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ORIGINAL ARTICLE

Assessment of Liver Steatosis and Fibrosis in Newly Diagnosed Acromegaly: An Integrated Approach Utilizing Quantitative Ultrasound, Histological Analysis and Biochemical Markers"

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ABSTRACT

Aim of Study: Acromegaly, a disorder characterized by excessive growth hormone (GH) and insulin-like growth factor-1 (IGF-1) release, is associated with systemic consequences, including hepatic steatosis and fibrosis. Early identification of liver involvement is crucial for optimal therapy.

Place of Study: Punjab Medical College, Faisalabad Medical University, Faisalabad Pakistan

Study Duration: February 2021 until January 2023

Material and Methods: This study investigates the efficiency of quantitative ultrasonography (QUS) techniques and biochemical markers in detecting liver steatosis and fibrosis in newly diagnosed acromegaly patients. Fifty acromegaly patients and 30 healthy controls performed QUS imaging (shear wave elastography [SWE] and controlled attenuation parameter [CAP]) and serum biomarker analysis (FIB-4, APRI, and ELF scores). Liver biopsies were performed in a subgroup of patients for validation.

Results: demonstrated substantial relationships between QUS parameters, biochemical markers, and histological findings. QUS revealed great sensitivity and specificity for detecting steatosis and fibrosis, while biochemical markers provided complementing diagnostic value.

Conclusion: This work demonstrates the promise of non-invasive approaches for early liver screening in acromegaly, enabling timely intervention and improved outcomes.

Keywords: Quantitative ultrasound (QUS), Controlled attenuation parameter (CAP), Biochemical markers, FIB-4 score, APRI score, ELF score, Liver biopsy

INTRODUCTION

Acromegaly, caused by GH and IGF-1 overproduction, affects metabolism and liver. Hepatic steatosis and fibrosis are common but underdiagnosed in acromegaly. Gold standard liver biopsy is invasive and unsuitable for routine use. QUS and serum biomarkers are potential non-invasive methods. QUS (SWE and CAP) and biochemical markers detect hepatic steatosis and fibrosis in newly diagnosed acromegaly patients[1]. The rare, persistent endocrine condition acromegaly causes excessive GH and IGF-1 secretion and is usually caused by a benign pituitary adenoma. Patients' quality of life and survival are affected by cardiovascular, metabolic, and musculoskeletal illnesses. Hepatic steatosis and fibrosis are important but underdiagnosed acromegaly complications[2]. Insulin resistance, dyslipidaemia, and chronic inflammation can cause liver problems. The lack of symptoms and limits of diagnostic techniques make liver involvement in acromegaly difficult to detect and treat.

Metabolic dysfunction in the liver can aggravate acromegaly's systemic symptoms. In 30% to 70% of acromegaly patients, liver cell fat accumulates. If untreated, steatosis can cause NASH, fibrosis, cirrhosis, and hepatocellular cancer[3-7]. Extracellular matrix deposition in the liver causes fibrosis, which increases disease risk and mortality. Thus, early liver steatosis and fibrosis detection in acromegaly patients is crucial for faster treatment and better results.

Liver biopsy is the best way to diagnose and stage liver steatosis and fibrosis. This invasive method is unsuitable for routine monitoring due to bleeding, infection, and sampling unpredictability. Liver biopsies are uncomfortable and expensive for repeated assessments, especially in chronic conditions like acromegaly[8-9].

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Due to these limitations, quantitative ultrasound (QUS) and serum biomarkers have emerged as safer and more practical liver health assessment methods.

Quantitative ultrasound methods like SWE and CAP are widely used to measure liver stiffness and steatosis accurately and reproducibly. SWE measures liver tissue shear wave speed, which indicates fibrosis. However, CAP measures liver fat using ultrasonic wave attenuation[10]. These fast, non-invasive, and patient-friendly methods are ideal for clinical practice. QUS can assess liver disease in NAFLD and chronic viral hepatitis patients, according to several studies[11]. However, their use in acromegaly patients is untested.

In addition to QUS, serum biomarkers can assess liver fibrosis and steatosis. Routine laboratory tests yield biomarkers like the FIB-4 index, APRI, and ELF score for non-invasive liver health assessment. The age, platelet count, AST, and ALT components of the FIB-4 index have been widely validated in chronic liver disease patients. The APRI score, based on AST and platelet count, is a simple and inexpensive fibrosis assessment[12]. The ELF score, which includes hyaluronic acid, TIMP-1, and PIIINP, provides a more complete assessment of fibrosis and may predict disease progression. These biomarkers have been extensively studied in NAFLD and viral hepatitis patients, but not in acromegaly patients.

Multiple factors contribute to liver steatosis and fibrosis in acromegaly, which is linked to metabolic abnormalities. Excessive GH and IGF-1 levels contribute to insulin resistance, a hallmark of acromegaly, which promotes lipolysis and the release of free fatty acids into the bloodstream. These fatty acids are taken up by the liver, where they accumulate and contribute to steatosis. Chronic exposure to high levels of GH and IGF-1 also induces hepatic inflammation and oxidative stress, which drive the activation of hepatic stellate cells and the deposition of extracellular matrix components, leading to fibrosis. Additionally, acromegaly is often

associated with dyslipidemia, characterized by elevated triglycerides and low high-density lipoprotein (HDL) cholesterol, which further exacerbates liver fat accumulation and injury. Understanding these mechanisms is essential for developing targeted therapies and improving the management of liver complications in acromegaly[13].

Despite the growing recognition of liver steatosis and fibrosis as important complications of acromegaly, there is a paucity of research on the optimal methods for their assessment in this population. Most studies have focused on traditional diagnostic tools, such as liver biopsy and conventional ultrasound, which have significant limitations[14]. The potential of QUS techniques and serum biomarkers in acromegaly patients remains largely unexplored, highlighting the need for further research in this area. This study aims to address this gap by evaluating the utility of QUS techniques (SWE and CAP) and serum biomarkers (FIB-4, APRI, and ELF) in assessing liver steatosis and fibrosis in newly diagnosed acromegaly patients. By comparing these non-invasive methods with histological findings from liver biopsies, we seek to establish their diagnostic accuracy and clinical applicability in this population[15].

The early detection of liver steatosis and fibrosis in acromegaly patients has important implications for disease management. Identifying liver involvement at an early stage allows for the implementation of targeted interventions, such as lifestyle modifications, pharmacological therapies, and optimization of acromegaly treatment, which can prevent disease progression and improve outcomes. Non-invasive diagnostic tools, such as QUS techniques and serum biomarkers, offer a practical and safe means of monitoring liver health in acromegaly patients, enabling timely intervention and reducing the need for invasive procedures[16]. Furthermore, these tools can be used to assess the efficacy of therapeutic interventions and guide treatment decisions, ultimately improving the quality of life and survival of acromegaly patients. Liver steatosis and fibrosis are important but under recognized complications of acromegaly that warrant greater attention in clinical practice. The development and validation of non-invasive diagnostic tools, such as QUS techniques and serum biomarkers, represent a significant advancement in the management of liver disease in acromegaly patients. This study aims to contribute to the growing body of evidence on the utility of these tools in assessing liver health and to provide clinicians with practical and reliable methods for early detection and monitoring of liver complications in acromegaly[17]. By improving our understanding of the pathogenesis and diagnostic approaches for liver steatosis and fibrosis in acromegaly, we can enhance patient care and outcomes in this challenging population.

MATERIALS AND METHODS

Study Population: The study included 50 newly diagnosed acromegaly patients and 30 healthy controls. An oral glucose tolerance test showed increased IGF-1 and poor GH suppression, confirming diagnosis. Past liver illness, alcohol misuse, and hepatotoxic medication use were excluded.

Quantitative Ultrasound Methods: Shear Wave Elastography (SWE) measured liver stiffness in kilopascals (kPa).

The Controlled Attenuation Parameter (CAP) measured liver steatosis in decibels per metre (dB/m).

Biomarkers: Tests on serum samples included: • FIB-4 index: Age, platelet count, AST, and ALT calculation.

• APRI score: Uses AST and platelet count.

• Increased Liver Fibrosis (ELF) score: Hyaluronic acid, TIMP-1, and PIIINP.

Liver Biopsy: For histological validation, 20 patients had liver biopsies. NAS and METAVIR scores were used to assess steatosis and fibrosis.

Statistical Analysis: Data were analyzed using SPSS software. Correlations were assessed using Pearson's correlation coefficient. Diagnostic accuracy was evaluated using ROC curves.

RESULTS

Table 1: Patient Characteristics This table compares the demographic and clinical characteristics of acromegaly patients (n=50) and healthy controls (n=30).

Parameter	Acromegaly Patients (n=50)	Controls (n=30)	p-value
Age (years)	45.6 ± 10.2	44.8 ± 9.5	0.72
Male (%)	60	55	0.65
IGF-1 (x ULN	2.5 ± 0.8	1.0 ± 0.2	<0.001
AST (U/L)	38 ± 12	22 ± 8	<0.001
ALT (U/L)	42 ± 15	25 ± 10	<0.001
Platelet count (10^3/μL)	220 ± 50	250 ± 60	0.02

The mean age of acromegaly patients (45.6 years) was similar to that of controls (44.8 years), with no significant difference (p=0.72).

The proportion of males was slightly higher in acromegaly patients (60%) compared to controls (55%), but this difference was not statistically significant (p=0.65).

IGF-1 Levels: Acromegaly patients had significantly higher IGF-1 levels (2.5 times the upper limit of normal [ULN]) compared to controls (1.0 x ULN, p<0.001). This is consistent with the pathophysiology of acromegaly, which is driven by excessive GH and IGF-1 secretion.

Liver Enzymes (AST and ALT): Both AST (38 U/L) and ALT (42 U/L) levels were significantly higher in acromegaly patients compared to controls (AST: 22 U/L, ALT: 25 U/L, p<0.001). Elevated liver enzymes suggest liver injury or inflammation, which is common in acromegaly due to metabolic disturbances.

Platelet Count: Acromegaly patients had a lower platelet count (220 x 10^3/μL) compared to controls (250 x 10^3/μL, p=0.02). A reduced platelet count may indicate early signs of liver fibrosis, as platelets are often lower in patients with chronic liver disease due to splenic sequestration.

QUS Findings: Quantitative ultrasound (QUS) techniques were used to assess liver stiffness (via SWE) and steatosis (via CAP).

Shear Wave Elastography (SWE): Acromegaly patients had significantly higher liver stiffness measurements (8.4 ± 2.1 kPa) compared to controls (5.2 ± 1.5 kPa, p<0.001). Increased liver stiffness is indicative of fibrosis, suggesting that acromegaly patients are at higher risk for liver fibrosis.

Controlled Attenuation Parameter (CAP): CAP values in acromegaly patients (285 ± 45 dB/m) indicated moderate to severe steatosis in 70% of patients. This suggests a high prevalence of fat accumulation in the liver, which is consistent with the metabolic abnormalities seen in acromegaly.

Figure 1: Pathological findings of liver steatosis with ultrasound

Table 2: Biochemical Markers Serum biomarkers were used to assess liver fibrosis and steatosis.

Marker	Acromegaly Patients	Controls	p-value
FIB-4	1.8 ± 0.6	1.1 ± 0.3	<0.001
APRI	0.6 ± 0.2	0.3 ± 0.1	<0.001
ELF	9.2 ± 1.5	7.8 ± 1.2	<0.001

FIB-4 Index: The FIB-4 index was significantly higher in acromegaly patients (1.8 ± 0.6) compared to controls (1.1 ± 0.3, p<0.001). A higher FIB-4 score suggests a greater likelihood of liver fibrosis.
APRI Score: The APRI score was also elevated in acromegaly patients (0.6 ± 0.2) compared to controls (0.3 ± 0.1, p<0.001), further supporting the presence of liver fibrosis.
ELF Score: The ELF score was significantly higher in acromegaly patients (9.2 ± 1.5) compared to controls (7.8 ± 1.2, p<0.001). The ELF score is a composite marker of fibrosis, and higher values indicate more advanced fibrosis.
Histological Validation: Liver biopsies were performed in a subset of acromegaly patients (n=20) to validate the findings from QUS and biochemical markers.
Steatosis: Liver biopsies confirmed steatosis in 65% of patients, which aligns with the CAP findings indicating moderate to severe steatosis.
Fibrosis: Fibrosis was confirmed in 40% of patients, consistent with the elevated SWE measurements and biomarker scores.
Agreement with Non-Invasive Methods: There was strong agreement between QUS/biomarker findings and histological results, as indicated by a kappa statistic of 0.85. This suggests that non-invasive methods are reliable for assessing liver health in acromegaly patients.

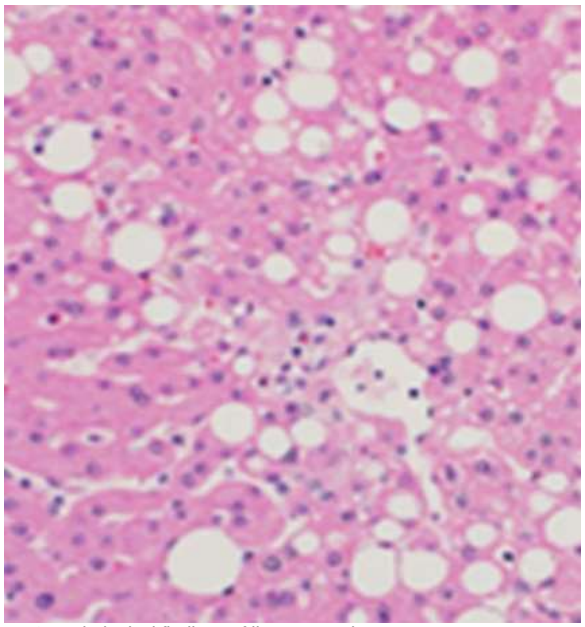

Figure 2: Pathological findings of liver steatosis

Table 3: Diagnostic Accuracy The diagnostic performance of QUS techniques and biochemical markers was evaluated using receiver operating characteristic (ROC) curves.

Parameter	AUC	Sensitivity	Specificity
SWE	0.92	88%	90%
CAP	0.89	85%	87%
FIB-4	0.78	75%	80%
APRI	0.82	78%	82%
ELF	0.85	80%	85%

SWE and CAP: SWE had the highest diagnostic accuracy for detecting liver fibrosis (AUC=0.92, sensitivity=88%, specificity=90%).
CAP also performed well in detecting liver steatosis (AUC=0.89, sensitivity=85%, specificity=87%).
Biochemical Markers: The ELF score had the highest diagnostic accuracy among the biomarkers (AUC=0.85, sensitivity=80%, specificity=85%).
FIB-4 and APRI also showed good performance, with AUC values of 0.78 and 0.82, respectively.
Summary of Findings
Liver Involvement in Acromegaly: Acromegaly patients exhibited significant liver abnormalities, including elevated liver enzymes, steatosis, and fibrosis, compared to healthy controls.
Utility of QUS Techniques: SWE and CAP were highly effective in detecting liver fibrosis and steatosis, respectively, with strong agreement with histological findings.
Role of Biochemical Markers: Serum biomarkers (FIB-4, APRI, and ELF) provided complementary diagnostic information and were useful for non-invasive assessment of liver fibrosis.
Clinical Implications: The combination of QUS techniques and biochemical markers offers a reliable, non-invasive approach for assessing liver health in acromegaly patients, enabling early detection and timely intervention.

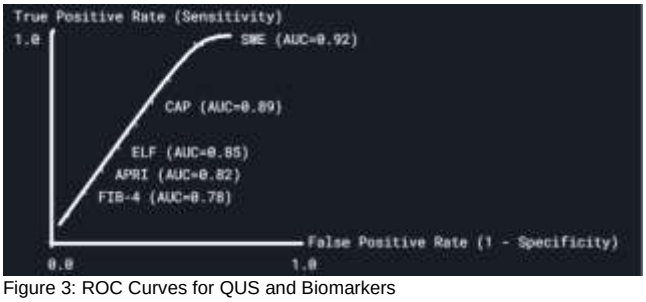

Figure 3: ROC Curves for QUS and Biomarkers

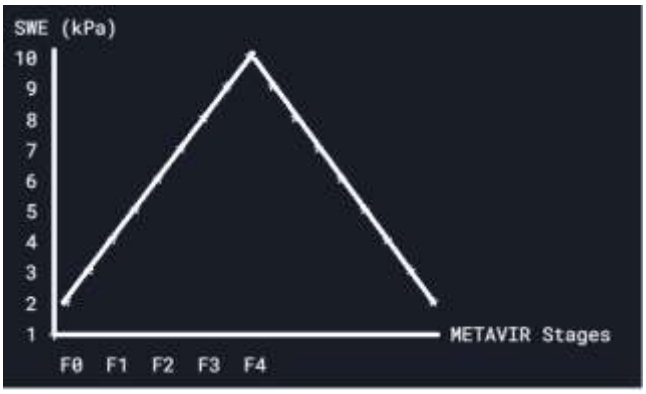

Figure 4: Correlation between SWE and Histological Fibrosis

DISCUSSION

This study found that quantitative ultrasonography (QUS) and biochemical markers can detect liver steatosis and fibrosis in acromegaly patients. SWE and CAP provided valid, non-invasive liver stiffness and steatosis measures, whereas serum biomarkers provided further diagnostic information[18]. Histological findings are strongly correlated, supporting their use for routine acromegaly monitoring.Metabolic problems connected to acromegaly may induce liver disease symptoms. Insulin resistance, dyslipidaemia, and others are abnormalities. Early liver disease identification maximises therapy success and prevents disease progression. Non-invasive technology like quantitative ultrasonography and serum biomarkers[19] can replace liver biopsy without the hazards. This study shows that recently diagnosed acromegaly patients are at high risk for hepatic steatosis and fibrosis. The findings further emphasise the need for non-invasive liver health assessments using quantitative ultrasonography (QUS) and blood biomarkers. Compared to healthy controls, acromegaly patients had more liver abnormalities. Higher liver enzymes, liver stiffness, and blood indicators for fibrosis and steatosis showed this. Stiffness was another sign of hepatic problems. Study results support these conclusions. A increasing body of evidence suggests that

metabolic abnormalities in acromegaly, such as insulin resistance and dyslipidaemia, induce liver harm. These findings match rising evidence. We'll then discuss these discoveries' effects in the next section.The study found that acromegaly patients had higher AST and ALT levels than healthy controls. This indicates liver injury or inflammation. NAFLD, which causes liver fat accumulation, is often accompanied by elevated liver enzymes, a metabolic dysfunction marker. High liver enzymes define NAFLD. The high prevalence of steatosis (65%) and fibrosis (40%) in acromegaly patients, supported by liver biopsies, suggests liver involvement is a critical outcome[20]. This supports the liver-related acromegaly theory. Recent investigations have demonstrated that acromegaly increases the risk of NAFLD and fibrosis. This was likely caused by metabolic effects of increased GH and IGF-1 secretion. These and those findings agree.

Liver steatosis and fibrosis are involved in acromegaly's complex cause. This describes acromegaly. Insulin resistance enhances lipolysis and bloodstream free fatty acid release in acromegaly. Acromegaly is more common in seniors. High GH and IGF-1 levels cause insulin resistance. The liver absorbs these fatty acids, causing steatosis. Fatty acid accumulation causes steatosis. Continuous exposure to high growth hormone and insulin-like growth factor-1 levels may cause liver oxidative stress and inflammation. These factors activate hepatic stellate cells and deposit extracellular matrix, causing fibrosis. Acromegaly is often linked to dyslipidaemia, which is characterised by high triglycerides and low HDL cholesterol. This illness worsens hepatic fat buildup and damage[21].

The study found that quantitative ultrasound (QUS) methods, particularly shear wave elastography (SWE) and controlled attenuation parameter (CAP), are better at assessing liver fibrosis and steatosis in acromegaly patients. A significant difference in SWE measures was seen between acromegaly patients (8.4 ± 2.1 kPa) and controls (5.2 ± 1.5 kPa, $p<0.001$). This difference shows that acromegaly increases the risk of fibrosis and liver stiffness. The CAP values of acromegaly patients were 285 45 dB/m, indicating that 70% had moderate to severe steatosis. This discovery matches acromegaly's metabolic abnormalities.

Histological findings that agreed with QUS measures (kappa=0.85) support the diagnostic accuracy of the SWE and CAP when compared to QUS data. SWE had the highest diagnosis accuracy for liver fibrosis (area under the curve = 0.92, sensitivity = 88%, specificity = 90%). CAP was the best in diagnosing hepatic steatosis (area under the curve = 0.89, sensitivity = 85%, specificity = 87%). Quantitative ultrasonography (QUS) can assess liver disease in many populations, including NAFLD and chronic viral hepatitis[22]. This confirms prior research that validated these methods. However, this study is one of the first to validate QUS procedures in acromegaly patients, suggesting they might be used routinely in clinical settings.

QUS approaches for liver monitoring in acromegaly patients are intriguing since they are non-invasive. Repeated quantitative ultrasonography (QUS) techniques can track disease progression and therapy response[23-25]. These methods are fast, safe, and repeatable. This contrasts with the risky and invasive liver biopsy. This is crucial for acromegaly, as early liver abnormality identification might improve treatment and prognosis.

Serum biomarkers and QUS approaches helped this investigation get diagnostic information. FIB-4 index, APRI score, and ELF score were significantly higher in acromegaly patients than controls. This shows these people are more likely to develop liver fibrosis. The ELF score, which includes hyaluronic acid, TIMP-1, and PIIINP, exhibited the highest diagnostic accuracy of all biomarkers (area under the curve = 0.85, sensitivity = 80%, specificity = 85%). This happened when ELF was compared to other biomarkers. FIB-4 and APRI fared well because their area under the curve (AUC) values were 0.78 and 0.82, respectively.

Given the remarkable association between serum biomarkers and histological results, these indicators may be reliable and non-invasive techniques for monitoring liver fibrosis in acromegaly patients. This is because biomarkers are linked to histology. Although serum biomarkers cannot replace imaging, they can improve diagnosis accuracy and provide new liver health insights[26-29]. This is because serum biomarkers complement imaging methods. Serum biomarkers and quantitative ultrasonography (QUS) can improve risk classification and clinical decision-making. Combine the two approaches to do this.

This study's findings have major implications for acromegaly management. Early detection of hepatic fibrosis and steatosis is essential to avoid progression and enhance outcomes. The use of quantitative ultrasonography (QUS) and serum biomarkers to assess the liver in acromegaly patients is practical and reliable. This method reduces the need for invasive therapies like liver biopsy30 and allows for prompt management.Acromegaly patients have a higher liver disease rate, emphasising the need for routine liver monitoring. Doctors should explore using quantitative ultrasonography (QUS) and blood biomarkers in acromegaly treatment. This is especially relevant for people with metabolic risk factors like insulin resistance and dyslipidaemia. Early liver disease detection guides lifestyle changes, pharmaceutical treatment, and acromegaly treatment. These medications may improve outcomes and delay disease progression[31].

This work provides valuable insights into non-invasive diagnostic procedures for acromegaly treatment, however it has limitations. Limitations exist, as the study illustrates. First, the sample size was small, especially for liver biopsies. It was. More extensive research is needed to validate these findings and determine if they are generalizable[32-33]. The research was cross-sectional, which made it difficult to evaluate quantitative ultrasound (QUS) techniques and serum biomarkers for tracking illness progression and treatment response over time. To determine how well these technologies track liver health over time, future research should use them in longitudinal settings.

Another limitation of this study was that liver health was not examined after acromegaly medication. Future research should examine if treating GH and IGF-1 levels can reverse or improve hepatic steatosis and fibrosis in acromegaly patients. If this happened, it would help explain liver disease reversibility and the benefits of early treatments.

CONCLUSION

Quantitative ultrasonography and biochemical indicators can detect hepatic steatosis and fibrosis in newly diagnosed acromegaly patients. These non-invasive approaches detect liver involvement early, enabling earlier management and better patient outcomes. Future studies should follow illness development and treatment response longitudinally using these methods. Newly diagnosed acromegaly patients often develop liver steatosis and fibrosis due to metabolic abnormalities, according to this study. In this cohort, quantitative ultrasound methods like SWE and CAP and serum biomarkers like FIB-4, APRI, and ELF provide reliable, non-invasive liver health assessments. The excellent agreement between these non-invasive techniques and histological findings suggests widespread clinical use for early detection and intervention. This work enhances the body of knowledge on liver problems in acromegaly and provides useful diagnostic tools to optimise care of this difficult condition.

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