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August 2012 Volume 8 Number 2
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Instructions for Contributors

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2. Rau JG, Wooten DC. Environmental impact analysis handbook. New York: McGraw-Hill; 1980.

3. Richardson AJ. Traffic planning and modeling: a twenty year perspective. Aust Road Res. 1990; 20(1):9-21.

4. Meyer MD. Public transportation in the 21st century. In: Gray GE, Hoel LA, editors. Public transportation. 2nd ed. Englewood Cliffs, New Jersey: Prentice Hall; 1992. p. 636-653.

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Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996, pp 30-45.
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The New Iraqi Journal of Medicine | **Research Article**
Pathology

Immunohistochemical expression of matrix metalloproteinase - 7 (MMP – 7) in human breast lesions

*Hanan Hussein Muhammad *, Alaa Ghani Hussein **, Ban Jumaa Qasim ****

Abstract

Objectives: to evaluate the Immunohistochemical expression of Matrix Metalloproteinase-7(MMP-7) in different breast lesions and to correlate this expression with different pathological parameters of invasive breast cancer "tumor size, tumor grade, lymph node involvement and lymphovscular permeation".
Methods: The study was retrospectively designed. A total of 70 paraffin blocks of breast lesions were included in the study, 30 cases were benign lesions and 40 cases were malignant tumors (insitu and invasive breast cancers). All cases were females.MMP-7 expression was assessed by immunohistochemistry using three steps- indirect streptavidin method.
Results: There was a statistically significant difference of MMP-7 Immunohistochemical expression in different breast lesions (P <0.001) .Frequency of cases with strong MMP-7 immunostaining was highest in invasive breast cancer (27.14%), followed by insitu carcinoma (11.42%), then atypical ductal hyperplasia (7.14 %). All cases of benign breast lesion did not show strong staining of MMP-7.
There was no significant correlation between MMP-7 immunohistochemical expression with tumor size, grade, lymph node involvement and lymphovascular permeation of invasive breast cancer .P-value is >0.05, 0.767 , 0.085 , 0.466, respectively.
Conclusion: MMP-7 immunohistochemical expression is sequentially increased during neoplastic progression from atypical ductal hyperplasia into insitu then invasive breast cancer; however, it is not related to tumor size, grade, lymph node involvement or lymphovascular permeation of invasive breast cancer.
The N Iraqi J Med, August 2012; 8(2):7-12
Keywords: *immunohistochemical, MMP-7, benign breast lesions, invasive breast cancer*

INTRODUCTION

Breast cancer is the most common cancer affecting women in the world today. It is the leading cause of cancer related death for women aged between 35 and 55 years worldwide [1]

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According to Iraqi Cancer Registry (2005), breast cancer in Iraq ranks the first among the commonest ten cancers by site and gender. There is a sharp increase in the incidence of this tumor in younger age group. [2]
Matrix-metalloproteinases (MMPs) are zinc-dependent enzymes responsible for the degradation of components of the basal membrane and extracellular matrix (ECM). While necessary for normal processes such as tissue remodeling during development, MMPs also facilitate pathologic states, such as tumor invasion and metastasis. Matrix-metalloproteinase-7 (MMP-7, matrilysin) is an important member of the MMP family that has broad substrate specificity against both extracellular matrix (ECM) and non-ECM components. Best known as a

contributor to tumor invasion and metastasis, a growing body of evidence also implicates MMP-7 in earlier stages of tumorigenesis, including cellular transformation, cell survival, tumor growth, angiogenesis, and evasion of immune surveillance [3, 4] Researchers have demonstrated that matrilysin is overexpressed in invasive cancers of the digestive organs and in cancers of other organs such as the lung, skin, breast, prostate, and head and neck. There is substantial evidence that the expression of matrilysin is associated with advanced clinicopathological stages and unfavorable prognosis. [5] MMP-7 is a small secreted metalloproteinase that differs from most other MMPs in that it is expressed in epithelial rather than only stromal cells [1]. MMP-7 is normally expressed in the breast, and has been shown to contribute to the development and proper branching of the mammary system in mice. In animals lacking MMP-7, reduced mammary lesions after chemical induction were found, while overexpression resulted in higher occurrences of mammary hyperplasia and accelerated tumor development. Significantly higher levels of expression have been found in breast carcinomas compared to adjacent non-tumor tissues. [4,6] It has been demonstrated that MMP -7 expression is higher in invasive breast cancer than in benign tumors and this overexpression is associated with invasion or metastasis and it is associated with advanced disease and decreased survival, by its ability to cleave extra-cellular matrix and extravasations at metastatic site. [7, 8] Studies reported that MMP-7 expression is associated with progression of carcinoma insitu from pre-invasive to invasive tumors. [9]

The aim of the present study is to evaluate the Immunohistochemical expression of Matrix Metalloproteinase-7(MMP-7) in different breast lesions and to correlate this expression with different pathological parameters of invasive breast cancer "tumor size, tumor grade, lymph node involvement and lymphovscular permeation".

Methods

The study was retrospectively designed. A total of 70 paraffin blocks of breast lesions were included in the study, 30 cases were benign lesions and 40 cases were malignant tumors (insitu and invasive breast cancers). All cases were females. The blocks were retrieved from archived material of Pathology unit of Al-Khadhmiya Teaching Hospital, Teaching Laboratories of Medical City Hospital, Al-Yarmook teaching hospital and private laboratories for the period 2008- 2010. The clinicopathological parameters were obtained from patients' admission case sheets and pathology reports. All cases underwent surgical operations for resection of tumors including 40 mastectomies and 30 excisional biopsies and all patients did not receive chemotherapy. An absolute confidentiality of the patients' vital information was maintained for ethical purposes and an ethical approval was obtained from institutions in which the study was carried out.

From each block, 2 sections of 5μm thickness were taken, one section was stained with Hematoxylin and Eosin (H&E) and slides were revised for type of tumor, histological grading (WHO grading system), and lymphovascular permeation of breast carcinoma cases. The other section was stained immunohistochemically using three steps- indirect streptavidin method for Monoclonal Mouse Anti-Human Matrix Metalloproteinase-7(MMP-7, Matrilysin); clone 3F264, manufactured by US Biological .Brown cytoplasmic staining is considered positive reaction. Positive control is gastric adenocarcinoma of intestinal type. Technical negative control was obtained by omission of primary antibody.

Scoring of immunohistochemical staining

Each immunohistochemically stained slide was scanned by a light microscope (Olympus, Japan) for the positive brown immunostaining and ten high power fields (40X) that reflect the best of the overall immunostaining were chosen for scoring of MMP-7 positive Immunohistochemical staining and the average of the ten fields was taken. Scoring scales 0-2 and included percentage of positively stained cells as well as staining intensity as follows: [10, 11]

0 = no staining

1=weak to moderate staining in 11–40% of tumor cells

2=strong staining in more than 40% of tumor cells

Statistical analysis

Data were analyzed using SPSS program (Statistical Package for Social Sciences) version 16 and Microsoft Office Excel 2007. Numeric data were expressed as mean± SEM, frequency was used to express discrete data. ANOVA was used to analyze numeric data while Chi-square was used to analyze discrete data. P< 0.05 was considered significant.

Results

Pathological study

The distribution of cases according to histopathological diagnosis is shown in table 1.

Type of breast lesion		No.[percentage]	Total
Benign	Fibrocystic disease	7 [10 %]	30[42.85 %]
	Fibroadenoma	6 [8.57 %]	
	Duct ectasia	1 [1.42 %]	
	Intraductal papilloma	3 [4.28 %]	
	Lactating adenoma	2 [2.85 %]	
	Tubular adenoma	1 [1.42 %]	
	Atypical ductal hyperplasia	10[14.28 %]	
Malignant	Ductal carcinoma insitu	9 [12.85 %]	40[57.14 %]
	Lobular carcinoma insitu	1 [1.42 %]	
	Invasive ductal carcinoma [NOS]	17[24.28 %]	
	Invasive lobular carcinoma	11 [15.71 %]	
	Invasive papillary carcinoma	1 [1.42 %]	
	Mucinous carcinoma	1 [1.42 %]	
Total		70[100%]	70[100%]

Table 1. Histopathological types of breast lesions

NOS=Not Otherwise Specified

Immunohistochemical study

There was a statistically significant difference of MMP-7 immunohistochemical expression in different breast lesions [P <0.001] .Frequency of cases with strong MMP-7 immunostaining was highest in invasive breast cancer accounting for 19 [27.14%], followed by insitu carcinoma in which 8 [11.42 %] cases showed strong MMP-7 staining then atypical ductal hyperplasia with 5[7.14 %] cases stained with strong intensity. No case of benign breast lesion showed strong staining of MMP-7. [(Figure 1 [Table 2)]. There was no significant correlation between MMP-7 immunohistochemical expression with tumor size, grade, lymph node involvement and lymphovascular permeation of invasive breast cancer [tables 3, 4, 5 and 6].

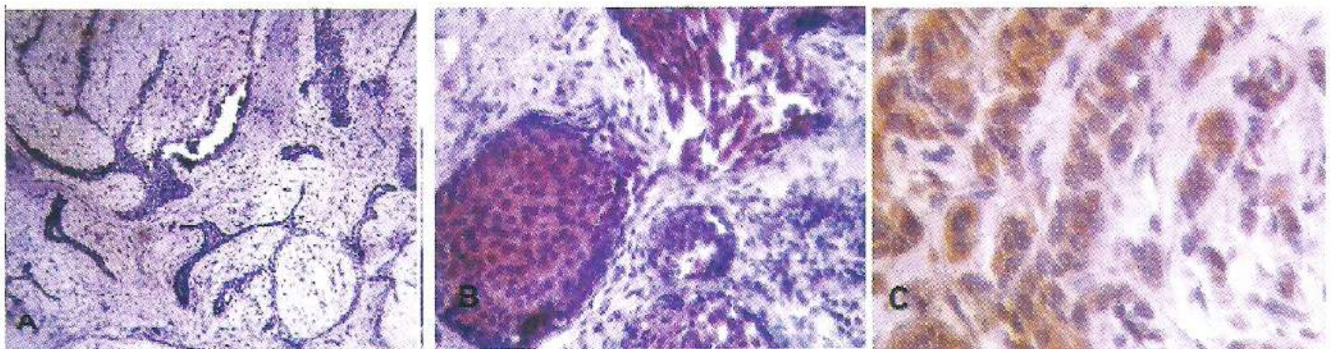

Figure 1. Immunohistochemical expression of MMP-7 in breast lesion. A. Fibroadenoma showing negative staining of MMP-7 [10X]. B. Insitu lobular carcinoma showing positive brown cytoplasmic staining with strong intensity [40X]. C. Invasive ductal carcinoma of no special type showing positive brown cytoplasmic staining with strong intensity [40X].

P=0.767 NS		MMP-7 stainingscore			Total
		0	1	2	
WHO grade	I	0 [0 %)	0 [0 %)	2[6.67%)	2 [6.67 %)
	II	2 [6.67 %)	7 [23.33 %)	14 [46.67 %)	23 [76.67%)
	III	0 [0 %)	2[6.67 %)	3 [10 %)	5[16.67%)
Total		2[6.67%]	9[30%]	19[63.33%]	30[100%]

Table 2. Immunohistochemical expression of MMP-7 in different breast lesions.

MMP7 staining score	Benign breast lesion	Atypical ductal hyperpalsia	Insitu carcinoma	Invasive carcinoma	Total	P-value
0	11 [15.71%]	2 [2.85 %]	0 [0%]	2 [2.85 %]	15[21.42%]	<0.001
1	9 [12.85 %]	3 [4.28 %]	2[2.85%]	9 [12.85 %]	23[32.85%]	
2	0 [0%]	5[7.14 %]	8 [11.42 %]	19 [27.14%]	32[45.71%]	
Total	20[28.57 %]	10 [14.28 %]	10 [14.28 %]	30[42.85 %]	70 [100%]	

Table 3. Correlation between MMP-7 immunohistochemical expression and size of invasive breast cancer (NS = Non-Significant).

MMP-7 score	No.[percentage)	Mean	SEM	Minimum	Maximum	P-value
0	2[6.67 %]	4.50	0.31	3.00	6.00	>0.05 NS
1	9[30 %]	3.50	0.84	2.50	6.00	
2	19[63.33%]	5.27	0.28	2.50	8.00	
Total	30[100%]	4.93	0.23	2.50	8.00	

Table 4. Correlation between MMP-7 invasive immunohistochemical expression and grade of breast Cancer (NS = Non-Significant).

Table 5. Correlation between MMP-7 immunohistochemical expression and lymph node involvement in invasive breast cancer.NS = Non-Significant

P=0.085 NS		MMP-7 staining score			Total
		0	1	2	
Lymph node involvement	negative	0 [0 %]	3 [10%]	3 [10 %]	6 [20 %]
	≥4	2 [6.67 %]	7 [23.33 %]	1 [3.33%]	10 [33.33 %]
	<4	0 [0 %]	9 [30 %]	5 [16.67 %]	14[46.67 %]
Total		2[6.67 %]	9[30%]	19[63.33 %]	30 [100%]

P=0.466		MMP-7 staining score			Total
NS		0	1	2	
Lymphovascular permeation	negative	0[0 %)	4[13.33 %)	6[20%)	10 [33.33 %]
	positive	2 [6.67%)	5 [16.67%)	13[43.33 %)	20 [66.67 %]
Total		2[6.67%)	9[30 %)	19[63.33%)	30 [100%]

Table 6. Correlation between MMP-7 immunohistochemical expression and lymphovascular permeation invasive breast cancer (NS = Non-Significant).

Discussion

This is, to the best of our knowledge, the first study in Iraq analyzing the immunohistochemical expression of MMP-7 in human breast cancer. It was shown that MMP-7 is aberrantly expressed in human breast tumors and that elimination of MMP-7 is associated with low invasiveness and slow tumor growth. [8] Likewise, it has been reported that MMP-7 overexpression in breast cancer [MCF-7] cells enhances cellular invasiveness and activation of proMMP-2 and MMP-9. [12]However, the potential role of MMP-7 in human breast cancer, and particularly in clinical breast cancer, has not been thoroughly investigated. [9]

In the present work, there was significant difference of MMP-7 expression among different breast lesion [P <0.001]. The highest frequency of cases with strong MMP-7 immunohistochemical staining was in invasive breast cancer, followed by insitu carcinoma then atypical ductal hyperplasia [27.14%, 11.42%, and 7.14 %, respectively] .All cases of benign breast lesions did not show strong staining of MMP-7. These findings are in accordance with other studies done by Luo et *al.*, Jiang *et al.* and Vizoso *et al.* [7,8,9]The significant increment of MMP-7 expression from atypical ductal hyperplasia into insitu breast cancer then invasive breast cancer suggests that MMP-7 is associated with progression of insitu carcinoma from pre-invasive to invasive tumors. [9]It has been reported that MMP-7 is overexpressed in late stages of breast tumor progression and often implicates metastasis. [13]On the other, Mylona *et al.* recorded that strong MMP-7 immunostaining was seen in 83% of invasive breast cancer cases with a non- significant correlation. This difference can be explained due to different sample size. [6]

Concerning the grade of invasive breast cancer ,strong MMP-7 was detected in mainly in grade II cases [46.67 %] ,however, statistically there were no significant correlation of MMP-7 expression and the grade of invasive breast cancer [P=0.767] in agreement with a study by Mavrommatis *et al*, which revealed that strong MMP-7 expression was seen mainly in grade II invasive cancer [51%]of cases but there was no significant correlation between the MMP-7 expression among the three grades of invasive breast carcinoma.[14] A study by Beeghly-Fadiel *et al.* showed that there was a strong association of MMP-7 expression with grade III invasive breast cancer .[3] Jiang *et al.* found that high MMP-7 expression was found to be associated with high grade tumors, advanced disease stage, and decreased survival in a study of 120 patients followed for a median of 120 months.[8]Mylona *et al.* reported an inverse association between MMP-7 expression and tumor grade. [6]These contradictory results could be explained by difference in the detection methods, sample size, scoring systems and small number of cases in different grades of breast cancer.

Regarding lymph node involvement and lymphovascular permeation, statistical analysis showed non- significant correlation between MMP-7 expression and these parameters of invasive breast cancer [P value = 0.466].This result is similar to the other studies [Mylona *et al.* Mourao *et al*,Vizoso *et al*]. [6, 9, 15]In conclusion, MMP-7 immunohistochemical expression is sequentially increased during neoplastic progression from atypical ductal hyperplasia into insitu then invasive breast cancer; however, it is not related to tumor size, grade, lymph node involvement or lymphovascular permeation of invasive breast cance

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P53 expression in cagA strain H. pylori gastritis (immunohistochemical and insitu hybridization study)

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Abstract

Objectives: To study the immunohistochemical expression of P53, as apoptosis makers in the gastric mucosa of patients infected with *Helicobacter Pylori* demonstrated by insitu hybridization method.

Materials and methods: Gastric antrum biopsies from 99 patients with dyspeptic symptoms (50 men, 49 women, median age 40) were analyzed for *H. pylori*, presence of chronic inflammation intestinal metaplasia and atrophy according to updated Sydney system. Insitu hybridization technique was done to detect cagA *H. pylori*. Immunostaining for p53 (Avidin- Biotin method) was performed on paraffin embedded tissue specimens.

Results: Forty four patients (44.44%) had H. pylori cagA positive starin. Atrophy of gastric mucosa was present in 14 (14.14 %) patients. Intestinal metaplasia was present in 8 (8.08%) patients. The frequency of atrophy was significantly higher in cagA H. pylori gastritis than non-cagA H. pylori gastritis ($p=0.041$). The frequency of intestinal metaplasia was significantly higher in cagA H. pylori gastritis than non-cagA H. pylori gastritis ($p=0.023$). P53 expression was significantly higher in H. pylori gastritis ($p= 0.001$), in cagA strain gastritis ($p= 0.001$), in the presence of atrophic gastritis ($p <0.001$), and in the presence of intestinal metaplasia ($p <0.001$).

Conclusions: CagA-positive H. pylori is associated with greater p53 expression. P53 protein is detectable in gastric mucosa before the appearance of dysplastic changes.

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Keywords: *cag H. pylori gastritis, p53 immunohistochemical expression.*

INTRODUCTION

Carriage of *Helicobacter Pylori* in the human stomach is associated with increased risk of peptic ulcer disease, distal gastric adenocarcinoma and gastric B-cell mucosa associated lymphoid tissue lymphoma.[1]

In developed countries, strains of *Helicobacter Pylori* that carry the cag pathogenesity island, a 35-40 Kb DNA fragment encoding a series of virulence-related gene associated with an extracellular secretory apparatus, are associated with a greater risk of peptic ulcer and adenocarcinoma than strains that are negative for cag island.[2.3] Because of the increasing realization that cell turnover is dependent not only on proliferation but also on apoptotic cell loss[4], and because it is now appreciated that many pathogenic bacteria are capable of interacting with the apoptotic program of epithelial cells[5], the effect of Helicobacter Pylori on gastric epithelial cells apoptosis also has been recently investigated. The presence of Helicobacter Pylori has been associated with a [2-5] fold increase in gastric epithelial apoptosis in vivo that returns to normal levels after eradication of the organism in most studies.[6,7] However in other studies, apoptosis was reported as unchanged[8] or even decreased in the presence of Helicobacter Pylori. [9]

The aim of this study is to study the immunohistochemical expression of P53, as apoptosis makers in the gastric mucosa of patients infected with Helicobacter Pylori demonstrated by insitu hybridization method.

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METHODS

The study was prospectively designed. A total of 99 adult patients presented with dyspeptic symptoms referred to the OGD (oesophagiogastroduodenoscopy) unit at Al-Kadhimiya teaching Hospital in Baghdad with an age range of 19-70 years (median 40 years) for upper endoscopy between June 2009 and March 2010 were included. In this study patients who had received anti-ulcer agents or antibiotics for up to two months before the examination and those who had histories of gastric cancer, gastric or duodenal ulcer, or gastric surgery, were excluded. The study was approved by the committee of ethical approval in the college.

Three tissue biopsies were obtained from each patient, two from the antrum and one from the corpus. Rapid urease test was performed on one of the antral biopsies. The other biopsy specimens were paraffin embedded and processed. One section from each block was stained by H&E to study the histopathological features and grading of gastritis was done according to the updated Sydney system. One section was used for In situ hybridization method to identify Cag-A starin *H. pylori*. One section was stained Immunohistochemically for P53.Two methods were used to identify H. pylori infection status; rapid urease test and histological sections stained with H&E stain. Patients were considered to be infected with *H pylori* if one or two of the tests were positive: rapid urease test, or histology. Patients were considered infection free when both of the two tests were negative. Immunohistochemical staining for p53 (fig. 7 and 8) was assessed semiquantitatively using a scoring system for both intensity (0, no staining; 1, weak staining; 2, moderate staining; 3, strong staining) and extent of staining (0, no nuclear staining; 1, greater than 10% nuclei staining; 2, 10–50% nuclei staining; 3, greater than 50% nuclei staining). The score for intensity and extent of staining was summed (total: 6) for each case.

In-situ hybridization (ISH) detection of cagA *H. pylori*:

In-situ hybridization technique uses biotinylated cDNA probe (for H. pylori cagA gene detection) together with Maxim's ISH detection kit. This complete hybridization and immune detection system, incorporates the biotion-streptavidin amplified technology to provide consistent results and maximum sensitivity to ensure economical and efficient use of the nucleic acid probs. A dark blue signal appears at specific site of the hybridized probe (fig.6).

Statistical analysis:

Statistical analysis was performed using SPSS 16 and Microsoft Excel 2007. Numeric variables were expressed as mean + SD. Chi-square test was used to study association between two discrete variables. T-test was used to compare the mean of numeric variables. A P-value of less than 0.05 was considered significant.

RESULTS

Histopathological assessment of gastritis

Histopathological assessment was done according to revised Sydney system. The results are shown in (table 1), and they were as follow:

1. Chronic inflammation was mild in 46 patients, moderate in 37 patients and severe in only 16 patients (fig. 1)
2. Active inflammation was present in only 34 out of 99 patients, and it was mild in most of the cases (29 patients) (fig. 2)

Relation between various histopathological parameters and cagA H. pylori status (cagA versus non cagA):

1. Chronic inflammation and CagA: The degree of chronic inflammation in the presence of cagA strain was significantly higher than that in the absence of cagA strain (mean score 2.11+0.65 versus 1.00+0.00; $p<0.001$).

2. Activity of inflammation and cagA: The activity of inflammation in the presence of cagA strain was significantly higher than that in the absence of cagA strain (mean score 0.90+0.64 versus 0.00+0.00; $p<0.001$).

3. Atrophy of gastric mucosa was present in only 14 out of 99 patients and was of mild degree.

4.Intestinal metaplasia was present in 8 out of 99 patients, and it was of mild degree (fig. 3).H. pylori infection was present in 69 out of 99 patients (44 were cagA positive), and it was of mild degree in most of the cases (fig. 4 and 5).

Score	Chronic inflammation	activity	atrophy	Intestinal metaplasia	H. pylori
0	0	65	85	91	30
1	46	29	14	8	60
2	37	4	0	0	9
3	16	1	0	0	0
Total	99	99	99	99	99

Table 1: The results of Histopathological scoring

Histological parameter		cagA H. pylori	Non-cagA H. pylori	p-value
Chronic inflammation	n	44	25	**<0.001**
	Mean score +SD	2.11+0.65	1.00+0.00	
Activity	n	44	25	**<0.001**
	Mean score +SD	0.90+0.64	0.00+0.00	
Atrophy	n	44	25	**0.041**
	Mean score +SD	0.22+0.42	0.16+0.37	
Intestinal metaplasia	n	44	25	**0.023**
	Mean score +SD	**0.18+0.39**	**0.00+0.00**	

Table 2: Relation between various histopathological parameters and cagA H. pylori status (cagA versus non cagA):

The degree of atrophy was significantly higher in cagA H. pylori gastritis than non-cagA H. pylori gastritis (0.22+0.42 versus 0.16+0.37; p=0.041). Also, the distribution of atrophy was more frequent among cagA H. pylori gastritis than non-cagA H. pylori gastritis (13/44 versus 1/25; p=0.011).

4. Intestinal metaplasia and cagA

The degree of intestinal metaplasia was significantly higher in cagA H. pylori gastritis than non-cagA H. pylori gastritis (0.18+0.39 versus 0.00+0.00; p=0.023). Also, the distribution of intestinal metaplasia was more frequent among cagA H. pylori gastritis than non-cagA H. pylori gastritis (8/44 versus 0/25; p=0.044).

P53 immunohistochemical expression

P53 expression was significantly higher in H. pylori gastritis than non- H. pylori gastritis (21/69 versus 0/30; p= 0.001). P53 expression was significantly higher in cagA strain gastritis than non- cagA strain gastritis (18/26 versus 3/22; p= 0.001). The p53 score was significantly higher in cag A strain H. pylori gastritis in comparison with cagA negative strain H. pylori gastritis (1.11+1.48 versus 0.24+0.59; p=0.006). P53 expression was significantly higher in the presence of atrophy in comparison with non-atrophic gastritis (13/14 versus 8/85; p <0.001). P53 expression was significantly higher in the presence of intestinal metaplasia in comparison with absence of intestinal metaplasia (8/8 versus 13/91; p <0.001

DISCUSSION

Atrophy and intestinal metaplasia

The sequence of events that have been suggested in the development of gastric carcinoma is chronic inflammation, mucosal atrophy, intestinal metaplasia, dysplasia and carcinoma [10].

The incidence of the precancerous lesions (atrophy and intestinal metaplsia) is variable in different studies. The percentage of atrophy, in those studies, ranged from 9 to 15 %; [11-13] while the percentage of intestinal metaplasia ranged from 35 to 42 %. [11-13].In the present study the percentages of intestinal metaplasia and atrophy were 8.8% and 14.14% respectively. Several studies have shown a significant positive association between *H. pylori* infection and development of gastric atrophy [14-17] and this finding is in accordance with the result of the present study. Other studies claimed that infection with *H. pylori* is responsible for higher rates of intestinal metaplasia [14, 17-19].Again this finding is in accordance with the result of the present study.

Some studies concluded that cag .A strain is the main pathogen behind the higher rates of gastric atrophy and atrophic gastritis; [18] which is again supports the result of the present study. Also those studies had attributed the higher rates of intestinal metaplasia to cag A strain. [18]This is also in accordance with the finding of the present study.

All of the eight cases of intestinal metaplasia were seen in chronic atrophic gastritis, and no intestinal metaplasia was present in chronic non-atrophic gastritis. According to these data, it can be concluded that *H. pylori* existence is an important factor for the development of atrophy and that atrophy can cause intestinal metaplasia. This finding is in accordance with Derya et al. [10]

P53 expression

Of greater controversy is the presence of immunohistochemically detectable p53 protein in *H. pylori* gastritis patients. Although it is generally agreed that p53 can be detected in dysplastic gastric epithelium [20-22] and intestinal metaplastic epithelium, [23, 24] its presence in nonmetaplastic, nondysplastic, and nonneoplastic epithelium is more debatable. In this study, 21 cases studied exhibited definite staining for p53. Besides staining for the glandular epithelium with intestinal metaplasia, it was also present in the adjacent nonmetaplastic, nondysplastic, and nonneoplastic gastric epithelium. Although this has not been the experience of Moss, our observations are similar to the findings of Jones et al [25] and Nardone et al [26] .This would imply that p53 immunohistochemical staining might not be used reliably to differentiate reactive epithelial atypia resulting from gastric erosions and/or inflammation and gastric dysplasia. A further controversy exists with regards to the nature of the p53 protein that is detected immunohistochemically in nonmetaplastic, nondysplastic, and nonneoplastic gastric epithelium. Jones et al [25]. considered this to be due to an accumulation of wild-type p53 protein that is detected because of the sensitivity of current antigen retrieval methods. However, there was no solid proof to support their contention that the protein is wild-type. In contrast, Murukami et al [27] sequenced exons 5, 6, 7, and 8 of the p53 gene in endoscopic samples of *H. pylori* gastritis patients without dysplastic or neoplastic changes. They identified non–hot spot codon mutations of the p53 gene in exons 7 and 8 in 11 of 21 endoscopic samples. This would indicate that *H. pylori* gastritis is associated with p53 point mutations and may be involved in the pathway leading to dysplasia or carcinoma. Nardone et al [26] also found positive immunohistochemical p53 staining in 15% of the *H. pylori* gastritis cases studied and attributed it to genomic instability associated with both chronic *H. pylori* infection and gastric atrophy. Further adding to the controversy are the recent findings of Marinone et al. [28] that were unable to find p53 mutations in their study of 130 patients with dyspepsia, of whom 47 had *H. pylori*-related gastritis. When we studied the patterns in p53 immunohistochemical staining in cagA-positive *H. pylori* gastritis cases and compared them with the cagA-negative gastritis cases, we observed that cases with more frequent p53 expression were from the cagA-positive cases. Overall, there seems to be a stronger association between p53 positive staining and cagA-positive than cagA negative strains. It is likely that some of our cases at least were due to accumulation of mutant p53 protein because of the higher rate of expression. We were also unable to detect the difference in the intensity of staining in intestinal metaplastic epithelium, which is associated with p53 mutations, and the adjacent inflamed but otherwise normal epithelium. This would be in accordance with the hypothesis advanced by Nardone et al. [26] that *H.pylori* infection can give rise to genomic instability and consequently p53 mutations. Nonetheless, the possibility that some of the p53 protein detected in our study, are wild-type proteins cannot be excluded

because p53 can be induced as a consequence of inflammation and cellular DNA damage. The cagA positive strain of *H. pylori* is more virulent and is associated with increased cell proliferation but decreased apoptotic activity when compared with cagA negative strains [29,30] However, this has been questioned by Moss et al [31] . who suggested that cagA positive *H. pylori* is associated with increased gastric epithelial cell apoptosis. If the p53 protein present in *H. pylori* gastritis patients is a consequence of mutation to a more stable mutant protein, this would explain the decreased apoptotic activity associated with infection by the cagA-positive strain. The strong presence of p53 protein in inflamed but otherwise normal gastric epithelium in *H. pylori* gastritis patients should also strongly caution against the use of immunohistochemical p53 staining as a diagnostic aid for the detection of gastric dysplasia.

CONCLUSION

GagA-Positive H. Pylori is associated with greater p53 expression. P53 protein is detectable in gastric mucosa before the appearance of dysplastic changes.

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Promoters and barriers to work: a comparative study of refugees versus immigrants in the United States

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Abstract

Background—Immigrants in general and refugees in specific are at risk for unemployment with detrimental effects on health and social well-being. Prior work has identified a series of barriers preventing employment among immigrants and refugees. However, these studies either fail to have a comparison group, or it is improper. The objective of this study is to compare unemployment determinants among culturally comparable Iraqi immigrants and refugees.

Method—A convenience sample of Iraqis residing in Michigan, who came to US after 2003, were surveyed covering socio-demographic aspects, prior and current job history, perceived barriers and facilitators to get a job, discrimination, and health.

Results—results show that refugees were twice as likely to be unemployed. Lack of language skills was a bigger barrier among refugees. The results indicate that immigrants are more successful than refugees in securing a job, even after taking their pre-migration and professional experiences into consideration.

Conclusion—This comparative study showed that refugees were more likely to have a difficult time in successfully finding a job. More attention is needed to help minimize the barriers that refugees face in the employment process.

Keywords

Professionals; Employment; Stress; Health

INTRODUCTION

According to both the United Nations and US government, a refugee is defined as a person who resides outside their place of birth and is unable to return to their place of birth due to

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racial, ethnic or religious persecution [1]. An immigrant, on the other hand, chooses to leave his or her country, often for economic reasons, and under the Immigration and Nationality Act (INA), they are granted legal immigrant status for three primary reasons: for family reunification, to provide a work force as U.S. employees, and for humanitarian concerns [2].

A refugee, like many people in the United States, must find employment enable to afford a decent living [3,4]. However, in addition to the employment troubles the United States is currently facing, refugees have added difficulties in finding jobs [3–6, 8] Prior research has shown that new refugees fall into one of two categories when seeking a professional vocation: either attain the same profession they held in their previous country of residence, or they are forced to work a low paying job. Many refuges, however, remain unemployed upon their migration to the US [4–8]. Several studies point out that language proficiency plays a critical role in the ability of refugees to attain a job. Due to the fact that many of them were not raised in the United States and have not been introduced to the English language well enough to communicate fluently, many refugees are having difficulties in obtaining a job. One of the top qualifications that employers seek is someone who masters the English language. A good background in English grammar and spelling is required in many jobs such as engineering, medicine, and teaching. It takes years of practice and schooling enable to fully master the English language. Unfortunately, refugees, specifically adults well past the grammar learning stag [8–10]. The difficult process of recertification of credentials and degrees was another stumbling block that decreased a refugee's chance of obtaining a job [8,11–14]. Refugees escape their place of birth in hope of escaping discrimination. Unfortunately, however, it seems that they also faced discrimination in the new country where they sought refuge. This discrimination played a role in their ability to gain an occupation, In fact, research has shown that discrimination proved to play a big role in affecting a refugee's chance of obtaining employment [5, 15–20] Strand reported that length of residence played a role in finding a job [3].

The study also showed that increased time will result in a higher utilization of programs, adaptation of the new culture, and increased knowledge of the labor market. This is in contrast to the study conducted by Krahn, which identified that factors such as language, work experience, and credential recognition to be the most important when finding a new job [8]. Having connections (networking) with people living in a culturally similar immigrant community who could potentially provide the refugee with a job could also promote employment [4–6] Other studies show that poor mental health is detrimental for many refugees in finding and maintaining a job in the new country [5, 6] Having a job is considered for many refugees as a source of satisfaction [5]. Physical problems (i.e. war injuries) could also adversely impact on their employability in the new country [5–20] Other interesting factors discussed are the individual's personality as well as work ethic, and determination [4, 5, 21] A major limitation of studies to date is the lack of either a comparison group of other immigrants or the comparison group consists of culturally and ethnically different immigrants. Some studies discussed above even compare refugees' job experiences with that of host country residents, clearly raising the concern for serious confounders. Since 2003, Iraqi refugees were ranked among one of the world's highest number of refugees.

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Data indicates that more than two million Iraqis have left Iraq since 2003 [22]. History shows that U.S. was able to overcome the problems generated by a growing number of refugee influx, notably when 1,330,000 Indochinese refugees entered the US in the spring of 1975 [4]. Other countries have had similar experiences particularly in Canada, United Kingdom and Australia [6, 8,19]. But refugees are not the only ones who are leaving their home country. The second group, immigrants are also leaving, possibly for the same reasons as the refugees, or, for different reasons. As these groups matriculate into their respective new countries, they will be differentiated based on their legal status. There is insufficient research comparing how these two groups fair in terms of employment, and whether obstacles and facilitators for employment differ between the two groups. The purpose of this paper is to explore this unknown, comparing culturally similar refugees and immigrant groups in terms of employment. Our hypothesis concludes that if given equal educational attainment, there would not be any observed difference between refugees and immigrant from Iraq. We further hypothesized that refugees, due to their higher level of assumed trauma exposure, would perceive more barriers to employment as compared to immigrants.

METHODS

Information about the study was announced on the local radio, after receiving approval from Wayne State University's Human Investigation Committee [Protocol # 0904007060]. One of the authors (H.J.) used the radio to reach out to the target audience, and then to contact and survey them either directly or by a phone number, which was provided by the surveyor. The information about the study was also disseminated to churches, mosques, party stores, gas stations, Arabic restaurants and other areas that Iraqi people usually attend, located in three Southeast Michigan counties (Wayne, Macomb, and Oakland).

Several Iraqi health care professionals, Iraqi graduated physicians, participated in the research project to conduct interviews on Iraqi refugees and immigrants. The volunteers were required to take a four hour training course on data collection. They were also responsible for contacting potential Iraqi participants to obtain further information and to secure consent. The Metropolitan Detroit area houses the largest population of Iraqis in the United States. Information regarding the name and address of the participants were not collected. However, the participants were required to write their first and last initials and their respective zip code to avoid duplication of the survey. The volunteer team was able to collect 396 surveys within a three month period (May–July, 2009). The survey included a range of questions regarding age, gender, health, and the occupation held before (Iraq) and after (Michigan) the migration process. The survey also questioned what the participant believed were factors involved in securing a job. A researcher reviewed the data to identify more recently immigrated persons, after 2003, in order not to work with a sample that had been in the United States for too long, irrespective of their legal status. We excluded participants (n=166) who entered the U.S. before 2003, those who were older than 65 years of age (n=11), and disabled (n=3). The remaining participants (n=218) represented the final study population. Some of the variables, e.g. number of years in the U.S., were dichotomized into those who arrived between 2003 to 2007 and 2008 to 2009, respectively. The reason for choosing 2008 as the cut-off point was because it marked the initiation of the global financial crisis. Data was analyzed using SPSS version 17.0. Chi-square tests, and

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Student's t-test, respectively, were used to compare differences in discrete and continuous variables between refugees and immigrants. Logistic regression was used to estimate the predictive value of various promoters and barriers between refugees and immigrants. We used logistic regression to predict dichotomous outcomes (e.g., employed vs. unemployed) after adjusting for pertinent socioeconomic factors, e.g., gender, as reported in the logistic regression models. Significance was set to a two-tailed p-value of <.05.

RESULTS

Table 1 shows demographic characteristics of both groups (refugees and immigrants). No significant differences between the two groups were found with respect to age, gender and education at attainment. There was, however, a significant difference between the two groups in terms of the period of residence in the U.S. Mean (±SD) for refugees was 1.86 (±1.31) years vs. immigrants 3.43 (±1.74). Furthermore, among refugees, 65.1 % were unemployed as compared to 39.9% of immigrants. Refugees were twice as likely to be unemployed compared to immigrants (OR 2.08; 95% C.I. 1.07–4.00), adjusting for age, gender and level of education. There were no correlations between immigration status and period of residency in terms of employment. Table 2 shows that before they came to America, most of the participants worked as professionals in Iraq. After immigrating to the US, refugees were less likely to secure a professional job than immigrants. Table 3 shows the results of the self-reported barriers to finding a job. There were significant differences between refugees and immigrant in terms of: language, lack of US professional knowledge, and health. Refugees were more likely to report poor language skills as a barrier to securing work as compared to immigrants (OR 3.61; 95%C.I. 1.21–10.73). There were no significant differences between the two groups in terms of having financial support or their ability to access professional training in order to help them find a job. As shown in table 4, refugees and immigrants rated their own health similarly. Immigrants were four times more likely to report that they enjoyed their jobs as compared to refugees (OR 3.72; 95% C.I., 1.38–10.06). Participants who worked as professionals, regardless of immigration status, were 18 times more likely to enjoy their work as compared to those who worked in non-professional jobs (OR 18.19; 95% C.I., 2.26–146.70). The results of this finding were taken after adjusting for age, gender and level of education.

DISCUSSION

The results indicate that immigrants were substantially more successful than refugees in securing a job. Moreover, immigrants were more likely to secure a job in accordance with their pre-migration and professional experience. Using logistic regression, control for age, gender, and level of education, refugees were also less likely to be satisfied with their job. Professionals in general, however, were more satisfied with their US jobs as compared to non-professionals. This is another consequence of being underemployed. Not only does society lack optimal return of human capital, it also results in more disenfranchised and dissatisfied immigrants. Refugees, despite their prior academic and professional achievements, had difficulties finding a matching job in the U.S. For example, none of the refugees holding doctoral degrees in medicine, pharmacy, or dentistry were able to find matching jobs in Michigan after an average of 1.8 years in the United States. In contrast,

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immigrants were substantially more successful in attaining the same job as the one they previously held back in their home country. Although the study identified numerous hindering factors for the refugees to acquire a job as compared to immigrant, those of primary concern include: language skills, lack of US professional knowledge, and health.

Additional research is needed to further elucidate the underlying mechanisms for these factors contributing to the higher unemployment rate among culturally and skills-based comparable refugees. Furthermore, in contrast to our hypothesis, there were no significant differences in job promoting factors between refugees and immigrants. The study thus suggests that more attention should be directed towards identifying barrier to securing work among refugees and not merely offering policy that focuses on job promotion. The latter strategy seems to be relevant for refugees and immigrants alike. Legal status appears to be a critical factor in the process of finding a job. This may be due to employers favoring an individual with regular immigrant status, or because immigrants are better prepared than refugees [4–6]. Immigrants clearly know well in advance which country they are relocating to, the steps that need to be taken in able to find a job, and the requirements they must meet enable to secure their job in the future. Refugees, on the other hand, are typically unaware of where they are moving to, and, as a result, are ill prepared [4–6]. This in fact may be the prime reason for the discrepancy between the success of refugees and immigrants. Even after adjusting for immigration status, age, gender, and education, those that had been in the US for 2 years or less were substantially less likely to have secured a job. This finding signifies the importance of early and proactive job and language training programs. It might be that immigrants, after a couple of years settling in, lose self-esteem and motivation, and consequently stop looking for a job. Our findings contrast to some earlier studies suggesting that length of stay in the new country is directly related to likelihood of employment [3], although other research supports our findings [8]. Neither group believed that their inability to find a job was due to poor health or discriminatory reasons. This is in contrast to some other studies [5, 6, 8, 20]. Poor health was discussed, as mentioned, to be a barrier to refugees' employment [5,6,20]. Refugees and immigrants alike strongly believe that having relevant labor market experiences in the United States were the most important factors in getting a job. Enrolling in training courses or making use of other support services did not appear to be helpful [4]. Immigrants reported that they were more satisfied with the jobs they held as compared to refugees. More immigrants were able to secure the same advanced jobs as they had held back home. For refugees, only 1 out of the 160 were able to successfully secure the same job as held back home, which might explain why refugees were substantially less satisfied with their current jobs [4]. In line with our findings, legal residence has been discussed in the literature as an important job promoting factor [4–6]. This factor plays a minor role in our study because all of our participants have legal residence in the United States. Language proficiency has also been identified as a critical factor for securing a job [8–10]. A much larger percentage of refugees in the current study reported that inadequate language skills were one of the main barriers. Some of our results do not support previously reported findings. As mentioned, employment plays a vital role in the wellbeing of an individual. Securing a job is the primary goal for immigrants and refugees alike Because of the rate of unemployment; we predicted that it would produce negative health effects, which was not the case, at least not over the short run. We

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specifically hypothesized that refugees would relate a great deal of their barriers to health issues, due to a multitude of reasons already mentioned in literature [5]. Overall, health was the least frequently reported barrier regardless of immigration status. Specific U.S professional knowledge has been considered in the literature as a powerful promoter of job success, but this finding was not substantiated in the current study [4–6]. The immigrants reported a much lower percentage of U.S. professional knowledge than refugees, but still were more successful. Early integration of refugees into the American society may also play an important role in improving language skills and improvement of socioeconomic status. If the newcomers integrate faster and more easily into the American culture, there will be measurable benefits to both the receiving country's social and economic structure and to the immigrants themselves [23] Refugees cannot expect full participation in the life of a new country if they are not recognized as a group with specific cultural and ethnic experiences and contributions. The analysis shows that threat to minority groups' identity is the greatest obstacle to social harmony [23] Social harmony is best achieved by maintaining, not weakening, subgroup identity [23].

Our results on discrimination does not support the notion that overt, or refugee-perceived discrimination, would contribute to refugees' higher unemployment [5, 8, 15, 20]. Overall, discrimination was the 2nd lowest barrier listed by the participants. Social networks may also provide information on alternatives to employment which may in fact facilitate economic assimilation. Bertrand found that larger communities who use welfare extensively encourage welfare usage among the new comers [24]. Montgomery's seminal theoretical work emphasizes the role of social networks in helping to overcome the problem of the lack of personal and professional references enable to resolve any doubts about unemployed individuals' capabilities. If members of a social network have better information about other members' credentials, then firms will use informal employee referrals to make hiring decisions [25].

We cannot assess precisely the effect of social networks on this population compared with other populations on the basis of the current study. However data from this study indicates that 28.6% of the immigrants included in this survey received some kind of support, especially family support, to find a job compared with 5.4% of the refugees. Thus, in conclusion, social networks seem to play an effective role in labor decision making of recently arrived refugees and immigrants.

Study limitation

Several study limitations are observed. First and foremost, is the use of convenience sampling. It is not clear if the data is representative of refugee and immigrant populations in general. Our results were based on a cross-sectional study, which limits our research. Finally, future studies need to cover a larger area of possible explanatory variables behind these findings.

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Conclusion and Recommendation

This comparative study showed that refugees were more likely to have a difficult time in successfully finding a job. More attention is needed to help minimize the barriers that refugees face in the employment process.

Service programs that expose refugees to the work force and provide "shadowing" opportunities in area of interest could prove to be very effective [15–19]. Such services would play a crucial role in informing newcomers about what they need to do to strengthen their likelihood of successfully competing for a job. Such programs could also implement other services like writing an effective resume, strengthening interviewing skills, and much more [15–19].

Finally, volunteering in the work force has been reported to be effective [8]. At the same time, policy and programs need to be adapted to the current economic situation with an overall high unemployment rate for both US born and immigrants. More research is needed in this area as both refugees and immigrants could play an important role in the economic development of countries, especially when they are highly educated.

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Table 1

Demography of Iraqi participants by legal status.

Logistic regression, adjusting for age, gender & education. There was no interaction between employment status and length of stay in U.S.

Variable	**Refugees (n=160)**	**Immigrant (n=58)**	**Total (n=218)**
Tears in U.S./Mean (±Std) ***	1.86 (±1.31)	3.43 (±1.74)	2.28 (±1.59)
Age/Mean (±Std) age *	41.85 (±9.72)	43.84 (±11.23)	42.38 (±10.14)
	No. (%)	No. (%)	No. (%)
Years arrived U.S. ***			
2003–2007	70 (43.8)	48 (82.8)	118 (54.1)
2008–2009	90 (56.3)	10 (17.2)	100 (45.9)
Gender			
Female	62 (61.3)	27 (53.4)	89 (59.2)
Male	98 (38.7)	31 (46.6)	129 (40.8)
Education *			
Bachelor's	103 (64.4)	30 (51.7)	133 (61.0)
MD, DDS, Pharmacy /	45 (28.1)	23 (39.7)	68 (31.2)
Master/Ph.D.	12 (7.5)	5 (8.6)	17 (7.8)
Work in U.S./Michigan ***			
Unemployed	104 (65.0)	23 (39.7)	127 (58.3)
Non-Profession	55 (34.4)	24 (41.4)	79 (36.2)
Profession	1 (0.6)	11 (19.0)	12 (5.5)
*P = n.s.; ***P< 0.001			
Likelihood of Unemployed	Sig.	Odds Ratios	95% C.I.
			Lower-Upper
Less than 2 years in U.S.	0.002	0.381	0.21–0.69
Refugees vs. Immigrant	0.029	2.08	1.08–4.00

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Table 2

Work status of Iraqi participants before and after immigrant to U.S. by legal status.

Work Status	Refugees (n=160)	Immigrants (n=58)	Total (n=218)
	No. (%)	No. (%)	No. (%)
Work in Iraq (P = n.s.)			
Non Professional Job	19 (11.9)	4 (6.9)	23 (10.6)
Professional Job	141 (88.1)	54 (93.1)	195 (89.4)
Work in U.S./Michigan (P <0.001)			
Non Professional Job	55 (34.4)	24 (41.4)	79 (36.2)
Unemployed	104 (65.0)	23 (39.7)	127 (58.3)
Professional Job	1 (0.6)	11 (19.0)	12 (5.5)

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Table 3

Major reported barriers or factors help to finding a job by legal status of Iraqi participants

Logistic regression, adjusting for age, gender, education, employment status, and length of stay in the U.S.

Self reported variable	Refugees	Immigrants	Total
	No. (%)	No. (%)	No. (%)
Major barriers to get employment			
No Job available *	57 (37.0)	21 (38.2)	78 (37.3)
Language ***	34 (22.1)	4 (7.3)	38 (18.2)
Lack of professional knowledge **	21 (13.6)	16 (29.1)	37 (17.7)
Financial support for training/family *	26 (16.9)	7 (12.7)	33 (15.8)
Discrimination *	11 (7.1)	7 (2.7)	18 (8.6)
Poor health **	5 (3.2)		5 (2.4)
Factor helping to get employment			
Have Experience *	32 (86.5)	9 (32.1)	41 (63.1)
Enter training course *	3 (8.1)	11 (39.3)	14 (21.5)
Different support * (E.g. family)	2 (5.4)	8 (28.6)	10 (15.4)
* P = n.s.; ** P < 0.02; *** P < 0.003			
Likelihood of language barrier	Sig.	Odds Ratios	95% C.I. for OR
			Lower-Upper
Refugees Vs Immigrant	0.021	3.612	1.21–10.71

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Table 4

Job satisfaction and self-rated health by legal status of Iraqis

Logistic regression, adjusting for age, gender, education, and length of stay in the U.S.

Self Report	**Refugees**	**Immigrant**	**Total**
	No. (%)	**No. (%)**	**No. (%)**
Enjoyment of work (P < 0.001)			
Strongly agree	1(1.8)	12(34.3)	13(14.4)
Agree	12(21.8)	10(28.6)	22(24.4)
Disagree	29(52.7)	10(28.6)	39(43.3)
Strongly disagree	13(23.6)	3(8.6)	16(17.8)
Self Rated Health (P = n.s)			
Excellent	30(19.1)	15(25.9)	45(20.9)
Very good	50(31.8)	12(20.7)	62(28.8)
Good	51(32.5)	18(31)	69(32.1)
Bad	22(14)	13(32.4)	35(16.3)
Very Bad	4(2.5)		4(1.9)
Likelihood Job enjoyment	Sig.	Odds Ratios	95% C.I. for OR
			Lower-Upper
Profession Vs Non profession	0.004	18.2	2.26–146.70
Immigrants vs. refugees	0.001	3.7	1.37–10.06

Vascular occlusive complications of homozygous homocystinuria and heterozygous hyperhomocysteinemia

*Anwar Sheikha**

Abstract

Background: Homocysteine has now evolved as an atherothrombotic risk factor standing in par with cholesterol and smoking in causing coronary, cerebrovascular, peripheral and venous occlusive vascular diseases. Homozygous homocystinuria is notorious for causing aggressive precocious arterial and venous occlusive complications. Despite some minor controversies, tens of major studies have recently shown that even mild and moderate hyperhomocysteinemia of the heterozygous variety could also be associated with major vaso-occlusive problems.

Patients and Methods: We report here a homocystinuria family whose two children were admitted with an aggressive course of arterial and venous atherothrombosis. One of the children was only three years old when she presented with a violent episode of gangrenous arterial vaso-occlusion. It is unusual for the vascular disease to antedate the other known features of this disease or show up in such a young age and with such a severity.

Results: Patients were found to have very high levels of homocysteine. This combined with the other phenotypic features of the disease, made the diagnosis clear. They both responded well to prompt diagnosis and aggressive management with anticoagulation and supplementation with folic acid, pyridoxine and vitamin B_{12}. They were discharged with minimal sequale of the thrombotic storm.

Conclusion: We conclude that although atherothrombosis is rare in children, one should always keep in mind the possibility of homocystinuria, especially if the other dysmorphic features are also noticed. If the homozygous form of this disease is so athero-thrombogenic, then there should be some grounds for the current homocysteine revolution as a cause for coronary, carotid and other atherosclerotic diseases.

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Keywords: *Homocystinuria,Hyperhomocysteinemia,Homocysteine,Vascular Occlusive Disease,Atherothrombosis*

INTRODUCTION

Hyperhomocysteinemia could be associated with both atherosclerotic arterial and thrombotic venous occlusive diseases [1,4]Homocystinuria is the rare homozygous form of the disease in which the homocysteine level is exceedingly high. The incidence of this inborn error of methionine metabolism is very rare at 5 per million live births. [5] It has remarkable clinical features and can easily be suspected on clinical grounds. It is this form of the disease that is usually associated with precocious atherosclerotic disease and symptomatic veno-occlusive complications at a relatively young age[1,2,6-8] Although normal at birth, with time, these children will develop ectopia lentis from inferior subluxation of the ocular lens, skeletal abnormalities resembling that of Marfan syndrome, scoliosis, pectus excavatum, high arched palate, mental retardation and malar flush [5] They are usually tall and thin with long limbs and arachnodactyly. They are usually seen wearing highly myopic eye-glasses. [5]

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The heterozygous form the disease is much more common in the population. Its incidence is reported to be between 5 and 10% of the population. [9-12] .The initial autopsy evidence of the association between homocystinuria and extensive arterial thrombosis triggered the search for a correlation between the much commoner heterozygous hyperhomocysteinemia and atherothrombotic vaso-occlusive diseases. [2] Since the initial report in 1976 of the association between hyperhomocysteinemia and coronary artery disease, numerous other reports emerged in favor of an independent link with cerebrovascular, carotid, coronary, peripheral arterial and veno-occlusive diseases [13, 4, 3, 6, 10,14-19] Hyperhomocysteinemia has now been identified as an independent risk factor linked with atherosclerotic heart and brain disease with an importance sometimes reaching that of high blood cholesterol and smoking. [18] Although enthusiasm about this strong pathophysiological role in atherosclerotic arterial disease has dwindled lately because of the presence of so many other associated adverse variables, but one cannot ignore tens of well-studied analysis that incriminated hyperhomocysteinemia as an atherothrombotic factor standing on its own.[4] If a disease is so thrombogenic in its homozygous state, then it is understandable to think about its heterozygous state as another risk factor for ischemic cardiac and cerebrovascular events. What makes this statement justifiable is the reward to be expected from prophylaxis against the ill effects of hyperhomocysteinemia. A tablet of multivitamins a day might be all that is needed against this evolving risk factor. [4, 3] We report here a homocystinuria family with two severely affected members. They presented with aggressive arterial and venous vascular occlusions. One of them was admitted with a profound athero-thrombogenic incident at a very early age of three years, even before showing the other known dysmorphic features of homocystinuria. This should forewarn us as to the speed at which this biochemical abnormality can lead to catastrophic occlusive vascular dilemmas. If the homozygous state has such a powerful atherosclerotic potential, then it should be a rule for every pediatrician to rule out the possibility of hyperhomocysteinemia in every child with coagulopathy and thrombosis. One-fifth of young children with thrombotic disease have heterozygous hyperhomocysteinemia and it is highly recommended to search for this possibility and manage it accordingly. [20]. it is noticed from this report, we could have easily missed the diagnosis in the second affected child if we were not aware of the presence of this inborn error of metabolism in the family. It is well warranted to consider starting the family on prophylactic multiple vitamin therapy, especially if they prove to have high homocysteine level, to avoid any possible long term ischemic problems. It is comforting to report that despite the aggressive nature of their presentation both of our patients responded well to our aggressive therapeutic anticoagulation and multivitamins and discharged with minimal sequale from the initial vascular damage.

PATIENTS AND METHODS

First Child: Patient was a ten year old girl who was referred from a peripheral hospital with a twelve hour history of inability to walk and swelling, pain and bluish discoloration of the toes of the left foot. Patient also showed swelling of the left thigh. She was seen by the vascular surgeon who thoroughly evaluated her and forwarded the diagnosis of deep vein thrombosis and distal arterial occlusion. On examination, the child was a tall thin girl with long limbs and arachnodactyly. Intellectually she did not seem bright. Her vital signs were normal. She showed swelling of the left lower limb with the diameter at the mid left thigh of 45 centimeters against 36 centimeter on a comparable point in the right thigh. Diameter of the left calf was 23 centimeter against 20 centimeter on the right calf. Toes of the left foot were bluish and shiny and the dorsalis pedis pulsation was absent. Other prominent features were scoliosis, high arched palate and pectus excavatum. She wore high myopic glasses and ophthalmic examination showed bilateral inferior sublaxation of the lens. The relevant points about her past medical history included: poor vision starting at the age of five years, for which she was prescribed glasses; diagnosis of mental subnormality in a referral hospital; nocturnal enuresis for which she put on Tofranil and the well-known fact in the family that she had a smelly urine. Family history was remarkable for having another younger sister with smelly urine. She had five siblings; all except one brother were tall and thin. Blood and biochemistry tests were all normal. Chest

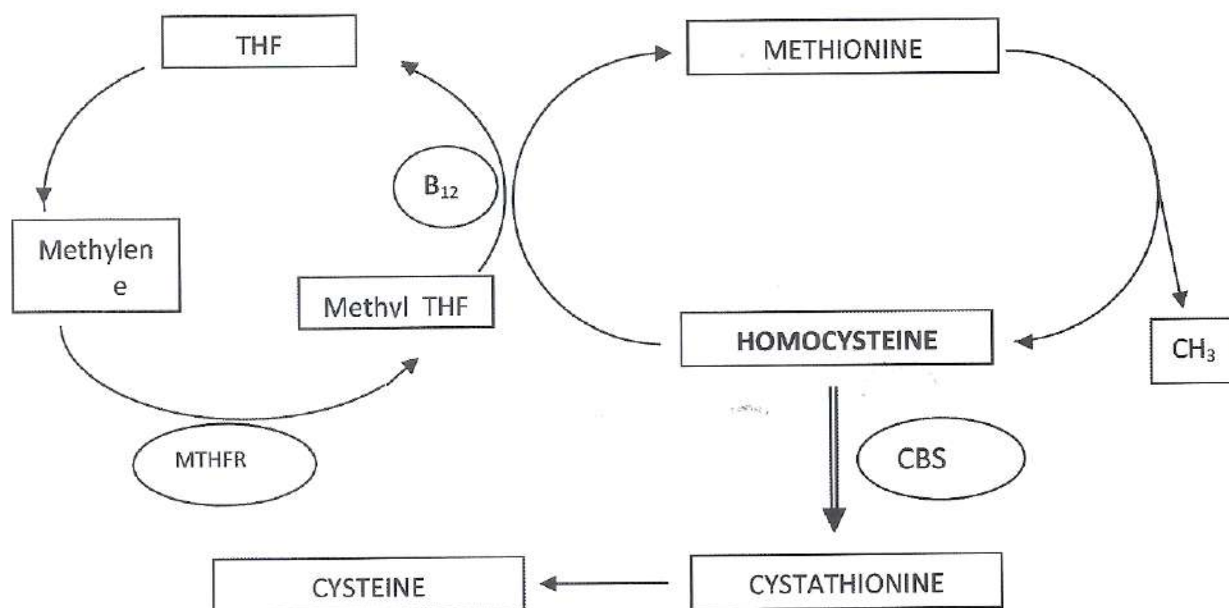
X-ray showed accentuated vascular markings. Abdominal ultrasound and echocardiography were normal. Venogram showed a large thrombus obstructing the femoral vein. It was difficult to tell about the proximal limit of the thrombus. Patency of the distal calf veins was normal. Based on these unique clinical presentations, the diagnosis of homocystinuria was clear. Tests done in a referral laboratory in Germany revealed a very high level of homocysteine. She was diagnosed as homocystinuria complicated by precocious thrombophilia and arterial occlusive disease. She was started on a full dose of therapeutic heparin followed by Warfarin. She responded well and discharged 16 days later with the swelling shrinking from the original 45 to 36 centimeters. She remained on Warfarin, Aspirin, vitamin B_6, vitamin B_{12} and folic acid. She did not show any more ill-effects of her disease in the outpatient follow up.

Second Child: A younger three year old sister of the first patient who was well-known to have smelly urine. She was urgently referred to our facility from a peripheral hospital after presenting with inability to walk and gangrenous right lower limb. She was conscious but looked quite sick and toxic. Her vital signs were in line with her clinical condition. Her weight was above 90% percentile at 15 kilograms. Unlike her previous sister, she did not show homocystinuria features of lens sublaxation, myopic glasses, high arched palate, arachnodactyly, mental problems or scoliosis. Short of very high creatinine phosphokinase, all other blood and biochemistry test results were normal. The right lower limb was cold and showed early evidence of gangrene. Right femoral pulse was absent. Angiogram showed embolic obstruction of the right iliac artery. Iliac and femoral artery embolectomy plus fasciotomy was performed by the vascular surgeon and then started on anticoagulation with heparin and Warfare. Skin grafting was done three weeks later with gratifying results. She was discharged on aspirin, folic acid, vitamin B_6 and vitamin B_{12}. She was seen on few occasions in the outpatient anticoagulant clinic with what seemed to be an excellent recovery.

DISCUSSION

Methionine is an essential sulfur-containing amino acid that can generate and donate methyl groups to variety of important reactions in the body. Homocysteine is an intermediate compound of methionine degradation. A detailed biochemical profile of the reactions involved in homocysteine metabolism cannot be accommodated in this article, but some knowledge of the main reactions is essential to understand this evolving issue (Fig. 1). The intracellular metabolism of homocysteine is regulated by two major pathways; it is either remethylated back to methionine with the help of methyl group donors like methyl tetrahydrofolate, vitamin B_{12} and the important enzyme methylene tetrahydrofolate reductase (MTHFR); or it will pass through the transsulfuration pathway to form Cystathionine and then cysteine. Cystathionine β-Synthase (CBS) is the enzyme required in this reaction and its deficiency is well known to cause homocystinuria and hyperhomocysteinemia [5]. Homozygous deficiency of CBS or MTHFR causes very high levels of homocysteine with the levels reaching above 100 μmol/L. The normal fasting value for homocysteine in the blood is 8-12 μmol/L in men and 6-10 μmol/L for women [20].Actually the level is said to be raised when it is two standard deviations above the normal mean. In suspicious hyperhomocysteinemia cases with normal fasting homocysteine level, methionine load test could be performed to increase sensitivity of detecting these patients [19].Homocystinuria is an inborn error of methionine metabolism due to homozygous CBS deficiency. This disease is highly athero-thrombogenic and the majority of these patients experience both arterial and venous thrombosis at a relatively young age. [21] Heterozygous deficiency of CBS and MTHFR creates hyperhomocysteinemia with the level of homocysteine far below what is seen in homocystinuria. Hyperhomocysteinemia of this type is also associated with major arterial and venous thrombovascular disease. [22,23] Other factors raising homocysteine level are folic acid deficiency, vitamin B_{12} deficiency, vitamin B_6 deficiency, renal failure and many drugs like nitrous oxide, methotrxate and antiepileptic druge [24,25] An interesting analysis combining the results of 38 studies greatly highlights the significance of association between hyperhomocysteinemia and vascular occlusion. 21.7% of coronary artery disease

patients, 26.6% of cerebrovascular disease patients, 32.8% of peripheral vascular disease patients and 13.8% of venous thromboembolism patients had a homocysteine level above 95% percentile[26,24] Hyperhomocysteinemia is a common abnormality and can interact with other atherogenic and hypercoagulable states to increase the chance of athero-thromboembolic diseases. Diabetes, high cholesterol, smoking, Antithrombin deficiency, Protein C and S deficiency and factor V Leiden can all synergistically compound vaso-occlusive complications of hyperhomocysteinemia .[18,20,27] A remarkable example emphasizes the magnitude of this synergism. The relative risk of deep vein thrombosis was 3.4 in the presence of hyperhomocysteinemia alone, 3.6 in the presence of factor V Leiden alone, but 21.8 when both hyperhomocysteinemia and factor V Leiden were present together.[27]The pathophysiological mechanisms responsible for vascular damage by homocysteine are complex. Hyperhomocysteinemia consumes and depletes nitrous oxide, induces subendothelial smooth muscle and collagen proliferation and inhibits repair of damaged endothelium.[4,28-30] Nitric oxide is an endothelium-derived relaxing factor that has many protective effects. It is a potent vasodilator; inhibits platelet activation and aggregation; inhibits proliferation of subendothelial smooth muscle cells, and neutralizes homocysteine. In hyperhomocysteinemia, nitric oxide is depleted and excess un-neutralized homocysteine inhibits glutathione peroxidase, resulting in formation of oxygen radicals that are directly toxic to the endothelium. [4] Hyperhomocysteinemia creates a hypercoagulable state through activation of clotting factors XII and V and increasing tissue factor activity. It also alters thrombomodulin function resulting in decreased protein C activation and reduced Antithrombin availability. It also impairs fibrinolysis thorough blocking of tissue plasminogen activity. [4] These events combined can easily explain the athero-thrombogenic potential of hyperhomocysteinemia. In this study, we report two sisters with homocystinuria who presented with severe arterial and venous thromboses at a relatively young age. They both had very high levels of homocysteine. With prompt diagnosis and aggressive management they went though the crises with minimal complications. With proper supplement of simple vitamins they did not show other vascular problems during the study period. These cases illustrate the destructive nature of homocysteine on the vasculature. The purpose of the study is to speculate from the severe form of the disease, what could happen with milder form of this biochemical abnormality. With hundreds of supportive studies there is little doubt now that hyperhomocysteinemia is a risk factor for both arterial and venous atherothrombosis.In conclusion, we stress on the importance of early diagnosis of homocystinuria and hyperhomocysteinemia in patients with atherothrombosis, because they can both be amenable to treatment. Even minor elevation of homocysteine is an independent risk factor for vascular occlusive disease and it should be taken seriously. Prophylaxis and treatment with folic acid, pyridoxine, vitamin B_{12} and betaine is cheap, safe, and appropriate and seems to be effective.



Homocysteine Metabolic Pathways

Abbreviations:

CBS:	**Cystathionine β- Synthase**
MTHFR:	**Methylene Tetrahydrofolate Reductase**
THF:	**Tetrahydrofolate**

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Research Article
Dermatology

Evaluation of the efficacy of 30% solution of trichloroacetic acid (TCA) in treatment of flat warts in comparison with 0.025% solution of tretinoin

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Abstract

Background: Treatment of plane warts is problematic, methods such as cryotherapy and cauterization is associated with high recurrence rate, risk of scar, pain and high cost. Topical tretinoin causes irritant contact dermatitis that limited its use. Trichloroacetic acid (TCA) is an analogue of acetic acid. It is widely used in biochemistry for the precipitation of macromolecules such as proteins, DNA, and RNA. Trichloroacetic acid in solutions of 50 to 90% is used in treating warts other than plane wart. The aim of this study is to evaluate the effectiveness of trichloroacetic acid (TCA) 30% solution and 0.025%: tretinoin solution in treatment of plane wart.

Materials and Methods: This study was a single blind, case-control study. Thirty-four patients with bilateral plane warts who signed informed consent were included The patients randomly used TCA and tretinoin solution at each side of the body for treatment period of 6 weeks Patients were examined at six weeks interval for 12 weeks and number of warts were recorded as well as side effects. The results were analyzed by Chi-square test statistically.

Results: After six weeks 46.7% of the lesions in TCA treated group disappeared versus 29.9% of the lesions in tretinoin treated group. This difference was significant (P-value <0.05).After 12 weeks 52.3% of the lesions in TCA treated group disappeared versus 48.3% of the lesions in tretinoin treated group.This difference was not significant.

Conclusion: Both tretinoin and TCA were effective in treatment of plane wart, but TCA seems to be more effective and need less duration i.e. Act faster than tretinoin.

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Keywords: *plane wart, TCA, tretinoin.*

INTRODUCTION

Warts are caused by human papilloma viruses(HPV) and more than 80 types of HPV have been described. Although some HPV types in the anogenital area can lead to dysplasia and cancer, most HPV infections cause histologically benign warts [1]. Flat (plane) warts or verruca plana are 2 to 4 mm, slightly elevated, flat-topped papules that have minimal scale. These are most frequent on the face, hands and lower legs. Wide spread flat warts occurs in patients with epidermodysplasia verruciformis (EV) that are usually caused by the same human papilloma virus (HPV) types as those found in flat warts in the general population(e.g., HPV 3, 10, 28 and49). In men who shave their beards and in women who shave their legs, numerous flat warts may develop as a result of autoinoculation[2].

Treatment of flat warts is a good idea because each lesion could be a source or reservoir for HPV and

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therapy will reduce the risk of spreading infection to the other parts of the body of the same patient and to the others. If lesions are few, light cryotherapy is used. Topical salicylic acid products can also be used. If the lesions are more extensive, treatment with topical tretinoin is indicated for its effects on epidermal growth. Imiquimod 5% has been recently introduced for the topical treatment of flat warts. Five-fluorouracil (5FU) cream 5% is also effective [3]. Pain, inconvenience and risk or scarring is associated with routine treatment methods such as caustics and acids application, cryotherapy and electrocautery. These problems are more in patients with face involvement due to cosmetic and psycho-social aspects of this area. All current treatments have about 50% complete response rate and 25-50% recurrence rate [4].trichloroacetic acid (TCA) 30% solute Trichloroacetic acid (TCA) is an analogue of acetic acid. It is widely used in biochemistry for the precipitation of macromolecules such as proteins, DNA, and RNA. Trichloroacetic acid in solutions of 50 to 90% is used in treating warts. Trichloroacetic acid application weekly for up to 6 weeks resulted in complete resolution of external genital warts in 70% of patients [5]. In concentration of 10-35%, TCA is used in light peel; while in concentration of 35-50% it is used for medium depth peeling [6].The aim of this study is to evaluate the effectiveness of trichloroacetic acid (TCA) 30%solution and 0.025% tretinoin solution in treatment of plane wart.

PATIENTS AND METHODS

A group of 34 patients (21female, 13 male) attending Department of Dermatology -Al Kadhimiyia teaching hospital- Baghdad from November 2010 till April 2011 were included after they had given written consent to take part in the study which was approved by the ethics commission of the Al Nahrain University-Collage of Medicine. The mean age of the patients was 18 years, ranging from 5 to 31 years. Warts had been present for 1 to 31 months before treatment, with a mean of 10 months in all groups. The diagnosis of flat warts was generally established clinically during the first visit; histological evaluation was only performed in doubtful cases. Exclusion criteria were pregnancy, breast-feeding, suffering from any systemic disease and the use of any other drug due to treatment of warts in past six weeks. Patients were then included in the study and seen every 2 weeks during the 6 weeks treatment period and at intervals of 6 weeks after the treatment period. For every patient admitted to the study, a detailed history was taken including age, sex, address , medical, drugs as well as number of the lesions in each area of the body which registered in checklist. In each patient, lesions of one side of the body were treated by application of 30% TCA solution which was prepared by adding 3o g of TCA crystals to 100 ml of distal water (TCA crystals from Riedel-de Haem- Germany) once every 2 weeks at clinic, while the other side were treated with 0.025% tretinoin solution (Domina-Syria), twice daily by patient himself. Solutions were applied on the lesions by the wood end of a cotton swab to minimize filtration of effective drug by cotton. A parent was applying tretinoin solution on the children who were aged less than ten years. The number of the warts in each side of the body and any adverse effect related to the study preparation such as burning sensation, pruritus, erythema or contact dermatitis were recorded in each visit. Evaluation of the efficacy of treatment was based on reduction of the number of warts. Statistical analysis was performed by the Chi-square test and value of P <0.05was considered significant.

RESULTS

Thirty four out of 40 patients participated in the entire study. Six patients were excluded due to irregular use of drug. Male to female ratio was13:21. The overall number of the lesions were 885.Four hundred and fifty lesions were treated by application of TCA solution and 435 lesions by tretinoin solution 0.025%.After 6 weeks, group treated by 30% TCA shows clinically significant improvement(the number of the lesions declined from 450 to 240) and the difference was statistically significant(P<0.05). Although tretinoin treated group shows decrease in lesion numbers from 435 to 305, this difference fail to reach statistical significance. At this point, all patients were asked to stop treatment and return back after further 6 weeks for follow up (Table 1).

After 12 weeks, the number of the lesions in group treated by 30% TCA declined from 240 to 215 which was statistically non significant. Although there is statistically significant difference when it is compared with pre-treatment values (P <0.05). Group treated by tretinoin shows clinically significant improvement (the number of the lesions declined from 305 to 225 and the difference was statistically significant (P <0.05) and such decline was also statistically significant when compared with pre treatment values (Table 1).After 6 weeks, chi-square test showed that efficacy of TCA 30% was superior and difference was significant statistically (P <0.05) in comparison with tretinoin treated

group. After 12 weeks, both agents seem to be effective and there is no statistical significant difference between effectiveness of both agents (Table 1).

*Statistically significant difference (P <0.05)

Lesion numbers	***TCA-treated group***		***Tretinoin-Treated group***	
	Count	Percentage	Count	Percentage
pre-treatment	450	100 %	435	100 %
Six weeks	240	53.3%*	305	70.1%
12 weeks	215	47.7%	225	51.7%

Table 1: Effectiveness of TCA and Tretinoin after 6 weeks treatment and after further 6 weeks of follow-up

Trichloracetic acid adverse effects were reported (percentage of occurrence) as follow: burning (12%), hypo or hyperpigmetation (9%), erythema (6%), dryness (6%), and pruritus (3%).Tretinoin adverse effects were reported (percentage of occurrence) as follow: burning (9%), hypo or hyperpigmetation (6%), erythema (9%), dryness (6%), and pruritus (6%).Table 2

Drug adverse effects	**TCA-treated group**	**Tretinoin-Treated group**
Burning	12%	9 %
Erythema	6%	9%
Pruritus	3%	6%
Dryness	6%	6%
Hyper-hypopigmentation	9%	6%

Table2: Incidence of adverse effects of both treatment groups

DISCUSSION

Since ancient times warts have represented a therapeutic problem. The contagious nature of warts was suspected as far back as 1823, but it was not until 1949 that virus particles in warts were first demonstrated. Today more than 50 subtypes of the HPV are known. The subtypes 3 and 10 are responsible for most cases of flat warts in infants and young adults [7].

The rate of spontaneous remission is very high in the first months of duration, but longstanding flat warts do not normally disappear by themselves. A number of therapies exist for such cases, but the cure rate is unfortunately low. Besides abrasive therapies, e.g. laser and curettage, cryotherapy is widely applied. Recurrence of flat warts occurs in 40-80% of patients after these conventional therapies and is therefore a major problem.[2] Topical tretinoin was first used in 1975. Subsequent experience suggests that higher than usual concentrations are needed for successful treatment, leading to more pronounced skin irritation[8].In this study, TCA 30% solution (applied topically once every 2 weeks) or tretinoin 0.025% solution (applied topically twice a day) for six week duration were evaluated in patients with plane wart. After 6 weeks, TCA seem to be more effective than tretinoin in reduction of wart lesion numbers. After 12 weeks, both TCA and tretinoin were almost equally effective in reduction of wart lesion numbers. Locally applied trichloracetic acid can be considered as a form of chemical cautery and is frequently used for treatment of anogenital warts. There are, however, no data on its efficacy compared with the most commonly used local application in treatment of plane wart. Trichloracetic acid, much like salicylic acid, cause focal destruction of the epidermis. Powell (1972) recommended trichloroacetic acid as a form of chemical cautery for the treatment of genital warts. It has an instant coagulant and desiccant action leading to necrosis of the superficial skin layers [9]. In addition to the local destruction associated with TCA, there is evidence that HPV DNA is damaged by TCA application. It is cheep, effective and safe during pregnancy [10].Up to our knowledge, this 1st time that effectiveness of TCA in treatment of plane wart is evaluated. Although, group treated by tretinoin shows some improvement after 6 weeks, such improvement fails to reach statistical significance. The peeling effect of tretinoin

could be an important therapeutic action, butit is possible that the peeling effect of tretinoin distributes virus to previously unaffected skin areas. Itching caused by tretinoin and followed by scratching could lead to the same phenomenon [11]. After12 weeks, statistical significant difference was found in both treatment modalities and this indicate that treatment with TCA need shorter duration than that with tretinoin because TCA was effective within 1st 6 weeks of therapy, while treatment with tretinoin need further 6 weeks to show statistical significant change. It has been well-documented that Tretinoin (all-trans retinoic acid) increases proliferation of basal keratinocytes and also the number of cell layers expressing the differentiation markers involucrine, loricrine, fillagrin and epidermal transglutaminase. These epidermal changes collectively translate to clinical desquamation and peeling and mediated by nuclear receptors of retinoids [12]. Many researchers have studied about plane wart treatment. In a randomized controlled study of 25 children, 85% of warts cleared with 0.05% tretinoin cream compared with 32% in controls [13]. In our study, efficacy of tretinoin was less (48.3%).Tolerability and patient satisfaction with both agents was comparable. Hyper-hypopigmentation and burning is the main adverse effects of TCA, while burning and erythema is the main tretinoin adverse effects.

CONCLUSION

Both tretinoin and TCA were effective in treatment of plane wart, but TCA seems to be more effective and need less duration i.e. act faster than tretinoin.

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Jordanian patients' and nurses' perceptions of cardiac patients' educational needs

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Abstract

Objectives: This study aims at comparing the perceptions of cardiac patients with those of cardiac nurses regarding the cardiac patients' educational needs.

Materials and Method: A research employing a questionnaire was conducted to find out what information categories first event cardiac patients and their nurses consider as being the most and least important. Accordingly, a non-probability convenience sample of 55 patients and 29 nurses was obtained from the Coronary Care Unit at Queen Alia Heart Institute (QAHI) at King Hussein Medical Center. The criteria for choosing nurses included (a) nurses who are licensed as Registered Nurses, and (b) work in the Coronary Care Unit at QAHI. For the cardiac patients, the inclusion criteria were being (a) adults of the age of 19 and above, (b) able to write and speak Arabic and (c) cardiac patients for the first time. The subjects of the sample completed the Cardiac Patients Learning Needs Inventory (CPLNI) which is composed of 37 questions categorized into eight groups. Each question was scored into one of five levels of importance. The results from the patient subjects were collected and compared with the results obtained from nurse subjects.

Results: The findings of this study revealed that there was no significant difference between responses of the patients and nurses at $P = 0.05$ in terms of what they perceived as the most and least important categories of information. Both patients and nurses ranked medication information as the most important and physical activities as the least important. There was agreement and congruency in the ranking order between the patients and the nurses in the four categories (medication information, anatomy and physiology, symptom management and physical activities).

Conclusion: The findings support the need for a cardiac rehabilitation program in Jordan that is based on the individualized patients' learning needs assessment.

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Keywords: Learning needs; cardiac rehabilitation program; educational needs; cardiac patient's perception

INTRODUCTION

Coronary Heart Disease (CHD) is highly prevalent in Jordan and is the leading cause of mortality and morbidity for both men and women [1].This show a similarity to the situation in the United State of America (USA) where it is responsible for the deaths of more than 2.3 million people each year [2, 3]. The risk factors associated with coronary artery diseases are smoking, hyperlipdemias, hypertension, obesity and diabetes mellitus. The combination of diabetes, hypertension, and smoking was associated with higher risk of CHD in women and men [3]. Some risk factors are modifiable and preventable through risk factors management [4]. Despite scientific research and technological advancements, Coronary Artery Disease remains the major cause of premature morbidity and mortality [2]. One approach to modify risk factors is through cardiac education, which aims at improving cardiac patients' survival, by means of bringing about changes in their life style, decreasing their anxiety and speeding up their post-cardiac events recovery (myocardial infarction) [4]. In order to gain the cardiac patients co-operation, cardiac education and rehabilitation should depend on patients' preference. Therefore, educational needs assessment of cardiac patients at the appropriate

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time can alleviate anxiety and stress [5]. According to Oermann [6], education benefits the cardiac patients in many ways. For instance, knowledge about their diagnosis helps them modify their life, enables them to care for themselves, and help them acquire information for making informed decisions that best suit their needs. Furthermore, due to the chronic nature of the coronary artery disease, risk factors modification is an area of educational importance that is found to be effective [7,8]. In which, early education of cardiac patients which is based on their educational needs can help patients reestablish the state of equilibrium and regain their social place within the society [8].

In USA and Europe, research which is based on the educational needs of cardiac patients suggest that after cardiac events, health education should focus on anatomy and physiology, lifestyle, medications, exercise, psychological effects and diet [8] Whereas, cardiac patients seek practical knowledge that helps them regain their normal life.

Nurses should identify patients' educational needs to enable them to develop a congruent health education program that focuses on the cardiac patients' perceptions of their own needs rather than focusing on their own personal perceptions of cardiac patients' needs. To achieve optimal level of cardiac patient's health education objective, nurses should possess the ability to identify the patient's perceptions and readiness to learn and accept the information which is relevant at this stage of the disease [3].

In Jordan, there is a lack of a well organized cardiac education program that is based on patients' educational needs assessment, depending mostly on nurses' and physicians' priority of educational needs. As a result, this study seeks to determine what information cardiac patients and nurses perceive to be of vital importance for them and whether the two groups differ in their views of the educational needs or not.

MATERIALS AND METHODS

The study utilizes a descriptive comparative approach in which a non-probability convenience sample of 55 patients (36 males, 19 females) and 29 nurses (6 males and 23 females) was rated according to CPLNI. The CPLNI is a questionnaire which was administered to the patients after uncomplicated attack of first cardiac event, and to nurses working at the coronary care unit at Queen Alia Heart Institute (QAHI) at King Hussein Medical Center. The study was conducted in 2009.The criteria for choosing nurses included (a) nurses who are licensed as Registered Nurses, and (b) work in the Coronary Care Unit at QAHI. For the cardiac patients, the inclusion criteria were being (a) adults of the age of 19 and above, (b) able to write and speak Arabic and (c) cardiac patients for the first time. Prior to conducting the study, it was approved by the Ethical Research Committee at QAHI/ King Hussein Medical Center /Coronary Care Unit. Obviously, there was no clear system or guidelines or any protocol concerning the type of educational information that cardiac patients received. Nurses and physicians were imposing their own beliefs about the educational needs or information to these patients. The CPLNI questionnaire, which was developed by Gerard (1984), was utilized in assessing patients' and nurses' perceptions of the importance of learning needs. The coefficient alpha, indicating reliability, for the total questionnaire was 0.91. The questionnaire consisted of 37 needs categorized into eight groups, and as follows; ("anatomy and physiology", "psychological factors", "lifestyle factors", "medication information", "dietary information", "physical activities", "symptom management", and "miscellaneous information"). Based on Likert scale, each of the 37 items, covering the aforementioned eight groups, was scored into one-to-five levels of importance, ranging from one (not important) to five (very important). The validity of the questionnaire in this study was reviewed by experts in QAHI. In addition, two demographic sheets were utilized within the study, one for the patients and one for the nurses. The cardiac patients' demographic sheet included: diagnosis, age of the patient, gender and educational level. The nurses demographic sheet included age, gender, number of years practicing as a registered nurse and cardiac nurse, degree in nursing, experience in teaching cardiac patients.

The researcher assistant approached the patients once their medical conditions allowed. The purpose of the study was explained, risk and benefits of participation in the study were described, and the right for voluntary participation and confidentiality were assured. Upon agreement, both cardiac patients and nurses signed a consent form, and then the questionnaire was administered. For special concerns of the patients' language, the researcher assistant helped the patients in clarifying any concerns related to the questionnaire. Upon the completion of filling out the questionnaire, the data was analyzed by using SPSS version 16. Descriptive statistics (mean and percentage) were used to characterize the sample in terms of demographics. Moreover, independent samples of *T*-test were used to examine differences in perceptions of educational needs cardiac patient's between cardiac patients and nurses.

RESULTS

Description of the sample

The sample consisted of 55 patients (36 males, 19 females) who were interviewed post-first cardiac events (myocardial infarction n=35, while angina n=20). The mean age of patients was 53 years (M=53) and their ages ranged from 23 to 84 years. Regarding the educational level of patients, thirty patients (54%) reported having a high school degree, ten patients (19%) had college level, and the remaining patients (n = 15) (27%) had secondary school level.

Table 1: Patient's characteristics N= 55.

Variable	Patients N	%
Gender		
Male	36	70
Female	19	30
Age in years		
Mean age	53	
Range	23-84	
Educational level		
College level	10	19
High school	30	54
Secondary school level	15	27
Diagnosis		
Myocardial infarction	35	64
Angina	20	36

Table 1, 2 summarize the patients and nurses demographic data:

The mean age the 29 (6 males, 23 females) nurses who filled out the questionnaire at the QAHI was 28 years ranging from 22-40 years. All of them are Registered Nurses and employed as military nurses. Their years of experience with cardiac patients ranged from 6 months to 10 years. Regarding the educational level of nurses, 26 nurses (90%) had diploma degree in nursing, 3 nurses (10%) had a bachelor's degree.). Table 2 summarizes the characteristics of the patients and nurses.

Variable	Nurses N	%
Gender		
Male	06	21
Female	23	79
Age in years		
Mean	28	
Range	22-40	
Educational level		
Diploma	26	
Bachelor's degree	90	
	3	10
Years as cardiac nurse (experience)		
1-5 years	20	69
6-10 years	9	31

Table 2 Nurses characteristics N=29

The results revealed that for the patients the most important educational needs were "medication information" (M= 4.35, SD=1.06). Symptom management (M= 4.23, SD=1.14), came second followed by "anatomy and physiology" (M= 4.20, SD=1.12), and Physical activity (M=3.47, SD=1.56) came last.

Learning needs category	Mean score out of 5	Standard Deviation
Medication information	4.35	1.06
Symptom management	4.23	1.14
Anatomy and physiology	4.20	1.12
Physical activities	3.47	1.56

Table 3 Learning needs as perceived by the patients N=55

Whereas, for the nurses the most important educational needs were "medication information" (M= 4.5, SD = .63). "Anatomy and physiology" came second (M= 4.4, SD= .60), then there was "symptom management" (M= 4.36, SD= .71), and finally "physical activities" (M= 3.76, SD=1.30).

Learning needs category	Mean score out of 5	Standard Deviation
Medication information	4.5	.63
Anatomy and physiology	4.4	.60
Symptom management	4.36	.71
Physical activities	3.76	1.30

Table 4Learning needs as perceived by the nurses N=29

The findings of the study revealed that, at alpha =0.05, there were no significant differences between the perceptions of the patients and nurses regarding the educational needs. Both patients and nurses ranked medication information as the most important and physical activities as the least important. See Table 5:

Learning needs category	T-test	*P value*
Medication information	3.44	.061
Anatomy and physiology	2.22	0.078
Symptom management	0.770	0.121
Physical activities	0.860	0.540

Table 5 Independent samples of *T test* for Differences between the Jordanian Patients' and Nurses' Perceptions of Learning Needs

Alpha=0.05 = *significance*. N of cardiac patients =55, N for nurses=29

DISCUSSION

The findings of the study provide information about how nurses and patients perceive the educational needs to be considered in developing health educational programs. Based on the data analysis, there was consistent evidence that the study subjects perceive the area of medication information as a top educational need. The patients in the study perceive that information regarding medications is the most important as an educational need (M =3.44, SD = .061) while they perceive physical activity (M = 3.76, SD = 1.30) as the least important. The overall results revealed that there is agreement and congruency in the ranking order between the patients and nurses in the four categories (medication information, Anatomy and physiology, Symptom management and Physical activities). Both nurses and patients perceive the medication information as the first educational need, followed by anatomy and physiology. Symptom management came third and the physical activities were deemed least important. The consistent findings of patients perceiving medication information as most important may be related to the nurses' own beliefs. The nurses may strongly emphasize the areas of medication information during discharge teaching, therefore, patients may perceive these areas most important. The findings of this study are consistent with and support the previous studies [5, 10, 9] although Turton's [11] found that there was congruency in the ranking order between nurses and patients, in which the risk factors were considered as the first priority. Hallstrom, and Elander [12] found no significant differences in the perception of learning needs between patients at medical and surgical wards and nurses working at different units. Other researcher found that nurses ranked medication information first whereas cardiac patients ranked medication information as the least important.

Ashton [7] conducted a study to assess the learning needs of men and women post-myocardial infarction and results indicated that women rated medication information as the most important learning needs while men rated risk factors as the most important learning needs. Gerard and Peterson [10] reported that cardiac nurses and nurses' educators ranked medication information as the top priority while patients ranked it as the least priority. Timmins and Kalizer [4] found that both patients and nurses gave the highest priority to symptom management and to "what to do to reduce the chance of another heart attack". Results of this study show that the overall responses of the patients differ to some extent regarding the physical activities from that of nurses'. Moreover, the results of the study revealed that both patients and nurses are more concerned about the medications. They might believe that medications can relieve signs and symptoms of the heart problem. Both nurses and patients focus on the physical aspects rather than the psychosocial aspects, and both of them are technically oriented. Furthermore, although nurses and patients placed physical activities as the lowest priority, it is crucial to emphasize the importance of physical activities that help patients in their recovery, adjustment of their daily lifestyle and prevention of further cardiac problems. According to Timmins and Kalizer [4], patients ranked physical activity at the bottom of their priority scale. Nevertheless, it is important to emphasize the importance of physical activity and its benefits for the overall wellbeing and survival of cardiac patients and it should be considered the core of health education programs for both patients and nurses. Since nursing and medical research focus on the importance of physical activity for rehabilitating cardiac patients, there is a need to educate the public and nurses to adopt healthy life styles. Cardiac patients and nurses were more technically oriented because they give the medication information the top priority, and they believe it is the best way to relive the symptoms. Also, both nurses and patients place physical activity as the least priority, which means that they are not well oriented to the importance of physical activity as one of the top priorities in rehabilitating the cardiac patients and adopting healthy life styles.

The small size of the sample of both patients and nurses and the fact that data is collected from a single site limit the diversity of the sample, therefore, limit the ability to generalize its findings.

CONCLUSION

This study is a preliminary study which used a small size sample; therefore, it needs to be replicated using a larger sample. However, the findings have the potential to assist nurses in designing tailored educational materials that are reflective of cardiac patient's educational needs. This will help cardiac nurses modify the patients' lifestyle and enable them to adapt to their conditions as well as to understand the importance of risk factors modification.

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Transverse excision with primary closure of pilonidal sinus: new surgical approach with review analyses of other surgical methods

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Abstract

Objective: To describe a new surgical technique for the treatment of pilonidal sinus in selected patients, with review analysis of other surgical methods.
Design: A prospective study.
Setting: From May 2000 to January 2006 at Al-Jamhori Teaching Hospital in Mosul.
Patients and Methods: Thirty-two patients with pre-sacral pilonidal sinus had been operated upon by a new surgical procedure after selection of patients from 80 sufferers according to special criteria.
Main outcome measures: The patients to whom the new surgical technique was applied had no acute infection, no previous operation in the natal cleft, no more than two sinuses and the distance between them not exceeded one centimeter. All other patients whom did not fit with these criteria were not involved in this study. The technique included a transverse excision of the sinus (es) down to the pre sacral fascia, washing the wound by povidon iodine, then by isotonic saline; the wound then is primarily closed by two layers transversely over a ridivag drain.
Results: There was no recurrence of pilonidal sinus after 48 months of follow up. Two patients developed wound infection (6%); one patient developed wound hematoma (4%). The hospital stay was not exceeded 8 hours. All the patients return back to their jobs within 10 days post operatively. The wounds appeared very cosmetic and acceptable by all the patients.
Conclusion: This type of surgery for pilonidal sinus is effective to those fit for the criteria used for their selection. It has fewer complications and no recurrence.

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Keywords: pilonidal sinus, natal cleft.

INTRODUCTION

Pilonidal sinus is a common disabling condition affecting young adults [1]. All surgical procedures for pilonidal sinus aimed for quick healing, no hospital admission, minimal patient's convenience, less complication and low recurrence rate. Although many different operative treatments have been suggested, still, no ideal one proved, since recurrence impairs the success of all form of therapy, as well as no method satisfies all the requirements for ideal treatment [2].

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PATIENTS AND METHODS

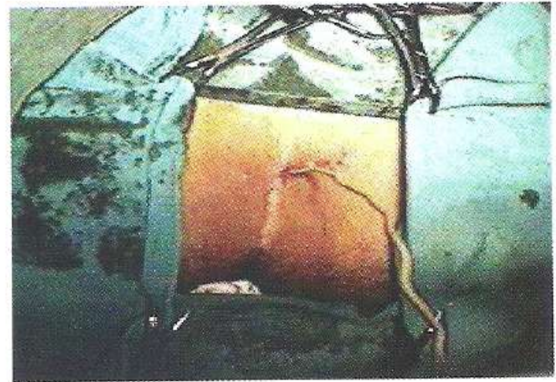
This is a prospective study that included 32 patients suffered from pilonidal sinus in the natal cleft. There were 29 male and 3 female (ratio of male to female was 9:1). The histories of pilonidal disease were extended between 3 months and 2 years with a mean of 10.5 months. There were 20 patients with single sinus (65%) and 12 patients with 2 sinuses (34%). Our patients were selected from 80 sufferers according to the following criteria:

1. *No previous operation in the natal cleft.*
2. No clinical evidence of acute infection or abscess at time of operation.
3. There should be no more than 2 sinuses.
4. The distance between the sinuses should be not more than 1 centimeter.
5. These criteria were fixed to about (45%) of patients with pilonidal sinus disease.

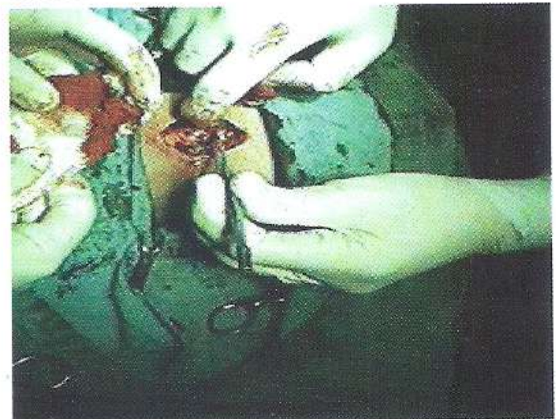
The operations were performed under general anesthesia in jack knife position, the hair were shaved at time of operation, the surgical procedure included a transverse excision of the tissue involving the sinus (es) with half to one centimeter of safety margin of normal tissue including the skin down to the pre-sacral fascia, adequate hemostasis were performed by electro-cauterization, the wound was irrigated by povidon iodine then washed by isotonic saline, the wound then closed in 2 layers, the subcutaneous layer by chromic cat gut and skin by interrupted silk suture with the avoidance of inserting stitches at the midline, the wound was closed over a redivag drain which was brought through one side of the wound and removed after 48 hours where the first dressing performed, as an out patient's visit.

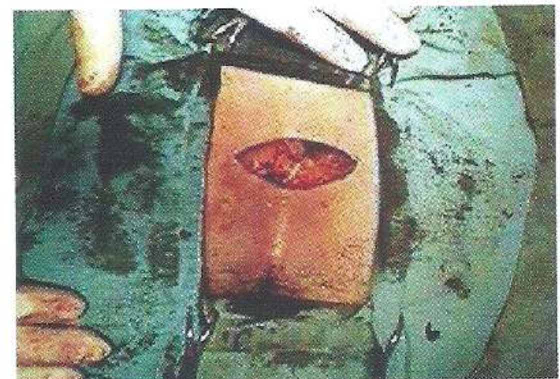
All the patients were discharged home in the same operative day (mean stay in the hospital was 8 hours),and received intramuscular diclofenac 75 mg post operatively and oral amoxicalve 500 mg with metronidazol 500 mg for 7 days after the operation. The silk suture was removed in the eighth post operative day during the second medication; they were allowed to take a bath and to return back to their usual physical activities in the tenth post operative day. The follow up of the patients continued for 48 months as an outpatient's visitors.

The following pictures demonstrate the operative procedures and post operative follow up.



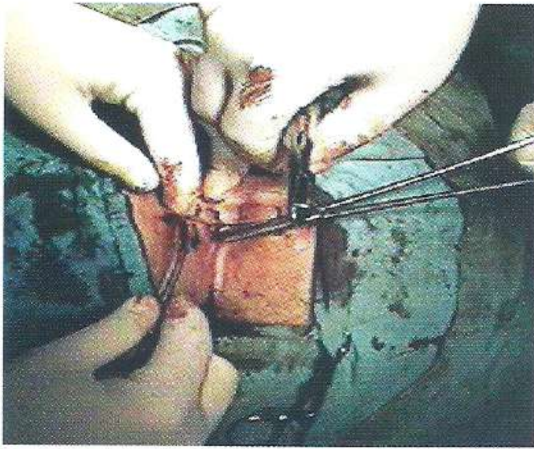
Probe inside the sinus

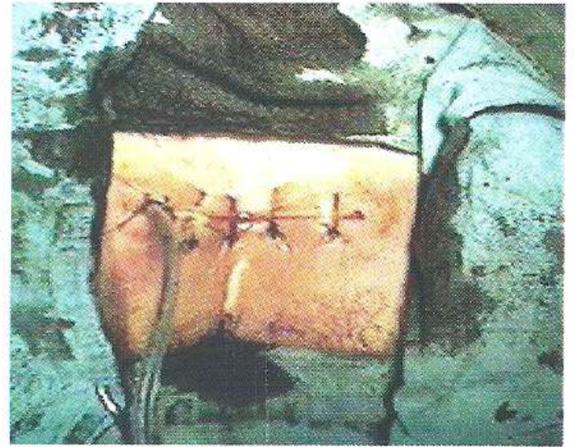




Transverse excision

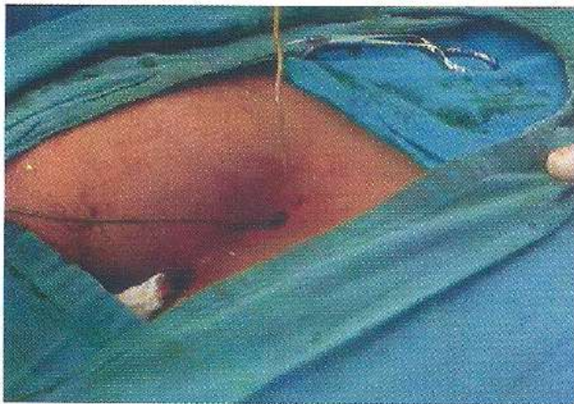
Hemostasis completed
Redivag drain inserted

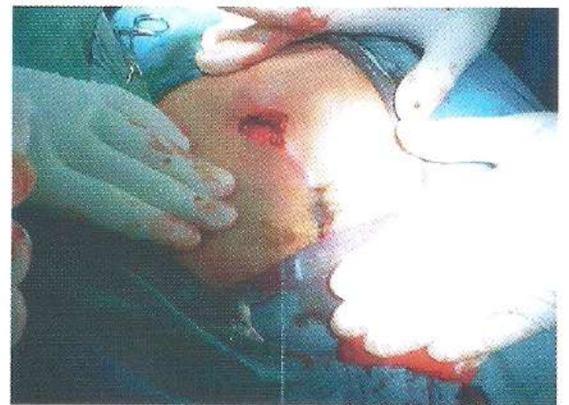




Skin suture

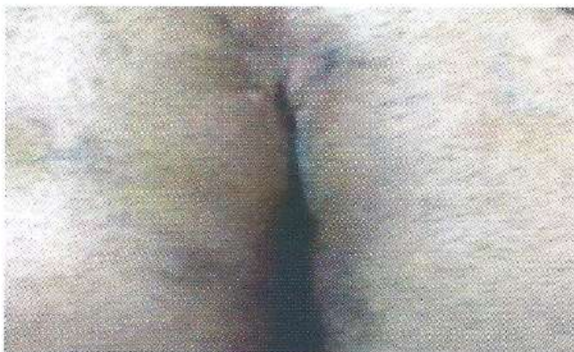
Operation completed

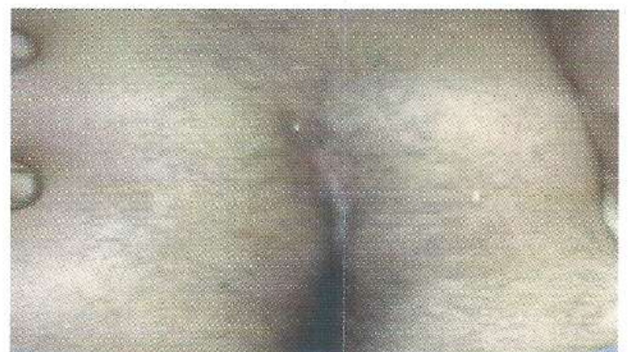




Patient with two sinuses

Removal of the hair tuft from the sinus





Six months after the operation

24 months after operation

RESULTS

Most of our patients were male (90%). Their age run with usual sufferers of pilonidal sinus (mean age was 27 years). All the patients under went uneventful recovery from anesthesia.

One patient (3.1%) developed wound hematoma with accidental fall of the drain early post operatively, the patient was treated conservatively and he did well. Two patients (6.52%) developed wound infection; their wounds became red, edmatous with induration. The silk sutures were removed, pus was sent for culture and sensitivity, the microorganism was staphylococcus in one patient and E coli in the other, their wounds were left opened and daily dressing were performed with the use of tailored antibiotic. Both patients did well and their wounds were closed by secondary intention within 3 weeks. No breakdown of wound was observed in any patients. All patients, except those with wound infection return to their daily work within 8 to 10 days' post operatively. During a period of 48 months of follow up, no evidence of recurrence of pilonidal sinus was reported.

DISCUSSION

Pilonidal sinus disease is a common problem; affecting mainly men from puberty to their early thirties [3].Definitely, there is no effective conservative treatment for pilonidal sinus[4], as well as it is not possible to identify a satisfactory surgical procedure for its management[3].Literatures agreed that, the ideal method of treatment should includes [1,2]:

1. Short hospital admission.
2. Less time of general anesthesia.
3. Quick healing.
4. Reduced number of complication.
5. Low risk of recurrence.
6. Minimal time off work.
7. Minimal inconvenience to the patients.

The majority of procedures can be classified in one of the four categories

Incision and drainage

Excision and healing by secondary intention

Excision and primary closure

Excision with reconstructive flap techniques.

In spite of ingenuous operative technique used for pilonidal sinus, no single one can rely upon to prevent recurrence of this benign, yet troublesome condition. The aim of surgery is to excise the sinus and crevice in which the hairs tend to accumulate, but the hair continue to present post operatively, which is the first post operative problem; the second problem is the weak scar and surface irregularity [5].

It is seems that recurrence is probably related to the anatomical status of the natal cleft. Distito-C et-al claimed that, modification of natal cleft by flattening it, together with meticulous hygiene and shaving of the pre sacral healing area as well as dietary regimen for obese patients-6- may decrease the recurrence rate.

The traditional method of surgical treatment of pilonidal sinus includes a wide longitudinal elliptical excision of the sinus with normal tissue down to the pre sacral fascia, the wound then closed primarily or left to heal by secondary intention. The advantage of primary closer are the early return to back to working activities, minor patient's discomfort, and reduced risk of infection-7-, as well as shorter healing time (10 days) in comparison with the open method (3 weeks)-8-. Actually there is no significant deference in the cure rate between the closed and opened methods -7-.

on the other hand, the recurrence rate after excision and primary closer is 17.5 to 20%-1-, while those with excision and secondary healing is 12 to 12.8% -8-9-.

The duration of work loss in primary closer is 1 to 3 weeks in comparison with 4 to 6 weeks in the open method-10-, apart from these, the wound in the open method needs a supervised wound care-4- until the scar become fully formed which may needs 45 days -11-. It is seems that, patients submitted to excision and primary suture had slightly but not significantly fewer early complication but there were less follow up visits, less sick leaves, quicker wound healing and it is cost effective-12-13, these finding are inconsistency with our work. The early post operative complication like infection and wound break down can be prevented by antibiotic, wound irrigation with antiseptic solution and wound drainage-10-.

From our study the primary closure (with transverse direction as in our series or longitudinal as in others) appeared to be the preferable surgical management, and the open method should be abandoned accordingly with other Authors-3-8-.

Because of the previous dilemma, new surgical procedures appeared, thinking that, changing in the anatomy of the natal cleft by flattening it or using asymmetrical closer of the wound may decrease the recurrence rate-2-. A lowest rate of recurrence was reported for reconstruction involving local flaps-14-. The aim is to divert the scar away from the midline.

Schoeller-T et al, by using modified fasciocutaneous V -Y advancement flap found an excellent functional result and acceptable scar without recurrence in his selected 24 patients within 4 years of follow up -15-.

Lemberg flap, which used by Ozgultekin et al, which direct the scar away from the midline, had no recurrence -16-. While the transposition rhomboid flap that used by Jemenez et al, showed no recurrence

within 12 months of follow up in his selected group but with 9 days of hospital stay-17-.

In the other hand, the use of gluteus maximumus muscular cuetaneous flap to facilitate wide excision and primary closer and to alter the anatomy of the natal cleft has been used in 5 selected patients and gained good results without demonstrable functional sequel-18-.

Lastly but not the least, Kitchen PRtechnique-19-, by using Karydakis flap or its modifications -20-21-, amid to lateralize the suture line and produce a shallow mid line furrow free from scar or suture holes (smeller to our technique) which become less vulnerable for hair penetration, this technique had only 4% recurrence rate in its 141 patients through 18 months of follow up.

From these views to the common and uncommon surgical procedures, we can say that, there is more than one right way for the treatment of pilonidal sinus-22-, the low risk of recurrence is certainly with the closed method and when the scar is minimum or away from the midline, the appropriate selection of the type of operation for each case appear to play an important role in prevention of recurrence-23-24-. This made the use of transverse excision with primary closer over a drain an acceptable procedure, after fulfillment of certain criteria, this procedure can be adapted to those without previous operation in the natal cleft in order to avoid weak scar, those with no more than 2 sinuses and the distance between them not more than 1 centimeter to facilitate primary closure without tension, as well as no infection at time of operation should present, to decrease the incidence of wound infection.

We can summarize the benefit of this technique by:

1- The scar well be parallel to the skin creases in the natal cleft, so the tension on the tissue become less; hence the breakdown of the wound well be abolished. (No wounds break down happened in our study) which is a reported complication in longitudinal closer-11-.

2- All researches regarding pilonidal sinus treatment agreed that, the weakest area is the midline scar, which is during friction, sweating or irritation, results in break down and production of a sinus and recurrence, as far as we use transverse incision, there is only one spot of scar at the midline (we avoid inserting stitches at the midline during suturing the skin), this may explain the absence of recurrence in this work.

3- The wound is far away from the anal verge, so the risk of infection from anal microorganism well be diminished (infection rate was 6% only in this study) which is more common problem in longitudinal incision where wound infection reported to be 13% - 13%.

4- The wound is above the setting site, this explain the less postoperative pain and the early mobilization and return back to the usual daily activities.

5- The end result of the scar appears to cause flattening of the natal cleft, which is a desired aim as a final result of the operation-2-.

6- This procedure can be applied to about 45% of patients with pilonidal sinus after adequate selection according to the criteria.

Lastly, it is worthy to say that hair removal from the natal cleft is very important procedure in prevention of recurrence of pilonidal sinus after operation regardless the surgical procedure used -25-, this can be achieved by many methods, actually, the efficacy of Alexandrite (755 nm wavelength) laser hair removal is now generally accepted and it is widely practiced in clinics with excellent results-26-.

CONCLUSION

Transverse excision with primary suture, a new technique for the surgical treatment of pilonidal sinus in selected patients appears to be save, simple and effective, it shows quick healing, less percentage of wound infection, early return to work and no recurrences, and we recommend it in patients fulfill the criteria for it.

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The nephroprotective activity of maidenhair, manna tree, and rowatinex in nephrocalcinosis model

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Abstract

Background: Nephrocalcinosis is a state of deposition of calcium phosphate or oxalate in the renal parenchyma with possible correlation to medicinal plants in the improvement of renal functions.
Materials and Methods: Thirty two healthy rabbits were used in the present study. Rabbits were allocated to four groups. Each group was given one of the followings: Maiden hair, Manna tree, Rowatinex, and distilled water. 2 hours later a large dose of oxalic acid administered orally and the same doses of aqueous extracts continued for 5 successive days. Blood samples were collected for biochemical analysis of renal functions before and after the induction at the 3rd and 5th days. Urine samples were examined to estimate the urine electrolytes in three occasions. Histopathological examination was conducted to check the deposited Ca^{++} in renal tissues and improvement of nephrocalcinosis.
Results: The obtained results revealed a highly significant reduction in the levels of BUN and both serum creatinine and K^+ and a highly significant elevation in the levels of both urine Na^+ and Ca^{++} as compared with the control group. The tested agents showed a significant increase in serum Ca^{++} levels except the Maiden hair also a reduction in Ca^{++} deposition of renal parenchyma with improvement in nephrocalcinosis severity.
Conclusion: Maiden hair, Manna tree, and Rowatinex showed nephroprotective activity due to their diuretic and antioxidant effect that reduce Ca^{++} deposition and improve the nephrocalcinosis with the possibility to be used for patients with renal stone.

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Keywords: *Maiden hair, Manna tree, Rowatinex, nephrocalcinosis, oxalic acid*

INTRODUCTION

Nephrocalcinosis (NC) is a state of deposition of calcium in the form of phosphate or oxalate in the parenchyma of the kidney. It is a process that can impair the kidney functions [1].It can occur in patients with hyperparathyroidism, renal tubular acidosis, vitamin D intoxication, and healing of renal tuberculosis [2]. The fragments of Ca^{++} salts may break freely from the kidney to provide nuclei for the formation of different types and sizes of stones accompanied with many symptoms [3]. These may be consequences of genetic, dietary, water intake, environmental, and occupational factors [4].It has been reported that barley and celery have nephroprotective effect due to their diuretic and antioxidant actions [5]. This study was carried out to explore the possible nephroprotective activity of *Adiantum capillus-veneris* (Maiden hair), *Alhagi graecorum Boiss* (Manna tree), and Rowatinex in experimental model of NC.

MATERIALS AND METHODS

Thirty two healthy rabbits, weighing 800-1000 gm were used. The animals were supplied by the animal house of veterinary collage. Each animal was kept in separated cages. They were fed standard oxoid pellets. Food and water was given *Ad libitum* to animals. The animals were allocated to four groups (each group contained 8 rabbits). All the extract of the tested agents were given at 9 am followed by oxalic acid 333 mg\kg orally administered at 11 am and then the same doses of aqueous extract continued for five days. Group-1 was given 3 ml of distilled water orally as a single dose before induction of NC by oxalic acid. Distilled water

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continued for 5 days.Group-2 was given aqueous extract of Maidenhair 1 gm/kg orally as a single dose followed by oxalic acid then the extract continued for 5 days. Group-3 was given aqueous extract of Manna tree 1 gm/kg orally as a single dose followed by oxalic acid then the extract continued for 5 days. Group-4 was given Rowatinex 0.1 ml/kg orally as a single dose followed by oxalic acid then Rowatinex continued for 5 days. The blood samples were collected from the heart for biochemical analysis and renal functions to determine blood urea nitrogen (BUN) and serum creatinine, K^+ and Ca^{++} in 3 occasions pre induction and post induction at the 3rd and 5th days by using spectrophotometer. Urine samples were taken from the animals by using metabolic cages, in which the animals were kept. Samples were measured in 3 occasions as in the blood samples. Histopathological examination was conducted to check the Ca^{++} crystals deposition in the renal tissues with the help of polarized microscope. The aqueous extract of medicinal plants was prepared by diluting one volume of well grinded plant (the roots of manna tree or the stem and leaves of Maiden hair) to 10 volume of water at 80 C^0 in stopper flask. After shaking well, it is allowed to stand for 10 minutes then cooled and filtered to be used within 12 hours [6]. Statistical analysis was done by using SPSS version 19. Analysis of variance (ANOVA) was used to compare between all the groups. Paired sample t-test used to find the difference between any treated group with control group with significance $P<0.05$.

RESULTS

The obtained results of Maiden hair, Manna tree, and Rowatinex as recorded in the 3rd and 5th days revealed a significant elevation in the levels of BUN and both serum creatinine and K^+. When compared with the normal values of analytes (Table -1) but they were significantly reduced when compared with control group-1 after induction of NC (Table -2). The serum Ca^{++} levels of all tested agents were significantly reduced at the 3rd and 5th days except Rowatinex when the results compared with the control group (Table -3). The urine Na^+ and Ca^{++} of the tested agents showed a significant increase at the 3rd and 5th day as compared with control group (Table -4).

The histopathological examination was achieved in the last day of the study to confirm the occurrence of NC and to compare between the control group and treated groups. There was no necrosis in all the tested groups with very mild inflammation and moderate Ca^{++} deposition when compared with the control group.

ANALYTES	MEAN LEVELS (mmol/L) ± S.D.
blood BUN	5± 0.7
serum creatinine	78.8± 1.25
serum potassium	4.5± 0.4
serum calcium	2.85± 0.16
urine sodium	88.4± 1.6
urine calcium	3± 0.5

Table (1): The blood BUN, serum creatinine, potassium, and calcium levels with urine sodium and calcium levels of the tested groups measured before induction of nephrocalcinosis by Oxalic acid.

Group	Agent	Dose	BUN (mmol/L)		Serum (mmol/L)	Creatinine
			After 3 day	After 5 days	After3 day	After 5 days
1	Oxalic acid	333mg/kg	8.2±0.05	9.5±0.4	96.5±0.6	103±1.2
2	Maidenhair	1gm/kg	6.9±0.2**	6.1±0.16**	87±0.2**	81.2±0.2**
3	Manna tree	1gm/kg	7±0.2**	6.2±0.16**	88.7±0.3**	79.9±0.8**
4	Rowatinex	0.1 ml/kg	6.59±0.1**	5.9±0.5**	90.1±0.5**	84.2±0.6**

Table 2: The mean of BUN and serum creatinine levels of the tested agents measured after induction of NC
** = Highly significant difference ($P \leq 0.001$) as compared with the control group.

Group	Agent	Dose	S K^+ (mmol/L)		S Ca^{++} (mmol/L)	
			After 3 day	After 5 days	After3 day	After 5 days
1	Oxalic acid	333mg/kg	5.1±0.19	5.4±0.35	1.58±0.1	1.4±0.07
2	Maidenhair	1gm/kg	5±0.12(NS)	4.6±0.12**	1.9±0.08**	1.69±0.16(NS)
3	Manna tree	1gm/kg	5.1±0.07(NS)	4.7±0.09**	1.9±0.1**	1.79±0.07*
4	Rowatinex	0.1 ml/kg	4.9±0.09*	4.6±0.19**	3.1±0.1**	3.2±0.2**

Table 3: The mean of serum K^+ and Ca^{++} levels of the tested agents measured after induction of NC
* = significant difference (0.001 < P ≤ 0.05), ** = highly significant difference (P ≤ 0.001), NS = No significant difference (P>0.05), as compared with the control group.

Group	Agent	Dose	urine Na^+ (mmol/L)		urine Ca^{++} (mmol/L)	
			After 3 day	After 5 days	After3 day	After 5 days
1	Oxalic acid	333mg/kg	89.5±0.6	90.9±0.7	3.8±0.11	4±0.13
2	Maidenhair	1gm/kg	99.2±0.7**	98.7±0.4**	4.4±0.2**	4.8±0.12**
3	Manna tree	1gm/kg	98.4±0.4**	97.7±0.8**	4.4±0.2**	4.7±0.18**
4	Rowatinex	0.1 ml/kg	95.7±0.9**	95.4±0.6**	4.17±0.18*	4.6±0.17**

Table 4: The mean urine Na^+ and Ca^{++} levels of the tested agents measured after induction of NC

* = significant difference (0.001 < P ≤ 0.05), ** = highly significant difference (P ≤ 0.001), as compared with the control group.

The histopathological examination was carried out in the last day of the study in order to detect any improvement in kidneys tissues after the toxic dose of oxalic acid see the pictures.

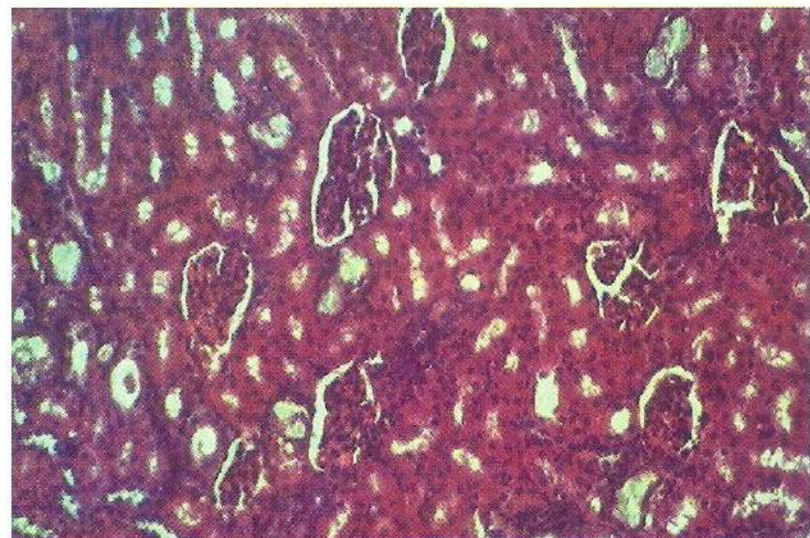

Figure (1): Normal rabbit kidney section. (20X, HandE stain)

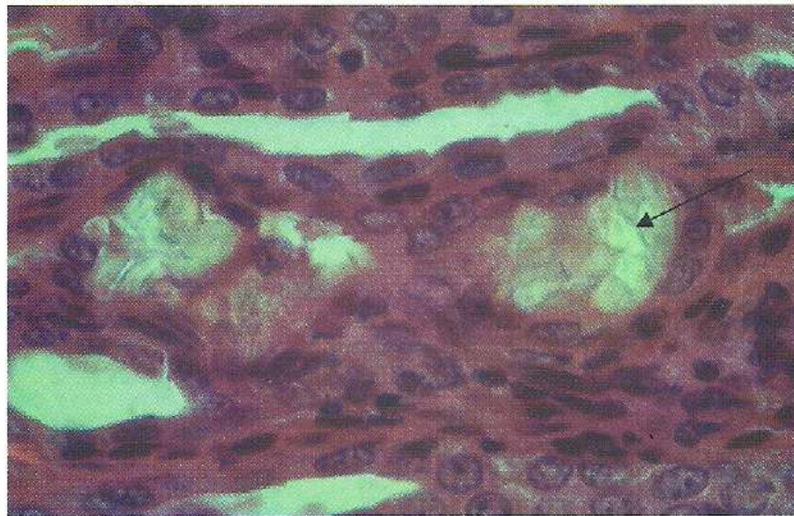

Figure (2): Heavy calcium oxalate crystals deposition in the renal tissue of rabbit receiving oxalic acid. (40X, HandE stain)

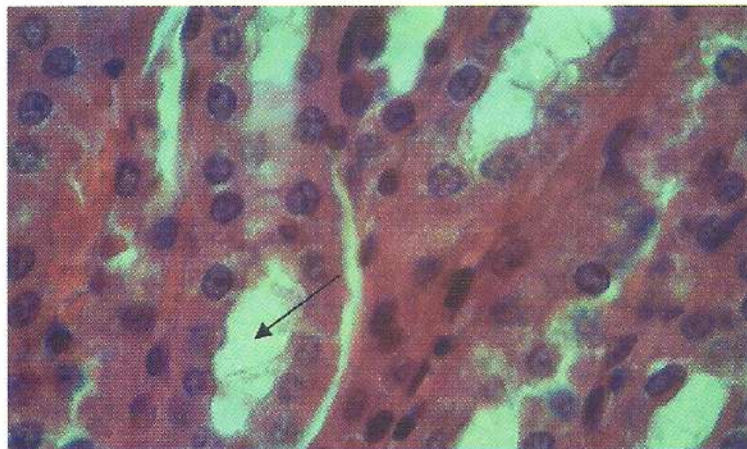

Figure (3): Mild calcium oxalate crystals deposition in the renal tissue of rabbits receiving Maidenhair and oxalic acid. (40X, HandE stain)

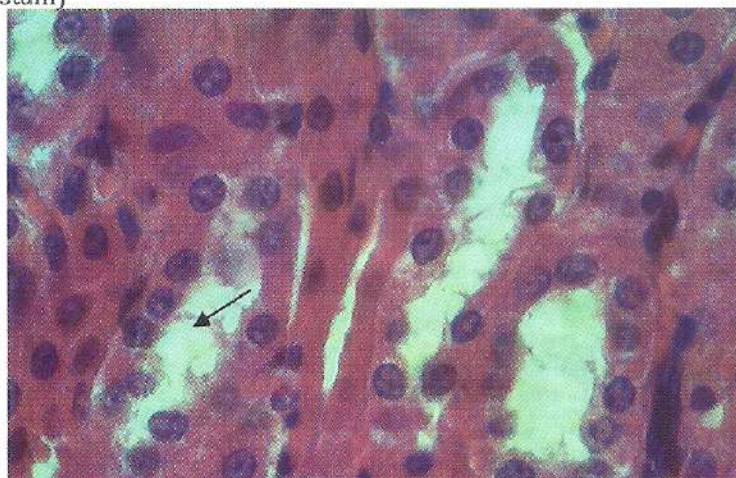

Figure (4): Mild calcium oxalate crystals deposition in the renal tissue of rabbits receiving Manna tree and oxalic acid. (40X, HandE stain)

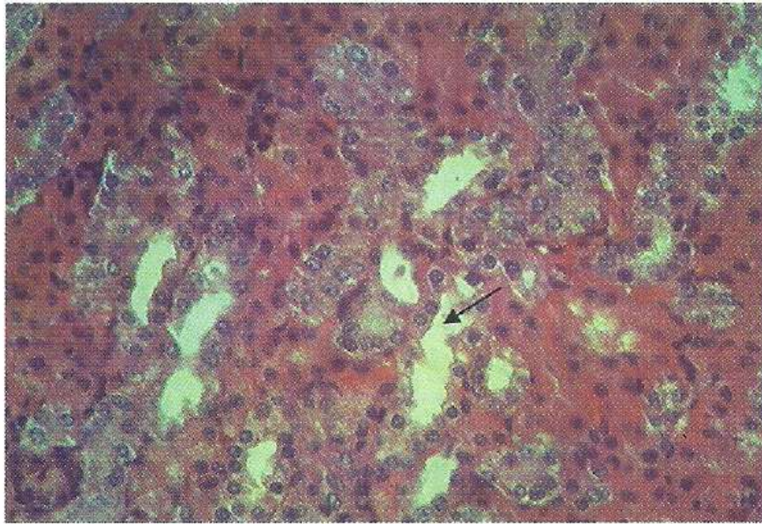

Figure (5): Mild calcium oxalate crystals deposition in the renal tissue of rabbits receiving Rowatinex and oxalic acid. (20X, HandE stain)

DISCUSSION

Oxalic acid is a highly oxidizing and powerful Ca^{++} chelating agent and it is one of the strongest organic acids. [7]It was used in a single large dose of 333 mg /kg to induce NC in rabbits (group-1). This effect was compatible to the work performed by others [8].who used 200 mg\day to produce NC in rats. Rowatinex is a terpene mixture drug (group-4) was used as treated control with its antioxidant properties which had been observed in terpene derivatives [9].Rowatinex was reported to increase renal blood flow and facilitate urine excretion leading to stone passage with additional antispasmodic activity [10].Therefore increasing urine $Ca^{++}$and Na^{+} levels. Maiden hair was tested as an aqueous extract (group-2). It exerts a diuretic and natriuretic effect which helps in the protection against gradual accumulation of Ca^{++} oxalate crystals within the renal tissues. In addition flavonoids are present in the constituents of this plant and well known to have antioxidant effect [11].Maiden hair contains proanthocyanidius antioxidant capability which is 20 time more potent than vitamin C [12]. antioxidant agents in prevention or attenuation of acute renal failure in rabbits. Manna tree was used in group-3 for its diuretic effect [15] with a significant reduction in BUN, serum creatinine and K^{+} levels and highly significant elevation in the levels of both, urine Ca^{++} and Na^{+} in comparison with control group-1. Really there is no available data about the effect of Manna tree on renal stone but our study showed that the diuretic effect of Manna tree was found to attenuate the renal damage and to provide promising results in NC. In addition to that the possibility to the present of antioxidant flavonoids in plant contents. The nephroprotective activity of Maiden hair, Manna tree, and Rowatinex in decreasing BUN, creatinine and K^{+} are similar to the results obtained by others [5] that used Barley and celery for this purpose. The histopathological results confirmed the nephroprotective effect of Maiden hair, Manna tree, and Rowatinex in induced NC by oxalic acid (see the figures 1-5)

Similar nephroprotective effect had been reported by others, [13, 14] who used some vasodilator and

CONCLUSION

All the tested agents posses nephroprotective activity at the tested doses in model of nephrocalcinosis by restoring the normal renal functions (through antioxidant and diuretic effects) and enhancing the bio-defensiveness of the kidney against the damaging effect produced by oxalic acid administration. Finally, Maiden hair, Manna tree, and Rowatinex can be used for patients with ureterolithiasis but these results should be confirmed by clinical trials.

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Reconstruction Of mandibular defects

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Abstract

Background: The goals of Maxillofacial and reconstructive surgeons are the restoration of function and esthetics in an expeditious manner with minimal surgical morbidity. The aim of this study was to present methods of reconstruction of the mandible.

Method: Thirty two patients (including 20 males and 12 females) who had partial mandibulectomies for malignant tumors or trauma that were treated at Maxillofacial Surgery Department at Ramadi Teaching Hospital. Different method used for reconstruction of mandibular defects.

Results: Of the 17 patients that had tumors including benign (4 cases) and malignant tumors (13 cases) while 15 patients had deformity of war injuries. Reconstruction of the mandible was done either by immediate bone graft from iliac crest, or by K-wire, direct approximation and assembling of bone pieces, or by the of reconstruction plate.

Conclusion: In all patients adequate results were achieved with adequate functional and aesthetic outcome with sufficient bone height and volume to facilitate prosthodontic treatment.

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keywords: Professionals, Employment, Stress, Health mandible, bone graft, K-wire, reconstruction plate, bone defect

INTRODUCTION

Maxillofacial defects were almost exclusively a problem for the maxillofacial prosthodontist, and few surgical options existed [1]. With the perfection and acceptance of vascularized free tissue transfer, with the perfection and acceptance of vascularized free tissue transfer, mandibular repair and replacement have become routine [2].

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After a decade of clinical experience, the fibula has emerged as most facial plastic and reconstructive Surgeons' donor site of choice for management of mandibular defects. When part or all of the maxilla or mandible is lost to disease or injury, it would be ideal to provide exact restoration or reconstruction [2,3] .Reconstruction of the mandible after ablative surgery or because of trauma or congenital defects poses a challenge to the oral and maxillofacial surgeon[2,4]. There are three important factors that play a role on the overall success of the reconstruction including rigid fixation of the graft is essential since where movement is predictable, bone healing will be impaired; adequate soft tissue cover must be available; and the volume and contour of the reconstructed bone should mimic the original or desired volume and contour of the resected or missing part as close as possible that can be achieved if the reconstructed mandible follows the original

contour or ,in case of congenital defects, is reconstructed in such a way that a proper intermaxillary relationship exists. In last years various modes of treatment have been introduced to reconstruct the mandible including bridging plates, free autogenous block bone grafts, particulate corticocancellous bone grafts using various scaffolds and mixtures with xenografts or biomaterials. Bone grafting is an essential step in the management of patients with a defect of the mandible that is widely accepted as a treatment for mandibular reconstruction [5, 6, 7].

METHODS

A total of 32 patient with mandibular defects that were treated in Maxillofacial Department at Ramadi Teaching Hospital including 20 males and 12 females; their ages ranged from 28 to 62 years. 17 patients had benign and malignant tumors while 15 patients had deformity of war injuries. Careful examination, Lab. investigations, conventional radiographs and / or CT examinations. Histopathological examinations (incisional and excisional biopsies) were carried out. chemotherapy followed by DXT depending on the evaluation during the patients' follow-up and prognosis. In the majority of the malignant cases, the mandible was reconstructed by K-wire for holding the 2 segments in position and to be used as substitute to the resected bone so it prevent any deformity or twisting of the jaw to the resected side and to get a proper occlusion while in cases of war injuries of the mandible, the defects were reconstructed by direct approximation and assembling of bone pieces with placement of direct trans-osseous wires with lower border wiring (Figure eight placement), or by a block of corticocancellous bone from iliac crest as monocortical or bicortical block of bone with or with out application of bone sliding technique. (Figures 1, 2, 3 and 4).

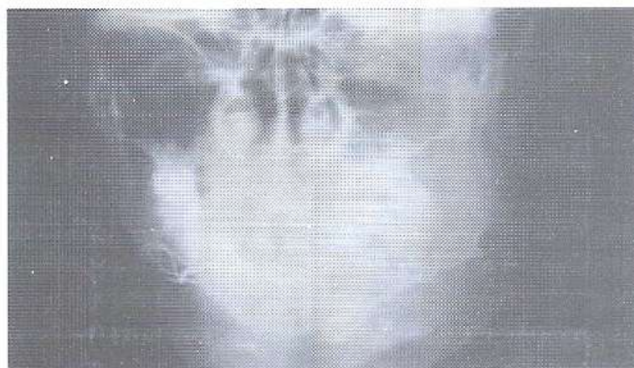

Figure 1. PA radiograph showed the placement of direct wiring and lower border wiring (figure eight).

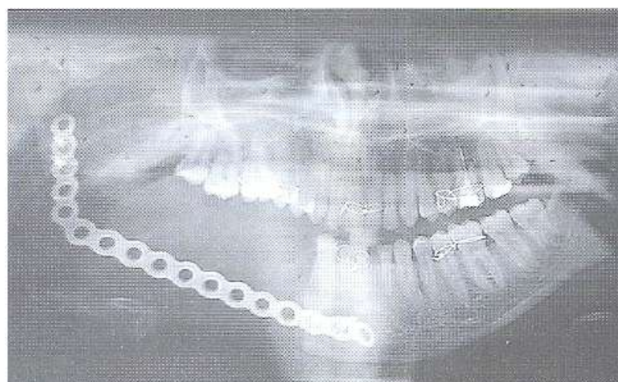

Figure 2. OPG showed the use of Reconstruction Plate

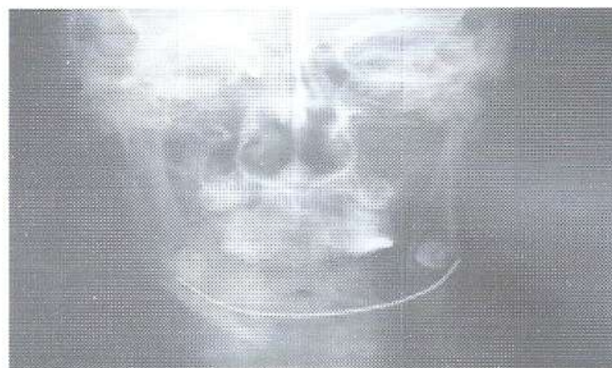

Figure 3. PA radiograph showed the insertion of K-wire

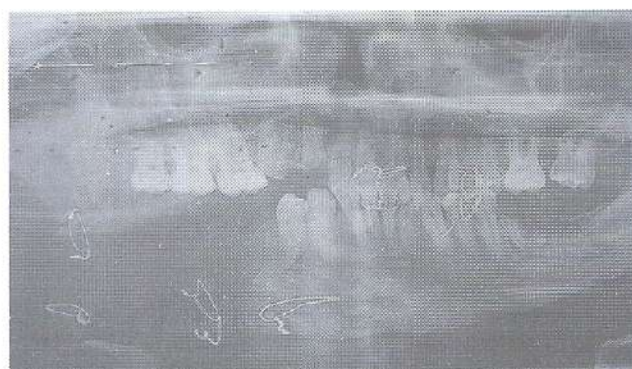

Figure 4. OPG showed the use of iliac bone graft with application of bone sliding technique

Age group	Sex		Cause of defect					Reconstruction				
			Tumor				War inj.	Tumor			War inj.	
	M	F	Bn	Mt								
				PD	MD	WD		BG	K	RP	DF	BG
25-34	4	1	0	0	0	2	3	0	1	1	0	3
35-44	8	6	1	0	1	4	8	2	3	1	3	5
45-54	6	5	3	2	1	1	4	1	2	4	1	3
55-65	2	0	0	1	0	1	0	1	0	1	0	0
Total	32(100%)											

Table 1. Patients' characteristics.

M=*male*, **F**=*female*, **Bn**=*benign*, **Mt**=*malignant*, **PD**=*poor differentiated*, *MD=moderate differentiated*, **WD**=*well differentiated*, **BG**=*bone graft*, **K**=*K-wire*, **RP**=*reconstruction plate*, **DF**=*direct wiring and figure eight*

RESULTS

These studies were conducted on 32 patients including 20 males and 12 females, aged 28 to 62 years that undergone surgical reconstruction of the mandible (Table 1). Of the 17 patients that had tumors including benign (4 cases) and malignant tumors (13 cases) while 15 patients had deformity of war injuries. Benign tumors including 4 cases of ameloblastoma while malignant tumors consisted of 3 cases of poor differentiated 2 cases of moderate differentiated and 8 cases of well differentiated squamous cell carcinoma. Reconstruction of the mandible was done by immediate bone graft from 6 cases were reconstructed by K-wire that used as temporary prosthesis for reconstruction of the mandible in malignant tumors while reconstruction plate was used in 7 cases of malignant tumors after radical surgery. In contrast the cases of war injuries were treated by use of a block of corticocancellous bone graft fixed by stainless steel wire in 11 cases with or without the use of bone sliding technique and 4 cases were reconstructed by direct approximation and assembling of bone pieces with placement of direct trans-osseous wires with lower border wiring (Figure eight placement).

DISCUSSION

The healing in the patients treated proves the versatility of the techniques described. The use of iliac crest as a donor site would have necessary to achieve continuity of the mandibles involved since postoperative complaints are generally less severe, whereas the amount of cancellous bone available is sufficient to surgical reconstruction[3,8,9] Although there have been no comparative studies on donor site morbidity; surgeons may assume that donor site morbidity is minimal. The soft tissue cover is essential to fill the defect in the desired shape and volume. The adequate height and width of the bony reconstructions allowed for proper prosthodontic rehabilitation or the insertion of dental implants [10, 11, 12]. There are many factors affecting the choice of reconstruction. These factors are associated with type of tumor, age, general condition and future follow-up, patient prognosis, and the loss of bone graft [6, 7, 13]. Reconstruction of the mandible with K-wire is an easy-way option, and shorter operation time is required for bony substitution and reconstruction, K-wire is easily applied and manipulated to form the shape of the resected part of the mandible while is has the disadvantages of loose screws, fractured K-wire. Impressive results were obtained by using block of corticocancellous bone graft from the iliac crest to provide a sufficient bulk of

bone to allow shaping and contouring of the graft to simulate the mandible. It has been advocated to the early mobilization of the mandible with the bone graft after 6 weeks of fixation and the graft subjected to force of mastication is more convenient for restoration of function, esthetics, and growth especially required in young patients, furthermore the early mobilization of the reconstructed jaws by bone graft will allow the graft to be exposed to functional stress and minimize the risk of disuse atrophy that is based on theory of functional demands of the periosteal matrix of the facial skeleton [14,15,16].

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Tooth loss and risk of hypertension in postmenopausal women

Widad F Jabber*

Abstract

Tooth loss has been associated with an increased risk of vascular diseases such as coronary heart disease and cerebrovascular disease. Little is known whether hypertension is an important factor linking 2 phenomena in postmenopausal women. We compared an incidence of hypertension and traditional risk factors for vascular diseases between 2 age-matched groups: 42 postmenopausal women with missing teeth and 19 without missing teeth. In addition to blood pressure, serum concentration of total cholesterol, high- and low-density lipoprotein cholesterol and triglycerides, and resting heart rate were measured as traditional risk factors for vascular diseases. Subjects without missing teeth had significantly lower diastolic blood pressure than did subjects with missing teeth (P= 0.022). The former tended to have lower systolic blood pressure than did the latter (P= 0.052). There were no significant differences in other variables between subjects with and without missing teeth. Our results suggest that hypertension may be an important factor linking tooth loss and an increased risk of vascular diseases in postmenopausal women.

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Keywords: *vascular diseases, hypertension, women*

INTRODUCTION

Vascular diseases such as coronary heart disease and cerebrovascular diseases are important causes of death in elderly women in Japan as well as in the United States. Premenopausal women are relatively at low risk for vascular diseases compared with men, but this risk increases with advancing age and with the onset of menopause[1] Risk factors for vascular diseases include menopause, smoking, diabetes mellitus, obesity, hypercholesterolemia , hypertriglyceridemia, and hypertension in women. Tooth loss has been associated with an increased risk of vascular diseases such as coronary heart disease[2-4] cerebrovascular disease[5,6] and peripheral arterial disease[7] One potential pathway linking tooth loss and vascular disease risk is oral infection-inflammation related to periodontal disease [6-18] Periodontal disease, a local chronic bacterial infection in the oral cavity, may contribute to endothelial dysfunction[12] carotid artery plaque formation [11,13,15,17] or deterioration of the antiatherogenic potency of HDL[18]A second pathway is that tooth loss may affect dietary quality and nutrient intake, leading to an increased risk of vascular disease [19-21] A third is confounding variables such as smoking or diabetes mellitus that largely affect both tooth loss and vascular

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diseases may produce spurious association between 2 phenomen[22-25]Tooth loss might lead to dietary pattern change, resulting in an increased risk of hypertension because the change of dietary pattern may be associated with hypertension[26] Systolic and diastolic blood pressure are important predictors for cardiovascular disease and stroke in the United States and Europe as well as in eastern Asia [27-30]Hypertension might be an important risk factor linking tooth loss and vascular disease risk in postmenopausal women. An analysis of postmenopausal,

METHODS

We evaluated 2 age -matched groups : 42 postmenopausal women with missing teeth (mean age ± SD 55.71 ± 4.05 years , range 50 to 63years) and 19 postmenopausal women without missing teeth (mean age ± SD 55.57 ± 3.68 years , range 48 to 60 years). Because third molars tend to be impacted completely or missed congenitally, these were excluded from tooth count. All of the subjects had no menstruation for at least 1 year. Excluded from the study were cigarette smokers and women with diabetes mellitus, clinical manifestations of arteriosclerosis (cardiovascular disease, peripheral artery disease, or cerebrovascular disease), liver disorders, significant renal impairment, trauma in the jaws, and orthodontic treatment. None had used medications that affect lipid metabolism or blood pressure. Subjects with secondary forms of hypertension were excluded on the basis of a complete history and physical examination, radiological and ultrasound examinations, and urinalysis.

Analytical Methods: Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg measured in a sitting position on at least 3 different occasions in the outpatient clinic of Amyria General Hospital. Normal blood pressure was defined as a systolic blood pressure<130 mm Hg and a diastolic blood pressure<80 mm Hg. Routine chemical methods were used to determine the serum concentration of total cholesterol, HDL cholesterol, and triglycerides (TGs). The serum concentration of LDL cholesterol was determined by the Freidewald method.[31] Resting heart rate, height, and weight were measured at sampling venous blood. Body mass index (BMI) was calculated as weight divided by the square of height (kilograms per meter squared).

Analysis

All characteristics were compared between subjects with and without missing teeth by unpaired *t* test subjects were divided into subgroups according to measurement values for vascular disease risk. Low BMI was defined as $<18.5 kg/m^2$, normal as ≥ 18.5 to $< 25 kg/m^2$, overweight as ≥ 25 to $<30 kg/m^2$, and obese as $\geq 30 kg/m^2$. Total cholesterol >220 mg /dL, HDL cholesterol <40 mg/dL, TG>150 mg/dL, and LDL cholesterol >140 mg/dL were considered traditional risk categories for vascular diseases. All traditional risk categories for vascular diseases were compared with tooth category by the *t* test. *P* values <0.05 were considered statistically significant. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 8.0 (SPSS).

Results

There were significant differences in the number of remaining teeth (*P*= 0.000) and diastolic blood pressure (*P*= 0.022) between subjects with and without missing teeth. Subjects without missing teeth tended to have lower systolic blood pressure than did subjects with missing teeth (*P*= 0.052); however, there were no significant differences in other characteristics between the 2 groups (Table 1).There was significant association between an incidence of hypertension and tooth loss (*P*=0.001); however, there were no significant associations among other traditional risk categories for vascular diseases and tooth loss (Table 2).

characteristics	Missing teeth(n=42)	No missing teeth(n=19)	p value
Number of teeth remaining	19.47±2.91	28.0±0.00	0.000
Years since menopause	6.71±4.05	5.94±2.97	0.463
Hight(cm)	155.14±3.91	147.4±32.93	0.139
Weight(kg)	69.00±14.03	62.23±7.59	0.343
Total cholesterol(mg|dl)	228.7±45.54	224.5±8.07	0.688
HDL cholesterol(mg/dl)	86.94±100.6	72.90±1.46	0.547
TGs(mg|dl)	124.10±14.9	108.30±25.19	0.120
LDL cholesterol (mg/dl)	137.49±5.22	143.32±8.29	0.262
Systolic blood pressure(mm Hg)	131.6±10.4	122.4±7.2	0.052
Diastolic blood pressure(mm Hg)	88.68±36.12	83.10±11.10	0.022
Heart rate (bpm)	65.5±14.36	65.3±2.86	0.125

TABLE 1.Differences in Characteristics Between Subjects With and Without Missing Teeth

*The results were shown as mean ±SD *P* value was calculated from *t* test.

Risk factor for vascular diseases	Missing Teeth(n=42)	No Missing Teeth(n=19)	P Value
BMI			
Low BMI	0(0%)	0(0%)	
Normal	19(45%)	13(68%)	0.224
Overweight	9(21%)	3(15.7%)	
Obese	14(33%)	3(15.7%)	
Total cholesterol >220 mg/dl	18(42%)	12(63.1%)s	0.75
HDL cholesterol <40 mg/dl	1(2.38%)	0(0%)	1.00
TGs >150 mg/dl	7(16%)	4(21%)	0.411
LDL cholesterol >140 mgldl	20(47%)	10(52.6%)	0.619
Hypertension	14(33.3%)	2(10.5%)	0.001

Table 2.Comparison of risk factors for vascular diseases. between subject with and without missing teeth*

*The results were shown as No. (%).
P value was calculated from *t* test.

Discussion

Tooth loss was significantly associated with an increased risk of hypertension in this study; however, there were no significant associations among other traditional risk factors for vascular diseases and tooth loss. The Eastern Stroke and Coronary Heart Disease Collaborative Research Group demonstrated that blood pressure is an important determinant of stroke risk in eastern Asian populations, whereas cholesterol concentration is less important, affecting the proportions of stroke subtypes more than overall stroke number [27]. Franklin et al reported that diastolic blood pressure was the strongest predictor of coronary heart disease in patients younger than 50 years of age, whereas systolic blood pressure, diastolic blood pressure, and pulse pressure were comparable predictors in patients aged 50 to 59 years in different age groups of the Framingham Heart Study participants [30, 31]. Diastolic blood pressure was significantly associated with tooth loss in our subjects who were relatively younger postmenopausal women. Our results suggest that postmenopausal women with missing teeth may have a higher risk of hypertension and subsequent vascular diseases than do those without missing teeth. On the basis of causal relationship, some hypotheses might be considered potential mechanisms linking tooth loss and an increased risk of hypertension. Intake of some nutrient-rich foods and beta carotene, folate, and vitamin C serum levels were significantly lower in denture wearers in the US civilian, no institutionalized population. [32] The decrease of serum antioxidant vitamins such as vitamin C in postmenopausal women with missing teeth in this study might contribute to an increased risk of hypertension. Subjects with missing teeth might have been at greater risk of periodontal disease than those without missing teeth, resulting in endothelial dysfunction through the oral infection-inflammation pathway and subsequent increased risk of hypertension. However, because Saito et al reported significant association between obesity and periodontitis in Japanese men and women,[33] there is less possibility that subjects with missing teeth had risk of periodontal disease than those without missing teeth at the time of examination in this study because there was no significant difference in obesity between subjects with and without missing teeth. Further, relatively younger women lost their teeth more likely by caries than by periodontal disease. [33,34] Tooth loss might be a reflection of previously continuous pain and mental stress that may contribute to an increased risk of hypertension.[35,36] On the basis of non-causal relationship, healthy bias might be considered 1 of confounding variables linking tooth loss and hypertension in this study. Postmenopausal women without missing teeth might have both good general and oral health consciousness compared with those with missing teeth, resulting in spurious association between tooth loss and hypertension. However, there were no significant differences in other risk factors for vascular diseases as well as basic characteristics between subjects with and without missing teeth. These suggest that tooth loss– hypertension association in this study may not be a spurious finding because of healthy bias. Our findings are limited to relatively healthy postmenopausal women because of restrictive exclusion criteria. A small number of subjects also may limit the interpretation of our findings. Second, we did not clarify the difference in the dietary patterns between subjects with and without missing teeth. Third, we did not measure endothelial function in this study. The estimation of dietary patterns and the measurement of endothelial function would be necessary to clarify as to which mechanisms contribute to an association between tooth loss and an increased risk of hypertension in postmenopausal women. In conclusion, there was significant association between tooth loss and an increased risk of hypertension in postmenopausal women, although there were no significant associations among tooth loss and other traditional risk factors for vascular diseases. Our results suggest that hypertension may be an important factor linking tooth loss and vascular disease risk in postmenopausal women.

Perspectives: Tooth loss was associated with an increased risk of hypertension in postmenopausal women. However, it was still unknown whether there was causal link between 2 phenomena because this study was cross-sectional. Some unknown confounding variables related to socioeconomic status, nutritional features, psychosocial factors, or

lifestyle might contribute to non-causal association. At the point of causal relationship, hypertension also might facilitate tooth loss. The strategy for tooth retention might play an important role in preventing hypertension and subsequent vascular diseases after menopause in women. Conversely, treating hypertension at an earlier age might promote tooth retention. Prospective longitudinal study including possible confounding variables would clarify the causal or non-causal relationship between tooth loss and hypertension in postmenopausal women.

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The New Iraqi Journal of Medicine

Research Article

Oral Medicine

The incidence of some oral Lesions and their treatments in children visit teaching dental hospital in Ramadi city

Dunia W. Alfayad

Abstract

Background: Children's oral health comprises a broad range of dental and oral disorders. The most common oral pathological conditions in children are periapical abscess; cellulitis and different oral anomalies like geographical tongue. Children's oral health comprises a broad range of dental and oral disorders. The most common oral pathological conditions in children are periapical abscess; cellulitis and different oral anomalies like geographical tongue.

Aim of the study: Study was conducted to evaluate the incidence of the frequent types of the oral lesions children visit Teaching Dental Hospital.

Materials and Method: The total number of patients who included in this study were 174 from October/3/2010 to June/1/2011. The age of the patients were ranged from 3-12 years with mean age of 7.5 years old. All of them attending College of Dentistry /Anbar university to be treated. All children were examined and diagnosis of the them was based on their signs; clinical symptoms and radio graphical evaluation.

Results : Out of 174 patients were examined 80 cases(45.97%) were with dental caries; 23 cases of them(13.21%)showed periapical abscess f 18 cases(10.34%) were geographical tongue and 53 cases(30.45%) were buccal cellulitis.

Conclusions: It was concluded from this study that oral lesions in children are highly occurred and their treatment is good and enough to have about 100% curing rate with good response.

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Keywords:

INTRODUCTION

Children's oral health comprises a broad range of dental and oral disorders. The most common oral pathological conditions in children are periapical abscess; cellulitis and different oral anomalies like geographical tongue [1]. The periapical abscess originates from the dental pulp, and is usually secondary to untreated dental caries [2].

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The abscess is an infection around the periapical area of a root. When it associated with the deciduous tooth it can be affect the development of the permanent tooth later on. An abscess generally appears as a pimple on the gum near the affected tooth, treatment is indicate [3]. Geographic tongue, is an inflammatory condition of the tongue affecting approximately 2% of the population, is usually characterized by discolored regions of papilla of the dorsum of the tongue [4]. The condition is usually chronic, and frequently manifests after eating any spicy food or may be associated with G.T. disorders such a lesion is treated by avoiding any stimulating food or by tongue brushing with follow up [5]. Buccal cellulitis most commonly associated with periapical abscesss [6].

Aim of the study

Study was conducted to evaluate the incidence of the frequent types of the oral lesions in children visit Teaching Dental Hospital. The aim of this study is to study the immunohistochemical expression of P53, as apoptosis makers in the gastric mucosa of patients infected with Helicobacter Pylori demonstrated by insitu hybridization method.

Methods

The total number of patients who included in this study were 174 from October/3/ 2010 to June/1/ 2011. The age of the patients were ranged from 3-12 years with mean age of 7.5 years old. All of them attending College of Dentistry /Anbar university to be treated. All children were examined and diagnosis of the them was based on their signs; clinical symptoms and radio graphical evaluation.

Results

Out of 174 patients were examined 80 cases(45.97%) were with dental caries; 23 cases of them (13.21%) showed periapical abscess figure-1; 18 cases(10.34%) were geographical tongue figure-2 and53 cases(30.45%) were buccal cellulitis figure-3 as showed in the table-1.The treatment were different for each group as required and the details were showed in the table-2.

No. of children	%	Type of the lesion
80	45.97	Dental caries
23	13.21	Periapical abscess
18	10.34	Geographical tongue
53	30.45	Buccal cellulitis
Total=174	99.97	

Table-1 shows number and the type of the oral lesions with their percentage.

Type of the oral lesion	Type of the treatment
Dental caries	Fillings or extractions
Periapical abscess	Extractions or root canal treat.
Geographical tongue	Oral health instruction and follow -up
Buccal cellulitis	Abscess drainage and antibiotic prescriptions or extraction of accused tooth

Table-2 shows types of the treatment.

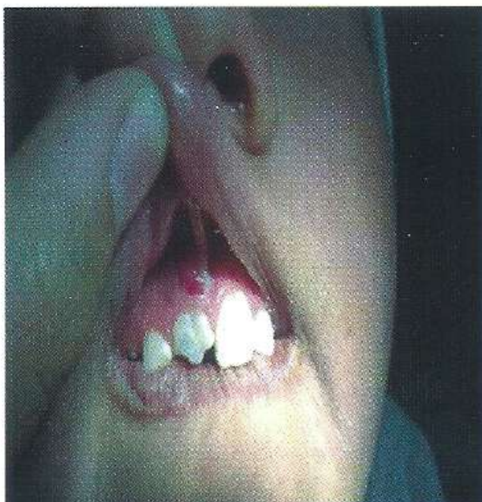

Fig.-1periapical abscess associated with upper right permanent central incisor due to trauma

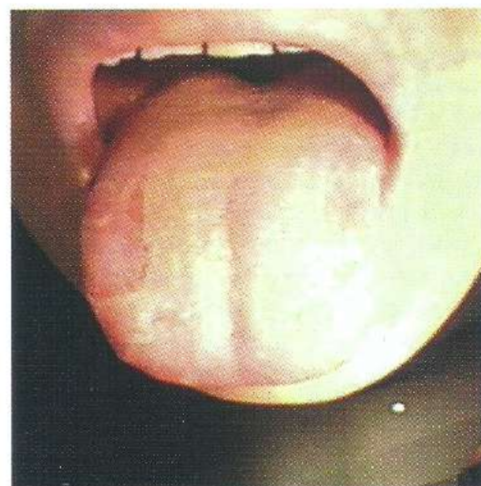

Fig.-2 clinical picture of patient with Geographical tongue on the right lateral border of the tongue.

Fig.-3 upper right buccal cellulitis due to dental infection

Discussion

The incidence of dental caries (45.97%) for children within this age is so high and required great attention. Similar observations have been reported by several workers also the percentage of periapical abscess as (13.21%) is required great attention [7, 8]. The occurrence of periapical abscess might be due to microbial infection [9].The results of treatments of 23 cases showed good response. This will agree with several authors [10, 11, 12, 13].The incidence of geographic tongue was (10.34) % similar results have been reported by Jonathan et. al. most often, patients were asymptomatic; however some patients report increased sensitivity to hot and spicy foods .The etiology and pathogenesis of geographic tongue are still poorly understood. It has been reported that geographic tongue was noted to be more prominent in adults than in children [14]. Its cause is uncertain, though it tends to run in families and is associated with several different genes, though studies show family association may also be caused by similar diets. Geographic tongue is more commonly found in people who are affected by environmental sensitivity, such as allergies, eczema, and asthma [15]. The tongue exhibits a well demarcated area of erythema, primarily affecting the dorsum and often extending to involve the lateral borders of it(Fig-1).The normal tongue architecture is affected, with loss of the filliform papillae and atrophy of the over lying mucosa. This might be linked to high sugars or processed foods. While there is no known cure or commonly prescribed treatment for geographic tongue, there are several ways to suppress the condition, including avoiding foods that exacerbate the problem [16, 17]. Some people affected by geographic tongue also report that taking vitamin B supplements causes the condition to go away temporarily. Steroid ointment may be applied topically for symptomatic patients [18] Burning may also be reduced by taking antihistamines. The condition is usually asymptomatic and insignificant; persistent pain is rare [19, 20]. About buccal cellulitis the condition Cellulitis (sell-you-lite-us) is an infection of the tissue just below the skin. Signs of cellulitis are swelling, redness, warmth, and tenderness of the skin [21, 22]. These signs can occur anywhere on the body. Children may also develop a fever and chills. Children with cellulitis on the face or near a joint usually need to go to the hospital for treatment [23]. This pathological condition required differential diagnosis from other lesions like lymphadenitis, sinusitis and odontogenic tumors [24] Cellulitis should be treated immediately. This indicates surgical treatment and drainage of pus to eliminate the source of infection and giving antibiotic therapy like amoxicillin, 500mg. or cephalosporin to sensitive patients will help to cure. Similar observations have been reported by others [25, 26]. Children with cellulitis may stay in the hospital up to 10 days and are usually allowed to eat a regular diet and participate in normal activities that are comfortable for them [27]. Buccal cellulitis showed in 53 children, (30.45) % might be occurs as a sequels of dental infection or might be due to trauma in most cases. Treatment of dental abscesses in children almost always involves tooth extraction +/- incision and drainage, particularly if primary dentition and similar studies have been made [28, 29].

Conclusion

It was concluded from this study that oral lesions in children are highly occurred and their treatment is good and enough to have about 100% curing rate with good response. However further studies is required to avoid such high percentage of lesions especially dental caries and their sequels. Consequently there is a definite need of data on dental treatment demands and wants for adequate planning of dental health care systems in their infancy in regions with limited financial resources

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Cytokines profiles including (TNF-α, IL-1αand IL-8) in patients with polymyositis

Fatin S. Maki , Yahya Y. Z , Adnan Anoze

Abstract

Background: Polymyositis is one of a group of muscle diseases known as the inflammation myopathies, which are characterized by chronic muscle inflammation accompanied by muscle weakness. In some cases of polymyositis, distal muscles may be affected as the disease progresses.
Aim of the Study: To estimate TNF-α and serum biochemical marker in sera of patients with polymyositis, and studying their relationship. And to bring the attention to use anti TNF-α as treatment for polymyositis.
Materials and Methods: There were 90 individuals participated in this study , 30 individuals represent the control group and other (60) were patients with polymyositis with muscle weakness. Cytokines profiles (including TNF-α, IL-1αand IL-8) were determined by enzyme linked immune sorbent assay (ELISA).
Results: The results were compared with those of healthy groups as controls. In the present study, it was noticed that the mean age for patients with active polymyositis was 51.75 years and 53.31 years with inactive polymyositis with female predominance (male: female ratio) 1: 7.56 where (53) 88.34% of patients were female and (7) 11.66% were male .The serum levels of TNF-α were elevated in patients with active and inactive polymyositis and decreased after treatment with methotrexate and low dose of steroid.
Data showed a highly significant elevation in serum IL-1α and IL -8 with active and inactive polymyositis compared to control.
Conclusion: Elevated levels of TNF-α is major factor in the causation of inflammatory polymyositis
TNF-α levels can be evidenced in patients with polymyositis and there was no correlation between its and other cytokines (IL-1α, IL-8) TNF-α concentration decreased after treatment with methotrexate and low dose of steroid.

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Keywords: TNF , IL – 1 α , IL- 8 , RF *rs*

INTRODUCTION

Polymyositis is one of a group of muscle diseases known as the inflammation myopathies , which are characterized by chronic muscle inflammation accompanied by muscle weakness(Engel et al 1994[1] . Polymyositis affects skeletal muscle (those involved with making movement) on both sides of the body. Slow, but progressive muscle weakness starts in the proximal muscles which eventually lead to difficulties climbing stairs, rising from a sitting position. In some cases of polymyositis, distal muscles may be affected as the disease progresses. (Oddis 2000[2], Dorph C. et al 2006 [3]

tumor Necrosis Factor-alpha (TNF) is cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. The primary role of TNF is in the

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regulation of immune cells. TNF is also able to induce apoptotic cell death, to induce inflammation, and to inhibit tumor regenesis and viral replication. Dysregulation and, in particular, over production of TNF have been implicated in a variety of human diseases, as well as cancer (Locksley RM et al 2001[4] Interleukins (cytokines) made by one leukocyte and acting on other leukocytes (Microvet et al 2007[5]. Cytokines activities are characterized using recombinant cytokines and purified cell populations in vitro, or with knock – out mice for). individual cytokine genes to characterize cytokine in vivo cytokines are made by many cell populations, but the predominant procedures helper T cells and macrophages (Microvet et al 2007[5]).

Aim of the Study:

To estimate TNF-α and serum biochemical marker in sera of patients with polymyositis, and studying their relationship with disease activity.

METHODS

The specimen was collected during the period from August 2008 to March 2009. There were 90 individuals participated in this study, 30 individuals represent the control group and other (60) were patients with polymyositis presented to the rheumatology department, Al-Kadhimiyia Teaching hospital with muscle weakness. cytokines profiles (including TNF-α, IL-1αand IL-8) were determined by enzyme linked immune sorbent assay (ELISA).

RESULTS

The results were compared with those of healthy groups as controls. In the present study , it was noticed that the mean age for patients with active polymyositis was 51.75 years and 53.31 years with inactive polymyositis with female predominance (male : female ratio) 1: 7.56 where (53) 88.34% of patients were female and[7] 11.66% were male .as in tab. 1The serum levels of TNF-α were elevated in patients with active and inactive polymyositis and decreased after treatment with methotrexate and low dose of steroid as shown in tab. 2 & Fig.1.Data showed a highly significant elevation in serum IL-1α and IL-8 with active and inactive polymyositis compared to control gp. as shown in tab.3 &4.After statistical analysis for obtained data there was lack of correlation Observed between pro inflammatory (TNF- α) and chemokine iL-8 &IL-1α.

DISCUSSION

The mean of age polymyositis patients of this study were 52.53 years old , and range from (33-77) years and that agree with a previous study done by Liang et al 2004[6] , which is stated that most patients who develop polymyositis are around and older than 65 years . And these patients have significantly greater esophageal involvement, bacterial pneumonia, and malignancies than younger patients afflicted with this disease. Marie J etal 1999 [7] showed that older patients experience complete remission less frequently and have a higher overall mortality rate associated with polymyositis Although the frequency of female patient group is higher than that of the male in this study (table.1) and male to female ratio was (1: 7.57) , this mean that the disease could affect both sexes but with propensity to female .This study agree with previous study done by Edelman C. et al 2004[8] , Who[8] stated that polymyositis like other autoimmune diseases , they occur predominantly in women . All patients included in this study have a high value of primary pro-inflammatory cytokine (TNF-α) ,A finding that agree with previous study done by Dalaskas MC et al 1998[9],which they showed that TNF-α resides at the apex of inflammatory cytokine cascade that is responsible for the pathophysiology of polymyositis .TNF-α may induce or augment the production of other pro – inflammatory cytokines such as interleukin -1α ,a study done by Efthimiou P et al , 2005[10].As shown in table.3) the concentration of IL-1α in patients with active and inactive polymyositis increase gradually which is in agreement with Efthimionu P et al ,2005[10] and Mackiewiez et al ,2004[11] who found that prominent expression of the pro inflammatory factors IL-1α is associated with muscle fiber damage .The result showed increase in concentration of chemokin (IL-8) in sera of patients with polymyositis , which is in agreement with Frederik Kreiner et al , 2008[12]. who showed that increase serum IL-8 levels associated with polymyositis.

CONCLUSION

Elevated levels of TNF-α is a major factor in the causation of inflammatory polymyositis

TNF-α levels can be evidenced in patients with polymyositis and there was no correlation between its and other cytokines (IL-1α , IL-8) TNF-α concentration decreased after treatment with methotrexate and low dose of steroid.

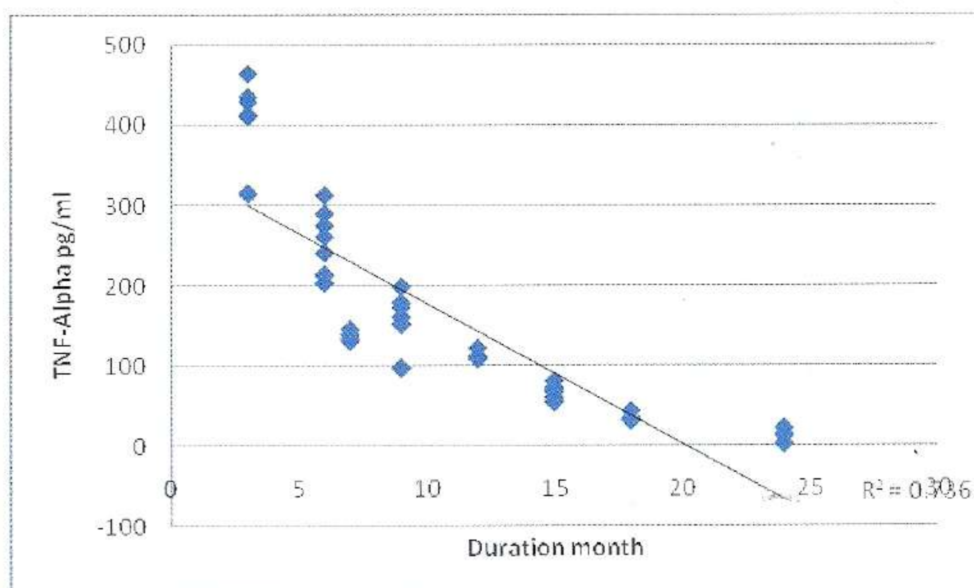

Figure (1) Correlation between TNF- alpha and duration time

	Male	Female	Total
Control (G1)	13	17	30
Active polymyositis(G2)	4	37	41
Inactive polymyositis(G3)	3	16	19
Total	20	70	90

Table (1) Gender distribution in all studied groups

TNF-α (pg/ml)			
Groups	Control G1	Active polymyositis G2	Inactive polymyositis G3
N	30	41	19
Mean	7.61	171.99	148.62
SE	0.381	22.34	27.4
Range	3.85 - 11.1	22 - 289	22 - 289
Comparison with control		P<0.00001	P<0.0001
Comparison between patients group		P<0.5129	
Comparison within study group	ANOVA (P<0. 00001)		

Table (2) serum TNF-α in active and inactive polymyositis and control groups

IL-1 alpha (pg/ml)			
Groups	Control G1	Active polymyositis G2	Inactive polymyositis G3
N	30	41	19
Mean	3.41	111.91	74.56
SE	0.58	14.70	17.86
Range	0.5 – 11.2	0.87 – 319.4	3.1 - 213
Comparison with control		P<0.00001	P<0.0012
Comparison between patients group		P<0.1152	
Comparison within study group	ANOVA P< 0.00001		

Table (3) Serum IL-1alpha in active, inactive and control groups

IL- 8 (pg/ml)			
Groups	Control G1	Active polymyositis G2	Inactive polymyositis G3
n	30	41	19
Mean	4.25	95.11	125.8
SE	0.72	23.28	44.11
Range	0.3 - 15	10 -156.2	10 -156.2
Comparison with control		P< 0.00001	P<0.0022
Comparison between patients group		P< 0.5976	
Comparison within study group	ANOV P < 0.00001		

Table (4) Serum IL-8 in active, inactive and control groups

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Serum level profile and pharmacokinetic parameters of single dose of amoxicillin in Type 2 diabetic patients

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Abstract

Background and Objectives: Many pathophysiological processes can affect the pharmacokinetic properties of drugs in people with diabetes. The present study was designed to evaluate the influence of diabetes mellitus on the pharmacokinetic parameters of amoxicillin administered as single oral dose.

Patients and Methods: Twelve healthy volunteers and twelve diabetic patients were enrolled in the present study. On day 1, a single oral dose of amoxicillin 500 mg was administered orally to all participants at 9:00 am after a 10-hour fasting. Over the following 24 hours, blood samples were taken at frequent intervals and serum amoxicillin concentrations were measured by a high-performance liquid chromatography method for assessment of pharmacokinetics of amoxicillin.

Results: The result indicated that the values of C_{max}, AUC_{total}, and AUClast were significantly decreased in diabetic patients compared with those reported in healthy subjects. At the same time, the values of T_{max} and $K_{elim.}$ were non-significantly affected compared with those in healthy subjects, while $T_{½}$ was significantly increased.

Conclusions: In conclusion, diabetes mellitus affects some of the pharmacokinetic values of orally administered amoxicillin, an event that point to the requirement for dose monitoring of some drugs in such cases.

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***Keywords:** diabetes mellitus, amoxicillin, oral absorption, pharmacokinetics*

INTRODUCTION

Many pathophysiological processes can affect the pharmacokinetic properties of drugs in people with diabetes [1]. Patients with diabetes have higher rates of cardiovascular, renal, gastrointestinal, neurological, and thyroid diseases and ophthalmological complications compared with individuals without diabetes. All may increase the chance of having drug-disease interactions [2]. Some physiological disorders, such as gastroparesis, decreased plasma albumin level, elevated plasma free fatty acid level, glycosylation of plasma proteins and changes in the hepatic microsomal cytochrome P-450 (CYP) contents were reported to occur in diabetes mellitus patients [3]; these changes could alter the pharmacokinetics and hence the pharmacodynamics of drugs in such patients [4]. Absorption of many orally administered drugs, such as metoclopramide and tolazoamide, was affected in diabetic patients with gastroparesis and autoimmune neuropathy [4, 5-8]. Amoxicillin is oral semisynthetic penicillin structurally related to ampicillin; it is widely used for treatment of

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bacterial infections and its plasma level is of critical importance for diabetic patients [9, 10]. There is a wealth of information regarding the pharmacokinetic parameters of amoxicillin in healthy subjects; however, limited information is available in diabetic patients. Since amoxicillin is often used to treat many types of bacterial infections in diabetics [11], the influence of the disease processes and consequent complications on the pharmacokinetic parameters of drugs, including amoxicillin, should be systematically evaluated. The present study was deigned to evaluate the influence of diabetes mellitus on the pharmacokinetics of amoxicillin administered as single oral dose.

METHODS

Patient's selection and design:

Twelve healthy volunteers and twelve diabetic patients were enrolled in the present study; all have an age of 55.3±5.78 years and with body mass index for each of 20.1±1.38 and 25.58±2.6 respectively. All healthy volunteers show a normal medical history and revealed no pathological abnormalities on clinical and biochemical examination. Meanwhile, all patients were selected for having type 2 diabetes mellitus for at least 5 years and have been treated with single daily dose of glibenclamide 5mg daily and metformin 500 mg three times daily. All patients had serum transaminase concentrations less than twice the upper limit of the laboratory reference range and a normal serum creatinine (<120 mmol/L). Written informed consent was obtained from each subject and the clinical protocol was approved by the Human Ethics Committee of the Iraqi Ministry of Health. All subjects were nonsmokers and were instructed not to drink caffeine or alcohol containing beverages for at least 10 hours before and during the study day. The study was performed according to an open, randomized clinical study design.

Blood sampling and analysis:

Following a 5-day screening period, healthy volunteers and patients with type 2 diabetes were enrolled in the study. On day 1, a single oral dose of amoxicillin 500 mg (Athlone, England) was administered orally to all participants at 9:00 a. m. after a 10-hours fasting. Blood samples were taken at zero-time and at frequent intervals over a period of 24 hours following the administration of amoxicillin (0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, and 24.0 hrs) and serum amoxicillin concentrations were measured by a high-performance liquid chromatography method for the assessment of pharmacokinetic of amoxicillin. Stock solution of amoxicillin (reference standard) 1mg/ml) was prepared by dissolving 100 mg in 100 ml of methanol. Working standard solutions were prepared from the stock solution by sequential dilution with methanol to yield final concentrations of 2.0, 4.0, 6.0, 9.0, and 12.0 µg /ml. Samples for the preparation of standard curve were prepared by mixing blank serum (specially prepared for this purpose) with different concentrations of standard amoxicillin solution to get the final required serum amoxicillin concentrations (2.0, 4.0, 6.0, 9.0, and 12.0 µg/ml). Calibration standards were obtained by addition of 300 µl of acetonitril to 100 µl of blank serum, then centrifuge at 10,000 rpm at 10°C for 5 minutes, then 1 ml of dichloromethane was mixed with the supernatant; mixed and centrifuged at 10,000 rpm at 10°C for 5 minutes; then 20 µl of supernatant was injected into HPLC column for determination of amoxicillin serum levels [11]. Analyses were performed using an HPLC system (Knauer, Germany) composed of a smartline pump 1000 and smartline U.V detector 2500 connected to smartline manager 5000. The separation was performed on a waters symmetry C19, 5µm (4.6 x150 mm) column. The drug analysis data were acquired and processed using CLASS-VP (v.6.2) software running under Windows 98 on a Pentium PC. The mobile phase was a mixture of 0.02 M disodium hydrogen phosphate buffer-methanol (10:90 vlv) adjusted to pH 3.0 at a flow rate of 1 ml/min. The wave length was set at 228 nm; run time was 10 min [11]. Calculation of the pharmacokinetic parameters analysis was performed using computer software kinetica PK- PD analysis version 5.0 (Microsoft -programs).

RESULTS

The effects of diabetes mellitus on absorption of amoxicillin was shown in table 1 and figure 1. The data showed that the values of C_{max}, AUC_{total}, AUC_{last} were significantly decreased ($P<0.05$) in the serum of diabetic patients compared with that in corresponding healthy subjects. At the same time, the values of T_{max}, K_{elim} were non-significantly affected ($P>0.05$) compared with healthy controls, while $T_{1/2}$ was significantly elevated ($P<0.05$) compared with that reported in healthy subjects.

Pharmacokinetic Parameters	Healthy subjects	Diabetic patients
C_{max} (µg/ml)	8.68 ± 0.05	8.51 ± 0.09*
T_{max} (hr)	2.5 ± 0.01	2.5 ± 0.01
AUC_{last}(µg. mL^{-1}. hr)	21.97 ± 1.18	20.83 ± 0.94*
AUC_{tot} (µg. mL^{-1}. hr)	21.99 ± 1.19	20.85 ± 0.94*
K_{elim} (hr^{-1})	0.41 ± 0.38	0.41 ± 0.37
$T_{½}$ (hr)	2.17 ± 0.60	2.21 ± 0.64*

Table 1. The pharmacokinetic parameters of orally administered amoxicillin in type 2 diabetic patients compared to healthy subjects

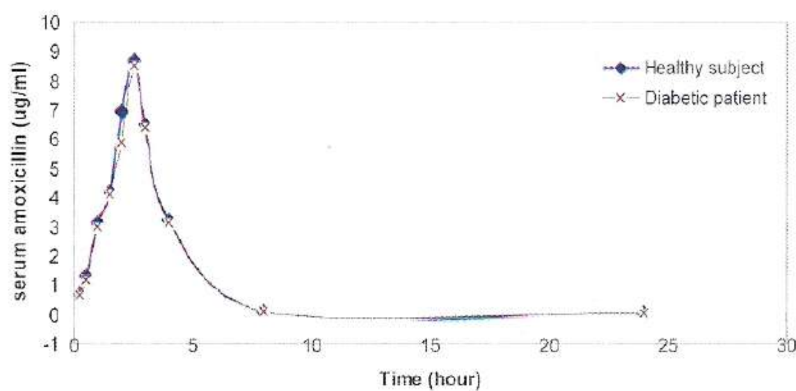

Figure 1. Serum-time profile of amoxicillin after 500 mg single oral dose in healthy subjects and patients with type II diabetes mellitus.

DISCUSSION

The data of the present study strongly indicated that diabetes mellitus alters some of the pharmacokinetic parameters of orally administered amoxicillin. The mechanism by which diabetes mellitus alters the pharmacokinetics of amoxicillin may be due to alterations in gastric emptying time induced by gastroparesis; since altered gastric emptying can modify the pharmacokinetic/pharmacodynamics profile of many orally administered drugs [12]. Erah in 2007 shows that alteration in body position which causes changes in gastric emptying time reduce the absorption of orally administered metronidazole and amoxicillin in rabbits [13]. Symptoms of diabetic gastroparesis include early satiety, nausea, vomiting, heart burn, anorexia, and severe gastric stasis may ultimately lead to gastric bezoars, bacterial over growth, and gastric candidiasis; this will lead to alter secretion of GI hormones, poor glycemic control, acidosis, and electrolyte disturbances [12]. These factors may alter the pH of stomach to a value of 5 which may alter the solubility of amoxicillin. Absorption of amoxicillin is less affected by changes in pH of GIT because of it is being a Zwitter ion with p*Ka* values of 2.68 (carboxylic acid), 7.49 (amine) and 9.63 (phenolic hydroxyl); it is often ionized across the whole range of pH in the GIT [13]. Amoxicillin is not susceptible to hepatic metabolism; also about 60% of an oral dose of amoxicillin is excreted unchanged in the urine within 6 hours by glomerular filtration and tubular secretion. Depending on the stage of diabetes, the glomerular filtration rate may be increased, normal, or decreased. In addition, a variety of renal tubular secretory abnormalities arise in both type 1 and type 2 diabetes that could potentially influence pharmacokinetics as well [14,15]. It has been previously reported that benzyl penicillin clearance was significantly higher in diabetic children than in controls and serum concentration of kanamicin, bekanamicin and amikacin were lower, and the half-life shorter, in diabetic children than in non diabetic children and studies in adults are more equivocal [4]. Twenty to 30% of diabetics develop abnormal gastric motility, resulting in disordered gastric emptying or gastroparesis [4]. Although the etiology of altered gastric motility remains obscure, many factors appear to be important including poorly controlled diabetes, and others [16]. Absorption of many orally administered drugs may or may not affected by the presence of diabetes; the extent of absorption of metoclopramide administered orally to diabetic patient with gastroparesis fell within the range of values reported in healthy subjects [4]. Meanwhile, absorption of tolazamide was 26% slower in diabetic patients with asymptomatic autonomic neuropathy than in healthy subjects [4], and a 26% decrease in the extent of absorption of orally administered ampicillin was reported compared with non-diabetics controls [17]. Therefore, it appears that diabetes can influence the gastrointestinal absorption of drugs, but the extent of influence of the disease on drug absorption may depend on the severity, duration and type of the disease [12]. Also, Daniyan *et al.* showed that diabetes induces an alteration in the pharmacokinetics of halofantrine and its major metabolite, especially the C_{max}, drug absorption parameters, and binding to plasma components [18]. In conclusion, the pharmacokinetic parameters of amoxicillin absorption after oral administration were altered in diabetic patients compared to healthy subjects. Therefore, the effect of diabetes mellitus on the pharmacokinetic parameters of drugs should be carefully evaluated to avoid clinical insignificance.

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Research Article
Clinical Pharmacology

Effectiveness of oliban, licorice, black seed and chamomile on chronic bronchial asthma

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Abstract

Background: Bronchial asthma is a clinical syndrome with possible correlation to medicinal plants in improvement of the asthmatic symptoms.

Methods: This study was carried out in the Al- Kadhimiyia teaching hospital between October 2008 to June 2009 on 90 patients of both sexes who were allocated to five groups plus 15 healthy volunteers as control. Each group was given one of the following agents: Prednisolone, Oliban, Licorice, Chamomile and Black seed and their pulmonary function tests were conducted as well as measuring the levels of serum electrolytes: Calcium (Ca), Magnesium (Mg), Potassium (K) and Selenium (Se) before and after the treatment.

Results: Most of the tested plants have positive effects on pulmonary function tests with significant elevation in the values of forced expiratory volume in first second (FEV_1%) and forced volume capacity (FVC) and clinical improvement of patients condition with marked reduction in asthmatic attacks.

Conclusion: Medicinal plants can reduce the symptoms of bronchial asthma and improve pulmonary functions with safety, less adverse effects.

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Keywords: *Oliban, Licorice, Chamomile, Black seed, Chronic asthma, Medicinal plants, Pulmonary function tests.*

INTRODUCTION

Bronchial asthma is a clinical syndrome with multiple causes etiology. It is characterized by paroxysmal or recurrent episodes of bronchial obstruction accompanied by wheezing caused by a spasm of muscles of bronchial tube or edema by swelling of their mucus membrane, both genetic and environmental factors are involve[1].

Asthma is caused also by other factors like many allergens, air pollutants, pollens, mold species and infections [2]. Exercise and emotional factor [3], gastroesophageal reflux and obesity [4] and some medications like Beta blockers and non-steroidal anti-inflammatory [5].

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The pathogenesis of chronic bronchial asthma is a complex; it may involve both airway inflammations with an oxidant-antioxidant imbalance [6]. Reactive oxygen species (ROS) have been shown to be associated with asthma pathogenesis by evoking bronchial hyperactivity, stimulating histamine release from the mast cells and mucus secretion from airway epithelial cells [7].

Some medicinal plants such as Thymus Vulgaris (Thyme) and Foeniculum vulgarae (Fennel) have been shown to cause elevation of the FEV% and FVC values. This action is explained by improvement of the pulmonary functions and decreasing of severity and frequency of asthmatic attacks in patients taking the plants [8].

The current study was performed to investigate the effect of some medicinal plants such as Oliban (Boswellia carteri), Black seed (Nigella sativa), Licorice (Glycyrrhiza glabra) and Chamomile (Anthemis nobilis) on patients with chronic bronchial asthma in order to improve their symptoms.

SUBJECTS AND METHODS

This study was performed in Al - Kadhemiya teaching hospital - Baghdad between October 2008 to June 2009. Ninty adult patients with 15 healthy volunteers of both sexes were involved in this study. Their age range was 33-55 years. Patients suffering from any disease other than chronic asthma were excluded, also pregnant women, cigarette smokers and alcohol consumers and were excluded from the study. This study was approved by ethical committee of college of medicine. The patients were advised to take special kinds of diet where it is possible and they were prevented from any exercise or exposure to any allergen. The patients were randomly allocated into five groups; each group was given one of the following tested drugs:

Group 1 (30 patients): they were given a single dose of Prednisolone 0.15 mg/Kg tablet orally once daily for a period of 7-10 days.

Group 2 (15 patients) : they were given Oliban 3 mg/Kg orally, 3 times daily for 7-10 days.

Group 3 (15 patients) : they were given Licorice 3.5 mg/Kg orally in 200 ml of water 3 times daily for 7-10 days.

Group 4 (15 patients) : they were given Chamomile 100 mg/Kg by inhalation once daily for 7-10 days.

Group 5 (15 patients): they were given Black seed 100 mg/Kg by inhalation once daily for 7-10 days.

Pulmonary function test was performed using a total computerized spirometer (Discom-14, Autospiron chest corporation Tokyo-Japan). The parameters used to assess the severity of asthma in the current study were forced volume capacity FVC and forced expiratory volume in first second FEV_1%. Blood samples were taken before the patients received any medication and after the improvement of the symptoms. Serum Mg^{2+} and Se^{2+} of all patients were measurement by using GFA-4B graphite tube with auto sample dispenser model 60 G flameless atomic absorption photometer. Serum Ca^{2+} and K^+ determined by using flame emission spectrophotometery (Gleenhomp). The tested plants were identified by Iraqi national center of herbs. All plants were cleaned to remove abnormal materials and selected parts of plants were used; seeds (Black seed), roots (Licorice). Plants were crushed and grounded well into powder. Most of the tested plants were used in the form of tea [9]. Licorice needs covering with boiling water for 15 minutes and mixing. Oliban needs boiling or to be soaked in water for 12 hours and used as gum. Chamomile and Black seed were boiled and immediately used by inhalation for 5-10 minutes using vapour machine.

All data were coded and analyzed using SPSS 10.01 statistical package for social sciences.

RESULTS

The results revealed significant elevation in FEV_1% and FVC of the tested plants Oliban, Licorice and Black seed with exception of Chamomile in addition to the control Prednisolone. The changes in the levels of serum electrolytes also confirming the results obtained. The serum Mg and Se of all the groups were significantly elevated Chamomile, at the mean time Serum Ca and K of all the groups significantly changed except Prednisolone and Chamomile (tables 1,2and3).

Discussion

Bronchial asthma is an inflammatory syndrome characterized by episodes of acute bronchoconstriction causing shortness of breath, cough, chest tightness, wheezing and rapid respiratory rat [10]. The diagnosis of asthma had been established in each patient and it was based on the above symptoms and clinical examination. Prednisolone is familiar corticosteroid used as control in group 1 to produce bronchial muscle relaxation. Its effect is indirect by decreasing the inflammatory processes, inhibiting the release of leukotrienes and reversing mucosal edema in asthmatic patients [11].

Parameters	Prednisolone		Oliban		Licorice	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
FEV_1%	72.75 ± 5.09	* 78.63 ±3.34	61.33 ± 6.04	*72.45 ± 5.83	58.30 ± 9.22	*81.10 ± 11.07
FVC / L	1.05 ± 0.15	* 2.25 ± 0.16	0.72 ± 0.16	*2.63 ± 0.82	1.08 ± 0.08	*3.60 ± 0.02
Ca / mmol/L	1.97 ± 0.07	2.10±0.10	1.93 ± 0.02	*2.20 ± 0.06	1.90 ± 0.06	*2.30 ± 0.08
K / mmol/L	3.5 ± 0.24	3.50 ± 0.08	3.60 ± 0.04	*3.90 ± 0.18	3.60 ± 0.03	*4.10 ± 0.12
Mg / mmol/L	0.73 ± 0.05	* 0.81 ± 0.15	0.73 ± 0.12	*0.97 ± 0.02	0.66 ± 0.17	*1.02 ± 0.10
Se µg / L	44.62 ± 6.35	* 49.17 ± 4.96	33.40 ± 8.54	*54.22 ± 4.12	28.19 ± 3.72	*51.70 ± 8.63

Table 1: The effect of Prednisolone (0.15 mg/Kg) , Oliban (3 mg/Kg) and Licorice (3mg/Kg) given orally for 7-10 days on pulmonary functions parameters and serum electrolyte levels.

* Results were significant at ($P<0.05$).

Parameters	Chamomile		Black seed	
	Before treatment	After treatment	Before treatment	After treatment
FEV_1%	77.41 ± 3.30	79.33 ± 4.40	53.80 ± 7.49	*74.91 ± 5.28
FVC / L	2.38 ± 0.27	2.75 ± 0.32	1.36 ± 0.12	*3.14 ± 0.05
Ca / mmol/L	2.06 ± 0.06	2.17 ± 0.07	1.97 ± 0.03	*2.10 ± 0.04
K / mmol/L	3.94 ± 0.05	3.61 ± 0.09	3.00 ± 0.18	*3.70 ± 0.06
Mg / mmol/L	0.78 ± 0.02	0.80 ± 0.02	0.90 ± 0.07	*1.08 ± 0.02
Se µg / L	54.66 ± 1.32	*60.05 ± 3.16	28.03 ± 7.01	*42.10 ± 9.18

Table 2: The effect of Chamomile (100 mg/Kg) and Black seed (100 mg/Kg) given by inhalational for 7-10 days on pulmonary functions parameters and serum electrolyte levels.

* Results were significant at ($P<0.05$).

The effect of Oliban (group 2) is related to presence of boswellic acid in its constituents that cause bronchial muscle relaxation [12]. Oliban also can interact with leukotrienes production from arachidonic acid [13].

The effect of Licorice (group 3) in relaxation of bronchial smooth muscle was similar to Prednisolone but more potent in treatment of asthma and to relieve the symptoms. The effectiveness of Licorice is related to corticosteroid like activity of glycyrrhizin [14]. While the antispasmodic effect is related to the flavonoid both are present in the plant [15].

The current results were compatible with results of others [17] but without reaching to the level of edema

and hypertension. The effect of Chamomile (group 4) is not significant when given by inhalation. No improvement occurs in asthmatic symptoms although it has relaxant effect on rabbit tracheal muscle contracted by histamine or acetylcholine when given by inhalation [17]. The effect of black seed (group 5) produced significant relaxing effect when given by inhalation with the relieve of the symptoms. This action is related to its chemical constituent thymoquinone that prevent histamine release from mast cell[18]and due to its well known antioxidant activity, these results were compatible with results of others[19] to prove the useful uses of antioxidants in chronic bronchial asthma. In assessment to the changes of serum electrolytes levels in asthmatic patients, it has been reported about positive correlation between serum Se levels and each of FEV_1% and FVC and if the Se levels decrease the possible risk of asthma would be increase due to reduction in glutathione peroxide and antioxidant activity [20].

It has been also reported about low plasma magnesium level that occurred in chronic bronchial asthma [21]. These results were similar to the results of our study before giving any medication. Both Se and Mg levels were greatly increased with typical improvement of asthmatic symptoms and reduction in severity and frequency of the attacks. Most of the asthmatic patients recorded low levels of serum Ca before any treatment and these results were similar to the results found by others. The increased intracellular Ca^{++}in leukocyte of asthmatic patients is directly correlated with severity of asthma [22].

In conclusion; medicinal plants can be used in prophylaxis or management of chronic bronchial asthma for their safety and less adverse effects but may take long time.

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Oral pyogenic granuloma- A case report

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Abstract

Pyogenic granuloma of the oral cavity is a relatively common entity, a localized granulation tissue overgrowth seen in the oral cavity arising in response to various stimuli such as local irritation, traumatic injury or hormonal factors. Clinically these lesions usually present as nodule or sessile papule with smooth or lobulated surface. These may be seen in any size from a few millimeters to centimeters. As lesions mature, the vascularity decreases and the clinical appearance is more collagenous and pink. Here, we report a case of Pyogenic granuloma in the lower right anterior edentulous region of jaw in 55 years old female which is rare location for this lesion

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Keywords: Pyogenic granuloma, granulation tissue overgrowth, sessile papule.

INTRODUCTION

Pyogenic granuloma of the oral cavity is a relatively common entity first described by Poncet and Dor in 1897 as human botryomycosis [1.2]. Then, Hartzell [1.3]introduced the term 'pyogenic granuloma' and some authors use the term 'lobular capillary hemangioma[1.4]. Pyogenic granuloma also known as a "Eruptive hemangioma," "Granulation tissue-type hemangioma "Granuloma gravidarum, "Pregnancy tumor, and "Tumor of pregnancy is a primarily oral disease which appears as an overgrowth of tissue due to irritation, physical trauma or hormonal factors. It is often found to involve the skin and nasal septum, and has also been found far from the head such as in the thigh[5].

Pyogenic granuloma is a localized granulation tissue overgrowth arising in response to various stimuli such as local irritation, traumatic injury or hormonal factors[6].

The term pyogenic granuloma is a misnomer since the condition is not associated with pus and does not represent a granuloma histologically, moreover the origin is traumatic, not infectious. Actually, it is a capillary hemangioma of lobular subtype. It is a benign lesion therefore surgical excision is the treatment of choice. It mainly involves the gingiva, extragingivally it can occur on the lips, tongue, buccal mucosa, palate. This article describes a case of oral pyogenic granuloma occurring in lower right edentulous region of jaw[7].

Clinically these lesions usually present as single nodule or sessile papule with smooth or lobulated surface. These may be seen in any size from a few millimeters to several centimeters. As lesions mature, the vascularity decreases and the clinical appearance is

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more collagenous and pink. The peak prevalence is in teenagers and young adults, with a female predilection of 2:1 .The increased incidence of these lesions during pregnancy may be related to the increasing levels of estrogen and progesterone [8].

CASE REPORT

A 55 years old female patient was came to department of ODMR with a chief complaint of a mild pain and swelling in lower anterior region of jaw since one month and difficulty in eating and speaking since 15 days. Patient had history of extraction of lower anterior teeth 1 month back and after teeth extraction, patient noticed swelling at same site. The growth was grown rapidly over the past 20 days to attain the present size of 5-6cm. The patient's medical history was unremarkable.

Clinical examination revealed an exophytic, sessile lesion that measured 5-6 cm in diameter. Growth extending from distal surface of lower lateral incisors to mesial surface of first molar region. Growth was lobulated in appearance due to indentation of upper anterior teeth and margins were well defined and regular. It was slightly tender on palpation and did not bleed easily. Consistency of growth was soft to firm and color was pale pink. There was generalized periodontal pocket and gingival recession. Calculus and stains were present in grade two degree. Missing teeth were Upper right 1st premolar and 2nd molar, lower right central incisor to 2nd molar and lower left central incisor to 3rd molar.

When growth is found in oral cavity, it is important to formulate the differential diagnosis since this would help further evaluation of the condition and management of the patient. After considering all clinical findings such as size, rapidity of growth and local factors, following lesions were considered in differential diagnosis - pyogenic granuloma, peripheral giant cell granuloma , peripheral ossifying fibroma , fibroma, epulis granulomatosum, fibrous epulis .

After that patient was advised for Orthopantomograph to rule out any bony pathology because of rapidity of growth and also advised excisional biopsy. Laboratory tests including calcium, alkaline phosphatase, phosphate, parathyroid hormone, hematological investigation and urine analysis were normal. Orthopantomograph showings a small radiolucent lesion with well defined sclerotic border causing resorption of alveolar process was seen in relation to lower right lateral incisor, canine, 1st premolar region with its smooth homogenous radiopaque soft tissue counterpart of swelling occupying upper and lower jaw bones. Lower right 1st premolar hiding clinically but visible radio graphically. Excisional biopsy was undertaken and lesion was removed along with concealed lower right 1st premolar.

The biopsy report was interpreted as a pyogenic granuloma as HandE section shows the mass of granulation tissue with chronic inflammatory cell infiltration ,endothelial proliferation and formation of numerous vascular spaces and surface epithelium was atrophic in some areas and hypertrophic in others suggestive of pyogenic granuloma. The lesion was completely excised to the periosteum level and there is no residual or recurrent, swelling apparent in the area of biopsy after a follow-up period of 6 months.

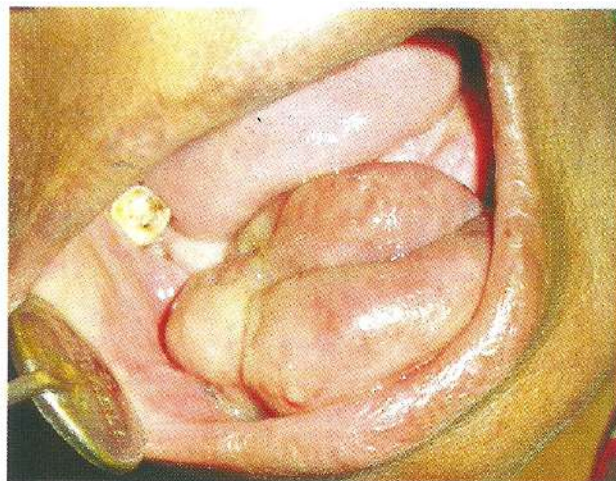

Fig-1- clinical intraoral photograph of pyogenic granuloma.

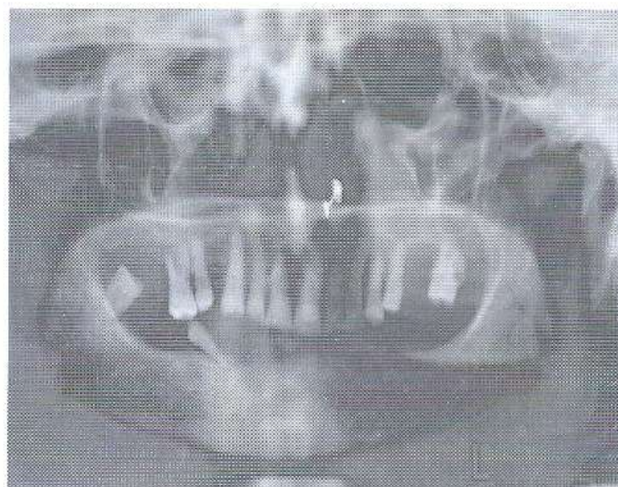

Fig-2-Orthopantomograph showing soft tissue counterpart of swelling occupying upper and lower jaw bones.

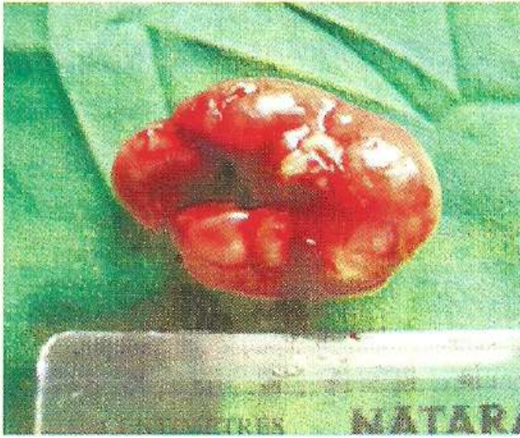

Fig-3- Specimen of pyogenic granuloma.

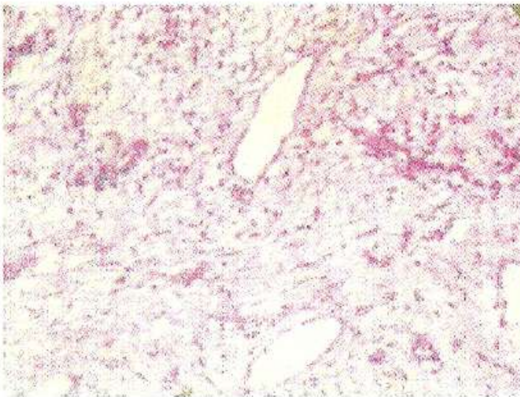

Fig-4-Photomicrograph (40X) of pyogenic granuloma

DISCUSSION

Pyogenic Granuloma, also known as granuloma pyogenicum, common soft tissue tumor of the skin and mucous membrane is a reactive inflammatory response in which there is an exurbent fibrovascular proliferation of the connective tissue, secondary to some low grade chronic irritant. In the oral cavity pyogenic granulomas show a striking predilection for the gingiva, with interdental papillae being the most common site in 70% of the cases .They are more common in the maxillary anterior area than any other area in the mouth.[8]

In the present case, the constant trauma due to mobility and local factor surrounding the hidden tooth could have been the etiology behind the growth in lower right region of jaw. Such atypical presentation, like rapidity of growth and old age, the case in discussion can be rather confusing and can lead to erroneous diagnoses of other more serious lesions. These include hemangioma and squamous cell carcinoma respectively. Although pyogenic granuloma can be diagnosed clinically with considerable accuracy, radiographic and histopathological investigations, aid in confirming the final diagnosis and treatment. Radiographs are advised to rule out bony destruction suggestive of malignancy or to identify a foreign body. All clinically suspected pyogenic granulomas must be biopsied to rule out more serious conditions as mentioned previously. [8]

Although many treatment technique have been described for pyogenic granuloma but management of PG depends on severity of symptom. If the lesion is small, painless and free of bleeding, clinical observation and follow up were advised. Although conservative surgical excision and removal of causative irritants are the usual treatment for gingival lesion.[9]

Recently some other treatment protocols, instead of excisional surgery have been proposed. Power et al [10], (1994) reported the use of ND:YAG laser for the excision of this lesion because of lower risk of bleeding compared to other surgical technique. They chose ND:YAG laser over the co_2 laser, because of its superior coagulation characteristic. Meffert et al [11],(1998) used flash lamp pulsed dye laser on mass of granulation tissue. Ishida and Ramos- E-Silva [12],(1998) believed that cryosurgery is very useful technique for the treatment for PG. They stated that oral mucosa because of its humidity and smoothness is an ideal site for this technique. Ichimiya et al. [13],(2004) attempted a approach using injection of absolute ethanol in patients with recurrence. Moon et.al. [14],(2005) reported that sodium tetradecyl sulphate, sclerotherapy successfully cleared the lesion in many patients. Parasi et al. [15],(2006) use series of intralesional corticosteroid injections for the treatment of PG particularly in highly recurrent lesion.

Although these are reactive hyperplasias, they have a relatively high recurrence rate of 16% after simple excision whereas, recurrences after surgery of extragingival pyogenic granulomas is however uncommon. Elimination of the causative agent is required[16].

CONCLUSION

Oral pyogenic granuloma is relatively common benign tumor, however their occurrence on gingival sites in the head and neck region is common. Proper diagnosis ,prevention, management and treatment of the lesion are very important . Pyogenic granuoma arises in response to various stimuli such as low grade local irritation, traumatic injury, sex hormones, so removal of causative agent is major line of treatment. Care must be taken to eliminate the causative agent along with the surgical excision of the lesion.

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Giant Bladder Stones, In Endourology Era : Single Institute Experience

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Abstract

Giant vesical stones are rare in contemporary urology practice. The armamentarium of vesical stone surgery has been widely expanded with current advances in endourology, and endoscopic lithotripsy by either a transurethral or percutaneous approach becoming the standard of care for bladder stone patients. Open surgery is still has a place in surgical management of vesical stones particularly in developing countries, where expertise and financial resources impact rules for managing patients. In this case series study, the clinical presentation, surgical management and outcome of six patients, pediatric and adult age group treated for large bladder stone more than 4 cm in diameter were retrospectively reviewed based on single institution experience.

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Keywords: *vesical stone; giant vesical stone; history of bladder stone; surgical treatment of vesical stone.*

INTRODUCTION

Vesical stones have been treated surgically and medically for many centuries.[1] Vesical calculi are a rare clinical entity, accounting for 5% of all urinary calculi in the Western world. [2,3] The armamentarium of vesical stone surgery has been widely expanded with current advances in urology. The range extends from the historical perineal lithotomy and blind insertion of crushing forceps passing through the traditional open approach to other minimally invasive interventions such as intracorporeal ,extracorporeal fragmentation and robotic surgery.[4] Despite this revolution in endourological instrumentation, a vesicolithomy is still the classical treatment for pediatric bladder stones and adults with large bladder stones of > 4 cm and hard stones.[2,5] Especially in developing countries where there is a lack or shortage of endourology set ups, Sylla et al.[6] reported that among 94 Senegalese patients with bladder stones, open procedures took place in 96%, and among 70 cases of pediatric bladder stones, open surgery was performed in 99%.[7]In this contribution, we review the literature and our experience in treated large bladder stones in both adult and pediatric population age groups.We specially focused upon clinical presentation ,surgical management and outcome of those patients based on a single institution experience .

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Case no.1

A 72-year-old man presented with a 2-year history of dysuria, hesitancy, a poor stream, straining, frequency, and intermittent hematuria. physical examination revealed a moderately enlarged prostate, and no hard nodule was felt. The kidney, ureter, and bladder ultrasound (KUB US) showed bilateral mild hydronephrosis, hydroureter, a huge bladder stone, and a prostate size of 45 cm^3. The KUB scout film showed a large pelvic radiopaque-shadow stone (9 x 8 cm).The patient was successfully managed with a vesicolithotomy as the stone occupied whole bladder.

There was no space to perform percutaneous cystolithripsy . Considerable difficulty was encountered during surgery, and the peritoneum was opened intraoperatively. This necessitated an extension of the incision and conversion to general anesthesia for proper inspection of the peritoneum and to exclude bowel injuries. The stone was broken into 3 pieces in situ using a pneumatic lithoclast (Richard Wolf,Knittlingen, Germany ™) and extracted in pieces, and TURP was performed. The patient wasdischarge home on day five postoperative. The weight of the stone pieces was 370 g.

Case no.2

A 63-year-old man was admitted because of acute urinary retention and renal impairment. Blood urea and serum creatinine were 9.1 mmol/L and 452 µmol/L, respectively. KUB US showed moderate bilateral hydronephrosis and hydroureter with a huge bladder stone of around 6.5 x 7 cm. The prostatic size was 37 cm^3.KUB scout film showed a large pelvic radiopaque shadow. After 2 weeks of continuous urethral bladder drainage, the patient underwent a cystolithotomy under spinal anesthesia. The stone was adherent to the posterior bladder wall, but we managed to push the stone into the operative field by inserting 2 fingers into the rectum. The stone was broken into 2 pieces in situ using a pneumatic lithoclast (Richard Wolf ™). The patient was discharge home on day 7 postoperative. The weight of the stone pieces was around 270 g.Serum creatinine and blood urea dropped to 136 µmol/L and 4.5 mmol/L, respectively, after 6 weeks of follow-up.

Case no.3

In a 66-year-old man, a bladder stone was incidentally discovered by KUB US. There was no hydronephrosis or hydroureter, and the bladder stone measured 5.4 x 4.7 cm. The KUB radiograph showed a pelvic radiopaque shadow .(Fig. 1).The stone was successfully removed by a percutaneouscystolithotomy (PCCL), and the suprapubic tract was dilated under direct vision up to 30 Fr. A 27-Fr.-size nephroscope (Richard Wolf ™) was used. A pneumatic lithoclast and forceps were used to extract the stone pieces. A postoperative KUB x-ray showed no residual stone, the patient was discharged on day one, and there was no leakage from the PCCL site. The stone was a mixed stone on analysis.

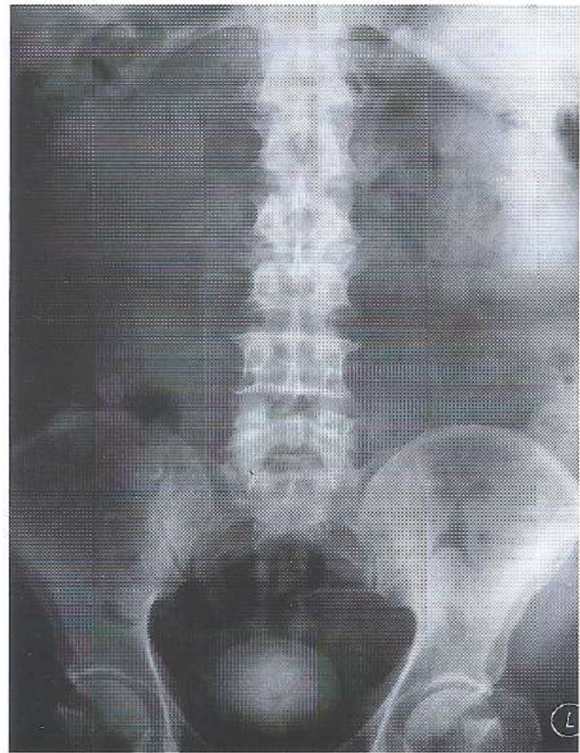

Figure 1 Kidney, ureter, and bladder radiograph of a 66-year-old man showing a radiopaque bladder stone, with the largest dimension of 5.3 cm.

Case no.4

A 56-year-old man presented with renal impairment. Preoperative blood urea exceeded 60 mmol/L and serum creatinine was 826 µmol/L. Serum potassium was 6.5 mmol/L, serum calcium was 2.28 mmol/L, and serum uric acid was 933 µmol/L. KUB US showed bilateral gross hydronephrosis and hydroureter and the presence of 2 large vesical stones, with the largest measuring around 5.7 cm in diameter . The KUB radiograph showed 2 large vesical stones.(Fig. 2).Physical examination revealed a hard mass at the lower abdomen, that was round and tender on a rectal examination. Peritoneal dialysis was started . After stabilization of his uremic status, the patient underwent a vesicolithotomy under spinal anesthesia.Difficulty was encountered intraoperatively because the stone was stuck to the posterior bladder wall and extended into the prostatic urethra, and there was no space to mobilize it. Theperitoneum was opened intraoperatively. A pneumatic lithoclast probe was used to break the stone into 3 pieces. Postoperative blood urea and serum creatinine decreased to 225 µmol/L.the patient was discharged on day 7 postoperatively. The weight of stone was 375 and it was a mixed type . At 12 months of follow-up, serum creatinine was 188 µmol/L.

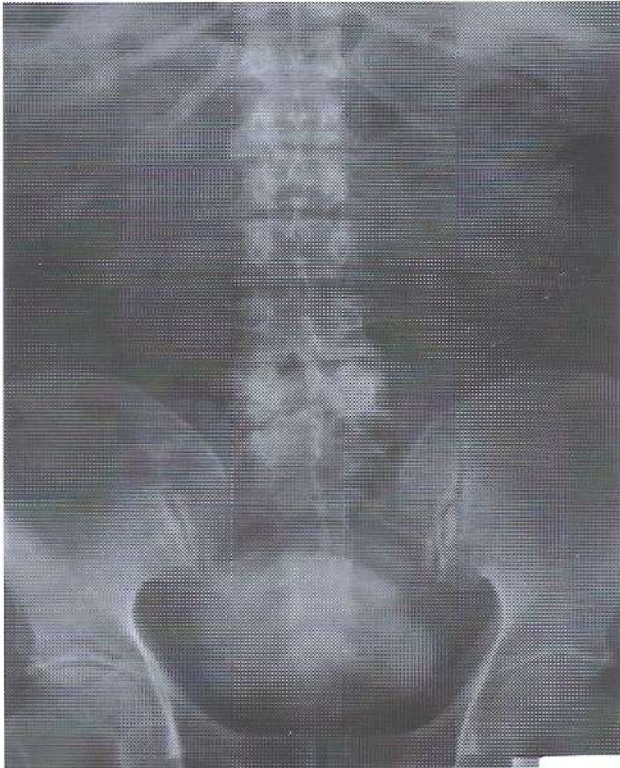

Figure 2 Kidney, ureter, and bladder radiograph of a 56-year-old man showing 2 large bladde r stones, with the largest dimension of 8.7 cm.

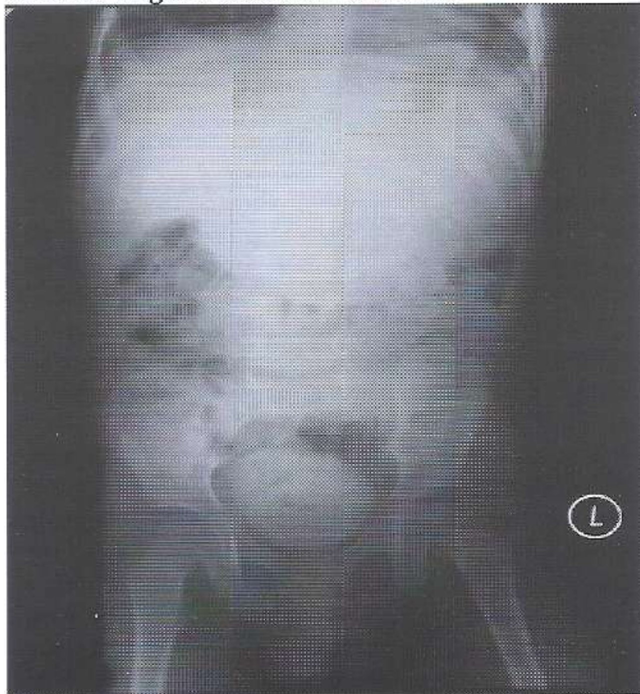

Figure 3 Kidney, ureter, and bladder radiograph of a 3-year-old boy showing a large bladder stone, with the largest dimension of 4.1 cm.

Case no.5

A 3-year-old boy, weighing 13 kg, presented with difficult micturition, an increased frequency of urination, and burning micturition for 1 year. A 24-h urine analysis showed no metabolic abnormalities. KUB US showed no hydronephrosis or hydroureter, but a large vesical stone, the largest dimension of which was 3.8 cm. The KUB radiograph showed a large vesical stone, A micturition cystourethrogram (MCU) showed grade-1 vesico-ureteric reflux (VUR)on the right side and grade-2 reflux on the left side. There was no evidence of the posterior urethral valves. A renal isotope scan (DMSA) found no evidence of renal scarring. The patient was electively admitted for PCCL under general anesthesia. The suprapubic tract was dilated under direct vision, the bladder was partially filled with glycine, and the tract was dilated up to 24 Fr. using a fascial dilator.A nephroscope sized 20.8 Fr and a pneumatic lithoclast (Richard Wolf ™) were used to blast the stone. At the end of the procedure, a Foley�s catheter was left to drain the bladder for 1 day. At 12 months of follow-up, MCU showed that VUR had resolved on both sides.

Case no.6

A 57-year -old man presented with lower urinary tract symptoms (frequency, dysuria, urgency) for one year duration,with unremarkable physical examination . KUB x-ray showed large pelvic radio opaque shadow ,largest diameter was 6.7 cm,KUB US showed bilateral moderatehydronephrosis hydroureter and presence of large bladder stone , urine analysis revealed pus cells more than 100/HPF,urine culture and sensitivity showed +ve growth for Escherichia coli .The patient was electively admitted for transurethral vesicolihotripsy under spinal anaesthesia ,the urethra was dilated up to 28 Fr ,A nephroscope size 27 Fr and pneumatic Lithoclast (Richard Wolf ™) were used to blast the stone transurethrally , The stone fragments were evacuated using Elik evacuator , the procedure took around 210 minutes and the vesicolihotripsy was abandoned as the procedure took a long time and there was shorting in operation time . Five days later the patient underwent a second transurethral vesicolihotripsy and stone clearance was achieved within 120 minutes.Postoperative KUB x-ray showed no evidence of radio opaque shadow ,the bladder irrigation stopped and urethral catheter was removed on day 2 postoperative .On 1 year follow up there was no recurrence of the stone .

Age (year)	Clinical presentation	Urine culture and sensitivity	Urea and creatine	KUB x-ray	KUB US	Operation	Stone weight (g)	Others
72	Lower urinary symptoms-LUTS	Mixed growth	Within the normal range	Largest dimension 6.5 cm	large bladder stone	Open vesicolithotomy		PSA 5 ng/dl
63	AUR and renal impairment	Mixed growth	9.1 mmol/L and 452 μmol/L	Largest dimension 8 cm	8.5 x 8 cm, BS	Open vesicolithotomy	270	
66	Urinary tract infection	*Escherichia coli*	Within the normal range	Largest dimension 5.5 cm	5.4 x 4.7 cm, BS	PCCL		
56	Renal impairment	Mixed growth	60 mmol/L and 826 μmol/L	Largest dimension8.5 cm	Bilateral HN, largest dimension 5.7 cm	Open vesicolithotomy	375	PSA 8.2 ng/dl
3	Urinary tract infection	*Proteus* sp.	Within the normal range	Largest dimension 5.5cm	Largest dimension 5.3 cm	PCCL		MCU, grade one Right and G2 left side
57	LUTS	*Escherichia coli*	Within the normal range	Largest dimension6.7 cm	Largest dimension 7 cm	Transurethral vesicolihotripsy		Two sessions to achieve stone free state

Table 1 Demographic data of all patients and their treatmentKUB,

kidney, ureter, and bladder; US, ultrasound; BPH, benign prostatic hyperplasia;

AUR, acute urinary retention; UTI, urinary tract infection; MCU, micturation cystourethrogram ;

BS, bladder stone; PCCL, percutaneous cystolithotomy; the normal range for blood urea is

3.3~7.5 mmol/L and serum creatinine is 62~124 μmol/L.

Discussion

Giant urinary bladder stones weighing more than 100 g are exceedingly rare in the era of modern urology practice.[8] Urinary bladder stones may be migrant, primary idiopathic, or secondary calculi.[9] Migrant bladder calculi are formed in the upper tract, pass into the bladder, and are retained there. In adults, bladder calculi rarely occur spontaneously; there must be a predisposing factor, such as bladder outlet obstruction, a recurrent urinary tract infection, or neurogenic bladder dysfunction.[2] Patients with intestinal mucosa or foreign bodies in the urinary tract are also at risk of development of calculi.[10] In the pediatric age group, bladder stones can occur as primary bladder calculi (endemic) in the absence of local disease, obstruction, neurologic lesions, or known primary infection.[11]The presenting symptoms and signs of bladder stones may include dysuria, suprapubic pain, terminal gross hematuria, intermittency, pelvic pain, and urine retention.[12] It is rare for a bladder stone to be asymptomatic or so large as to cause bilateral hydronephrosis hydroureter and renal impairment (cases 2, 3, and 4).Vesical stones can be detected by plain radiography of the KUB, intravenous urography (IVU), US, un-enhanced spiral computed tomographic (CT) scan, pelvic magnetic resonance imaging (MRI), and cystoscopy.[1] Cystoscopy remains the most commonly used tool to confirm the presence of stones, their number, size, position, assessment of bladder capacity, and plan of treatment.There are several treatment modalities for giant vesical stones, ranging from a cystolithotomy,[12] to endoscopic cystolithotripsy and combined procedures.[13] Endoscopic cystolithotripsy can beused to fragment bladder calculi either percutaneously or transurethrally using a variety of methods including pneumatic, US, electrohydraulic (EHL), and laser lithotripsy.[14-15] A cystolithotomy can be performed through a small lower midline or a transverse suprapubic incision (cases 1, 2, and 4). The advantages of a suprapubic cystolithotomy include rapidity, easy removal of several calculi at one time, 100% stone clearance, removal of calculi that are adherent to the bladder mucosa, the ability to remove large stones that are too hard or dense to fragment, and the ability to manage the underlying pathology.[2]The major disadvantages include postoperative pain, a longer hospital stay, and longer bladder catheterization times. Awkward manipulation can occur with attempts to extract large impact stones as intact stones, thus the peritoneum was opened in cases

that underwent a cystolithotomy, which necessitated wound extension with conversion to general anesthesia for proper dissection and to exclude bowel injury.In the era of endourology, endoscopic cystolithotripsy has become the preferred option for treating bladder stones more than 4cm . Teichman et al.[15] and Grasso et al.[16] reported that the use of a Holmium: YAG laser is safe and can successfully treat bladder stones with mean diameters of 5.5 and 6 cm, respectively.Menon and Resnick[17] documented that pneumatic lithotripsy is effective in fragmenting large, hard calculi with minimal tissue injury, Although it is effective in fragmenting hard and large stone but the main drawback was time consuming in evacuated stone pieces from the bladder transurethral with possibility of urethral injury and subsequent urethral stricture (case 6). EHL can be promising in fragmenting large bladder stones as reported by Juan et al.[18] However it is associated with high rates of bladder mucosal injury and bleeding, and it is not an option in our institution. For paediatric and adult bladder stones, the preferable approach is percutaneous suprapubiccystolithotripsy (cases 3 and 5). The percutaneous route allows the use of shorter and larger-diameter endoscopic equipment, which allows rapid fragmentation and evacuation of calculi.[19] Percutaneous lithotripsy is the primary choice of treatment for paediatric bladder stones as it avoids potential injury to the small- caliber urethra while providing an approach less invasive than open surgery, thus reducingpostoperative pain, hospital stay, and cost of treatment, as reported by Salah et al.[11] and Al-Marhoon.[20] A combined transurethral and percutaneous approach is also effective in managing large bladder stones and can be used to aid stone stabilization and facilitate irrigation of the stone debris.[21] In conclusion for large bladder stones >4 cm, the percutaneous approach is the primary treatment option as it is safe and effective with short hospital stay and low morbidity in both adult and paediatric population . However, when there is a shortage in expertise , endourological instruments and operation time , a cystolithotomy is alterative treatment for large bladder stones of > 4 cm in both age groups with longer hospital stay and convalescence period .

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