The role of Cytomegalovirus Infection in Diabetic Acromegaly Patients

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A R T I C L E   I N F O

A B S T R A C T

Introduction: Acromegaly is often associated with alterations in carbohydrate metabolism, ranging from impaired glucose tolerance to overt diabetes mellitus (DM). This study aimed to evaluate the serum concentrations of TNF-α and IL-10, along with other biochemical parameters, in patients with acromegaly and concomitant diabetes. Furthermore, we sought to investigate the associations between these parameters. Additionally, this study investigated the prevalence of Cytomegalovirus (CMV) infection and its potential correlation with TNF-α, IL-10, and other biochemical parameters in this patient population. **Methods:** Serum concentrations of TNF-α and IL-10 were measured in 50 patients with acromegaly and concomitant diabetes and 50 healthy controls using commercially available ELISA kits. CMV DNA was detected in serum samples using a qualitative PCR assay targeting the CMV late antigen *gp64* gene. **Results**: Patients with acromegaly and concomitant diabetes exhibited significantly higher levels of IGF-1, insulin, HOMA-IR, cholesterol, triglycerides, LDL, VLDL, ALT, AST, bone-specific alkaline phosphatase (BALP), TNF-α, and IL-10 compared to the control group (all *P*<0.05). CMV infection was detected in 1.9% (1/50) of the healthy control group and 23.5% (12/50) of the acromegaly and diabetes group. Within the acromegaly and diabetes group, CMV-positive patients had significantly higher levels of TNF-α and IL-10 compared to CMV-negative patients (both *P*<0.05). **Conclusion**: This study demonstrated a significant association between elevated levels of TNF-α and IL-10 and acromegaly with concomitant diabetes. Further research is needed to determine if these cytokines play a causal role in the pathogenesis of these comorbidities. The observed increase in ALT, AST, and BALP levels in patients suggests potential liver and bone involvement in acromegaly with concomitant diabetes. Moreover, a higher prevalence of CMV infection was observed in patients with acromegaly and concomitant diabetes compared to healthy controls, suggesting a potential link between CMV infection and this patient population. Further research is warranted to elucidate the nature of this association and its potential clinical implications.

INTRODUCTION

Acromegaly is a rare, chronic disease characterized by the overproduction of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), most commonly due to a GH-secreting pituitary adenoma [1]. Although uncommon, acromegaly is clinically significant because chronic GH excess has widespread systemic effects, leading to various complications that can significantly impact a patient's quality of life and increase mortality risk [1]. Pituitary adenomas causing acromegaly are typically sporadic, though rarely, they can be associated with familial genetic syndromes [2].

GH exerts its effects on the human body primarily through IGF-1. Both GH and IGF-1 play complex and multifaceted roles in regulating metabolism, particularly influencing insulin sensitivity. Although GH levels in serum fluctuate significantly throughout the day in response to factors like diet and physical activity, IGF-1 levels remain relatively stable, making it a more reliable marker of GH action [3]. Chronic GH excess, as seen in acromegaly, directly impairs pancreatic beta-cell function and induces insulin resistance, contributing to the development of diabetes in a significant proportion of

Abulmahdi Zaghir et al.

patients. This acromegaly-induced diabetes, also known as acromegalic diabetes, further increases the risk of cardiovascular disease and mortality [1, 4].

GH directly elevates glucose levels by promoting hepatic gluconeogenesis, glycogenolysis, and lipolysis, while simultaneously reducing insulin sensitivity in the liver and peripheral tissues [5]. Exogenous IGF-1 administration has been shown to increase glucose uptake in peripheral tissues, leading to decreased serum glucose levels in both healthy individuals and those with type 2 diabetes mellitus (T2DM) and insulin resistance [6, 7]. Although IGF-1 promotes glucose uptake, this effect alone is insufficient to counteract insulin resistance in the presence of excessive GH, as seen in acromegaly. GH directly contributes to insulin resistance by reducing the expression of key insulin signaling pathway components, such as insulin receptor substrate (IRS) proteins and glucose transporter type 4 (GLUT4), thereby impairing glucose uptake in muscle and fat tissue [8].

Initially, pancreatic β-cell hypersecretion may compensate for GH-induced insulin resistance. However, persistent GH excess can eventually lead to β-cell dysfunction and impaired insulin secretion, ultimately contributing to the development of overt dysglycemia, including diabetes [1, 8, 9]. T2DM, a highly prevalent metabolic disorder, arises from a complex interplay of two major factors: impaired insulin secretion by pancreatic β-cells and insulin resistance, characterized by reduced insulin sensitivity in peripheral tissues [10].

While both acromegaly and classic T2DM can involve insulin resistance, their underlying pathophysiology differs significantly. In acromegaly, chronic GH excess directly impairs insulin signaling and β-cell function, playing a dominant role in the development of acromegalic diabetes. Further research is needed to fully elucidate the specific contributions of GH/IGF-1, visceral adiposity, and other factors in the development of acromegalic diabetes compared to other forms of diabetes [11].

Chronic hyperglycemia, as seen in T2DM, can impair the phagocytic activity of macrophages, contributing to an increased risk of infections [10]. Viral infections trigger a type I interferon (IFN) response, characterized by the production of cytokines such as TNF-α, IFN-γ, and IL-6. These cytokines can induce transient insulin resistance in muscle and liver. While the pancreas may initially compensate for this resistance by increasing insulin secretion, prolonged or chronic viral infections, particularly with viruses like human cytomegalovirus (HCMV), may contribute to the development of diabetes. This link is likely due to multiple factors, including persistent inflammation and direct or indirect viral impacts on pancreatic β-cell function [12].

Furthermore, T2DM is associated with impaired immune function and delayed wound healing, which can increase susceptibility to viral infections. This susceptibility may be further exacerbated by the dysregulated inflammatory milieu often observed in T2DM, characterized by altered levels of cytokines such as IL-1β, IL-1Ra, IL-18, IL-4, IL-6, IL-10, and TNF-α [13, 14]. While systemic inflammation is also recognized as a feature of acromegaly, the specific cytokine profiles and their implications in the context of viral infections and diabetes development remain incompletely understood.

The coexistence of acromegaly, T2DM, and CMV infection presents a unique clinical challenge. Patients with acromegaly already face significant metabolic dysregulation due to chronic GH excess, which induces insulin resistance and impairs pancreatic beta-cell function, leading to acromegalic diabetes. When these patients also contract CMV, a virus known to induce insulin resistance through pro-inflammatory cytokine release, the management of glucose metabolism becomes even more complex [11-14].

While IL-10, a potent anti-inflammatory cytokine, typically improves insulin sensitivity by suppressing pro-inflammatory pathways, some studies suggest a potential link between elevated IL-10 levels and insulin resistance [15]. This paradoxical relationship warrants further investigation, particularly in the context of acromegaly, to elucidate the precise role of IL-10 and its potential impact on glucose metabolism in this complex clinical setting.

This study aims to evaluate serum levels of TNF-α, IL-10, the TNF-α/IL-10 ratio, Insulin-like growth factor 1 (IGF-1), and insulin in patients with acromegaly and concomitant diabetes. We will investigate the associations between these parameters and assess their potential relevance to disease severity and metabolic control. Furthermore, we will determine the prevalence of cytomegalovirus infection in this patient population and explore its potential correlations with the aforementioned inflammatory markers, hormonal profiles, and metabolic parameters.

MATERIAL AND METHODS

Sample collection. Ten milliliters (10 mL) of fasting blood samples were collected from each of the 50 patients with acromegaly and concomitant diabetes and the 50 healthy controls using disposable plastic syringes. For each participant, 2 mL of whole blood was collected into an EDTA tube for plasma extraction (centrifuged at $1000 \times g$ for 15 min), and 8 mL was collected into a serum separator tube for serum extraction (allowed to clot for 30 min at room temperature and then centrifuged at $1000 \times g$ for 15 min). Serum samples were stored at -20°C until analysis.

Determination of TNF-α and IL-10 cytokines by ELISA. Serum concentrations of TNF-α and IL-10 were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Diaclone, Besançon, France; TNF-α: Cat# 950.090.096; IL-10: Cat# 950.060.096) according to the manufacturer's instructions [16, 17]. Measurements were performed for both the

acromegaly with concomitant diabetes group and the healthy control group.

IGF-1 assay. Serum IGF-1 concentrations were measured using a commercially available ELISA kit (Elabscience, Wuhan, China; Cat# E-EL-H0086) based on the sandwich ELISA technique. In this assay, microplates were pre-coated with a monoclonal antibody specific to human IGF-1. The assay was performed according to the manufacturer's instructions [18, 19].

Insulin assay. Serum insulin concentrations were measured using a commercially available ELISA kit (Monobind Inc., Lake Forest, CA, USA; Cat# 5825-300). The assay was performed according to the manufacturer's instructions, which utilize specific enzyme-conjugated and immobilized antibodies that recognize distinct epitopes on the insulin molecule with different affinities [17].

Biochemical parameters assay

Assessment of Insulin Resistance (HOMA-IR). All 50 patients with acromegaly and concomitant diabetes and the 50 healthy controls underwent an oral glucose tolerance test (OGTT). Fasting blood samples were collected, and serum glucose and insulin concentrations were measured using the immunofluorometric method. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated using the following formula [20, 21]:

HOMA-IR = [Fasting insulin (μU/mL) × Fasting glucose (mmol/L)] / 22.5.

Assessment of liver function. Serum levels of alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured using commercially available diagnostic kits and a spectrophotometry system. ALP was measured using a kit from DiaSys Diagnostic Systems (Holzheim, Germany; Cat# 10401 9910021). AST and ALT were measured using kits from Randox Laboratories (Crumlin, UK; AST: Cat# AS 101; ALT: Cat# AL 100). These assays were based on kinetic photometric tests optimized according to the recommendations of the German Society of Clinical Chemistry (DGKC) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [21].

Measurement of other biochemical parameters. Fasting blood glucose (FBS), total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured in all serum samples using commercially available kits from Linear Chemicals S.L. (Barcelona, Spain). The following kits were used: FBS (Cat# 1129005), TC (Cat# 1118005), TG (Cat# 1155010), and HDL-C (Cat# 1133010). Low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) were calculated using the Friedewald formula [22].

Detection of CMV DNA by PCR. CMV DNA was detected in serum samples using a qualitative PCR assay targeting the late antigen *gp64* gene. DNA was extracted from serum samples using a commercially available kit (DNAVIRO, Kiagene Fanavar, Cat: FPKT004.0100). A previously characterized CMV-positive DNA sample and a CMV-negative DNA sample (DNase RNase Free water was used) were used as positive and negative controls, respectively. These control samples were stored in DNase/RNase-free microtubes with TE buffer at -40°C.

Oligonucleotide primers targeting the CMV gp64 gene were synthesized (GenScript Biotech, China) with the following sequences [23]:

Forward: 5′-CCGCAACCTGGTGCCCATGG-3′

Reverse: 5′-CGTTTGGGGTTGCGCAGCGGG-3′

PCR amplification was performed using 2x Taq PerMix (Parstous, Tehran, Iran; Cat# 101081) with a thermal cycling protocol consisting of an initial denaturation step at 94°C for 30 seconds, followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 63°C for 30 seconds, and extension at 72°C for 60 seconds.

PCR products (139 bp) were analyzed by electrophoresis on a 1.5% agarose gel in TBE buffer at 100 V alongside a 100 bp DNA ladder plus (Sinaclon, Tehran, Iran). The gel was stained with ethidium bromide (10 µg/mL) and visualized under UV light. The presence of a single band at the expected size indicated a positive result for CMV DNA.

Statistical analysis. Data are presented as mean ± standard deviation. Differences between the acromegaly with concomitant diabetes group and the healthy control group were analyzed using an unpaired two-tailed Student's t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. Multiple comparisons, where applicable, were performed using Tukey's post hoc test. All statistical analyses were performed using GraphPad Prism version 8.4.2 (GraphPad Software, San Diego, CA, USA). *P*-values < 0.05 were considered statistically significant.

Ethics considerations. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Arak University (Ethical code: IR.ARAKU.REC.1401.113). All participants provided written informed consent before enrollment in the study. The informed consent forms are available upon request from the corresponding author.

RESULTS

Demographic, clinical, and laboratory characteristics of the study participants are presented in (Table 1). This includes data on IGF-1 and insulin levels, HOMA-IR, inflammatory cytokines (IL-10 and TNF-α), liver function tests (AST, ALT, and ALP), anthropometric measurements (age, height, weight, and BMI), and lipid profile (cholesterol, HDL-C, LDL-C, and VLDL-C). The prevalence of CMV infection, as determined by PCR, is also presented and compared between the acromegaly with concomitant diabetes group and the healthy control group.

Table 1. Demographic, clinical, and laboratory characteristics of patients with acromegaly and concomitant diabetes and healthy controls

| Parameter	Control (n=50)	Patients (n=50)	P-value
Age (years)	43.52 ± 7.67	45.06 ± 10.47	P >0.9999
Weight (kg)	78.82 ± 13.29	92.84 ± 15.48	P =0.9949
Height (cm)	167.56 ± 6.24	167.44 ± 10.18	P >0.9999
BMI (kg/m²)	28.08 ± 4.64	33.07 ± 4.52	P >0.9999
IGF-1 (ng/mL)	233.22 ± 71.39	606.56 ± 166.83	P <0.0001
Insulin (μU/mL)	5.71 ± 1.48	15.64 ± 3.37	P >0.9999
HOMA-IR	1.19 ± 0.34	8.29 ± 3.00	P >0.9999
AST (U/L)	25.7 ± 5.87	50.0 ± 6.00	P =0.9142
ALT (U/L)	32.1 ± 9.23	44.8 ± 15.00	P =0.9992
ALP (U/L)	56.7 ± 9.53	163.0 ± 12.00	P <0.0001
Cholesterol (mg/dL)	169.02 ± 21.29	262.04 ± 59.17	P <0.0001
TG (mg/dL)	112.76 ± 26.63	214.20 ± 63.29	P <0.0001
HDL-C (mg/dL)	48.14 ± 7.74	45.96 ± 10.81	P >0.9999
LDL-C (mg/dL)	98.33 ± 23.64	163.67 ± 50.30	P <0.0001
VLDL-C (mg/dL)	22.55 ± 5.33	52.41 ± 11.83	P=0.0138
IL-10 (pg/mL)	6.34 ± 1.34	15.38 ± 0.30	P >0.9999
TNF-α (pg/mL)	0.81 ± 4.97	23.24 ± 5.96	P =0.3606
CMV positive (%)	2 (4%)	24 (48%)	P <0.0001
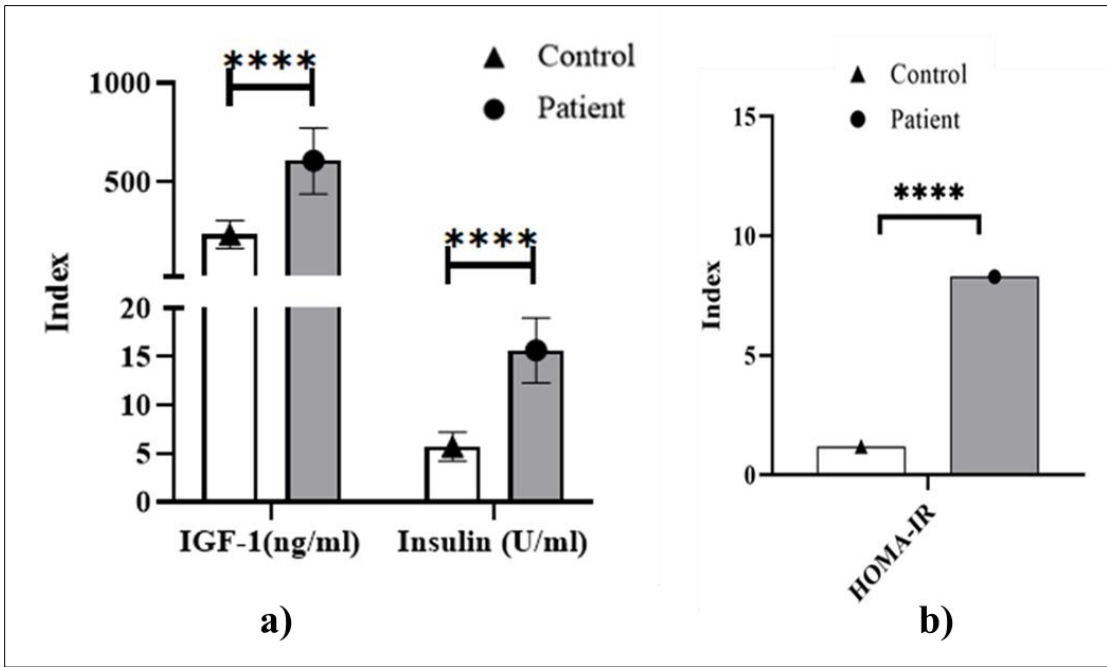
Fig. 1. Serum levels of IGF-1, insulin (a), and HOMA-IR (b) in patients with acromegaly and concomitant diabetes and healthy controls

Insulin resistance in patients with acromegaly and concomitant diabetes. Serum levels of IGF-1 and insulin were compared between patients with acromegaly and concomitant diabetes and healthy controls. There was a significant difference in both IGF-1 and insulin levels between the two groups (both *P*<0.0001). As shown in Figure 1a, the concentrations of IGF-1 and insulin were significantly higher in patients compared to healthy controls (both ****P* <0.0001).

HOMA-IR was calculated for both groups using the formula: [fasting insulin (μU/mL) × fasting glucose (nmol/L)] / 22.5 [20]. Figure 1b shows that HOMA-IR was significantly higher in patients with acromegaly and concomitant diabetes compared to healthy controls (****P < 0.0001*).

Inflammatory cytokine levels in patients with acromegaly and concomitant diabetes. To investigate the potential role of inflammatory cytokines in the pathogenesis of acromegaly with concomitant diabetes, serum levels of IL-10 and TNF-α were measured and compared between patients and healthy controls. Statistical analysis revealed that both IL-10 and TNF-α levels were significantly higher in patients with acromegaly and concomitant diabetes compared to healthy controls (both ****P*<0.0001) (Figure 2 and Table 1).
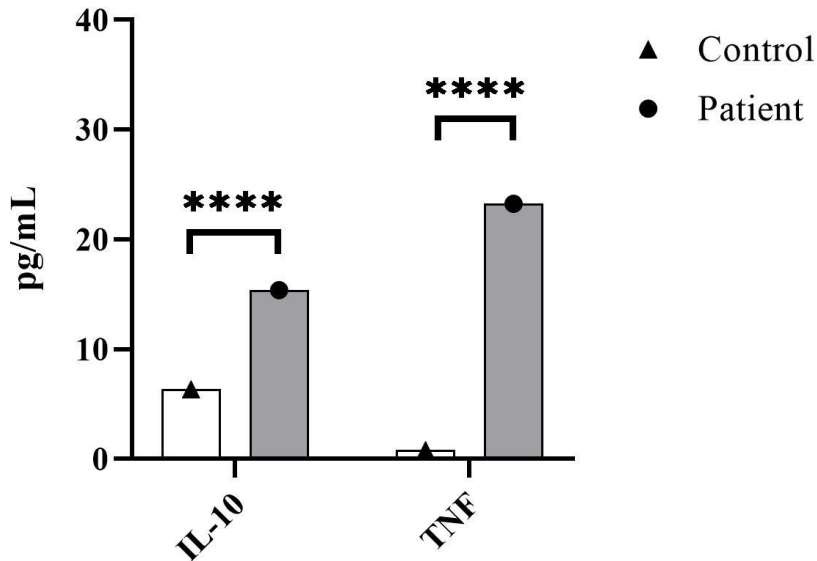
Fig. 2. Serum levels of IL-10 and TNF-α in patients with acromegaly and concomitant diabetes and healthy controls

Association of liver function tests with acromegaly and concomitant diabetes. To assess liver function, serum levels of AST, ALT, and ALP were measured in patients with acromegaly and concomitant diabetes and healthy controls. As shown in Figure 3a and Table 1, the concentrations of all three enzymes were significantly higher in patients compared to controls (AST and ALP: ****P<0.0001; ALT: ****P=0.0008). These differences were statistically significant based on an unpaired two-tailed ANOVA test.

Association of lipid profile with acromegaly and concomitant diabetes. To investigate the association between lipid profile and acromegaly with concomitant diabetes, serum levels of cholesterol, TG, HDL-C, LDL-C, and VLDL-C were measured and compared between patients and healthy controls. As shown in Figure 3b, there was a significant increase in cholesterol, TG, LDL-C, and VLDL-C in patients with acromegaly and concomitant diabetes compared to controls (all ****P<0.0001). However, there was no significant difference in HDL-C levels between the two groups.

The similar HDL-C levels in patients and controls, despite the observed increases in other lipid parameters, may be due to several factors. HDL-C metabolism is complex and can be influenced by various factors beyond lipolysis, such as liver function, hormonal balance, and compensatory mechanisms. For example, it's possible that the increased lipolysis in acromegaly primarily affects other lipid fractions, while HDL-C metabolism is maintained through compensatory pathways. Additionally, insulin resistance and other metabolic alterations in acromegaly may differentially affect HDL-C compared to other lipids.

The mean and standard deviation for each lipid parameter in both the acromegaly with concomitant diabetes group and the control group are presented in Table 1.

Association of anthropometric measurements with acromegaly and concomitant diabetes. Age, sex, weight, height, and BMI were measured and compared between patients with acromegaly and concomitant diabetes and healthy controls. As shown in Figure 3c, there was a significant increase in weight and BMI in patients compared to controls (weight: **P=0.004; BMI: ***P=0.0008). However, there were no significant differences in height or age between the two groups.

Association of CMV infection with acromegaly and concomitant diabetes. A total of 100 participants were included in this study: 50 patients with acromegaly and concomitant diabetes and 50 healthy controls. CMV DNA was detected in 12 out of 50 patients (24%) and 1 out of 50 controls (2%). This difference in CMV prevalence between the two groups was statistically significant (Figure 4a). PCR amplification of the CMV *gp64* gene yielded a 139 bp product, which was visualized as a single band on a 1.5% agarose gel after electrophoresis.

To investigate the potential role of IL-10 and TNF-α in the inflammatory response to CMV infection, serum levels of these cytokines were compared between CMV-positive and CMV-negative patients with acromegaly and concomitant diabetes. As shown in Figure 4b, both IL-10 and TNF-α concentrations were significantly higher in CMV-positive patients compared to CMV-negative patients (IL-10: **P=0.004; TNF-α: ***P=0.0008).

Furthermore, we investigated the association between CMV infection and various metabolic parameters in

Abulmahdi Zaghir et al.

patients with acromegaly and concomitant diabetes. Our analysis revealed that CMV-positive patients had significantly higher levels of cholesterol, TG, LDL-C, and

IGF-1 compared to CMV-negative patients. All statistical details, including *P*-values, are presented in Table 2.
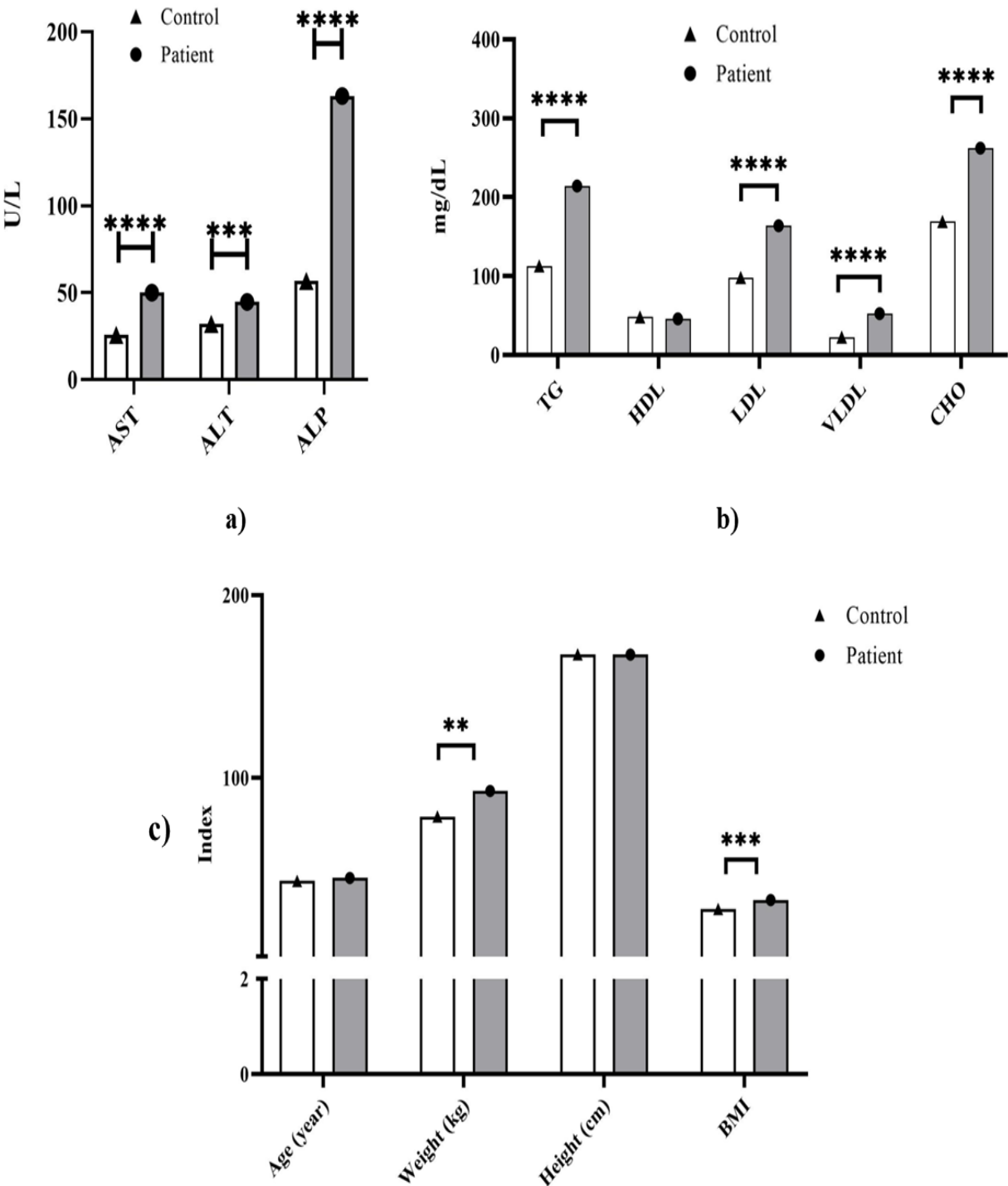

Fig. 3. Comparison of biochemical and anthropometric parameters between patients with acromegaly and concomitant diabetes and healthy controls. (a) Liver enzymes (AST, ALT, and ALP). (b) Lipid profile (cholesterol, TG, HDL-C, LDL-C, and VLDL-C). (c) Anthropometric measurements (age, sex, weight, height, and BMI)

Table 2. Comparison of metabolic parameters between CMV-positive and CMV-negative patients with acromegaly and concomitant diabetes

Parameter	Mean Difference (CMV⁺ vs. CMV⁻)	95% CI of Difference	Adjusted *P*-value
Cholesterol (mg/dL)	-124.9	-176.4 to -73.27	<0.0001
TG (mg/dL)	-67.26	-118.8 to -15.68	0.0018
LDL-C (mg/dL)	-101.1	-152.7 to -49.52	<0.0001
IGF-1 (ng/mL)	-215.8	-267.4 to -164.2	<0.0001

Note: Data are presented as mean differences with 95% confidence intervals. Adjusted *P*-values were calculated using Tukey's multiple comparisons test following a two-way ANOVA. Statistically significant *P*-values (*P* < 0.05) are shown in table.
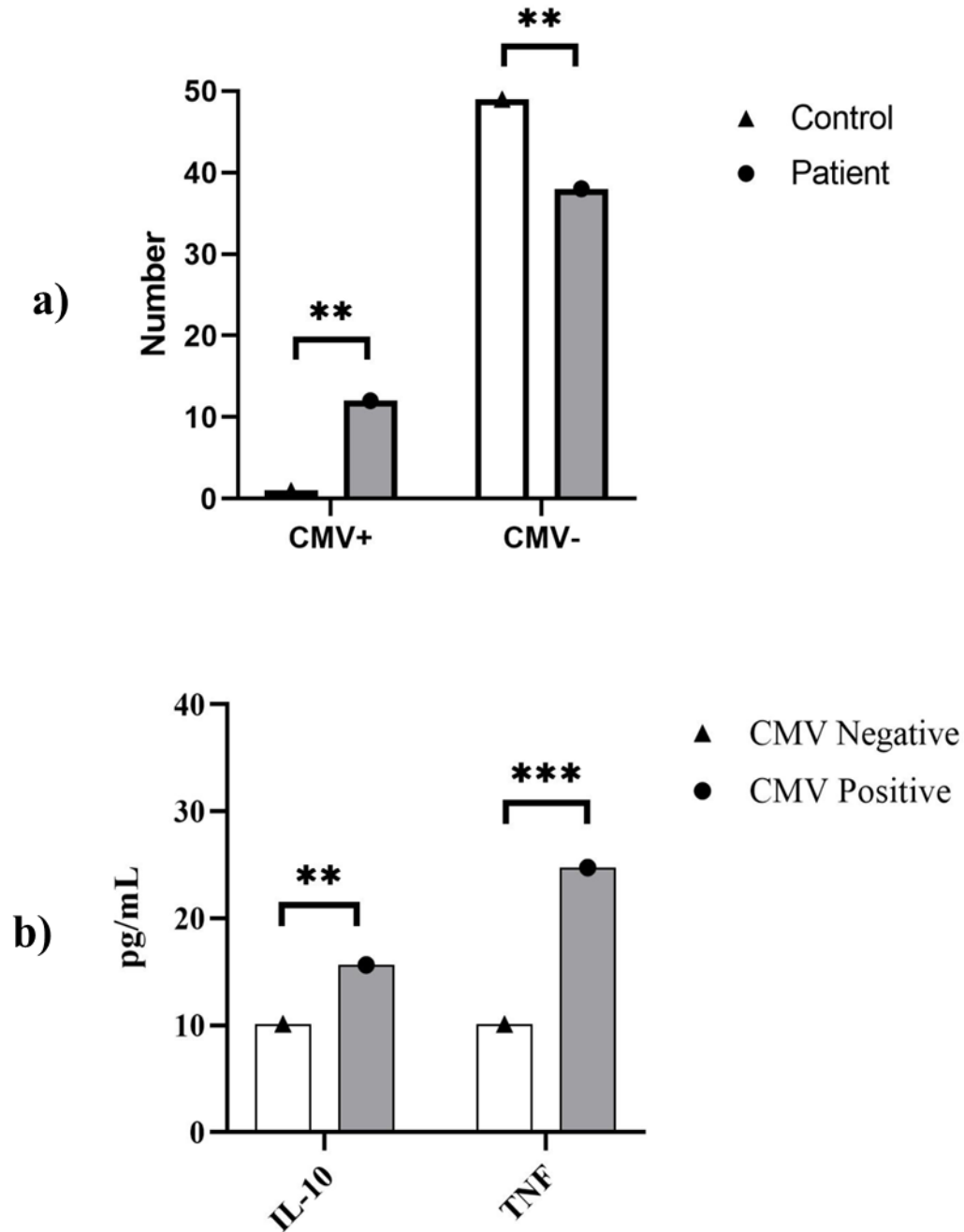
Fig. 4. Comparision of CMV status and inflammatory markers betwwen patient and control groups (top) and cytokine levels (IL-10 and TNF) in CMV positive vesus negative subjects (bottom)

Abulmahdi Zaghir et al.

DISCUSSION

Our findings demonstrate that patients with acromegaly and concomitant diabetes exhibit significantly elevated levels of IGF-1 and insulin compared to healthy controls (both **P < 0.0001), which is indicative of insulin resistance. This observation is consistent with previous studies that have reported elevated IGF-1 levels in acromegaly patients [24, 25]. While elevated IGF-1 may contribute to the development of insulin resistance in these patients, it is important to acknowledge that other factors, such as growth hormone excess and the inherent metabolic dysregulation associated with acromegaly, also play a significant role. Our findings demonstrated elevated production and activity of IGF-I in patients with diabetic acromegaly, a hallmark of this condition. This observation is consistent with the understanding that acromegaly is characterized by insulin resistance, which can progress to diabetes if left untreated [25].

We observed significantly elevated levels of both TNF-α and IL-10 in patients with diabetic acromegaly compared to the control group (P < 0.0001). This observation aligns with previous research that has implicated TNF-α and IL-10 in the inflammatory profile and pathogenesis of acromegaly [26]. Our findings suggest an association between elevated levels of IL-10 and IGF-1 and the pathogenesis of diabetic acromegaly. This is consistent with the study by Wolters et al. (2020) which demonstrated a pro-inflammatory shift in immune cell function characterized by decreased production of anti-inflammatory IL-10 following normalization of IGF-1 levels in acromegaly patients [27].

Our findings are also consistent with those of other studies, which have demonstrated that insulin resistance is prevalent in inflammatory liver diseases [28], often characterized by increased production of TNF-α [29]. Indeed, TNF-α can promote insulin resistance by directly inhibiting insulin receptor signaling [30], suggesting that the metabolic alterations observed in these patients are likely primarily driven by inflammation-mediated effects.

Our biochemical assays demonstrated significantly higher levels of liver enzymes (AST, ALT, and ALP) in patients with diabetic acromegaly compared to the healthy control group, as shown in Fig. 3.

While all of these liver enzymes can be indicators of liver function, ALT is often used specifically in epidemiological studies as a surrogate marker for liver abnormalities. In line with this, recent prospective epidemiological studies have demonstrated that ALT levels are associated with an increased future risk of type 2 diabetes mellitus and metabolic syndrome [31, 32]. Elevated serum alkaline phosphatase levels have also been reported in patients with diabetes mellitus for many years [33]. In line with these findings, our data also demonstrate that elevated levels of these enzymes are associated with diabetic acromegaly. This suggests that liver enzyme assessments may be a valuable tool for assessing the early metabolic risk associated with this condition.

When investigating the biochemical profiles of patients with diabetic acromegaly, we observed significantly higher concentrations of cholesterol, triglycerides (TG), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) compared to the healthy control group (****P<0.0001) (Fig. 3). This observation may be explained by the fact that elevated IGF-1 levels in these patients may induce adipocyte breakdown and inhibit lipid uptake, leading to increased circulating lipid concentrations [34]. In contrast to our findings, a study by Berg et al. (2010) reported that patients with acromegaly had lower LDL levels and no significant difference in TG levels compared to healthy individuals [35].

Ectopic fat deposition in the liver and muscle has been proposed as one of the mechanisms involved in the pathogenesis of insulin resistance in acromegaly [36-38] although the evidence for this is mixed. For instance, while some studies suggest hepatic lipid accumulation occurs in active acromegaly [39], others have shown that liver lipid content is significantly lower in acromegaly patients compared to healthy subjects [40].

Another objective of this study was to investigate the potential association between diabetic acromegaly and CMV infection. Interestingly, we found a positive correlation between diabetic acromegaly and CMV infection. This finding raises the question of whether CMV infection might play a role in the development or progression of diabetic acromegaly.

While the mechanisms underlying this potential association are unclear, it is worth noting that the relationship between persistent CMV infection and autoimmune type 1 diabetes has been attributed to several factors. For example, CMV infection might trigger an immune response to viral antigens expressed on host cells or to host-cell-specific antigens that are revealed as a result of infection. Moreover, in certain conditions, such as a specific genetic background or exposure to certain environmental factors (e.g., drugs, nutrition, toxins, other infections), recurrent CMV infection may contribute to the development of beta-cell-specific autoimmune disease [41].

Consistent with the idea that CMV can infect pancreatic beta cells, experimental evidence indicates that CMV can infect these cells both in vivo and in vitro [41]. Moreover, Wang et al. (2022) showed that chronic viral infection of beta cells led to the synthesis and secretion of alpha-interferon, which in turn triggered class I MHC hyperexpression on neighboring endocrine cells. This finding is similar to observations of aberrant class II MHC antigen expression on beta cells in patients with type 1 diabetes [42].

Our findings suggest that CMV infection may influence lipid metabolism and potentially contribute to lipid deposition, as evidenced by the observed increases in cholesterol, triglyceride, and LDL levels. This is consistent with previous studies, which have shown that CMV infection can lead to significant elevations in cholesterol and triglycerides in humans, promoting their accumulation within the arterial wall [43-45]. For example, CMV infection has been shown to alter the host lipidome profile and modulate the expression of several genes and microRNAs involved in cholesterol metabolism, highlighting the potential for viral influence on lipid homeostasis [43-45]. However, further research is needed to elucidate the precise mechanisms by which CMV infection may contribute to dyslipidemia in the context of diabetic acromegaly.

This study is limited by the relatively small sample size and the lack of direct liver function assessments. While histological examination of liver biopsy samples is considered the gold standard for diagnosing liver abnormalities, it was not feasible to include it in this study due to the invasive nature of the procedure, potential risks to patients, high cost, and the possibility of sampling errors [46].

In conclusion, patients with diabetic acromegaly exhibited insulin resistance, as evidenced by significantly elevated levels of IGF-1, insulin, and HOMA-IR. This insulin resistance may be further exacerbated by increased lipolysis, as suggested by the elevated levels of cholesterol, triglycerides, LDL, and VLDL observed in these patients. Furthermore, we observed significantly elevated levels of TNF-α and IL-10, suggesting a role for inflammatory dysregulation in diabetic acromegaly. These elevated cytokine levels are consistent with the presence of insulin resistance and may serve as potential immunological markers for this condition. Additionally, the significantly elevated liver enzymes (ALT, AST, and ALP) in our patient cohort suggest that liver function may be impacted in diabetic acromegaly and could contribute to the pathogenesis of this disorder. Our finding that CMV infection was more prevalent in the acromegaly group (23.5%) compared to healthy controls (1.9%), coupled with the observation of significantly elevated TNF-α and IL-10 levels in CMV-positive samples, raises the possibility that CMV infection may contribute to the pathogenesis of diabetic acromegaly, potentially by increasing susceptibility to viral infections or exacerbating inflammation. However, further research is warranted to elucidate the precise mechanisms underlying these associations.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests associated with this manuscript.

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