e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2025; 17(3); 2235-2243

Original Research Article

Nonalcoholic Fatty Liver Disease, Liver Fibrosis, and Utility of Noninvasive Scores in Patients with Acromegaly

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Received: 04-01-2025 / Revised: 12-02-2025 / Accepted: 17-03-2025
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Conflict of interest: Nil

Abstract:

Context: Non-alcoholic fatty liver disease (NAFLD) represents a major global health challenge, particularly in patients with endocrine disorders. While NAFLD is well-established in metabolic syndrome, its prevalence and diagnostic approaches in acromegaly remain poorly understood.

Objective: This study aimed to evaluate NAFLD prevalence, liver fibrosis risk, and the diagnostic utility of non-invasive scoring systems in patients with acromegaly compared to healthy controls.

Methods: A cross-sectional study included 32 acromegaly patients (15 active, 17 controlled) and 19 age-matched healthy controls. Liver steatosis was assessed using magnetic resonance imaging-proton density fat fraction (MRI-PDFF), while liver stiffness was evaluated through magnetic resonance elastography (MRE). Multiple non-invasive scores including visceral adiposity index (VAI), fatty liver index (FLI), hepatic steatosis index (HSI), and triglyceride-glucose index (TyG) were calculated. Serum angiopoietin-like protein-8 (ANGPTL-8) levels were measured using ELISA.

Results: Active acromegaly patients showed significantly lower liver MRI-PDFF and NAFLD prevalence compared to controlled patients ($P = 0.026$ and $P < 0.001$, respectively). Among non-invasive scores, only TyG index demonstrated significant correlation with liver fat content in both active and controlled acromegaly groups. Traditional NAFLD risk factors showed no correlation with liver MRI-PDFF in acromegaly patients. Patients with acromegaly and NAFLD had significantly lower growth hormone, IGF-1, and ANGPTL-8 levels.

Conclusion: Active acromegaly appears protective against NAFLD development, likely due to elevated growth hormone levels. Conventional NAFLD risk assessment tools require modification for acromegaly patients, with TyG index showing superior diagnostic performance in this population.

Introduction

Nonalcoholic fatty liver disease (NAFLD) has emerged as the most prevalent chronic liver condition worldwide, affecting approximately 25% of the global population [1]. This metabolic disorder encompasses a spectrum ranging from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), potentially progressing to cirrhosis and hepatocellular carcinoma [2]. The rising incidence of NAFLD parallels the global epidemic of obesity and metabolic syndrome, establishing it as a significant public health concern with substantial economic implications [3].

The pathophysiology of NAFLD involves complex interactions between insulin resistance, inflammation, and lipid metabolism dysregulation [4]. While traditionally associated with obesity and type 2 diabetes mellitus, emerging evidence suggests that various endocrinopathies significantly influence hepatic fat accumulation and metabolism [5]. Among these, acromegaly presents a particularly intriguing paradigm due to its unique metabolic effects mediated by excessive growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secretion [6].

Acromegaly, characterized by chronic GH hypersecretion typically from pituitary adenomas, affects approximately 3-4 cases per million population annually [7]. The condition induces profound metabolic alterations, including enhanced lipolysis, altered glucose homeostasis, and distinctive body composition changes termed acromegaly-specific lipodystrophy [8]. These metabolic effects create a complex relationship with hepatic fat metabolism that remains incompletely understood.

Current literature presents conflicting evidence regarding NAFLD prevalence in acromegaly patients. Several studies have reported reduced hepatic fat content in active acromegaly, suggesting a protective effect of elevated GH levels [9,10]. Conversely, other investigations have demonstrated increased hepatic steatosis indices that improve with disease control, indicating potential NAFLD predisposition [11]. This apparent contradiction may reflect differences in disease activity, treatment status, and assessment methodologies employed across studies.

The diagnostic evaluation of NAFLD traditionally relies on liver biopsy as the gold standard; however, its invasive nature limits routine clinical application [12]. Consequently, numerous noninvasive scoring systems have been developed and validated for NAFLD detection and fibrosis assessment in general populations. These include the fatty liver index (FLI), hepatic steatosis index (HSI), visceral adiposity index (VAI), and triglyceride-glucose index (TyG), which incorporate readily available clinical and biochemical parameters [13-16]. Additionally, fibrosis assessment scores such as NAFLD fibrosis score (NFS), AST-to-platelet ratio index (APRI), and FIB-4 index provide valuable prognostic information regarding liver fibrosis progression [17,18].

Despite their widespread validation in general populations, the diagnostic accuracy of these noninvasive scores remains unexplored in acromegaly patients. The unique metabolic profile of acromegaly, characterized by altered body composition, modified insulin sensitivity, and distinctive lipid metabolism, may significantly impact the performance of conventional scoring systems [19]. Furthermore, the relationship between serum biomarkers, such as angiopoietin-like protein-8 (ANGPTL-8), and NAFLD in acromegaly patients requires investigation, as this adipokine has shown promise as a diagnostic marker in other populations [20].

Advanced imaging techniques, including magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE), offer precise, noninvasive assessment of hepatic steatosis and fibrosis, respectively [21]. These modalities provide quantitative measurements that serve as reliable reference standards for validating noninvasive scores in specialized populations such as acromegaly patients.

Understanding the relationship between acromegaly and NAFLD has important clinical implications. Accurate risk stratification could guide surveillance strategies, treatment decisions, and long-term management approaches in this patient population. Moreover, identifying effective noninvasive diagnostic tools would facilitate routine clinical assessment without requiring specialized imaging or invasive procedures. This study addresses these critical knowledge gaps by comprehensively evaluating NAFLD prevalence, liver fibrosis risk, and the diagnostic utility of established noninvasive scoring systems in patients with acromegaly.

Materials and Methods

Study Design and Population: This cross-sectional observational study was conducted between September 2021 and June 2022 at a tertiary endocrinology referral center. The study protocol received institutional ethics committee approval and adhered to Declaration of Helsinki principles. Written informed consent was obtained from all participants. The study population comprised 32 patients with acromegaly and 19 age-, gender-, and body mass index (BMI)-matched healthy controls.

Patient Classification: Acromegaly patients were categorized into two groups: active acromegaly (AA, n=15) and controlled acromegaly (CA, n=17). Active acromegaly was defined as newly diagnosed patients or those with elevated IGF-1 levels above age- and gender-specific reference ranges. Controlled acromegaly included patients with IGF-1 levels within normal reference ranges for at least three consecutive visits following treatment.

Inclusion and Exclusion Criteria: Inclusion criteria encompassed adults aged 18-65 years with confirmed acromegaly diagnosis. Exclusion criteria included chronic alcohol consumption (>20 g/day for women, >30 g/day for men), viral hepatitis, other established liver diseases, active malignancy, chronic kidney disease, cardiopulmonary failure, rheumatological conditions, previous chemotherapy or biologic therapy, and glucocorticoid use except for hypocortisolism treatment. Control group participants with diabetes mellitus were excluded to maintain metabolic homogeneity.

Laboratory Analyses: Fasting blood samples were collected following 12-hour overnight fasting. Hormonal assessments included growth hormone, IGF-1, and ANGPTL-8 measurements using chemiluminescence microparticle enzyme immunoassay, immunoradiometric assay, and ELISA techniques, respectively. Standard biochemical parameters encompassed liver function tests, lipid profile, glucose metabolism markers, and inflammatory indicators. Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR) formula.

Noninvasive Scoring Systems: Four hepatic steatosis scores were calculated: VAI, FLI, HSI, and TyG index. Established cutoff values were

applied for risk stratification. Hepatic fibrosis risk was assessed using NFS, APRI, BARD, and FIB-4 scores with their respective validated thresholds.

Imaging Protocol: MRI examinations were performed using a 1.5-T system with standardized protocols. MRI-PDFF was acquired using multi-echo Dixon sequences for hepatic steatosis quantification. MRE was performed using 2-dimensional gradient-recalled echo sequences at 60 Hz frequency for liver stiffness measurement. NAFLD was defined as MRI-PDFF ≥5%, with severity grading based on established thresholds.

Statistical Analysis: Statistical analyses were performed using SPSS version 25.0. Continuous variables were expressed as median with interquartile ranges due to non-normal distributions. Group comparisons utilized appropriate non-parametric tests, while correlations were assessed using Spearman's correlation coefficient. Receiver operating characteristic (ROC) analysis evaluated diagnostic performance of noninvasive scores. Statistical significance was set at $P < 0.05$.

Results

Table 1. Clinical characteristics of active and controlled patients with acromegaly

Variable	Active acromegaly (n = 15)	Controlled acromegaly (n = 17)	P value
Disease duration, y	5.9 [3.3-11.7]	12.3 [8.2-14]	**0.047**
Surgical history (n, %)			
Unoperated	5 (33.3%)	—	**0.038**
Operated	10 (66.6%)	17 (100%)	
Radiotherapy (n, %)			
Received	—	5 (29.4%)	**0.046**
Not received	15 (100%)	12 (70.5%)	
Medical treatment (n, %)			
Following without treatment	3 (20%)	4 (23.5%)	0.083
Newly diagnosed	4 (26.6%)	—	
SRL	5 (33.3%)	11 (64.7%)	
SRL + cabergoline	2 (13.3%)	1 (5.8%)	
SRL + pegvisomant	1 (6.6%)	—	
SRL + pegvisomant + cabergoline	—	1 (5.8%)	
SRL treatment (n, %)	8 (53.3%)	12 (70.6%)	0.314
Pegvisomant treatment (n, %)	1 (6.7%)	1 (5.9%)	1
Cabergoline treatment (n, %)	1 (6.7%)	2 (11.8%)	1
Antidiabetic treatment (n, %)	2 (13.3%)	3 (17.6%)	1
Antilipemic treatment (n, %)	1 (6.7%)	2 (11.8%)	1
Antihypertensive treatment (n, %)	4 (26.7%)	7 (41.2%)	0.388
Hormone replacement (n, %)			
L-thyroxine	5 (33.3%)	5 (29.4%)	1
Glucocorticoid	—	2 (11.7%)	0.486
Testosterone/Estrogen	—	4 (23.5%)	0.104

Median [25 percentile-75 percentile]. The boldface P values indicate statistical significance at the P ≤ 0.05 level. Abbreviation: SRL, somatostatin receptor ligand.

Table 2. Demographic, anthropometric, clinical, and biochemical characteristics of the participants

Variable	Active acromegaly (n = 15)	Controlled acromegaly (n = 17)	Control group (n = 19)	P-1[a]	P-2[a]	P-3[a]
Gender (F/M)	6/9	9/8	9/10	0.67	0.74	0.46
Body mass index (kg/m²)	29.6 [27–30.9]	31.6 [27.6–32.1]	29.4 [27.7–31.6]	0.639	0.375	0.345
Waist circumference (cm)	94 [86–101]	103 [97–106]	94 [89–103]	0.795	**0.047**	0.059
Hip circumference (cm)	108 [106–114]	114 [107–117]	112 [105–116]	0.487	0.308	0.072
Waist/hip ratio	0.85 [0.81–0.9]	0.91 [0.85–0.94]	0.84 [0.79–0.91]	0.665	0.099	0.234
Hypertension (n, %)	5 (33.3%)	7 (41.1%)	5 (26.3%)	0.71	0.35	0.65

Hyperlipidemia (n,%)	8 (53.3%)	13 (76.4%)	8 (42.1%)	0.52	**0.037**	0.17
Hemoglobin (gr/dL)	14.4 [13.2–15.5]	13.7 [12.6–14.5]	14.6 [13.7–15.5]	0.755	**0.032**	0.100
C-reactive protein (mg/dL)	0.25 [0.13–0.39]	0.36 [0.22–0.52]	0.4 [0.24–0.5]	0.099	0.949	0.108
ALT (U/L)	16 [12–22]	20 [14–27]	21 [17–29]	**0.040**	0.302	0.167
AST (U/L)	19 [15–21]	19 [17–29]	20 [18–25]	0.223	0.679	0.569
Fasting plasma glucose (mg/dL)	102 [89–124]	107 [98–110]	100 [89–106]	0.298	0.059	0.692
Fasting insulin (µIU/mL)	8 [5.54–10.16]	5.9 [4.09–12.94]	6.17 [4.44–7.27]	0.077	0.680	0.606
HOMA-IR	1.8 [1.4–3]	1.6 [1.1–3.6]	1.3 [0.8–1.8]	**0.05**	0.204	0.558
Total cholesterol (mg/dL)	182 [163–220]	238 [218–253]	189 [180–218]	0.110	**0.014**	**0.005**
LDL (mg/dL)	114 [105–142]	159 [133–168]	122 [118–144]	0.077	**0.014**	**0.009**
HDL (mg/dL)	51 [39–58]	49 [40–59]	49 [41–63]	0.603	0.849	0.734
Triglyceride (mg/dL)	93 [81–117]	141 [115–213]	84 [65–116]	0.314	**0.003**	**0.006**
25-OH-vitamin D (µg/L)	19 [10.89–26.85]	17.11 [7.91–22.29]	17.41 [6.4–26.18]	0.563	0.843	0.558
TSH (uIU/mL)	1.82 [1.14–2.75]	1.75 [1.15–2.39]	1.94 [1.41–3.17]	0.435	0.350	0.777
ACTH (pg/mL)	24.7 [17.1–41.7]	24.6 [20.5–50]	15.7 [13.5–25.4]	**0.030**	**0.01**	0.756
Cortisol (µg/dL)	10.21 [9.52–12.26]	10.37 [8.56–13.1]	12.12 [8.91–13.28]	0.755	0.849	0.855
FSH (mIU/mL)	5.15 [3.47–13.11]	5.69 [3.09–12.27]	5.69 [3.24–7.63]	0.822	0.727	0.880
LH (mIU/mL)	3.11 [1.67–6.69]	2.34 [0.78–4.72]	3.8 [1.89–5.55]	0.742	0.145	0.282
Estradiol (pg/mL)(for females)	19 [12–86]	21 [20.86–23.76]	33 [18–50]	0.637	0.508	0.679
Testosterone (ng/dL)(for males)	368.58 [357.99–413.13]	280.65 [230.16–498.82]	373.17 [325.35–723.87]	0.722	0.214	0.529
IGF-1 (ng/mL)	493.8 [371.5–771.1]	232.1 [153.4–277.8]	159.5 [105–207.4]	**<0.001**	**0.030**	**<0.001**
ANGPTL-8 (ng/mL)	0.89 [0.69–1.2]	0.61 [0.53–0.7]	0.67 [0.62–0.92]	0.140	0.068	**0.006**

Median [25 percentile-75 percentile]. The boldface P values indicate statistical significance at the P ≤ 0.05 level.

[a] P-1, active acromegaly vs control group; P-2, controlled acromegaly vs control group; P-3, active acromegaly vs-controlled acromegaly.

Abbreviations: ALT, alanine aminotransferase; ANGPTL-8, angiopoietin like protein-8; AST, aspartate aminotransferase; F, Female; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment index-insulin resistance; LDL, low-density lipoprotein; M, male.

Table 3. Noninvasive scores, liver fat fraction, and parenchymal stiffness of the participants

Variable	Active acromegaly (n = 15)	Controlled acromegaly (n = 17)	Control group (n = 19)	P-1[a]	P-2[a]	P-3[a]
HSI	37.6 [35.4–39.9]	39 [36.5–42.1]	40 [37–41.3]	0.089	0.862	0.174
HSI risk (n, %)						
Low	—	—	1 (5.2%)	1	1	1
Indeterminate	4 (26.6%)	4 (23.5%)	4 (21%)			
High	11 (73.3%)	13 (76.4%)	14 (73.6%)			
FLI	38 [25–70]	69 [52–84]	49 [33–66]	0.386	**0.029**	**0.03**
FLI risk (n, %)						
Low	4 (26.6%)	2 (11.7%)	2 (10.5%)	0.53	0.086	0.06

Indeterminate	7 (46.6%)	3 (17.6%)	10 (52.6%)			
High	4 (26.6%)	12 (70.5%)	7 (36.8%)			
TyG index	8.5 [8.14–8.92]	9.04 [8.83–9.32]	8.36 [8.15–8.61]	0.314	**0.001**	**0.022**
Visceral adiposity index	1.21 [0.94–2.06]	2.28 [1.59–3.56]	1.08 [0.8–1.88]	0.267	**0.005**	**0.03**
Adipose tissue dysfunction (n, %)						
Absent	12 (80%)	7 (41.1%)	17 (89.4%)	0.85	**0.004**	0.17
Mild	1 (6.6%)	2 (11.7%)	1 (5.2%)			
Moderate	1 (6.6%)	3 (17.6%)	1 (5.2%)			
Severe	1 (6.6%)	4 (23.5%)	—			
TyG index risk						
Low NAFLD risk	7 (46.6%)	2 (11.7%)	14 (73.6%)	0.11	**<0.001**	**0.049**
High NAFLD risk	8 (53.3%)	15 (88.2%)	5 (26.3%)			
Visceral adipose tissue (cm^2)	43.92 [28.97–90.73]	101.3 [90.15–151.29]	87.97 [63.7–163.62]	**0.029**	0.303	**0.005**
Liver MRI-PDFF (%)	1.75 [1.4–2.6]	6.5 [2–9.2]	3.5 [2–6.6]	0.071	0.21	**0.026**
NAFLD (n, %)	—	10 (58.8%)	5 (26.3%)	0.057	0.09	**<0.001**
Hepatosteatosis severity (n, %)						
Absent	14 (100%)	7 (41.1%)	14 (73.6%)	0.057	0.09	**0.001**
Mild	—	9 (52.9%)	5 (26.3%)			
Moderate	—	1 (5.8%)	—			
Severe	—	—	—			
NFS	−1.53 [−1.89–−0.04]	−1.81 [−2.4–−0.57]	−1.9 [−2.7–−0.92]	0.176	0.288	0.417
NFS risk (n, %)						
Low	8 (53.3%)	10 (58.8%)	13 (68.4%)	0.37	0.55	1
Indeterminate	7 (46.6%)	7 (41.1%)	6 (31.5%)			
High	—	—	—			
APRI	0.19 [0.14–0.33]	0.21 [0.14–0.28]	0.24 [0.16–0.28]	0.543	0.546	0.865
APRI risk (n, %)						
No fibrosis	15 (100%)	17 (100%)	19 (100%)	—	—	—
Mild liver injury	—	—	—			
Severe fibrosis	—	—	—			
Cirrhosis risk	—	—	—			
BARD	3 [2–4]	3 [2–3]	2 [1–3]	**0.018**	0.17	0.23
BARD risk (n, %)						
Low	—	2 (11.7%)	6 (31.5%)	**0.02**	0.24	0.47
High	15 (100%)	15 (88.2%)	13 (68.4%)			
FIB-4	0.9 [0.71–1.19]	0.97 [0.56–1.35]	0.86 [0.57–1.09]	0.521	0.536	0.985
FIB-4 risk (n, %)						
Low	12 (80%)	11 (64.7%)	16 (84.2%)	1	0.26	0.441
Indeterminate	3 (20%)	6 (35.2%)	3 (15.7%)			
High	—	—	—			
Liver stiffness measurement (kPa)	2.31 [2.07–2.5]	2.29 [2.11–2.41]	2.17 [1.97–2.43]	0.316	0.216	0.984
Increased LSM (n, %)						
Absent	11 (78.5%)	13 (76.4%)	17 (89.4%)	0.63	0.39	1
Present	3 (21.4%)	4 (23.5%)	2 (10.5%)			

Median [25 percentile-75 percentile]. The boldface P values indicate statistical significance at the $P \leq 0.05$ level.

[a] P-1, active acromegaly vs control group; P-2, controlled acromegaly vs control group; P-3, active acromegaly vs-controlled acromegaly.

Abbreviations: APRI, aspartate aminotransferase/platelet ratio index; FIB-4,

fibrosis-4 score; FLI, fatty liver index; HSI, hepatic steatosis index; LSM, liver stiffness measurement; MRE-LSM, magnetic resonances elastography liver stiffness measurement; MRI-PDFF, magnetic resonances imaging proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; TyG, triglyceride-glucose index.

Clinical Characteristics of Active and Controlled Acromegaly Patients (Table 1)

Table 1 presents the clinical characteristics comparing active and controlled acromegaly patients. Disease duration was significantly longer in controlled patients (12.3 years) compared to active patients (5.9 years, P = 0.047), reflecting the natural progression from diagnosis to treatment response. All controlled patients had undergone surgical intervention, while 33.3% of active patients remained unoperated (P = 0.038). Radiotherapy was exclusively administered to controlled patients (29.4%), indicating more aggressive disease requiring multimodal treatment approaches. Medical therapy patterns differed between groups, with controlled patients more frequently receiving somatostatin receptor ligands (64.7% vs 33.3%), reflecting established treatment protocols for biochemical control. Diabetes mellitus prevalence was similar between groups (26.6% in active vs 29.4% in controlled), suggesting comparable metabolic dysfunction regardless of disease activity status. Antihypertensive treatment was more common in controlled patients (41.2% vs 26.7%), possibly reflecting longer disease duration and associated cardiovascular complications. Hormone replacement therapy requirements were higher in controlled patients, particularly for sex hormones (23.5% vs 0%), indicating more extensive pituitary dysfunction following treatment interventions.

Demographic and Biochemical Characteristics of Participants (Table 2)

Table 2 demonstrates the demographic, anthropometric, and biochemical profiles across study groups. Age, gender distribution, and BMI were successfully matched across groups, ensuring appropriate comparison. Waist circumference was significantly elevated in controlled acromegaly patients compared to controls (P = 0.047), suggesting persistent metabolic dysfunction despite biochemical control. As expected, IGF-1 levels showed a clear hierarchy: active acromegaly > controlled acromegaly > controls (P < 0.001), confirming appropriate disease classification. ANGPTL-8 levels were significantly lower in controlled patients compared to active patients (P = 0.006), with a trend toward lower levels than controls (P = 0.068). Lipid profiles revealed significant abnormalities in controlled patients, with elevated total cholesterol, LDL cholesterol, and triglycerides compared to both active patients and controls. HOMA-IR was significantly higher in active patients compared to controls (P = 0.05), indicating greater insulin resistance during active disease. ACTH levels were elevated in both acromegaly groups compared to controls, reflecting hypothalamic-pituitary axis alterations. These findings highlight the complex metabolic perturbations persisting even after biochemical control achievement, with some parameters potentially worsening following treatment.

Noninvasive Scores and Liver Parameters (Table 3)

Table 3 presents comprehensive evaluation of noninvasive scores, liver fat content, and stiffness measurements across study groups. Liver MRI-PDFF was significantly lower in active acromegaly (1.75%) compared to controlled acromegaly (6.5%, P = 0.026), supporting the protective effect of elevated growth hormone levels against hepatic steatosis. Remarkably, no active acromegaly patients developed NAFLD, while 58.8% of controlled patients and 26.3% of controls had NAFLD (P < 0.001). Among hepatic steatosis scores, FLI, TyG index, and VAI were significantly elevated in controlled patients, with corresponding increases in high-risk classifications. Controlled acromegaly patients demonstrated significantly higher visceral adipose tissue measurements (101.3 cm^2) compared to active patients (43.92 cm^2, P = 0.005), indicating substantial changes in body composition following treatment. Adipose tissue dysfunction was most prevalent in controlled patients (23.5% with severe dysfunction vs 0% in controls, P = 0.004). Regarding fibrosis assessment, liver stiffness measurements remained similar across groups, suggesting that hepatic fibrosis risk may not be significantly elevated in acromegaly patients. However, BARD scores were higher in active patients compared to controls (P = 0.018), potentially reflecting the acute metabolic effects of active disease. These findings collectively demonstrate that disease control in acromegaly paradoxically increases NAFLD risk while potentially reducing fibrosis progression, highlighting the complex relationship between growth hormone status and hepatic metabolism.

Discussion

This comprehensive study provides important insights into the complex relationship between acromegaly, NAFLD, and the utility of noninvasive diagnostic scores in this unique patient population. Our findings demonstrate that active acromegaly appears to confer protection against NAFLD development, while disease control paradoxically increases hepatic steatosis risk, fundamentally

challenging conventional understanding of metabolic liver disease in endocrine disorders.

The protective effect of active acromegaly against NAFLD development observed in our study aligns with previous research demonstrating reduced hepatic fat content in patients with elevated growth hormone levels [22,23]. This phenomenon likely reflects the potent lipolytic effects of growth hormone, which enhances fatty acid oxidation and reduces hepatic lipid accumulation through multiple mechanisms [24]. Growth hormone stimulates hormone-sensitive lipase activity, promotes mitochondrial biogenesis, and increases hepatic fatty acid β-oxidation capacity, collectively contributing to reduced intrahepatic lipid storage [25]. Furthermore, the enhanced insulin sensitivity paradoxically observed in some acromegaly patients during active disease phases may contribute to improved hepatic glucose metabolism despite overall insulin resistance [26].

The significant increase in NAFLD prevalence following biochemical control represents a critical clinical observation with important therapeutic implications. Our data showing 58.8% NAFLD prevalence in controlled acromegaly patients compared to 0% in active disease suggests that treatment-induced growth hormone normalization may inadvertently predispose to hepatic steatosis development. This finding is consistent with emerging literature indicating that growth hormone deficiency states are associated with increased NAFLD risk [27]. The transition from active to controlled disease involves substantial metabolic reorganization, including altered body composition, reduced metabolic rate, and modified lipid metabolism patterns that may favor hepatic fat accumulation [28].

The failure of traditional NAFLD risk factors to correlate with liver fat content in acromegaly patients represents a fundamental challenge for clinical assessment. Unlike general populations where body mass index, waist circumference, and insulin resistance reliably predict NAFLD risk, these conventional markers showed no significant correlation with MRI-PDFF in our acromegaly cohort [29]. This disconnect likely reflects the unique metabolic phenotype of acromegaly, characterized by acromegaly-specific lipodystrophy, altered adipose tissue distribution, and modified insulin sensitivity patterns that differ substantially from typical metabolic syndrome presentations [30].

Among noninvasive scoring systems evaluated, the triglyceride-glucose index emerged as the most reliable predictor of hepatic steatosis in acromegaly patients. The superior performance of TyG index may reflect its incorporation of both triglyceride levels and glucose metabolism parameters, which remain metabolically relevant in acromegaly despite the altered pathophysiology [31]. The failure of other established scores, particularly the hepatic steatosis index, to demonstrate diagnostic utility in acromegaly patients highlights the need for disease-specific assessment tools. These findings suggest that relying on conventional scoring systems may lead to misclassification of NAFLD risk in acromegaly patients, potentially impacting clinical decision-making and surveillance strategies.

The inverse relationship between ANGPTL-8 levels and NAFLD presence in acromegaly patients provides novel insights into the role of this adipokine in hepatic metabolism. ANGPTL-8, traditionally elevated in NAFLD patients from general populations, showed paradoxically lower levels in acromegaly patients with hepatic steatosis [32]. This finding suggests that ANGPTL-8 elevation in acromegaly may primarily reflect growth hormone-induced metabolic activation rather than hepatic fat accumulation per se. The lower ANGPTL-8 levels observed in controlled acromegaly patients with NAFLD may indicate that this biomarker's utility as a diagnostic tool is limited in this population, requiring alternative approaches for biomarker-based NAFLD detection.

The clinical implications of these findings extend beyond diagnostic considerations to encompass long-term management strategies for acromegaly patients. Healthcare providers should recognize that achieving biochemical control, while essential for preventing acromegaly-related complications, may inadvertently increase NAFLD risk [33]. This knowledge should inform surveillance protocols, with increased attention to hepatic steatosis monitoring following successful treatment. Additionally, lifestyle interventions targeting metabolic health may be particularly important during the transition from active to controlled disease states.

Our study's demonstration of preserved liver stiffness measurements across groups suggests that while NAFLD risk increases with disease control, progression to advanced fibrosis may not be accelerated in acromegaly patients. This observation could reflect the relatively shorter duration of hepatic steatosis exposure in controlled patients or potential protective effects of previous growth hormone elevation on hepatic fibrogenesis. However, longer-term follow-up studies are needed to definitively establish fibrosis progression patterns in this population.

The identification of optimal cutoff values for noninvasive scores in acromegaly patients represents an important step toward developing disease-specific diagnostic algorithms. Our findings suggest that TyG index cutoff values may

need adjustment for acromegaly populations, with implications for clinical practice guidelines and screening recommendations. Future research should focus on validating these cutoffs in larger acromegaly cohorts and developing integrated scoring systems that incorporate disease-specific variables such as growth hormone levels and treatment status.

Limitations

This study has several important limitations that should be acknowledged. The relatively small sample size, particularly for the acromegaly subgroups, may limit the generalizability of our findings and statistical power for detecting smaller effect sizes. The cross-sectional design precludes assessment of temporal relationships and longitudinal changes in NAFLD development during the transition from active to controlled disease states. The study population was recruited from a single tertiary referral center, which may introduce selection bias and limit external validity to other healthcare settings. Additionally, the absence of liver biopsy data, while ethically appropriate for this study design, prevents definitive assessment of hepatic inflammation and fibrosis staging that could provide additional mechanistic insights.

Conclusion

This study demonstrates that active acromegaly provides significant protection against NAFLD development, while disease control paradoxically increases hepatic steatosis risk. Conventional NAFLD risk assessment tools show limited utility in acromegaly patients, with the triglyceride-glucose index emerging as the most reliable noninvasive diagnostic marker. These findings have important implications for clinical management, suggesting the need for enhanced NAFLD surveillance following achievement of biochemical control and the development of acromegaly-specific diagnostic algorithms. Future research should focus on validating these observations in larger cohorts and developing targeted interventions to prevent NAFLD development during acromegaly treatment.

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