

**Education-Family Physician Corner****Growth Hormone and the Cardiovascular System: The Balance**

Abeer Al-Saweer, CABFM\*

Growth hormone (GH) possesses anabolic effects that render its excess or its deficiency pathological. In the normal population, low GH might be harmful. Pathological high and low levels of GH might exert harmful influences on cardiovascular structures.

In this review an outline of the pathophysiology of GH, cardiovascular mortality and morbidity due to GH deficiency or excess will be presented. An outline of evidence-based recommendations of GH deficiency and excess in relation to the cardiovascular system will be reviewed.

**Pathophysiology of GH in Relation to Cardiovascular System**

GH is a protein consisting of 191 amino acids produced by the anterior part of the pituitary gland. The anabolic effect of GH on muscle, bone and cartilage is mediated by Insulin Growth Factor (IGF-1). The GH receptor is more abundant and more active in the heart than in many other tissues. GH exerts its action by inducing local synthesis of IGF-1 in cardiac tissue. IGF-1 is a well-established cardiac growth factor. Cardiac mass is augmented in transgenic mice showing over expression of IGF-1<sup>1</sup>.

In neonatal cardiomyocytes, IGF-1 induces protein synthesis and cell hypertrophy. Moreover, IGF-1 stimulates myofibril development and raises the number of new sarcomeres in adult cardiomyocytes<sup>1</sup>. Cardiac IGF-1 release might be due to local mechanical stimuli. For example, IGF-1 is over expressed in the myocardium following exposure to increased blood pressure or volume<sup>1</sup>.

In a study, it was found that GH deficient patients manifest increased abdominal fat, even in patients with normal weight. Cardiac function might be affected in the form of decreased cardiac ejection volume and reduction of arterial distensibility. The lipid profile is also worsened, along with increased inflammatory markers, such as highly sensitive C-reactive protein<sup>2</sup>.

Hypopituitary GH-deficient adults have an increased number of atheromatous plaques in carotid and femoral arteries, compared with control individuals<sup>3</sup>.

On the other hand, in most patients with acromegaly a specific cardiomyopathy is present,

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\* Assistant Professor, Arabian Gulf University  
Consultant Family Physician  
Ministry of Health  
Kingdom of Bahrain  
Email: ASaweer@health.gov.bh

which is characterized by myocardial hypertrophy with interstitial fibrosis, lymphomononuclear infiltration and areas of monocyte necrosis results in biventricular concentric hypertrophy<sup>4</sup>.

Hypertension is present in approximately 30% of acromegalic patients, presumably attributable to volume overload and structural changes in the vascular system. The high prevalence of hypertension and diabetes mellitus in association with acromegaly contribute to progression of coronary artery disease<sup>4</sup>.

### **The Balance**

According to recent studies, patients with long-term disturbance of growth hormone secretion have an increased risk of cardiovascular morbidity and mortality.

### **Epidemiology of GH Deficiency and Cardiovascular System**

The data of cardiovascular morbidity and GH deficiency is scarce. In a study of adult patients with hypopituitarism and GH deficiency, an increased CV risk (odds ratio of 2 for men and 3.5-4 for women) was found<sup>2,4</sup>.

A study focused on cerebrovascular and cardiovascular morbidity in hypopituitary patients; cerebrovascular morbidity had increased in hypopituitary patients without GH replacement therapy compared with the control population. The increase in the total number of myocardial infarctions was less than the increase in cerebrovascular events<sup>4</sup>. The study carries appropriate credibility since the sample size is big enough to draw conclusions. In another study of 289 hypopituitary patients who received GH replacement therapy, the risk ratio for cerebrovascular events was higher than that of the control population<sup>5</sup>. The relative risk for myocardial infarctions had decreased in hypopituitary GH treated patients in comparison to control population. The former two studies illustrate that GH replacement therapy may reduce the risk of myocardial infarctions in GH deficient patients<sup>4,5</sup>.

Cardiovascular risk markers are improved with GH replacement therapy as shown by meta analysis, which revealed overall beneficial effects on lean body mass, improved low-density lipoprotein and diastolic pressure<sup>4,5</sup>.

The American Association of Clinical Endocrinologist (AACE) recommended the following in GH deficient patients: “Annual measurements of BMI, waist circumference, waist-to-hip ratio and cardiovascular risk markers in all patients, with the cardiovascular treatment targets being similar to the general population. Cardiovascular parameters needed to be monitored include systolic and diastolic blood pressure, heart rate and electrocardiogram results. More expensive and complex examinations (echocardiogram, carotid echo-Doppler) should be performed only if clinically indicated”<sup>5</sup>.

### **GH Excess and Cardiovascular System**

In a study in normal population, increased plasma IGF-I was associated with increased incidence of chronic heart failure; this increase did not influence the development of other cardiovascular diseases<sup>6</sup>. In a group of acromegalic treated patients for as little as six months, the risk of heart failure was completely ameliorated. The GH excess effect on the heart was totally reversed<sup>7</sup>.

The mortality rate of patients with acromegaly is 2 to 4 times higher than normal population. The increase is due primarily to cardiovascular disease<sup>8</sup>. Treatment that retain serum IGF-I levels to normal abolishes this risk. In addition, reduction of circulating GH levels to less than 2.5 ng/mL leads to mortality rates comparable to those of the normal population. These data emphasize the importance of timely diagnosis and appropriate treatment<sup>5,6</sup>.

The American Association of Clinical Endocrinologist recommended the following to monitor and treat cardiovascular comorbidity in acromegalic patients: “Standard therapy for patients with left ventricular hypertrophy, impaired cardiac systolic and diastolic function, arrhythmias, conduction abnormalities, valvular heart disease and ischemic heart disease should be used”<sup>9</sup>. Limited information is available about the role of screening cardiac stress tests or echocardiography in patients with acromegaly. With lowering of GH concentrations, left ventricular size and function might improve<sup>9</sup>.

Hypertension and diabetes mellitus, if present, may improve if GH and IGF-I levels are lowered. Standard dietary strategies and medical therapies for hypertension, diabetes mellitus and hyperlipidemia should be used. In the absence of definitive interventional studies in this patient population, it seems prudent to attempt to achieve the goals for high-risk cardiac patients: blood pressure, < 130/80 mmHg, hemoglobin A1c < 6.5%, low-density lipoprotein cholesterol < 100 mg/dL, triglycerides < 150 mg/dL and high-density lipoprotein cholesterol > 40 mg/dL<sup>9</sup>.

## CONCLUSION

**Disturbed cardiovascular function has been demonstrated to decrease life expectancy both in GH deficiency and excess. Studies have provided the evidence that GH normalization leads to significant reduction in both cardiovascular mortality and morbidity. These studies have suggested that the cardiovascular abnormalities can be partially reversed by suppressing GH and IGF-I levels in acromegaly or after GH replacement therapy in growth hormone deficiency patients.**

**Clinical studies have recommended the meticulous cardiovascular surveillance and adherence to treatment in GH disturbed patients in order to reduce the cardiovascular morbidity and mortality risk.**

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**Competing Interest:** None **Sponsorship:** None

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## REFERENCES

1. Gupta V. Adult Growth Hormone Deficiency. Indian J Endocrinol Metab 2011; 15(Suppl3): S197-202.
2. Abs R, Feldt-Rasmussen U, Mattsson AF, et al. Determinants of Cardiovascular Risk in 2589 Hypopituitary GH-Deficient Adults - A KIMS Database Analysis. Eur J Endocrinol 2006; 155(1): 79-90.

3. Van Bunderen CC, van Nieuwpoort IC, Arwert LI, 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(10): 3151-9.
4. Stochholm K, Gravholt CH, Laursen T, et al. Mortality and GH Deficiency: A Nationwide Study. *Eur J Endocrinol* 2007; 157(1): 9-18.
5. Svensson J, Bengtsson BA, Rosen T, et al. Malignant Disease and Cardiovascular/Morbidity in Hypopituitary Adults with or without Growth Hormone Replacement Therapy. *J Clin Endocrinol Metab* 2004; 89(7): 3306-12.
6. Forman K, Vara E, García C, et al. Effect of a Combined Treatment with Growth Hormone and Melatonin in the Cardiometabolic Aging on Male SAMP8 Mice. *J Gerontol A Biol Sci Med Sci* 2011; 66(8): 823-34.
7. Dutta P, Bhansali A, Kumar BV, et al. Effects of Short Term Growth Hormone Therapy in Adult Growth Hormone Deficiency. *J Assoc Physicians India* 2010; 58: 670-3.
8. Di Somma C, Rivellese A, Pizza G, et al. Effects of Short-Term Treatment with Orlistat on Growth Hormone/Insulin-Like Growth Factor-I Axis in Obese Post-Menopausal Women. *J Endocrinol Invest* 2011; 34(2): 90-6.
9. Cook DM, Yuen KC, Biller BM, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Growth Hormone Use in Growth Hormone-Deficient Adults and Transition Patients - 2009 Update. *Endocr Pract* 2009 15(Suppl 2): 1-29.