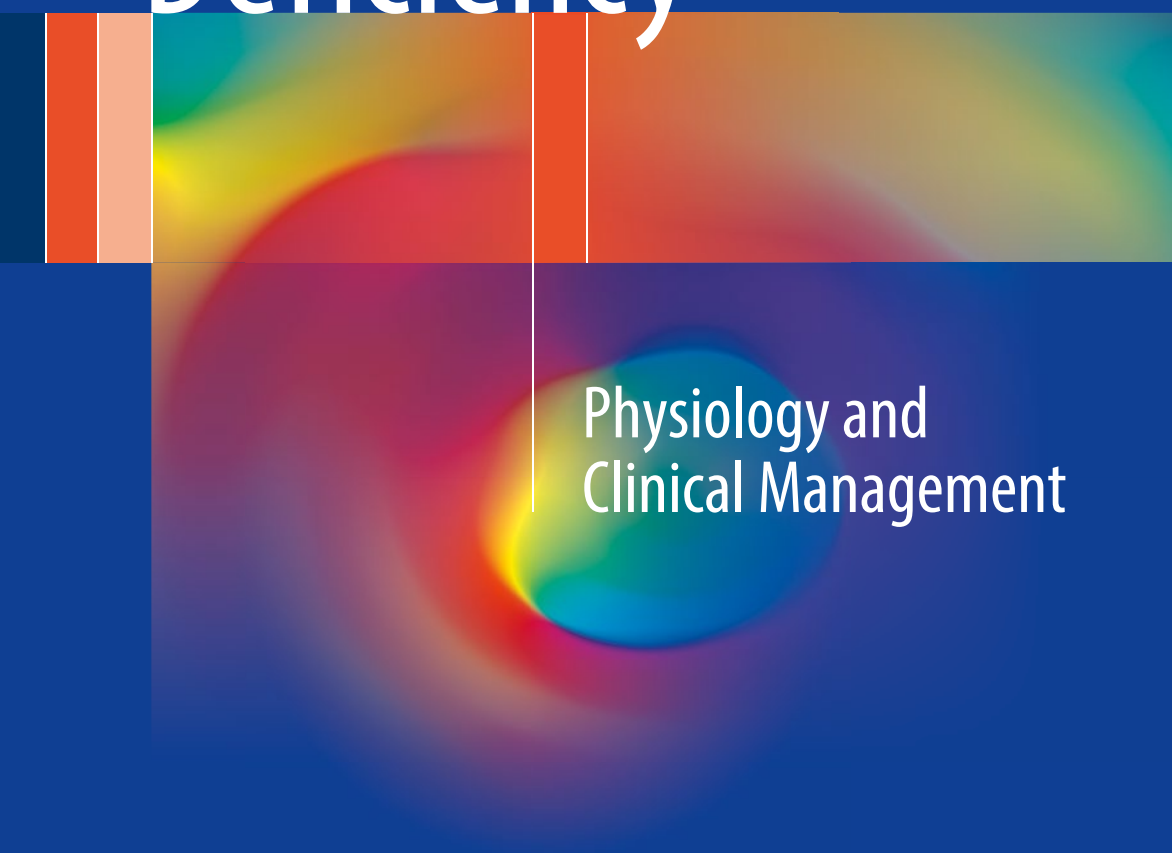
Laurie E. Cohen
Editor

Growth Hormone Deficiency



Physiology and Clinical Management

Springer

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ISBN 978-3-319-28036-3 ISBN 978-3-319-28038-7 (eBook)
DOI 10.1007/978-3-319-28038-7

Library of Congress Control Number: 2016936684

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Preface

While it has been known for close to 100 years that the pituitary gland regulates growth and for almost 60 years that human growth hormone (GH) stimulates growth in GH-deficient children, our knowledge about GH function and GH-deficient states continues to grow. Both basic science and clinical research have contributed to our understanding about GH, although the interactions between various systems are complex, and some mechanisms remain unclear. The goal of this book is to provide up-to-date information to the clinical endocrinologist on GH function and what occurs in GH deficiency.

After the Introduction, the book is divided into three parts. The first describes the mechanisms of human GH secretion and action. Growth hormone structure and function are explained, along with various important regulators of GH secretion, including sex steroids and thyroid hormone. Additionally, insight into how undernutrition, inflammation, and catabolic illness affect GH secretion is discussed; as well as how the opposite state, obesity, affects GH function and testing. Included in this part are the metabolic effects of GH on body composition and on cardiovascular risk factors.

The second part deals with the diagnosis of GH deficiency, both in children and in adults. It describes both the tests that can be utilized and their interpretation and points out the challenges faced in using these studies to make a diagnosis. A chapter is devoted to magnetic resonance imaging of the pituitary gland.

The third part explains various etiologies of GH deficiency, from molecular mechanisms to cranial radiation to traumatic brain injury, as well as syndromes associated with GH deficiency where the molecular defect is less clear.

The definition of "GH deficiency" remains a challenge. This book should guide clinicians in understanding their patients' underlying pathology. In the future, additional insights into the hypothalamic-pituitary-GH axis and GH signaling, plus newer technologies (e.g., whole exome sequencing) to determine molecular defects, may help us better determine which individuals have a defect in the GH signaling pathway and which individuals do not.

Boston, MA, USA — Laurie Cohen

Abbreviations

aa	Amino acid
BPS	Branching point site or branch point sequence
cAMP	Cyclic adenosine monophosphate
CHT	Compound heterozygous
CRH	Corticotropin-releasing hormone
CSS	Cryptic splice site
D1	Type 1 5′-deiodinase
D2	Type 2 5′-deiodinase
D3	Type 3 5′-deiodinase
ERK	Extracellular signal-regulated kinases
ESE	Exonic splice enhancer
GH	Growth hormone
GHD	Growth hormone deficiency
GHRH	Growth hormone-releasing hormone
GHRHR	Growth hormone-releasing hormone receptor
GHRP	Growth hormone-releasing peptides
GHRP-2	Growth hormone-releasing peptide-2
GHRP-6	Growth hormone-releasing peptide-6
GHS	Growth hormone secretagogues
HGMD	Human Gene Mutation Database
HGVS	Human Genome Variation Society
HM	Homozygous
HT	Heterozygous
IGF-I	Insulin-like growth factor-1
IGHD	Isolated growth hormone deficiency
ISE	Intronic splice enhancer
LCR	Locus control region
PKC	Protein kinase C
RTH	Resistance to thyroid hormone
SDS	Standard deviation score
SP	Signal peptide

T1DM	Type 1 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine
TR	Thyroid hormone receptor
TRE	Thyroid response element
TRH	Thyrotropin-releasing hormone

Contents

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Chapter 1
Introduction: Discovery of Growth Hormone and Synthesis of Recombinant Human Growth Hormone

Laurie E. Cohen

The most famous likely growth hormone (GH)-deficient individual was Charles S. Stratton (born February 4, 1838), nicknamed General Tom Thumb by P.T. Barnum who discovered him at age of 10. He was born to parents of normal height who were first cousins. His birth weight was nine and a half pounds, and he grew steadily until age 18 months. Thereafter, he grew poorly and had delayed puberty, growing several inches in his late twenties; he achieved an adult height of only 3 ft 2 in. He married Lavinia Warren Bump (born October 31, 1842) on February 10, 1863, in a highly publicized affair. Ms. Bump had grown normally until age 1 year but then only slowly, until cessation of growth at age 10 years and achieving an adult height of 2 ft 8 in. Her parents were third cousins of normal height. Due to their proportionate short stature, normal birth length and weight, growth retardation starting late in the first year of life, normal intelligence, and normal sexual development, it is assumed that both Stratton and Bump had autosomal recessive growth hormone deficiency (GHD) [1, 2].

In the nineteenth century, individuals with growth stunting were defined as "dwarfs" if disproportionate and as "midgets" if proportionate. At the turn of the nineteenth to twentieth centuries, an English physician, Hastings Gilford, created the term "ateliosis" to describe those with normal proportions and subdivided them into "sexual" (displayed normal sexual development) and "asexual" (did not display normal sexual development) [2].

While it was determined in 1922 that the pituitary gland regulates growth, GH was not isolated until 1944, and human GH was not isolated until 1956. Attempts to use GH to promote growth began in 1932, but success did not occur until 1958 when human GH was utilized. Cadaveric human GH was used until 1985, when Creutzfeldt–Jakob

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L.E. Cohen (ed.), *Growth Hormone Deficiency*,
DOI 10.1007/978-3-319-28038-7_1