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Autoimmune Hepatitis Prevalence among Patients from Saudi Arabia with Chronic Liver Disease Referred for Transient Elastography

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Abstract

Background and study aim: Autoimmune hepatitis (AIH) is a chronic liver disease that can lead to progressive liver damage. The prevalence of AIH among the general population and among chronic liver disease (CLD) patients is variable worldwide. Currently, no published data on the prevalence of AIH among Saudi or among liver disease patients from the region. In this study, we aimed to assess the prevalence of AIH among CLD patients who were referred for transient elastography (FibroScan) in Saudi Arabia. **Patients and methods:** A retrospective study was conducted among CLD patients who had a transient elastography (FibroScan) during the 3-year study period. We obtained demographic data and test results for serum alanine aminotransferase (ALT), bilirubin, hemoglobin (Hgb), platelets, and international normalized ratio (INR) from all patients. We compared the results of the AIH patients to those of the non-AIH patients with CLD. In addition, for AIH patients, we measured serum immunoglobulin G (IgG), antinuclear antibody (ANA), smooth muscle antibody (SMA) and ALT at 2 - 6 weeks and at 3 - 4 months. **Results:** We included 494 patients, who were predominantly female (271 (60%)) and Saudi (299 (60.5%)). Thirty patients (6.1%) had AIH, which represented the 4th most common liver disease. Compared to non-AIH patients, AIH patients were younger (mean ages 49.9 years, SD 14.22 years, and 40.4 years, SD 13.94 years, respectively, $P = 0.001$). Patients with AIH had significantly lower Hgb and platelets ($P = 0.008$ for both) and higher ALT, bilirubin and INR ($P = 0.05$, 0.047 and 0.019, respectively). More than 50% of the AIH patients had cirrhosis. Older age was not associated with advanced disease stage among the AIH patients ($P < 0.001$). AIH represents the 4th most common cause of CLD in patients referred for transient elastography in Saudi Arabia. AIH tends to be severe in patients at a young age, with a marked biochemical response to steroids and azathioprine treatment.

Keywords

Autoimmune Hepatitis, Chronic Liver Disease, Saudi Arabia, Prevalence, Transient Elastography (FibroScan)

1. Introduction

Autoimmune hepatitis (AIH) is chronic inflammatory liver disease with an unknown etiology. AIH can present as either acute or chronic hepatitis along with liver cirrhosis or end-stage liver disease [1] [2] [3] AIH is more common in young and middle-aged females with a female to male ratio of 3 - 4:1 [4] [5] [6]. However, the age at diagnosis varies widely, affecting individuals from childhood to old age [1] [2] [3]. The prevalence of AIH in Western Europe is variable and is estimated at approximately 10 - 17 cases/100,000 people [7] [8]. A higher prevalence rate of 42.9/100,000 people was reported from the state [9]. In Asia and New Zealand, the prevalence rate was 24.5 cases/100,000 people, while in contrast, Singapore had a much lower prevalence of 4 cases/100,000 people [10] [11]. The estimated global incidence and prevalence of AIH are 1.7 - 1.9 cases/100,000 people per year and 16.9 - 42.9/100,000 people, respectively [12]. The global prevalence of AIH among individuals with liver disease is not well studied; however, AIH is much less common than viral hepatitis and alcoholic and nonalcoholic fatty liver disease, representing only 4% of all indications for liver transplantation [12] [13] [14]. Several national reports from Saudi Arabia have addressed the clinical characteristics of AIH; however, the prevalence of AIH among the general population and among patients from Saudi Arabia with liver disease is not known [3] [4] [5]. The spectrum of clinical presentations of AIH ranges from asymptomatic disease to acute severe liver failure or severe advanced liver cirrhosis [1]-[6]. AIH is characterized by elevated transaminases, liver infiltration with lymphocytes and plasma cells, and positive serum autoantibodies [1] [2] [3]. The standard treatment for AIH is steroids and immunomodulation with azathioprine [1] [2] [3]. In Saudi Arabia, the prevalence of AIH might be underestimated due to the high prevalence of chronic hepatitis B and C and the increasing burden of nonalcoholic fatty liver disease (NAFLD) [15] [16]. This study was conducted at King Abdulaziz University Hospital (KAUH), the largest academic medical center in western Saudi Arabia, and aimed to study the prevalence of AIH among patients with chronic liver disease (CLD).

2. Patients and Method

Ethical approval was obtained from the research ethics committee of the Faculty of Medicine, King Abdulaziz University.

This is a retrospective study that was conducted at the Gastroenterology/Hepatology Unit at KAUH, Jeddah. The study was conducted over a 3-year period from April 2015 to April 2018. The study population was composed of adult patients above 18 years of age with stable CLD who did not show any clinical evidence of decompensation and who had received transient elastography using FibroScan within the study period. We excluded patients who had FibroScan examinations at KAUH but had incomplete data in their files because of parallel follow-ups in other hospitals. Patients who had a superimposed acute liver injury (such as drug-induced injury on top of stable CLD) were also excluded. The data were obtained from the gastroenterology and hepatology unit documents and from patients' electronic files in the hospital information system.

Demographic data were collected, which include age, gender, and nationality (Saudi or non-Saudi). We gathered the following information for all patients: hemoglobin (Hgb), platelet count, serum alanine transaminase (ALT), serum glutamyl transferase (GGT), serum albumin, and serum bilirubin. These results were obtained from tests that were conducted within one month of the FibroScan examination. We also assessed associated comorbidities or autoimmune diseases and evidence of hepatocellular carcinoma, cirrhosis or fatty liver in the imaging examination.

For the AIH patients, we also included the results of the serum immunoglobulin G (IgG) test that was conducted within 1 month of the FibroScan examination. In addition, we obtained serum ALT levels at 2 - 6 weeks posttreatment and at 3 - 4 months posttreatment.

The FibroScan (Echosens; Paris, France; 2005) examination was performed by one expert examiner with more than 5 years of experience in performing the examination. A successful examination was defined as showing at least 10 valid readings with at least a 70% success rate (interquartile range (IQR) of less than 30%). The result was read in kilopascals (kPa). Different stages of fibrosis were defined as F0 (less than 6 kPa), F1 (6 - 7.1 kPa) for mild fibrosis, F2 (7.2 - 9.4 kPa) for moderate fibrosis, F3 (9.5 - 12.4 kPa) for severe fibrosis, and F4 (>12.5 kPa) for cirrhosis [17] [18]. The fat content was determined from the captured attenuation parameter (CAP). Radiological examination was performed using an abdominal ultrasound, and fatty liver was defined as fatty infiltration or attenuation of the liver image with or without hepatomegaly. Portal hypertensive features and cirrhosis were defined with an ultrasound examination if there were dilated portal veins, the presence of collaterals or splenomegaly.

The patients were divided into two groups (the AIH group and the non-AIH group), and a comparison of the two groups was performed in terms of clinical features and laboratory results.

CLD was defined as persistently abnormal liver enzymes for 3 - 6 months, positive serological markers for viral hepatitis, and/or the presence of laboratory features of portal hypertension (HTN) (such as thrombocytopenia) together with positive serological markers for AIH or viral hepatitis. Nonalcoholic fatty liver disease was diagnosed based on the following criteria: persistently elevated liver enzymes for more than three months, the presence of metabolic syndrome or obesity, a lack of viral and autoimmune markers, and a negative history of hepatotoxic medication use or radiological examination with an ultrasound or computerized tomography (CT) abdominal examination.

AIH was defined according to the international group for AIH criteria and the modified criteria for the diagnosis of AIH [19] [20].

Chronic viral hepatitis B and chronic viral hepatitis C were diagnosed based on the presence of a serological viral marker for hepatitis B virus (HBV) or hepatitis C virus (HCV) and a positive viral load detected by the TaqMan polymerase chain reaction (PCR) method.

Patients who had long lasting Rheumatoid arthritis and were on methotrexate for 10 years or more, they were assessed for methotrexate induced liver fibrosis using fibroscan.

Patients with overlap syndrome were defined on the bases of presence of biochemical and immunological features of two autoimmune liver diseases at the same time. Those include AIH-PBC overlap 2 patients. And AIH-PSC overlap 1 patient.

Statistical Method

IBM SPSS 22 was used for statistical analysis. Descriptive statistics are described by frequencies, means, and standard deviations. The chi-square test was used to compare the differences in nominal variables between the AIH patients and the patients with other liver diseases. Student's t-test was used to compare the continuous variables between the AIH patients and the patients with other liver diseases. Linear regression analysis was used to study the effect of different variables on the presence of cirrhosis. A P value ≤ 0.05 was considered significant.

3. Result

The total number of patients was 509, and 494 patients were included in the final analysis according to the inclusion criteria. The total number of AIH was 35 and 5 were excluded because of none availability of their laboratory and follow up data on the hospital information system. The majority of the patients were female (271; 60%), and the majority of patients were Saudi (299; 60.5%). The mean age was 49.46 years (SD 14.21; range 18 - 87 years). The majority of patients were in their forties.

The most commonly identified liver disease among our cohort was chronic hepatitis B (CHB), followed by chronic hepatitis C (CHC). Thirty patients with AIH were identified, making AIH the fourth most common liver disease, representing 6.1% of all patients (**Table 1**). All the patients in our cohort were type I AIH based on the serological markers.

Other baseline characteristics of all patients are shown in **Table 2**, which compares the characteristics of AIH patients to those of the patients with other liver diseases. In both groups, there were more Saudi patients than non-Saudi patients, and 73% of AIH patients were Saudi. Sixty percent of patients were females, and forty percent of patients had cirrhosis based on an ultrasound examination. For the continuous variables the data was normally distributed apart from the serum IgG and IgM. There was a significant difference between the

AIH patients and patients with other liver diseases in terms of age, Hgb, platelet count, serum ALT, serum GGT, serum bilirubin, INR, and CAP (**Table 3**). The biochemical parameters were normal in 310 (66.8%) of the non-AIH patients. On the other hand, the laboratory test results of the AIH patients varied from a modest elevation in ALT and serum bilirubin to very high levels (P = 0.05 and 0.047, respectively) compared to the levels of the non-AIH group (**Table 3**).

The mean serum IgG value for AIH patients was 24.1 g/L (SD 12.44 SE 2.6) (normal up to 16.1 g/L) and the median was 21.4 g/L. The mean serum IgM for AIH patients was 1.78 g/l (SD 1.25 SE 0.26) (normal range 0.5 - 1.9 g/l.) and the median was 1.36 g/l.

Twenty patients had moderately to strongly positive ANA, and 13 patients had moderately to strongly positive SMA.

The distribution of the two groups according to the stage of fibrosis is shown in **Table 4**, and there was a significant difference between the AIH and non-AIH patients (P < 0.001).

Table 1. Distribution of patients according to the underlying liver disease.

Diagnosis	Number of patients	Percent
CHB	166	33.6
CHC	153	31.0
AIH	30	6.1
NAFLD	111	22.5
Methotrexate	19	3.8
Chronic cholestasis of unknown cause	1	0.2
Overlap syndrome	4	0.8
PBC	3	0.6
CHB + CHC	6	1.2
DILI-induced AIH	1	0.2
Total	494	100.0

Table 2. Baseline characteristics of AIH patients compared to those of non-AIH patients.

Variable		AIH, number (%)	Non-AIH, number (%)	P value
Nationality	Saudi	22 (73.3%)	277 (59.7%)	0.18
	Non-Saudi	8 (26.7%)	187 (40.3%)	
Sex	Male	12 (40%)	211 (45.5%)	0.35
	Female	18 (60%)	253 (54.5%)	
Age (years)		40.5 SD 13.940	49.9 SD 14.22	0.001
Diabetes		7	124	0.62
Cirrhosis on ultrasound		12 (40%)	20 (4.31%)	0.044
Autoimmune disease		6 (20%)	39 (8.4%)	0.014

Table 3. Baseline laboratory test results of AIH patients compared to those of non-AIH patients.

	Patients	Mean	Std. Deviation	Std. Error Mean	P Value
Hgb Normal 12 - 15 g/dL	AIH	12.07	2.487	0.488	0.008
	Non-AIH	12.96	2.536	0.120	
Platelet count Normal 150 - 450 K/μL	AIH	216.46	117.505	23.045	0.008
	Non-AIH	258.43	117.993	5.581	
Albumin Normal 35 - 50 g/L	AIH	31.91	12.468	2.445	0.245
	Non-AIH	34.84	5.532	0.260	
ALT Normal 30 - 65 U/L	AIH	83.69	79.307	15.553	0.05
	Non-AIH	51.13	66.981	3.161	
GGT Normal 5 - 85 U/L	AIH	237.92	265.655	52.099	0.004
	Non-AIH	72.87	203.724	9.701	
Bilirubin Normal 0 - 17 μmol/L	AIH	50.13	85.957	17.191	0.047
	Non-AIH	14.03	25.499	1.202	
INR Normal 1.1 - 1.4 Seconds	AIH	1.35	0.474	0.106	0.019
	Non-AIH	1.08	0.285	0.016	
CAP	AIH	217.67	64.420	15.184	0.033
	Non-AIH	253.33	69.995	3.281	
kPa Stiffness score	AIH	13.91	9.415	1.883	0.10
	Non-AIH	10.57	12.021	0.558	

Table 4. The chi square test for the different stage of fibrosis between the two groups.

F Score	Number in None AIH	Number in AIH	Total
0	191	3	194
1	99	5	104
2	45	2	47
3	33	4	37
4	96	16	112
	464	30	494

Of the AIH patients, 20 patients had available results for follow-up ALT values at 2 - 6 weeks and at 3 - 4 months posttreatment with immune suppression. These patients showed a significant reduction in ALT values (P = 0.01 and 0.004, respectively).

Of the non-AIH CLD patients, 337 (72.6%) were older than 40 years, and this age group was associated with a higher stiffness score of 11.72 kPa compared to 7.58 kPa for patients 40 years or younger (P > 0.001).

However, in the AIH group, 11 (36.6%) patients who were older than 40 years did not have a higher stiffness score than the patients who were 40 years or younger (14.62 kPa and 13.35 kPa, respectively, P = 0.75).

4. Discussion

Our study showed that AIH represents the 4th most common cause of CLD in patients referred for Fibroscan. AIH prevalence among the general population and among patients with CLD is variable in different countries. Some reports have shown that AIH is the cause of 4% of all indications for liver transplantation [12]. On the other hand, the prevalence within the general population, which ranges from 10.7 - 16.9 cases per 100,000 people in Europe, has been reported [13]. Higher prevalence rates have been reported in some areas such as Alaska, with prevalence rates of 42.9 cases per 100,000 people, and New Zealand, with 24.5 cases per 100,000 people [9] [10]. Similar general population prevalence studies on liver disease have not been conducted in Saudi Arabia. However, the annual Ministry of Health statistics and other reports show a significant burden of CHB and CHC, which are the two most common liver diseases, as shown in our report [15] [21]. On the other hand, the prevalence of AIH among our cohort is lower than the figure reported by Khalaf *et al.* [22] and Al Sebayel *et al.* [23] (14.3% and 10%, respectively) among liver transplant patients from Saudi Arabia. This difference can be explained by the severity of AIH among Saudi patients, with more than one-third to more than half of patients having advanced fibrosis or decompensated cirrhosis at a young age [4] [5] [6]. The predominance of AIH hepatitis among females is similar to what has been shown in several national and international studies. On the other hand, we have shown that AIH tends to be a severe disease that has severe fibrosis. This finding is similar to previously published data on AIH from different regions from Saudi Arabia [4] [5] [6]. All patients in our cohort were type I AIH and this is similar to the previously reported data on AIH from our center [5].

The clinical and laboratory features of AIH patients from our cohort are similar to those in the published data on AIH from Saudi Arabia, and they also indicate advanced disease severity compared to the disease severity in non-AIH patients. The disease severity is reflected by lower platelet counts, lower Hgb, and a high rate of patients with advanced fibrosis [4] [5] [6]. On the other hand, the higher serum ALT, GGT and serum bilirubin levels of AIH patients, compared to those of non-AIH patients, may reflect ongoing disease activity in AIH patients in the first set of laboratory testing. The prevalence of severe fibrosis in patients aged older than 40 years was not different from that of younger patients; this lack of difference is another reflection of the prevalence of severe AIH at young ages. This finding is similar to the results discussed in our previous report on AIH patients [5]. AIH is known to respond to steroids and azathioprine in most patients, even those with advanced fibrosis and stable cirrhosis [1] [2] [3], and we have shown a significant biochemical response in serum ALT during a short-term follow-up. However, assessing a longer treatment response was not an aim of our study, and this was previously documented by several national and international studies [1] [2] [3]. Multiple regression analysis showed that among AIH patients, age was associated with evidence of cirrhosis in ultrasound examinations. This finding could reflect a long-term ongoing active disease prior to developing cirrhosis at a relatively young age, as shown in most of our AIH patients. This result, in addition to what we have mentioned above, is additional evidence of the aggressive nature of AIH among Saudis [3] [5]. On the other hand, none of the AIH patients had an elevated CAP, which can be explained by the presence of a large number of NAFLD patients representing the most common liver disease after viral hepatitis B and C. The prevalence of serum autoantibody positivity is similar to what has been shown from previous national data on AIH [3].

Our study may not reflect the real prevalence of AIH and other chronic liver disease from Saudi Arabia, however it gives a reflection on the most common chronic liver disease in Saudi Arabia. In addition, we have shown that AIH though not common but it tends to present with severe form of chronic liver disease. National prevalence studies are lacking about AIH and other liver disease from Saudi Arabia. It is important to have National prevalence studies on AIH since early diagnosis and initiation of immune suppression will delay the progression to advance liver disease in young population. This study might be similar to countries that had high prevalence of viral hepatitis B and C and NAFLD with lower prevalence of AIH and other autoimmune liver disease, like European countries.

In conclusion our study showed that AIH represents the 4th most common liver disease among patients with liver disease from Saudi Arabia. AIH tends to result in advanced disease in a large percent of patients. Treatment with immunosuppression results in a marked early biochemical response in AIH patients.

Limitations of the Study

The retrospective nature of the study resulted in failure to include patients who had incomplete data.

The study was conducted in one center, and a similar multicenter national study will more accurately reflect the prevalence of AIH liver disease in the Kingdom of Saudi Arabia.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

AIH: autoimmune hepatitis, CLD: chronic liver disease, ALT: alanine aminotransferase, Hgb: hemoglobin, INR: international normalized ratio, IgG: immunoglobulin G, ANA: antinuclear antibody, SMA:smooth muscle antibody.

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Effect of Knee Valgus Angle during Single Leg Squat and Horizontal Hop for Distance in Patients with Patellofemoral Pain and Controls

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Abstract

Background: Patellofemoral pain (PFP) is considered one of the most common dysfunctions of the lower extremities. Faulty lower limb mechanics and increased of knee valgus on loaded tasks are believed to play an important role in the development of PFP. Objective: To figure out if male PFP patients during single leg horizontal hop for distance and squat with greater knee valgus than controls, and if the nature of the task changes the angles of knee valgus. Methods: Twenty males with unilateral PFP formed the patient group and forty-five asymptomatic males formed the control group. Two dimensional (2-D) frontal plane projection angle (FPPA) was used during single leg squatting and horizontal hop for distance tasks. Results: For the single leg squat, the mean of 6.96˚, 9.80˚, 15.04˚ was reported in the control, PFP asymptomatic knee, and PFP symptomatic knee, respectively. For the single leg horizontal hop for distance, the mean of 11.63˚, 13.72˚, 19.17˚ was reported in the control, PFP asymptomatic knee, and PFP symptomatic knee, respectively. These differences were significant ($p < 0.002$) for both tasks. Conclusions: Patients with PFP represented with greater knee valgus angle than what was found in either their asymptomatic limb or in the control group.

Keywords

Knee Valgus, Hop Tests, Squat, Patellofemoral Pain, Controls

1. Introduction

Patellofemoral pain (PFP) is one of the most common dysfunctions and disorders of lower extremities, mainly affecting young physically active athletes [1]. The presence of PFP usually limits participation in sporting activities [2]. This disorder has been reported to develop patellofemoral osteoarthritis [1] [3]. The mechanisms are still not clearly understood, however, faulty lower limb mechanics and increased of knee valgus on loaded tasks are believed to play an important role in the development of PFP [4].

As the patella passes through the trochlear groove, it has been thought that abnormality in lower limb biomechanics is claimed to negatively affect the alignment of the patella [5]. Wilson *et al.* [5] reported that PFP patients had increased lateral patellar subluxation and tilting during squatting with the neutral aligned position knee. Tanamas *et al.* [6] found that increased lateral patellar tilt being correlated with both increased stress on loading and decreased medial and lateral patella facet cartilage volumes. Noehren *et al.* [7] found a significant relationship between lateral patella translation and knee abduction and external rotation when asymptomatic participants squatted with knees aligned in a valgus or neutral position. Abnormal distribution of the stresses on the patellofemoral joint will happen when the load-bearing surface areas are changed, with different patellar tracking [8]. This abnormal distribution of stresses is believed to have a strong relationship with patellar dysfunctions such as osteoarthritis [9]. Lee [10] reported that patients with PFP showed significant greater knee valgus angle on the affected limb during loading tasks than that reported in either their sound limb or in the asymptomatic control group.

In clinical research, two-dimensional (2-D) motion-analysis system is used to measure different functional movement tasks and can be easily found in clinical practice. 2-D motion-analysis system has been used in the literature to evaluate dynamic knee valgus in many screening tests [10] [11] [12] [13]. These tests involved the single leg squat [10], drop vertical jump [11], single-leg horizontal hop for distance [12], and drop landing [13]. Moreover, 2-D analysis has been used to evaluate knee-valgus angle in healthy, athletic, and injured populations [11].

Poor limb alignment, especially an increased knee valgus during single leg squat [14], running [15], and bilateral landing tasks [16], has been correlated with PFP. Therefore, one of the mentioned studies [10] investigated different movement patterns happened in different single leg movement tasks and how they link to the presence of PFP in female patients. However, none of the above-mentioned studies investigated the changes happened in knee valgus angle between different single leg movement tasks in male participants and how that might relate to the presence of PFP, especially when there are differences in knee valgus angles between gender according to the body constitution. Therefore, the aim of this study is to evaluate the knee valgus angle of male PFP patients and asymptomatic controls while undertaking two tasks, single leg horizontal hop for distance and single leg squat tasks. The objective of the study being to find if male PFP patients perform single leg squat and horizontal hop for distance with greater knee valgus angle than controls, and if the nature of the task changes the degree of knee valgus angle.

2. Materials and Methods

2.1. Subjects

Forty-five asymptomatic male participants (control) involved in the study testing (age mean 25.2 ± 3.98 year, height mean 171.96 ± 5.37 cm, and weight mean 74.80 ± 6.33 kg). All subjects had no any history of anterior cruciate ligament (ACL) injury or other knee pathology, lower limb pathology, lower limb fractures, lower limb surgeries, and had no sever injuries for 3 months prior to the data collection. Twenty male patients with unilateral patellofemoral pain (age mean 25 ± 3.9 year, height mean 172.1 ± 4.93 cm, and weight mean 73.6 ± 6.44 kg) were recruited from hospital clinics, who were the symptomatic comparison group. These patients have been already examined by experienced musculoskeletal doctors to establish that they have met the required inclusion and exclusion criteria mentioned in **Table 1** [17], and they are only having unilateral knee pain. To minimize the risk of any symptom aggravation with testing, participants with relatively mild symptoms (pain is less than 8 out of 10 on a 10 cm visual pain scale, whereas 0 equals no pain and 10 worse perceivable pain) were selected to take part in the study. All participants were recreational athletes participated at least 3 hours of sporting activity per week. A written informed consent was obtained from all subjects and the project was approved by Najran University Research Ethics Committee with approval number (10 – 05-01 – 2020 EC).

2.2. Procedures

2.2.1. Frontal Plane Projection Angle (Video Capture)

The frontal plane projection angle (FPPA) was assessed using a single camera, capturing at a standard sampling frequency of 30 fps, positioned on a tripod at a height of 80 cm from the floor to the middle of the lens, and 2.5 m away from an X-shaped marker which was placed as a reference for the central point on the floor. The zoom lens of the video camera was set at a standard 1x optical zoom throughout all trials in order to standardize the camera position between participants. The reason behind placing the camera on a tripod at a height of 80 cm and 2.5 m away is to ensure that the video included the lower limbs, trunk, and shoulders of the participants with different heights. Each participant was filmed before starting any of the individual tests using a calibration frame (1 m ×1 m) for five seconds. The calibration distance was set 2.5 m away from a camera (frontal plane) just above the X mark which was placed on the floor. This calibration was used for data analysis.

In order to examine the FPPA, three markers were placed directly on the participants' skin before starting the test using a black marker on the following points:

1) Anterior superior iliac spine (ASIS).

2) Middle of the tibiofemoral joint (not middle of the patella).

3) The middle of the ankle mortise anatomical landmark.

Table 1. Inclusion exclusion criteria for patellofemoral pain patient group (Herrington and Al-Shehri 2007).

Inclusion criteria
• Symptoms of anterior knee pain for at least 1 month
• Average pain level of 3 or more on a 10-cm visual analog scale during stepping up and down of a 30 cm high bench
• Anterior or retropatellar knee pain on at least 2 of the following activities: prolonged sitting, climbing stairs, squatting, running, kneeling, and hopping/ jumping
• Presence of two of the following clinical criteria on assessment: pain during apprehension test, pain during the patellar compression test, and crepitation during the compression test
Exclusion criteria
• Previous knee surgery or arthritis
• History of patellar dislocation or subluxation, or ligament laxity
• Patellar tendon pathology or chondral damage
• Spinal referred pain
• History of other abnormalities such as leg length inequalities (N 2 cm)
• Medication as a part of the treatment
• Previous physical therapy or acupuncture treatment for the knee within the previous 30 days

All markers were placed by the same experimenter, and the midpoints were determined using a standard tape measure (**Figure 1**). Participants were asked to perform 3 test trials for all tasks onto their right (dominant in all cases) leg for the control group and both symptomatic and asymptomatic limbs for the PFP group. The reason why the control group has to be right dominant in all cases is that to standardize the test protocol and to make sure that there were no variations might occur when conducting the tests between both limbs (right and left). Moreover, to make sure that the reference values provided in the current study can be generalized to one limb (right) only. The analysis of the FPPA was undertaken in Quintic Biomechanics Software (v21, Quintic, Sutton Coldfield, UK) where FPPA was taken at the maximum knee flexion angle after landing from hop and squat (defined as the lowest point the pelvis reached). After recording the results from the three successful trials for each participant, the mean value over the three trials was calculated and reported. The test-retest reliability of the following tests for evaluating an individual's repeatability of performance of the knee valgus has been reported previously and shows that are reliable tests [12] [18].

1) Single-Leg Squat Task

Participants were instructed to stand on one leg, keep the other limb off the floor, with hands crossed behind their trunk in order to allow all markers to be visible. They were asked to squat down to 45˚ (estimated visually) but not greater than 60˚, and then return to a normal position without losing their balance. During practice trials (from three to five trials maximum), knee flexion angle was checked using a standard goniometer (Gaiam-Pro) then observed by the examiner throughout all trials. There was also an electronic counter used for each trial over five second period in which the first count starts the movement,

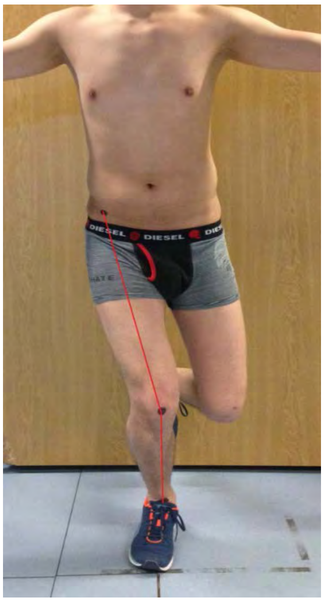

Figure 1. Anatomical marker placement to determine the FPPA.

the third shows the lowest point of the squat and the fifth shows the end. In order to control the degree of lower limb rotation during squatting, the participants were instructed to place their foot on the X-shaped marker, which is placed on the floor, with their foot pointing straight ahead. Acceptable trials were when participants maintained balance and squatted to the desired depth of approximately 45˚ of the knee joint. The control group applied this task on their dominant (right dominant in all cases) leg, while the PFP group applied the task on both legs. While carrying out the task perceived pain was recorded (scored after completion) by the subject marking perceived pain level on a 10 cm visual pain scale (0 equals no pain, 10 worse perceivable pain).

2) Single-Leg Hop Landing Task

The FPPA was assessed during the single-leg horizontal hop for distance test. Participants were asked to perform a unilateral horizontal hop for distance task as far as possible, and land with complete stabilization within the area of the X-shaped marker which was placed on the floor 2.5 m far away from a camera (the hop was applied after adjusting the starting point). The participants hopped to the X-shaped marker (or nearby) from a starting point based on their individual hop distance achieved during the practice trials (from three to five trials maximum), to ensure that the landing was at a point ±30 cm from the X-shaped marker, to accommodate the calibration.

After landing, the participants were free to move their arms as required and to help with balance following landing. Unsuccessful attempts were when the participant hopped and touched the ground with their non-weight bearing leg during landing, or failed to hop within the limited marked distance. The participants needed to land with their foot in line with the camera to ensure that the appropriate calculation of the FPPA was achieved. If the individual landed with their foot too abducted or adducted this trial was repeated as this will affect the measurement of the FPPA. The control group applied this task on their dominant (right dominant in all cases) leg, while the PFP group applied the task on both legs. While carrying out the test perceived pain was recorded (scored after completion) by the subject marking perceived pain level on a 10 cm visual pain scale (0 equals no pain, 10 worse perceivable pain).

2.3. Data Analysis

All statistical analysis was conducted using SPSS for Windows version 25 (SPSS Inc., Chicago, IL). The relationship between knee valgus angle during single leg squat and single leg horizontal hop for distance for both controls and PFP patients was analyzed using factorial ANOVA two factors; task (single leg squat and single leg horizontal hop for distance) and condition (control, PFP or uninjured). Paired t-tests were used to evaluate specific differences within conditions and student t-test between group comparison with the Bonferroni correction ($\alpha = 0.0125$). The significance p-value was set at 0.05.

3. Results

The mean, standard deviation, and the range of the values for the asymptomatic control group and PTP group for both tests the single leg squat and single leg horizontal hop for distance were as shown in Table 2. There is increase in knee pain reported by the subjects who participated in the current study, with more pain is seen when undertaking hop landing tasks. Therefore, it is shown that increasing knee valgus angle during loaded taskes will significantly increase the knee pain. The numeric rating pain score for all limbs including all tasks was shown in Table 3.

Table 2. The mean, standard deviation, and the range of values for both groups.

Group/Test	Single Leg Squat			Single Leg Horizontal Hop for Distance				
	Mean	SD	Range	Mean	SD	Range	Cohen's d	P-value
Control Group	6.96˚	1.56˚	3.9˚ - 10.7˚	11.63˚	1.84˚	8.0˚ - 14.6˚	−2.74	0.002*
PFP Group Asymptomatic Knee	9.80˚	1.37˚	7.1˚ - 11.9˚	13.72˚	1.53˚	10.9˚ - 16.4˚	−2.70	0.001*
PFP Group Symptomatic Knee	15.04˚	1.67˚	12.3˚ - 17.3˚	19.17˚	1.74˚	16.3˚ - 22.7˚	−2.42	0.001*

SD = Standard Deviation, ˚ = Degree, * Significant difference between tasks ($p < 0.05$).

Table 3. Visual pain rating scale score for all tasks (mean ± standard deviation).

Group/Test	Single Leg Squat		Single Leg Horizontal Hop for Distance			
	Mean	SD	Mean	SD	Cohen's d	P-value
Control Group	0.71	0.73	0.89	0.75	−0.24	0.670*
PFP Group Asymptomatic Knee	0.85	0.59	1.15	0.88	−0.40	0.266*
PFP Group Symptomatic Knee	4.50	0.83	6.00	0.65	−2.01	0.681*

SD = Standard Deviation, * No significant difference between tasks ($p > 0.05$).

No significant interaction was shown between factors using factorial ANOVA (P = 0.65, 95% CI [0.58 - 0.72]). There was a significant effect for both tasks (P = 0.006, 95% CI [0.003 - 0.008]), and for conditions (P = 0.001, 95% CI [0.0005 - 0.0009]). Paired t-tests reported among the control knees (P = 0.002) with the mean −4.67 ± 2.26, injured knees (P = 0.001) with the mean −4.13 ± 2.45, and uninjured knees (P = 0.001) with the mean −3.92 ± 2.03, that there was a significant differences in FPPA between tasks. It was also found a significant difference between FPPA on single leg squat task between the control and injured knee (P = 0.0001, with the mean −8.62 ± 2.31), the injured and uninjured knee (P = 0.002, with the mean 5.24 ± 1.61), and between the control and uninjured limb (P = 0.007, with the mean −3.38 ± 1.45). For single leg horizontal hop for distance FPPA there was a significant difference between the control and injured knee (P = 0.0003, with the mean −7.67 ± 2.48), the injured and uninjured knee (P = 0.001, with the mean 5.45 ± 1.89), and between the control and uninjured limb (P = 0.009, with the mean −2.22 ± 2.27).

4. Discussion

The aim of the study was to investigate if male PFP patients single leg squat and horizontal hop for distance with greater knee valgus angle than controls, and if the nature of the different task changes the degree of knee valgus angle. Current study showed patients with unilateral PFP had significantly greater knee valgus angles than either their asymptomatic limb or asymptomatic controls when undertaking unilateral loading tasks.

This study found that patients with PFP showed significantly greater FPPA during single leg squats and single leg horizontal hop for distance than their contralateral asymptomatic limb or controls. Moreover, FPPA also showed to increase between tasks. Few previous studies have evaluated the effect of different tasks on PFP patient's individual performance. Lee [10] used 2-D motion analysis to assess FPPA in a unilateral single leg squat and single leg land tasks in patients with PFP and controls (females only). The main outcome in his study was to investigated the changes in knee valgus in PFP patients and controls across the tasks of single leg squat and single leg land. Lee [10] found that patients with PFP reported significantly greater FPPA during single leg squats and single leg land than their contralateral asymptomatic limb or controls. In line with this, our study demonstrated significant increases in knee FPPA between our tasks (single leg squats and single leg horizontal hop for distance), with the knee valgus increasing with the increased load to lower limbs. This finding is similar to what was reported by Lee [10] although we used in our study a horizontal hop land task and he used a land from a 30 cm step, similar outcomes have been noted.

In addition, Willson and Davis [4] used three-dimensional (3-D) motion analysis to evaluate changes in knee angle in PFP patients across the tasks of single leg squat, running, and single leg hopping. They reported that the PFP patients have significant greater knee motion, however across these tasks the magnitude of that motion did not change. This was also similar to our findings, but the differences between our study and that of Willson and Davis [4] might be because of the differences in load in the respective tasks. They have patients hopping on the spot to an average height of 9.2 cm, while in our study the subjects landing from a maximum horizontal hop for distance task. Maximum horizontal hop for distance appear to be more changeable and difficult than landing from a step, as it requires the limb to control the horizontal forces in addition to maintain the balance when landing. Therefore, this would potentially increase the stress on patellofemoral joint with the more load being focused on a specific contact area during landing [8]. This can be confirmed by the noticeable increase in knee pain reported by the PFP patients who participated in the current study (**Table 3**). This finding is in line with the work conducted by Salsich *et al.* [19] who found that increasing knee valgus angle during single leg squat will significantly increase the knee pain.

The mean FPPA between groups in a single leg squat task appeared to be lower in our study than Lee's [10] study (as this is the only similar task matched between the two studies). For the single leg squat task in our study we reported a mean of 6.96˚, 9.80˚, 15.04˚ in the control, PFP asymptomatic knee, and PFP symptomatic knee, respectively. However, in Lee [10] study he reported a higher mean than our study of 8.4˚, 10˚, 16.8˚ in the control, PFP asymptomatic knee, and PFP symptomatic knee, respectively. This variations and higher mean results in Lee's [10] study are expected as he got female participants in his study and we had males only, females on their nature have higher knee valgus angle than men as been reported by Nguyen & Shultz [20] who found that the mean standing Q-angle in females is 13˚ and it was higher about 4˚ than what was reported by males (9˚), thus, considering these variations reported in knee angle between gender in different tasks are normal. Regarding biomechanical models for male participants (controls) during standing task, the mean clinical measure reported for the Q-angle was 9.0˚ ± 4.1˚ [20]. This is very close to the mean knee valgus angle reported in our study during squat task for the controls at 6.96˚ ± 1.56˚, and for the asymptomatic knees for the PTP group at 9.80˚ ± 1.37˚. However, it was different than (lower) to what was reported in our study during single leg hop land task by the controls 11.63˚ ± 1.84˚ and asymptomatic knees for the PTP group 13.72˚ ± 1.53˚. These findings would confirm that higher knee valgus angle is obtained during high force loaded exercises such as hop land tasks than lower force loaded exercises like squats.

Furthermore, it was found for single leg squat and single leg horizontal hop for distance FPPA tasks that there was a significant difference between the control and uninjured limb ($P < 0.009$). The mean FPPA for the single leg squat was reported to be higher in uninjured limb than the control limb 9.80˚, 6.96˚, respectively, and for the single leg horizontal hop for distance was 13.72˚ for the uninjured limb and 11.63˚ for the control limb. This means that the PFP patients are representing with higher knee valgus even with their sound limbs in comparison to the controls, hence they have already more abnormal pressure on their patellofemoral joint which may contribute to the presence of the pain on their injured limbs.

5. Limitations

There are possible limitations with using a 2-D for motion analysis. Although 2-D analysis was reported previously to be an accurate in measuring several tasks, the accuracy and magnitude of 3-D lower limb motion analysis during any movement cannot be fully replicated by 2-D FPPA applications. However, in the absence of the 3-D methods 2-D analysis still can provide a reliable and valid measures for lower limb kinematics [18]. Another limitation is that this study only included male participants, but the possible reason for this is because the previous study by Lee [10] was conducted on females only, hence we need to investigate if different gender will enhance the overall findings. Another limitation in the current study is that the number of participants in the control group far exceeds the symptomatic group and this may have affected the results. However, the control group was collected with almost similar characteristics to the symptomatic group to minimize any effect that may be presented with any variations of the age, height, and weight. Moreover, inter-limb testing for the symptomatic subjects was not performed and this is considered as another limitation of the current study.

6. Conclusion

Patients with PFP were represented with greater knee valgus angle on the injured limb (unilateral load) than what was found in either their sound asymptomatic limb or in the control group. More attention is needed to be taken for the knee valgus angle when treating/ rehabilitating patients or train athletes during any screening tasks such as a unilateral squatting, hop landing, or horizontal hop for distance task. If patients presented with higher knee valgus (more than 9.80˚ according to our findings) treatment plan should be set. Treatment methods including patients' feedback in front of a mirror, stretching hip adductors, strengthening of hip abductors, and core strengthening exercises. If not corrected (the higher knee valgus), it may lead to more patellofemoral joint stress and ongoing pain.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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- Clinical Interventions in Aging
- Clinical Laboratory Analysis
- Clinical Linguistics & Phonetics
- Clinical Lipidology
- Clinical Microbiology and Antimicrobials
- Clinical Microbiology and Infection
- Clinical Microbiology and Infectious Diseases
- Clinical Molecular Pathology
- Clinical Monitoring and Computing
- Clinical Neurology and Neurosurgery
- Clinical Neurophysiology
- Clinical Neuropsychology
- Clinical Neuroradiology
- Clinical Neuroscience
- Clinical Nursing
- Clinical Nutrition
- Clinical Obstetrics and Gynaecology
- Clinical Oncology and Cancer Research
- Clinical Ophthalmology
- Clinical Oral Implants Research
- Clinical Oral Investigations
- Clinical Orthopaedics and Related Research
- Clinical Otolaryngology
- Clinical Pathology
- Clinical Pediatric Emergency Medicine
- Clinical Periodontology
- Clinical Pharmacology & Toxicology
- Clinical Pharmacy and Therapeutics
- Clinical Physiology and Functional Imaging
- Clinical Practice and Epidemiology in Mental Health
- Clinical Psychology and Psychotherapy
- Clinical Psychology in Medical Settings
- Clinical Radiology
- Clinical Rehabilitation
- Clinical Research and Regulatory Affairs
- Clinical Research in Cardiology
- Clinical Respiratory
- Clinical Rheumatology
- Clinical Simulation in Nursing
- Clinical Sleep Medicine
- Clinical Techniques in Small Animal Practice
- Clinical Therapeutics
- Clinical Toxicology
- Clinical Transplantation
- Clinical Trials
- Clinical Ultrasound
- Clinical Virology
- Complementary Therapies in Clinical Practice
- Consulting and Clinical Psychology
- Contemporary Clinical Trials
- Controlled Clinical Trials
- Diabetes Research and Clinical Practice
- Evaluation in Clinical Practice
- Fundamental & Clinical Pharmacology
- Hereditary Cancer in Clinical Practice
- Human Psychopharmacology: Clinical and Experimental
- Innovations in Clinical Neuroscience
- Laboratory and Clinical Medicine
- Neurophysiologie Clinique/Clinical Neurophysiology
- Nutrition in Clinical Practice
- Pacing and Clinical Electrophysiology
- Psychiatry in Clinical Practice
- Therapeutics and Clinical Risk Management
- Veterinary Clinical Pathology

We are also interested in short papers (letters) that clearly address a specific problem, and short survey or position papers that sketch the results or problems on a specific topic. Authors of selected short papers would be invited to write a regular paper on the same topic for future issues of the ***IJCM***.

Notes for Intending Authors

All manuscripts submitted to IJCM must be previously unpublished and may not be considered for publication elsewhere at any time during IJCM's review period. Paper submission will be handled electronically through the website. All papers are refereed through a peer review process. Additionally, accepted ones will immediately appear online followed by printed in hard copy. For more details about the submissions, please access the website.

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