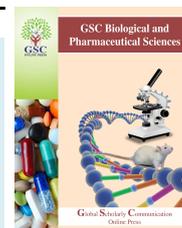


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(REVIEW ARTICLE)



## Recombinant human growth hormone: a medical miracle or cause for concern?

Subramanian Ganesh Chidambar \*, Mat Yusoff Yuslina, Esa Ezalia, Zakaria Zubaidah and Ponnampalam Stephen N.

*Haematology Unit, Cancer Research Centre, Institute for Medical Research, Jalan Pahang, 50588 Kuala Lumpur, Malaysia.*

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### Abstract

The availability of recombinant human growth hormone (GH) has expanded the use beyond growth hormone deficiency (GHD) to conditions that include, use in anti-aging formula and in sports to enhance athletic performance. The long-term safety and efficacy of GH use for these conditions has not been demonstrated. The objective of this review is to explore evidence from clinical and epidemiological studies to determine the safety of GH and current updates on any adverse effects including cancer risk. The primary concern with GH use for healthy adults without proven GHD is the lack of long-term studies evaluating its safety and efficacy. An association with cancer has been shown in limited studies that highlight the need for caution on long term use in healthy adults without GHD. GHD efficacy has not been established in anti-aging or enhancing athletic performance but adverse effects have been documented in these uses.

**Keywords:** Growth hormone; Growth hormone deficiency; Adverse effects; Anti-aging; Cancer

### 1. Introduction

Human growth hormone (hGH) plays an important role in cell regeneration, growth and maintaining healthy human tissue. The hormone is naturally produced by somatotrophic cells in the anterior pituitary gland. The hGH which is a polypeptide residue of 191 amino acids is formed by cleavage of a 26 N terminal amino acid peptide from a 217 amino acid precursor protein. The mature hGH is circulated throughout the body and interacts with surface receptors on various cells including muscle, bone and cartilage. Once secreted, HGH remains active in the bloodstream for a few minutes, before it is converted by the liver into growth factors such as the insulin-like growth factor (IGF-1), which has growth-promoting properties on every cell in the body. There exist several hypothalamic hormones that regulate growth hormone release. The two well-known of these are the growth hormone release factor (GHRF) that stimulates release and somatostatin that suppresses release of GH [1].

Diseases associated with GH are related to deficiency or overproduction of the hormone. Congenital deficiency is associated with an abnormal pituitary gland or other syndromes and conditions, including mutations to residues within the signal peptide that affects the secretion of GH from cells. Acquired deficiency can be multifactorial. These factors include, infection, brain tumours or injury. Symptoms of GHD in children include dwarfism or short stature, slow growth, delayed onset of puberty, delayed tooth development [2]. In adults, GH deficiency (GHD) is associated with pituitary tumours and treatment with surgery or radiation. Signs and symptoms include low energy and stamina, decreased muscle mass, weight gain especially abdominal obesity, depression, memory loss, dry skin and hair loss. Studies have also indicated lipoprotein metabolism is altered in adults by GHD, resulting in increased total cholesterol, low density lipoprotein and triglyceride levels that increase the risk for cardiovascular disease. HGH is also responsible for male reproductive function and sexual maturation while deficiency is associated with sexual dysfunction. [3, 4]. The ability to extract GH from human pituitary glands enabled therapy for GHD in the 1950s. Human GH was initially

\*Corresponding author

E-mail address: [dr.ganeshchidambar@gmail.com](mailto:dr.ganeshchidambar@gmail.com)

extracted from human cadavers but supply was scarce. In 1985, the pituitary derived GH was discontinued because of the reports of Creutzfeldt-Jakob disease occurrence in several recipients from different countries [5, 6].

Bio-recombinant hGH via recombinant DNA technology was developed in the 1980s and approved by the Food and Drug Administration (FDA), United States, for specific uses in adults and children. The United States FDA has approved hGH therapy for the treatment of selected disorders that impair physical growth and development; these include Turner's syndrome, (a congenital condition in which a female does not have two complete X chromosomes), Prader-Willi syndrome (a congenital disease, that causes mental disability and obesity), for chronic renal deficiency, and Human Immunodeficiency virus associated wasting disease.

Reports have shown that hGH is well tolerated and treatment with GH replacement increased growth rate, improved body composition (higher muscle mass, lower fat mass); improved weight management; increased energy and physical activity and improved strength [7, 8]. Administration of hGH has been shown to speed up the regeneration of bone which is important in bone healing. HGH has also been known to stimulate collagen synthesis in the skeletal muscle and tendons. In HGH-deficient adults, participants who were administered long-term HGH therapy experienced normalization of muscle strength, increased exercise capacity, and improved thermoregulation and body composition [9, 10]. Growth hormone (GH) replacement therapy has become an established form of treatment in GH-deficient (GHD) patients. It is evident that adults with untreated GH deficiency are both physically and psychologically compromised and benefit from GH replacement.

Although the beneficial effects of GH replacement therapy has been well documented, the long term outcomes and adverse effects of long term therapy has not been well characterized. In recent years there has been much concern and controversy on hGH and risk of cancer; either in individuals with no previous history of malignancy or increased risk of recurrence in cancer survivors [11-14]. It has been demonstrated that GH and the mediator peptide IGF-1 have the ability to influence regulation of cellular growth [15]. *In vitro* studies have showed that GH causes transformation of normal cells and proliferation of leukemic cells; IGF-I acts both as a strong mitogen and as an anti-apoptotic agent in a wide variety of cancers [16]. There are many published reports on studies of the possible association between GH/IGF-1 status and cancer risk, however the data remains inconclusive. Some studies have shown a correlation between high plasma concentrations of the GH-dependent growth factor insulin-like growth factor I (IGF-I) and an increased risk for the common cancers of adulthood such as breast, colorectal, and prostate cancers.

The availability of bio-recombinant GH has also expanded the use beyond GHD to conditions, including use in anti-aging formula and sports to boost performance; however data regarding its efficacy and safety in these conditions are still lacking [17].

The objective of this review is to explore evidence from clinical studies and epidemiological studies to determine the safety of GH and current updates on any adverse effects including cancer risk.

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## 2. Methodology

An exhaustive literature search was conducted using key words and phrases that included, "growth hormone", "growth hormone factors", "growth hormone replacement therapy", "benefits and adverse effects of growth hormone" including "growth hormone and cancer" from various search engines including Google Chrome, Google scholar, Pubmed and Medline. More than 80 articles were retrieved; the search was refined to include only original articles between 2007 and 2017 that were relevant to this study. Some earlier publications were also reviewed for historical perspectives and relevance. A total of 38 articles were studied and evaluated for this review.

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## 3. GH treatment in paediatric GHD

GH is licensed for use in many countries for treatment of patients diagnosed with GH deficiency (GHD). Diagnosis of GHD in childhood requires a combination of clinical criteria, biochemical tests and radiological evaluation. GHD results from developmental abnormalities or diseases affecting the hypothalamus and pituitary gland. The causes may be genetic defects affecting the genes that regulate development of pituitary cells secreting GH or may be acquired causes such as pituitary tumours, craniopharyngioma, infection of the central nervous system, traumatic head injury and cranial irradiation. The most common presentation of GHD in children is stunted growth. After initial approval in 1987 for children with GHD, GH treatment has been approved for a number of conditions that result in stunted growth for growth failure associated with Turner syndrome, short stature homeobox-containing (*SHOX*) gene deficiency, Prader-Willi syndrome, and chronic renal insufficiency and in children born small for gestational age (SGA).

The Malaysian Clinical Practice Guidelines, Ministry of Health (2010) recommend that GH treatment in children should be monitored closely by a paediatric endocrinologist in partnership with the paediatrician or primary care physician and should be conducted on a 3- to 6-monthly basis, to document auxological data, monitor treatment response, compliance and safety. Many studies have showed that side effects are rare. These include acute pancreatitis, gynaecomastia, oedema, lymphoedema and carpal tunnel syndrome [18]. Girls with TS on rhGH therapy were at increased risk for diabetes mellitus, slipped capital femoral epiphyses (SCFE), idiopathic intracranial hypertension, oedema, lymphoedema or scoliosis [19].

### 3.1. GH treatment and risk of malignancy

There has been increasing concern regarding the potential influence of GH therapy on neoplasia due to the general growth-inducing effects of GH. Recombinant GH is both anabolic and mitogenic whilst IGF-1 is antiapoptotic. There is much experimental data to suggest that GH treatment acting via local tissue might enhance tumour cell growth. There are concerns that GH treatment may cause new malignancy (*de-novo*), tumour recurrence or second malignancy in those already treated for one tumour.

The majority of studies that evaluated the risk of *de novo* neoplasms in patients without previous malignancy who received childhood treatment with recombinant GH detected no increase in rates of *de novo* neoplasms either during treatment or in post-treatment follow-up. The studies have reported the rates of primary cancer in GH-treated patients without risk factors to be similar to those of the general population.

One of the earliest studies was conducted by Howell *et al* in 1998 in Sweden involving 102 patients with neurofibromatosis (NF) [20]. GH deficiency and short stature is a feature of NF patients, commonly associated with the presence an intracranial tumour or the management of the tumour by radiation. The data for the study was obtained from the Pharmacia and Upjohn International Growth Database, set up in 1987 to monitor the progress of patients receiving GH replacement therapy. The study reported that 5 out of 102 patients had a recurrence of an intracranial tumour or a second intracranial tumour. It was concluded that incidence of tumour occurrence is comparable to that reported previously in similar patients with NF and that GH therapy did not influence the progression of any of the features of NF including intracranial tumours. The retrospective study design including lack of controls was a limiting point of this study.

Child *et al.*, in 2016, reported their findings on primary cancer assessment from a large observational study of GH treated children [21]. A cohort of 19,054 GH-treated children were obtained from an observational Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS). This study evaluated the incidence of primary malignancies The GH-treated children without a history of previous malignancy did not have a higher risk of all-site primary cancer during the study when compared to general-population cancer registries. Wilton *et al* in 2010 assessed the incidence of cancer in GH treated patients, in an observational survey (KIGS—the Pfizer International Growth Database study) [22]. The authors analyzed data from patients with growth disorders who had no known increased risk of developing cancer before starting recombinant human GH treatment. This study also concluded that there was no evidence that GH treatment in young patients with growth disorders resulted in an increased risk of developing cancer, relative to that expected in the normal population.

A recent large scale and long term follow up study, “Safety and Appropriateness of Growth Hormone Treatments” in Europe (SAGhE) was conducted in Europe to determine the association of GH and cancer risk [23]. The European cohort study involved 8 countries, Belgium, France, Netherlands, Sweden, United Kingdom, Switzerland, Germany, and Italy, and a cohort of 23,984 patients who had received treatment with recombinant hGH since 1984. Data was obtained from national population-based registries for mortality and cancer incidence. The study reported 251 deaths from cancer and 137 cancer incidences in the countries. The authors concluded that, although there was a significant increase in cancer mortality with increasing mean daily r-hGH dose for patients with previous cancer, the results could not establish that GH treatment affects the risk of cancer incidence. Caution for their inference was based on weaknesses of the study that included complexity of heterogeneity in patients and treatments from 8 countries and limiting information from aggregated data especially GH treatment beyond paediatric ages for some patients and IGF-1 levels.

In a retrospective cohort multi-centre study in the United States. Sklar and co-workers investigated the risk of second neoplasms among GH treated cancer survivors who were enrolled in a Childhood Cancer Survivor Study [24]. The first phase of their study, a long-term follow-up of 5 year cancer survivors involved 361 cases from a total of 13,539 cancer survivors. The study concluded that GH therapy did not increase the risk of disease recurrence or death in survivors, however an increase in number of secondary osteogenic sarcomas were observed among leukemia survivors treated

with GH (15 out of 361). This study reported that cancer survivors who were treated with GH had a three-fold increased risk of developing a second neoplasm (SN) compared with cancer survivors who had not received GH treatment.

In the second phase of their study, the 361 patients who had received GH treatment were again selected from 14,108 cases enrolled in the Childhood Cancer Survivor Study and followed up for another 32 months [25]. An additional 5 patients developed solid tumours; meningiomas were the most common SN among the GH-treated group. This updated study confirmed their earlier finding that childhood cancer survivors treated with GH appear to have an elevated risk of developing a secondary solid tumour compared with survivors not so treated. The elevation of risk due to GH use appears to diminish with increasing length of follow-up and overall risk was small.

### 3.2. Insulin like growth factor and association with malignancies

IGF-I over-expression occurs in tumours diagnosed in childhood such as osteosarcoma, Wilms tumour and neuroblastoma [26]. Several large-scale epidemiological studies have shown a link between high levels of IGF-I and some common cancers of adulthood, including of prostate, lung, breast and colon cancers. Data from these studies have demonstrated that high levels of IGF-I and low levels of IGFBP-3 are predictive of a heightened cancer risk. Further, Shevay and Laron in 2007 have reported that congenital IGF-I deficiency acts as a protecting factor for the development of cancer [27]. In their survey of 222 patients with congenital IGF-I deficiency and 338 first and second-degree relatives, none of the IGF-I deficient patients had cancer, whereas 9-24% of the family members had a history of malignancy. Individuals with Laron syndrome (GH receptor [GHR] deficiency) have a greatly reduced cancer risk compared with family members without the receptor deficiency. Laron syndrome is due to a mutation in the GHR resulting in low circulating IGF-1 and consequent short stature. Steuerman *et al.*, in 2011 examined 230 individuals with this disorder and found no cases of cancer, while family members without the disorder had developed various forms of cancer [28].

A prospective study was conducted in United Kingdom by Allen and coworkers to determine the associations between serum concentrations of insulin-like growth factor-I (IGF-I), IGF-II and IGF-binding proteins (IGFBP)-3 and breast cancer risk [29]. One hundred and seventeen cases involving 70 premenopausal and 47 postmenopausal women and 350 matched controls were investigated in a nested case-control study from the island of Guernse. Their data showed that premenopausal women with a relatively high circulating IGF-I that premenopausal women with a relatively high circulating concentration of IGF-I and low levels of IGFBP-3 were at an increased risk of developing breast cancer. Their results also showed that IGF-I and IGFBP-3 was not associated with risk in postmenopausal women and serum IGF-II concentration was not associated with risk in pre- or postmenopausal women. In a Sweden nested case control study, Stattin and co-workers investigated the role of GH factors, IGF-I, IGFBPs-1, -2, and -3 as well as insulin as possible etiologic factors for prostate cancer [30]. Plasma levels of IGF-I, IGFBP-1, IGFBP-2, IGFBP-3, and insulin were measured from 298 control men and 149 men who had a diagnosis of prostate cancer between 1 month and 10 years after blood collection. In this study case subjects had statistically significantly higher mean levels of IGF-I and IGFBP-3 than control subjects. The study reported that prostate cancer risk is increased in men with elevated plasma IGF-I. Since the association was strong in younger men in the study, circulating IGF-I may be specifically involved in the early pathogenesis of prostate cancer.

Enriori *et al.*, conducted a study in Argentina, to compare serum IGF-I concentrations in patients with gross cystic disease (type I and type II cyst) and healthy women [31]. This study involved 24 patients with type I cysts, 17 with type II cysts and 25 healthy women. Their results showed that serum IGF-I concentrations were significantly higher in sera from patients with type I cysts than in patients with type II cysts. A highly significant decrease of IGFBP-3, the major IGFBP, was found in patients with type I cysts with respect to healthy women. The IGF-I/IGFBP-3 ratio, an estimate of biologically active IGF-I, was very significantly higher in patients with type I cysts than in both type II patients and healthy women. The IGF-I/IGFBP-1 ratio was also significantly higher in patients with type I cysts than in type II bearers and healthy women. The study concluded that the enhanced levels of IGF-I/IGFBP-3 found in patients with type I cysts could eventually be associated with the increased risk of breast cancer. Giovannucci *et al.*, conducted a prospective study between 1989 and 1990 to examine whether plasma levels of IGF-1 and IGFBP-3 influence risk of colorectal cancer and adenoma in women [32]. A total of 32,826 women from the Nurses' Health Study were followed up from 1989 to 1994. During the study period, 79 new cases of colorectal cancer, 90 cases of intermediate/late stage adenoma and 107 cases of early-stage adenoma were documented. The study reported that high levels of circulating IGF-1 and particularly low levels of IGFBP-3 are associated independently with an elevated risk of colorectal adenoma and cancer.

Several studies have published the association of acromegaly and cancer. Acromegaly is a medical condition characterized by excess growth of distal bones, soft tissue and viscera, caused by hypersecretion of GH, which stimulates the release of IGF1. Glucose intolerance and diabetes are well-documented complications of acromegaly. In a study of

acromegaly patients in Iran, Larijani *et al.*, investigated 23 acromegaly patients by colonoscopy and detected colonic polyps in 3 of these patients [33].

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#### 4. Non-prescription uses of GH in anti-aging and sports

Adults with GHD present with a wide spectrum of clinical presentation that may overlap with a variety of other conditions [34]. GHD syndrome in adults is associated with increased risk for cardiovascular mortality, osteopenia, fracture rates, fat mass and decreased muscle mass. Untreated GH deficiency in adults is associated with increased morbidity and mortality. Successful GH replacement therapy ameliorates many symptoms of GH deficiency

GH levels in circulating blood are high early in life, corresponding to the period of rapid somatic growth, and begin to decline soon after attainment of puberty and full physical and reproductive maturation. This decline continues during adult life and aging due to reduced hypothalamic secretion of GH-releasing hormone (GHRH) with consequent decline of GH biosynthesis and release by the anterior pituitary. Some of the symptoms of aging include decrease in muscle mass, increased adiposity, reduced libido and energy and resemble symptoms of adult GHD. This association between declining levels of plasma IGF-1 and aging symptoms was reported by Rudman *et al.*, in 1990 [35]. In this study involving elderly men aged between 61 and 81 years, with low levels of plasma IGF-1, recombinant GH treatment improved general well-being, reduced adiposity and increased muscle mass and bone density. These results elicited enormous general interest by raising the possibility of using hormonal replacement therapy to slow down, halt or perhaps even reverse aging, or at least some of its symptoms. Marketing claims of its anti-aging properties has spiralled the enthusiasm for GH use in healthy individuals. GH has also been used in sports based on its anabolic properties to enhance performance. The misuse of GH in sports, often termed “sports doping” is banned by sports associations including the International Olympic Committee.

GH use for anti-aging and sports has not been approved. Data regarding its efficacy and safety in these conditions are still lacking. Published literature on randomized, controlled trials evaluating GH therapy in the healthy elderly is limited. A systematic review was carried out by Liu *et al.*, (2007), to evaluate the safety and efficacy of GH among healthy elderly reported that GH use is associated with small changes in body composition and increased rates of adverse events and did not recommend its use as an anti-aging therapy [36]. Considering limited literature on the subject, the benefits on athletic performance is not supported by any scientific evidence. Liu *et al.*, (2008), conducted a systematic review on GH use and athletic performance and concluded that GH may not improve strength but may worsen exercise capacity and increase adverse events [37]. Melmed *et al.*, (2008), have reported a case of metastatic colon cancer in a patient had been receiving HGH therapy for anti-aging purposes for 7 years before clinical presentation [38].

Another alarming concern is that HGH sold illegally may be impure with a combination of other unknown products, which are potentially dangerous.

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#### 5. Conclusion

GH replacement therapy in both children and adults is well tolerated and improves most of the alterations observed in GH deficiency (GHD). Despite the positive effects of GH on body composition, HGH therapy may cause one or more side effects such as gynecomastia, carpal tunnel syndrome, joint pain, oedema, and impaired glucose tolerance. The clinical usefulness of any therapeutic intervention has to be considered on the relationship of benefits to risks, which will depend on the age and gender of the patient, the disease condition in which it is assessed, the doses and regimen employed as well as the severity of adverse effects encountered.

The primary concern with GH use for healthy adults without proven GHD is the lack of long-term studies evaluating its safety and efficacy. Weak study design, small scale studies, short term evaluations, patients lost to follow-ups and mismatched controls, further lead to incomplete ascertainment and lack of validation of the outcomes of studies. The benefits of long-term use of GH to improve health outcomes in healthy aged individuals, for example, to reduce age related symptoms such as sarcopenia, osteoporosis, cardiovascular disease or dementia, has not been conclusively demonstrated scientifically. Safety concerns have been raised about whether GH treatment increases the risk of cancer. There has been a large number of studies conducted to determine the association between GH therapy and cancer. Although some progress has been made in investigating the role of GH and factors in cancer, there is still limiting evidence to establish a definite link. Data from most of these studies do not show a higher than expected risk of cancer in people treated with GH therapy when compared with the risk of cancer in the general population; Whilst some studies did show significant cancer incidence in adults with GH deficiency treated with GH, the results of these small studies

certainly do not confirm that GH therapy is associated with cancer but does highlight the need for further long-term investigation.

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## Compliance with ethical standards

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### *Disclosure of conflict of interest*

The authors declare that they have no conflict of interests. Ganesh Chidambar Subramanian conducted the review and wrote the manuscript. Dr Yuslina, Dr Ezalia, Dr Zubaidah and Dr Stephen participated in the internal review of the manuscript.

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