



Health and Humanitarian crisis in Yemen ... page 20

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In this issue of the journal there are a number of papers from the Region dealing with various topics including surgical and medical.

Azar BH. et al., reported and compared early experience of surgery and endovascular ablation combined with sclerotherapy. They followed a retrospective multicenter cohort study included patients diagnosed as cases of primary lower limb varicosities. The study included 71 patients, with mean age of 36.26. The most common finding was bilateral affection (27, 38%). Forty patients (56.3%) underwent surgical intervention and other 31 (43.7%) had endolaser ablation and sclerotherapy. Although early complications occurred more with the surgical intervention, the difference was not reached statistical significance. Over all, the late complications were not significantly different in both arms of interventions. Both (late and early complications) were highly significantly related to the severity of the CEAP classifications (both p-values were less than 0.001). The authors concluded that endolaser ablation with sclerotherapy is starting in Iraq. Although it is in the early stage of its development, it has better outcome compared to the classical surgical intervention.

Younis SN, et al.; carried a study to evaluate the relationship between apparent diffusion coefficient (ADC) values of renal parenchyma and different stages of chronic kidney disease and compare it with serum creatinine and estimated GFR among patients who referred to Rizgary Teaching Hospital in Erbil. An analytic cross-sectional study that was carried out from November 2017 to April 2018. In so doing, 12 individuals (control group) and 38 patients (patient group) diagnosed with known chronic

kidney disease (CKD) were selected. After they had undergone magnetic resonance imaging of the upper abdomen, the patient group subjects were classified in different stages of CKD based on estimated glomerular filtration rate (eGFR) calculated using chronic kidney disease epidemiology (CKD-EPI) equation. The results of the present study revealed a significant inverse correlation between ADC values and serum creatinine in the patient group. Also, there was a strong positive correlation between ADC and eGFR in the patients with CKD. Moreover, the patient group had a significantly lower mean ADC compared to the control group. The authors concluded that the observed correlation between ADC values and serum creatinine and eGFR in the patients under investigation in the present study indicated that the presence and degree of renal dysfunction can be determined through ADC values.

Rashid SA. et al., investigated the capacity of diffusion-weighted magnetic resonance imaging (DW-MRI) in differentiating hepatic hydatid and simple cysts among patients. According to the results of DW-MRI (b=0, 400, and 800), most of the cysts were hyperintense. Moreover, the results of comparing mean DW cyst at b0, b400, and b800 among types of hepatic cysts showed that CE2 and CE4 had the highest prevalence. Also, comparing mean DW cyst to parenchyma ratio at b0, b400, and b800 among types of hepatic cysts revealed that the highest prevalence belonged to CE3 and CE4. Moreover, comparison of mean ADC cyst at b0 and b800 among types of hepatic cysts showed the highest prevalence for CE3 and CL. Finally, comparing mean ADC cyst to parenchyma ratio at b0 and b800 among types of hepatic cysts revealed the highest prevalence for CL and SHC. The authors concluded that DW-MRI may have the capacity to differentiate between hepatic hydatid and simple cysts.

Mehmet Rami Helvaci, MR et al., looked at the effect smoking on weight. Smoking may cause loss of appetite via endothelial inflammation all over the body. Consecutive patients with coronary artery disease (CAD) were studied. Study included 2860 cases (1620 females). Prevalence of CAD were similar in females and males (3.8% versus 4.4%, respectively, $p > 0.05$) with mean ages of 61.5 versus 63.5 years, respectively ($p > 0.05$). Smoking and chronic obstructive pulmonary disease (COPD) were significantly higher in males with CAD (54.5% versus 9.6%, $p < 0.001$ and 18.1% versus 6.4%, $p < 0.05$, respectively).

Whereas low density lipoprotein cholesterol (LDL-C) (132.6 versus 115.6 mg/dL, $p = 0.008$), triglyceride (TG) (250.3 versus 150.1 mg/dL, $p = 0.002$). The authors concluded that smoking and excess weight may be the major underlying causes of metabolic syndrome in Turkey, and they may cause similar degree of clinical severity.

Mehmet Rami Helvaci, MR et al., tried to understand whether or not there is a significant relationship in between urolithiasis and smoking. Consecutive patients with urolithiasis were collected into the first, and age and sex-matched controls were collected into the second groups. Fifty-one patients with urolithiasis and 66 controls were studied, totally. When we looked at the urolithiasis patients, 56.8% of them (29 patients) were female with a mean age of 47.2 ± 12.7 (22-70) years. Interestingly, although the lower prevalence of smoking in females in population, the prevalence of smoking was significantly higher in the urolithiasis group, here (45.0% versus 30.3%, $p < 0.05$). The authors concluded that Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract, and cause a low-grade vascular endothelial inflammation all over the body including the gastrointestinal and urinary tracts. The low-grade vascular endothelial inflammation eventually terminates with an accelerated atherosclerosis and relative immunosuppression. The prolonged vascular endothelial inflammation, accelerated atherosclerosis, relative immunosuppression, and sympathetic nervous system activation may induce motility, absorption, and infectious problems in the gastrointestinal and urinary tracts those may terminate with urolithiasis in smokers.

In our Education and Training section, Maurice Brygel, General Surgeon, provides an update and overview of the treatment of haemorrhoids, including rubber band ligation. This will be useful to family doctors undertaking day surgery in the office and for medical and surgical students.

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Table of Contents

- 2 **Editorial**
DOI: 10.5742MEWFM.2018.93505
- Original Contribution**
- 4 **Surgery or combined endolaser ablation and sclerotherapy for varicose veins, a new trend in a developing country (Iraq); a cohort study**
Bashar Hanna Azar, Ashur Yohanna Izac Oraha, Emad Abdulrahman Hussen
DOI: 10.5742MEWFM.2018.93509
- Population and Community Studies**
- 9 **Urolithiasis and smoking**
Mehmet Rami Helvaci, Orhan Ayyildiz, Mustafa Cem Algin, Yusuf Aydin, Abdulrazak Abyad, Lesley Pocock
DOI: 10.5742MEWFM.2018.93507
- 14 **Excess weight or smoking**
Mehmet Rami Helvaci, Orhan Ayyildiz, Mehmet Gundogdu, Yusuf Aydin, Abdulrazak Abyad, Lesley Pocock
DOI: 10.5742MEWFM.2018.93510
- 20 **Health and humanitarian crisis in Yemen**
Lesley Pocock
DOI:
- Clinical Research and Methods**
- 23 **An investigation into the differentiation of hepatic hydatid and simple cysts via diffusion-weighted MRI**
Sameeah A. Rashid, Hamdy Ismat Tahir
DOI: 10.5742MEWFM.2018.93511
- 33 **An exploration into the role of diffusion weighted MRI imaging in the assessment of chronic kidney disease**
Saeed N. Younis, Safa Ezzidin Norouldin Almukhtar, Dendar Khudhur Rashid
DOI: 10.5742MEWFM.2018.93508
- Education and Training**
- 43 **Surgical Skills Series - Haemorrhoids**
Maurice Brygel
DOI: 10.5742MEWFM.2018.93512

Surgery or combined endolaser ablation and sclerotherapy for varicose veins, a new trend in a developing country (Iraq); a cohort study

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Abstract

Introduction: Management of varicose veins has changed in the last few decades in favor of minimal invasive interventions. The developing world lately became part of this revolution. The aim of this study is to report and compare early experience of surgery and endovascular ablation combined with sclerotherapy.

Patients and methods: A retrospective multicenter cohort study included patients diagnosed as cases of primary lower limb varicosities. The patients underwent either of two procedures: Surgical intervention and endolaser ablation combined with sclerotherapy. Sociodemographic and clinical data as well as outcomes, were compared.

Results: The study included 71 patients, with mean age of 36.26. Thirty-nine patients (54.9%) were male. The most common finding was bilateral affection (27, 38%). Forty patients (56.3%) underwent surgical intervention and the other 31 (43.7%) had endolaser ablation and sclerotherapy. Although

early complications occurred more with the surgical intervention, the difference did not reach statistical significance. Overall, the late complications were not significantly different in both arms of the interventions. Both (late and early complications) were highly significantly related to the severity of the CEAP classifications (both p-values were less than 0.001).

Conclusion: Endolaser ablation with sclerotherapy is starting in Iraq. Although it is in the early stage of its development, it has a better outcome compared to the classical surgical intervention.

Key words: endolaser, sclerotherapy, varicose vein, saphenofemoral junction

Introduction

Lower limb varicose veins are defined as dilated subcutaneous veins, more than three millimeters in diameter assessed in the standing position. They can affect the principal axial superficial veins being the small and great saphenous veins or other superficial tributaries. The majority of varicosities are related to primary venous diseases. The leading cause is probably an intrinsic biochemical or biologic anomaly in the venous wall, however other multifactorial causes can lead to it.

Secondary causes are also well-known contributors to the development of varicose veins and these include, deep venous obstruction, deep venous thrombosis, arteriovenous fistula or superficial thrombophlebitis. Congenital cases may present as venous malformations [1].

For a long time, varicose veins have been well known for their cosmetic issues only. However, nowadays, it is well-known that they are frequent causes of pain, disability, loss of working days and declining of the quality of life.

Precedently, the standard treatment for varicosity was operation. The latter involves high ligation and stripping near the knee level with multiple phlebectomies. In the last decade, newer treatments arose in the form of endovenous ablation of great saphenous vein with laser, radiofrequency ablation and ultrasound guided foam sclerotherapy [2].

Regardless of the type of management, all share common aims, which can be summarized as: ablation of the varicosities, boosting venous function, treatment and prevention of complications of chronic venous disorders, relief and/or improvement of venous symptoms, attaining better quality of life, and gaining better aesthetic appearance [3].

The aim of this study was to compare early and late outcomes of the patients undergoing endovascular ablation with sclerotherapy in a developing country (Iraq) compared with those undergoing surgical intervention.

Patients and Methods

Study design and protocol: This was a retrospective multicenter cohort study that included patients diagnosed as cases of lower limb varicosities. Doppler ultrasound was done for all patients before the intervention to confirm the diagnosis, determine the level of the incompetence and exclude deep venous thrombosis. Secondary varicosities were excluded. The patients underwent either of two procedures. Surgical intervention or endolaser and sclerotherapy.

Surgical intervention included saphenofemoral junction ligation (or sapheno-popliteal junction ligation according to the level of incompetence) with multiple stab venous avulsion under spinal anesthesia, followed by bandaging for 12 days. The second type of intervention included under spinal anesthesia, cannulation of the great or small

saphenous vein at the most accessible part below the knee, followed by localization of the saphenofemoral junction under duplex ultrasound guide. While keeping the probe on, the endovenous laser catheter is advanced over a guide wire and the ablation of the junction was performed, through the same port. Foam sclerosing agent is injected using a 1%, 2% or 3% polidocanol, then the catheter is drawn slowly with continuous laser pulses till the whole main stem of the vein is completed.

In the area where the vein was very superficial, we used normal saline injection to separate and cool the tissues. The remaining varices and spider veins were managed by foam sclerotherapy in the same session.

The patients were discharged on the same day and compression stockings were advised to be applied for a week.

Clinical data: For each of the cases, information regarding sex, age, past medical and surgical history, clinical presentation, features of varicose vein, investigations, clinical stage of the diseases (CEAP), types of interventions and follow up were obtained from the medical record. For missed data, the patients were contacted whenever feasible.

Data analysis: Data entry and coding were performed using Microsoft Excel, version 2013; later, the data were transferred to and analyzed by Statistical Package for the Social Sciences (SPSS) software, version 24. Descriptive statistics (percentage, mean, and standard deviation) were calculated to present socio-demographic and clinical data. Chi square test was analyzed to compare categorical data.

Results

The study included 71 patients, with mean age and standard deviation of 36.26 ± 11.28 . Thirty-nine patients (54.9%) were male and 32 (45.1%) were female, 29 (40.8%) of the cases had positive family history for varicose vein. Regarding laterality, the most common finding was bilateral affection (27, 38%), followed by left leg (24, 33.8%) and the least one was the right leg lower limb (20, 28.2%). Pain was the most common clinical manifestation (53, 74.6%), followed by swelling (11, 15.5%), eczema and pigmentation found in 4 (5.6%) cases, ulcer in 1 (1, 1.4%) and in 2 (2.8%) cases there was more than one clinical sign and symptom. Forty patients (56.3%) underwent surgical intervention and the other 31 (43.7%) had endolaser ablation and sclerotherapy. The severity of the varicosity was not significantly related to the types of the procedure (Table 1). Pain was the most common early and late complication (Figures 1 and 2). Although early complications occurred more with the surgical intervention, the difference did not reach statistical significance (Table 2). The most common late complication which significantly differed across the groups was residual varicosity (1 (2.5%) case in surgical group and 7 (22.6%) cases in the group with laser ablation and sclerotherapy, P-value 0.008). Overall, the late

Table 1: Relationship of severity of the varicosity with the types of procedure

Occupation	N					P.Value
	1	2	3	4	5	
Housewife	0	22	6	2	0	0.148
Worker	0	16	1	1	1	
Employee	0	5	3	0	1	
Military	0	2	3	1	0	
Student	1	2	0	0	0	
Unemployed	1	4	0	0	0	

Table 2: Early complications and types of interventions.

Early complications	Surgical producer N		P.Value
	Surgical	Endolaser ablation	
No complication	36	30	0.622
Pain	2	1	
Hematoma	1	0	
Wound infection and hematoma	1	0	

Table 3: Late complications in the two different treatment modalities

Late complications	Surgical producer N		P. Value
	Surgical	endolaser ablation	
NO	28	13	0.057
Recurrence varicose veins	3	1	
Pain	6	4	
Residual varicosity	1	7	
Skin discoloration	0	2	
Oedema	0	1	
Parathesia and pain	0	1	
Parasthesia and itching	0	1	
Parathesia	1	1	
Pain and edema	1	0	

complications were not significantly different in both arms of interventions (Table 3). Neither early nor late complications were significantly related to the site of incompetence (p-value 0.125, p-value 0.894 respectively) while both (late and early complications) were highly significantly related to the severity of the CEAP classifications (both p-values were less than 0.001).

Discussion

In VEDICO (Venous Disease Control) trial, a statement was made in its first part, clarifying that, even in centers of excellence; there are no golden rules for the treatment of varicose veins. Different regional and national variations

exist related to different aspects, being medical or financial [4]. In some developing countries (at least in Iraq) still the operation, in the form of saphenofemoral junction ligation and multiple stab venous avulsion, is the standard method of intervention for management of primary varicosity of the lower limbs whenever intervention is indicated.

During the past decade, the revolution in endovascular technology has changed the ways of treatment and evaluation of varicose veins worldwide. Endovenous ablations and foam sclerotherapy have been considered as a less invasive alternative to vein stripping, and has already gained popularity among vein surgeons in developed countries [1][5].

In trying to keep up with the updates in this subject as a developing country, we tried to present our experience of both techniques. The present study confirmed that overall, minimal invasive therapy (endolaser ablation and sclerotherapy) is preferred over the surgical intervention although the difference has not reached a statistically significant level. This may be explained by the small sample size and short period of follow up.

In a prospective randomized trial performed by Rasmussen et al, comparing EVLA without high ligation and stripping with high ligation, a noticeable reduction in postoperative bruising and pain following laser ablation has been reported [5]. In the current study, hematoma and pain was observed as twice in the surgical group as compared to the endolaser and sclerotherapy arm.

Recurrent varicosity following treatment is considered a serious problem. In a randomized trial by Carradice et al, that discussed the clinical and technical outcomes of endovenous laser ablation, they confirmed the higher rates of recurrence post surgery in comparison with EVLA [6].

In the clinical practice guidelines of the society for vascular surgery and the American venous forum that were published in 2011, recurrent rate ranging from 6.6% to 37% has been reported. This picture decreased afterwards [1]. Two patients complained of residual varices

after endovenous laser ablation in a randomized clinical trial comparing endovenous laser ablation to conventional surgery by D. Carradice et al [6]. In another prospective study that studied EVLA, with a patient sample of 280, only three patients were documented to have residual varicosity [7]. In this study, one patient (2.5%) had residual varicosity following surgical treatment while 7 patients (22.6%) complained of residual varicosity after combined endolaser and foam sclerotherapy treatment. This high rate of residual varices might be explained by the fact that the latter form of therapy in this region is in the early stage and extensive experience is lacking.

Considering post treatment hematoma, we had only one patient with hematoma following surgical intervention, treated by evacuation; comparing this to the literature, in a study published by Manfred Kalteis et al, comparing surgical management versus EVLA, rates of 10% and 12% were reported respectively [5].

Conclusion

Endolaser ablation with sclerotherapy is starting in Iraq. Although it is in the early stage of its development, it has better outcome compared to the classical surgical intervention. Sharing experience within the region is highly recommended.

Figure 1: Distribution of the early complications

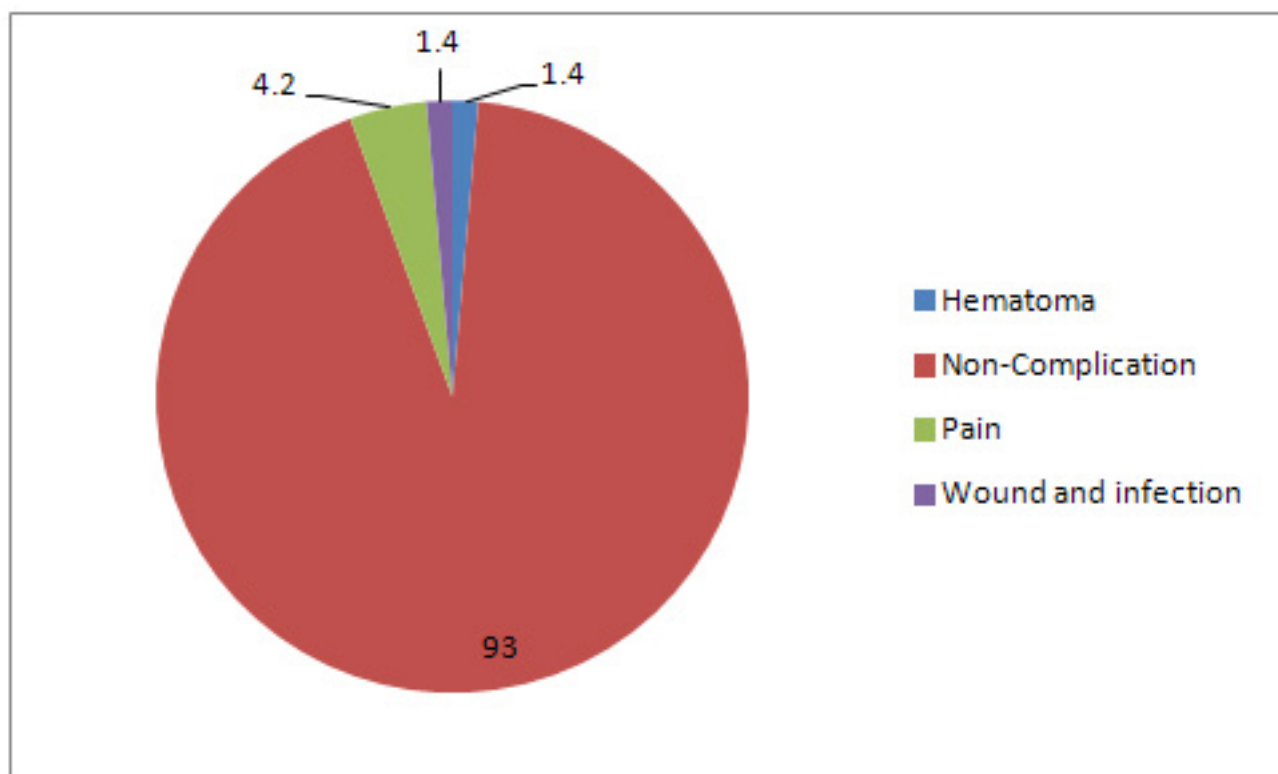
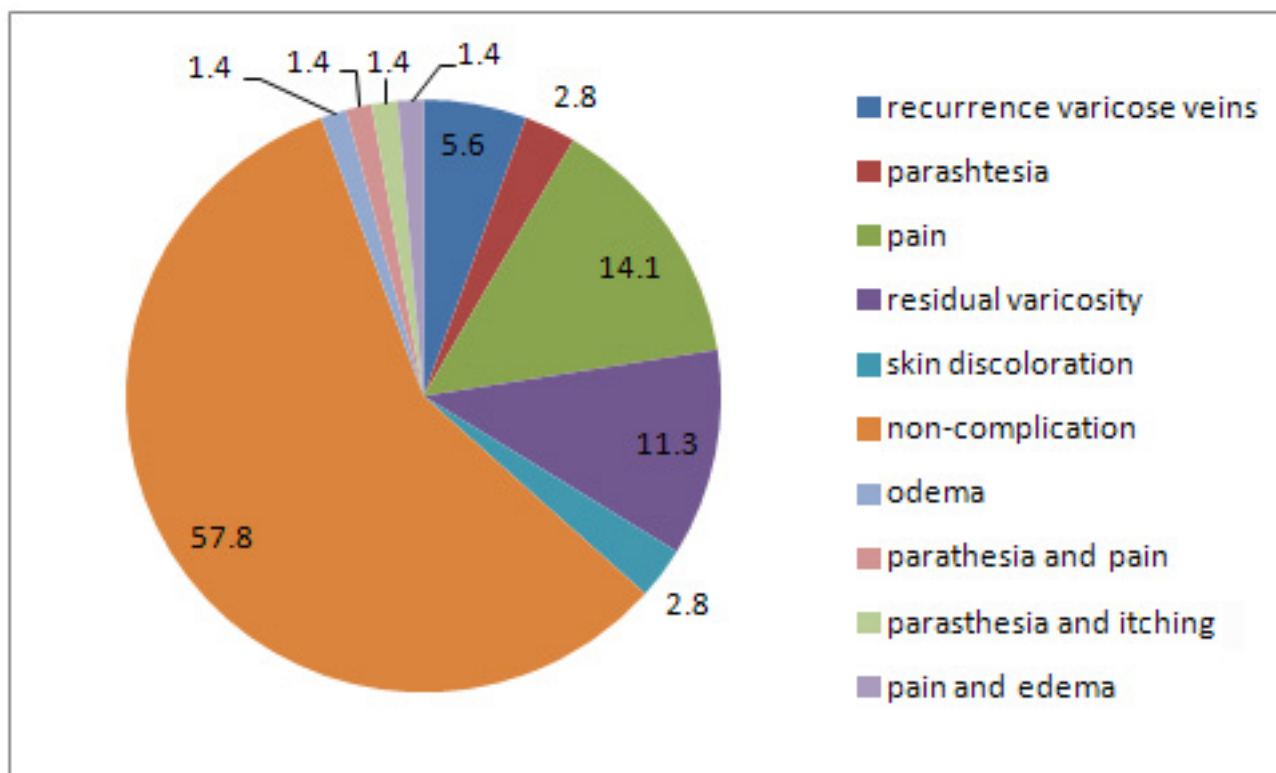


Figure 2: Distribution of the late complications

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Urolithiasis and smoking

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Abstract

Background: Urolithiasis and smoking are common pathologies in society. We tried to understand whether or not there is a significant relationship in between.

Methods: Consecutive patients with urolithiasis were collected into the first, and age and sex-matched controls were collected into the second, groups.

Results: Fifty-one patients with urolithiasis and 66 controls were studied, in total. When we looked at the urolithiasis patients, 56.8% of them (29 patients) were female with a mean age of 47.2 ± 12.7 (22-70) years. Interestingly, although the lower prevalence of smoking in females in the population, the prevalence of smoking was significantly higher in the urolithiasis group, here (45.0% versus 30.3%, $p < 0.05$). On the other hand, there was non-significant difference according to the mean body weight between the groups (77.3 versus 76.4 kg, $p > 0.05$).

Conclusion: Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract, and cause a low-grade vascular endothelial inflammation all over the body including the gastrointestinal and urinary tracts. The low-grade vascular endothelial inflammation eventually terminates with an accelerated atherosclerosis and relative immunosuppression. The prolonged vascular endothelial inflammation, accelerated atherosclerosis, relative immunosuppression, and sympathetic nervous system activation may induce motility, absorption, and infectious problems in the gastrointestinal and urinary tracts; those may terminate with urolithiasis in smokers.

Key words: Urolithiasis, smoking, chronic endothelial inflammation, accelerated atherosclerosis, early aging

Introduction

Urolithiasis is a common pathology in society, and the lifetime risk of urolithiasis is 12-15% for a white man and 5-6% for a white woman with an up to 50% of lifetime recurrence ratio (1). We detected the prevalence of urolithiasis as 13.7% in women and 15.2% in men among the patients applying to internal medicine polyclinic (2). Approximately 80% of the stones are composed of calcium oxalate (CaOx) and calcium phosphate, and CaOx is the main constituent of them. Beside that, 10% of struvite (magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme, urease) and 9% of uric acid stones are seen. The majority of the CaOx stone formers do not suffer from any systemic disease (3), and the minority of the patients have primary hyperparathyroidism or hyperoxaluria secondary to bowel disease (enteric hyperoxaluria) or genetic disorders of oxalate metabolism (primary hyperoxaluria). Although the relatively higher prevalence of urolithiasis in society, there is not any known exact underlying cause of it. There are just some reported systemic illnesses associated with an increased risk of urolithiasis in the literature. For example, patients with chronic diarrheal illnesses such as ulcerative colitis and Crohn's disease can develop enteric hyperoxaluria; those result with an increased risk of renal stones (4). Oxalate may be the primary problem in such patients, since excess oxalate is absorbed through the inflamed bowel wall. Similarly, a low-grade inflammation induced increased absorption of oxalate may be the primary mechanism of urolithiasis in irritable bowel syndrome (IBS), since it was shown in the above study that there is a significant relationship between urolithiasis and IBS (2). Although indirectly, increased oxalate absorption induced urolithiasis has also been shown previously (5, 6). On the other hand, smoking is a well-known cause of chronic vascular endothelial inflammation all over the body. We tried to understand whether or not there is a significant relationship between urolithiasis and smoking in the present study.

Material and Methods

The study was performed in the Internal Medicine Polyclinic of the Mustafa Kemal University between August 2008 and January 2009. Consecutive patients were taken into the study and patients above the age of 70 years were excluded to avoid debility induced weight loss in elders. Their medical histories including smoking habit were learnt, and current smokers for the last six-months and cases with a history of five pack-years in the past were accepted as smokers. A routine check up procedure including hematologic and biochemical tests, urinalysis, and an abdominal X-ray graphy in supine position was performed, and patients with devastating illnesses including type 1 diabetes mellitus (DM), malignancies, acute or chronic renal failure, cirrhosis, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on body weight. An additional intravenous pyelography was obtained just in suspected cases from urolithiasis at the moment as a result of the urinalysis and abdominal X-ray graphy. So urolithiasis was diagnosed either by medical history or as a result of current laboratory tests. Eventually, cases with urolithiasis were collected into the first, and age and sex-matched controls were collected into the second groups. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Results

Fifty-one patients with urolithiasis and 66 controls were studied, totally. When we looked at the urolithiasis patients, 56.8% of them (29 patients) were female with a mean age of 47.2 ± 12.7 (22-70) years. Interestingly, although the lower prevalence of smoking in females in the population, the prevalence of smoking was significantly higher in the urolithiasis group, here (45.0% versus 30.3%, $p < 0.05$). On the other hand, there was nonsignificant difference according to the weight in between (77.3 versus 76.4 kg, $p > 0.05$).

Table 1: Characteristic features of the study cases

Variables	Cases with urolithiasis	p-value	Control cases
Number	51		66
Female ratio	56.8% (29)	Ns*	56.0% (37)
Mean age (years)	47.2 ± 12.7 (22-70)	Ns	45.6 ± 13.1 (20-67)
Mean body weight (kg)	77.3 ± 16.5 (45-114)	Ns	76.4 ± 12.2 (50-98)
<i>Prevalence of smoking</i>	<i>45.0%</i> (23)	<i><0.05</i>	<i>30.3%</i> (20)

*Nonsignificant ($p > 0.05$)

Discussion

Smoking may be found among one of the most common causes of vasculitis in the world. It is a major risk factor for the development of atherosclerotic endpoints including coronary artery disease (CAD), peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease (CRD), stroke, cancers, early aging, and premature death (7, 8). Its atherosclerotic effects are the most obvious in Buerger's disease. It is an obliterative disease characterized by inflammatory changes in small and medium-sized arteries and veins, and it has never been reported in the absence of smoking in the literature. Although there are well-known strong atherosclerotic effects of smoking, some studies reported that smoking in humans and nicotine administration in animals are associated with a decreased body mass index (BMI) (9). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (10), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (11). According to an animal study, nicotine may lengthen intermeal time and simultaneously decreases amount of meal eaten (12). Additionally, BMI seems to be the highest in former, the lowest in current and medium in never smokers (13). Smoking may be associated with postcessation weight gain but evidence suggests that risk of weight gaining is the highest during the first year after quitting and declines over the years (14). Similarly, although the CAD was detected with similar prevalence in both genders in a previous study (15), prevalence of smoking and COPD were higher in males with CAD against the higher prevalence of BMI, white coat hypertension (WCH), low density lipoprotein cholesterol, triglyceride, hypertension (HT), and DM in females with CAD as the other atherosclerotic risk factors. This result may indicate both the strong atherosclerotic and weight decreasing roles of smoking (16). Similarly, the incidence of a myocardial infarction is increased sixfold in women and threefold in men who smoke at least 20 cigarettes per day compared to the never smoked cases (17). In other words, smoking is more dangerous for women regarding the atherosclerotic endpoints probably due to the higher BMI and its consequences in them. Parallel to the above results, the proportion of smokers is consistently higher in men in the literature (8). So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite. Smoking-induced weight loss may be related with the smoking-induced vascular endothelial inflammation all over the body, since loss of appetite is one of the major symptoms of inflammation in the body. Physicians can even understand healing of their patients from their returning appetite. Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract, and cause a low-grade vascular endothelial inflammation all over the body until clearance from the circulation. But due to the repeated smoking habit of the individuals, the clearance process never terminates. So the patients become ill with loss of appetite, permanently. In another explanation, smoking-induced weight loss is an indicator of being ill instead of being healthy (11-13).

After smoking cessation, normal appetite comes back with a prominent weight gain in the patients but the returned weights are their physiological or 'actual' weights. On the other hand, smoking as a pleasure in life may also show the weakness of volition to control eating so it comes with additional weight excess and its consequences. Similarly, prevalence of HT, DM, and smoking were the highest in the highest triglyceride having group as another significant component of the metabolic syndrome (18).

There may be several mechanisms increasing the incidence of urolithiasis in smokers. First of all, smoking may cause a chronic low-grade inflammation in the gastrointestinal tract epithelium by disturbing the normal balance between intestinal flora and circulatory defence mechanisms. The low-grade inflammation induced increased absorption of oxalate, as in chronic diarrheal illnesses, may be the development mechanism of urolithiasis in smokers. Smoking induced sympathetic nervous system activation may cause motility disorder that may aggravate this instability, since diarrheal losses induced lower urinary pH and citrate levels increase urinary CaOx and uric acid supersaturations since citrate may inhibit calcium crystallization by binding to it. Secondly, accelerated atherosclerosis may disturb both gastrointestinal and urinary tracts' epithelial functions for absorption and excretions of elements, so facilitating directly a stone or just a nidus formation for stone. Even the accelerated atherosclerosis induced electrolyte imbalance in urine may facilitate urolithiasis. Thirdly, immunosuppression secondary to accelerated atherosclerosis induced urinary tract infections may cause urolithiasis since some types of bacteria can provoke urinary supersaturation and modify the environment thus leading to formation of crystal deposits that may be a factor promoting urolithiasis. In fact, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme, urease. Lastly, accelerated atherosclerosis induced glomerular dysfunctions may alter urinary contents, facilitating urolithiasis. So there may be hundreds of mechanisms with variable priorities for urolithiasis in smokers, thus the result of the study should not be surprising.

It is a well known entity that excess weight causes a high cost on physical health even in early decades. Persons with excess weight have a higher prevalence of elevated blood pressure than lean persons, and well-known complications of HT are left ventricular hypertrophy, CAD, heart failure, chronic renal failure, and stroke (19, 20). Similarly, atherogenic dyslipidemia is commonly seen in cases with excess weight, and it is characterized by increased levels of triglycerides and/or low density lipoprotein cholesterol, or a decreased level of high density lipoprotein cholesterol in serum (19). On the other hand, excess weight is accompanied by a large number of coagulation and fibrinolytic abnormalities suggesting that it induces a prothrombotic and proinflammatory state (21). The low-grade chronic vascular endothelial inflammation is characterized by lipid-induced injury that initiates invasion of macrophages followed by proliferation of smooth muscle

cells, endothelial dysfunction, and increased atherogenicity (22, 23). As a supporting evidence of the role of inflammation in atherosclerosis, elevations of serum C-reactive protein (CRP) carry predictive power for the development of major cardiovascular events (24). In particular, excess weight is considered as a strong factor for controlling of circulating CRP concentrations because adipose tissue is involved in the regulation of cytokines (25), so individuals with excess weight have elevated levels of CRP (26). Furthermore, excess weight is highly correlated with dietary intake of increased calories and fat, both of which have been linked to several types of cancer including breast, colon, and prostate (27). Although excess weight is associated with an increased risk of all-cause mortality (28), there was no significant difference according to the mean body weight between the urolithiasis patients and control cases in the present study.

Due to the prolonged survival of human beings, systemic atherosclerosis probably will be the main health problem all over the world in this century, and its associations with sedentary life style, excess weight, smoking, and alcohol are researched under the title of metabolic syndrome in the literature, extensively (29, 30). The syndrome is characterized by a low-grade inflammatory process on vascular endothelium initiated in early years of life (31). The syndrome includes sedentary life style, overweight, WCH, impaired fasting glucose, impaired glucose tolerance, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, smoking, alcohol, and chronic infections and inflammation for the development of irreversible consequences including obesity, HT, DM, COPD, cirrhosis, CRD, PAD, CAD, stroke, early aging, cancers, and premature death (32, 33). In another perspective, the metabolic syndrome may be the most significant disease of human life decreasing its quality and duration at the moment. The syndrome has become increasingly common all over the world, for example 50 million people in the United States are affected (34). Metabolic syndrome can be slowed down with appropriate non-pharmaceutical approaches including lifestyle changes, diet, and exercise in early years of life (35). If not, the syndrome induced accelerated atherosclerotic process all over the body may be the leading cause of early aging and premature death for both genders. For example, CAD and cancers are the leading causes of death in developed countries. Similarly, although the well-known mutagenic effects of smoking, its role in cancers may also be related to the systemic atherosclerotic process that immune cells can not eradicate cancer cells, effectively, due to the insufficient blood supply of the tissues (7).

As a conclusion, several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract, and cause a low-grade vascular endothelial inflammation all over the body including the gastrointestinal and urinary tracts. The low-grade vascular endothelial inflammation eventually terminates with an accelerated atherosclerosis and relative immunosuppression. The prolonged vascular endothelial inflammation, accelerated atherosclerosis, relative immunosuppression, and sympathetic nervous system activation may induce motility,

absorption, and infectious problems in the gastrointestinal and urinary tracts which may terminate with urolithiasis in smokers.

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Excess weight or smoking

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Abstract

Background: Smoking may cause loss of appetite via endothelial inflammation all over the body.

Methods: Consecutive patients with coronary artery disease (CAD) were studied.

Results: Study included 2,860 cases (1,620 females), totally. Prevalence of CAD was similar in females and males (3.8% versus 4.4%, respectively, $p>0.05$) with mean ages of 61.5 versus 63.5 years, respectively ($p>0.05$). Smoking and chronic obstructive pulmonary disease (COPD) were significantly higher in males with CAD (54.5% versus 9.6%, $p<0.001$ and 18.1% versus 6.4%, $p<0.05$, respectively). On the other hand, body mass index (BMI) and white coat hypertension (WCH) were higher in females with CAD (29.7 versus 28.3 kg/m² and 30.6% versus 23.6%) but differences were non-significant ($p>0.05$ for both) probably due to small sample sizes of CAD groups. Whereas low density lipoprotein cholesterol (LDL-C) (132.6 versus 115.6 mg/dL, $p=0.008$), triglyceride (TG) (250.3 versus 150.1 mg/dL, $p=0.002$), hypertension (HT) (58.0% versus 30.9%, $p<0.001$), and diabetes mellitus (DM) (51.6% versus 38.1%, $p<0.05$) were all higher in females with CAD, significantly.

Conclusion: Smoking and excess weight may be the major underlying causes of metabolic syndrome in Turkey, and they may cause a similar degree of clinical severity. Smoking and COPD were higher in males with CAD against the higher BMI, WCH, LDL-C, TG, HT, and DM in females terminating with similar prevalence of CAD in both genders. To be able to understand the clear effects of smoking on BMI and its consequences, the next study should be performed on non-smokers in both genders.

Key words: Excess weight, smoking, atherosclerosis, metabolic syndrome, early aging, premature death

Introduction

Due to the prolonged survival of human beings, systemic atherosclerosis may be the main health problem in this century, and its associations with some metabolic disorders and smoking are collected under the title of metabolic syndrome in the literature (1, 2). The syndrome is characterized by a low-grade chronic inflammatory process on vascular endothelium initiated in early years of life (3). The inflammatory process is initiated by some factors including overweight, obesity, smoking, alcohol, and chronic infections and inflammations (4, 5). The syndrome can be slowed down with appropriate non-pharmaceutical approaches including lifestyle changes, diet, and exercise (6). The metabolic syndrome may contain white coat hypertension (WCH), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, overweight, alcohol, and smoking for the development of irreversible consequences including hypertension (HT), type 2 diabetes mellitus (DM), obesity, chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease (CRD), peripheral artery disease (PAD), coronary artery disease (CAD), and stroke (7). In another perspective, the metabolic syndrome may be the most significant disease of human life decreasing its quality and duration at the moment. The syndrome has become increasingly common all over the world, for example 50 million people in the United States have it (8). The syndrome induced accelerated atherosclerotic process all over the body may be the leading cause of early aging and premature death for both genders. For example, CAD is the leading cause of death in developed countries. Although CAD may be equally seen in both genders (7), there may be some gender differences about the risk factors of CAD. We tried to understand whether or not there are some gender differences according to the atherosclerotic risk factors in patients with CAD in the present study.

Material and Methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. We took consecutive patients above the age of 15 years. Their medical histories including smoking habit were learnt, and a routine check up procedure including fasting plasma glucose (FPG), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), and an electrocardiography was performed. Current smokers with six pack-months and cases with a history of five pack-years were accepted as smokers. COPD was diagnosed via the pulmonary function tests in suspected cases in which the ratio of forced expiratory volume in the first second of expiration to forced vital capacity is lower than 70%. Body mass index (BMI) of each case was calculated by the measurements of the same physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (9). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already using antidiabetic medications were

defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 126 mg/dL, and diagnosis of cases with a two-hour plasma glucose level of 200 mg/dL or higher is DM. An office blood pressure (OBP) was checked after a 5-minute rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous two hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked HT after education about proper BP measurement techniques (10). A 24-hour ambulatory blood pressure (ABP) monitoring was not required due to its equal effectiveness with HBP measurements (11). Eventually, HT is defined as a mean HBP value of 135/85 mmHg or greater, and WCH as an OBP of 140/90 mmHg or greater, but a mean HBP value of lower than 135/85 mmHg (10). A stress electrocardiography was performed in cases with an abnormal electrocardiography and/or history of angina pectoris. A coronary angiography was obtained just for the stress electrocardiography positive cases. So CAD was diagnosed either angiographically or with a history of coronary artery stenting and/or coronary artery bypass graft surgery. Eventually, all cases with CAD were divided into two groups according to gender distribution, and they were compared in between. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 1,620 females and 1,240 males. Mean ages were 41.7 and 40.8 years, respectively ($p > 0.05$). Prevalence of CAD was similar in females and males (3.8% versus 4.4%, respectively, $p > 0.05$). Mean ages of the CAD cases were 61.5 versus 63.5 years, respectively ($p > 0.05$) (Table 1). Prevalence of smoking was significantly higher in males with CAD (54.5% versus 9.6%, $p < 0.001$). Parallel to the higher prevalence of smoking, prevalence of COPD was also higher in males, significantly (18.1% versus 6.4%, $p < 0.05$). On the other hand, although the mean weight of males with CAD was significantly higher (79.1 versus 74.4 kg, $p = 0.027$), the females had a higher mean BMI value (29.7 versus 28.3 kg/m², $p > 0.05$), but the difference was statistically non-significant probably due to the small sample sizes of the CAD groups. Similarly, the mean LDL-C and TG values were significantly higher in females with CAD, too (132.6 versus 115.6 mg/dL, $p = 0.008$ and 250.3 versus 150.1 mg/dL, $p = 0.002$, respectively). Although prevalence of WCH was also higher in females, the difference was non-significant probably due to the small sample sizes of the CAD groups again (30.6% versus 23.6%, $p > 0.05$). Although the small sample sizes of the CAD groups, prevalence of HT and DM was significantly higher in females with CAD (58.0% versus 30.9%, $p < 0.001$ and 51.6% versus 38.1%, $p < 0.05$, respectively).

Table 1: Characteristic features of the study cases

Variables	Males with CAD*	Females with CAD	p-value
Prevalence	4.4% (55/1,240)	3.8% (62/1,620)	Ns†
Mean age (year)	63.5 ± 10.8 (43-82)	61.5 ± 11.2 (42-88)	Ns
<u>Prevalence of smokers</u>	<u>54.5% (30)</u>	<u>9.6% (6)</u>	<u><0.001</u>
<u>Prevalence of COPD‡</u>	<u>18.1% (10)</u>	<u>6.4% (4)</u>	<u><0.05</u>
<u>Mean weight (kg)</u>	<u>79.1 ± 12.9 (58-116)</u>	<u>74.4 ± 18.7 (42-129)</u>	<u>0.027</u>
Mean BMI§ (kg/m ²)	28.3 ± 4.7 (20.6-46.9)	29.7 ± 6.7 (19.0-48.6)	Ns
<u>Mean LDL-C (mg/dL)</u>	<u>115.6 ± 38.5 (43-192)</u>	<u>132.6 ± 47.3 (10-232)</u>	<u>0.008</u>
<u>Mean TG¶ (mg/dL)</u>	<u>150.1 ± 113.4 (53-594)</u>	<u>250.3 ± 233.9 (81-1380)</u>	<u>0.002</u>
Prevalence of WCH**	23.6% (13)	30.6% (19)	Ns
<u>Prevalence of HT***</u>	<u>30.9% (17)</u>	<u>58.0% (36)</u>	<u><0.001</u>
<u>Prevalence of DM****</u>	<u>38.1% (21)</u>	<u>51.6% (32)</u>	<u><0.05</u>

*Coronary artery disease †Nonsignificant (p>0.05) ‡Chronic obstructive pulmonary disease §Body mass index ||Low density lipoprotein cholesterol ¶Triglyceride **White coat hypertension ***Hypertension ****Diabetes mellitus

Discussion

Vascular endothelial inflammation is actually caused by some metabolic risk factors for the development of systemic atherosclerosis, and the symptomatic atherosclerosis is probably the leading cause of early aging and premature death for both genders in human beings. Smoking, alcohol, and excess weight are probably the most common causes of the systemic endothelial damage (12). Definition of the metabolic syndrome or aging syndrome or accelerated endothelial damage syndrome includes metabolic risk factors including overweight, smoking, alcohol, WCH, IFG, IGT, hypertriglyceridemia, hyperbetalipoproteinemia, and dyslipidemia for the development of irreversible endpoints including HT, DM, obesity, COPD, cirrhosis, CRD, PAD, CAD, stroke, early aging, and premature death (13, 14). In a previous study, prevalence of hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, IGT and WCH had a parallel fashion to excess weight by increasing until the seventh decade of life and decreasing afterwards, significantly (p<0.05 nearly in all steps) (15). On the other hand, prevalence of HT, DM, and CAD always continued to increase by aging without any decrease (p<0.05 nearly in all steps) indicating their irreversible properties (15). After development of one of the irreversible consequences, the nonpharmaceutical approaches will provide little benefit to prevent development of the others probably due to

cumulative effects of the risk factors on the endothelial system for a long period of time all over the body (13, 14).

Obesity is probably found among one of the irreversible consequences of the metabolic syndrome since after the development of obesity, non-pharmaceutical approaches provide limited success either to heal obesity or to prevent its complications. Overweight and obesity probably lead to a chronic and low-grade inflammatory process on vascular endothelial system, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of weight excess in all age groups (16). The low-grade chronic inflammation may cause genetic changes on epithelial cells, and the systemic atherosclerosis may decrease clearance of malignant cells by the immune system, effectively (17). For example, effects of excess weight on BP were shown in a study that the prevalence of sustained normotension (NT) was significantly higher in the underweight (80.3%) than the normal weight (64.0%) and overweight cases (31.5%, p<0.05 for both) (18), and 52.8% of cases with HT had obesity against 14.5% of cases with NT (p<0.001) in another study (19). So the dominant underlying risk factor of the metabolic syndrome appears as weight gaining, which is probably the main cause of insulin resistance, dyslipidemia, IGT, and WCH

by means of a chronic inflammatory process (6). Even prevention of the accelerating trend of weight gaining with diet or exercise, even in the absence of a prominent weight loss, will probably result with resolution of many adverse parameters of the syndrome (20, 21). But according to our opinion, limitation of excess weight as an excessive fat tissue in and around the abdomen under the heading of abdominal obesity is meaningless, instead it should be defined as overweight or obesity by means of BMI since adipocytes function as an endocrine organ that produces a variety of cytokines and hormones anywhere in the body (6). The resulting hyperactivities of sympathetic nervous system and renin-angiotensin-aldosterone system are probably associated with chronic endothelial inflammation, insulin resistance, and an elevated BP. Similarly, the Adult Treatment Panel III reported that although some people were classified as overweight with a large muscular mass, most of them also have excess fat tissue, and excess weight does not only predispose to CAD, stroke, and other endpoints, it also has a high burden of other CAD risk factors including dyslipidemia, HT, and DM (9).

Smoking is a major risk factor for the development of atherosclerotic endpoints such as CAD, PAD, COPD, cirrhosis, CRD, and stroke (17, 22). Its atherosclerotic effects are the most obvious in Buerger's disease (thromboangiitis obliterans). It is an obliterative disease characterized by inflammatory changes in small and medium-sized arteries and veins, and it has not been documented in non-smokers, implicating cigarette smoking as a primary etiologic factor. Although the known strong atherosclerotic effects of smoking, some studies reported that smoking in humans and nicotine administration in animals are associated with a decreased body weight (23). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (24), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (25). According to an animal study, nicotine may lengthen intermeal time and simultaneously decreases amount of meal eaten (26). Additionally, body weight seems to be the highest in former, the lowest in current and medium in never smokers (27). Smoking may be associated with postcessation weight gain, but evidence suggests that risk of weight gain is the highest during the first year after quitting and declines over the years (28). Similarly, although the CAD was detected with similar prevalences in both genders in the previous study (7), prevalence of smoking and COPD were higher in males with CAD against the higher prevalence of BMI, WCH, LDL-C, TG, HT and DM in females as the other atherosclerotic risk factors. This result may indicate both the strong atherosclerotic and weight decreasing roles of smoking. Similarly, the incidence of a myocardial infarction is increased sixfold in women and threefold in men who smoke at least 20 cigarettes per day compared to the never smoked cases (29). In other words, smoking is more harmful for women regarding CAD, probably due to the associated higher BMI and its consequences in women. Similar to our results, the proportion of smokers is consistently higher in men in the literature (22). So smoking is probably a powerful

atherosclerotic risk factor with some suppressor effects on appetite.

Smoking-induced weight loss may be related with the smoking-induced endothelial inflammation all over the body, since loss of appetite is one of the major symptoms of inflammations in the body. Physicians can even understand healing of their patients from their returning appetite. Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory system, and they probably cause a subclinical vascular endothelial inflammation until their clearance from the circulation. But due to the continuous smoking habits of the individuals, the clearance process never terminates. So the patients become ill with loss of appetite, subclinically. In another explanation, smoking-induced loss of weight is an indicator of being ill instead of being healthy during smoking (25-27). After smoking cessation, loss of appetite comes back with a prominent weight gaining in the patients but the returned weight is their physiological or 'usual' weights, actually. On the other hand, smoking as a pleasure in life may also show the weakness of volition to control eating in the metabolic syndrome, so it comes with additional weight excess and its complications although there are some inhibitory effects of it on appetite. Similarly, prevalence of HT, DM, and smoking were the highest in the highest TG having group as another significant component of the metabolic syndrome in another study (14).

Alcohol may also cause severe endothelial damage not only in the vasculature of gastrointestinal tract instead all over the body (30, 31). It may have similar adverse effects with smoking on vascular endothelium with different severity in different organs (17). In other words, alcohol causes COPD and smoking causes cirrhosis, too. Both of them affect both arterial and venous endothelial cells all over the body. Buerger's disease alone is clear evidence to show the strong atherosclerotic effects of smoking since this disease has not been shown in the absence of smoking in the literature. Similarly, the alcoholic cirrhosis alone is clear evidence to show strong atherosclerotic effects of alcohol. The effects of smoking and alcohol on vascular endothelium terminate with a symptomatic atherosclerosis, end-organ insufficiencies, early aging, and premature death, therefore they must be included among the parameters of the metabolic syndrome. We did not study the effects of alcohol due to its low prevalence in Turkey in the present study.

Male gender alone may also be a significant factor for the accelerated atherosclerotic process since females live longer than males all over the world (32). Concern to protect his family is a feature of male sex in human beings and even in animal kinds. The feature probably comes from testosterone. You rarely see females fighting with each other for a male but you can easily see some fighting males for a female in human beings and especially in animal species. You can see soldiers or coalmine workers in males but rarely in females. Males use their physical force more in daily life. The dominant physical role of male sex is also seen during sexual activities. The overuse of body probably

causes an accelerated atherosclerosis and a shortened lifespan in males. The shortened survival of male gender was even shown in the sickle cell patients although they have significantly shorter mean life expectancy with the current health services (33). Due to some antidepressive properties of smoking and alcohol, they are also more common in males all over the world which may also indicate presence of some additional stresses on the male gender in society. But the longer lifespan of females cannot be explained by the strong atherosclerotic effects of smoking and alcohol alone. Effects of testosterone may also be important in the shortened survival of males. So the dominant role of male gender, smoking, and alcohol put them into the accelerated atherosclerotic process whereas excess weight is the major problem in females regarding the accelerated aging process. In other words, overuse of the body in males and underuse of the body in females may accelerate the endothelial inflammation and damage, atherosclerosis, early aging, and premature death. Avoidance of smoking, alcohol, and excess weight are essential in protection from the metabolic syndrome. On the other hand, the term of regular exercise should be replaced with daily and essential activities in the protection of females since they actually need a lifestyle change instead of exercise. Avoidance of animal-rich diet, walking as much as possible, avoidance of elevators, eating fruit with its peel even to escape chronic constipation, drinking tea, finding daily responsibilities, finding new aims to live, and not using taxis should be the lifestyles of people under the risk of syndrome.

As a conclusion, metabolic syndrome or aging syndrome or accelerated endothelial damage syndrome is a systemic and inflammatory atherosclerotic process. Smoking and excess weight may be the major underlying causes of the syndrome in Turkey, and they may cause similar degrees of clinical severity. Smoking and COPD were higher in males with CAD against the higher BMI, WCH, LDL-C, TG, HT, and DM in females terminating with a similar prevalence of CAD in both genders. To be able to understand the clear effects of smoking on BMI and its consequences, the next study should be performed on non-smokers in both genders.

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Health and Humanitarian crisis in Yemen: The Health system in Yemen is close to collapse and 13 million people are at risk of starvation. Most affected are children

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Amara is held by her father, Omar*, in the Save the Children-supported health facility. 10-month-old Amara* is from Hajjah governorate in northern Yemen and suffers from Severe Acute Malnutrition.*

PHOTO CREDIT: Claire Nicoll / Save the Children

The United Nations has issued a warning that Yemen could experience the worst famine seen in the past 100 years.

Despite the cessation of major hostilities in April this year, ground fighting is still taking place in Marib, Al-Jawf and Taiz, claiming dozens of lives and overburdening existing health facilities. Yemen is facing a growing humanitarian catastrophe as health workers are either forced to leave the area or are staying and risking their lives to help innocent civilians caught up in the deadly conflict. Yemen's

health system was already struggling and is now under enormous strain. The health workers who remain in the country are unable to provide even basic care.

Fighting has reached 21 of the country's 22 governorates (provinces) and more than 4,000 people have been killed by weapons of war, according to the United Nations.

More than half of the people have little access to basic health care, and less than 45% of the hospitals are still able to provide any form of health care.

Thousands of people have died from the outbreak of cholera in 2017. By December 2017, the outbreak of cholera in Yemen had infected one million people. Despite cholera being a treatable disease, thousands of people have died due to lack of availability of basic medical facilities.

In addition to cholera, other contagious diseases such as diphtheria are spreading in the country. A lack of access to safe drinking water is compounding the ongoing health crisis as is absence of immunisation and preventive programs.

More than 80% of Yemen's population lacks food, fuel, drinking water and access to health care services, leaving the population vulnerable to diseases that can generally be cured or eradicated elsewhere in the world.

Yemeni children are literally starving to death and the world has seen the dreadful images of small children just skin and bones, their bodies bloated, and too weak to lift their heads and limbs, on the nightly news on their television screens. Yet the world has failed to act as this disaster has been brought about by politics, not failure of crops due to droughts that have raised the sympathy of the world in other famines. While mass convoys of food, medicine and health workers are needed, the political situation is not

conducive to their entry given the prior attacks on these forms of aid.

Update: October 23. Closing of the Port city of Hudaydah (Hodeidah) has further exacerbated the problem by closing one of the last entry points for food and medicine.

Helping these gentle and good people requires a few brave steps. The ordinary people of Yemen require, peace and normalcy and a great deal of assistance to restore their ordinary lives that have been robbed from them.

Some NGOs are currently working in Yemen. For those who cannot directly assist, NGOs working in Yemen's conflict and disaster zones need to be supported. Save the Children welcomes such support from world doctors and the public and can be contacted on:

<https://www.savethechildren.org.au/donate/more-ways-to-give/current-appeals/yemencrisis>

Lesley Pocock

The following pictures and reports come from Save The Children currently working on the ground.



Razan was seriously injured in an airstrike when fleeing violence in Hodeidah, Yemen.*

Eight-year-old Razan seriously injured her eye when she was hit by shrapnel during an airstrike in Hodeidah. When she was injured, she was fleeing the violence with her family. After she was injured, she suffered at home in pain for five days as her family couldn't afford the cost of transport to hospital. Save the Children referred Razan to a specialist hospital for emergency surgery and is providing psychosocial support to help her begin to come to terms with her experiences.*

PHOTO CREDIT: Mohammed Awadh / Save the Children



Sabreen*, one year old, suffers from Cholera.
PHOTO CREDIT: Ali Ashwal / Save the Children



Suha*, two and a half, lives in Haboor district in Amran governorate, Yemen.
She suffers from severe malnutrition and, as a result, is unable to eat, walk or sit. Suha is receiving treatment at the Save the Children-supported health facility in Haboor.
PHOTO CREDIT: Mohammed Awadh / Save the Children

An investigation into the differentiation of hepatic hydatid and simple cysts via diffusion-weighted MRI

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Abstract

Background and objective: As opposed to simple hepatic cysts (SHC) that are benign, hydatid hepatic cysts are associated with serious complications such as bacterial infection, anaphylactic shock, and spread of new cysts. However, both simple and hydatid cysts are asymptomatic and diagnosed accidentally. The present study was carried out in order to investigate the capacity of diffusion-weighted magnetic resonance imaging (DW-MRI) in differentiating hepatic hydatid and simple cysts among patients who referred to Azadi Teaching Hospital in Duhok, the Kurdistan Region of Iraq from October 2017 to April 2018.

Materials and methods: Performing DW-MRI on 60 patients led to diagnosis of 108 cysts (16 completely liquid (CL) hydatid cysts, 14 cystic echinococcosis CE1, 10 CE2, 17 CE3, 15 CE4, and 36 simple hepatic cysts), and apparent diffusion coefficients (ADCs) were measured. A comparison between the signal intensity on the cysts and the liver was carried out by employing a 3-point scale (0=hypointense, 1= isointense, & 2=hyperintense). The results of the diagnosis were supported by surgery and/or ELISA test. Mean and standard deviation of different types of cysts using DW-MRI (b=0, 400, and 800) were calculated using SPSS 22.0, and the results were presented in tables and diagrams.

Results: According to the results of DW-MRI (b=0, 400, and 800), most of the cysts were hyperintense. Moreover, the results of comparing mean DW cyst at b0, b400, and b800 among types of hepatic cysts showed that CE2 and CE4 had the highest prevalence. Also, comparing mean DW cyst to parenchyma ratio at b0, b400, and b800 among types of hepatic cysts revealed that the highest prevalence belonged to CE3 and CE4. Moreover, comparison of mean ADC cyst at b0 and b800 among types of hepatic cysts showed the highest prevalence for CE3 and CL. Finally, comparing mean ADC cyst to parenchyma ratio at b0 and b800 among types of hepatic cysts revealed the highest prevalence for CL and SHC.

Conclusion: According to the results of the present study, it can be stated that DW-MRI may have the capacity to differentiate between hepatic hydatid and simple cysts.

Key words: hepatic hydatid cysts, hepatic simple cysts, diffusion-weighted MRI, apparent diffusion coefficient

Table 1: Classification of hydatid cysts based on Gharbi and WHO-Informal Working Group of Echinococcosis (WHO-IWGE)

Gharbi	WHO	Ultrasonography characteristics
-	CL	Unilocular cyst, anechoic, no wall depicted
Type I	CE1	CL characteristics + wall + mobile internal echogenicities
Type II	CE2	Multivesicular, multiseptated cyst, daughter cysts, honeycomb pattern
Type III	CE3	Detached-floating membrane (water-lily sign)
Type IV	CE4	Heterogeneous hypo/hyperechoic cyst, no daughter cyst
Type V	CE5	Cyst with a partial or complete wall calcification

Introduction and Background

The general prevalence of hepatic cysts, as indicated by research, is about 5% all over the world, which rises with age, particularly after the age of 80 [1,2]. Cystic lesions involving the liver may be classified into developmental, neoplastic, inflammatory, and miscellaneous lesions. Because the clinical presentations and management strategies of cystic liver lesions differ significantly according to their causes, the need to differentiate non-invasively different types of cysts is extremely important [3,4]. It should also be noted that hydatid cysts cause serious complications such as bacterial infection, anaphylactic shock, and spread of new cysts [5].

As a zoonotic infection caused by the larvae of cestodes of the genus *Echinococcus*, hydatid cysts usually afflict the lungs and liver and can cause chronic disease and death if they are not diagnosed early and managed efficiently [6].

Based on their sonographical characteristics, hydatid cysts are classified into 5 groups (See Table 1) [7, 8]. According to this classification, 25 to 40% of hydatid cysts fall into type 1 which are almost indistinguishable from simple cysts because they have sonographic similarity [9].

Since both types of cysts are asymptomatic, they are mostly diagnosed incidentally through imaging technologies including computed tomography (CT) scan, ultrasound (US), and magnetic resonance imaging (MRI) [8]. US has been introduced as the gold standard method to diagnose and determine the number, placement, and size of cysts [7]. However, this method cannot detect cysts until they form their wall and become completely solid, which practically restricts its capacity to detect cysts in their early stage because cysts are liquid in initial stages [11]. Therefore, the results of US depend on the maturity of the cysts [9].

On the other hand, due to high contrast resolution on images obtained from conventional MRI, it is introduced as a helpful method to differentiate different types of hydatid cysts particularly CE1, CE2, and CE3; however, liquid hydatid cysts and simple cysts are difficult to distinguish from each other through this method [12]. Recently, diffusion-weighted magnetic resonance imaging (DW-MRI) has been introduced to be useful in distinguishing simple cysts from liquid hydatid cysts because it can measure intracellular water molecules and extracellular

and intravascular movements [13]. Through ADC values calculated based on the images obtained from DW-MRI using different b factors (the gradient strength and time), it is possible to carry out quantitative analysis of the images of the cysts [14].

The present study was an experiment to check the capacity of DW-MRI in differentiating hepatic hydatid and simple cysts among patients who referred to Azadi Teaching Hospital in Duhok, the Kurdistan Region of Iraq from October 2017 to April 2018.

Materials and Methods

The present cross-sectional study was carried out on 60 patients (23 men and 37 women) who had referred to the radiology department of the Hospital in Duhok, the Kurdistan Region of Iraq from October 2017 to April 2018. Following relevant examinations, a total of 108 cysts (36 simple cysts and 72 hydatid cysts except for CE5) were included.

In the beginning and before the initiation of the examinations, written informed consent was taken from each patient, and those patients who had contraindications to MRI (due to claustrophobia) or had undergone treatment or surgery for hydatid disease were excluded from the study. Other exclusion criteria were solid liver lesions, type-5 hydatid cyst (CE5) due to the effect of its calcific content on DWI, and cyst diameter less than 1 cm.

First, ultrasound was carried out for all of the patients, and the detected hydatid cysts were classified based on their radiological characteristics according to the WHO-IWGE classification presented in Table 1 above. Afterwards, DW-MRI was conducted with a 1.5 tesla MR unit (Achieva, Philips medical systems).

For DW-MRI, axial non-breath holding (NBH) spin echo planar EPI DW images were obtained with sensitivity encoding SENSE at three different b values (0, 400 and 800 s/mm²). Afterwards, those images were utilized to generate ADC maps. In addition, a comparison between the signal intensity on the cysts and the liver was carried out by employing a 3-point scale (0=hypointense, 1=isointense, & 2=hyperintense).

In order to analyze the collected data, a region of interest (ROI) was generated and placed in the center of the cysts in order to measure the signal intensities of the cysts for

each b factor (i.e. 0, 400, and 800 s/mm²). Afterwards, ADC maps were created, and the mean ADC values were measured. The statistical analysis was carried out through SPSS 22.0. In so doing, different groups were compared regarding the ratio of cysts signal intensity and cyst/parenchyma signal intensity and the ratio of cyst ADC and cyst/parenchyma ADC. Mean \pm standard deviation was employed to present the DW trace and ADC values.

Afterwards, Kruskal Wallis variance and the Mann-Whitney U test were utilized to analyze the differences of DW cysts signal intensity, cyst/parenchyma signal intensity ratio, cyst ADC and cyst/parenchyma ADC ratio. The level of statistical significance was set at $p < 0.05$.

Results

The present study was carried out on 62 patients (23 men and 37 women) with hydatid cysts and simple hepatic cysts. The patients were aged from 10 to 64 years. A total number of 108 cysts were included in the study. According to the results, the median number of cysts per each patient was 1, with a range from 1 to 9 cysts per patient. The results revealed 16 completely liquid (CL) hydatid cysts, 14 cases of cystic echinococcosis CE1, 10 cases of CE2,

17 cases of CE3, 15 cases of CE4, and 36 simple hepatic cysts. The results also showed that 88% of the lesions were seen in the right lobe of liver, 18% in the left lobe, and 2% in the caudate lobe. It was also observed that the smallest and largest diameters were 1.3 and 11 cm, respectively (See Table 2).

Comparing the signal intensities on the cysts and the liver using DW quality b0 showed that 100% of the signals of the cysts were hyperintense. According to DW quality b400, it was seen that 2, 11, and 87% of the signals of the cysts were respectively hypointense, isointense, and hyperintense. Also, based on analysis using DW quality b800, 25, 5, and 70% of the signals of the cysts were respectively hypointense, isointense, and hyperintense (See Table 1).

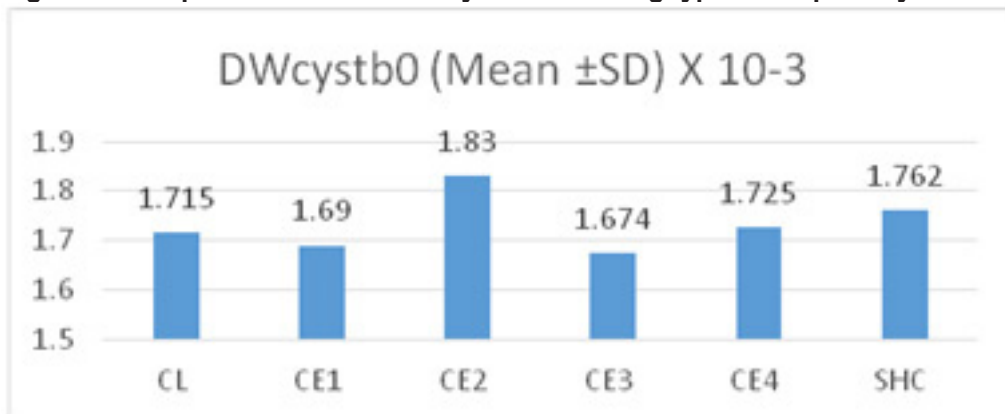
The quantitative results of the present study indicated that mean DW signal intensities of liver parenchyma at b0, b400, and b800 s/mm² were respectively $0.617 \pm 0.203 \times 10^{-3}$, $0.290 \pm 0.156 \times 10^{-3}$, and $0.175 \pm 0.061 \times 10^{-3}$. Moreover, the mean ADC signal intensities of liver parenchyma at b0 and b800 s/mm² were respectively $1.334 \pm 0.421 \times 10^{-3}$ and $0.358 \pm 0.259 \times 10^{-3}$ (See Table 2).

Table 2: Demographic characteristics

Characteristic	Value
Number of patients	60
Number of cysts	108
Age	(10-64)
Gender (Male /Female)	23 / 37
Number of Cyst/ patients (Median) (range)	1 (1-9)
Cyst type	
Completely liquid (CL) hydatid cyst	16
Cystic echinococcosis CE1	14
CE2	10
CE3	17
CE4	15
Simple hepatic cyst	36
Site Rt lobe/Lt lobe/ caudate	88/ 18/ 2
Size (minimum diameter) cm	1.3
Size (maximum diameter) cm	11
DW quality b0 (hypo/iso/hyper)	0/0/100
DW quality b400 (hypo/iso/hyper)	2/11/87
DW quality b800 (hypo/iso/hyper)	25/5/70
DW P b0 (Mean \pm SD) $\times 10^{-3}$	0.617 ± 0.203
DW P b400 (Mean \pm SD) $\times 10^{-3}$	0.290 ± 0.156
DW P b800 (Mean \pm SD) $\times 10^{-3}$	0.175 ± 0.061
ADC P b0 (Mean \pm SD) $\times 10^{-3}$	1.334 ± 0.421
ADC P b800 (Mean \pm SD) $\times 10^{-3}$	0.358 ± 0.259

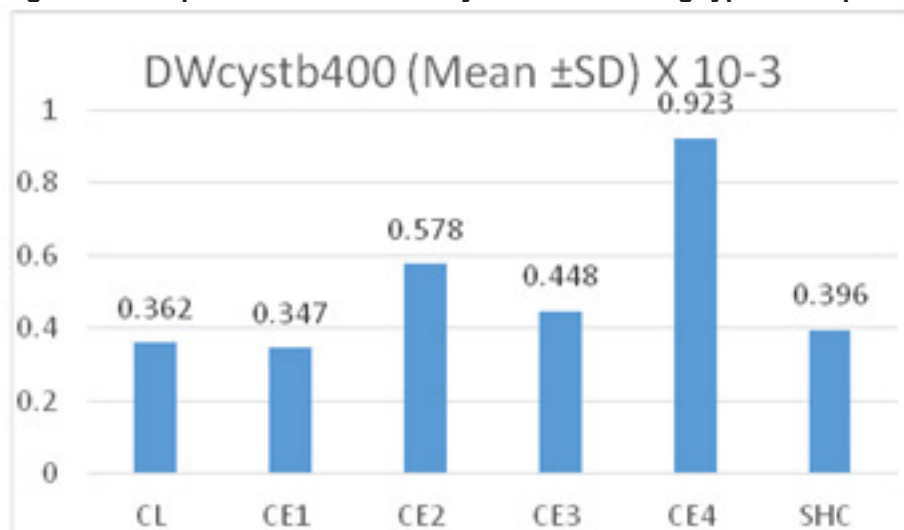
Figures 1 to 10 present the results of comparing mean DW and ADC signal intensities. Moreover, Kruskal Wallis test was run to carry out the overall comparisons. Also, Mann Whitney U test was used to compare two types of cysts. Comparing mean DW cyst signal intensities at b0 s/mm² factor showed that there was no significant difference between types of cyst (p>0.05) (See Figure 1).

Figure 1: Comparison of mean DW cyst at b0 among types of hepatic cysts



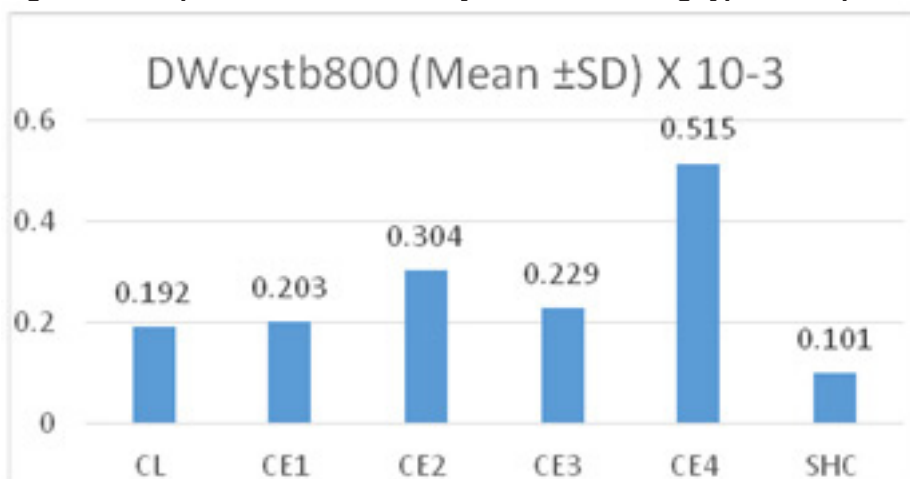
Comparing mean DW signal intensities at 400 s/mm² was successful in differentiating CE4 and CE2 from other types of hydatid cyst and from simple hepatic cysts (SHC); however, SHC could not be differentiated from CL hydatid cysts (See Figure 2).

Figure 2: Comparison of mean DW cyst at b400 among types of hepatic cysts



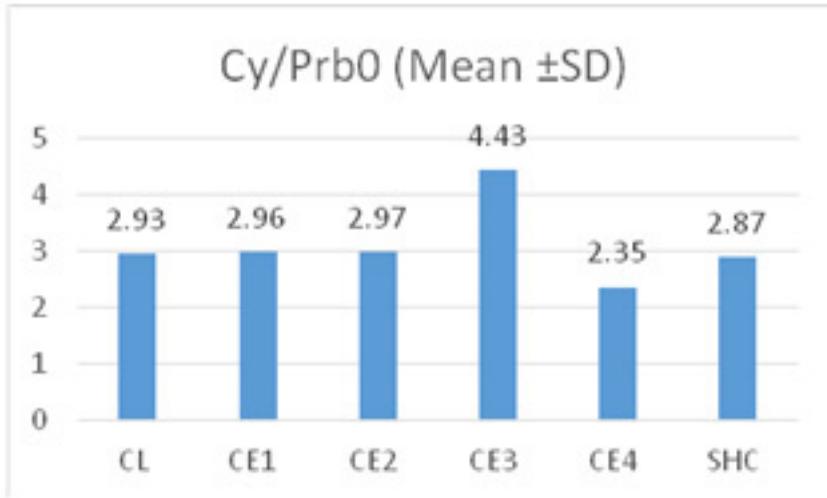
Also, mean intensity of DW signal at b800 s/mm² could successfully differentiate CE4 and CE2 from other hydatid cysts. However, it failed to differentiate SHC from CL hydatid cyst (See Figure 3).

Figure 3. Comparison of mean DW cyst at b800 among types of hepatic cysts



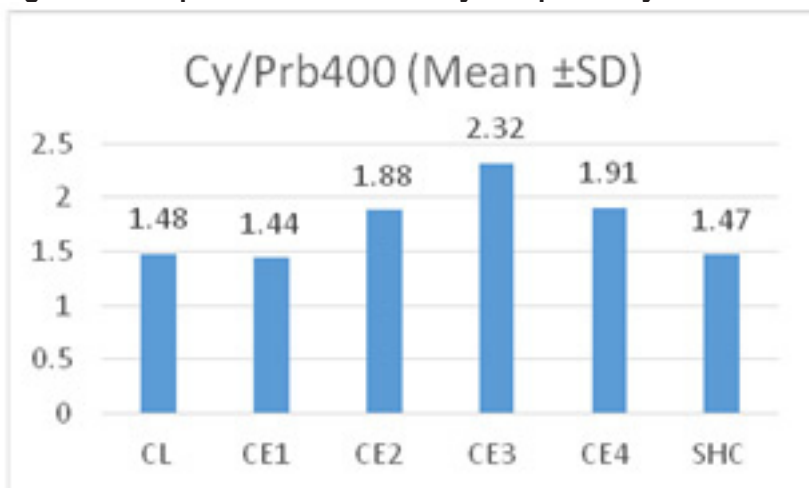
The results also showed that the mean signal intensity cyst/parenchyma ratio and b_0 s/mm² could only differentiate CE3 from other hydatid cysts types, but it could not differentiate between SHC and CL hydatid cyst (See Figure 4).

Figure 4: Comparison of mean DW cyst to parenchyma ratio at b_0 among types of hepatic cysts



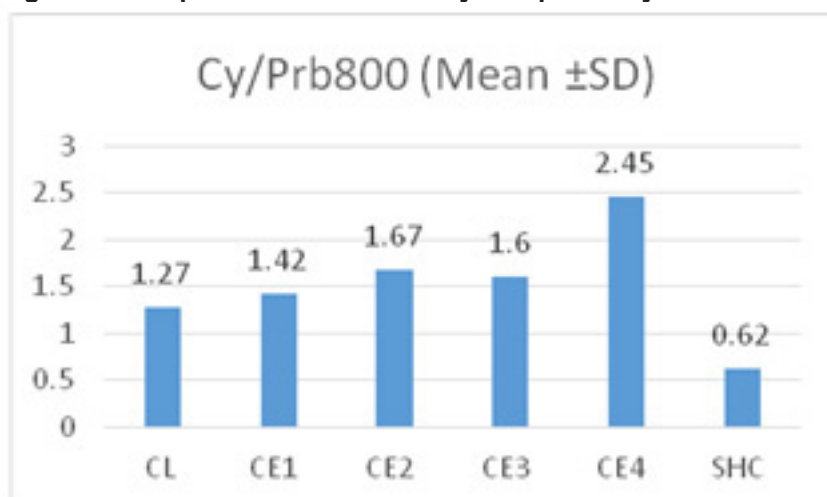
Moreover, CE3, CE2, and CE4 could successfully be differentiated from other types of hydatid cysts through the mean signal intensity cyst/parenchyma ratio and b_{400} s/mm². It failed to differentiate SHC from CL (See Figure 5).

Figure 5: Comparison of mean DW cyst to parenchyma ratio at b_{400} among types of hepatic cysts



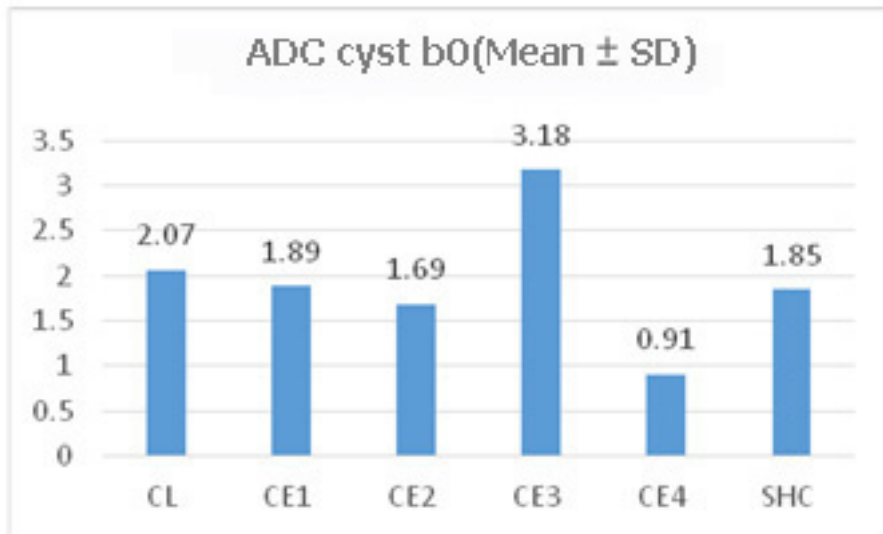
The mean signal intensity cyst/parenchyma ratio and b_{800} s/mm² could successfully differentiate SHC from all other types of hydatid cysts (Figure 6).

Figure 6: Comparison of mean DW cyst to parenchyma ratio at b_{800} among types of hepatic cysts



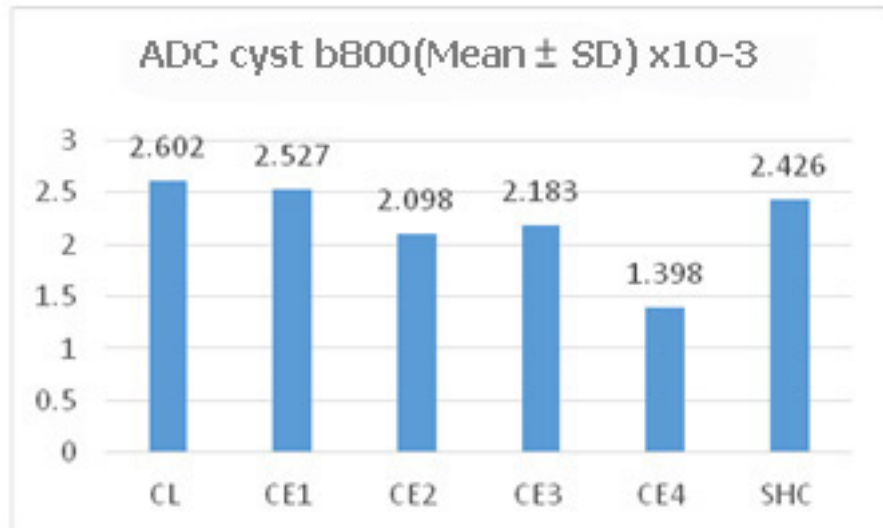
The results also indicated that at b_0 s/mm² mean ADC signal intensity of cysts and cyst/parenchyma ADC ratio could successfully differentiate CE3 and CE4 from other hydatid cyst types but failed to differentiate SHC from CL (See Figure 7).

Figure 7: Comparison of mean ADC cyst at b_0 among types of hepatic cysts

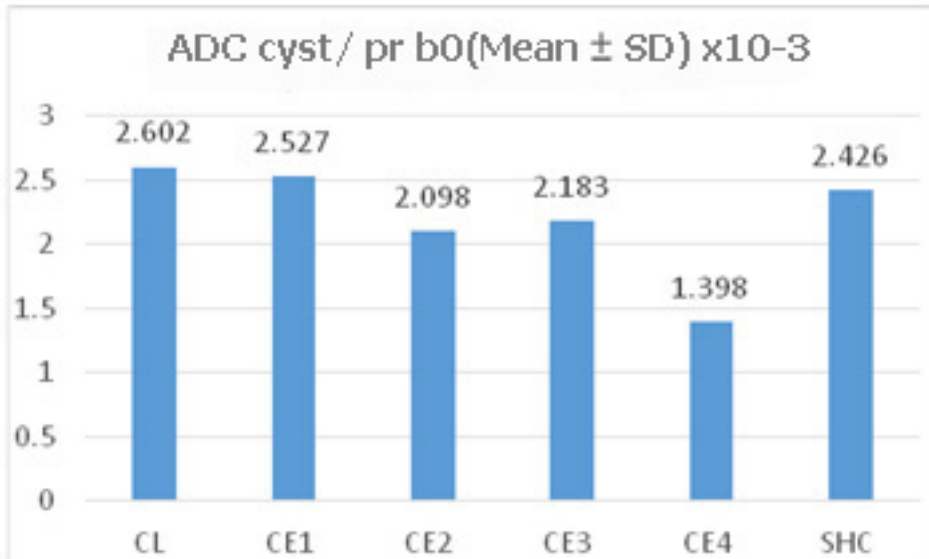


Moreover, mean ADC signal intensity at b_{800} s/mm² factor was successful in differentiating CE4 from other hydatid cysts and CL hydatid cyst from SHC (See Figure 8).

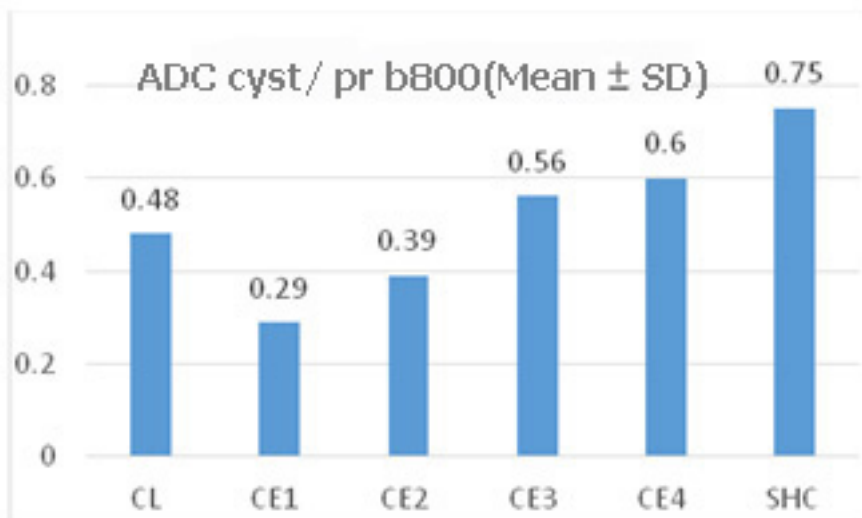
Figure 8: Comparison of mean ADC cyst at b_{800} among types of hepatic cysts



In addition, mean ADC cyst to parenchyma ratio at b_0 s/mm² factor could CE3 and CE4 from other hydatid cyst types but failed to differentiate SHC from CL (See Figure 9).

Figure 9: Comparison of mean ADC cyst to parenchyma ratio at b0 among types

Finally, mean ADC cyst to parenchyma ratio at b800 s/mm² factor could differentiate CE4 from other hydatid cysts and CL hydatid cyst from SHC (See Figure 10).

Figure 10: Comparison of mean ADC cyst to parenchyma ratio at b800 among types of hepatic cysts

In line with the figures presented above, Table 3 (next page) presents the mean and standard deviation of DW and ADC and ratios among all types of cysts.

Table 3: The mean and standard deviation of DW and ADC and ratios among all types of cysts

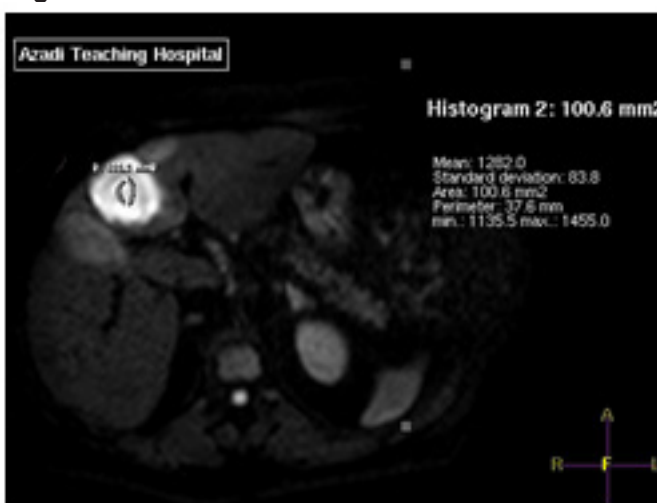
Parameter	CL	CE1	CE2	CE3	CE4	SHC
DWcystb0 (Mean ±SD) X 10 ⁻³	1.715 ±0.417	1.690 ±0.403	1.830 ±0.304	1.674 ±0.566	1.725 ±0.487	1.762 ±0.373
DWcystb400 (Mean ±SD) X 10 ⁻³	0.362 ±0.065	0.347 ±0.056	0.578 ±0.420	0.448 ±0.116	0.923 ±0.625	0.396 ±0.144
DWcystb800 (Mean ±SD) X 10 ⁻³	0.192 ±0.037	0.203 ±0.034	0.304 ±0.325	0.229 ±0.037	0.515 ±0.298	0.101 ±0.021
Cy/Prb0 (Mean ±SD)	2.93 ±0.78	2.96 ±0.70	2.97 ±0.65	4.43 ±3.98	2.35 ±0.57	2.87 ±0.63
Cy/Prb400 (Mean ±SD)	1.48 ±0.45	1.44 ±0.38	1.88 ±1.12	2.32 ±1.18	1.91 ±0.63	1.47 ±0.49
Cy/Prb800 (Mean ±SD)	1.27 ±0.54	1.42 ±0.37	1.67 ±1.67	1.60 ±0.76	2.45 ±1.22	0.62 ±0.29
ADCcystb0 (Mean ±SD) X 10 ⁻³	2.602 ±0.595	2.527 ±0.547	2.098 ±0.806	2.183 ±0.564	1.398 ±0.566	2.426 ±0.525
ADCcystb800 (Mean ±SD) X 10 ⁻³	0.157 ±0.178	0.078 ±0.032	0.155 ±0.167	0.137 ±0.115	0.228 ±0.076	0.220 ±0.086
ADC Rb0 (Mean ±SD)	2.07 ±0.46	1.89 ±0.28	1.69 ±0.87	3.18 ±3.65	0.91 ±0.60	1.85 ±0.59
ADC Rb800 (Mean ±SD)	0.48 ±0.43	0.29 ±0.07	0.39 ±0.37	0.56 ±0.49	0.60 ±0.47	0.75 ±0.19

Figure 1 (below) DW MRI image & Figure 2 (below) corresponding ADC map of a case from this study of a 10-year-old female with hepatic hydatid cyst, shows restricted diffusion. Selection of the ROI for measurement of the signal intensity of the cyst is also shown.

Figure 1



Figure 2



Discussion

According to the results of research studies, cystic echinococcosis (CE) is one of the most important parasitic diseases which threatens human health all over the world. Ultrasound as the gold standard method to detect cysts fails to differentiate different types of CE and completely liquid (CL) hydatid cysts from simple hepatic cysts (SHC) [7]. In these cases conventional MRI and diffusion-weighted MRI come to be quite useful [13]. In this regard, the present study was an attempt to investigate the capacity of diffusion-weighted magnetic resonance imaging (DW-MRI) in differentiating hepatic hydatid and simple cysts.

The results of the present study showed that the average ADC values of normal liver parenchyma at b0 and b800 factors were respectively $1.334 \pm 0.421 \times 10^{-3}$ and $0.358 \pm 0.259 \times 10^{-3}$, which proved that the ADC values were significantly different at different b factors. This finding proves that ADC values vary with different b factors (especially at minimum and maximum b factors). Similar results were reported by Yamada et al [15].

Moreover the results of the current experiment indicated that the signal intensity of the images obtained from DW-MRI of different types of cysts successfully differentiated types of hydatid cysts from simple hepatic cysts (SHCs) at b800 factor. This finding is in complete agreement with the results of the study carried out by Inan et al [16]. Also, as indicated by the results of the present study, completely liquid (CL) hydatid cysts could successfully be differentiated from simple hepatic cysts (SHC) through ADC values at b800 factor. This finding was in line with those of the studies conducted by Inan et al and Oruç et al [17, 18]. However, as seen above, ADC values could not differentiate between CL hepatic cysts and simple hepatic cysts at b0 and b400 factors, which is in line with previous studies [17, 18].

Study Limitations

The present study had one limitation which was related to using the echo-planar sequence with a higher b value and a lower SNR which might have led to greater image distortion.

Recommendations

In the present study, the echo-planar sequence was utilized, which may have caused anatomic distortion as a result of its susceptibility effects; therefore, future studies are recommended to employ a single-shot spin-echo echo-planar sequence with ECG triggering in order to minimize cardiac pulsation effect. Moreover, in the present study, the ADC values were measured manually, which may include a degree of subjectivity; therefore, utilization of computerized method of ROI demarcation is advised in future studies.

Conclusion

In conclusion, ADC values obtained from DW-MRI images can be helpful to differentiate type-4 hepatic cysts from other cysts and from simple cysts. The can also be utilized to differentiate between completely liquid (CL) hydatid cysts and simple hepatic cysts (SHC).

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An exploration into the role of diffusion weighted MRI imaging in the assessment of chronic kidney disease

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Abstract

Background and objective: Research has shown that diffusion-weighted magnetic resonance imaging (DW-MRI), one of the functional MRI techniques, can be utilized to evaluate renal function; however, more investigation is needed to understand its potential and capacity. The present study was carried out in order to evaluate the relationship between apparent diffusion coefficient (ADC) values of renal parenchyma and different stages of chronic kidney disease and to compare it with serum creatinine and estimated GFR among patients who referred to Rizgary Teaching Hospital in Erbil, the Kurdistan Region of Iraq.

Materials and Methods: The present experiment was an analytic cross-sectional study that was carried out from November 2017 to April 2018. In so doing, 12 individuals (control group) and 38 patients (patient group) diagnosed with known chronic kidney disease (CKD) were selected. After they had undergone magnetic resonance imaging of the upper abdomen, the patient group subjects were classified into different stages of CKD based on estimated glomerular filtration rate (eGFR) calculated using chronic kidney disease epidemiology (CKD-EPI) equation. Both control and patient groups underwent DW-MRI at b values of 40, 400, and 800, and ADC values were calculated for both groups. Afterwards, the control and patient groups were compared regarding their ADC values.

Results: The results of the present study revealed a significant inverse correlation between ADC values and serum creatinine in the patient group. Also, there was a strong positive correlation between ADC and eGFR in the patients with CKD. Moreover, the patient group had a significantly lower mean ADC compared to the control group.

Conclusion: The observed correlation between ADC values and serum creatinine and eGFR in the patients under investigation in the present study indicated that the presence and degree of renal dysfunction can be determined through ADC values.

Key words: chronic kidney disease (CKD), diffusion-weighted magnetic resonance imaging (DW-MRI), apparent diffusion coefficient (ADC), renal dysfunction

Introduction and Background

As one of the leading threats to, and problems in public health all over the world [1], chronic kidney disease (CKD) is increasingly prevalent worldwide and puts a lot of financial pressure on countries [2]. A variety of acute and chronic conditions can cause parenchymal kidney disease resulting in nephron loss followed by adaptive hyperfiltration in the remaining nephrons. This adaptive hyperfiltration in turn leads to long-term glomerular damage causing proteinuria and progressive loss of kidney function [3].

Renal function can be estimated through serum markers like blood urea nitrogen level, creatinine level, and estimated glomerular filtration rate (eGFR) [4]. However, it should be noted that single kidney function cannot be evaluated via blood tests which are significantly affected by the patients' age and body mass index (BMI). Therefore, and given the limitations of serum markers, imaging techniques have recently obtained significance in evaluating renal function and renal parenchymal disease [6].

Although good anatomic images can be obtained through computed tomographic (CT) scan and ultrasonography (USG), the information provided by them is of limited functional value. Moreover, changes in renal echogenicity can be observed through USG; however, the final results lack objectivity and can be significantly influenced by operator dependency. Furthermore, due to using iodinated contrast material in CT scan, its utilization is limited due to the adverse effects of iodinated contrast material on kidneys [6]. Both structure and function can be shown objectively via magnetic resonance imaging (MRI) without exposing the patient to radiation. Renal function can be evaluated through functional MRI techniques like blood oxygen level-dependent (BOLD) imaging, contrast-enhanced MRI renography, and diffusion-weighted imaging (DWI) [6].

As a widely utilized method of neuroimaging, diffusion-weighted magnetic resonance imaging (DW-MRI) can particularly be used to evaluate intracranial tumors, acute cerebral stroke, and demyelinating diseases [7]. Since DW-MRI is extremely sensitive to motion, its application outside the central nervous system is limited [8]; therefore, it cannot be in the abdomen because the effect of diffusion is obscured due to the presence of spontaneous motion such as peristalsis, respiration, and blood flow. However, motion-related problems have recently been overcome and reliable diffusion-weighted images of the abdominal organs can be obtained as a result of advances in ultrafast MRI methods [9].

Changes in the diffusion properties of water molecules in tissues are the basis for diffusion-weighted magnetic resonance imaging (DW-MRI) which is commonly employed in neuroradiology for early diagnosis of cerebral ischemia and characterization of cerebral tumors and infections [10].

Since available techniques are usually inadequate for abdominal imaging especially for focal lesion detection and characterization, and the evaluation of diffuse parenchymal diseases; therefore, diffusion-weighted imaging (DWI) is employed. The potential value of DWI in evaluating different renal diseases, such as renal ischemia, renal infection, diffuse renal disease, and pyonephrosis, has been proved in recent studies [10-14].

Recent studies have pointed out that there is an association between nephrogenic systemic fibrosis (NSF) and the use of gadolinium chelate contrast agents [15-19] in patients with renal failure, especially those with acute or chronic renal disease and glomerular filtration rate (GFR) of lower than 30 mL/min/1.73 m² [20-21]. Moreover, there has been a relationship between apparent diffusion coefficient (ADC) values and eGFR [22-25].

So far few studies have focused on the relationship between apparent diffusion coefficient (ADC) values and different stages of chronic kidney disease (CKD), and they have suggested various cut-off ADC values [26-30]. In this regard and to fill the research gap, the present study was carried out in order to evaluate the relationship between apparent diffusion coefficient (ADC) values of renal parenchyma and different stages of chronic kidney disease and compare it with serum creatinine and estimated GFR among patients who referred to Rizgary Teaching Hospital in Erbil, the Kurdistan Region of Iraq.

Materials and Methods

Subjects and data collection

The present analytic cross-sectional study was carried out at the Radiology Department of Rizgary Teaching Hospital located in Erbil, the Kurdistan Region of Iraq from September 2017 to April 2018. The statistical population consisted of 62 patients who referred to Rizgary Hospital during the above mentioned period. Out of those 62 patients, 12 were excluded from the study due to severe renal atrophy (3 patients), polycystic kidney disease (3 patients), single kidney (3 patients), hydronephrotic kidneys (2 patients), and claustrophobia (1 patient), which led to a net study population of 50 patients who were divided into two groups.

Group 1 was regarded as the control group and consisted of 12 patients who referred to the radiology department for abdominal MRI for different reasons and were diagnosed with normal renal function parameters. Their serum creatinine level was measured within 1 week before imaging. The second group which was regarded as the patient group consisted of 38 patients who were diagnosed with chronic kidney disease (CKD) with a mean age of 54±15.79 years. All of the patients were informed about the MRI examination to which none of the patients had contraindication. After the subjects were ensured about the privacy of their information, informed consent was obtained from them.

According to K/DOQI CKD (kidney disease outcomes quality initiative) classification [13], the subjects in the patient group were classified into 5 stages of disease severity including Stage 1: eGFR; 90mL/min/1.73m² (kidney damage with normal or increased eGFR); Stage 2: eGFR; 60–89mL/min/1.73m² (kidney damage with a mild reduction in eGFR); Stage 3: eGFR; 30–59mL/min/1.73m² (moderate reduction in eGFR); Stage 4: eGFR; 15–29mL/min/1.73m² (severe reduction in eGFR); and Stage 5: eGFR; < 15mL/min/1.73m² (kidney failure).

Chronic kidney disease epidemiology (CKD-EPI) equation was employed to calculate the estimated glomerular filtration rate (eGFR).

DW-MRI protocol

All MRI examinations were performed using a 1.5-T scanner (MAGNETUM Aera, Siemens Healthcare, Germany). Parameters including repetition time (TR) of 2000ms, echo time (TE) of 65 ms, slice thickness of 6 mm, receiver bandwidth of 1964 Hz/pixel, field of view (FOV) of 380 mm, and matrix size of 164×159 were taken into account in all MRI scans.

All of the images were obtained through respiratory triggering and synchronization with diaphragm motion in order to reduce artefacts from respiratory motion and using parallel imaging based on generalized auto-calibrating partially parallel acquisition (GRAPPA) using a twofold acceleration factor.

It should be noted that all MRI scans were evaluated by the same radiologist. ADC values of the kidneys were calculated with diffusion gradient b-values of 50, 400, and 800 s/mm². Moreover, the standardized diffusion sequence provided by the manufacturer for abdominal and pelvic scanning was employed in order to obtain DW images and ADC maps of good quality. In addition, no intravenous contrast material was used on the acquisition of DWI-ADC sequences.

Image analysis

The ADC values were measured directly from regions of interest (ROIs) manually outlined in the renal parenchyma. As circular ROIs of size 1 cm² were taken into account, three such ROIs were placed in each kidney; one at the upper, interpolar, and lower pole in axial imaging. However, it is stated that it can be hard to place ROI cursor accurately in cortex or medulla separately [30]. Afterwards, a total of 6 ROIs were obtained from each individual. Finally, the mean of these six ADC values was calculated. The standard laboratory assay was utilized to calculate serum creatinine. The mean ADC values were recorded for each patient, and the relationship of ADC values with CKD stage and serum creatinine levels were evaluated.

Results

According to the results of descriptive statistics, the patient group included 38 subjects whose mean age was 54±15.79 years with a range of 20 to 70 years. Regarding their gender, 17 were men and 21 were women. The descriptive statistics also showed that none of the 12 subjects in the control group had any known risk factors of kidney disease, and all of them had normal blood urea and serum creatinine level which were tested within the first week of MRI examination. With regard to their gender, half of them (n=6) were women and half men (n=6). Their age ranged from 26 to 59 with a mean of 42.6±9.9 years.

The results of K/DOQI CKD (kidney disease outcome quality initiative) classification indicated that out of the 32 CKD patients, 9 belonged to stage 5, 10 to stage 4, 7 to stage 3, 4 to stage 2, and 2 to stage 1.

According to our result, the mean ADC values of normal individuals and different stages of chronic kidney disease were as follows.

Normal: the mean ADC value in both kidneys ranges (1891-2103) with a mean and SD of 1981±52.1

Stage 1: the mean ADC value in both kidneys' ranges (1972-2103) with a mean and SD of 2015±32.5

Stage 2: the mean ADC value in both kidneys ranges (1818-1980) with a mean and SD of 1849±25.32

Stage 3: the mean ADC value in both kidneys ranges (1750-1865) with a mean and SD of 1800.2± 39.5

Stage 4: the mean ADC value in both kidneys ranges (1654-1735) with a mean and SD of 1677±0.13

Stage 5: the mean ADC value in both kidneys ranges (1485-1645) with a mean and SD of 1560±45.5

The results of Pearson correlation coefficient in the patient group (n=38) revealed that there was a significant inverse correlation between serum creatinine (eGFR) and ADC value (r=-0.78) (See Figure 1).

The results also showed that in the CKD group (n=32) there was a strong positive correlation between ADC and eGFR (R=0.88) (See Figure 2).

Moreover, the results indicated that the patient group had a significantly lower mean ADC value compared to the control group (1648±115.5(x10⁻⁶ mm²/s) vs. 1981 ±135.0(x10⁻⁶ mm²/s)). Also, the results of Pearson correlation coefficient test in the CKD group revealed that there was a correlation between mean ADC value and stages of CKD. It was also observed that there was a significant difference among stages of CKD regarding mean ADC value (mean ADC value dropped with advance in CKD stages) (See Figures 3 & 4).

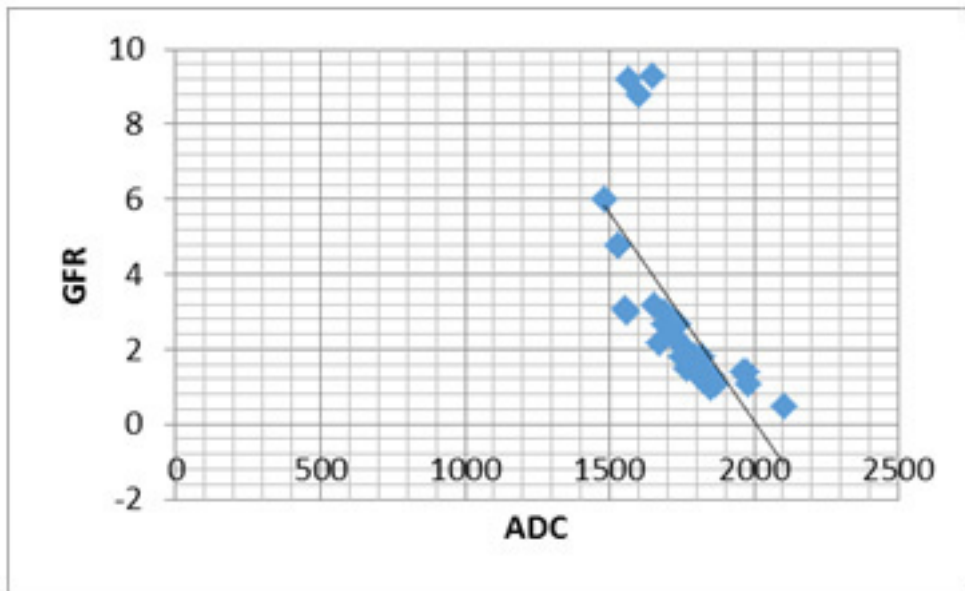


Figure 1: Correlation between ADC value and serum creatinine (eGFR) in the patient group (Stages 1, 2, 3, 4, & 5)

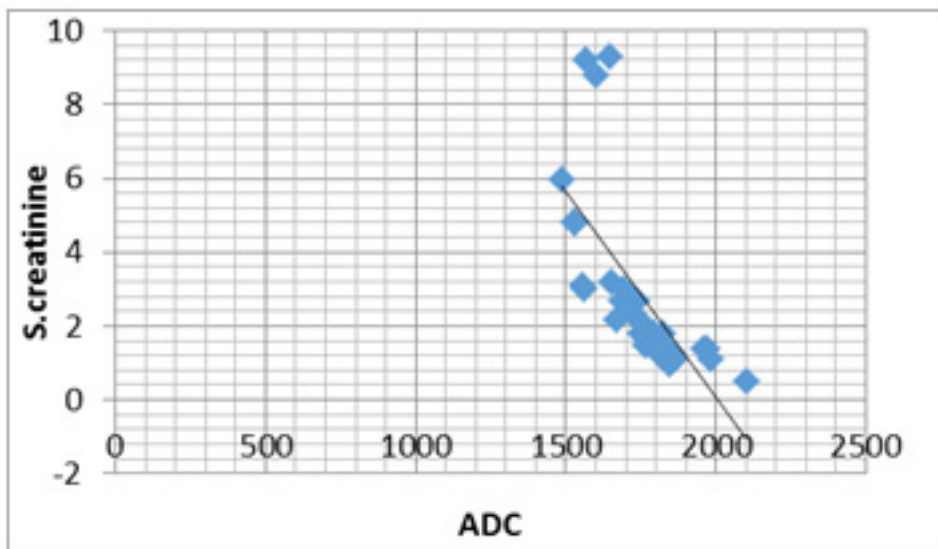


Figure 2: Correlation between ADC and eGFR in the CKD patients

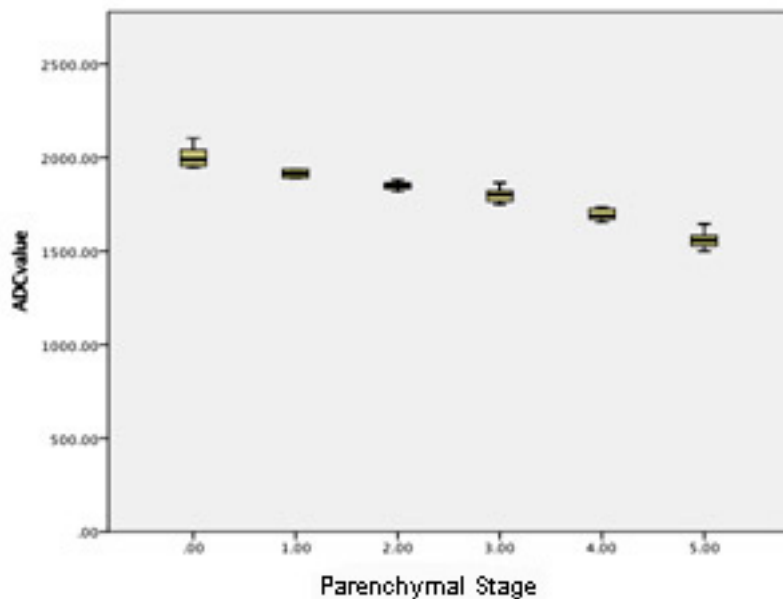
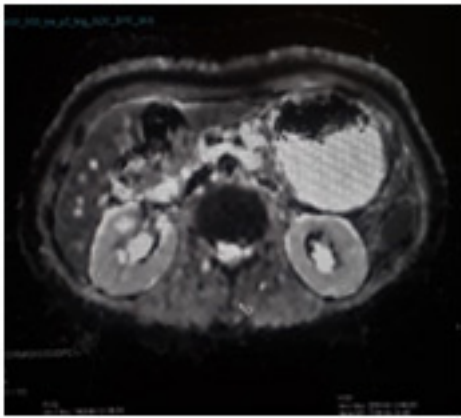
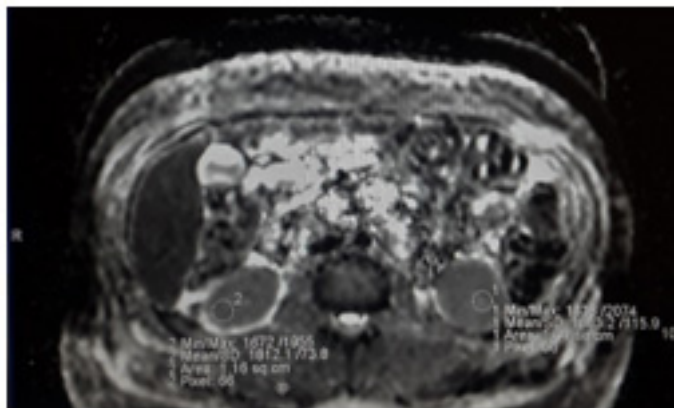


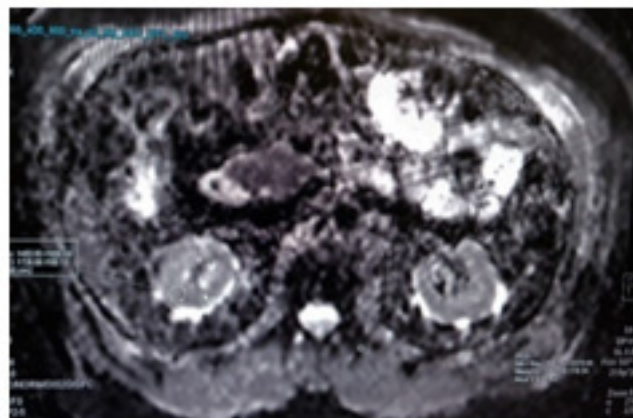
Figure 3: Box plot of mean ADC in different stages of CKD showing decreasing ADC values with increasing stage of CKD



(a)



(b)



(c)

Figure 4. (a) ADC map in a 40-year-old female with normal kidney function (healthy individual), showing no restriction of diffusion, and mean ADC value was 2085 ($\times 10^{-6}$ mm²/s). (b) ADC map in a 45-year-old male with CKD (stage 2), showing restricted diffusion in the kidney parenchyma bilaterally with a mean ADC value of 1845 ($\times 10^{-6}$ mm²/s). The circles show examples of ROI placement. (c) ADC map in a 62-year-old male with CKD (stage 5), showing restricted diffusion in the kidney parenchyma bilaterally with more decrease in mean ADC value of 1636 ($\times 10^{-6}$ mm²/s). It also shows decrease in parenchymal thickness.

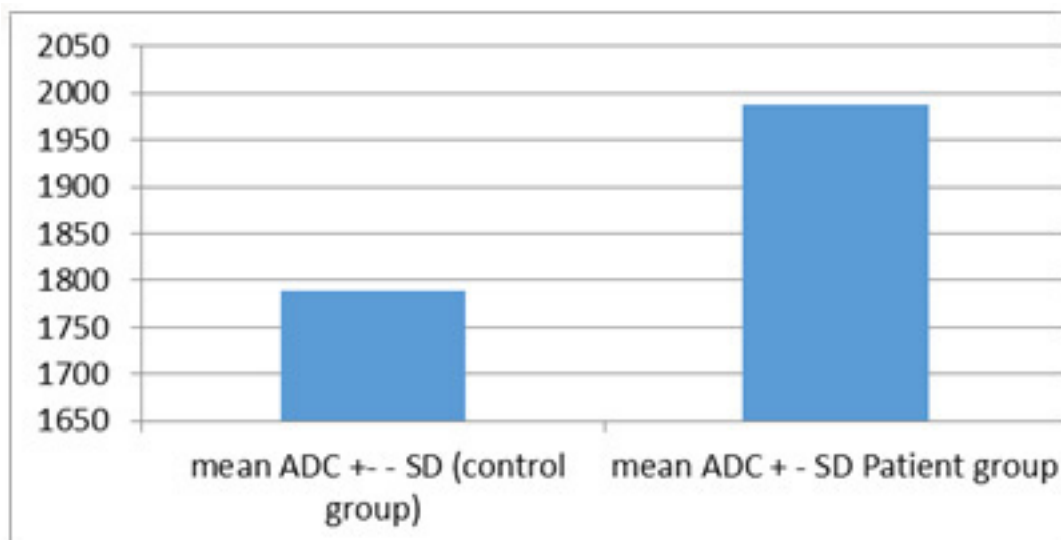


Figure 5. Difference between mean ADC values in the control and patient groups

The results of the present study also indicated that there was a strong positive significant relationship between serum creatinine level and chronic kidney disease stages ($r=0.83$; $p<0.05$). There was also a strong positive significant correlation between eGFR and mean ADC value in the patients with CKD at all stages from 1 to 5 ($r=0.88$; $p<0.05$) (See Table 1). The results also proved that there was a significant difference between the control and patient groups in terms of their mean ADC values (See Figure 5).

According to the results, there was a moderate negative correlation between serum creatinine level and ADC value in the CKD subjects ($r=-0.78$), while there was a very weak positive correlation between serum creatinine level and ADC value in the control group ($r=0.18$), and this difference between the two groups was statistically significant ($P<0.05$) (See Figures 2 and 3 above).

As indicated in Table 1, an increase in parenchymal stages leads to a rise in the coefficient of the correlation between eGFR and ADC value from 0.22 in the normal group to 0.92 in the worst CKD group (stage 5). Similarly, the coefficient of the correlation between serum creatinine level and ADC value rises from 0.18 in the normal group to 0.87 in the worst CKD group (stage 5). Therefore, it can be concluded that ADC value is a useful diagnostic factor to detect and staging of CKD. As the difference was statistically significant between mean ADC value in patients with stage 3 versus stage 4 and between stage 4 versus 5 because there is a strong significant correlation between ADC in these groups of CKD and both eGFR and serum creatinine level ($p<0.05$). However, we failed to find significant difference regarding mean ADC values between patients with stage 2 and stage 3. And there was overlap in ADC values between stage 1 and 2 which may be attributed to small number of patients in stage 1 (2) and stage 2 (4) (See Table 1).

Discussion

The results of the present study indicated that there was a significant inverse correlation between serum creatinine (eGFR) and ADC value ($r=-0.78$) in the patient group, which is in line with the results of previously conducted studies [14, 27, 29]. A strong positive significant relationship between ADC and eGFR ($R=0.88$) was observed in the CKD group. This finding was also reported by another study [26], while another experiment [28] reported an opposite finding, i.e.

lack of significant relationship between eGFR and ADC values.

Furthermore, as the results of the present study indicated, the subject of the patient group with renal dysfunction had a significantly lower mean ADC value compared to the control subjects with normal kidney function. This finding is in agreement with the results of other studies [14, 25, 26, 27, 29]. In justifying this finding, it can be stated that decreased water diffusion and reduced perfusion in renal parenchymal disease lead to a drop in mean ADC value. According to this finding, cut-off ADC values can be used to identify renal dysfunction.

Moreover, different mean ADC values were observed in different stages of CKD, with a decrease in mean ADC value with increase in CKD stages. A similar finding was reported in another study [29]. It should be stated that the obtained cut-off ADC values were similar to those of previously conducted studies [26-30]; therefore, these values can be employed to diagnose stages of CKD.

Also, the results of the present study showed a moderate negative correlation between serum creatinine level and ADC value in the CKD subjects, a very weak positive correlation between serum creatinine level and ADC value in the control group, and a strong significant correlation between ADC and both eGFR and serum creatinine level in the patient group; therefore, ADC values can be employed to distinguish between different stages of CKD. This finding was also reported by another study [29].

Conclusion

In short, ADC values can be employed to examine the degree of renal inefficiency and distinguish different stages of chronic kidney disease (CKD). Therefore, ADC values taken from ADC images can increase the accuracy of examination results and be used as a valuable investigation for assessment of renal function along with serum markers of renal function.

Limitations of the study

The present study had several limitations which should be dealt with in future similar studies. First, the study sample was small; therefore, there were very few patients with stage-1 and stage-2 CKD ($n=2$ and $n=4$, respectively) which restricted the possibility of comparing cut-off ADC values in

Table 1. Correlation between ADC value and eGFR and serum creatinine

Chronic kidney disease stages	eGFR-ADC correlation coefficient	P-value	serum creatinine-ADC correlation coefficient	P-value
Normal 0	0.22	0.001	0.18	0.003
Stage 1	0.41	0.0002	0.39	0.001
Stage 2	0.48	0.0001	0.34	0.0003
Stage 3	0.56	0.00007	0.59	0.0002
Stage 4	0.72	0.00006	0.65	0.00003
Stage 5	0.92	0.00004	0.87	0.00002

different stages. Second, the function of each kidney was not evaluated separately, and the correlation between mean ADC values and eGFR was investigated in individual patients. Third, the study did not include acute renal failure cases. Fourth, ADC values were measured manually, which may have involved a degree of subjectivity. Therefore, utilization of computerized ROI demarcation methods with better accuracy are recommended in future studies. Finally, standardized protocol for renal DW-MRI has not been established by manufacturers yet, and this contributes to variation in the absolute ADC values with some changes in expression in different studies including the present research.

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Haemorrhoid Treatment including Rubber Band Ligation

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Abstract

A practical guide for surgical students and trainees.
An information guide for the haemorrhoid patient.

Key words: haemorrhoids, HAL RAR repair, injection sclerotherapy, rubber band ligation

Haemorrhoids - Introduction and Background

Have a rich blood supply from the superior and middle rectal vessels. They have been compared with protruding varicose veins. They bleed or prolapse with the straining associated with constipation. The lack of fibre in the modern diet is thought to play a role.

Haemorrhoids may: bleed, prolapse or thrombose. Staging reflects the severity and is used as a guide to advise on treatment.

The bleeding is typically bright red and spurts into the toilet pan. It discolours the toilet paper red. Should the blood be mixed with the faeces this suggests bleeding from a higher source. This requires further investigation.

Stage 1 - Bleed, particularly at the toilet - the red blood may drip or splash into the bowl or colour the toilet paper.

Stage 2 - Prolapse - usually with straining at the toilet. They return inside spontaneously

Stage 3 - Need to be pushed back in after bowel action

Stage 4 -Thrombose and prolapse - this is very painful and the haemorrhoid cannot be returned inside

Perianal haematoma

This is a different problem. It is a rupture of the perianal venous plexus. It is situated separate to the anal verge. There may be some overlap with internal or internal-external haemorrhoids. They are painful but the pain usually settles within 5 days – thus they are called a 5 day wonder. They may be treated by drainage in the office.

Treatment for haemorrhoids depends on their severity (stage or degree). The main measures consist of:

STAGE 1 High fibre diet and use of local shrinking and soothing applications such as local anaesthetic or Cortisone creams or suppositories.

STAGE 2 Diet and applications help but banding or injection is often recommended. We prefer banding over injection.

STAGE 3. Injection sclerotherapy, Rubber banding or Haemorrhoidectomy.

STAGE 4. Haemorrhoidectomy.

Newer Treatment - HAL RAR

HAL RAR (Haemorrhoid artery ligation and recto anal repair)

The rectal vessels are transixed under the guidance of an ultrasound probe. The larger skin tags are hooked up. No incisions are required. General anaesthesia is required. In assessing the type of treatment the presence of large skin tags may be a factor in decision making.

Radical operative haemorrhoidectomy. This is the most effective method of treating large or thrombosed haemorrhoids permanently. However, surgery does involve hospitalization and up to two to three weeks of postoperative discomfort and time off work. Cost factors and pressure on beds has led to early discharge with some even being treated as a day case.

Advancing technology has led to a stapled haemorrhoidectomy which is not always popular and still has similar complications to the standard haemorrhoidectomy.

Following haemorrhoidectomy possible early complications include bleeding or acute retention of urine, then later secondary haemorrhage.

Before any anal procedure a full history and examination is required to exclude other causes of the bleeding such as rectal or bowel cancer.

This includes a full assessment, abdominal examination, rectal examination, proctoscopy and at least sigmoidoscopy. Young age is not a reason to exclude these as rectal cancer not infrequently occurs aggressively even in the twenties. Other risk factors such as family history and inflammatory bowel disease must also be noted in making management decisions.

In western society rubber band ligation would be carried out by a surgeon.

Rubber band ligation

Rubber band ligation strangulates the blood supply and the haemorrhoids shrink or drop off within a few days. Because internal haemorrhoids have an autonomic nerve supply they do not have the sensitive pain nerve fibres of the skin. Thus the technique is usually not painful. It is however useful to give some light analgesia such as paracetamol as this reduces the suprapubic referred discomfort which can occur. It also reduces the need to defaecate immediately post op which would dislodge the bands. However, the external skin is painful and for this reason banding is not suitable for those haemorrhoids which are thrombosed. Banding does not deal with the large skin tags.

Banding is usually carried out in the office. It does not require an anaesthetic. Some patients go into anal spasm and the proctoscope cannot be inserted thus anaesthesia is required. Banding can also be performed together with colonoscopy under general anaesthetic particularly if there is an indication for colonoscopy.

A latex rubber band is placed around the neck of the haemorrhoid, through a proctoscope. There are 2 techniques. With one an assistant holds the proctoscope while the surgeon needs both hands to grasp the haemorrhoid and fire the band applicator. The second technique uses suction on the gun, thus only one hand is required and the surgeon can hold the proctoscope with the other hand.

Procedure

At the first visit a rectal examination with a well lubricated glove is performed. Then the bowel above the haemorrhoids is examined with a sigmoidoscope to exclude other causes of bleeding from the bowel. A colonoscopy may need to be arranged to ensure no other cause for the bleeding is present.

A suitable time to carry out the rubber band ligation is then arranged. It is preferable for the patient to be driven, as occasionally patients can feel faint after the procedure. There may be some lower abdominal discomfort.

Advantages

1. No hospitalisation.
2. No anaesthetic required. Minimal pain.
4. Minimal time off work.

Possible Disadvantages

May require more than one course of treatment.

Does not deal with external skin tags and loose skin of haemorrhoids.

There is a small risk of complications such as aggravation of other haemorrhoids, bleeding, pain or infection. There is still the remote possibility of secondary haemorrhage.

The pain is difficult to predict and is usually not severe. However if the bands are too low the somatic nerves are involved and it is extremely painful. The bands may need to be removed.

There is a bearing down sensation sometimes and analgesics taken just before or after the procedure is helpful.

Recurrence is more common than following surgery

After the Procedure

The patient should be asked to rest in the office to ensure all is okay for 15 minutes or so. It is best to be driven home.

The following is suitable patient information to be given to the patient:

1. Try not to use your bowels the same day; the rubber band may fall off with the straining. Occasionally you will see the band very soon after the procedure suggesting the treatment was ineffective. On most occasions you will not even notice the rubber band.
2. Avoid getting constipated or straining. Two to three teaspoons of bran a day or other stool softeners Coloxyl or Agarol may help.
3. If there is excessive bleeding, lie down with your bottom up in the air. Gravity usually stops the bleeding. However, if it persists notify the office. Anusol or Rectinol ointments may help minor bleeding.
4. A burning or irritating sensation may be present. Stop all coffee, alcohol and spices and the use of Anusol or Rectinol suppositories.

For pain use Panadol, Panadeine, Digesic, Codral Forte or anti-inflammatories such as Neurofen or Neurofen Plus. If another haemorrhoid becomes inflamed, try to push it back inside and use a suppository.

For painful external swelling:

- Warm baths are helpful.
- Ice packs help the haemorrhoids shrink.
- Rest,

The situation may be reassessed in about three weeks to determine how successful the procedure has been. An examination is not usually carried out until then, because there is a wound inside where the haemorrhoid has dropped off. This wound can bleed severely about 8-10 days after the procedure - rarely.

For this reason it is advisable not to have the banding done if you are going away on holidays or travelling during that time.

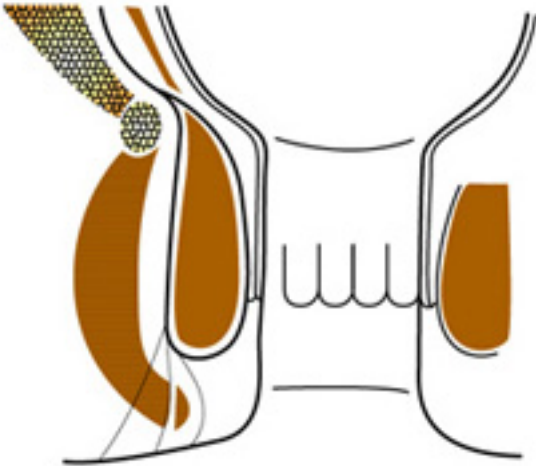
If you have other specific medical problems such as being on Warfarin or Aspirin these will need to be considered and probably stopped. Also if you have a heart valve problem or cardiac murmur an antibiotic cover may be required.

Injection sclerotherapy

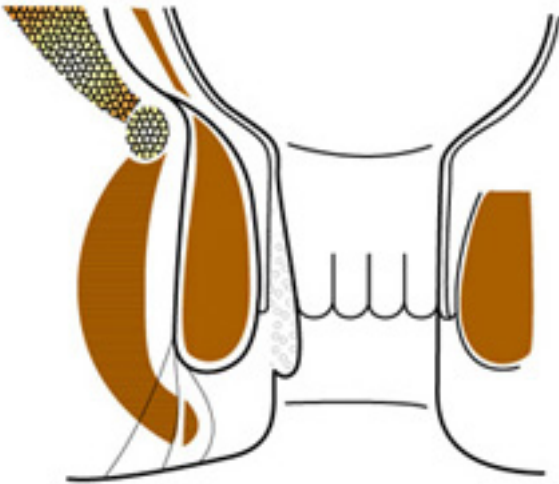
A solution of 4% phenol in almond oil is used. Some prefer this to banding. The phenol thromboses the vessels. It can only be injected above the dentate line. Below would cause severe pain. There are similar results and complications to banding, but another severe complication can be prostatitis if it is injected into the prostate.

Diagram of the ano-rectal region

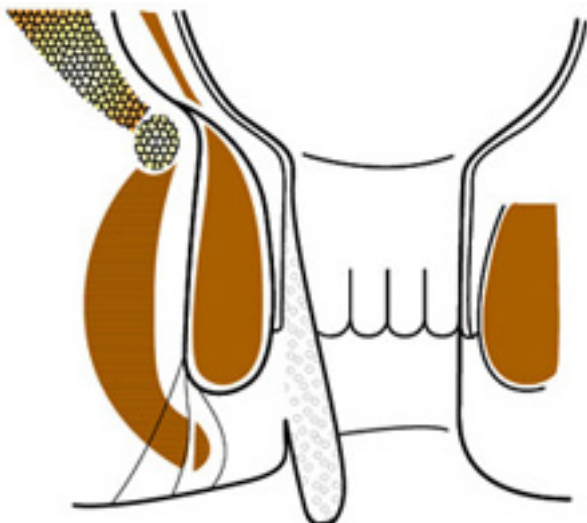
Normal anatomy. Note dentate line (pectinate line), internal and external anal sphincters



Does not prolapse - 1st degree



Reduces spontaneously - 2nd degree



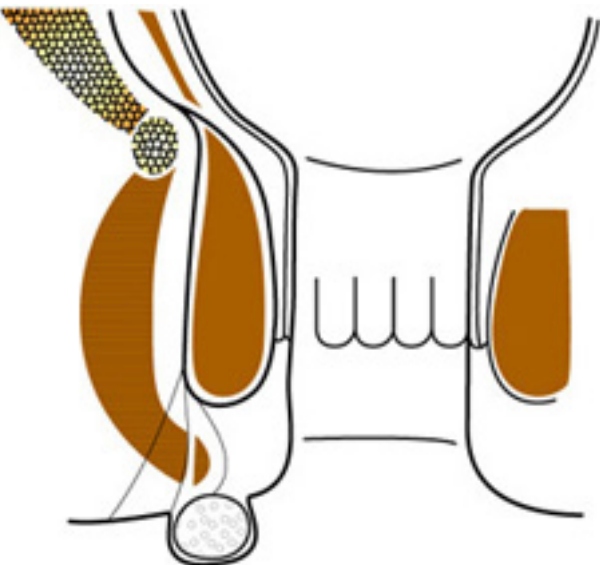
Needs to be pushed back in - 2nd to 3rd degree



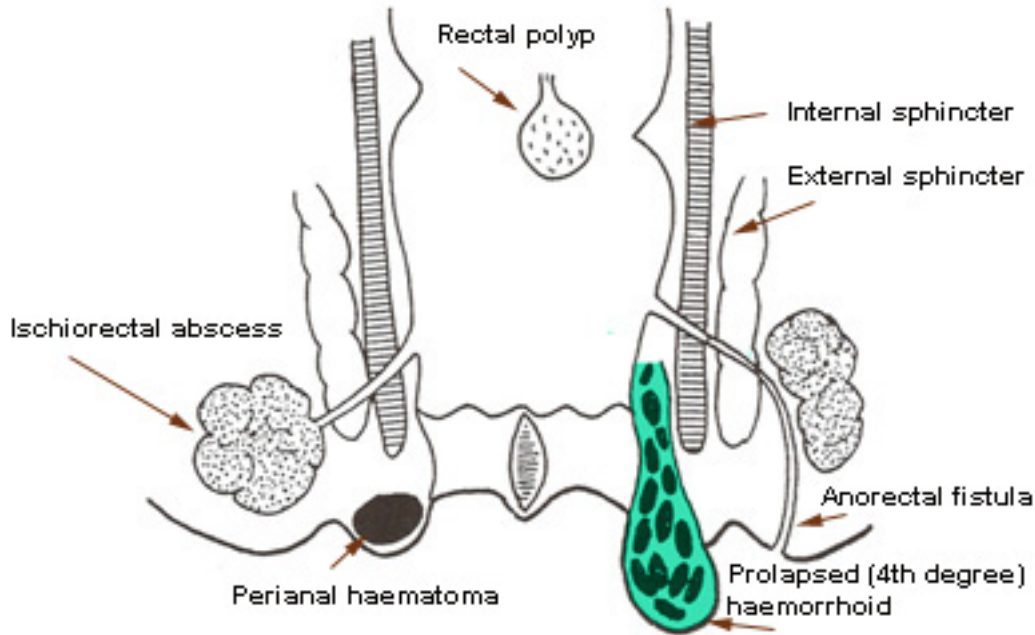
Strangulated thrombosed - larger - 3rd to 4th degree



Perianal Haematoma - external haemorrhoid



Perianal haematoma and other conditions and landmarks



Rubber Band Ligation for Haemorrhoids

This is a simpler office or room's treatment for haemorrhoids as opposed to surgery, which usually takes place in hospital. No anaesthetic is required and the patient is able to go home almost immediately.

When surgery (hospitalisation and anaesthesia are required) the post-operative course is often more painful.

Banding has many advantages over the haemorrhoid operation. However not all haemorrhoids are suitable for rubber band ligation. Haemorrhoids are formed just within the anus.

Physical Examination



Figure 1. Thrombosed single haemorrhoid.
Note: has an internal component thus not strictly a perianal haematoma



Figure 2. Another example of thrombosed haemorrhoid. Note: extra skin tags



Figure 3. Prolapsing haemorrhoid. Note: Different stages of thrombosis and prolapse.



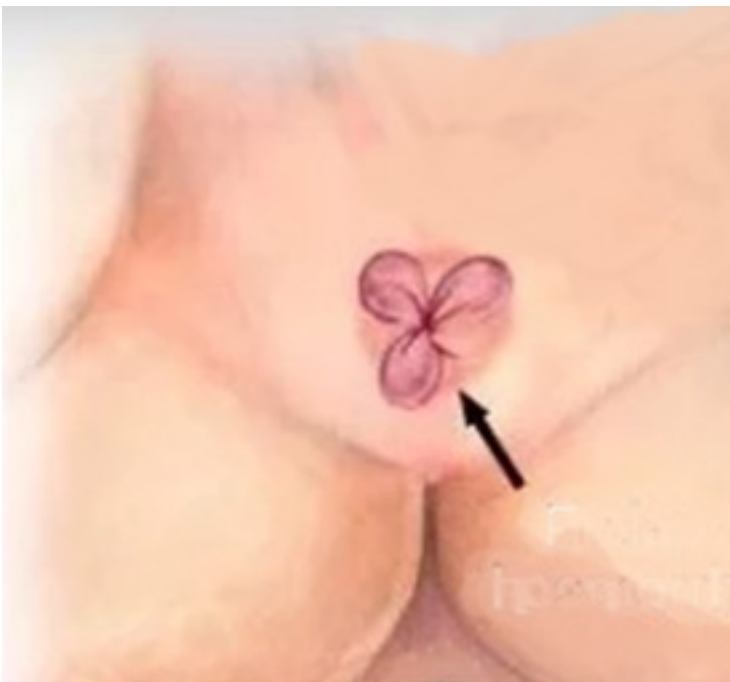
4. Prolapsed thrombosed intero external haemorrhoid in right lateral position. Note: Swelling and oedema of skin

Pain and swelling with past history of repeated episodes were indications for surgery.



Thrombosed haemorrhoid on day 4 - mostly perianal. Discharging blood, may be an indication for surgery, particularly if it continues to bleed. But pain and swelling are resolving therefore treated conservatively without surgery.

(Patient's decision)



This shows three primary haemorrhoids in 3, 7 and 11 o'clock positions with accessory haemorrhoids in between.

Note the external skin swelling and the corresponding mucosal haemorrhoidal engorgement. It may be appropriate to wait until the swelling resolves - treat with ice packs, bath sitz baths) and analgesics.

Operative Procedure

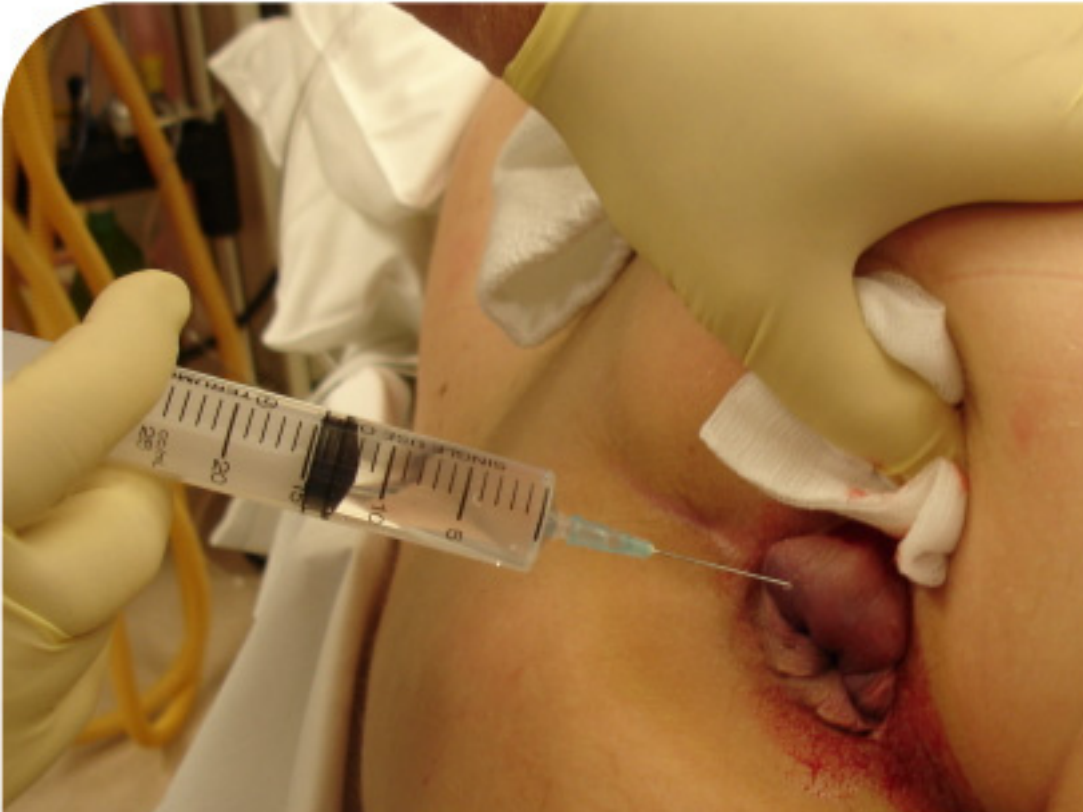
Operative procedure required, (although one could wait and it may resolve).



Prolapsed thrombosed internal hemorrhoid in right lateral position. NB: Swelling of skin. Pain and swelling with past history of repeated episodes were indications for surgery. Surgery can be carried out under local anaesthetic and sedation. Patient shaved whilst in left lateral position. Proposed to excise only one hemorrhoid to reduce post-operative pain and promote early return to work.



Pudendal nerve block plus local infiltration using long acting local anaesthetic such as bupivacaine



Then local anaesthetic is injected directly into haemorrhoid for rapid onset of action and haemostasis. Adrenaline reduces bleeding.



A haemorrhoid has been excised in the office and the wound is now healing.

Risk management

The risk management here is to:

- a) Establish a diagnosis,
- b) Recommend treatment.

Not all haemorrhoids require surgical intervention and alternative treatments for each problem should be offered.

It should be remembered for any anal procedure that the post-operative recovery can be very painful particularly if a complication occurs. Thus the patient needs to be adequately warned about the possibility of pain and the possibility of fainting with pain or due to psychological responses.

The patient often comes for reassurance that they have not got a cancer. If cancer cannot be completely ruled out as a local cause of the problem then further examination with sigmoidoscopy and colonoscopy will be required.

For haemorrhoids, the treatment may consist of diet alone and review may be required. Other alternative treatments are local applications, which may sting, injection sclerotherapy, rubber band ligation and surgical intervention.

Haemorrhoids may be treated with injection or rubber band ligation but it should be remembered that either technique can be painful and complications such as infection or bleeding may occur - in particular secondary haemorrhage eight to ten days later or even reactionary haemorrhage within 24 - 48 hours of the procedure.

There needs to be adequate explanation for the procedure. If an office procedure is to be carried out the patient needs to be fully informed about the extent of the procedure and the aftercare. In particular risks of fainting and causing damage to oneself. The appropriate supervision afterwards is required.

