dietary treatment would be appropriate for patients in the zone of moderately increased risk with TC: HDL ratio of 5 -6.5 for men and up to 7.5 for women.

In contrast, our study indicated dietary treatment for cholesterol >250 mg/dl and ratio >5.0 in both sexes.

As shown in this study, HDL-cholesterol even at a low level of total cholesterol may be associated with high risk of CHD. Comparing this result with the result of PROCAM, Assman studies and modified Sheffield tables, our study shows that the ratio > 5.0 and CHD risk > 15% indicates a high risk in CHD, MI hypercholesterolemic patients.

Conclusion
There are gender differences in lipid profile in patients and healthy individuals.

The total cholesterol to HDL-cholesterol ratio is a good practical way for the management of the patient suffering from mild-to-moderate hypercholesterolemia and it is useful to the clinician when combined with detailed knowledge of the patient’s other risk factors.

It can also be applied to patients at high risk of CHD, MI and to patients with normal to low levels of total cholesterol.

This study has demonstrated that raised cholesterol, TC:HDL ratio and lowered HDL-cholesterol are associated with CHD, MI, and hypercholesterolemic patients in both sexes.

We recommend that patients should follow dietary treatment when the TC: HDL ratio is > 5.0.

References


ABSTRACT

Background: Although metabolic syndrome is related with several metabolic parameters and chronic diseases, little is known about its relationship with cataract.

Methods: The study was performed in the Internal Medicine Polyclinic on patients applying for any complaint. All operated cases for cataract and an age and sex-matched control group were determined, and their smoking habits, metabolic parameters, and chronic diseases were compared.

Results: There were 55 operated cases for cataract (28 females) among all of the 2,888 cases. So prevalence of cataract operations was 1.9%. Thirty-five of the cases had been operated bilaterally, eight of them from the left and 12 of them from the right sides alone. The mean age of the cataract cases was 67.6 ± 10.4 years. So it is a health problem of the elderly with similar prevalences in both sexes and both sides of the eyes. When we compared the two groups, there was no significant difference according to the prevalence of smoking, overweight, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, obesity, hypertension (HT), and diabetes mellitus (DM) between the cataract and control cases.

Conclusion: Metabolic syndrome may be a reversible progression step between complete physical health and irreversible chronic diseases such as obesity, type 2 diabetes mellitus (DM), hypertension (HT), coronary heart disease (CHD), and stroke with the components of overweight, hypertriglyceridemia, hyperbetalipoproteinemia, impaired fasting glucose, impaired glucose tolerance, smoking, and white coat hypertension. Although the syndrome is significantly related with many terminal diseases, cataract cases do not have higher prevalence of any reversible component or terminal disease of the syndrome.

Key words: Cataract, metabolic syndrome, smoking, aging

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Introduction

Metabolic syndrome may be a reversible progression step between complete physical health and terminal chronic diseases such as obesity, type 2 diabetes mellitus (DM), hypertension (HT), coronary heart disease (CHD), and stroke with the components of overweight, hypertriglyceridemia, hyperbetalipoproteinemia, impaired fasting glucose, impaired glucose tolerance, smoking, and white coat hypertension (WCH). Probably initiation of weight gain is the most significant promoter factor, and hypertriglyceridemia and WCH are the most significant reversible indicators of the syndrome (1,2). In recent years, regulation of body weight is rapidly becoming the center of attention for public health experts in the industrialized world as well as in developing countries (3). The current prevalence of obesity in the general population, is estimated at 19.9% and 24.9% in men and women, respectively (4). Certain calculations suggest that, given trends over the past 30 years, the entire United States population could be obese by the year 2230 if these trends persist (5). A more disturbing trend is the increased obesity in children. This alarming trend has prompted the World Health Organization to declare obesity as a worldwide epidemic (6). On the other hand, cataract is opacity of lenses which interferes with vision, and is the most common cause of visual impairment worldwide especially for elders, since the prevalence of cataract increases with age (7). In a study performed on 8,571 patients in Turkey, cataract was found responsible for 50% of cases with blindness (8). Thus from a public health perspective, it is important to identify risk factors that affect development and progression of cataract. Although many studies have shown that the metabolic syndrome is associated with numerous medical complications and increased all-cause mortality (9-11), little is known about its relationship with cataract, and there are various reports about this topic in the literature (12-16).
Materials and Methods
The study was performed in the Internal Medicine Polyclinic of the Medical Faculty of the Dumlupinar University, on patients applying for any complaint between August 2005 and March 2007. Their medical histories, including operation for cataract, HT, DM, dyslipidemia, and already used medications were studied, and a routine check up procedure including fasting plasma glucose (FPG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) was performed. Current daily smokers, smoking at least six pack-month, and cases with a history of five pack-year were accepted as smokers. Body mass index (BMI) of each case was calculated by the measurements of the physician instead of verbal expressions, because there is evidence that heavier individuals systematically under-report their weight relative to lighter individuals (17). Weight in kilograms is divided by height in meters squared, and obesity is defined as a BMI of 30.0 or greater and overweight as 25.0–29.9 kg/m(2) (18).

Cases with an overnight FPG level of 126 mg/dL or greater on two occasions, or already receiving antidiabetic medications, were defined as diabetics (18). An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level of 200 mg/dL or greater is DM (18). Additionally, a 10-day twice daily measurement of blood pressure at home (HBp) was obtained in all cases, even in normotensives in the office due to the risk of masked HT, after a 10-minute education session about proper BP measurement techniques (19). The education included recommendation of upper arm while discouraging wrist and finger devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest for at least a period of 5-minutes in the seated position, before measurement. HT is defined as a blood pressure (BP) of 135/85 mmHg or greater on mean HBp values (19). Additionally patients with dyslipidemia were detected, and we used the National Cholesterol Education Program Expert Panel’s recommendations for defining dyslipidemic subgroups (18). Dyslipidemia is diagnosed with a LDL-C value of 160 or greater and/or a TG value of 200 or greater and/or a HDL-C value of lower than 40 mg/dL. Eventually, all operated cases for cataract and an age and sex-matched control group were determined, and their smoking habits, metabolic parameters, and comorbid disorders were compared. Independent-Samples T Test and comparison of proportions were used as the methods of statistical analyses.

Results
There were 55 operated cases for cataract (28 females) among all of the 2,888 cases, totally. So the prevalence of cataract operations was 1.9%. Thirty-five of the cases had been operated bilaterally, eight of them from the left and 12 of them from the right sides alone. Mean age of the cataract cases was 67.6 ± 10.4 years (Table 1). So it is a health problem of the elderly with similar prevalences in both sexes and both sides of the eyes. Although there was a presence of a slightly higher prevalence of smoking in the control group (29.0 versus 20.0%), the difference was nonsignificant (p>0.05). Similarly, there was no significant difference according to the prevalences of overweight, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, obesity, HT, and DM between the cataract and control groups in the present study (Table 2).

Discussion
Although there is no universally accepted definition for the metabolic syndrome, it basically includes five features: excess weight, high glucose and insulin levels, low HDL-C, high TG, and high BP values (20). But the already used definitions such as excess weight, a BP of 135/85 or 140/90 mmHg or above, and a FPG of 100 or 110 mg/dL or above also includes patients with obesity, DM, and HT. But actually the syndrome is a collection of risk factors instead of a terminal chronic disease, and it is a reversible condition with appropriate nonpharmacological approaches, whereas the chronic diseases including HT, DM, symptomatic atherosclerosis, and obesity are irreversibly and have final states which almost always require drug therapy to delay their complications. So metabolic syndrome alone is a disadvantageous but reversible status but not a final disease, and after the development of one of the terminal chronic diseases, the term of metabolic syndrome probably loses most of its significance, since from now on the nonpharmaceutical approaches will provide little benefit to prevent development of the other conditions, probably due to the cumulative effects of the risk factors on systems for a long period of time. On the other hand, we saw in a previous study that prevalence of smoking was significantly higher in the hypertriglyceridemia group (42.2% vs. 28.4%, p<0.01) parallel to the higher prevalences of excess weight, DM, and HT (21). So, smoking, as a pleasure in life, may show the weakness of volition of the individuals to control eating in the syndrome, but eventually the smoking habit comes with the terrible effects on health such as atherosclerosis to facilitate CHD, peripheral artery disease, and stroke. So definition of the metabolic syndrome should be as a collection of reversible risk factors including overweight, hypertriglyceridemia, hyperbetalipoproteinemia, smoking, and WCH for several terminal chronic diseases such as obesity, HT, type 2 DM, CHD, and stroke.

Obesity is a disorder characterized by increased adipose tissue that results from a systemic imbalance between food intake and energy expenditure (22), and is a public health problem. It is associated with many terminal complications including type 2 DM, HT, CHD, certain types of cancers, and an increased all-cause mortality (9-11). On the other hand, obesity can be reversed only by a few individuals and most of them are transient. This small percentage of reversibility can also be achieved with a prominent weight loss even in type 2 DM and HT, although they are mainly accepted as irreversible end points of the metabolic syndrome. Additionally, obesity is usually acquired after a long period of time, and usually initiated to develop in early childhood and adolescence. Probably due to its long duration, it brings many irreversible changes in body. Since excess weight leads to both structural and functional abnormalities in many systems of the body, risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of moderate to severe weight excess in all age groups (10).
Table 1: Characteristic features of the study cases

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cataract group</th>
<th>p-value</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>55</td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>Female ratio</td>
<td>50.9% (28)</td>
<td>ns*</td>
<td>50.9% (28)</td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>67.6 ± 10.4 (45-88)</td>
<td>ns</td>
<td>67.6 ± 8.2 (45-81)</td>
</tr>
<tr>
<td>Prevalence of smoking</td>
<td>20.0% (11)</td>
<td>ns</td>
<td>29.0% (16)</td>
</tr>
</tbody>
</table>

*Nonsignificant (p>0.05)

Table 2: Metabolic parameters and comorbid disorders of the study cases

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cataract group</th>
<th>p-value</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of overweight</td>
<td>40.0% (22)</td>
<td>ns*</td>
<td>47.2% (26)</td>
</tr>
<tr>
<td>Prevalence of hyperbetalipoproteinemia</td>
<td>20.0% (11)</td>
<td>ns</td>
<td>20.0% (11)</td>
</tr>
<tr>
<td>Prevalence of hypertriglyceridemia</td>
<td>16.3% (9)</td>
<td>ns</td>
<td>21.8% (12)</td>
</tr>
<tr>
<td>Prevalence of dyslipidemia</td>
<td>32.7% (18)</td>
<td>ns</td>
<td>30.9% (17)</td>
</tr>
<tr>
<td>Prevalence of obesity</td>
<td>30.9% (17)</td>
<td>ns</td>
<td>30.9% (17)</td>
</tr>
<tr>
<td>Prevalence of HT†</td>
<td>32.7% (18)</td>
<td>ns</td>
<td>38.1% (21)</td>
</tr>
<tr>
<td>Prevalence of DM‡</td>
<td>27.2% (15)</td>
<td>ns</td>
<td>27.2% (15)</td>
</tr>
</tbody>
</table>

*Nonsignificant (p>0.05) †Hypertension ‡Diabetes mellitus

For example, effects of body weight on BP were previously shown by us (23) that the prevalence of sustained normotension (NT) was significantly higher in the underweight (80.3%) than the normal weight (64.0%) and overweight cases (31.5%) (p<0.05 for both). Similarly, 55.1% of cases with HT had obesity against 26.6% of cases with NT (p<0.001) in another study (24). Again, the mean age increased gradually and significantly from the normal weight towards the obesity cases, parallel to the increased prevalences of WCH, dyslipidemia, hyperbetalipoproteinemia, HT, type 2 DM, and CHD in another study (25).

Eye diseases disproportionately affect the elders, who account for more than half of the persons visiting the ophthalmologists. The world population is aging rapidly with the number of persons aged above 65 years expected to be more than doubled from 2000 to 2035. As the population is aging, work of health care, particularly ophthalmology services, will increase as a consequence. Thus, determination of risk factors of diseases is important to decrease the increased demand on health services. Although the effects of metabolic syndrome on overall health is well documented, less is known about the ocular manifestations of the
syndrome. Among different eye diseases, obesity was linked with age-related cataract, glaucoma, age-related maculopathy, and diabetic retinopathy (16). Cataract is a multifactorial disease, influenced from various toxic factors, environmental stresses, and gene mutations (17). There are three principal mechanisms by which lens cells are damaged leading to cataract: oxidative stress, osmotic gradients, and glycosylation. The established risk and protective factors for age-related cataract such as DM, steroid use, and heavy smoking are all associated with one or more of these mechanisms. Excess weight may influence these physiological processes as well. Animal models support a role of calorie restriction for prevention of cataract (15). Although numerous population-based studies support an association between obesity and risk of age-related cataract (15,16), we detected neither a parallel nor an inverse relationship between reversible parameters or terminal diseases of the metabolic syndrome and cataract in the present study.

As a conclusion, metabolic syndrome may be a reversible progression step between complete physical health and terminal chronic diseases such as obesity, type 2 DM, HT, CHD, and stroke with the components of overweight, hypertriglyceridemia, hyperbetalipoproteinemia, impaired fasting glucose, impaired glucose tolerance, smoking, and WCH. Although the metabolic syndrome is significantly linked with many physical health problems, cataract cases do not have a higher prevalence of any reversible component or terminal chronic disease of the syndrome.

References
Central Corneal Thickness in Glaucoma Patients

ABSTRACT

Objectives: To investigate the relationship between central corneal thickness and intraocular pressure in glaucoma patients.

Patients and methods: This study was conducted at the Royal Medical Services during the period between March 2009 and March 2010. One hundred and thirty two patients diagnosed to have glaucoma were enrolled in the study. Exclusion criteria included patients with corneal pathology. Ocular examination included Snellen’s visual acuity, Goldmann’s applanation tonometry, slit lamp anterior segment examination and fundus examination using +78 lens. Central corneal thickness was measured using pachymetry.

Patients were classified into four groups according to intraocular pressure level. Group 1, for those with less than 10 mmHg, group 2 between 10-20 mmHg, group 3 between 20-30 mmHg and group 4 above 30 mmHg.

Results: The mean age was 54 years with a male to female ratio of 1.1:1. Central corneal thickness was highest in patients in group 1 (614.3 micron). Patients in group 4 had the lowest central corneal thickness (512.7 micron).

Conclusion: Central corneal thickness is an important test to be done in ocular hypertensive and glaucoma patients when they have their intraocular pressure measured by applanation tonometry, as patients with thick corneas may have false high intraocular pressure.

Keywords: central corneal thickness, glaucoma and applanation

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Introduction

Glaucoma is a disease where intraocular pressure is at a level sufficient to cause optic nerve damage and visual field loss (1-2). The most important factor when evaluating glaucoma patients is assessment of intraocular pressure. The universal technique of measuring intraocular pressure is applanation tonometry using Goldmann’s tonometer (3).

Goldmann’s tonometer measures the force required to applanate the eye to 3.06 mm diameter. The force required is a combination of opposition to intraocular pressure plus the force needed to bend the cornea (4). Therefore, the thicker the cornea the higher the force needed to bend and the thinner the cornea, the lower the force needed to bend (5).

Previous studies investigated the role of central corneal thickness measurement in patients with glaucoma (6-7). Corneal thickness can aid classification in glaucoma suspects between primary open angle glaucoma, ocular hypertension and normal pressure glaucoma. Measuring central corneal thickness was recommended by the ocular hypertension studies as it is a predictive factor for the conversion of ocular hypertensive patients to glaucoma (8).

The aim of this study was to investigate the relationship between central corneal thickness and intraocular pressure in glaucoma patients.

Patients and Methods

This was a prospective study that was conducted at the Royal Medical Services during the period between March 2009 and March 2010. One hundred and thirty two patients diagnosed to have glaucoma were enrolled in the study. Patients were randomly selected from those attending adult glaucoma clinics. Exclusion criteria included patients with corneal pathology. Ocular examination included Snellen’s visual acuity, Goldmann’s applanation tonometry, slit lamp anterior segment examination and fundus examination using +78 lens. Central corneal thickness was measured using pachymetry. Patients were classified into four groups according to intraocular pressure level. Group 1, for those with less than 10 mmHg, group 2 between 10-20 mmHg, group 3 between 20-30 mmHg and group 4 above 30 mmHg.
Results

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Percentage</th>
<th>Central corneal thickness (micron)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>8</td>
<td>6.3%</td>
<td>614.3</td>
</tr>
<tr>
<td>(IOP &lt;10 mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>65</td>
<td>51.2%</td>
<td>560.7</td>
</tr>
<tr>
<td>(10-20 mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>45</td>
<td>35.4%</td>
<td>543.1</td>
</tr>
<tr>
<td>(20-30 mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>9</td>
<td>7.1%</td>
<td>512.7</td>
</tr>
<tr>
<td>(IOP&gt;30 mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>127</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

The mean age of patients was 54 years, with a male to female ratio of 1.1:1. Five patients were excluded from the study due to corneal pathology. Central corneal thickness was highest in patients in group 1 (614.3 micron). Patients in group 4 have the lowest central corneal thickness (512.7 micron). Those in groups 2 and 3 had central corneal thickness of 560.7 micron and 543.1 micron respectively (Table 1).

Discussion

In clinical practice, the applanating pressure measured using an applanation tonometer is considered to be equal to the intraocular pressure (9). However, this is not true as there is a force required to bend the cornea. Patients with thick corneas have to use higher force to bend the cornea while those with thin corneas need a lower force.

Various methods have been used in past studies to measure central corneal thickness. They include optical pachymetry, ultrasound pachymetry, orbscan, optical coherence tomography, laser interferometry and ultrasound biomicroscopy (10-13). We used ultrasound pachymetry in our study. Ultrasound pachymetry is considered to be the standard of measuring central corneal thickness. The advantage is that it is fast and very convenient to repeat several measurements to minimize measurement error. It can also be used to measure peripheral corneal thickness (14). After topical anaesthesia with Novesin (0.4% benoxinate hydrochloride), an average of five contact measurements was made with the probe perpendicular to the cornea, similar to a previous study. The ultrasonic A-scan velocity was set at 1640 m/s for all measurements. Ehlers et al performed a number of studies in the 1970s assessing the effect of central corneal thickness and intraocular pressure. They found a deviation from this of IOP of 7 mmHg per 100 ?m. Johnson and his colleagues reported a patient with a central corneal thickness of 900 ?m with IOP of 11 mmHg but when measured by applanation, the IOP had ranged from 30 to 40 mm Hg.

The patients enrolled in our study were selected from glaucoma patients attending the glaucoma clinic at the King Hussein Medical Center. One hundred and thirty two patients were diagnosed to have glaucoma based on their intraocular pressure level, optic disc appearance and visual field findings. All patients were assessed by one glaucoma specialist. Cornea was examined using slit lamp and five patients were excluded from the study as they had corneal pathology. Slightly more than half of the patients had IOP between 10-20 mmHg with central corneal thickness of 560.7 micron. Nine patients had IOP of more than 30. This group of patients has thin corneas (central corneal thickness of 512.7 micron). Patients with low intraocular pressure have thick corneas.
In conclusion, central corneal thickness is an important test to be done in ocular hypertensive and glaucoma patients when they have their intraocular pressure measured by applanation tonometry as patients with thick corneas may have false high intraocular pressure.

References
Zinex cream as a prevention and treatment of uncomplicated skin lesions in infants

ABSTRACT

Objective: to determine the clinical efficacy of Zinex cream for the prevention and treatment of uncomplicated skin lesions in infants.

Patients and methods: The study was conducted at the Jordanian field hospital in Gaza from the period of 1st of September 2010 to 1st of January 2011. A total number of 233 patients were included in the study.

The inclusion criteria were as following: mild to moderate skin dermatitis with no signs of infection or complications. Male to female ratio was (1:1.4). Patients were categorized into two main groups; group (A) n=144 for whom clinical diagnosis was mild dermatitis, while group (B) n=89 who were suffering from moderate dermatitis. Age group for infants and children ranged from newborns to 12 months. Diagnosis was mainly based on clinical grounds. A specially designed form was used for each patient separately, which included age, gender, source of referral, presentation and diagnosis. Applications of Zinex cream 4-5 times daily were advised to mothers until symptoms disappeared. Follow up for patients after 5, 10 and 20 days were done.

Results: Most children had already tangible signs of improvement noted at 2-3-days from initiation of treatment. After 4 to 5 days treatment dermatitis manifestations disappeared in all children with mild dermatitis, while children with moderate dermatitis lasted slightly longer by 6 to 7 days. All children were encouraged to continue the use of Zinex for preventive purposes after symptoms disappeared.

Conclusions: Zinex cream is effective for prevention of most uncomplicated dermatitis in infants,(especially mild disease), and is safe to use with no adverse implications.

Key words: Zinex cream, dermatitis, infants

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Introduction

Dermatitis in general is a common disease in children less than two years of age. Its manifestations are observed in virtually every infant (1).

The protective function of skin in a young child is not sufficient because of its anatomical and physiological characteristics: a thin surface layer of the epidermis and a rich blood supply along with the different nature of the immune response to the impact of foreign antigens (2).

Dermatitis is usually provoked by the impact on the baby’s skin by the following factors: mechanical (cloth diapers), physical (humidity and temperature), chemicals (ammonia, digestive enzymes, and bile salts) and microbial factors acting within the cradle or nappy. The influences of these adverse factors make the skin of children vulnerable and easily prone to inflammation (3).

A lot of local treatment for dermatitis is by using various creams and ointments on the basis of zinc and talc, which acts through its adhesive properties that protect the skin from constant exposure to urine and faeces (3,4).

The high prevalence of irritant, xerotic and atopic dermatitis determines the need for improved methods of treatment.

Patients and Methods

The study was conducted at the Jordanian field hospital in Gaza from the period of 1st of September 2010 to the 1st of January 2011.

A total number of 233 patients were included in the study, who had the following diseases: irritant napkin dermatitis, xerotic eczema, and atopic dermatitis. The inclusion criteria...
was no recurrence during the follow up period. Factors, manifestations of dermatitis quickly faded and there were no re-observed with a new onset of dermatitis at day 20. Applications of Zinex cream 4-5 times a day were advised to patients until symptoms disappeared. Follow up for patients after 5, 10 and 20 days were done.

Results
A total of 231 patients out of 233 completed the study; two patients were excluded, one died from neonatal sepsis while the other had a complication in the form of infantile gluteal granuloma. Both patients were from the moderate grade group (B). Male to female ratio was (1:1.4) males n=98, while females were n=125. Most children already had tangible signs of improvement noted at 2-3-days from treatment initiation: decreased erythema and infiltration, dry and peeling skin rash disappeared, reduced (approximately twofold) affected area. At day five from treatment dermatitis manifestations disappeared in all children with mild dermatitis, however treatment of children with moderate dermatitis lasted slightly longer by 6-7-days, hence manifestations of dermatitis disappeared in 65 of 87 (74.7%) children at day five, while for the 22 (25.3%) remaining patients we extended the treatment for 5-6-days. All children after symptoms disappeared were encouraged to continue the use of Zinex cream for preventive purposes. Most children were not re-observed with a new onset of dermatitis at day twenty. Only in 4 children was a renewed slight erythema and papular rash in the crotch area observed. This was explained by their mothers due to irregularities in the diet (consumption of allergenic foods), reducing the frequency of nappy changes (up to 2 times a day). After elimination of these negative factors, manifestations of dermatitis quickly faded and there was no recurrence during the follow up period.

Table 1: Distribution of patients according to grade of severity

<table>
<thead>
<tr>
<th>Grade of severity</th>
<th>No. of patients</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild</td>
<td>144</td>
<td>61.8%</td>
</tr>
<tr>
<td>moderate</td>
<td>89</td>
<td>38.2%</td>
</tr>
<tr>
<td>total</td>
<td>233</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Table 2: Response of patients group to treatment during the follow up period

<table>
<thead>
<tr>
<th>Group (A)</th>
<th>Day five</th>
<th>Day ten</th>
<th>Day twenty</th>
</tr>
</thead>
<tbody>
<tr>
<td>144(100%)</td>
<td>144(100%)</td>
<td>144(100%)</td>
<td></td>
</tr>
<tr>
<td>65(74.7%)</td>
<td>87(100%)</td>
<td>83(95.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion
Among the most common uncomplicated skin lesions in infants is contact irritant dermatitis (CD), the frequency of which varies from 75 to 95% (5, 6). The most important mechanism, in triggering CD according to modern ideas is simultaneous action of urine and feces on the baby skin (7).

CD has a tendency to recur with some diseases in children, either due to increased sensitivity of skin and mucous membranes, or through predisposition to allergies, i.e. diseases of the gastrointestinal tract, that increase ammonia content in urine. Other skin lesions such as atopic eczema, seborrheic dermatitis, candidiasis, may also play a big role in the development of CD (8). Provoking factors for the occurrence of CD is also transferring the child to artificial feeding (pH feces in children on artificial feeding is shifted to the alkaline side with increasing ammonia content in urine), disorders of the skin micro flora, diarrheal diseases, in which the frequency of defecation, increases content and increases activity of enzymes that irritate the skin(9).

Atopic dermatitis (AD) is one of the most common allergic diseases of childhood. Its prevalence in children of developed countries ranges from 10 to 25%, while in the structure of allergic diseases the proportion of AD is 50-75% (5,10). Clinical manifestations of AD are rash, varying in nature (often vesiculopapular), intense prurigo (itching), dryness and infiltrative skin changes. The reasons that lead to the emergence of AD in infants, most often are: poor nutrition, early artificial feeding, early introduction of fruit juices and products, lack of knowledge of the rules of skin care of...
the baby, disturbances of normal skin flora and functional disorders of the gastrointestinal tract, infectious diseases, taking medications, as well as the presence of allergic diseases in parents or other close relatives. Without proper treatment of the early mild manifestations of AD it will be transformed into the full blown picture of children's eczema (10).

Even minor skin lesions, poor care (wet, dirty diapers), breaching the skin barrier, often leads to allergic (including severe forms of AD, infant eczema) and infection (pyoderma, furunculosis) disease and may cause the child anxiety, sleep disturbance, and decreased excretory function of skin. The biggest threat is the appearance of pathological changes of the skin in the neonatal period as they may be the cause of such extremely serious infectious diseases like pemphigus neonatal exfoliative dermatitis, Richter necrotic phlegmon, gluteal granuloma and neonatal sepsis (11).

Therefore, prevention and early treatment of uncomplicated skin lesions, especially in newborns and infants are extremely important. In this study we used Zinex cream to treat and prevent these mild manifestations and this was obvious in Table (2) which shows that at day 5 all patients with mild grade of dermatitis group (A) were cured, n=144, while in group (B), n=65 patients were cured at day five, however when time had been extended to ten days all of the patients were cured, n=87, so it is important to use effective and safe skin care for a baby.

We used Zinex cream in this study depending upon the physiological characteristics of infant’s skin; baby creams should have the following properties:

- Antiinflammatory (decrease signs of inflammation of the skin)
- Moisturizers and emollients (to remove dry skin)
- Antimicrobial (prevention and treatment of secondary infection of damaged areas of skin)
- Recover damaged epithelium; along with improve skin barrier function
- Should not contain components of dermal absorption which could have a negative impact on a child’s body (2, 4).

Zinex cream contains: zinc oxide, dimethicone, panthenol, soft surfactant, chamomile extract, wheat proteins, moisturizers, emollients and anti-inflammatory components (12).

The main components that are part of the Zinex formula have the following effects: mild surfactant provides efficient hydrophilic barrier to skin, chamomile extract works as anti-inflammatory and soothing effect, chamomile oil has anti-inflammatory effect and promotes wound healing; phospholipids, which are an important part of the natural moisture factor affecting the skin and skin surface pH regulation, Panthenol is a tool for outdoor use, stimulating epithelization of the skin, has an anti-inflammatory effect and also serves as a source of neutral fats. The active principle is a precursor of vitamin D-pantothenic acid. Pantothenic acid is essential for the formation of antibodies and it promotes the growth of the epidermis (1, 12, 13).

Conclusions
Zinex cream is effective for prevention of most uncomplicated dermatitis in infants, including newborns. It is also effective in the treatment of uncomplicated atopic, seborrheic, xerotic dermatitis (especially mild disease), safe in use and with no adverse implications, including allergies.

This study strongly recommends Zinex cream for a wide use in infants in the neonatal period.

References
Firstly we thank all regional academics and readers who took part in this survey and who contributed survey questions. The reply/return rate from academics was 73% and participating academics came from a range of universities and medical schools representing Iraq, Egypt, Lebanon, Saudi Arabia, Libya, Iran, Turkey, Pakistan, UAE and Jordan.

Your needs and wishes
Data from the survey returns, and comments, were remarkably consistent and showed clear needs and preferences of readers, practitioners and academics.

On the academic side, the free to air archives of previous issues were used ‘often’ by all but one respondent, (the highest response of the survey) making this a clear need as a research tool. While these archives can be accessed free on our own websites many respondents (also) wanted them on various databases that were either used or preferred by their national academic bodies.

Database presence
We are currently listed on Ebsco databases (including EbscoHost, DynaMed and Cinahl), and Al Manhal database and we have applied for listings on ISI. We will advise further once we hear.

While most of these databases are closed commercial entities we are seeking access to all databases requested by our readers.

All articles are being given a DOI (Digital Object Identifier) as they go on to the Al Manhal database.

In one Middle East country we have submitted the journals to the national academic bodies and have had them meet the national academic criteria, and become accepted, making this another route of journal acceptance for academics publishing their research.

Most readers wanted ‘an email reminder of new issues out’ and more CME. Both of these will be implemented as from next issue (February 2012) and you can click the following email address to be put onto the email distribution list for the Journal Alerts emails. Contact: admin@mediworld.com.au.

These Alerts will carry journal titles and their authors, for the current issue, with the ability to click directly to the online article.

Readers almost unanimously liked the variety of topics, the relevance of topics and the fact that regional issues were covered. They were also appreciative of the journals as a free resource and most have requested no advertising on the journals. A full report of both surveys can be found further below.

Impact factor / Health Index
These tend to be produced on a publishers’ own database (and therefore reflect that company’s or databases journals only) or can be worked out via formulae/statistics or via Google search engine.

The accepted formula is:

The impact factor for a journal is calculated based on a three-year period, and can be considered to be the average number of times published papers are cited up to two years after publication. For example, the impact factor 2011 for a journal would be calculated as follows:

\[ \text{Impact factor 2011} = \frac{A}{B} \]

A = the number of times articles published in 2009-2010 were cited in indexed journals during 2011

B = the number of articles, reviews, proceedings or notes published in 2009-2010

Impact factor 2011 = A/B

You can also use the following formula to find out the number of citations on an (your) individual author’s /academic’s own articles:

http://code.google.com/p/citations-gadget/

Take a sample 3 year old issue and apply these formulae to it.

Webstats
The other report we will make available to you on a quarterly basis will be sourced from our ‘webstats’ software which has been running behind the journals since their launch and where we’ve seen our combined journal readership grow until its current level of circa 1,000,000 readers / month.
The top (8) MESA/MENA countries reading the journal are: India, Egypt, Pakistan, Jordan, Saudi Arabia, Yemen, Turkey, United Arab Emirates, and Bangladesh.

The top international reader countries are: USA, Australia, United Kingdom, Russian Federation, Indonesia, Malaysia, Canada and South Africa.

Most used search engines are: b3090789.crawl.yahoo.net; crawl-66-249-67-18.googlebot.com; 213.186.122.2.ute1.net.ua; imparser12.yandex.ru; msnbot-207-46-199-37.search.msn.com

Most common access points (after a direct request for the website) are for articles on surgical management, antibiotic sensitivity, and CME.

Academic Survey
The reply/return rate from academics was 73% and contributing academics came from a range of universities and medical schools from Iraq, Egypt, Lebanon, Saudi Arabia, Libya, Iran, Turkey, Pakistan and Jordan.

Top three most read journals were: (1) Middle East Journal of Family Medicine/ World Family Medicine (MEJFM/ WFM),(2) Middle East Journal of Nursing (ME-JN) and (3) the Middle East Journal of Psychiatry and Alzheimers (ME-JPA). The latter was only launched in 2011 but its early high readership shows a regional need for information on this topic.

Most academic readers (75%) read ‘articles of interest’ mainly, but 10% read every article. All but one respondent accesses the archives ‘often’.

In regard to ‘new titles’ there was most interest in, in order, a Journal of Public Health, a Journal of Epidemiology and a Journal of Paediatrics. Other journal topics of interest to the region are: Medical Education and Accreditation; Women’s health and other issues related to women, Emergency Medicine; Social medicine.

Most academics did not want to see advertising in the journal.

Preferred article types were consistently:
* Original contribution/Clinical investigation
* Review articles
* Education and training
* CME

New topics academic readers would like to see covered include: Medical education research and operational research; Special Education and Evaluation

Consistently readers like the diversity of the topics, the relevance of the topics and the coverage of regional research.

Negative comments were: many wanted ‘theme issues’ and some wanted a colour cover/image. While the possibility of ‘theme issues’ will depend on the quality, number and type of articles submitted - we will in future provide a colour cover, but are conscious that this may add a cost to those organisations who print them out for their members so we would like to hear any negative feedback on this point.

Comments ticked in agreement (top 6 in order):
* I would like an email reminder that there is a new issue out.
* I appreciate that it is a free resource for doctors of the region.
* I would like to see more research
* The MEJFM deals in real medicine relevant to the Middle East region
* I am happy with the publication in its current form
* I would like to see theme issues

Most readers or authors would also like a pdf copy of the individual articles, in addition to the full pdf. This will be instituted from February 2012.

Academic Competencies
As some respondents answered nationally and others for their particular medical school we could not make national assumptions from the data collected. The following is a link to a recent article and survey done on this topic which probably provides a more complex overview. See: www. mejfm.com/July2010/globalcompetencies.htm

Research in the Region
Data showed:
Allocation of research budget to academic institutions has been graded as average to poor
Allocation of qualified personnel was graded as average to good
Most students have free access to online medical databases and a variety of databases are used, and there are no limits on which can be used free in most institutions
Most existing research facilities (computer and other) were graded average.

Most have compulsory research activities for students and most have established guidelines.

Most countries have: Subsidised medicine, Spreading/diffusion of medical insurance and Universal access to medical facilities and most found the focus of their medical school as socially accountable.

National situation
There were widespread shortages of both nurses and GPs/ family physicians reported across the region and primary care was undertaken in either hospital outpatients (mostly) or a variety of other locations such as government provided health centres, schools, health houses, industry, armed forces and other. The percentage of health and medical care provided through primary care was reportedly between 39% (Egypt) and 80% (Iraq).