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Article

Twenty-Four-Month rhGH Intervention: Insights into Redox Regulation, Vascular Biomarkers, and Body Composition in Adult GHD Patients

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Abstract

Adult growth hormone deficiency (GHD) is linked to increased cardiovascular and metabolic risk due to oxidative stress (OS), endothelial dysfunction, and adverse body composition. Long-term systemic effects of recombinant human growth hormone (rhGH) therapy remain insufficiently defined. This study assessed the impact of 24-month rhGH replacement on OS, vascular markers, body composition, and bone mineral density (BMD) in adults with severe GHD. Fifteen adults with confirmed GHD received rhGH for 24 months. Serum insulin-like growth factor -1 (IGF-1), oxidized LDL (Ox-LDL), thioredoxin (Trx), 8-oxoguanine DNA glycosylase (OGG1), E-selectin, ICAM-1, and VCAM-1 were measured at baseline, 12, and 24 months. Body composition and BMD were evaluated by DXA. IGF-1 increased significantly at 12 and 24 months ($p < 0.001$). Ox-LDL decreased markedly ($p < 0.00001$), while Trx and OGG1 increased ($p < 0.05$). Levels of E-selectin, ICAM-1, and VCAM-1 declined, indicating improved endothelial function. Lean body mass and BMD (lumbar spine and femoral neck) increased, whereas body fat percentage decreased. Lipid profiles were unchanged. Significant correlations were observed between vascular markers and adiposity, and between BMD, triglycerides, and IGF-1. A 24-month rhGH therapy improves redox balance, vascular function, and body composition in adults with severe GHD, supporting the use of redox and vascular biomarkers to monitor treatment efficacy.

Keywords: growth hormone deficiency; oxidized low-density lipoprotein; thioredoxin; vascular cell adhesion molecule-1; intercellular adhesion molecule-1; 8-oxoguanine DNA glycosylase 1

1. Introduction

Growth hormone deficiency (GHD) is a clinically recognized syndrome characterized by inadequate secretion of growth hormone (GH). In adults, it may represent the persistence of childhood-onset deficiency (CO-GHD) or arise de novo as adult-onset GHD (AO-GHD), with an estimated prevalence of approximately 2–3 cases per 10,000 individuals [1]. AO-GHD is consistently associated with increased cardiovascular risk, driven by dyslipidemia, visceral adiposity, endothelial dysfunction, and chronic low-grade inflammation [2–4]. Beyond these metabolic disturbances, GHD is marked by a broadened profile of vascular abnormalities that further amplify cardiovascular vulnerability. A central feature of its pathophysiology is endothelial dysfunction, reflected by reduced nitric oxide (NO) bioavailability and upregulated expression of adhesion molecules, including selectins, which collectively contribute to early atherogenic processes.

As demonstrated in our previous study and supported by existing literature, patients typically exhibit an atherogenic lipid profile—marked by elevated low-density lipoprotein cholesterol (LDL-

C) and triglycerides (TG), alongside reduced high-density lipoprotein cholesterol (HDL-C) - together with increased arterial stiffness, oxidative stress (OS), and diminished NO bioavailability [5]. These factors collectively accelerate atherogenesis [6–8]. Considering the central role of atherosclerosis in cardiovascular disease (CVD), heart failure, and thrombotic complications, understanding its underlying mechanisms in GHD remains essential. The interplay between oxidized low-density lipoprotein (ox-LDL), thioredoxin (Trx), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin offers valuable mechanistic insights into atherosclerosis pathogenesis within the GHD context. Ox-LDL contributes significantly to endothelial dysfunction, inflammation, and plaque formation by reducing NO availability and increasing OS [9–11]. Additionally, it induces the expression of adhesion molecules, facilitating leukocyte adhesion and transmigration into the vascular intima, thereby promoting inflammation and plaque progression [12]. Trx, a major endogenous antioxidant, counteracts OS by scavenging reactive oxygen species (ROS), thereby protecting endothelial integrity and limiting oxidative damage [13,14]. Moreover, it inhibits pro-inflammatory pathways involved in atherogenesis [15]. Adhesion molecules VCAM-1, ICAM-1, and E-selectin are upregulated in response to oxidative and inflammatory stimuli, enhancing immune cell recruitment to the endothelium and aggravating vascular inflammation and remodeling [16–18]. Furthermore, 8-oxoguanine DNA glycosylase 1 (OGG1) plays a critical role in the base excision repair pathway by removing oxidatively damaged guanine from DNA, thus preserving genomic stability [19]. Reduced OGG1 activity has been associated with increased susceptibility to doxorubicin-induced cardiotoxicity, accelerated vascular aging, and worsened endothelial dysfunction in atherosclerosis models [20]. OGG1 deficiency leads to accumulation of oxidative DNA lesions, intensifying vascular inflammation and contributing to CVD pathogenesis [21]. Given the pivotal role of atherosclerosis in CVD, heart failure, and thrombotic events, elucidating molecular mechanisms of vascular dysfunction in GHD remains a research priority. Although recombinant human growth hormone (rhGH) therapy has demonstrated improvements in metabolic and vascular parameters, the specific contributions of Trx, OGG1, VCAM-1, ICAM-1, and E-selectin—and their interactions with lipid metabolism and body composition—are yet to be fully defined [22–24]. Consequently, data on endothelial and OS biomarkers in this setting remain limited.

This study aimed to evaluate the effects of 24-month rhGH therapy on cardiovascular and metabolic parameters in adults with severe GHD, with particular focus on biomarkers of OS and endothelial dysfunction, including ox-LDL, Trx, OGG1, VCAM-1, ICAM-1, and E-selectin. By characterizing changes in these markers during long-term treatment, the research seeks to enhance understanding of the mechanisms linking GHD to increased cardiovascular risk. The findings may facilitate integration of these biomarkers into clinical monitoring, enabling improved risk stratification and supporting personalized therapeutic strategies to reduce long-term CVD risk in this population.

2. Results

2.1. Biochemical Analysis

2.1.1. Lipid Profile

No statistically significant changes in the lipid profile were observed (Table 1).

Table 1. The investigated biochemical parameters in the studied group.

Parameter				
s	Initially	After 12 mth	After 24 mth	
				p* value (0 vs 12 mth)
				p** value (0 vs 24 mth)

IGF-1 (ng/mL)	47.07 (8.57-138.8)	155.1 (36.04-265.1)	153.19 (58.02-303.9)	<0.001	<0.001
Ox-LDL (ng/mL)	1643 (1233-1910)	1623 (1066-2154)	1187 (919.5-1887)	<0.05	<0.00001
Trx (ng/mL)	3.90 (2.66-6.88)	4.59 (2.18-11.6)	5.1 (2.7-10.2)	0.38	<0.05
E-selectin (pg/mL)	5736 (1043-14414)	5649 (2040-9500)	3828 (717.4-7692)	0.54	<0.001
P-selectin (pg/mL)	83493 (35819-147352)	95089 (37656-188437)	91296 (41620-121511)	0.20	0.37
ICAM-1 (pg/mL)	99269 (44598-130792)	102415 (38572-146950)	79565 (23092-129154)	0.79	<0.05
VCAM-1 (ng/mL)	953.8 (753.1-1258)	1001 (761-1394)	838.1 (532-993.7)	0.62	=0.05
OGG-1 (ng/mL)	4.14 (2.53-5.7)	5.42 (2.4-8.63)	6.8 (3.7-12.8)	0.65	<0.05
Cholesterol (mg/dL)	201 (114-302)	199 (114-295)	200.4 (114-302)	0.69	0.13
LDL (mg/dL)	126 (65-219)	131 (58-216)	127 (65-219)	0.20	0.49
HDL (mg/dL)	43 (24-85)	50 (27-80)	46.6 (24-79)	0.20	0.09
TG (mg/dL)	120 (51-684)	120.5 (45-326)	153.3 (51-684)	0.67	0.35

Abbreviations: **IGF-1**: insulin like growth factor type 1; **Ox-LDL**: oxidized low-density lipoprotein, **Trx**: thioredoxin; **VCAM-1**: vascular cell adhesion molecule-1; **ICAM-1**: intercellular adhesion molecule-1; **OGG-1**: 8-oxoguanine DNA glycosylase 1; **LDL**: low-density lipoprotein; **HDL**: high-density lipoprotein; **TG**: triglycerides.

2.1.2. IGF-1

Serum insulin-like growth factor-1 (IGF-1) concentrations increased significantly after both 12 and 24 months of rhGH therapy compared with baseline values ($p < 0.001$ for both time points; Table 1).

2.1.3. Ox-LDL

A significant reduction in Ox-LDL levels was observed after 12 months of rhGH therapy ($p < 0.05$), followed by an even more pronounced decrease after 24 months compared with baseline ($p < 0.00001$; Table 1, Figure 1).

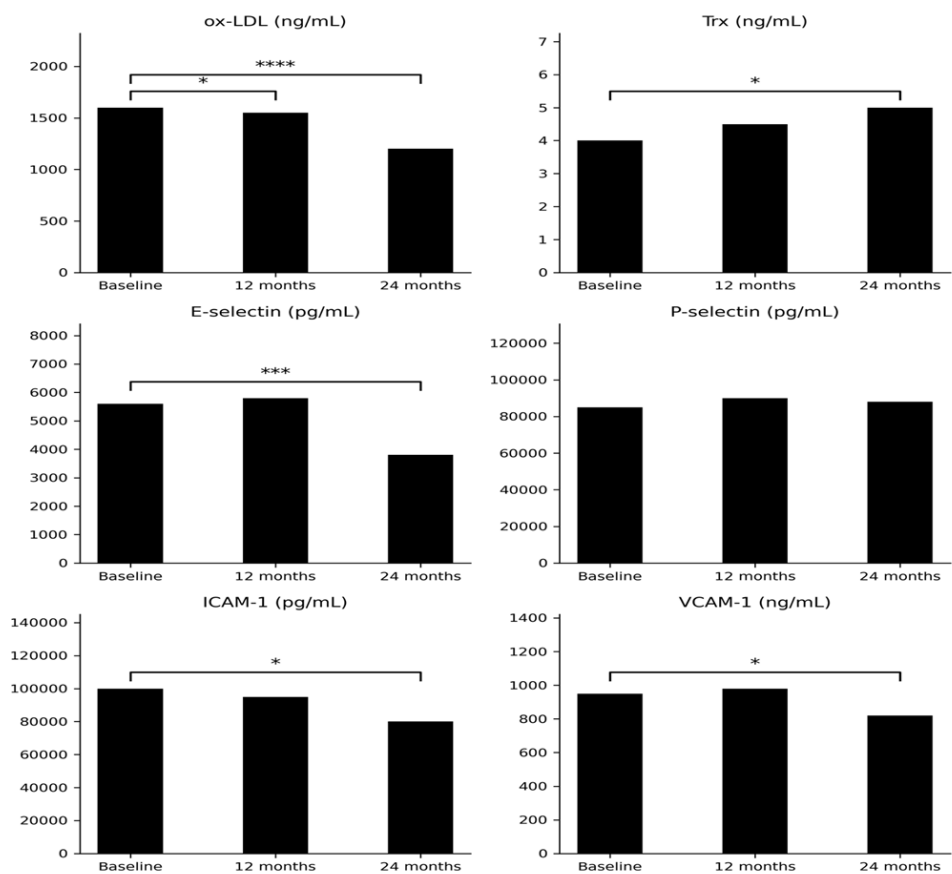


Figure 1. Longitudinal changes in ox-LDL, Trx, E-selectin, P-selectin, ICAM-1, and VCAM-1 during 24-month rhGH therapy at baseline, 12 months, and 24 months. Statistical significance is indicated by brackets; $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***), $p < 0.0001$ (****) vs. baseline.

2.1.4. Thx

A significant higher concentration of Trx after 24 months therapy was observed compering to baseline value ($p < 0.05$) (Table 1, Figure 1).

2.1.4. OGG-1

A statistically significant increase in OGG-1 concentration was observed after 24 months of therapy compared with baseline ($p < 0.05$; Table 1).

2.1.4. E-selectin and P-selectin

E-selectin concentrations decreased significantly after 24 months of rhGH therapy compared with baseline ($p < 0.001$), whereas no statistically significant changes were observed in P-selectin levels across the studied groups (Table 1, Figure 1).

2.1.4. I-CAM1 and VCAM-1

After 24 months of rhGH therapy, the GHD patients demonstrated a statistically significant reduction in both ICAM-1 ($p < 0.05$) and VCAM-1 ($p = 0.05$) concentrations compared with baseline (Table 1, Figure 1).

Body Composition Evaluation

Total body mass changed significantly after 24 months of therapy ($p = 0.05$). Fat mass (%) decreased significantly at 12 and 24 months compared with baseline ($p = 0.04$ and $p < 0.001$,

respectively), although an increase in absolute fat mass (g) was noted at 24 months ($p = 0.05$). Lean mass (g) increased significantly after 24 months of treatment ($p = 0.0008$). Significant improvements were also observed in L1–L4 BMD, femoral neck BMD, and femoral neck Z-score at 24 months compared with baseline ($p = 0.04$, $p = 0.0002$, and $p = 0.0018$, respectively). However, no statistically significant changes in BMC were detected (Table 2).

Table 2. The investigated bioimpedance parameters in the studied group.

Parameters	Initially	After 12 mth	After 24 mth	p* value (0 vs 12 mth)	p** value (0 vs 24 mth)
Total mass (kg)	78.6 (39.6-167.3)	78.0 (62.3-156)	86.9 (59.8-167.3)	0.51	0.05
Tissue fat %	37.5 (27.4-50.4)	38.4 (26.7-48.7)	39.7 (27.4-60.4)	0.04	0.001
Fat tissue (g)	28434 (13891-82462)	29937 (16939-67385)	33868 (16881-82462)	0.08	0.05
Lean mass (g)	48646 (23996-81228)	45550 (36530-84977)	50021 (34296-81228)	0.49	0.0008
BMC	2547 (1261-3778)	2568 (1770-3650)	2731 (1844-3778)	0.42	0.72
L1-L4 BMD	1.09 (0.8-1.6)	1.1 (0.9-1.5)	1.2 (0.9-1.6)	0.73	0.04
L1-L4 T score	-1.1 (-3.4-3.2)	-0.3 (-2.0-2.4)	-0.1 (-2.5-3.2)	0.17	0.1
L1-L4 Z score	-1.1 (-3.7-3.0)	-0.9 (-2.3-2.0)	-0.3 (-2.2-3.0)	0.73	0.13
Neck BMD	0.95 (0.7-1.4)	0.96 (0.77-1.5)	1.04 (0.74-1.4)	0.29	0.0002
Neck T score	-0.8 (-2.1-2.3)	-0.6 (-1.9-2.5)	-0.63 (-2.1-2.3)	0.79	0.92
Neck Z score	-0.9 (-2.2-2.0)	-1.0 (-2.0-2.3)	-0.43 (-2.1-2.0)	0.72	0.0018

Abbreviations: **BMC**: bone mineral content; **BMD**: bone mineral density; “-”: minus.

2.2. Correlations

2.2.1. Ox-LDL and Related Correlations

A significant positive correlation was observed between ox-LDL and P-selectin after 24 months of therapy ($p = 0.02$, $R = 0.60$). Additionally, ox-LDL correlated positively with lean mass (g) at 12 months ($p = 0.02$, $R = 0.63$) (Table 3).

Table 3. Spearman`s correlation coefficients between parameters and other metabolic markers in group initially and during the treatment.

Parameters	Initially	After 12 months	After 24 months
Ox-LDL (ng/mL) vs P-selectin (pg/mL)	NS	NS	$p=0.02$ $R=0.60$
Ox-LDL (ng/mL) vs Lean (g)	NS	$p=0.02$ $R=0.63$	NS
E-selectin (pg/mL) vs VCAM-1 (ng/mL)	NS	NS	$p=0.05$ $R=0.57$

E-selectin (pg/mL) vs HDL (mg/dL)	NS	NS	p=0.01 R=-0.67
E-selectin (pg/mL) vs Waist (cm)	NS	NS	p=0.04 R=0.57
Trx (ng/mL) vs Tissue (g)	NS	NS	p=0.04 R=0.71
Trx (ng/mL) vs Vitamin D (mg/dL)	NS	NS	p=0.01 R=-0.69
Trx (ng/mL) vs Fat (g)	NS	NS	p=0.01 R=0.71
ICAM-1 (pg/mL) vs BMI (kg/m2)	NS	NS	p=0.04 R=0.55
ICAM-1 (pg/mL) vs Waist (cm)	NS	p=0.03 R=0.58	p=0.04 R=0.57
ICAM-1 (pg/mL) vs Hip (cm)	NS	NS	p=0.02 R=0.61
ICAM-1 (pg/mL) vs LDL (mg/L)	NS	NS	p=0.04 R=-0.57
P-selectin (pg/mL) vs BMI (kg/m2)	NS	NS	p=0.02 R=0.64
P-selectin (pg/mL) vs Tissue (g)	NS	NS	p=0.03 R=0.63
P-selectin (pg/mL) vs Fat (g)	NS	p=0.04 R=0.57	NS
VCAM-1 (ng/mL) vs glucose (mg/dL)	NS	NS	p=0.03 R=0.58
LDL (mg/dL) vs L1-L4 Z-score	NS	NS	p=0.03 R=-0.58
LDL (mg/dL) vs Lean (g)	NS	NS	p=0.01 R=-0.33
HDL (mg/dL) vs IGF-1 (ng/mL)	NS	NS	p=0.02 R=-0.59
HDL (mg/dL) vs Lean (g)	NS	p<0.01 R=-0.73	p=0.01 R=-0.68
TG (mg/dL) vs L1-L4 T-score	NS	NS	p=0.03 R=0.60
TG (mg/dL) vs L1-L4 Z-score	NS	NS	p=0.05 R=0.54
Lean (g) vs L1-L4 BMD	NS	p<0.001 R=0.78	p=0.05 R=0.55
Lean (g) vs L1-L4 T-score	NS	p=0.01 R=0.67	NS
Lean (g) vs L1-L4 Z-score	NS	p=0.04 R=0.53	NS
Lean (g) vs Neck BMD	NS	p<0.01 R=0.72	p=0.01 R=0.69
Lean (g) vs Neck T-score	NS	p=0.02 R=0.68	p=0.03 R=0.60
Lean (g) vs Neck Z-score	NS	p=0.01 R=0.67	NS

Abbreviations: IGF-1: insulin like growth factor type 1; Ox-LDL: oxidized low-density lipoprotein, Trx; thioredoxin; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; OGG-1:

8-oxoguanine DNA glycosylase 1; **LDL**: low-density lipoprotein; **HDL**: high-density lipoprotein; **TG**: triglycerides; **BMC**: bone mineral content; **BMD**: bone mineral density; “-”: minus; **BMI**: body mass index.

2.2.2. Endothelial Adhesion Molecules

E-selectin demonstrated significant positive correlations with VCAM-1 ($p = 0.05$, $R = 0.57$) and waist circumference ($p = 0.04$, $R = 0.57$), as well as a negative correlation with HDL-C at 24 months ($p = 0.01$, $R = -0.67$). It also correlated positively with BMI ($p = 0.02$, $R = 0.64$) and tissue mass (g) ($p = 0.03$, $R = 0.63$) at 24 months, and with fat mass (g) at 12 months ($p = 0.04$, $R = 0.57$). VCAM-1 was positively associated with glucose concentration at 24 months ($p = 0.03$, $R = 0.58$). ICAM-1 levels correlated positively with BMI ($p = 0.04$, $R = 0.55$) and hip circumference ($p = 0.02$, $R = 0.61$) at 24 months, as well as with waist circumference at 18 months ($p = 0.03$, $R = 0.58$). A significant negative correlation with LDL-C was also observed ($p = 0.04$, $R = -0.57$). The above correlations are presents in Table 3.

2.2.3. Redox-Related Marker

Trx showed positive correlations with tissue mass (g) and fat mass (g) ($p = 0.04$, $R = 0.71$; $p = 0.01$, $R = 0.71$, respectively), and a negative correlation with serum vitamin D levels ($p = 0.01$, $R = -0.69$) (Table 3).

2.2.4. Lipid Profile Correlations

LDL-C demonstrated inverse correlations with the L1–L4 Z-score ($p = 0.03$, $R = -0.58$) and with lean mass (g) at 24 months ($p = 0.01$, $R = -0.33$). HDL-C correlated negatively with IGF-1 ($p = 0.02$, $R = -0.59$) and with lean mass (g) at both 12 months ($p < 0.01$, $R = -0.73$) and 24 months ($p = 0.01$, $R = -0.68$). Moreover, positive associations were found between TG levels and both the L1–L4 T-score ($p = 0.03$, $R = 0.60$) and L1–L4 Z-score ($p = 0.05$, $R = 0.54$) at 24 months (Table 3).

2.2.5. Body Composition and Bone Parameters

Lean mass (g) showed consistent positive correlations with L1–L4 BMD, femoral neck BMD, and femoral neck T-score at both 12 and 24 months (all $p < 0.05$). At 12 months, additional correlations were observed between lean mass and the L1–L4 T-score ($p = 0.01$), L1–L4 Z-score ($p = 0.04$), and femoral neck Z-score ($p = 0.01$) (Table 3).

3. Discussion

Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

In patients with GHD, numerous studies have demonstrated vascular alterations typical of early atherosclerosis. The most frequently reported findings include impaired endothelium-dependent vasodilation, increased intima-media thickness (IMT), elevated indices of arterial stiffness, and heightened vascular inflammatory activity [25,26]. These changes are driven by upregulated pro-inflammatory cytokine activity, increased expression of adhesion molecules, enhanced leukocyte adhesion and infiltration within the vascular wall, and lipid abnormalities—such as low HDL and elevated LDL—that further exacerbate endothelial inflammation. Collectively, these disturbances promote a distinctly pro-atherogenic and pro-thrombotic endothelial phenotype. Treatment with rhGH in adults with GHD has been shown to improve endothelial function, enhance NO bioavailability, reduce IMT and arterial stiffness, and ameliorate lipid profiles while diminishing vascular inflammation [25].

By evaluating a combination of traditional biochemical markers and less commonly assessed redox and vascular indicators, our findings contribute to a more integrated understanding of GH's therapeutic impact. An early and important finding of this study was the marked rise in IGF-1

concentrations at both 12 and 24 months ($p < 0.001$), demonstrating the effective biological action of rhGH and its broad metabolic influence. IGF-1, as the main mediator of GH effects, plays a crucial role in reducing inflammation and OS by suppressing pro-inflammatory cytokines such as IL-6 and TNF- α and by boosting antioxidant defenses, including enzymes like superoxide dismutase (SOD) [27–29]. These protective mechanisms help maintain endothelial health and slow down the development of atherosclerosis. It is worth noting that obesity—particularly with a BMI between 30 and 35 kg/m²—is linked to decreased IGF-1 levels, likely due to factors such as fatty liver, increased insulin levels, and changes in IGF-binding proteins [30,31]. Conversely, some studies, including that of Andersen et al., have reported normal or even elevated IGF-1 levels in individuals with obesity [32]. In this context, given that 26.6% of our study participants were classified as obese, IGF-1 values were interpreted using a -2 SDS cutoff, in accordance with current clinical guidelines [33]. Numerous prior investigations have consistently demonstrated substantial increases in serum IGF-1 levels following rhGH therapy in adults with GHD, underscoring the biological efficacy of treatment. Bengtsson et al. reported a significant rise in IGF-1 after long-term rhGH administration, particularly among male patients, accompanied by improvements in body water and overall body composition [34]. Similarly, Christiansen et al. observed early increases in IGF-1, lean body mass, and total body water, together with reductions in fat mass after just 12 months of GH therapy ($p < 0.001$) [35]. These findings are consistent with our results, which demonstrated a significant increase in IGF-1 levels at both 12 and 24 months ($p < 0.001$), further supporting IGF-1 as a robust early biomarker of metabolic and vascular responsiveness to rhGH in adults with GHD.

Body composition analysis in our study confirmed the dual anabolic and lipolytic effects of rhGH therapy. Lean mass increased significantly ($p = 0.0008$), while fat percentage decreased markedly ($p < 0.001$), indicating an improved muscle-to-fat ratio. Interestingly, total fat mass showed a slight but significant increase ($p = 0.05$), which may reflect redistribution between visceral and subcutaneous compartments or compensatory adaptations in fat storage. These findings are consistent with the results of Johannsson et al. and Salomon et al., who reported improved body composition following GH replacement, although they contrast with observations by Jørgensen et al., who documented sustained reductions in total fat mass without evidence of redistribution [36–38]. The positive correlations observed between P-selectin and both BMI and fat mass ($R = 0.64$ and 0.57 , respectively) further highlight the inflammatory burden imposed by adiposity, emphasizing the role of adipose tissue as an active endocrine organ contributing to vascular activation.

Skeletal outcomes were similarly favorable. BMD increased significantly at both the lumbar spine (L1–L4; $p = 0.04$) and femoral neck ($p = 0.0002$), aligning with findings from Rahim et al., who demonstrated enhanced bone turnover and mineralization during GH therapy [39]. Strong positive correlations between lean mass and BMD (e.g., $R = 0.78$ for L1–L4) reinforce the interdependence between muscle and bone tissue, particularly in the context of GHD, where mechanical loading and anabolic signaling are impaired. In contrast, BMC remained unchanged, supporting previous evidence that early skeletal responses to GH are driven predominantly by improvements in bone architecture and density rather than by increases in absolute mineral content. This distinction is especially relevant during the initial phases of treatment, when structural remodeling precedes mineral accrual. Additionally, the positive correlations between TG and both L1–L4 T- and Z-scores ($R = 0.60$ and 0.54) suggest that lipid availability may influence bone metabolism, potentially through pathways involving PPAR activation or adipokine signaling, as proposed by Zhou et al. [40]. The inverse associations observed between HDL and both IGF-1 and lean mass further illustrate the complex systemic effects of GH on lipid transport, energy utilization, and tissue remodeling.

A following notable finding in our study was the marked reduction in Ox-LDL concentrations observed after both 12 and 24 months of rhGH therapy ($p < 0.00001$), highlighting a potential protective effect of GH on vascular health. Ox-LDL is a key mediator of atherogenesis, promoting endothelial dysfunction, inflammation, and foam cell formation [41,42]. Its decline suggests improved oxidative balance and reduced lipid peroxidation, which are consistent with previously reported GH-mediated enhancements in endothelial function. Colao et al. demonstrated that long-

term GH replacement in GHD patients significantly improved endothelial-dependent vasodilation, partly via increased NO bioavailability and attenuation of OS markers [43]. Similarly, Wu et al. described how GH and IGF-1 signaling can downregulate ROS production and inflammatory responses in the vascular endothelium, thereby mitigating Ox-LDL-induced injury [44]. These findings support the hypothesis that rhGH therapy not only corrects hormonal deficiency but also exerts systemic antioxidant effects, which may contribute to the reduced cardiovascular risk observed in treated GHD patients. The consistent decline in Ox-LDL levels throughout the study period reinforces its potential utility as a sensitive biomarker of vascular response to GH replacement therapy.

The increase in Trx levels observed after 24 months of rhGH therapy ($p < 0.05$), together with a concurrent decrease in Ox-LDL, indicates a strengthened antioxidant response to treatment. Trx is a key intracellular redox regulator that protects cells from oxidative injury by reducing ROS, maintaining protein thiol homeostasis, and modulating redox-sensitive signaling pathways [45]. Therefore, the rise in Trx suggests that rhGH therapy may enhance endogenous antioxidant defenses, potentially counteracting OS associated with GHD. This interpretation is consistent with findings by Andoh et al., who demonstrated a protective role of Trx against oxidative injury in vascular tissue, particularly through its ability to preserve endothelial integrity and limit lipid peroxidation [46]. The simultaneous reduction in Ox-LDL further reinforces this protective profile, as Ox-LDL is a well-established marker and mediator of atherosclerotic progression. Lower Ox-LDL levels may reflect decreased oxidative modification of lipids, improved lipoprotein handling, or enhanced scavenging of ROS—all of which support the notion that rhGH treatment mitigates vascular OS.

The inverse correlation between Trx and vitamin D ($R = -0.69$; $p = 0.01$) observed in our cohort may indicate a complex hormonal and nutritional interplay in redox regulation. Although the underlying mechanism remains unclear, one possibility is that lower vitamin D levels stimulate compensatory upregulation of antioxidant pathways such as the Trx system. Alternatively, vitamin D may modulate redox signaling indirectly through effects on inflammation, calcium homeostasis, or adipose tissue function, thereby influencing Trx expression. Further mechanistic studies are needed to elucidate whether this relationship is causal, compensatory, or merely reflective of broader metabolic alterations in adults with GHD undergoing rhGH therapy.

Our findings suggest a potential role of GH in DNA repair mechanisms, as evidenced by a significant increase in OGG1 levels after 24 months of therapy ($p < 0.05$). OGG1, a key glycosylase involved in the excision of oxidized guanine lesions, is upregulated in response to OS [47]. The observed positive correlation between Ox-LDL and OGG1 supports the notion that lipid peroxidation may trigger compensatory DNA repair pathways. This aligns with data from González-Duarte et al., who reported reduced OGG1 activity in GHD patients and linked it to increased cardiovascular vulnerability [48]. Similar trends were also described by Mancini et al., who observed impaired redox-related DNA repair in untreated GHD, suggesting that GH replacement may partially restore genomic stability under oxidative conditions [49].

Despite clear improvements in redox status and endothelial markers, no significant changes were observed in traditional lipid parameters (LDL, HDL, TG) over the course of therapy. This is consistent with findings by Rudling et al., who proposed that GH modulates lipid metabolism primarily through hepatic LDL receptor expression and regulation of VLDL turnover—effects that may not be fully captured by standard fasting lipid profiles [50]. Interestingly, we observed an inverse correlation between IGF-1 and HDL levels ($p = 0.02$; $R = -0.59$), which contrasts with the results of Capaldo et al., who documented an increase in HDL following GH replacement [51]. Additionally, HDL showed a strong negative correlation with lean mass at both 12 and 24 months ($p < 0.01$; $R = -0.73$ and $p = 0.01$; $R = -0.68$, respectively), suggesting a complex, potentially bidirectional interaction between anabolic processes and lipid remodeling. This may reflect a shift in lipid distribution or function rather than concentration, emphasizing the need to interpret static lipid values within a broader metabolic context.

Endothelial function improved significantly in our study, as indicated by the reduction in circulating adhesion molecules E-selectin, ICAM-1, and VCAM-1. These molecules play key roles in leukocyte adhesion, transmigration, and the propagation of vascular inflammation, and are well-established markers of endothelial dysfunction. Their decline following rhGH therapy suggests a restoration of endothelial homeostasis and a reduction in subclinical vascular inflammation. Our results are consistent with previous reports by Christ et al. and Pfeifer et al., who observed time-dependent improvements in endothelial markers in adult GHD patients treated with GH [52,53]. These effects have been attributed to enhanced NO bioavailability, reduced OS, and improved insulin sensitivity—factors that collectively support endothelial repair. However, Franco et al. found no significant changes in E-selectin levels after 12 months of treatment, highlighting potential variability based on therapy duration, baseline inflammation, or individual response [54]. It is possible that improvements in endothelial biomarkers occur gradually and may only become evident with prolonged GH exposure. Additionally, early effects of GH on vascular function may be functional (e.g., NO-mediated vasodilation) rather than structural (e.g., reduced expression of adhesion molecules), which could explain the delayed changes observed in circulating markers.

Correlation analyses in our study further highlight the pro-inflammatory role of adiposity in endothelial dysfunction. E-selectin showed a positive association with waist circumference and VCAM-1, and a negative correlation with HDL ($R = -0.67$, $p = 0.01$), suggesting that central fat accumulation contributes to vascular inflammation and impaired lipid handling. Similarly, ICAM-1 correlated positively with BMI and waist-to-hip ratio, and negatively with LDL ($R = -0.57$), indicating that increased adiposity may promote chronic low-grade inflammation while altering lipid transport or clearance. These findings are consistent with earlier studies by Mulhem et al. and Matsumoto et al., which identified elevated adhesion molecule levels as early indicators of cardiovascular risk in individuals with obesity or metabolic syndrome [55,56]. The observed positive correlation between VCAM-1 and fasting glucose in our cohort reinforces the link between glycemic dysregulation and endothelial stress, suggesting that metabolic disturbances may amplify vascular inflammation through upregulation of adhesion molecules. Collectively, these associations underscore the complex crosstalk between adipose tissue, lipid metabolism, and endothelial activation in GHD.

Summarizing, this study demonstrates that 24-month rhGH therapy in adults with severe GHD improves redox status, endothelial function, and body composition. Significant reductions in Ox-LDL and adhesion molecules, together with increases in Trx and OGG1, indicate that rhGH replacement exerts antioxidant and vascular-protective effects that extend beyond its classical metabolic actions. Positive changes in BMD and lean mass further support its anabolic and skeletal benefits. The strengths of this study include its multidimensional evaluation of biochemical, vascular, and structural parameters, as well as the incorporation of less commonly investigated markers such as Trx and OGG1. However, several limitations should be acknowledged. The relatively small sample size and lack of a placebo-controlled group reduce the generalizability of the results, and the observational design precludes causal inference. Variability in lipid responses may reflect unmeasured confounders, including diet, physical activity, and genetic predisposition. In addition, the absence of detailed lipoprotein subfraction assessment and inflammatory cytokine profiling limits the resolution with which GH-related metabolic and vascular changes can be characterized. Contemporary research on the molecular effects of rhGH in adult GHD remains limited, with much of the existing evidence derived from earlier trials lacking mechanistic depth.

Despite these limitations, the present work advances current understanding by integrating vascular, redox, and genomic markers, offering new insights into the potential mechanisms underlying the long-term systemic benefits of rhGH replacement. Further studies with larger cohorts and mechanistic endpoints are warranted to validate and expand upon these findings.

4. Materials and Methods

4.1. Studied Population

The study was conducted at the Department of Endocrinology, Diabetology, and Internal Medicine, Medical University of Bialystok, Poland, and was supported by grant APK.002.393.2021. A total of 15 participants (4 females, 11 males), aged 18–60 years, with a confirmed diagnosis of GHD were enrolled. Severe GHD was diagnosed based on clinical features, low IGF-1 concentrations—defined as values below –2 standard deviation scores (SDS) from the age- and sex-adjusted reference range, in accordance with current clinical guidelines—and peak GH levels below 3 ng/mL during hypoglycemia induced by insulin and/or glucagon stimulation tests. Hormonal assessments were performed after appropriate replacement of cortisol, thyroxine, and sex steroids, as per current recommendations. Three patients were diagnosed with de novo AO-GHD, while the remaining individuals had a history of CO-GHD and had received rhGH therapy during childhood, which had been discontinued between 1 and 20 years prior to the study. Fourteen participants had multiple pituitary hormone deficiencies (MPHD), while one patient had isolated GHD, confirmed by two GH stimulation tests (Table 4). Participants had no history of cardiovascular events, no current diagnosis of CVD, and were not receiving any medications known to influence cardiovascular risk (e.g., statins, ezetimibe, or antiplatelet therapy). In accordance with World Health Organization (WHO) guidelines, all patients were advised to engage in at least 150 minutes of moderate-intensity physical activity per week, distributed over several days, or at least 75 minutes of vigorous activity, or an equivalent combination using a 2:1 ratio (e.g., 75 minutes of vigorous plus 150 minutes of moderate activity). Obese individuals received dietary counseling to follow a calorie-reduction diet targeting a daily energy deficit of 500–1000 kcal. Two male patients (aged 18 and 25 years) had type 1 diabetes, diagnosed 6 months before study enrollment and treated with intensive functional insulin therapy using insulin analogs. Both achieved adequate metabolic control (glycated hemoglobin (HbA1c) < 6.5%). Exclusion criteria included poor general condition, uncontrolled diabetes (HbA1c > 7%), pre-proliferative or proliferative diabetic retinopathy, pregnancy, and any history of malignancy. All patients initiated rhGH therapy at starting doses of 0.2 mg/day (males) and 0.3 mg/day (females), with dose titration based on IGF-1 concentrations. The mean daily maintenance doses were 0.4 mg/day for men and 0.5 mg/day for women. Personalized rhGH substitution was well tolerated, and no adverse events were reported during the treatment period. Anthropometric measurements, including height and weight, were performed using standardized instruments. BMI was calculated by dividing body weight (kg) by height squared (m²). BMD and body composition were assessed using DXA. The patients were non-smokers, did not abuse alcohol, and had no other conditions affecting peripheral markers assessment. These data were collected from medical history, physical examination, and patient records. Venous blood samples (5.5 mL) were taken after fasting, centrifuged, and serum stored at -80°C.

Table 4. The investigated biochemical parameters in the studied group.

	Sex	Age (years)	Treatment (before rhGH)	Dose of rhGH	Etiology GHD	IGF-1 (ng/ml) initially	BMI (kg/m2) initially	CO-GHD in history
P1	F	41	HCT, L, D, Es/Pg	0.5 mg	CPGP	68.6	30.9	+
P2	M	25	L,T	0.5 mg	NFPM	62.8	24.8	+
P3	M	18	T	0.4 mg	CPH	27.3	22.8	+
P4	F	26	HCT, L, Es/Pg	0.6 mg	CPH	40.1	29.0	+
P5	M	19	D, L, T, HCT	0.3 mg	CPGP	74.8	34.9	+
P6	F	60	HCT, L	0.4 mg	ES	15.11	24.3	-
P7	M	20	L, HCT, T	0.3 mg	CPH	91.8	28.1	+
P8	M	23	-	0.3 mg	I	138.8	25.9	-
P9	F	38	L, HCT, Es/Pg	0.5 mg	NFPM	47.07	24.9	-

P10	M	18	T	0.2 mg	I	120.2	20.4	+
P11	M	28	L, HCT, T, D	0.3 mg	CPGP	22.6	27.1	+
P12	M	42	L, T, D	0.3 mg	CPGP	63.0	54.1	+
P13	M	36	HCT, L, T	0.5 mg	CPGP	48.9	21.5	+
P14	M	18	L, HCT, D, T	0.7 mg	CPGP	54.4	24.4	+
P15	M	25	L, HCT, T	0.5 mg	CPGP	8.6	35.8	+

Abbreviations: **GHD**: growth hormone deficiency; **rhGH**: recombinant human growth hormone; **P**: patient; **F**: female; **M**: male; **HCT**: hydrocortisone; **L**: levothyroxine; **Es/Pg**: estrogen/progesterone; **D**: desmopressin; **T**: testosterone; **CPH**: congenital pituitary hypoplasia; **CPGP**: craniopharyngioma postsurgical; **ES**: empty sella; **NFPM**: non-functioning pituitary macroadenoma; **CO-GHD** - childhood-onset growth hormone deficiency; **I**: idiopathic; **IGF-1**: insulin like growth factor type 1; **BMI**: body mass index.

4.2. Biochemical Measurement

Serum concentrations of IGF-1, total cholesterol (CHOL), LDL-C, HDL-C, TG, ox-LDL, Trx, OGG1, VCAM-1, ICAM-1, P-selectin, and E-selectin were assessed at baseline, after 12 months, and following completion of the 24-month rhGH therapy.

Serum IGF-1 levels were measured using the electrochemiluminescence immunoassay (ECLIA) method on a Roche Cobas e411 analyzer (Roche Diagnostics, 05061313 190; Sussex, UK) in accordance with the manufacturer’s protocol.

Lipid profile parameters, including CHOL, LDL-C, HDL-C, and TG, were determined using the enzymatic colorimetric method on a Roche Cobas c111 analyzer (Roche Diagnostics, Basel, Switzerland), with the following reagent kits: CHOL: 03039773190; LDL-C: 03039073390; HDL-C: 03037973219; TG: 03039773190.

OS and endothelial markers were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits, according to the manufacturers’ instructions: ox-LDL (Novus Biologicals, Bio-Techne, NBP3-18794; Minneapolis, MN, USA), Trx (XpressBio, XPEH0291; Frederick, MD, USA), OGG1 (Cloud-Clone Corp., SEC704Hu; Wuhan, China), VCAM-1 (Cloud-Clone Corp., SEA547Hu; Wuhan, China), ICAM-1 (Cloud-Clone Corp., SEA548Ca; Wuhan, China), and E-selectin (Cloud-Clone Corp., SEA029Hu; Wuhan, China).

All samples were analyzed in duplicate. Intra- and inter-assay variability were within the acceptable range specified by the respective manufacturers.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 9.0 software. Statistical significance was set at $p < 0.05$. Data distribution was assessed with the Shapiro-Wilk test, indicating non-normal distribution. Consequently, nonparametric tests, including the Mann-Whitney (**) and Kruskal-Wallis (*) tests, were used for inter-group comparisons. Spearman correlation analysis was conducted to evaluate relationships between parameters. Observational statistical analysis involved repeated-measures ANOVA and post hoc tests with Bonferroni corrections.

Dual-Energy X-Ray Absorptiometry and Body Composition

Body composition was assessed using DXA with a Hologic medical body analyzer (Hologic Inc., USA). This method allows for the precise measurement of BMD, bone mineral content (BMC), body mass, total body water (TBW), fat mass, lean mass, and BMI.

5. Conclusions

This study confirms that 24 months of rhGH therapy in adults with severe GHD leads to sustained increases in IGF-1 levels, demonstrating effective hormonal replacement and biological

responsiveness. GH therapy was associated with significant improvements in OS markers, including reductions in Ox-LDL and increases in Trx and OGG1, suggesting enhanced antioxidant capacity and activation of DNA repair pathways. Long-term treatment also resulted in decreased concentrations of endothelial adhesion molecules (E-selectin, ICAM-1, VCAM-1), indicating improved endothelial function and reduced vascular inflammation. Anabolic effects were reflected by increases in lean body mass and BMD at both the lumbar spine and femoral neck. While body fat percentage declined significantly, total fat mass showed variable responses, likely reflecting inter-individual differences in fat redistribution or metabolic adaptation. Classical lipid parameters (LDL, HDL, TG) remained unchanged, underscoring the need for more sensitive markers to capture GH-related changes in lipid metabolism. Correlations between lipid indices, adiposity, inflammatory markers, and endothelial function highlight the complex interplay among GH action, metabolic status, and cardiovascular risk.

Collectively, these findings demonstrate the broad multisystem benefits of rhGH therapy in adult GHD and provide new insights into its potential mechanisms, particularly in redox regulation, vascular protection, and tissue remodeling.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board. The Bioethics Committee of the Medical University of Bialystok approved the protocol for specimen collection.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript: IGF-1, insulin-like growth factor 1; Ox-LDL, oxidized low-density lipoprotein; Trx, thioredoxin; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; OGG-1, 8-oxoguanine DNA glycosylase 1; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; GHD, growth hormone deficiency; rhGH, recombinant human growth hormone; P, patient; F, female; M, male; HCT, hydrocortisone; L, levothyroxine; Es/Pg, estrogen/progesterone; D, desmopressin; T, testosterone; CPH, congenital pituitary hypoplasia; CPGP, craniopharyngioma postsurgical; ES, empty sella; NFPM, non-functioning pituitary macroadenoma; CO-GHD, childhood-onset growth hormone deficiency; I, idiopathic; “–”, minus.

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