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Review Article

Unveiling the Cardiovascular Impact of Growth Hormone: Insights into Physiology, Pathology, and Therapy

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ABSTRACT

The significance of height in boosting self-confidence has prompted some families to seek medical interventions to enhance their children's stature. One such intervention is hormone therapy using recombinant human growth hormone (rhGH), which has been employed in clinics since 1985, primarily for treating growth hormone deficiency (GHD). Over time, rhGH therapy has been utilized for various conditions where childhood short stature is not solely a result of inadequate growth hormone secretion, such as small for gestational age (SGA) or idiopathic short stature (ISS).

In addition to its effects on the skeletal system, growth hormone (GH) also plays a vital role in regulating cardiovascular function. There is growing evidence suggesting a correlation between abnormal GH levels—both elevated and deficient—and increased cardiovascular morbidity and mortality among patients with GH disorder. Notably, cardiovascular complications are not limited to pathological GH levels; even slight increases within the normal range have been linked to increased cardiovascular disease (CVD) events in healthy individuals.

These findings raise concerns about the potential long-term cardiovascular effects of rhGH therapy, especially among children without GH disorders. In this comprehensive review, we summarized recent research findings to provide insights into the physiological and pathophysiological effects of GH on the heart. We aimed to elucidate the long-term side effects of GH therapy and identify associated risk factors.

Keywords:
Growth Hormone
Insulin-Like Growth Factor I
Cardiovascular Diseases
Hormone Replacement Therapy

Introduction

The growth hormone (GH) is a peptide consisting of a single chain with 191 amino acids, characterized by a molecular weight of 22 kilodaltons (kDa). Structurally, it comprises four alpha helices, a hydrophobic core, and two disulfide bonds (Chen et al., 1989; De Vos et al., 1992). The gene encoding human growth hormone is situated on chromosome 17 and is expressed in the

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somatotropic cells of the anterior pituitary gland (Hartman et al., 1993). The regulation of GH secretion involves a negative feedback mechanism within the hypothalamic-pituitary axis. Specifically, the hypothalamus stimulates the pituitary gland to release GH by secreting growth hormone-releasing hormone (GHRH) in the ventromedial hypothalamic nucleus (VMN) (Fodor et al., 1994). Subsequently, GH promotes the synthesis and release of insulin-like growth factor-1 (IGF-I) in the liver. Elevated levels of IGF-I provide negative feedback by increasing somatostatin in the arcuate nucleus of the hypothalamus, thereby reducing GH secretion (Ceda et al., 1987).

Beyond its role in regulating GH secretion, IGF-1 mediates many of GH's anabolic effects, such as promoting linear growth and protein synthesis across various tissues (Dixit et al., 2021). IGF-1 primarily circulates in plasma bound to a family of proteins known as IGF-binding proteins (IGFBPs) (Allard and Duan 2018; Jehle et al., 2003). More than 90% of circulating IGF-1 is bound to IGFBPs, with only about 1% in free, unbound form. Six IGFBP types have been identified, each containing 200–300 amino acids. These binding proteins extend IGF-1's half-life while also modulating its interaction with its receptor (Allard and Duan 2018).

The receptors for GH and IGF-1 belong to the tyrosine kinase receptor family and are widely distributed throughout the body, including in bone, skeletal muscle, and cardiac tissue (Carter-Su et al., 2016; Giustina et al., 2008; Higaki et al., 1997; Obradovic et al., 2019). GH binding to its receptor initiates receptor dimerization and phosphorylation, subsequently activating Janus kinase 2 (JAK-2) and triggering multiple signaling pathways involving STAT proteins, MAPK, IRS, and PI3K (Carter-Su et al., 2016). While the signaling pathways activated by IGF-1 may vary, they generally exhibit similarities to those activated by GH (Kenchegowda et al., 2018; Werner 2023).

GH and IGF-1 effects on the heart are particularly complex. Under physiological conditions, GH and IGF-1 support cardiac hypertrophy in response to physical stress and offer protection against arrhythmias. Conversely, abnormal levels of GH and IGF-1 can promote maladaptive cardiac remodeling and increase the risk of severe arrhythmias (Troncoso et al., 2014). This review focuses on the physiological and pathological effects of GH and IGF-1 on the mechanical and electrical properties of the heart. Additionally, we will highlight long-term cardiac complications that may occur following recombinant GH therapy.

Physiological Effects of GH/IGF-1 on Cardiac Electrical Activity

Animal studies indicate that GH and IGF-1 exert cytoprotective and antiarrhythmic effects in models of acute myocardial infarction (MI). Pre-treatment with GH reduces infarct size and ventricular tachyarrhythmias (VTs) in post-MI rats (Elaiopoulos et al., 2007; Jin et al., 2002; Råmunddal et al., 2008) (Table 1). The exact mechanisms behind the antiarrhythmic effects of GH and IGF-1 are not fully understood. Some experimental studies suggest that GH pre-treatment reduces norepinephrine (NE) release at sympathetic nerve endings, thereby lowering NE levels in both cardiac tissue

TABLE 1: Growth Hormone, Insulin-Like Growth Factor I, Cardiovascular Diseases, Hormone Replacement Therapy

Ion Channel/Mechanism	Effect of GH/IGF-1	Mechanism	References
Voltage-gated Na^+ Channels	Increased expression	Enhances cardiomyocyte excitability, aiding in action potential initiation and propagation	D'Amario et al., 2011a
T-Type Ca^{2+} Channels	Increased expression and phosphorylation	Phosphorylation via protein kinase C pathway, leading to increased Ca^{2+} influx and contractility	D'Amario et al., 2011b; Solem and Thomas 1998; Xu and Best 1990; Yang et al., 1995
L-Type Ca^{2+} Channels	Increased expression and phosphorylation	Phosphorylation via protein kinase C pathway, enhancing Ca^{2+} influx and contractility	D'Amario et al., 2011b; Solem and Thomas 1998; Xu and Best 1990; Yang et al., 1995
I(to), IK1, IKir (Potassium Currents)	Decreased currents (I(to), IK1, IKir)	Activation of MAPK and PI3K pathways leading to the reduction of these currents, contributing to altered heart rate	Ma et al., 2012; Teos et al., 2008; Xu and Best 1991
Norepinephrine Release	Reduction in norepinephrine levels during acute MI	Prevent disruption in membrane potential and repolarization	Kolettis, 2013 Stamatis et al., 2020

TABLE 2: Impact of GH/IGF-1 on Cardiac Mechanical Function

GH/IGF-1 Effect	Mechanism	References
Enhance Systolic Contraction Forces	Increase Ca^{2+} influx via L-type Ca^{2+} channels Induce Ca^{2+} release from nuclear envelop Increase Ca^{2+} sensitivity of myofibrils. Stimulate the synthesis of contractile proteins	Cittadini et al., 2013; Cittadini et al., 2006; Troncoso et al., 2014; Teos et al., 2008; Lu et al., 2001; Hallengren et al., 2014
Accelerate Diastolic Relaxation	Prompt Ca^{2+} reuptake into the SR and mitochondria	Cittadini et al., 2006; Sánchez-Aguilera et al., 2023

and plasma during acute MI (Elaiopoulos et al., 2007; Råmunddal et al., 2008). This reduction in local norepinephrine, as shown in models such as ex vivo Langendorff-perfused hearts and in vivo sympathetic denervation, plays a critical role in preventing myocardial necrosis and reducing VT occurrence (Ravingerova et al., 1993; Stamatis et al., 2020). Elevated interstitial norepinephrine levels have complex electrophysiological consequences, including increased resting membrane potential, delayed afterdepolarizations, and disrupted repolarization, all of which contribute to functional re-entrant circuit formation (Kolettis 2013).

GH/IGF-1 can induce their effects via alterations in the expression and gating behavior of ion channels in cardiomyocytes (Table 1). IGF-1, for instance, boosts expression of voltage-gated Na^{+} channels in cardiomyocytes which are crucial for the initiation and propagation of action potentials in cardiomyocytes, thereby affecting cardiomyocytes excitability (D'Amario et al., 2011a). Additionally, these hormones enhance the expression and phosphorylation of T and L-type Ca^{2+} channels in cardiomyocytes. Phosphorylation of the L-type Ca^{2+} channel occurs via the protein kinase C signaling pathway resulting in increased Ca^{2+} influx and contractility in these cells (D'Amario et al., 2011b; Solem and Thomas 1998; Xu and Best 1990; Yang et al., 1995).

Furthermore, GH/IGF-1 initiates activation of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways, leading to reduction of transient outward potassium current (I(to)), delayed rectifying potassium current (IK1), and inward rectifying potassium current (IKir) in ventricular myocytes (Ma et al., 2012; Teos et al., 2008; Xu and Best 1991). These alterations in potassium currents contribute to changes in heart rate and mediate GH/IGF-1 anti-arrhythmic effects (Danielsson et al., 2013; Råmunddal et al., 2008; Salari et al., 2018). The antiarrhythmic properties of these hormones have been investigated in animal models of myocardial infarction. Intra-myocardial GH administration preserves action potential shape and duration at infarcted borders, suggesting protection against post-infarction arrhythmias (Kontonika et al., 2017).

Physiological Effects of GH/IGF-1 on Cardiac Mechanical Activity

The benefits of GH/IGF-1 extend beyond their antiarrhythmic properties. At physiological levels, these hormones support adaptive cardiac hypertrophy in response to physical stress (Table 2). The prolonged action potential resulting from GH increases Ca^{2+} influx via L-type Ca^{2+} channels, promoting cardiomyocyte hypertrophy (Cittadini et al., 2006; Solem and Thomas 1998; Xu and Best 1991). IGF-1, on the other hand, heightens the calcium sensitivity of myofibrils, effectively enhancing myocardial contractile strength (Cittadini et al., 2013; Cittadini et al., 2006). Disruption in the GH/IGF-1 signaling pathway can impair the cardiac response to physical stress. For instance, mice lacking IGF-1 receptor genes fail to undergo hypertrophy in response to exercise, and inhibition of the IGF-1/PI3K/Akt pathway interferes with adaptive hypertrophy under stress conditions (Teos et al., 2008; Xu and Best 1991) (Table-2).

In addition to L-type Ca2+ channels on the cell membrane, intracellular ion channels contribute to GH/IGF-1-induced cardiac hypertrophy. Ion channels within the membranes of intracellular organelles play a critical role in regulating cytosolic calcium concentrations, which are essential for cardiac contraction and hypertrophic responses (Fahanik-Babaei et al., 2024; Fahanik-Babaei et al., 2011; Salari et al., 2011; Salari et al., 2015). IGF-1 induces a rapid and transient increase in cytosolic calcium level via the IP_3 signaling pathway, with the calcium increase initially detected in the nuclear envelope before

TABLE 3: Impact of GH/IGF-1 on the Heart in Pathological Conditions

High GH secretion		GH deficiency
Gigantism	**Acromegaly**	**Dwarfism**
Ventricular hypertrophy	Ventricular hypertrophy	Dilated cardiomyopathy
Valvular disease	Cardiomyopathy	Systolic dysfunction
Diastolic dysfunction	Valvular disease	Arrhythmia
Systolic dysfunction	Diastolic dysfunction	
Arrhythmia	Systolic dysfunction	
	Arrhythmia	

spreading to the cytosol. This effect of IGF-1 persists even in the absence of extracellular calcium and is unaffected by ryanodine, suggesting its reliance on the release of calcium from intracellular reserves (Troncoso et al., 2014) (Table 2).

Elevated cytosolic Ca^{2+} levels during systole may impair cardiac function by hampering heart relaxation in the subsequent diastolic phase. Sarcoplasmic reticulum calcium pumps (SERCA2) are crucial in terminating contraction during diastole. GH/IGF-1 accelerates calcium reuptake into the sarcoplasmic reticulum and promotes diastole via the Akt signaling pathway, while enhancing SERCA2 density(Cittadini et al., 2006).

IGF-1 also increases mitochondrial Ca^{2+} uniporter (MCU) activity, augmenting calcium entry into mitochondria and strengthening oxidative metabolism and ATP production in cardiomyocyte mitochondria(Sánchez-Aguilera et al., 2023).

In addition, GH and IGF-1 contribute to improved cardiac mechanical function by stimulating the synthesis of contractile proteins. A transient increase in IGF-1 levels enhances myocardial contractility by boosting the synthesis of heavy-chain myosin and actin in myocytes without affecting heart rate(Lu et al., 2001). These hormones also promote the expression of genes associated with light chain myosin, α-actin, and troponin I in neonatal cardiomyocytes (Hallengren et al., 2014; Ito et al., 1993).

Pathological Impacts of GH/IGF-1 on Heart Electrical and Mechanical Characteristics

Chronic elevation of growth hormone (GH) can lead to maladaptive cardiac changes collectively known as cardiac remodeling. This process includes cardiomyocyte hypertrophy, which thickens the ventricular walls without expanding chamber size, limiting diastolic relaxation. Additionally, fibrotic alterations in the extracellular matrix increase myocardial stiffness, further impairing cardiac function and heightening heart failure risk. These structural changes can also disrupt the heart's electrical pathways, elevating the likelihood of arrhythmias (Mizera et al., 2018b; Wolters et al., 2020) (Table 3).

Cardio-graphic studies indicate that 7–40% of patients with acromegaly may experience cardiac rhythm abnormalities, such as ectopic beats, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, sick sinus syndrome, ventricular tachycardia, and bundle branch block (Ramos-Leví and Marazuela 2017). Ventricular arrhythmias, in particular, are more common than supraventricular premature complexes (Kahaly et al., 1992; Lombardi et al., 2002). In a case series by Dutta et al., 50% of deaths among patients were attributed to ventricular arrhythmias linked to abnormal ventricular remodeling (Dutta et al., 2012). Another case study by Subramanian et al. similarly reported idiopathic premature ventricular contractions (PVCs) and ventricular tachycardia (VT) as cardiac complications in acromegaly (Subramnaian et al., 2021).

Structural changes, including left ventricular hypertrophy (LVH) and fibrosis, further increase arrhythmia risk by promoting collagen deposition, a recognized factor in rhythm disturbances (Mizera et al., 2018b). Slow and uneven action potential conduction, due to myofibrillar disarray and cardiomyocyte uncoupling, amplifies this risk (Mizera et al., 2018b). Additionally, QT interval variability is implicated in arrhythmogenesis in acromegaly. Orosz et al. demonstrated that patients with acromegaly exhibit increased beat-to-beat short-term QT variability, which may serve as a predictor for ar-

rhythmias or sudden cardiac death (Orosz et al., 2015). Treating excess GH secretion can be helpful in decreasing the occurrence of arrhythmia (Wolters et al., 2020).

Sex differences also correlate with cardiovascular outcomes in GH disorders. Long-term follow-ups reveal higher mortality rates among women, despite their generally milder tumor characteristics and better treatment response (Galoiu et al., 2024; Ritvonen et al., 2016). Sex hormones, especially androgens and estrogens, influence GH and IGF-1 production (Birzniece and Ho 2017; Ciresi et al., 2018). Testosterone enhances GH secretion and IGF-1 levels by upregulating GH receptor expression in liver and growth plate tissues, promoting muscle and bone growth. IGF-1, in turn, reduces GH release in the pituitary via negative feedback (Yu et al., 1996). Estrogens stimulate GH secretion but reduce hepatic IGF-1 production and GH receptor sensitivity, resulting in higher GH levels but with limited IGF-1 effects. Moreover, estrogen lowers somatostatin receptor expression in the pituitary, further promoting GH secretion (Djordjijevic et al., 1998). Consequently, women generally have higher baseline GH secretion than men (Ciresi et al., 2018).

Duration of GH disorder is another factor that can affect cardiovascular complications. Acromegaly, due to its longer duration, induces more severe cardiovascular complications compared to gigantism (Liliya et al., 2018; Mizera et al., 2018a). Women tend to be diagnosed with acromegaly later than men, partly because milder symptoms may delay diagnosis, leading to extended exposure to GH excess and its systemic effects over time (Găloiu et al., 2024).

Importantly, long-term cardiovascular complications are not exclusive to pathological GH levels. Even slight increases in GH secretion within the normal range have been linked to a higher incidence of cardiovascular disease (CVD) events in healthy individuals (Hallengren et al., 2014).

In addition to gigantism and acromegaly, GH deficiency (GHD) can also result in severe cardiovascular issues, including reduced left ventricular mass, decreased cardiac output, dilated cardiomyopathy, and arrhythmias (Isgaard et al., 2015; Lombardi et al., 2012; Vance and Mauras 1999). Recent studies indicate that GHD may alter cardiac electrophysiology, potentially raising arrhythmic risk. Children with GHD display prolonged T wave peak-to-end (Tp-e) intervals and elevated Tp-e/QT and Tp-e/QTc ratios, reflecting increased ventricular repolarization heterogeneity, a precursor for arrhythmogenesis (Yilmaz et al., 2023). While hormone therapy improves heart function in GHD patients, full normalization of cardiac parameters may remain elusive even after a year of treatment (Alkan et al., 2021; Alkan et al., 2023).

Benefits and Side Effects of GH Therapy

GH therapy initially aimed at treating GHD has been extended to conditions like small for gestational age (SGA) and idiopathic short stature (ISS) (Danowitz and Grimberg 2022; Richmond and Rogol 2010). Long-term follow-up studies have shown that GH therapy may result in gender- and dose-dependent cardiovascular complications in the patients. (van Bunderen and Olsson 2021; van Bunderen et al., 2011). In a 2012 study, Carel et al. highlighted the importance of GH dosage in the context of cardiovascular risks. They revealed that GH doses over 50 μg/kg/day were associated with increased mortality (Carel et al., 2012). A recent study in a Swedish population further confirmed the impact of cumulative GH dose and treatment duration on cardiovascular outcomes. Additionally, it found a gender-dependent effect, with women experiencing more cardiovascular events than men after GH therapy (Tidblad et al., 2021). As discussed, gender plays a significant role in GH/IGF-1 physiology, with boys generally responding more effectively to GH therapy during prepubertal years, showing greater height increases after two years of treatment (Sävendahl et al., 2012a). This gender difference is partially attributed to estrogen, which limits GH-induced IGF-1 release in the liver, thereby reducing GH's effectiveness on growth. During puberty, females often require higher GH doses and longer treatment durations, which heightens their risk of GH-related side effects (Ciresi et al., 2018; Johansson et al., 1999; Span et al., 2000).

However, there is some controversy regarding GH therapy's cardiovascular risks (Goedegebuure et al., 2022; Sävendahl et al., 2020; Sävendahl et al., 2012b). Goedegebuure et al. followed 167 adults born SGA who underwent 12 years of recombinant human growth hormone (rhGH) treatment and found no significant differences in metabolic or cardiovascular health profiles compared to adults without GH therapy (Goedegebuure et al., 2022; Tidblad et al., 2021). However, the popula-

tion size in this study was small and their finding has not been confirmed by studies which assessed larger populations (Sävendahl et al., 2020).

Conclusion

In conclusion, this review highlights the intricate role of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in cardiac physiology and pathology. These hormones have profound effects on heart function, regulating cardiac excitability, contractility, and structural integrity. While physiological GH levels confer benefits, such as promoting adaptive hypertrophy and arrhythmia resilience, chronic dysregulation in GH—whether excessive or deficient—predisposes individuals to a range of adverse cardiovascular outcomes, including ventricular remodeling, fibrosis, and heightened arrhythmogenic risk.

Our review underscores the significance of gender-specific responses to GH therapy, revealing that females may be more susceptible to cardiovascular side effects, emphasizing the need for tailored therapy based on gender. This aspect, along with patient-specific factors like baseline cardiovascular health and genetic predispositions, should guide GH therapy to optimize safety and effectiveness.

There's still debate about the cardiovascular safety of recombinant GH (rhGH) therapy, especially in people without GH deficiency. Some research supports its safety, while other studies raise concerns. This makes it clear that we need further studies and better tools to monitor heart health in those receiving GH therapy. In the meantime, a thoughtful, individualized approach is essential, especially for children and adults with idiopathic short stature or those born small for their age, as these groups might carry unique risks.

Future research should aim to clarify the precise mechanisms through which GH and IGF-1 influence the heart, identify innovative methods for detecting early cardiac changes, and devise alternative strategies to reduce potential risks. By personalizing GH therapy to each individual's unique profile, we can work to enhance the therapeutic benefits while protecting long-term cardiac health.

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Conflicts of interest

The authors have nothing to declare.

References

Alkan F, Ersoy B, Kızılay D O, Coskun S. Cardiac functions in children with growth hormone deficiency: Effects of one year of GH replacement therapy. Growth Horm IGF Res 2021; 60-61: 101432. https://doi.org/10.1016/j.ghir.2021.101432

Alkan F, Ersoy B, Kızılay D O, Ozyurt B C, Coskun S. Evaluation of cardiac structure, exercise capacity and electrocardiography parameters in children with partial and complete growth hormone deficiency and their changes with short term growth hormone replacement therapy. Pituitary 2023; 26: 115-123. https://doi.org/10.1007/s11102-022-01295-z

Allard J B, Duan C. IGF-binding proteins: why do they exist and why are there so many? Frontiers in endocrinology 2018; 9: 117. https://doi.org/10.3389/fendo.2018.00117

Birzniece V, Ho K K Y. Sex steroids and the GH axis: Implications for the management of hypopituitarism. Best Pract Res Clin Endocrinol Metab 2017; 31: 59-69. https://doi.org/10.1016/j.beem.2017.03.003

Carel J C, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguelidou F, Rey G, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. J Clin Endocrinol Metab 2012; 97: 416-425. https://doi.org/10.1210/jc.2011-1995

Carter-Su C, Schwartz J, Argetsinger L S. Growth hormone signaling pathways. Growth Horm IGF Res 2016; 28: 11-5. https://doi.org/10.1016/j.ghir.2015.09.002

Ceda G P, Davis R G, Rosenfeld R G, Hoffman A R. The growth hormone (GH)-releasing hormone (GHRH)-GH-somatomedin axis: evidence for rapid inhibition of GHRH-elicited GH release by insulin-like growth factors I and II. Endocrinology 1987; 120: 1658-1662. https://doi.org/10.1210/endo-120-4-1658

Chen E Y, Liao Y-C, Smith D H, Barrera-Saldaña H A, Gelinas R E, Seeburg P H. The human growth hormone locus: nucleotide sequence, biology, and evolution. Genomics 1989; 4: 479-497. https://doi.org/10.1016/0888-7543(89)90271-1

Ciresi A, Radellini S, Guarnotta V, Mineo M G, Giordano C. The metabolic outcomes of growth hormone treatment in children are gender specific. Endocr Connect 2018; 7: 879-887. https://doi.org/10.1530/EC-18-0135

Cittadini A, Marra A M, Arcopinto M, Bobbio E, Salzano A, Sirico D, et al. Growth hormone replacement delays the

progression of chronic heart failure combined with growth hormone deficiency: an extension of a randomized controlled single-blind study. JACC: Heart Failure 2013; 1: 325-330. https://doi.org/10.1016/j.jchf.2013.04.003

Cittadini A, Monti M, Iaccarino G, Di Rella F, Tsichlis P, Di Gianni A, et al. Adenoviral gene transfer of Akt enhances myocardial contractility and intracellular calcium handling. Gene therapy 2006; 13: 8-19. https://doi.org/10.1038/sj.gt.3302589

D'Amario D, Cabral-Da-Silva M C, Zheng H, Fiorini C, Goichberg P, Steadman E, et al. Insulin-like growth factor-1 receptor identifies a pool of human cardiac stem cells with superior therapeutic potential for myocardial regeneration. Circ Res 2011b; 108: 1467-1481. https://doi.org/10.1161/circresaha.111.240648

Danielsson C, Brask J, Skold A C, Genead R, Andersson A, Andersson U, et al. Exploration of human, rat, and rabbit embryonic cardiomyocytes suggests K-channel block as a common teratogenic mechanism. Cardiovasc Res 2013; 97: 23-32. https://doi.org/10.1093/cvr/cvs296

Danowitz M, Grimberg A. Clinical Indications for Growth Hormone Therapy. Adv Pediatr 2022; 69: 203-217. https://doi.org/10.1016/j.yapd.2022.03.005

De Vos A M, Ultsch M, Kossiakoff A A. Human growth hormone and extracellular domain of its receptor: crystal structure of the complex. Science 1992; 255: 306-312. https://doi.org/10.1126/science.1549776

Dixit M, Poudel S B, Yakar S. Effects of GH/IGF axis on bone and cartilage. Mol Cell Endocrinol 2021; 519: 111052. https://doi.org/10.1016/j.mce.2020.111052

Djordjijevic D, Zhang J, Priam M, Viollet C, Gourdji D, Kordon C, et al. Effect of 17beta-estradiol on somatostatin receptor expression and inhibitory effects on growth hormone and prolactin release in rat pituitary cell cultures. Endocrinology 1998; 139: 2272-2277. https://doi.org/10.1210/endo.139.5.5990

Dutta P, Das S, Bhansali A, Bhadada S K, Rajesh B V, Reddy K S, et al. Congestive heart failure in acromegaly: A review of 6 cases. Indian J Endocrinol Metab 2012; 16: 987-990. https://doi.org/10.4103/2230-8210.103007

Elaiopoulos D A, Tsalikakis D G, Agelaki M G, Baltogiannis G G, Mitsi A C, Fotiadis D I, et al. Growth hormone decreases phase II ventricular tachyarrhythmias during acute myocardial infarction in rats. Clin Sci (Lond) 2007; 112: 385-391. https://doi.org/10.1042/CS20060193

Fahanik-Babaei J, Bagheri M, Salari S. Characterization of a novel Ca(2+)-Activated potassium channel in rat brain rough endoplasmic reticulum. Arch Biochem Biophys 2024; 759: 110105. https://doi.org/10.1016/j.abb.2024.110105

Fahanik-Babaei J, Eliassi A, Jafari A, Sauve R, Salari S, Saghiri R. Electro-pharmacological profile of a mitochondrial inner membrane big-potassium channel from rat brain. Biochim Biophys Acta 2011; 1808: 454-460. https://doi.org/10.1016/j.bbamem.2010.10.005

Fodor M, Csaba Z, Kordon C, Epelbaum J. Growth hormone-releasing hormone, somatostatin, galanin and beta-endorphin afferents to the hypothalamic periventricular nucleus. J Chem Neuroanat 1994; 8: 61-73. https://doi.org/10.1016/0891-0618(94)90036-1

Galoiu S, Toma I D, Tanasie D I, Barbulescu A, Baciu I, Niculescu D A, et al. High mortality risk among women with acromegaly still persists. Front Endocrinol (Lausanne) 2024; 15: 1348972. https://doi.org/10.3389/fendo.2024.1348972

Găloiu S, Toma I D, Tănasie D I, Bărbulescu A, Baciu I, Niculescu D A, et al. High mortality risk among women with acromegaly still persists. Front Endocrinol (Lausanne) 2024; 15: 1348972. https://doi.org/10.3389/fendo.2024.1348972

Giustina A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. Endocr Rev 2008; 29: 535-559. https://doi.org/10.1210/er.2007-0036

Goedegebuure W J, van der Steen M, Smeets C C J, Hokken-Koelega A C S. Childhood growth hormone treatment and metabolic and cardiovascular risk in adults born small for gestational age after growth hormone cessation in the Netherlands: a 12-year follow-up study. Lancet Child Adolesc Health 2022; 6: 777-787. https://doi.org/10.1016/S2352-4642(22)00240-1

Hallengren E, Almgren P, Engström G, Hedblad B, Persson M, Suhr J, et al. Fasting levels of high-sensitivity growth hormone predict cardiovascular morbidity and mortality: the Malmö Diet and Cancer study. J Am Coll Cardiol 2014; 64: 1452-1460. https://doi.org/10.1016/j.jacc.2014.03.063

Hartman M L, Veldhuis J D, Thorner M O. Normal control of growth hormone secretion. Horm Res 1993; 40: 37-47. https://doi.org/10.1159/000183766

Higaki K, Matsumoto Y, Fujimoto R, Kurosaki Y, Kimura T. Pharmacokinetics of recombinant human insulin-like growth factor-I in diabetic rats. Drug Metab Dispos 1997; 25: 1324-1327.

Isgaard J, Arcopinto M, Karason K, Cittadini A. GH and the cardiovascular system: an update on a topic at heart. Endocrine 2015; 48: 25-35. https://doi.org/10.1007/s12020-014-

0327-6

Ito H, Hiroe M, Hirata Y, Tsujino M, Adachi S, Shichiri M, et al. Insulin-like growth factor-I induces hypertrophy with enhanced expression of muscle specific genes in cultured rat cardiomyocytes. Circulation 1993; 87: 1715-1721. https://doi.org/10.1161/01.CIR.87.5.1715

Jehle P M, Schulten K, Schulz W, Jehle D R, Stracke S, Manfras B, et al. Serum levels of insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-1 to -6 and their relationship to bone metabolism in osteoporosis patients. Eur J Intern Med 2003; 14: 32-38. https://doi.org/10.1016/S0953-6205(02)00183-8

Jin H, Yang R, Lu H, Ogasawara A K, Li W, Ryan A, et al. Effects of early treatment with growth hormone on infarct size, survival, and cardiac gene expression after acute myocardial infarction. Growth Horm IGF Res 2002; 12: 208-215. https://doi.org/10.1016/S1096-6374(02)00042-4

Johansson A G, Engström B E, Ljunghall S, Karlsson F A, Burman P. Gender differences in the effects of long term growth hormone (GH) treatment on bone in adults with GH deficiency. J Clin Endocrinol Metab 1999; 84: 2002-2007. https://doi.org/10.1210/jcem.84.6.5743

Kahaly G, Olshausen K V, Mohr-Kahaly S, Erbel R, Boor S, Beyer J, et al. Arrhythmia profile in acromegaly. Eur Heart J 1992; 13: 51-56. https://doi.org/10.1093/oxfordjournals.eurheartj.a060047

Kenchegowda D, Legesse B, Hritzo B, Olsen C, Aghdam S, Kaur A, et al. Selective insulin-like growth factor resistance associated with heart hemorrhages and poor prognosis in a novel preclinical model of the hematopoietic acute radiation syndrome. Radiat Res 2018; 190: 164-175. https://doi.org/10.1667/RR14993.1

Kolettis T M. Coronary artery disease and ventricular tachyarrhythmia: pathophysiology and treatment. Curr Opin Pharmacol 2013; 13: 210-217. https://doi.org/10.1016/j.coph.2013.01.001

Kontonika M, Barka E, Roumpi M, La Rocca V, Lekkas P, Daskalopoulos E P, et al. Prolonged intra-myocardial growth hormone administration ameliorates post-infarction electrophysiologic remodeling in rats. Growth Factors 2017; 35: 1-11. https://doi.org/10.1080/08977194.2017.1297432

Liliya R, Adrian D, Nalini S, Luciana A N, Anne B, Marie-Lise J-R, et al. Cardiovascular complications in pituitary gigantism (results of an international study). Journal 2018; 57. https://doi.org/10.1530/endoabs.57.021

Lombardi G, Colao A, Marzullo P, Biondi B, Palmieri E, Fazio S. Improvement of left ventricular hypertrophy and arrhythmias after lanreotide-induced GH and IGF-I decrease in acromegaly. A prospective multi-center study. J Endocrinol Invest 2002; 25: 971-976. https://doi.org/10.1007/BF03344070

Lombardi G, Di Somma C, Grasso L, Savanelli M, Colao A, Pivonello R. The cardiovascular system in growth hormone excess and growth hormone deficiency. Journal of endocrinological investigation 2012; 35: 1021-1029.

Lu C, Schwartzbauer G, Sperling M A, Devaskar S U, Thamotharan S, Robbins P D, et al. Demonstration of direct effects of growth hormone on neonatal cardiomyocytes. J Biol Chem 2001; 276: 22892-22900. https://doi.org/10.1074/jbc.M011647200

Ma Y, Zhang L, Launikonis B S, Chen C. Growth hormone secretagogues preserve the electrophysiological properties of mouse cardiomyocytes isolated from in vitro ischemia/reperfusion heart. Endocrinology 2012; 153: 5480-5490. https://doi.org/10.1210/en.2012-1404

Mizera L, Elbaum M, Daroszewski J, Bolanowski M. Cardiovascular complications of acromegaly. Acta Endocrinol (Buchar) 2018a; 14: 365-374. https://doi.org/10.4183/aeb.2018.365

Obradovic M, Zafirovic S, Soskic S, Stanimirovic J, Trpkovic A, Jevremovic D, et al. Effects of IGF-1 on the cardiovascular system. Current Pharmaceutical Design 2019; 25: 3715-3725. https://doi.org/10.2174/1381612825666191106091507

Orosz A, Csajbók É, Czékus C, Gavallér H, Magony S, Valkusz Z, et al. Increased short-term beat-to-beat variability of QT interval in patients with acromegaly. PLoS One 2015; 10: e0125639. https://doi.org/10.1371/journal.pone.0125639

Ramos-Leví A M, Marazuela M. Cardiovascular comorbidities in acromegaly: an update on their diagnosis and management. Endocrine 2017; 55: 346-359. https://doi.org/10.1007/s12020-016-1191-3

Råmunddal T, Gizurarson S, Lorentzon M, Omerovic E. Antiarrhythmic effects of growth hormone--in vivo evidence from small-animal models of acute myocardial infarction and invasive electrophysiology. J Electrocardiol 2008; 41: 144-151. https://doi.org/10.1016/j.jelectrocard.2007.09.002

Ravingerova T, Slezak J, Tribulova N, Dzurba A, Uhrik B, Ziegelhoffer A. High arrythmogenesis during early reperfusion of ischaemic myocardium: participation of oxygen free radicals. J Basic Clin Physiol Pharmacol 1993; 4: 335-346. https://doi.org/10.1515/JBCPP.1993.4.4.335

Richmond E, Rogol A D. Current indications for growth hormone therapy for children and adolescents. Endocr Dev 2010; 18: 92-108. https://doi.org/10.1159/000316130

Ritvonen E, Loyttyniemi E, Jaatinen P, Ebeling T, Moilanen L, Nuutila P, et al. Mortality in acromegaly: a 20-year follow-up study. Endocr Relat Cancer 2016; 23: 469-480. https://doi.org/10.1530/ERC-16-0106

Salari S, Eliassi A A, Saghiri R. Evidences on the existence of a new potassium channel in the rough endoplasmic reticulum (RER) of rat hepatocytes. Physiology and Pharmacology 2011; 15: 16-26.

Salari S, Ghasemi M, Fahanik-Babaei J, Saghiri R, Sauve R, Eliassi A. Evidence for a KATP channel in rough endoplasmic reticulum (rerKATP Channel) of rat hepatocytes. PLoS One 2015; 10: e0125798. https://doi.org/10.1371/journal.pone.0125798

Salari S, Silverå Ejneby M, Brask J, Elinder F. Isopimaric acid - a multi-targeting ion channel modulator reducing excitability and arrhythmicity in a spontaneously beating mouse atrial cell line. Acta Physiol (Oxf) 2018; 222. https://doi.org/10.1111/apha.12895

Sánchez-Aguilera P, López-Crisosto C, Norambuena-Soto I, Penannen C, Zhu J, Bomer N, et al. IGF-1 boosts mitochondrial function by a Ca(2+) uptake-dependent mechanism in cultured human and rat cardiomyocytes. Front Physiol 2023; 14: 1106662. https://doi.org/10.3389/fphys.2023.1106662

Sävendahl L, Blankenstein O, Oliver I, Christesen H T, Lee P, Pedersen B T, et al. Gender influences short-term growth hormone treatment response in children. Horm Res Paediatr 2012a; 77: 188-194. https://doi.org/10.1159/000337570

Sävendahl L, Cooke R, Tidblad A, Beckers D, Butler G, Cianfarani S, et al. Long-term mortality after childhood growth hormone treatment: the SAGhE cohort study. The lancet Diabetes & endocrinology 2020; 8: 683-692. https://doi.org/10.1016/S2213-8587(20)30163-7

Sävendahl L, Maes M, Albertsson-Wikland K, Borgström B, Carel J C, Henrard S, et al. Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. J Clin Endocrinol Metab 2012b; 97: E213-E217. https://doi.org/10.1210/jc.2011-2882

Solem M L, Thomas A P. Modulation of cardiac Ca2+ channels by IGF1. Biochemical and Biophysical Research Communications 1998; 252: 151-155. https://doi.org/10.1006/bbrc.1998.9626

Span J P, Pieters G F, Sweep C G, Hermus A R, Smals A G. Gender difference in insulin-like growth factor I response to growth hormone (GH) treatment in GH-deficient adults: role of sex hormone replacement. J Clin Endocrinol Metab 2000; 85: 1121-1125. https://doi.org/10.1210/jcem.85.3.6463

Stamatis K V, Kontonika M, Daskalopoulos E P, Kolettis T M. Electrophysiologic effects of growth hormone post-myocardial infarction. Int J Mol Sci 2020; 21. https://doi.org/10.3390/ijms21030918

Subramnaian M, Shah V, Saggu D K, Yalagudri S, Narasimhan C. Looking above the heart: A rare cause of ventricular tachycardia. J Arrhythm 2021; 37: 1120-1122. https://doi.org/10.1002/joa3.12546

Teos L Y, Zhao A, Alvin Z, Laurence G G, Li C, Haddad G E. Basal and IGF-I-dependent regulation of potassium channels by MAP kinases and PI3-kinase during eccentric cardiac hypertrophy. Am J Physiol Heart Circ Physiol 2008; 295: 1834-1845. https://doi.org/10.1152/ajpheart.321.2008

Tidblad A, Bottai M, Kieler H, Albertsson-Wikland K, Sävendahl L. Association of childhood growth hormone treatment with long-term cardiovascular morbidity. JAMA pediatrics 2021; 175: e205199-e205199. https://doi.org/10.1001/jamapediatrics.2020.5199

Troncoso R, Ibarra C, Vicencio J M, Jaimovich E, Lavandero S. New insights into IGF-1 signaling in the heart. Trends in Endocrinology & Metabolism 2014; 25: 128-137. https://doi.org/10.1016/j.tem.2013.12.002

van Bunderen C C, Olsson D S. Growth hormone deficiency and replacement therapy in adults: Impact on survival. Rev Endocr Metab Disord 2021; 22: 125-133. https://doi.org/10.1007/s11154-020-09599-w

van Bunderen C C, van Nieuwpoort I C, Arwert L I, Heymans M W, Franken A A, Koppeschaar H P, et al. Does growth hormone replacement therapy reduce mortality in adults with growth hormone deficiency? Data from the Dutch National Registry of Growth Hormone Treatment in adults. J Clin Endocrinol Metab 2011; 96: 3151-3159. https://doi.org/10.1210/jc.2011-1215

Vance M L, Mauras N. Growth hormone therapy in adults and children. New England Journal of Medicine 1999; 341: 1206-1216. https://doi.org/10.1056/NEJM199910143411607

Werner H. The IGF1 Signaling pathway: From basic concepts to therapeutic opportunities. Int J Mol Sci 2023; 24. https://doi.org/10.3390/ijms241914882

Wolters T L C, Netea M G, Riksen N P, Hermus A, Netea-Maier R T. Acromegaly, inflammation and cardiovascu-

lar disease: a review. Rev Endocr Metab Disord 2020; 21: 547-568. https://doi.org/10.1007/s11154-020-09560-x

Xu X P, Best P M. Decreased transient outward K+ current in ventricular myocytes from acromegalic rats. Am J Physiol 1991; 260: H935-942. https://doi.org/10.1152/ajpheart.1991.260.3.H935

Xu X P, Best P M. Increase in T-type calcium current in atrial myocytes from adult rats with growth hormone-secreting tumors. Proc Natl Acad Sci U S A 1990; 87: 4655-4659. https://doi.org/10.1073/pnas.87.12.4655

Yang R, Bunting S, Gillett N, Clark R, Jin H. Growth hormone improves cardiac performance in experimental heart failure. Circulation 1995; 92: 262-267. https://doi.org/10.1161/01.CIR.92.2.262

Yilmaz M, Gurses D, Ata A. Electrocardiographic findings in children with growth hormone deficiency. Cureus 2023; 15: e36385. https://doi.org/10.7759/cureus.36385

Yu Y M, Domené H M, Sztein J, Counts D R, Cassorla F. Developmental changes and differential regulation by testosterone and estradiol of growth hormone receptor expression in the rabbit. Eur J Endocrinol 1996; 135: 583-590. https://doi.org/10.1530/eje.0.1350583