


Hepatic steatosis in patients with acromegaly

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Abstract

Objective: Comorbid NAFLD is increasingly being diagnosed in patients with diabetes and nondiabetic endocrinopathies. The aim of this study was to assess hepatic steatosis noninvasively by transient elastography in patients with acromegaly.

Design: A cross-sectional study including 22 patients with acromegaly.

Methods: Hepatic steatosis was quantified using controlled attenuation parameter (CAP) during elastography. Anthropometric measurements were obtained, serum liver function tests and lipid and hormone profiles were measured, and prosteatogenic gene variants were genotyped using standard assays.

Results: In total, 41% of patients were women (mean age 60 ± 14.7 years, mean BMI 31.2 ± 4.6 kg/m²). Hepatic steatosis, as defined by CAP > 248 dB/m, was present in 66% of patients. Five (45%) of the patients with hepatic steatosis also had fibrosis, and one presented with cirrhosis. Nine patients were carriers of the *PNPLA3* p.I148M prosteatogenic [M] risk allele, eight of whom were heterozygotes. CAP values were significantly ($P = .045$) higher in these patients and corresponded to advanced steatosis, as compared to patients with the wild-type genotype, who demonstrated CAP values consistent with mild steatosis (311 ± 33 dB/m. vs 254 ± 62 dB/m). CAP values did not differ significantly in carriers of distinct *TM6SF2* and *MBOAT7* genotypes; however, carriers of the risk alleles displayed higher CAP as compared to wild-type patients.

Conclusions: This study shows that in patients with acromegaly, carriers of the *PNPLA3* susceptibility allele are at risk of developing hepatic steatosis, as assessed by CAP. Comorbid NAFLD might compound prognosis in such patients; thus, further research into the pathomechanisms and treatment of NAFLD in acromegaly is warranted.

KEYWORDS

adiponutrin, controlled attenuation parameter, *MBOAT7*, nonalcoholic fatty liver disease, *TM6SF2*, transient elastography

Abbreviations: ACTH, adrenocorticotrophic hormone; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; FSH, follicle-stimulating hormone; γ -GT, gamma-glutamyl transpeptidase; GH, growth hormone; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1; IQR, interquartile range; LDL, low-density lipoprotein; LH, luteinizing hormone; LSM, liver stiffness measurement; *MBOAT7*, membrane-bound O-acyltransferase domain-containing 7; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovarian syndrome; *PNPLA3*, patatin-like phospholipase domain-containing 3; SHBG, sex hormone-binding globulin; STH, somatotrophic hormone; TC, total cholesterol; TG, triglyceride; *TM6SF2*, transmembrane 6 superfamily member 2; VCTE, vibration-controlled transient elastography; WC, waist circumference.

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1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of liver conditions, ranging from bland steatosis to nonalcoholic steatohepatitis (NASH), which results in progressive hepatic fibrosis. Patients with NAFLD are at risk of liver cirrhosis and hepatocellular carcinoma.¹ The pathogenesis of NAFLD is still not entirely understood. The risk is increased by environmental risk factors such as metabolic-related challenges but also in the presence of genetic variations.² For instance, the mutation p.I148M in the gene encoding the triglyceride hydrolase patatin-like phospholipase domain-containing 3 (PNPLA3) rs738409 (also referred to as adiponutrin) is reported to be a major risk factor for NAFLD.² In addition, common genetic variations in the membrane-bound O-acyltransferase domain-containing 7 (MBOAT7) and in the transmembrane 6 superfamily member 2 (TM6SF2) genes have also been associated with increased susceptibility to NAFLD and its severity.³

Comorbid NAFLD is becoming progressively more prevalent in certain conditions such as the metabolic syndrome, which is a well-established risk factor.⁴ NAFLD has also been reported in up to 80% of patients with type 2 diabetes.⁵ Nondiabetic endocrinopathies are also increasingly being linked to fatty liver.^{6,7} Hypothyroidism has been associated with NAFLD,⁶ as have patients with increased circulation of androgens, evidenced by occurrence rates of up to 70% in women with polycystic ovarian syndrome (PCOS).⁸

Acromegaly is another endocrinopathy of interest, which is characterized by the hypersecretion of growth hormone (GH). GH triggers hepatic and systemic insulin-like growth factor 1 (IGF-1) production.⁹ Both GH and IGF-1 are suggested to play an important role in the metabolism of hepatic fat.¹⁰ Treatment-naïve patients with acromegaly are reported to commonly have elevated serum triglyceride concentrations in addition to insulin resistance and visceral adipose tissue accumulation—factors associated with NAFLD.¹¹ Furthermore, certain treatments for acromegaly can compound this clinical picture, as they have been associated with altered hepatic fat accumulation and liver dysfunction.^{12–14} This has been illustrated in a randomized study that reported increased accumulation of hepatic fat after cotreatment of somatostatin analogue with the GH receptor antagonist, pegvisomant.¹⁴

Overall, there has been a little attention on the role of NAFLD in patients with acromegaly; thus, the objective of this cross-sectional study was to investigate the associations between the clinical features of acromegaly and NAFLD, taking into account the genetic make-up of the individual patients.

2 | PATIENTS AND METHODS

This study recruited adult patients diagnosed with acromegaly from within the Department of Medicine II at Saarland University Medical Center, who were willing to provide informed consent for participation. The diagnosis of acromegaly was based on IGF-1 concentrations in blood and the absence of growth hormone suppression

during an oral glucose tolerance test (OGTT). Patients were excluded if they presented with chronic hepatitis B or C virus infection; had significant long-term alcohol consumption that surpassed 21 and 14 standard alcoholic drinks per week for men and women, respectively¹⁵; were taking steatogenic medications; or presented with monogenic hereditary liver diseases.¹⁵ The study was approved by the Ärztekammer des Saarlandes local ethical committee (Refs. #271/11 and #67/16) and conducted within the framework of the Declaration of Helsinki.

2.1 | Anthropometric, clinical and biochemical assessments

Height and weight were recorded together with transient elastography using a stadiometer and a scale (seca 217 and seca 701, respectively; Seca), from which body mass index (BMI) was calculated. Waist circumference (WC) was obtained, and a full medical history was taken, which included previous and current medications. Fasted blood samples were collected for routine analyses including liver function tests, serum lipids and relevant hormones. Specifically, the following parameters were quantified: surrogate markers for liver function, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) and γ -glutamyl transpeptidase (γ -GT); the following lipid status markers: triglycerides (TGs), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol; and glucose-related markers and hormones: HbA1c, total testosterone, free testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, sex hormone-binding globulin (SHBG), cortisol, adrenocorticotrophic hormone (ACTH), somatotrophic hormone (STH), insulin-like growth factor 1 (IGF-1; concentration and standard deviation (SD) score) and prolactin.

2.2 | Noninvasive assessment of hepatic steatosis and fibrosis

Hepatic steatosis and liver stiffness were simultaneously quantified using the noninvasive vibration-controlled transient elastography (VCTE; FibroScan[®], Echosens), which yields liver stiffness measurements (LSMs) ranging from 1.5 to 75.0 kPa and controlled attenuation parameter (CAP) values between 100 and 400 dB/m. The full technique has been described previously.¹⁶ CAP results were only included if they were based on 10 valid measurements. Furthermore, if the success rate surpassed 60% and the interquartile range (IQR) for LSM was $\leq 30\%$, then LSM results were also included, as per the EASL-ALEH Clinical Practice Guidelines.¹⁷ For LSM values < 7.1 kPa, the IQR/LSM ratio was not a criterion for inclusion.¹⁸

2.3 | Genotyping of risk variants

For genotyping, we followed the membrane-based QIAamp protocol (Hilden, Germany) for the DNA isolation from EDTA blood.

PCR-based assays based on 5'-nuclease and fluorescence detection (Thermo Fisher; rs738409: C_7241_10; rs58542926: C_894635_10; rs641738: C_8716820_10) were used to genotype the following single nucleotide polymorphisms: *PNPLA3* rs738409 (c.444C > G, resulting in the amino acid substitution p.I148M); *TM6SF2* rs58542926 (c.549G > A, resulting in the amino acid substitution p.E167K) and *MBOAT7* rs641738 (c.50G > A, resulting in the amino acid substitution p.G17E), respectively.

2.4 | Statistical analysis

The software programs SPSS 20.0 (SPSS) and GRAPHPAD PRISM 7.04 (GraphPad Software) were used for all statistical analyses. Results based on continuous data are presented as mean \pm SD or median (range), based on the data distribution. According to a recent meta-analysis of individual participant data, the CAP cut-off 248 dB/m is used to differentiate steatosis from no steatosis, corresponding to the histological S0 and \geq S1 categories.¹⁹ Therefore, we carried out subgroup analysis using this cut-off. Furthermore, we interpreted LSM > 6.0 kPa to indicate the presence of fibrosis, where we categorized values between 6 and 12 kPa as manifest liver fibrosis and values >12.0 kPa as liver cirrhosis.¹⁷ Based on the data distribution, either the *t* test or Mann-Whitney *U* test was used to assess for significance between two unpaired groups and ANOVA or the Kruskal-Wallis test was used for comparing three such groups. Categorical variables were evaluated using contingency tables. Univariate regression analysis was planned a priori for the two variables BMI and *PNPLA3* genotype to assess for associations with hepatic steatosis in acromegaly patients. A two-sided *P*-value < .05 was defined as statistical significance.

3 | RESULTS

3.1 | Patient characteristics

A total of 22 patients with acromegaly who were treated at our centre were included in this cross-sectional analysis. Table 1 summarizes their characteristics. The mean age of the patients was 60.0 \pm 14.7 years, and nine patients (41%) were women. One patient had a BMI in the normal range (<25 kg/m²), eight patients were overweight (BMI 25.0-29.9 kg/m²), and the remaining 13 patients were categorized as obese (BMI \geq 30 kg/m²). Waist circumference values were within the normal range for five men, and the remaining men and women were above the normal thresholds (<94 cm for men; <80 cm for women). Approximately one-third of the cohort had a diagnosis of diabetes type 2, and two-thirds presented with arterial hypertension.

3.1.1 | Liver profiles

Figure 1A summarizes the CAP and LSM results of the noninvasive transient elastography. Using the CAP cut-off 248 dB/m to

TABLE 1 Patient characteristics for sample of acromegaly patients

	Entire sample
Sociodemographic characteristics	
N (men/women)	22 (13/9)
Age (y)	60.0 \pm 14.7
Diabetes	8 (36%)
Hypertension	14 (64%)
Anthropometry	
Body weight (kg)	91.4 \pm 16.8
BMI (kg/m ²)	31.2 \pm 4.6
WC (cm)	104.6 \pm 18.3
Endocrine markers	
Testosterone (pg/mL)	2.5 \pm 1.6
Free testosterone (pg/mL)	1.5 (0.0-66.2)
Oestradiol (pg/mL)	14.2 \pm 13.8
FSH (mIU/mL)	4.7 (0.4-56.8)
LH (mIU/mL)	2.6 (0.1-28.1)
Prolactin (μ iu/mL)	67 (3-379)
SHBG (mmol/L)	46.4 \pm 24.6
Cortisol (μ g/dL)	10.6 (1.7-41.1)
ACTH (pg/mL)	13.3 \pm 7.8
STH (ng/mL)	0.9 (0.1-29.0)
IGF-1 (ng/mL)	164.4 \pm 76.4
Liver markers	
CAP (dB/m)	276 \pm 56
LSM (kPa)	5.6 (3.5-15.8)
ALT (U/L)	27 (10-96)
AST (U/L)	24 (17-67)
AP (U/L)	72 (45-251)
γ -GT (U/L)	32 (14-186)
Metabolic markers	
HbA1c (%)	6.1 \pm 0.7
Triglycerides (mg/dL)	186 (66-686)
Total cholesterol (mg/dL)	215 \pm 45
LDL cholesterol (mg/dL)	124 \pm 45
HDL cholesterol (mg/dL)	52 (23-147)

Abbreviations: ACTH, adrenocorticotrophic hormone; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1; LDL, low-density lipoprotein; LH, luteinizing hormone; LSM, liver stiffness measurement; SD, standard deviation; SHBG, sex hormone-binding globulin; STH, somatotrophic hormone; WC, waist circumference; γ -GT, gamma-glutamyl transpeptidase.

determine the presence of hepatic steatosis, 11 patients were diagnosed with fatty liver. Of these, five patients also had manifest liver fibrosis (LSM between 6 and 12 kPa), and one patient presented with liver cirrhosis (>12 kPa). Figure 1B demonstrates that the median

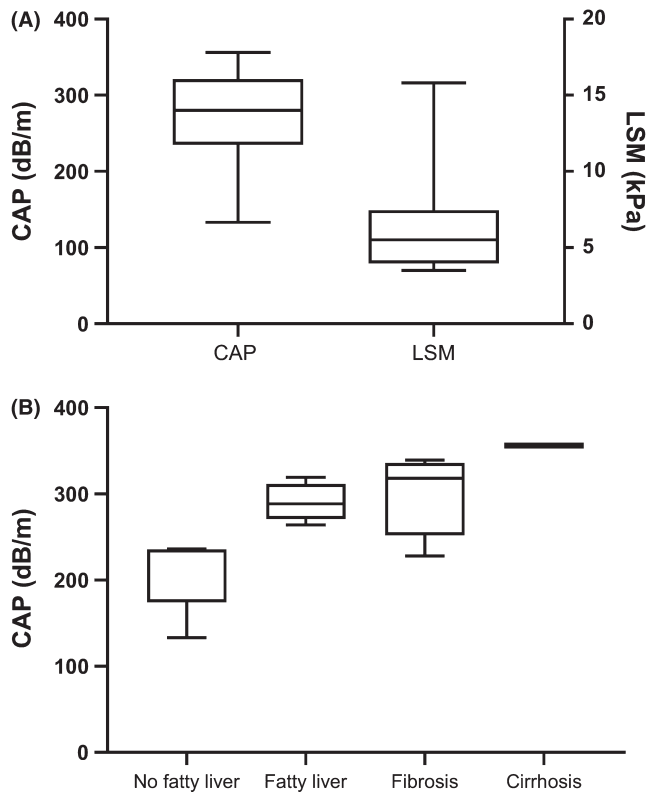


FIGURE 1 A, Boxplots depicting noninvasive transient elastography results for controlled attenuation parameter (CAP) and liver stiffness measurements (LSMs) in the entire study group. B, Boxplots comparing CAP values for the four different groups of patients with acromegaly: patients without fatty liver compared to patients with fatty liver, and with fibrosis and cirrhosis. The CAP cut-off for fatty liver was 248 dB/m. Liver fibrosis was defined by LSM > 6.0 kPa, and LSM > 12.0 kPa indicated cirrhosis

CAP values increase with advancing liver disease. In terms of liver function tests, one patient had elevated ALT, AST and AP activities, and three patients had increased AST levels only; finally, raised γ -GT activities were documented in six patients.

3.1.2 | Lipid profiles

Overall, 68.2% of the patients displayed elevated serum TG (>150 mg/dL) and 63.6% raised TC concentrations (>200 mg/dL). LDL cholesterol was above the normal threshold of 120 mg/dL in 40.9%, and 9.0% of the patients had HDL cholesterol values <40 mg/dL. HbA1c was above the normal range in six patients (all of which had a diagnosis of diabetes). Incidentally, not all the diabetic patients presented with hepatic steatosis.

3.1.3 | Endocrine markers

IGF-1 concentrations were within the normal range for 18 of the 22 patients (82%) on treatment. When comparing serum cortisol concentrations between patients, only three patients demonstrated elevated values. Prolactin concentrations were within the normal

range for six patients and were elevated in one patient, whilst 15 patients had values below normal. Both STH and SHBG concentrations were raised in two and four patients, respectively, and three patients had SHBG levels below the normal threshold. Only one patient had elevated ACTH concentrations. Two patients displayed total testosterone levels above the threshold, four were below, and 10 patients were in the normal range (there were missing values for six patients).

The majority of patients had FSH values within the normal range ($n = 16$), and one and four patients had values above and below this range, respectively. Likewise, 13 patients had normal LH concentrations and seven displayed elevated values (cut-off could not be determined for two patients). Finally, six patients had normal oestradiol levels, whereas this was below the normal threshold for one patient (the cut-off could not be determined for 15 patients).

3.1.4 | Medications

The patient sample was documented as taking the following medications: seven patients were receiving octreotide only, four were on octreotide and cabergoline cotreatment, and one patient received octreotide together with pegvisomant. Two patients were taking pegvisomant alone, and one was receiving pegvisomant with cabergoline. Seven patients were untreated.

3.1.5 | Genotyping results

Genotyping results were available for 21 of the 22 patients and are summarized in Table 2. Nine patients were carriers of the *PNPLA3* p.I148M risk allele, of whom only one was homozygous (MM) and eight were heterozygous (IM). The remaining 12 patients did not carry the risk allele (wild type [II]). For the *TM6SF2* gene, six patients were heterozygous (EK) and 15 did not carry the risk allele (EE). Three patients were homozygous (EE) for the *MBOAT7* risk allele, with 11 patients being heterozygous (GE) carriers, and seven carried the wild-type genotype (GG).

3.2 | Hepatic steatosis is influenced by risk genotypes in patients with acromegaly

CAP values were available for 18 of the 21 patients who were genotyped. From these, 17 were included based on fulfilling our criteria for CAP inclusion. Heterozygous carriers of the prosteatogenic (M) *PNPLA3* risk allele had significantly ($P = .045$) higher CAP as compared to the wild-type group (Figure 2). A comparison of CAP values based on *MBOAT7* and *TM6SF2* genotypes revealed no significant differences between wild-type, heterozygous and homozygous groups and the wild-type and heterozygous groups, respectively. Nevertheless, mean CAP values were lower in carriers of the wild-type genotype than in heterozygous patients for both genotypes, as illustrated in Figure 2. Additionally, the *MBOAT7* genotype included patients homozygous for the risk allele, in whom the mean CAP value was highest.

TABLE 2 Number of patients based on genotype

	Number of patients per genotype		
	Wild-type	Heterozygote	Homozygote
<i>PNPLA3</i> p.I148M	12	8	1
<i>TM6SF2</i> p.E167K	15	6	0
<i>MBOAT7</i> p.G17E	7	11	3

Abbreviations: *MBOAT7*, membrane-bound O-acyltransferase domain-containing 7; *PNPLA3*, patatin-like phospholipase domain-containing 3; *TM6SF2*, transmembrane 6 superfamily member 2.

3.3 | *PNPLA3* p.I148M risk allele is associated with higher CAP

Table 3 summarizes the patient characteristics based on the presence or absence of the *PNPLA3* p.I148M risk allele (M) (of note, comparisons with the homozygous group have been omitted due to only one patient being present in that category). The seven patients with one prosteatogenic (M) risk allele who had valid CAP values were all above the threshold for diagnosing hepatic steatosis (CAP > 248 dB/m). This contrasted with only four out of the nine patients in the wild-type group. Moreover, three of these patients in the risk group had liver fibrosis and one was categorized as having cirrhosis, as per the valid transient elastography results.

Concentrations of IGF-1 also differed significantly ($P = .031$) between groups, with the *PNPLA3* risk allele carriers displaying lower values 112 (50-377) ng/mL vs 171 (82-292) ng/mL. Though the remaining comparisons were not significantly different, Table 3 further illustrates that acromegaly patients with the *PNPLA3* risk allele presented with markedly higher BMI and WC. Additionally, LFTs were higher in these patients, who also had lower median HbA1c when compared to the wild-type group.

3.4 | Clinical phenotypes do not differ based on the presence of hepatic steatosis

A subgroup comparison was carried out based on the presence or absence of hepatic steatosis, as defined by CAP cut-off 248 dB/m. This corresponded to 12 vs 6 patients; however, when comparing the clinical characteristics between these two groups, no significant differences were observed.

A further analysis comparing CAP scores in patients receiving pegvisomant with those not on medications or with those receiving somatostatin analogues or cabergoline revealed no differences.

3.5 | Univariate regression analysis reveals associations with CAP

Linear univariate regression analysis for CAP values as continuous variable was carried out for two variables (*PNPLA3* genotype and BMI), agreed on a priori; however, no significant associations were observed.

4 | DISCUSSION

This cross-sectional study evaluated the clinical features of patients with acromegaly and assessed for hepatic steatosis as well as for genetic determinants related to NAFLD. Hepatic steatosis was present in 66% of the patients when using a CAP cut-off of 248 dB/m, this finding is similar to another recent study that reported hepatic steatosis in 61% of acromegaly patients using the hepatic steatosis index.²⁰ Furthermore, five of the included patients with hepatic steatosis also had fibrosis and one had cirrhosis. Moreover, the *PNPLA3* risk allele was highly prevalent in this small sample (in 41% of the patients). Indeed, all patients who carried one *PNPLA3* p.I148M prosteatogenic [M] risk allele had CAP values above the suggested

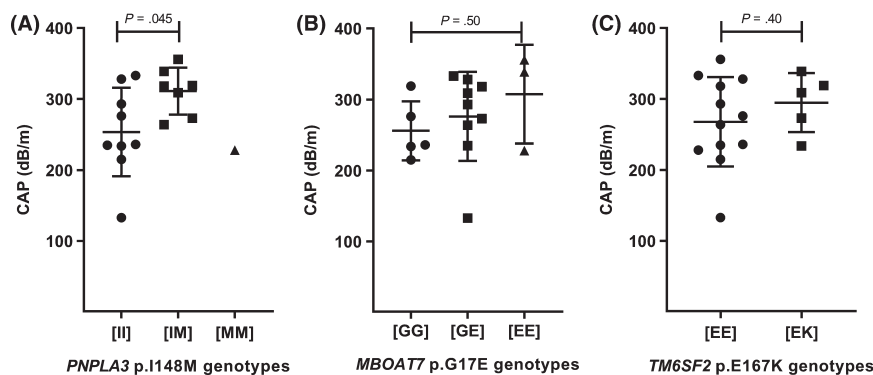


FIGURE 2 Individual patient CAP scores (as well as mean \pm SD) based on genotype for the following single nucleotide polymorphisms: patatin-like phospholipase domain-containing 3 (*PNPLA3*) p.I148M; membrane-bound O-acyltransferase domain-containing 7 (*MBOAT7*) p.G17E; and transmembrane 6 superfamily member 2 (*TM6SF2*) p.E167K. CAP values differed significantly ($P = .045$) between patients who were heterozygous carriers of the *PNPLA3* risk allele (IM) as compared to the wild-type patients (II). No significant differences in CAP were demonstrated between the three *MBOAT7* genotypes, where the lowest mean CAP value was observed in carriers of the wild-type genotype (GG) and the highest in patients homozygous for the risk allele (EE). No difference in CAP was observed between the *TM6SF2* genotypes

TABLE 3 Patient characteristics based on *PNPLA3* p.I148M risk genotype

	Patients with one <i>PNPLA3</i> risk allele	Patients with no <i>PNPLA3</i> risk allele
Sociodemographic characteristics		
N (men/women)	8 (3/5)	12 (8/4)
Age (y)	58.5 ± 10.2	60.1 ± 18.5
Diabetes	3 (38%)	4 (33%)
Hypertension	6 (75%)	7 (58%)
Anthropometry		
Body weight (kg)	95.2 ± 22.2	88.6 ± 12.4
BMI (kg/m ²)	31.3 ± 4.8	30.1 ± 3.9
WC (cm)	109.0 ± 19.7	99.6 ± 16.2
Endocrine markers		
Testosterone (pg/mL)	2.4 ± 1.8	2.5 ± 1.8
Oestradiol (pg/mL)	16 (5 - 44)	5 (0 - 10)
FSH (mIU/mL)	5.0 (1.0 - 50.2)	4.7 (0.4 - 56.8)
LH (mIU/mL)	2.5 (0.1 - 21.0)	2.6 (0.1 - 28.1)
Prolactin (µIU/mL)	67 (5 - 196)	68 (4 - 379)
SHBG (nmol/L)	47 (20 - 55)	41 (11 - 107)
Cortisol (µg/dL)	10.2 (6.3 - 41.1)	9.9 (1.7 - 26.6)
ACTH (pg/mL)	9.0 ± 4.2	14.5 ± 8.4
STH (ng/mL)	1.5 (0.1 - 29.0)	0.9 (0.1 - 12.6)
IGF-1 (ng/mL)	112 (50 - 377)*	171 (82 - 292) [§]
Liver markers		
CAP (dB/m)	311 ± 33**	254 ± 62**
LSM (kPa)	5.3 (3.8-15.8)	5.4 (3.5-10.3)
ALT (U/L)	29 (18-59)	23 (10-96)
AST (U/L)	27 (22-34)	23 (17-67)
AP (U/L)	74 (61-97)	72 (45-251)
γ-GT (U/L)	36 (14-86)	28 (14-186)
Metabolic markers		
HbA1c (%)	5.7 (5.2-7.8)	6.1 (5.4-7.3)
Triglycerides (mg/dL)	219 (66-686)	186 (77-309)
Total cholesterol (mg/dL)	224.8 ± 55.2	213.1 ± 41.0
LDL cholesterol (mg/dL)	117 (81-215)	114 (51-211)
HDL cholesterol (mg/dL)	51 (23-90)	50 (38-147)

Abbreviations: ACTH, adrenocorticotrophic hormone; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1; LDL, low-density lipoprotein; LH, luteinizing hormone; LSM, liver stiffness measurement; SHBG, sex hormone-binding globulin; STH, somatotrophic hormone; WC, waist circumference; γ-GT, gamma-glutamyl transpeptidase.

**P* = .030.

***P* = .045.

threshold for hepatic steatosis (>248 dB/m). Moreover, the mean CAP value for these patients corresponded to advanced steatosis (S3) and was significantly higher (*P* = .045) when compared to the mean CAP value of the wild-type patients who did not possess the risk allele, which corresponded to mild steatosis, S1.¹⁹

How acromegaly is associated with increased risk of hepatic steatosis is not entirely understood, but might be mediated by the presence of obesity. Moreover, we previously reported significantly higher CAP values in carriers of the *PNPLA3* risk allele in patients with chronic liver diseases.¹⁶ Moreover, metabolic and endocrine factors may interact and have dynamic effects on hepatic steatosis in acromegaly. Specifically, growth hormone (GH) stimulates insulin resistance via its induction of gluconeogenesis and glycogenolysis, and indeed, hepatic lipid accumulation has been associated not only with GH deficiency but also with GH excess.²⁰ Detrimental consequences on glucose metabolism, insulin signalling and adipose tissue have been documented in patients with acromegaly and GH excess. For instance, insulin resistance is associated with increased lipolysis and elevated circulating free fatty acids are seen in acromegaly patients.²¹ On the contrary, deficiencies of both GH and IGF-1 have been associated with an increased risk of NAFLD, as shown in animal models with GH deficiency, in whom hepatic steatosis is reversed upon correction of GH and IGF-1 concentrations.²² Indeed, lower GH concentrations have been reported in human studies with participants diagnosed with NAFLD.^{23,24} Moreover, low serum IGF-1 concentrations have also been associated with NAFLD and it has been suggested that hepatic insulin resistance modulates hepatic GH production and thus IGF-1 concentrations.^{25,26} A recent study showed hepatic steatosis (as assessed by a surrogate marker, the hepatic steatosis index) to be related to insulin resistance and the reduction of IGF-1 and GH levels; after 12 months of follow-up, improvements to insulin sensitivity paralleled reductions of hepatic steatosis.²⁰

The observed risk with GH and IGF-1 deficiencies would imply that treated patients with acromegaly might be prone to develop NAFLD, because treatment does, in some cases, lead to the development of GH deficiency, as illustrated in a recently published case study.²⁷ Moreover, an intervention study and another case study both report histological NASH resolution upon GH correction in patients with GH deficiency.^{28,29} None of the patients herein had a deficiency in IGF-1 concentrations; therefore, other mechanisms must exist through which NAFLD risk is amplified.

The GH receptor antagonist, pegvisomant, has also been associated with intrahepatic lipid accumulation. In a randomized prospective study by Madsen et al.¹⁴, cotreatment of somatostatin analogue with pegvisomant in 12 patients resulted in increased intrahepatic lipid concentrations, as quantified using proton magnetic resonance spectroscopy (¹H MRS). Moreover, the authors found the weekly dose of pegvisomant correlated positively with accumulation of intrahepatic fat and speculated that the intermittent elevations in liver enzymes might be partially responsible for this effect. A subgroup analysis of our sample of patients with acromegaly did not reveal any significant differences in CAP values based on the medications taken. However, as described in Results section, there was a significant overlap between

several medications (eg, pegvisomant, somatostatins and cabergoline), which might have obviated any associations. We found elevations in liver enzymes to occur in a small number of patients only, despite high occurrence of hepatic steatosis. This finding reinforces that hepatic steatosis can occur in the absence of elevated LFTs. Moreover, when comparing the general characteristics of patients with versus without hepatic steatosis (based on CAP cut-off 248 dB/m), we could not find any significant differences between the two groups.

The current study is limited by the small sample size and the chance of false-positive findings. Moreover, being a cross-sectional design, the longer-term hepatic and extrahepatic implications could not be evaluated. Studies with larger patient samples are needed to confirm the findings reported herein. Moreover, a comparison of the prognosis for acromegaly patients with NAFLD versus patients without NAFLD is needed. It is known that acromegaly is associated with acromegalic cardiomyopathy³⁰ and that NAFLD is an independent risk factor for cardiovascular disease.³¹ Therefore, it would be beneficial to screen patients with acromegaly for the presence of NAFLD and manage accordingly. This is important because hepatic steatosis can be effectively mediated via lifestyle interventions, as recommended in the official guidelines.¹⁵

The significant genetic associations reported herein also warrant further investigation due to the small sample size included. We demonstrated that the *PNPLA3* gene was significantly associated with higher CAP values in carriers of the risk allele. The *PNPLA3* gene is a strong risk factor, not only for developing hepatic steatosis but also for NASH, fibrosis and cirrhosis.³² Moreover, the *PNPLA3* gene has been associated with increased risk of cardiovascular disease in the setting of type II diabetes.³³ Thus, lifestyle interventions for patients with the inherently increased risk of a poorer prognosis would be advantageous. Interestingly, we and others have shown that lifestyle interventions appear to be more effective in carriers of the *PNPLA3* risk allele when compared to noncarriers, as evidenced in several studies.^{34,35} We did not find differences in CAP values based on the *TM6SF2* and *MBOAT7* genotypes; however, a trend for higher CAP was observed based on the presence of risk alleles. This finding is in line with recent research supporting a stronger role of *PNPLA3* as compared to *TM6SF2* and *MBOAT7* genotypes in terms of severity of hepatic-related injury.³⁶

5 | CONCLUSION

Patients with both acromegaly and *PNPLA3* genetic risk present with a greater degree of hepatic steatosis as compared to patients with acromegaly without this genetic risk. This association should be investigated in larger patient cohorts. Since comorbid NAFLD might compound prognosis in such patients, further research into the role of NAFLD in acromegaly is warranted.

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CONFLICTS OF INTERESTS

The authors of this study explicitly declare that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

F. Lammert designed the study. A. Koutsou-Tassopoulou recruited patients and collected the data. I. Papapostoli-Sklavounou and B. Friesenhahn-Ochs assisted with the patient recruitment. S. Weber and M. Krawczyk assisted with the genetic analyses. CS Stokes analysed the data and drafted the manuscript, which was then critically revised by all authors. The final draft submitted has been approved by all authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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