Evaluation of Serological Factors and their Relationship with Constant Shoulder Score in Frozen Shoulder Patients

Abstract

Introduction: Frozen Shoulder is a painful and debilitating illness that affects 2 to 5% of the general population, characterized with significant shoulder pain and reduced mobility, resulting in loss of passive and active movements. This is a cross-sectional study to evaluate serological factors in these patients and their relationship with Constant Shoulder Score (CSS) which may be of diagnostic benefit.

Materials & Methods: Frozen shoulder (Adhesive Capsulitis) cases referring within 4 months of the disease were considered for the study (referred sample). Diagnostic criteria for adhesive capsules included: 1) limited and painful shoulder for at least 4 weeks, 2) severe shoulder pain that interfered with daily life or work performance, 3) nocturnal pain, 4) painful limitation of raising active and passive to less than 100 degrees, and 5) limitation of at least 50% in external rotation. After primary clinical evaluations, a series of specific blood tests were requested and the shoulder range of motion and scores were recorded The mean levels of fasting blood glucose (FBS), Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) CRP levels and associated with constant shoulder score (CSS) were documented.

Results & Discussion: Fifty patients with frozen shoulder referred to the orthopedics clinic of a tertiary teaching hospital within one year period were included. A total of 29 patients with adhesive capsulitis were assigned to the study, of whom 22 were female (76%) and 7 male (24%). The mean levels of fasting blood glucose (FBS), Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) were 100.61 ± 17.29 mg/dL, 16.89 ± 13.14 mm/h and 2.85 ± 6.88 mg/L, respectively. CRP levels were inversely associated with constant shoulder score (CSS).

Conclusion: The serum level of CRP might be a reliable biomarker for predicting the qualitative state of pain and range of motion in patients with adhesive capsulitis.

Keywords: Adhesive capsulitis, Frozen shoulder, Serologic tests, Hematologic tests.

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Introduction

Frozen shoulder, also known as adhesive capsulitis, is an inflammatory disorder that causes shoulder stiffness and pain, described as "A syndrome of varied severity defined by the gradual development of global restriction of active and passive shoulder mobility where radiographic signs other than mild osteopenia are absent," according to the American Academy of Orthopedic Surgeons[(1)].

The majority of patients exhibit a severe decrease of passive range of motion, which is an important diagnostic criterion. In the general community, adhesive capsulitis affects two to five percent of the population. The average age of onset is around 55 years old. Females have a somewhat higher prevalence (1.4:1). The non-dominant hand is usually affected. Interestingly, various autoimmune comorbid diseases, such as thyroid problems and diabetes mellitus, have been proven to predispose people to this syndrome. Furthermore, depending on the duration of their diabetes, patients with diabetes often have worse treatment outcomes[(2)].

Adhesive capsulitis' exact pathogenesis is uncertain. Inflammation begins in the joint capsule and synovial fluid, according to the most widely accepted theory. Reactive fibrosis and adhesions of the synovial lining of the joint follow the inflammation. Pain results from the capsule's initial inflammation, and capsular fibrosis and adhesions result in a reduction in range of motion[(3)].

Some studies report patients with frozen shoulder to have high ESR (28%), CRP (34%), fibrinogen (21%), and WBC (53%) compared to otherwise healthy individuals[4]. Finding a significant relationship between lab tests and clinical state of frozen shoulder is valuable information which helps physician in assessing patients with frozen shoulder and making more accurate clinical judgement about their functional state and possibly help in choosing better treatment options. In the present study, we intended to measure certain laboratory markers in patients with frozen shoulder and evaluate these markers' relationship with clinical state of the disease which is represented with CSS.

Materials & Methods

This cross-sectional study was performed to evaluate the blood factors, and CSS in patients with froze shoulder. Patients with frozen shoulder referred to the orthopedics clinic of a referral tertiary institutional hospital from March 2019 to March 2020 were included.

Inclusion criteria

Having met the clinical diagnostic criteria and having been visited at the outpatient clinic of a tertiary referral university-based hospital at least once Exclusion criteria: Patients referring to the clinic 9 months after the onset of the disease; patients' dissatisfaction to participate in the study. After explaining the purpose of the study and obtaining written informed consent, 50 patients who had been referred in the first 4 months of their disease (in the freezing phase) were considered and assigned to the study. However, only 29 cases met the criteria. Sampling was done by convenience method. Diagnostic criteria for adhesive capsules included: 1) limited and painful shoulder for at least 4 weeks, 2) severe shoulder pain that interfered with daily life or work performance, 3) nocturnal pain, 4) painful limitation of raising active and passive to less than 100 degrees, and 5) limitation of at least 50% in external rotation[5]. Radiography was also requested to rule out other possible causes for all patients. A file was created for these patients and basic patient information such as age, sex, education and occupation, along with the Constant Shoulder Score (CSS) questionnaire was collected. CSS is a multi-item functional scale assessing pain, ADL (activity of daily living), ROM(range of motion) and strength of the affected shoulder. Its score ranges from 0 to 100 points, representing worst and best shoulder function, respectively[6]. Visual analogue scale (VAS) was used for pain evaluation. Also, clinical findings such as patient examinations and complaints and laboratory findings and other modalities and imaging were recorded as needed. Patients were referred to the same laboratory for ESR, CRP and other parameters' level. Finally, the obtained data were statistically analyzed using SPSS version 26 statistical analysis software. Independent t test was used for quantitative variables such as the level of requested tests, and Pearson test and Spearman coefficient were used to determine the relationship between data. Significance level was considered $P < 0.05$.

Ethical considerations

The present study was approved by the regional ethics committee of Tabriz University of Medical Sciences based on the Helsinki Declaration with the ethics code IR.TBZMED.REC.1398.990.The purpose of the study were explained and written informed consent was obtained. Admission to the study was completely optional. Data confidentiality and having the right to quit the research anytime intended were warranted.

Results

In this study, 50 patients were diagnosed clinically with frozen shoulder over the span of one year, of whom 29 patients met the criteria for the study. None of the patients gave a family history of the disease in close relatives. Most patients were right-handed (75.9%). 14 patients had right shoulder (48.3%), 13 patients left shoulder (44.8%) and 2 patients had both shoulders (6.9%) involved. The hand dominancy had no statistically significant relationship with the involved shoulder ($P = 0.242$). Table 1 summarizes demographic information of the participants such as age, gender, BMI, comorbidities, the patients' handedness and the affected shoulder's side, and type of treatment they received. In 15 patients behind the shoulder (51.7%), 7 patients (24%) above, 3 patients in front (10.3%), 3 patients at lateral shoulder (10.3%) and in one patient neck were reported as the pain site. Nine patients (31%) had moderate pain, 7 patients (24%) severe pain, 7 patients very severe pain (24%), 3 patients (10.3%)

had unbearable pain and 2 patients (6.9) had mild pain and one patient (3.4%) had very little pain.

Only 6 patients (20.7%) had a history of recent shoulder trauma and 23 patients (79.3%) had no trauma to the shoulder.

Statistically, the relationship between constant shoulder score and the requested experiments was evaluated, which was significantly related to CRP (P = 0.025).

Collectively, it can be postulated that 1 mg/L decrease in the level of CRP would increase CSS by about 41.4 points, the mean value of which was 53.37 ± 15.41. Table 2 reports Laboratory factors values and their relationship with Constant shoulder score.

Table 1: Demographic information of the participants enrolled at the study.

Variable			Participants (n = 29)			
			Number (n =)		Percent (%)	
Age			55.59 ± 9.57			
Sex	Female		22		75.9	
	Male		7		24.1	
BMI		Mean Value	27.78 ± 4.59			
		Normal	7		24.1	
		Overweight	10		34.5	
		Moderate Obesity	5		17.2	
		Severe Obesity	2		6.9	
Comorbidity		Diabetes Mellitus	1		3.4	
		Cardiovascular Disease	2		6.9	
		Epilepsy	1		3.4	
		Hypothyroidism	1		3.4	
		Hyperlipidemia	1		3.4	
		Diabetes + Hyperlipidemia	3		10.3	
		None	20		69	
			Dominant Hand		Dominant Hand	
			Left	Right	Left	Right
Affected Shoulder		Left	5	8	17.2	27.6
		Right	2	12	6.9	41.4
		Both	0	2	0	6.9
Type of Treatment		Medication	7		24.1	
		Physiotherapy	4		13.8	
		Corticosteroid Injection	4		13.8	
		Laser Therapy	1		3.4	
		Combination Therapy	4		13.8	
		None	9		31.1	

Table 2: Laboratory factors values and their relationship with Constant Shoulder Score

Blood Values	Minimum	Maximum	Mean±Std. Deviation	Adopted range of normality	P value
FBS	83	150	100.61±17.29	70-110 mg/dl	0.78
Platelets	$214*10^3$	$450*10^3$	$240*10^3$±$59*10^3$	150-450 10^3/ µl	0.75
WBC	4.200	16.200	6.445±2.399	4-11 10^3/µl	0.86
Neut.	1.50	7.30	3.235±1.484	2-8 10^3/µl	0.75
Lymph	1400	3000	2119.8±418.17	0.9-5.2 10^3/µl	0.69
ESR	1	48	16.89±13.14	0-22 mm/h	0.07
CRP	0	36	2.85±6.88	0-10 mg/L	0.02
LDL	22	195	125.96±38.11	0-150 mg/dl	0.66
VLDL	11.5	120	41.60±28.65	2-30 mg/dl	0.34
TG	50	479	160.72±100.67	30-150 mg/dl	0.3
Cholesterol	75	350	216.13±62.04	0-200 mg/dl	0.6
Fibrinogen	200	472	300.26±66.09	200-400 mg/dl	0.73
RF	0	36	4.65±8.14	0-15 IU/ml	0.34
CSS	16	75	53.37±15.41		

Discussion

In this study, we measured certain laboratory parameters in patients afflicted with shoulder adhesive capsulitis and also evaluated the relationship between those parameters with clinical state of frozen shoulder, measured through Constant Shoulder Score (CSS). Among several markers, only CRP showed statistically significant association with CSS. Several researches have been conducted to evaluate the relationship between biomarkers and frozen shoulder. By obtaining an estimation of markers' level in frozen shoulder patients, they can also be compared with other shoulder pathologies.

The Frozen shoulder inflammatory process hypothesis was confirmed by Bulgen et al. In 1982, who reported high CRP levels in 25% of patients and ESR in 20% of patients with normal lymphocyte counts[7]. In the present study, ESR was reported to be high in 7 patients (24%) and CRP in 2 patients (7%). Park et al. in 2020 investigated the levels of CRP in a group of 202 patients with idiopathic adhesive capsulitis (IAC), along with 606 healthy individuals, finding increased levels of CRP (> 1 mg/L) in these patients, while also suggesting that the level of CRP in IAC was associated with diabetes, FBS, hypertriglyceridemia and hypolipoproteinemia[8]. Park et al. also conducted a case-control study to evaluate association between fasting glucose levels and idiopathic adhesive capsulitis in a normoglycemic population[9]. They concluded idiopathic adhesive capsulitis is positively associated with fasting glucose levels of 90-99 mg/dL, which are currently considered normoglycemic. Hyperglycemia is a known risk factor for adhesive capsulitis, and Park et al. study concludes that higher level of blood glucose even in normal range is a risk factor. In our study, fasting glucose of 5 (17.2%) patients was above the upper limit, as compared to that of the remaining 24 (82.8%) patients which was within the normal range (70 – 100 md/dL), but the statistical analysis did not show any significant relationship between FBS and CSS.

In a study by Gumina et al., who looked at the relationship between blood tests and CSSs in the first phase of the disease, about 56 patients who were treated conservatively at the first visit in the first phase of the disease were evaluated for their requested tests and CSS, then after 4 months the tests and examinations were repeated[4].

There was no statistically significant relationship between blood parameters of FBS, cholesterol, LDL, triglyceride, fibrinogen, white blood cells, ESR, CRP, rheumatoid factor and constant score. However, in the present study, there was a significant relationship between CRP and constant score (P = 0.025). In the above study, no treatment other than physiotherapy was performed for patients for 4 months to prevent any reduction of inflammatory factors in blood. But after 4 months, a significant inverse relationship was recorded between Constant score and glycemia (P = 007), triglyceride (P = 0.05), ESR (0.017), CRP (0.013)[4]. The association between frozen shoulder and blood lipids has been investigated by Bunker and Esler[10]. Because some pathological diseases such as diabetes[11], epilepsy[12], alcoholism[13] and heart disease[14] are more common among people with hyperlipidemia, the authors concluded that hyperlipidemia may be a common strand that binds adhesive capsules to these pathologies. They reported that fasting triglyceride and cholesterol levels were significantly increased in the frozen shoulder group compared with the control group. Unfortunately, they did not mention the percentage of patients with adhesive capsules and hyperlipidemia. Our data also confirms this association, showing that two-thirds and almost half of patients with adhesive capsules have high levels of cholesterol and triglycerides, respectively. Although we have confirmed this relationship, other studies are needed to gain a more accurate understanding of the factors that link the two conditions.

Conclusion

Based on our findings, although adhesive capsulitis is significantly associated with the level of pro-inflammatory marker of CRP, white blood cell counts and serum levels of lipoproteins were not found to be reliable predictors of the disease. The serum level of CRP might be a reliable biomarker for predicting the qualitative state of pain and range of motion in patients with adhesive capsulitis, as it is correlated with CSS. Of note, it can be postulated that 1 mg/L decrease in the level of CRP would increase CSS by about 41.4 points.

Limitations of the Study

Limitations of the present investigation are being a cross-sectional single center study on a small group of patients with adhesive capsulitis, which was

limited in its scope due to the relatively low number of its participants. Further large-scale studies on this subject matter are warranted.

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