Sickle cell disease is one of the commonly inherited hemoglobinopathies worldwide and has a variable spectrum of severity. It is caused by a genetic defect in the hemoglobin molecule. The difference between normal hemoglobin A (HbA) and hemoglobin S (HbS) lies in only one amino acid of the beta-chain. This abnormality leads to polymerization of the hemoglobin when the oxygen saturation is lowered, resulting in red blood cell deformity, vaso-occlusion, ischemia, and infarction. Chronic hemolysis is also a consequence of the sickling phenomenon, particularly with homozygous HbS disease. Although acute painful abdominal crisis is the commonest cause of acute abdominal pain in sickle cell patients, other common abdominal manifestations include acute splenic sequestration crisis, splenic infarction, splenic abscess, cholelithiasis, hepatic crisis, pancreatitis, and ischemic colitis. The incidence of acute appendicitis does not appear to be increased in the SCD population. However, reports have suggested that when acute appendicitis develops, it has a rapid course with a high incidence of gangrene and perforation. Al-Salem et al reported a 67% increase in gangrene and perforation in patients with acute appendicitis in SCD versus 5% of the remaining population. These studies have suggested that sickle cell patients with abdominal pain should be evaluated carefully and frequently, and when acute appendicitis appears they should proceed to an early operation. Delayed diagnosis of this condition has serious consequences and appendiceal perforation

Distinct sonographic features of acute appendicitis in sickle cell disease

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Ann Saudi Med 2013; 33(1): 22-27
DOI: 10.5144/0256-4947.2013.22

BACKGROUND AND OBJECTIVES: The purpose of this study was to report sonographic findings of appendicitis in patients with positive screening tests for sickle cell compared to normal control patients.

DESIGN AND SETTING: A retrospective study of the medical records of 396 patients who underwent appendectomy during a 3-year period from March 2005-2008.

PATIENTS AND METHODS: The study included 216 males and 180 females, whose ages ranged from 7 to 55 years. Four patients (0.9%) had sickle cell disease (SCD), 101 had sickle cell trait (SCT) (25%) and 291 (74%) patients were without sickle cell anemia (control group).

RESULTS: Positive sonographic findings of appendicitis were identified in 95 (90%) SCT patients and in 253 (87%) control patients. The mean maximal mural thickness was higher in sickle cell patients (4.5 [1.4] mm) in comparison with the control group (3.0 [2.2] mm) (P<.0001). Appendicolith was significantly detected in 53% of the control group and in 8.5% of the sickle cell group (P<.0001). Color Doppler showed hypervascularity in 72% of patients with appendicitis in the control group with a significant difference compared to only 12 cases (11%) of SC patients (P<.05). Ultrasonography findings suggesting perforation were found in 35 sickle cell patients and in 75% (3 of the 4 patients) with SCD. Findings suggesting perforation were found only in 49 patients (17%) of the control group. Perforated appendix was significantly higher in sickle cell patients in preoperative US and intraoperatively (P<.05)

CONCLUSION: Positive sonographic findings of appendicitis in sickle cell patients are different from the general population. These findings include mural thickening with a low incidence of appendicolith and wall hypervascularity. Also sonographic features of perforation in sickle cell patients are more common suggesting a need for more urgent operative intervention.
is associated with increased morbidity and mortality.\textsuperscript{11}

Despite the familiarity of the signs and symptoms of acute appendicitis, the overall diagnostic accuracy achieved by traditional history, physical examination, and laboratory tests has been approximately 80\%.\textsuperscript{11} Imaging examination such as gradual compression ultrasonography (US) and contrast-enhanced thin-section CT can reduce the number of misdiagnoses and negative laparotomies. In atypical cases, US and CT may help to lower the rate of false-negative appendicitis diagnoses, reduce morbidity from perforation, and lower hospital expenses.\textsuperscript{11} Graded-compression US of the right lower quadrant (RLQ) has been shown to be a useful examination because of its safety and high diagnostic sensitivity approaching 90\% and specificity of 98% in the diagnosis of acute appendicitis.\textsuperscript{12} Advantages of US include lack of radiation exposure, noninvasiveness, short acquisition time, and a potential for diagnosis of other causes of abdominal pain, particularly in the subset of women of childbearing age. Opinion varies as to whether these diagnostic imaging modalities should be performed in all patients with suggested appendicitis or if radiology should be reserved for selected patients with atypical or confusing clinical presentations. Recently, contrast-enhanced thin-section (0.5 mm) helical CT has become the preferred imaging technique in the diagnosis of acute appendicitis and its complications, with a high diagnostic accuracy of 95\% to 98\%.\textsuperscript{13,14}

There is a paucity of literature on imaging findings of acute appendicitis in sickle cell patients. In this study, we have compared the US findings of appendicitis in sickle cell patients to a normal population to show if these findings differ, in order to be able to nominate acute appendicitis as a cause of acute abdomen in sickle cell patients, to be operated upon without delay.

**PATIENTS AND METHODS**

This study was performed at the Gulf Specialist Hospital, Qatif (Eastern Province, Saudia Arabia). The study group included all patients who underwent appendectomy in the period from March 2005 to March 2008, including children and pregnant women, depending on Alvarado score which is a safe, noninvasive, simple, fast, reliable and repeatable diagnostic scoring system with high sensitivity (87\%), specificity (60\%) and high diagnostic value (83\%).\textsuperscript{15} On admission, all patients agreed to undergo abdominal and pelvic US examination. The study included 396 patients (216 male and 180 female) aged 7 to 55 years. Screening for sickle cell anemia (performed routinely) was negative in 291 patients (control group) and positive in 105 patients (sickle cell patients group). By hemoglobin electrophoresis, 4 patients had SCD and 101 had sickle cell trait (SCT). We reviewed medical records, sonography and histopathology results. Blood studies and sonography were part of the routine assessment in patients with right-side abdominal pain in our hospital. CT was reserved as a problem-solving tool.

All US examinations included in this study were performed by a senior radiologist (RD). Examinations were performed on a Hitachi EUP-6000 unit (Hitachi Medical Systems, Tokyo, Japan) using both curved array 3-5-MHz and linear array 7-10-MHz transducers. The radiologists used the graded compression technique previously described by Puylaert.\textsuperscript{16} Color Doppler US was performed at the end of the gray-scale US examination by using a low-velocity scale (pulse repetition frequency, 1500 Hz) and a low wall filter (100 Hz) to detect slow blood flow. The sonographic criteria used for diagnosis of appendicitis included enlarged appendiceal diameter, lack of compressibility, and the presence of appendicolith.\textsuperscript{16,17} We also evaluated the color Doppler of the wall (appendiceal wall signal) as follows: Color gain was increased until clutter was observed and then was reduced just enough to remove clutter from the image of the appendix.\textsuperscript{18} We also measured the appendiceal maximal mural wall thickness (MMT) from the outer wall to the luminal surface on transverse sections without compression. The US features of perforation include loss of the echogenic submucosal layer and the presence of a loculated periappendiceal or pelvic fluid collection or abscess.\textsuperscript{19,20} US reports describing equivocal findings of appendicitis were analyzed with the positive cases. The surgeon was aware of the results of both US and laboratory evaluations before the decision to operate was taken.

Appendectomy was performed for all patients included in this study. The operative reports were used as the reference standard for comparison with the sonographic reports. The US findings were compared with surgical results in sickle cell patients and the control group. The sonographic findings and operative reports in the sickle cell patients and control group were tabulated and compared. Statistical comparison was done using the chi-square test and the t test as appropriate. Results were considered statistically significant at $P < .05$.

**RESULTS**

The sickle cell anemia screening test was positive in 105 patients for all 396 patients who underwent appendectomy within a period of 3 years in our hospital. Hemoglobin electrophoresis of these 105 patients
showed SCD in 4 patients only (HbS range from 75% to 90% and HbO was 0%). The remaining 101 patients had SCT (HbS ranged from 45% to 75 % and HbO 25% to 55%). The demographic findings of the study population are shown in Table 1. The sonographic findings of both groups of patients are listed in Table 2. Positive sonographic findings of appendicitis were identified in 90% (n=95) of sickle cell patients and in 87% (n=253) of patients without sickle cell anemia.

In all patients with appendicitis, sickle cell patients had a statistically significantly smaller diameter, higher MMT, and lack of an appendicolith (P<.05). A statistical difference was also found in the color Doppler hypervascularity—72% of patients with appendicitis in the control group while in sickle cell patients, appendiceal wall hypervascularity was shown only in 11% (n=12, P<.05) (Figure 1). US showed findings of perforated appendicitis in 33% (n=35) of sickle cell patients (Figure 2). In patients in the control group, sonography revealed appendiceal perforation in 49 patients (17%) (P<.05).

The difference in US-measured outer appendiceal calibers and MMT were statistically significant between the sickle cell patients and the control group (Table 3). The outer appendiceal caliber between the sickle cell and control groups was 6.5±1.2 mm vs. 9.8±4.5 mm, (P<.05) and the MMT difference was 4.5±1.4 mm vs. 3.0±2.2 mm (P<.05). Thus the sickle cell patients had a thinner outer appendiceal caliber and a wider maximal mural thickness when compared to the control group (Figures 3, 4). The perforation rate in sickle cell patients was significantly increased compared to the controls both sonographically and operatively (Table 4). In the sickle patients (105 patients), 95 had positive findings on sonography, and 10 had negative findings. According to the operative database positive appendicitis was detected in 99 patients. In the control group, 253 patients had positive findings on sonography, and 38 had negative findings with no statistical significance between groups, while perforated appendicitis was significantly higher in sickle cell patients by preoperative sonography.

DISCUSSION
Appendicitis is the most common cause of acute abdominal pain that necessitates surgical intervention. Although there are many causes of abdominal pain in sickle cell patients, the incidence of acute appendicitis does not appear to be increased in the sickle cell population. In the last two decades, imaging examinations had a big role in the diagnosis of appendicitis. However, there is paucity of literature about imaging findings of
patients was 26.5% of the total appendectomies in our hospital. This incidence is similar to the combined incidence of both SCT and SCD, which is 22% to 27% of the population in the Eastern Province of Saudi Arabia. However, only four patients had SCD (1% of the total appendectomies done in our hospital), while the rate of appendectomies in SCD patients is lower than the general incidences of SCD in our community (about 2%). This confirms the previous suggestion that incidence of acute appendicitis is lower in the SCD population. However, this rate is slightly higher than that of the study of Al-Salem et al, who reported an incidence of appendicectomy in SCD patients of 0.43% of 2102 appendectomies performed, and also the study of Al Nazer et al who found only 8 patients with SCD out of 1563 (0.5%) patients with acute appendicitis. Our relatively higher rate may be attributed to the lower number of cases in our study.

The use of sonography for the diagnosis of appendicitis has increased in the past 20 years. A large set of appendiceal and periappendiceal criteria are used to diagnose acute appendicitis, with the most sensitive and specific being a diameter of 6 mm or greater (sensitivity 98%; specificity 98%), lack of compressibility (sensitivity 96%; specificity 98%), and inflammatory fat changes (sensitivity 91%; specificity 76%). Also appendicitis was diagnosed if the appendiceal maximal mural thickness (MMT) was 3 mm or more in a non-compressible appendix. Views about the utility of sonography examination in the diagnosis of appendicitis vary. In some institutions, sonography is considered routine, whereas other groups have claimed that clinical examination by an experienced surgeon has an accuracy of 71% to 97% and recommend sonography in only select cases. In our study, a dilated appendix more than 6 mm was noted in 50 patients (47.6%) in the sickle cell group and in 253 patients (86.9%) in the control group. The outer appendiceal caliber was higher in the control group patients than in the sickle cell patients while the maximal mural thickness was higher in sickle cell patients than controls. Appendicolith was detected in 155 cases of the control group (53%) and in 9 cases (8.5%) in the sickle cell group. These sonographic findings suggest that the inflammatory changes of appendicitis in sickle cell patients differed from the general population in the form of more wall thickening rather than luminal and caliber dilatation as observed in the control group. These observations suggest that the etiology of appendicitis might differ in both groups of patients.

Appendiceal obstruction, which is the most common cause of appendicitis in the general population, could lead to retention of pus or appendiceal secretion
within the distended lumen with resorption of appendiceal gas and subsequent luminal and outer caliber dilatation. While in sickle cell patients, appendicitis appears to be attributable to blockage of appendiceal vessels by the abnormal sickled red blood cells, causing extensive transmural hemorrhage and congested blood vessels with subsequent wall thickening without luminal distension. In our study, the highly significant incidence of the presence of appendicolith in the control group relative to sickle cell patients group confirms this explanation. According to these observations, we suggest measuring the maximal mural thickness in addition to outer appendiceal diameter to diagnose cases of suspected appendicitis in sickle cell patients.

Color Doppler sonography can be a useful adjunct to gray scale sonography for improving observer confidence in the diagnosis of appendicitis. Visualization of an increased color Doppler flow signal in the appendiceal wall and/or a right lower quadrant mass is supportive of a diagnosis of appendicitis. This likely reflects increasing perfusion of the appendiceal wall accompanying inflammation. Hyperemia in the appendiceal wall shown on color Doppler images was a specific finding for appendicitis that was very rarely encountered in patients without appendicitis. Another published study reported that flow was never identified in the normal appendiceal wall. These observations were also seen in our study where appendiceal wall hypervascularity was noted in 72% of patients with appendicitis in the control group, while in sickle cell patients, appendiceal wall hypervascularity was observed in only 11% (12 cases), a highly statistically significant difference that can be attributed to blockage of appendiceal vessels by the abnormal sickled red blood cells, causing transmural ischemia. However, this observation should be taken with caution as in initial appendiceal inflammation in patients without sickle cell; there may be no detectable increase in color Doppler flow signal. Therefore, the absence of a color Doppler flow signal is nondiagnostic as it can be seen in both normal and abnormal appendices.

Al Salem et al in 1997 suggested that when acute appendicitis develops in sickle cell patients, it has a rapid course with a high incidence of gangrene and perforation and they recommended that patient with SCD and abdominal pain should be evaluated carefully and frequently, and when acute appendicitis appears they should probably be operated upon early. In the sickle cell patients in our study, sonography revealed appendiceal perforation in one third of patients (n=35); among them three of the four patients had SCD (75%). At the time of operation appendiceal perforation was noted in 41 patients (39%), while in control group, sonographic signs of appendiceal perforation were evident in 49 patients (16%) and the number increased to 65 patients (22%) at the time of surgery. The low perforation rate detected by sonography in comparison to the operative results in both groups of patients confirms the opinion that US features of perforation occur in 50% to 70% of cases of perforated appendicitis and the appendix.

### Table 4. Comparison between the sonographic and the operative findings in sickle cell patients and control.

|                      | SC patients (n=105) | Control (n=291) | P      | SC patients (n=105) | Control (n=291) | P      |
|----------------------|--------------------|-----------------|--------|--------------------|-----------------|--------|
| Negative appendicitis| 10 (9.5%)          | 38 (13%)        | NS (.44)| 6 (5.7%)           | 27 (9.2%)       | NS (.36)|
| Positive appendicitis| 95 (90.4%)         | 253 (86.9%)     | NS (.87)| 99 (94.2%)         | 264 (90.7%)     | NS (.93)|
| Perforated appendicitis| 35 (33.3%)        | 49 (16.8%)      | .0004  | 41 (39%)           | 56 (22.3 %)     | .0027  |

Statistically comparisons by chi-square test.

### Figure 4. Abdominal ultrasonography (sagittal view) of a 17-year-old girl with SCD and acute appendicitis showing a dilated appendix with a markedly thick wall without a distended lumen.
ACUTE APPENDICITIS IN SCD

itself is visible in only 40%-to 60% of patients with appendicular perforation.19,20 Although sonography is relatively limited in detection of perforated appendix, our sonographic findings suggest that perforations are more common in SCD patients and may reach up to 75% in patients with SCD in comparison to the general population. The very high perforation rate in SCD patients was comparable to those reported by El Salem et al which was 67% of their nine patients with SCD30 and to that of Al Nazer et al who reported perforation in 87% of their eight SCD patients.24 One explanation could be the possible delay in diagnosis of appendicitis due to spending more time excluding other more common causes of abdominal pain in patients with SCD. Another possible explanation is that SC patients usually take painkillers to decrease the severity of the disease and this may mask the appearance of the appendix. Moreover, the recurrent attacks of pain due to sickling and its complications may increase the pain threshold of these patients, which further masks the characteristic pain of appendicitis. Finally, sickle cell patients are usually underbuilt and this makes abdominal sonography easier as obesity is a well-recognized factor that severely limits the interpretation of any sonographic examination. El Salem et al in 1998 and Al Nazer et al in 2003 suggested another explanation: They claimed that blockage of appendicular vessels by the abnormal sickled red blood cells causes congestion, hemorrhage, and subsequent transmural ischemic necrosis, leading to perforation; this was later proved by histological studies.10,24

A number of limitations in our study must be considered. Because of the retrospective design of our study, we were not able to control for other variables, such as clinical findings, symptom duration or body mass index. Furthermore, there was no reliable way to confirm the false-negative results, which were excluded (all our patients underwent appendicectomy). There were some additional sonographic criteria not included in our protocol that may have been interesting to evaluate, especially the presence of air in the appendicular lumen, and the noncompressibility of the peripappendiceal fat.

We conclude that sonographic findings of appendicitis in sickle cell patients differ from the general population. These findings include mural thickening rather than luminal or outer caliber dilatation with a low incidence of appendicolith and wall hyperervascularity. Also sonographic features of perforation in sickle cell patients are more common than in the general population. When sonographic findings of acute appendicitis are detected in sickle cell patients, delay of appendicectomy should be avoided, even in view of the possibility of negative appendicectomy, still the outcome will be better than that with appendicular perforation.

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