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Challenges and future for the delivery of growth hormone therapy

Andrés Caicedo[a,b,*], Ron Rosenfeld[c]

[a] Colegio de Ciencias de la Salud, Universidad San Francisco de Quito, Quito, Ecuador
[b] Mito-Act Research Consortium, Universidad San Francisco de Quito, Quito, Ecuador
[c] Oregon Health and Science University, Portland, OR 97239, United States

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ABSTRACT

Growth hormone (GH) has multiple roles in sustaining human development and homeostasis. Its pulsatile secretion stimulates growth and contributes to an equilibrium in a process tightly regulated and coordinated by many organs. GH deficiency is a medical condition affecting all ages, with not only significant consequences in the health of the patient but also impact on the quality of life. This review gathers the different strategies used today with a glance at future technologies to treat GH deficiency. We present key aspects for consideration when developing new methods to deliver GH, mimicking or replacing its pulsatile activity. Today and in the future, the fusion of biochemistry, biology and nanotechnology will provide hybrid devices using microfluidic systems. But, until new technologies for GH delivery will become available, current methods must be reinforced in conjunction with the development of better communication strategies between the health system and patients. Treating GH deficiency represents a multidisciplinary effort for which this review provides a glance at potential future directions for this therapy.

1. Introduction

Growth hormone (GH) is essential for human development and health, as it mediates cell metabolism, body growth, and circadian clock rhythmicity, among other actions [1]. The secretion and actions of GH are tightly regulated in children by the need to increase in size and in both children and adults to maintain tissue homeostasis [2]. Secretion of GH is also dependent on a variety of external factors, such as nutrient intake, and by behavioral patterns, such as sleep, physical activity and stress [2,3]. These factors activate the hypothalamus, which controls GH secretion via GH releasing hormone (GHRH), somatostatin (SRIF), and GH releasing peptide (Ghrelin). The hypothalamus, together with insulin-like growth factor (IGF-I), which is produced in the liver and other tissues, participates in a negative feedback loop with GH, thereby controlling its secretion and decreasing GH production [4]. Once GH is secreted by the pituitary gland, it binds to GH-binding protein (GHBP) and is transported to the entire body by the circulatory system [5]. Cells susceptible to react to GH stimulation express the GH receptor, which activates the Janus Kinase 2 (JAK2) and Src family kinases signaling pathways [6]. Perturbations in GH secretion or downstream after its receptor activation can cause suboptimal growth, decreased bone density, delayed puberty and decrease the quality of life of affected individuals [7].

Clinical approaches to the treatment of GH deficiency have overcome many difficulties, beginning from where to obtain it or how to synthesize it, to determining the appropriate dosage and availability once inside the body. Cadaveric human pituitaries were the only viable source for human GH isolation in the 1950s, but this method was not sustainable and safe [8]. Cadaveric tissue was rapidly unavailable due to the demand and it represents a potential risk of transmitting diseases from the donor of the pituitary gland to the patient [9]. In the 1980s the method to obtain GH synthetically via recombinant Deoxyribonucleic Acid (DNA) technology was refined and very quickly this procedure was available to the public, appearing in the market as Recombinant Human Growth Hormone (rhGH) and administered by intramuscular or subcutaneous injection [9]. rhGH helps children and adults benefit from its effects and many treated patients attain normal size or achieve sustained growth with age [10]. Many studies have shown that compliance to the rhGH treatment is the most important factor in measuring the success of the therapy, in terms of growth and growth velocity [10–12]. For example, in New Zealand a 6–8 month follow up of 12-year old children with GH-deficiency, compliant patients, i.e. patients having missed no more than one dose, showed significant improvement: patients gained on average 3 cm while uncompliant patients, i.e. patients having missed more than 3 doses per week, grew less than 1 cm [13]. In a multicenter study, follow up assessments at 3, 6 and 12 months

* Corresponding author at: Universidad San Francisco de Quito USFQ, Colegio de Ciencias de la Salud, Escuela de Medicina, Vía Interoceánica km 12.5 and Av. Florencia, 17-12-841, Quito, Ecuador.
E-mail address: acaicedo@usfq.edu.ec (A. Caicedo).

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showed that compliant patients (0% missed doses) had a significantly faster growth compared to uncompliant patients (more than 10% missed doses) [14]. But, daily injections, frequency of administration, and cost of rhGH influence the compliance of patients to the treatment, frequently resulting in sub-optimal growth or limited metabolic effects [13,14,11].

It remains unclear whether ideal treatment with rhGH must mimic the normal pulsatile secretion, dosage and persistence in circulation. Normal GH pulsatility in peripheral blood is tightly regulated, with discrete bursts approximately every 3 h, and achieving the highest concentrations during sleep [4,15,16]. Different strategies of administration try to mimic this regulated process by prolonging the activity of rhGH in the circulation but longer action of GH goes further away from normal physiology and represents a challenge for its application. So far long-acting rhGH has solved the need for every day injections and has shown promising results [17]. It is possible to extend rhGH viability (long-acting GH) by stabilizing its molecular structure with the addition of Zinc (Zn2 + -hGH dimeric complexes) or using carrier solvents, such as hydrogels, microspheres or microcapsules that allow a sustained availability of rhGH in the circulation [9]. Ideally, injections should be delivered weekly, biweekly or monthly via a small-bore needle; volume of drug should be capable of administration via a single injection. rhGH efficacy should not to be inferior to daily rhGH conventional therapy [18].

It has been observed that the device used to deliver GH is important in increasing adherence of the patient to the prescribed therapy. New options are constantly being developed as easy-to-use devices, such as injection pens, electronic injectors and needle-free injectors [19]. These devices must not cause local reactions, such as lipodystrophy or pain, which influence patient comfort and long-term persistence to the treatment. New technologies could be employed to provide minimally invasive treatments and will improve the delivery of GH by combining sensors, actuators and microelectronics in a device that could be practical, useful and painless for the patient [20]. Providing a treatment for GH deficiency has been a health challenge from the first isolation of cadaveric pituitary glands to the future adaptation of Micro Electromechanical Systems (MEMS) devices for pain-free GH delivery. This will represent a combined effort of biochemical, nanotechnological, and clinical know-how. The purpose of this review is to provide an overview of the current delivery methods of GH, the challenges and the directions for future development towards successful therapy.

2. Current challenges and solutions for a successful rhGH treatment

Every day administration of GH by intramuscular or subcutaneous injections is still the most effective and most widely used strategy to treat patients with growth deficiency [21,22]. This means of GH administration has seen little change over the last 30 + years and has always being burdensome for patients [9]. The most significant change in the application of GH treatment was the introduction in 1985 of biosynthetic GH or rhGH and the more recent development of new formulations to extend GH activity in the form of long-acting GH [5,9]. Many pharmaceutical companies now offer rhGH in a safe biosynthetic formulation, but its cost is high and especially problematic for low-income countries and public health systems [23,24]. Even if the administration of rhGH is burdensome and expensive, from the time of its isolation until today, GH treatment has helped thousands of children to recover normal growth and affected adults to achieve appropriate metabolic equilibrium [9]. Daily injections of rhGH with a concentration of 0.025 to 0.05 mg/kg/day are recommended to treat most pediatric GH deficiencies, but most patients don't consistently follow the prescribed treatment, even if they know that regular administration will help them to obtain the desired results [9,19,12].

The development of better strategies to facilitate access to rhGH therapy and increase the compliance of the affected population represents a priority for public health systems, pharmaceutical companies and health professionals [25]. One available option, as a public health strategy, is to continue the use of current delivery methods for rhGH, but educate and communicate better with patients and their families about the use of GH therapy and the need for maximal adherence to treatment protocols [26]. Improving the education of patients and facilitating communication with the practitioner would help reduce misperceptions about the consequences of missed GH doses and unfulfilled expectations [13,27]. The practitioner must be prepared to discuss all the questions and concerns that the patient might have, provide help, advise on device selection, understand specific patient needs, offer training sessions, improve the follow up of treatment by up-to-date options, and organize and cooperate to create support groups of patients and families, giving them the opportunity to share treatment complications or successes [28].

Doctor to patient communication is a key aspect in building a trustful relationship between the affected child or adult, their family and the practitioner [29]. The ability and competency to effectively transmit information to the patient has been shown to have positive associations with patient outcome, recall, understanding and adherence to therapy [30]. As patient to physician communication is important in clinical practice, formal training programs could be ideal as part of academic and professional training to transmit the important factors and guidelines about GH treatments to the patient and family [31]. As a long-term relationship is established between the patient with growth hormone deficiency and the physician, it would be recommended that the practitioner and young health professionals improve their communication skills, especially when treating children and dealing with their evolving attitude towards their condition as they approach puberty and adulthood.

The follow-up of the patient by the physician is typically limited to assessing the standard check points for the treatment and evaluation of the success of therapeutic intervention [32]. In practice, however, many patients do not follow their doctor's recommendations, negatively affecting success of treatment [33]. Little attention is paid to the fact that today's society receives constant information, news, health updates, exercise programs, and nutritional and activity follow-up through the use of current electronic technologies, such as smart phones, the internet and social media [34,35]. This represents a potential goldmine for transmitting information to the patient and following the progress of any treatment [36]. eHealth represents a term that involves the development and use of any type of communication technology (ICT) to improve health and all related purposes [37]. The development of eHealth approaches to increase adherence in patients to treatment has been shown to improve the outcome of many diseases [38–41]. “Mobile health” or “mHealth” is part of the eHealth strategies to deliver information, educational games, and reminders to patients' mobile phones, smart phones or tablets [39]. Also, eHealth strategies could improve patient to practitioner communication and provide a detailed follow up of treatment [42]. To our knowledge, none of these approaches has been used systematically to improve adherence to GH treatment.

Many strategies have been developed and studied in an effort to improve adherence to therapy in GH deficient patients, from developing devices that reduce the discomfort of GH administration to modifying the GH molecule and extending its activity in the body. The development of a GH infusion pump was an early option to daily administration of GH by injection. The continuous infusion of rhGH showed to induce levels of IGF-I slightly higher than daily injections [15]. In relatively short-term studies, the GH infusion pump has been shown to give comparable results to therapy with daily injections, but carrying a pump every day could decrease the quality of life in patients, especially children [15,43]. In a biochemical approach to increase the life-time in circulation of GH, rhGH was stabilized with biodegradable microspheres containing polylactic-*co*-glycolic acid (PLGA) [9]. The stabilization of rhGH with PLGA induced higher serum levels of rhGH