Growth Hormone & IGF Research 25 (2015) 149–157

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Review article

Reviewing the safety of GH replacement therapy in adults

Kirstine Stochholm [a], Gudmundur Johannsson [b,c,*]

[a] Department of Internal Medicine and Endocrinology, Aarhus University Hospital, 8000, Aarhus C, Denmark
[b] Department of Endocrinology, Grstr 8, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden
[c] Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Göteborg, Grstr 8, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden

ARTICLE INFO

Article history:
Received 19 May 2015
Received in revised form 17 June 2015
Accepted 17 June 2015
Available online 19 June 2015

Keywords:
Growth hormone
Hypopituitarism
Mortality
Morbidity
Safety
Adults

ABSTRACT

Context: Systematic data on safety of growth hormone (GH) replacement therapy in adult GH deficiency is lacking.
Objective: To systematically describe safety of adult GH replacement therapy on glucose metabolism and long term safety.
Design: A systematic web-based search of PubMed was performed guided by the Standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).
Outcome: Randomised controlled trials of ≥3 months and open trials for ≥12 months with more than 50 adult patients (50 patient years, prospective and retrospective) including adverse event reporting as well as articles on mortality primarily on adult onset patients, reporting mortality ratios on GH treated patients, were included for the review.
Results: Based on the defined selection criteria 94 studies were included. The short-term early placebo controlled trials did not demonstrate an increased frequency of diabetes mellitus (DM) and the long-term open studies did not consistently show an increased incidence of DM during GH replacement. The concern that long-term GH replacement might increase the risk of primary cancer, secondary neoplasia after tumour treatment and recurrence of previous tumours was not evident in the study data.
Conclusion: Based on available data, short- and long-term adult GH replacement in patients with severe GH deficiency and hypopituitarism is safe. However, the small number of subjects, limitation of long-term of GH treatment data and absence of an adequate control population is still a limitation for the interpretation of these data.

1. GH deficiency in adults — background

Growth hormone deficiency (GHD) in adults caused by a hypothalamic–pituitary disorder is an infrequent syndrome characterized by an adverse body composition, an unfavourable lipid profile, impaired physical capacity, reduced bone mineral density (BMD) and compromised self-reported quality of life [1].

Incidence data on adult onset GHD is scarce. A population-based estimate from the North-Western part of Spain suggests an incidence rate of adult hypopituitarism of 4.2 per 100,000 per year [2], and a Danish incidence study on adult onset GHD suggests an incidence rate of 1.9 per 100,000 in men and 1.4 per 100,000 in women [3].

2. GH replacement — efficacy

The efficacy of GH replacement therapy for adults with well-defined hypothalamic–pituitary disorder and GHD is well documented [4]. A meta-analysis of the efficacy of GH replacement on cardiovascular risk factors in adults based on randomised placebo controlled trials showed that GH treatment had beneficial effects on lean and fat body mass, total and low-density-lipoprotein (LDL) cholesterol concentrations, and diastolic blood pressure, but with reduced insulin sensitivity [5]. The increase in bone mineral content and BMD and the improvement in quality of life have also been well-described, but mainly based on long-term open studies [6–10]. The studies showing efficacy of GH replacement therapy has formed the base of increasing use of GH for replacement in adult hypopituitary patients and many long-term open surveillance studies have demonstrated continuing long-term effects in terms of favourable impact on lipids, increased BMD and improvement in quality of life. The long-term use of GH replacement in adults has therefore been adopted in many centres, which also has increased the interest in long-term safety of this replacement therapy.

3. GH replacement — safety

Direct effects of GH and GH-induced synthesis and secretion of IGF-I from the liver as well as the stimulation of local production of IGF-I in most tissues mediate the well-known effects of GH [11–14]. The safety concerns related to GH replacement therapy comes in particular from the sodium and water retaining effects, the reduction in insulin

* Corresponding author at: Department of Endocrinology, Grstr 8, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden.

http://dx.doi.org/10.1016/j.ghir.2015.06.006
1096-6374/

sensitivity and the induction of cell growth and proliferation in response to GH and IGF-I. The short-term adverse event reporting has mainly supported fluid related side-effects and impairment in glucose metabolism whereas the long-term concerns are mainly related to increased frequency of diabetes mellitus (DM) and a possible impact on progression on the underlying tumour causing the GHD as well as on de novo neoplasia.

GH and IGF-I through their action on the distal nephron induce the retention of salt and water and the sustained increase in extracellular fluid that is seen during GH replacement in adults [15]. Adult patients with GHD have reduced extracellular fluid volume [16], which is restored by GH replacement therapy [17]. The rapid increase in extra cellular water in response to GH treatment is the mechanism behind the early dose related side effects seen in adult patients when GH replacement is initiated. In the first trials with adult GHD, the dose was based on body weight, which resulted in high daily GH doses in patients with high body weight. Side-effects were therefore more frequently seen in patients with high BMI and in patients with adult-onset disease and in older patients [18]. The most frequently reported fluid related side-effects are peripheral oedema, arthralgia, muscle stiffness, myalgia, paresthesia and carpal tunnel syndrome [19].

We undertook a systematic search for publications addressing safety of adult GH replacement therapy. Based on the search criteria and review of the abstracts and papers, 92 full papers were included for review [6,8,12,13,18–105]. The report focuses on glucose metabolism and long-term safety.

3.1. Search methods

Standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed [106]. The main study objectives were formulated according to the PICO (Patient, Intervention, Comparison, Outcomes) model before the web-based search was performed. The following criteria were used: P — Hypopituitarism or GHD adults, I — GH treatment or replacement, C — placebo, no treatment, open with no controls, O — all cardiovascular surrogate markers, glucose metabolism, fracture data, cancer, pituitary tumour progression, and mortality. A detailed web-based search of PubMed was last performed on 18 Otober 2014. Search strategies combined the following terms: I. GH replacement (filters: clinical trial, human, English, adults +19) and II. GH deficiency and mortality (filter: adults). I: Based on the title of the studies and abstracts, reviews, letters, editorials and case reports and short-term (<3 months) experimental trials unlikely to have any safety report were excluded. Randomised controlled trials of ≥3 months and open trials for ≥12 months with more than 50 patients (50 patient years, prospective and retrospective) including adverse event reporting were included for the review. Full articles of interest were retrieved and analysed (Fig. 1). II: Based on the title of the studies and abstracts, reviews, letters, editorials and case reports were excluded. Articles on mortality primarily on adult onset patients, reporting mortality ratios on GH treated patients, were included. Two additional reports were manually included into this review, as they did not appear in the web-based search (Fig. 1).

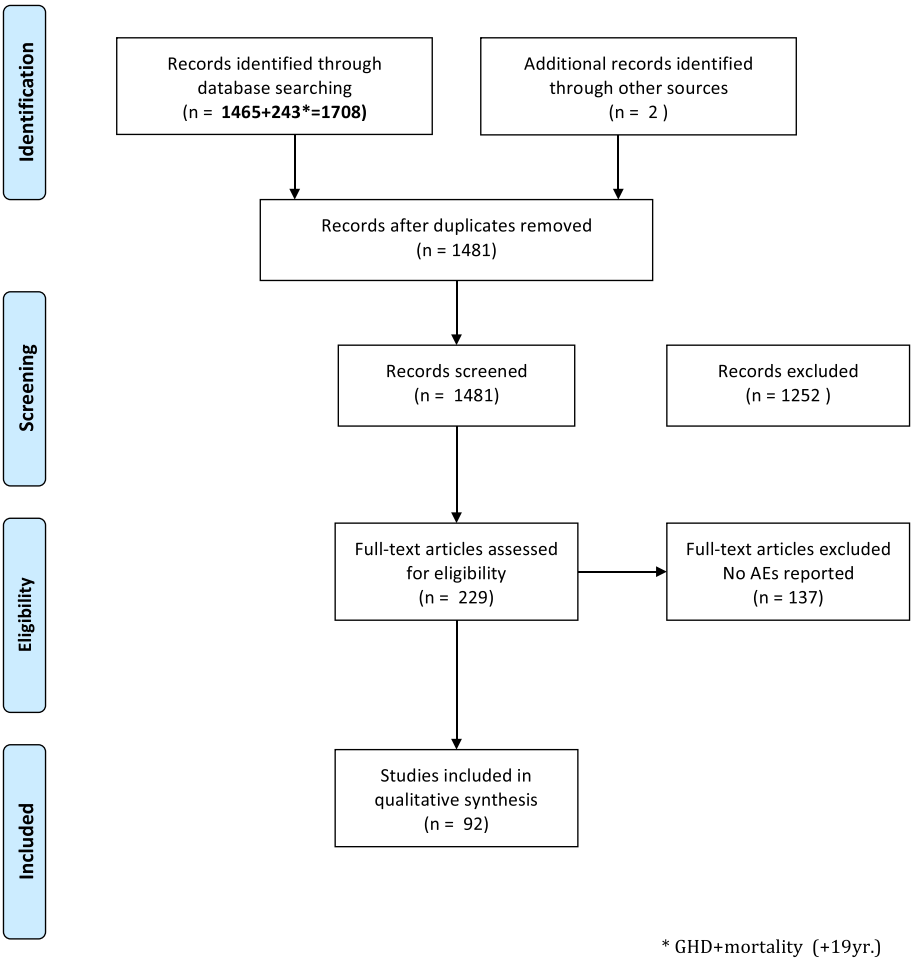

Fig. 1. Flow diagram of selected studies.