Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism Genetics

Affiliated Journal of the Pediatric Endocrine Society (PES)

Recommended by ISPED and SIMA

Pediatric Endocrinology Reviews

Diabetes Nutrition Metabolism Genetics

Affiliated Journal of the Pediatric Endocrine Society (PES-USA)
Affiliated Journal of the Japanese Society of Pediatric Endocrinology (JSPE)

Recommended by ISPED and SIMA

Published by: Y.S. Medical Media Ltd.

8 Hamelacha St., Kiryat-Nordau Industrial Area, PO Box 8214, Netanya 42504, Israel, Tel: +972-9-8641111, Fax: +972-3-5217462
E-mail: per@medmedia.co.il, Website: www.pediatricendoreviews.com
Indexed in PubMed/MEDLINE, SCIE, EMBASE/EXCERPTA MEDICA, EBSCO and SCOPUS Databases

Founders: Zvi Laron, MD, PhD (h.c.)
Delbert A. Fisher, MD

Publisher: Yoel Shamos

Editorial Manager
Irit Lipner

Design
Rina Yashar

Accounting
Sima Ben-Or

PEDIATRIC ENDOCRINOLOGY REVIEWS (PER) publishes scholarly review articles in all areas of clinical and experimental Endocrinology, Diabetes, Nutrition, Metabolism and Genetics.
PER is intended for practicing pediatricians, pediatric endocrinologists, pediatric diabetologists, pediatric gastroenterologists, neonatologists, pediatric gynecologists, nutritionists, sport physicians, Geneticists and pediatricians-in-training.
PER will also publish topics on specific subjects or as proceedings of scientific meetings in the above fields of interest. All articles, whether invited or direct contributions, are peer-reviewed.
PER publishes correspondence, book reviews, a meeting calendar and meeting reports.

Submissions

Submit manuscripts online to email: irit.lipner@medmedia.co.il
or to the Editor-in-Chief, Zvi Laron, MD, E-mail: laronz@clalit.org.il

Manuscripts

Must be typewritten in English in Arial 12 font on one side 8 ½ x 11 inch (22 x 28 cm) heavy-duty white bond paper sequentially numbered, (including references, tables legends and footnotes). Abstract, references, tables and legends should each begin on a new page. Manuscripts should not exceed 16 printed pages including references, tables and figures. (4300 characters with spaces/page)
All accepted manuscripts are subject to editing.

Meeting Report

Same rules as for manuscripts

Transfer of Author Copyright

Copyright release should be addressed to Y.S. Medical Media, Ltd., which should include the article title, date and must be signed by all the authors.

Title Page

Include: authors' names, academic degrees and departmental and institutional affiliations of each. Designate one author as the corresponding author and provide address: business and phone; telephone numbers, fax numbers and email.
Include a running title and up to 8 keywords.

Abstract

Not exceeding 150 words, should incorporate data on background, Objective or hypothesis and main data. The abstracts will be available on the web.

Disclosures

PubMed requires all authors include a "conflict of interest statement" preceding the Reference section.

References

Should be cited consecutively in the text in parentheses, regular size, and listed in the same numerical order at the end of the paper.
List the names of all authors.
Reference Example
Journal article:
van der Kooi AL, van den Heuvel-Eibrink MM, van Noortwijk A, Neggers SJ, Pluijm SM, van Dulmen-den Broeder E, van Dorp W, Laven JS. Longitudinal follow-up in female Childhood Cancer Survivors: no signs of accelerated ovarian function loss. Hum Reprod 2017;32:193-200
Book
Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 6th Ed, Zitelli BJ, McIntire SC, Nowalk AJ, eds, Amsterdam, New York, Elsevier Saunders USA 2012; pp.1067
Chapter in book:
Shevah O, Laron Z. Genetic Aspects in Z. Laron and J. Kopchick (eds), Laron Syndrome - From Man to Mouse, Berlin Heidelberg, Springer 2011; pp.29-52
Personal communications should not be included in the Reference list, but may be cited in the text in parentheses.
Papers accepted and in press may be listed mentioning the journal.

Tables & Figures

Each table with a heading must be typed on a separate sheet and numbered consecutively.

Illustrations

Illustrations should be of a high quality (jpg/pdf/power point). The cost of color illustrations will be charged to the author.
The legends should be typed together on a separate page.

Galley Proofs

After submission of all authors' final corrections, only printer's errors may be corrected.

Reprints & Copyrights

Reprint order and copyright form will be provided with the Galley Proofs.

Enquiries, Subscriptions, Reprints

Enquiries concerning manuscripts in press, reprints or submission may be addressed to: Irit Lipner, Tel: 972-9-864-1119, Fax: 972-9-521-7462, E-mail: irit.lipner@medmedia.co.il, or to the Editor-in-Chief, Zvi Laron, MD, Tel: 972-3-9253670/1, Fax: 972-3-9222996, E-mail: laronz@clalit.org.il.
All editorial correspondence, including Supplements, should be addressed to the Editor-in-Chief.

Advertising

Advertising by commercial firms should be addressed to email: per@medmedia.co.il.

See our website: www.pediatricendoreviews.com

Table of Contents

Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism Genetics

Forthcoming Articles

In Memoriam: Hans Akerblom, MD

Osteoclasts in Health and Disease
Ulf Lerner

Programing of the Autoimmune Diabetogenic Response in the Thymus during Fetal and Perinatal Life
Vincent Geenan, et al

Primary School Performance of Girls with Turner Syndrome: a Transcultural Assessment
Jan Lebl, et al

Endocrine Management of Ovotesticular DSD, an Index Case and Review of the Literature
Maria Vogiatzi, et al

Forthcoming Supplements

99 Years of Human Insulin
Guest Editors: Zvi Laron, Johnny Ludvigsson

Psychological Factors Influencing Clinical Management and Outcomes in People with Disorders/Differences of Sex Development (DSD)
Guest Editors: David E. Sandberg, Larry Mullins

Message from the Editors

To Our Readers,

Having received the previous issue you will certainly have observed that PER has become an Affiliated Journal to two large Pediatric Endocrine Societies: PES (USA) and JSPE (Japan). This will bring news from PER to an additional 2,200 colleagues.

In this issue, we remember John Crigler, an eminent pediatric endocrinologist and excellent teacher.

The articles range from metabolic actions of GH and FGF23 to the effect of GH on sleep, the genetics and physiology of osteoclasts, and hyperphosphatemia. The Meeting Report reviews selected lectures from the 2019 Endocrine Society Meeting.

We wish to acknowledge the receipt of an educational grant from Ascendis.

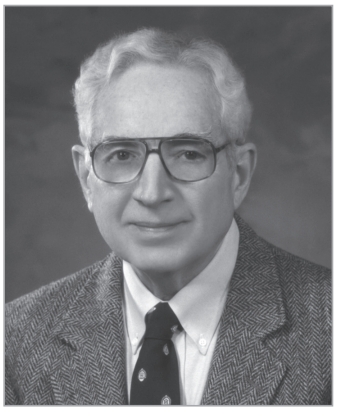
We hope that you have had a pleasant summer vacation.
Enjoy the reading.

Zvi Laron, MD, PhD (h.c.) *Mitchell E. Geffner, MD* *Tatsuhiko Urakami, MD, PhD*
and the Medical Media Team

In Memoriam

John Fielding Crigler, Jr, MD (1919-2018)

Ref: *Ped. Endocrinol. Rev. 2019;17(1):2-3*



John Fielding Crigler, Jr, MD, who co-identified the eponymous Crigler-Najjar Syndrome and was one of the founders of the field of pediatric endocrinology, died on May 13, 2018 at his home in Needham, Mass. He was 98. Dr. Crigler retired in 2007 as Chief (Emeritus) of the Division of Endocrinology at Boston Children's Hospital and Associate Professor of Pediatrics (Emeritus) at Harvard Medical School. He founded the Division in 1955, serving as its Chief for 34 years, and helped to establish the field of pediatric endocrinology nationally and internationally.

One of six children, Dr. Crigler was born in Charlotte, North Carolina on September 11, 1919. He was an accomplished cellist and was torn between choosing a career in music or medicine. His decision to pursue a career in medicine was no doubt heavily influenced by his relatives. His mother's sister was one of the three pediatric house staff in the first internship class of the Harriet Lane Home at Johns Hopkins School of Medicine in 1912. Dr. Crigler's other maternal aunt attended nursing school at Hopkins. Thereafter, with the support of the Rockefeller Foundation, she founded the School of Nursing at Peking Union Medical College in China, and upon her return to the United States successively became Head of Nursing at the University of Chicago, Cornell-NY Hospital, and Johns Hopkins, before retiring.

Dr. Crigler graduated from Duke University in 1939 and entered Johns Hopkins School of Medicine that same year. He met his future wife, Mary Adele Sippel, during his first days of medical school, a coincidence that he described throughout his life as "stumbling on happiness." After an internship at University Hospital in Boston in 1943, where Dr. Crigler and his fellow house staff oversaw the distribution of the entire world's supply of penicillin, Dr. Crigler joined the U.S. Navy as a Medical Officer, seeing action in the amphibious forces of both the Atlantic and Pacific theaters of World War II.

After completing his military service, Dr. Crigler pursued pediatric residency training at Hopkins between 1946 and 1950. As a resident, Dr. Crigler's meticulous attention to patients' histories and physical examinations, dogged perseverance and insatiable curiosity led to the discovery, with Victor Najjar, of the defect in bilirubin metabolism that bears their names. Throughout his career, his careful analysis of historical data and physical signs in comprehensive longitudinal studies became hallmarks of Dr. Crigler's clinical investigation, scholarship and teaching. He remained at Hopkins to receive training in pediatric endocrinology as the first Endocrine Fellow of Dr. Lawson Wilkins, the founder of the discipline of pediatric endocrinology. Working with Dr. Wilkins, Dr. Crigler defined the life-saving properties of glucocorticoids, which had just become available, in salt-losing congenital adrenal hyperplasia. This work, published in 1952, was chosen in 1998 by Pediatrics as the most important endocrinology paper published in the journal's first 50 years.

In 1955, after 3 years at MIT studying biophysical chemistry and molecular biology, Dr. Crigler, upon the request of Dr. Charles Janeway, joined the faculty of Boston Children's Hospital and Harvard Medical School as the founding Chief of the Division of Endocrinology. He was the first program director and principal investigator of the General Clinical Research Center at Children's Hospital from 1964-76 and Associate Director from 1976-89. During his tenure he established one of the first training programs in pediatric endocrinology through which he trained over 70 endocrinologists. Dr. Crigler attracted an impressive array of fellows, and his disciples became professors of departments of pediatrics or medicine, chairpersons, and deans, making significant contributions to the field. Dr. Crigler modestly reminisced towards the end of his career, "a few were destined to become leaders in their countries and have realized their goals."

He trained many of the current faculty of the Division of Endocrinology, including two of the authors of this Memorial Minute (JM and JW). Always the consummate teacher and scholar, Dr. Crigler's mentoring qualities included a unique blend of insight, humor, integrity, wisdom, passion, precision,

generosity, and pathos. Indeed, he relished and taught many the sheer joy of human interaction. Those who had the good fortune to work with and learn from Dr. Crigler were imbued with his uncompromising commitment to excellence. Indeed, being the student of one of Dr. Crigler's uncompromising lessons was not always pleasant. But as many of our senior current faculty can attest, Dr. Crigler elevated our standards and thereby contributed to our successes, and for this we are grateful.

After stepping down as Division Chief in 1989, Dr. and Mrs. Crigler took a six-month sabbatical at the Sydney Children's Hospital in Australia, both to enjoy a well-deserved respite from the hustle-bustle of Boston, and also to give the new Chief (JM) time to find his bearings. When he returned from sabbatical, Dr. Crigler worked actively until 1992, when he became a dynamic emeritus member of the Division, attending conferences and giving career advice to Fellows and faculty. To the new Division Chief, he was a constant supporter, not without suggestions and the gentlest of criticisms, which helped wisely guide the Division over the ensuing 25 years. In 2007, Dr. Crigler retired from Boston Children's Hospital.

In 1972 Dr. Crigler made a key observation which changed the way in which we think of disorders of metabolism: in patients with type 1 glycogen storage disease (von Gierke) whom he and Dr. Judah Folkman were preparing for portocaval shunt, then standard therapy for this disorder, he noted that the metabolic derangements improved markedly following parenteral hyperalimentation, which led to the concept that these derangements were but a futile attempt to compensate for the underlying disorder. These concepts form the basis for the current treatment of glycogen storage diseases as well as many of other metabolic diseases affecting glucose metabolism. His early studies changed glycogen storage disease from one of lethality in childhood, until today, when under the care of Dr. Crigler's students, Drs. Joseph Wolfsdorf and David Weinstein, these patients are now parents, and are on the cusp of being cured by gene therapy. Dr. Crigler authored over 70 clinical research papers and made important contributions to the pathophysiology and treatment of many other endocrine disorders throughout his career. Principal among these were long-term, cross-institutional studies of central precocious puberty using gonadotropin-releasing hormone agonists led by Dr. William Crowley (Massachusetts General Hospital) in collaboration with Drs. John Crawford (also at MGH) Robert Blizzard (University of Virginia) James Tanner (University College London) and their colleagues.

Dr. Crigler was a founding member of the Pediatric Endocrine Society as well as its 8th president, and was the recipient of the Judson Van Wyk Prize, given by the Pediatric Endocrine Society in recognition of outstanding career achievement in the field that he had helped establish. This award stands in tribute to an exceptional leader whose career is marked by scientific excellence, leadership, integrity, and dedication to the health of children. In 2007, Boston Children's Hospital honored Dr. Crigler and his wife with the creation of the John Fielding Crigler, Jr, and Mary Adele Sippel Crigler Chair in Pediatric Endocrinology at Children's Hospital Boston. Dr. Crigler requested that the endowed chair bearing his name also honor his beloved wife and life partner. She died shortly after the awarding of this honor to her and her husband. This Chair was (and still is) the largest endowment bestowed upon the Division of Endocrinology. Dr. David Ludwig, Professor of Pediatrics at HMS and Professor of Nutrition at Harvard School of Public Health, has served brilliantly as the first incumbent since its inception.

More personally, John and Mary Adele Crigler were loving friends of many of the Division's families, supporting them through their personal lives by welcoming them into their home, offering wise advice, providing emotional support and inspiring them in so many other ways. Most importantly, Dr. Crigler was devoted to Mary Adele, his wife of 63 years, and his children. He is survived by his four children, Catherine Drury Crigler Greenwood of Brookline, MA, John Fielding Crigler III of Irvine, CA, Ann Norris Crigler of South Pasadena, CA, and Virginia Ijams Crigler Guenette of Lenox, MA; four grandchildren, two great grandchildren, and many nieces and nephews.

Joseph A. Majzoub, Chair

E-mail: joseph.majzoub@childrens.harvard.edu

Thomas Carpenter

E-mail: thomas.carpenter@yale.edu

Joseph I. Wolfsdorf

E-mail: joseph.wolfsdorf@childrens.harvard.edu

Emerging Mechanisms of GH-Induced Lipolysis and Insulin Resistance

Vishva M. Sharma, PhD

Department of Biomedical Sciences and Diabetes Institute, Ohio University, Athens, OH 45701, USA

Correspondence author: Vishva M. Sharma, PhD, Department of Biomedical Sciences and Diabetes Institute, Ohio University, Athens, OH 45701, USA, Tel: +1-740-593-2227, E-mail: sharmav@ohio.edu

Abstract

Growth hormone (GH) is a pleiotropic hormone that coordinates an array of physiological processes including growth and metabolism. GH promotes anabolic action in all tissues except adipose, where it catabolizes stored fat to release energy for the promotion of growth in other tissues. However, chronic stimulation of lipolysis by GH results in an increased flux of free fatty acids (FFAs) into systemic circulation. Hence, a sustained release of high levels of GH contributes significantly to the development of insulin resistance by antagonizing the anti-lipolytic action of insulin. The molecular pathways associated with the lipolytic effect of GH in adipose tissue however, remain elusive. Recent studies have provided molecular insights into GH-induced lipolysis and impairment of insulin signaling. This review discusses the physiological and metabolic actions of GH on adipose tissue as well as GH-mediated deregulation of the FSP27-PPARγ axis which alters adipose tissue homeostasis and contributes to the development of insulin resistance and Type 2 diabetes.

Ref: *Ped. Endocrinol. Rev. 2019;17(1):4-16*
doi: *10.17458/per.vol17.2019.s.ghlipolysisandinsulinresistance*
Key words: *Growth hormone, PPARγ, FSP27, CIDEC, Lipid droplets, AKT, Insulin resistance, Fat metabolism, Metabolic disease, Type 2 diabetes*

Introduction

Historically, elegant work by Evans and Long in 1922 was one of the first demonstrations that an intraperitoneal injection of fresh bovine anterior hypophyseal extract accelerated growth in rats (1). A series of experiments by Houssay, Biasotti, Young and others dating back to the 1930's and early 1940's established that either hypophyseal extracts or crude anterior pituitary extracts accelerate growth as well as diabetes in dogs and cats (2-5). In 1942, Houssay reported that these pituitary extracts induced histological changes in many tissues and damaged Langerhans islands in the pancreas, indicating their diabetogenic potential (6). In 1944, Li and colleagues successfully isolated growth hormone (GH) from the anterior pituitary (7). Afterwards, a series of studies by multiple groups reported that GH has the potential to induce growth, diabetes and hyperglycemia in animals (7-11).

The physiological actions of GH are pleiotropic and involve multiple organs and physiological systems. Kastin et al in the 1970's showed that lipid mobilizing substances present in the hypothalamus and pituitary of mammals are involved in central neuronal control of obesity (12). They further hypothesized that GH-releasing hormone (GH-RH) may influence lipolysis secondarily by regulating pituitary hormones (e.g GH) release. Pituitary GH is the major regulator of liver-produced IGF-I, which is transported via circulation to peripheral tissues where it acts in an endocrine manner. GH exerts many metabolic

effects that persist throughout life (13,14). Although GH acts in nearly every tissue of the body, its growth promoting effects on cartilage and bone are most notable, especially during the adolescent years. In addition to promoting growth, GH exerts profound anabolic actions during postnatal skeletal development, in-part through stimulating insulin-like growth factor-1 (IGF-1) (15). Multiple studies have shown that GH acts in two steps: GH directly activates growth hormone receptor (GHR) to stimulate IGF1 synthesis and then IGF-1 acts on target cells to exert physiological effect of GH (16-18). GH and IGF-1 exert their effect on osteogenic cells via binding to their cognate receptors [(GHR) and IGF-1 receptor (IGF-1R)] respectively, which activate an array of genes that mediate cellular differentiation and function (19). GH induces skeletal IGF-1 synthesis, sulfate uptake, osteoblast hypertrophy, proliferation of prechondrocytes, widening of epiphyseal plate, stimulation of cartilage growth, mineralization and bone remodeling (20,21). Alterations in the GH-GHR-IGF-1 signaling axis can cause growth failure and changes in body composition (22-25). Although GH promotes growth, it unevenly effects protein, lipid and carbohydrate metabolism. Recombinant human GH therapy in GH-deficient children results in decreased body fat and increased fat-free mass, including muscle and bone. Growth hormone induces a rapid loss of fat due to the stimulation of lipolysis and reciprocal antagonism of the lipogenic actions of insulin (26).

Recent studies have shown that GH destabilizes PPARγ, the master transcriptional regulator of adipogenesis (27,28). This results in the deregulation of fat metabolism and promotes the progression of insulin resistance, a key precipitating factor for the development of Type 2 diabetes, cardiovascular problems and metabolic diseases (29-32). This review provides an update on recent studies that involve human subjects, primary human adipocytes, and mouse 3T3-L1 differentiated adipocytes to reveal signaling pathways and molecular entities involved in GH-mediated development of insulin resistance, a pre-requisite for the progression of metabolic diseases.

Growth Hormone Action

Somatic growth was thought to be controlled by pituitary GH-mediated production of somatomedin-C, insulin like growth factor 1 (IGF-1) expressed exclusively in liver. Liver IGF-1 therefore, was considered to be the prime mediator of GH action (33). However, later studies showed that extra-hepatic tissues can also produce IGF-1 and exert autocrine/paracrine effects in the local environment to promote growth (13,34,35). GH regulates metabolically diverse processes by binding to the GHR, a member of the cytokine receptor superfamily that is abundantly expressed in various tissues (36-38). Upon stimulation by GH binding, GHR tyrosine phosphorylates Janus Kinase 2 (Jak2). Activated Jak2 then phosphorylates GHR on tyrosine residues which in turn recruit members of the signal transducer and activator of transcription (STAT) family of transcription factors; of these, the STAT5 family has widely been associated with GH actions (39,40). Phosphorylation of STATs by Jak2 results in their dissociation from the GHR and subsequent homo/hetero-dimerization and translocation to the nucleus where they modulate transcription of an array of genes including IGF-1, acid labile subunit (ALS) and suppressor of cytokine signaling (SOCS) among others. IGF-1 then binds to its receptor on the cellular surface and activates intracellular signaling pathway, which results in the phosphorylation of various proteins leading to increased metabolism, anabolism, cellular replication and division (41). SOCS on the other hand acts as a negative regulator and terminates GH-induced signaling (42). In addition to JAK-STAT, GH action is also propagated via linkage of GHRs to several cellular effector systems, including Src/SHC, MAPK, PI3K-Akt, and PKC. Differential activation of these pathways under varied physiological conditions determines the anabolic versus catabolic actions of GH (43-49). Alterations in GH or GHR action is associated with Laron Syndrome and Acromegaly in humans.

Laron Syndrome

Laron syndrome (LS) was first described by an Israeli physician Dr. Zvi Laron in 1966. It is a rare genetic disorder inherited in an autosomal recessive manner that is caused by mutations which inactivate the GHR gene and leads to severely depressed GH/IGF-1 action. The serum of patients with LS have high GH and low IGF1 levels, thus, they are GH insensitive or resistant (50,51). Laron patients are characterized by dwarfism, facial phenotype, obesity and hypogenitalism (52,53). Interestingly, multiple studies have shown that Laron patients have a significantly reduced risk of cancer and insulin resistance compared to their unaffected relatives, despite having obesity, a risk factor for both cancer and type 2 diabetes (54-58).

Gigantism and Acromegaly

Gigantism and acromegaly are rare disorders that are caused by excessive GH secretion and/or high levels of its mediator, IGF-1. Gigantism occurs when excess GH or IGF-1 leads to an increase in linear growth, and epiphyseal growth plates are not fused before the end of puberty. Often children with GH secreting adenomas that are not treated display pituitary gigantism or acromegalic gigantism (59). However, most patients with acromegaly develop it in adult life which does not result in gigantism. Both disorders have common clinical manifestations since acromegalics can be tall, and most giants

have acromegalic features. In both conditions, the primary cause is a benign GH-secreting pituitary tumor, and less likely a pituitary hyperplasia, ectopic GH or GH releasing hormone (GHRH) secretion (59). Interestingly, both disorders alter adipose tissue metabolism significantly. These patients despite having less fat and more lean mass, suffer from diabetes, cardiovascular and other metabolic problems (60-63).

Growth Hormone and Sexual Dimorphism

Neonatal as well as adult sex steroid environments in males and females influence the adult GH secretory pattern by modulating growth hormone releasing hormone (GHRH) and somatostatin (SS). GHRH and SS mRNA levels can be altered by changes in testosterone levels suggesting that sex steroids in adults alter the GH secretory pattern and modulate sexual dimorphism ((64-66). In male rats, GH is secreted in pulses occurring at regular 3 to 4-hour intervals with high peaks and low plasma GH levels in between. Female rats produce lower GH pulses but maintain higher plasma GH levels between the pulses as compared to males (67). The continuous presence of testosterone in males appears to be necessary to maintain low basal GH levels (68). On the contrary, estrogen elevates basal plasma GH levels and suppress the GH pulses under some conditions. High amplitude GH pulses with low plasma GH levels (i.e. a masculine plasma GH pattern) promotes growth more effectively than a constant, intermediate level of plasma GH (i.e. a feminine plasma GH pattern) (67). Interestingly, serum GH concentrations are significantly higher in women than in men (69). Two studies in human subjects which employed different assays showed that females exhibited significantly greater irregularity in GH concentration than their male counterparts, implying that mass and mode of GH secretion are regulated differently in males and females (70,71). The consistency and statistical significance of these findings suggest that sexual dimorphism is broadly present in higher animals (69).

Physiological and Metabolic Effects of Growth Hormone on Adipose Tissue

In mammals, triglycerides (TGs) are stored in lipid droplets in the adipose tissue, where they serve as the primary source of energy during periods of food deprivation. Adipose tissue can be broadly divided into two main categories – white adipose tissue (WAT) and brown adipose tissue (BAT). WAT acts as an energy reservoir and is distributed throughout the body and can be further categorized into subcutaneous (subQ) or intra-abdominal WAT. SubQ WAT is located beneath the skin and accounts for approximately 80% of the total WAT while intra-abdominal (visceral and non-visceral) fat accounts for about 20% of total WAT (72,73). Similarly, brown adipose tissue (BAT) is also located at multiple locations (intrascapular, supraclavicular, neck, para-aortic, paravertebral and suprarenal) in humans and is involved in thermogenesis (74-77). Whole-body energy homeostasis depends on the precisely regulated balance of lipid storage and mobilization. Lipolysis is the catabolic process of triglyceride breakdown mediated by lipolytic enzymes, which catabolize adipose TGs into glycerol and fatty acids (FAs) for release into systemic circulation. To date, there are three primary lipases known to carry out adipose-stored TG breakdown and act in a sequential manner. Adipose triglyceride lipase (ATGL) is the rate limiting lipase that cleaves the first fatty acid from the TG, while hormone sensitive lipase (HSL) and mono glyceride lipase (MGL) act to release the second and third fatty acid respectively finally releasing the glycerol backbone (78).

GH is required for the differentiation of adipocytes during development. However, GH contributes differentially to fat depot development at different anatomical locations. For example, GH's effect on the development of the subcutaneous fat depot is twice as pronounced as the internal (visceral) fat depots (79). Interestingly, after adulthood GH levels inversely correlate with the adipose tissue mass in both mice and human. In acromegaly, increased GH levels cause a decrease in the total body fat mass with most significant reduction in the visceral adipose depot (80). Similarly, bGH mice with elevated GH levels display much less body fat mass compared to the control littermates (81). This is consistent with the results in obese mice showing reductions in the inguinal and mesenteric fat depots upon GH treatment in a dose dependent manner (82). On the contrary, decreased GH action increases visceral as well as total adiposity as observed in LS patients (56,83). Interestingly, mouse models with reduced GH action (such as growth hormone receptor knockout (GHR-/-), growth hormone antagonist (GHA) and Ames dwarf mice display increased whole body adiposity (84-90).

As discussed above, GH exerts anabolic effects directly and through stimulation of IGF-I, insulin, and free fatty acids (FFA). When subjects are well nourished, GH-induced stimulation of IGF-I and insulin is important for anabolic nutrient storage and growth of lean body mass (LBM), adipose tissue, and glycogen reserves. During fasting and other catabolic states, GH predominantly stimulates the release and oxidation of FFA, which leads to decreased glucose and protein oxidation and preservation of LBM and glycogen stores. During fasting and stress, the effects of GH on protein metabolism become more pronounced; lack of GH during fasting increases protein loss and urea production rates by approximately 50%, with a similar increase in muscle protein breakdown. GH is classified as a counter-regulatory hormone in that it antagonizes the hepatic and peripheral effects of insulin on glucose metabolism via

mechanisms involving a concomitant increase in FFA flux and uptake (24).

Studies have shown that nutritional state modulates the lipolytic responsiveness of cells by adjusting GH-induced intracellular signal transduction pathways. For example, under fed conditions GH in hepatocytes activated JAK-STAT, PI3K-Akt, and ERK pathways, whereas under fasting conditions it activated PLC/PKC and ERK pathways. Blocking PLC/PKC and ERK pathway inhibited GH-stimulated lipolysis in fasting state (91,92). In human subjects, fasting-induced changes in hormonal sensitivity are mediated in-part by GH, which is significantly elevated during prolonged fasting (93-95). Fasting has been found to be associated with increased GH levels in systemic circulation, enhanced lipolysis, decreased insulin sensitivity, reduced IGF-1 bioactivity and blunted activation of the JAK-STAT pathway (96). Diurnal fluctuations in serum FFA levels mirror the pulsatile secretion pattern of GH while the nocturnal increase in FFA during sleep is absent in GH-deficient patients, strongly linking lipolysis to GH (97). Fasting and exercise both induce lipolysis – elevated levels of GH are observed during fasting, resulting in a reduction of anti-lipolytic gene G0 switch 2 (G0S2) mRNA and protein expression but an induction of adipose triglyceride lipase (ATGL) protein expression with a concomitant rise in circulating fatty acids. Interestingly, both ATGL and G0S2 remain unchanged during exercise suggesting that the ATGL-G0S2 complex is an important long-term regulator of lipolysis under physiological conditions (such as fasting) in humans (98).

GH may mediate its actions in adipocytes via growth hormone receptors, or through the GH-mediated secretion of insulin-like growth factor-I (IGF-I) in an autocrine/paracrine manne (99-102). GH-induced lipolysis of adipose tissue in combination with reduced triglyceride accumulation via inhibition of lipoprotein lipase activity appears to be the dominant mechanism in the reduction of visceral adipose fat mass. GH induces lipolysis to a lesser degree in sub-cutaneous adipose tissue in human subjects as well as in mouse models (80,81,99-103). Since GH levels are inversely related to adipose tissue mass in both mice and humans, one would expect that GH-mediated reduction of adipose tissue would have health benefits. However, mounting evidence suggests that despite a reduction in fat mass caused by GH, the metabolic health of mice or humans is compromised (60). In fact, patients with acromegaly have elevated levels of GH, and therefore have reduced body fat and increased lean body mass but still develop insulin resistance (22,24,25,104,105). bGH mice mimic acromegalic patients and have less total body fat mass with higher muscle mass than littermate controls and develop insulin resistance (81,106,107). Additionally, administration of GH to GH-deficient children is associated with a redistribution of adipose tissue from an abdominal (android) to a more peripheral (gynoid) distribution, a significant reduction in abdominal adipocyte size, a significant reduction in overall basal rates of lipogenesis and a reduction in the anti-lipolytic actions of insulin (108).

Studies involving human subjects have shown that GH potently stimulates adipose tissue lipolysis in a dose dependent manner (109,110). Additionally, GH increases lipolysis by increasing the activity of hormone sensitive lipase (HSL) in adipose tissue (111-114). Also, GH produces a pronounced inhibition of adipose tissue lipoprotein lipase activity (LPL). LPL hydrolyzes plasma triglycerides (TG) in adipose tissue and causes an accumulation of TG in adipocytes. GH receptor knockout mice (GHR-/-) are susceptible to obesity while GH overexpressing mice (bGH) have a leaner phenotype (81,115). Whether the observed lipolytic effect in bGH mice is a direct effect of GH or a consequence is currently unknown.

Transcriptional Regulation of Lipid Droplet (LD) Associated Proteins and GH-Induced Lipolysis

LDs are considered as intracellular TG storage organelles in adipocytes. These organelles are composed of a core of TGs and cholesterol esters that is surrounded by a phospholipid monolayer. Various proteins have been shown to be associated with LDs (116). The majority of LD-associated proteins in adipocytes are involved either in lipogenesis, lipolysis or in maintaining LD homeostasis. They are primarily regulated by a set of transcription factors called Peroxisome Proliferator-Activated Receptors (PPARs), which have the ability to sense and interpret fatty acid signals derived from dietary lipids, pathogenic lipoproteins or essential fatty acid metabolites (117,118). PPARs belong to the nuclear hormone receptor family of transcription factors that are activated by ligands. PPARs consist of three members namely; PPARα, PPARβ/PPARδ and PPARγ. They differ with respect to ligand specificity and their expression pattern in various tissues; however, all PPARs bind to a conserved sequence of DNA called the PPAR response element (PPRE) in the proximal promoter region of target genes and help recruit transcription machinery (119). Exogenous and endogenous lipid species as well as synthetic compounds such as thiazolidinediones (TZDs) can act as PPAR ligands. Therefore, alterations in the intracellular concentration of these lipid species or treatment with TZDs has a direct impact on PPAR-dependent gene regulation (120).

Several LD-associated proteins have been shown to be regulated by PPARγ in adipocytes and therefore are direct transcriptional targets of PPARγ (117). FSP27 (also known as CIDEC) is expressed at high levels in WAT where it regulates fat storage (121-123), lipid droplet dynamics (124,125) and lipolysis (126,127). siRNA-mediated silencing of

FSP27 in cultured white adipocytes leads to the formation of multilocular LD, increases in systemic FFA flux due to excessive lipolysis and decreases in triglyceride storage, while FSP27 overexpression suppresses lipolysis and increases LD size (122,126-128). Chromatin immunoprecipitation (ChIP) assays have confirmed that FSP27 is a direct transcriptional target of PPARγ (129).

Recent studies in human subjects, primary human adipocytes and 3T3-L1 adipocytes have shown that GH treatment downregulates FSP27 expression, resulting in LD fragmentation and elevations in systemic flux of FFAs (27,28). Mechanistically, GH binding to its receptor activates multiple signaling pathways including the Ras-Raf-MEK-ERK1,2 pathway (43,92,130,131). MEK1 has been shown to interact with and phosphorylate PPARγ leading to its nuclear export and degradation upon tetradecanoyl phorbol acetate or TNF-α stimulation (132,133). GH-mediated activation of MEK/ERK signaling lead to PPARγ Ser273 phosphorylation and subsequent degradation, FSP27 downregulation, increased HSL phosphorylation and excessive lipolysis in human adipocytes (28). Enforced expression of FSP27 by adenoviral transfection or blocking MEK/ERK signaling with the MEK1 inhibitor U0126 stabilized PPARγ in the nucleus, improved insulin signaling and restored GH-induced lipolysis to normal levels (27,28).

Counterintuitively, GH administration also results in FSP27 mRNA upregulation suggestive of an additional transcription regulation mechanism for FSP27 expression (27). Such a mechanism is physiologically obligatory in order to optimally regulate lipolysis and maintain adipose tissue homeostasis. Absence of a counter-regulatory mechanism would otherwise lead to sustained flux of FFAs causing lipotoxicity and insulin resistance as observed in mice overexpressing bGH. GH signaling phosphorylates STAT5 proteins which can homodimerize or heterodimerize with other STAT family members and translocate to the nucleus in a MEK- and PPARγ-independent manner to regulate gene expression and mediate GH effects (43). A recent study by Sharma et al. elegantly demonstrated that inhibiting STAT5 phosphorylation with a subsequent GH stimulation nearly abolishes FSP27 mRNA expression in 3T3-L1 adipocytes. These results suggest that GH-mediated STAT5 phosphorylation upregulates FSP27 expression under physiological conditions to keep GH stimulated MEK/ERK signaling under check and maintain an optimal level of lipolysis. Furthermore, qPCR analysis of RNA isolated from subcutaneous and perigonadal fat of $STAT5^{\Delta N/\Delta N}$-mutant mice, which express hypomorphic forms of both Stat5a and Stat5b, demonstrated that FSP27 is significantly reduced in the perigonadal fat and tends to be reduced in subcutaneous fat (27). These studies provide molecular insights into how GH-mediated activation of MEK/ERK causes destabilization of the transcription factor PPARγ resulting in downregulation of FSP27, G0S2 and other lipid droplet associated genes while simultaneously phosphorylating STAT5 to regulate LD homeostasis and prevent excessive lipolysis at the same time.

Growth Hormone and Insulin Resistance

Visceral WAT positively correlates with an increased risk of insulin resistance and type 2 diabetes (134-138), while subQ WAT has been suggested to be protective (73,139,140). Although GH contributes to the growth and development during adolescent years, IGF-I levels in boys and girls rise and fall in concert with the rise and fall of insulin resistance across the entire spectrum of normal puberty. This trend suggests that the GH/IGF-1 axis acts as a prime mediator of insulin resistance during puberty (141). Multiple cross-sectional and longitudinal studies have shown that insulin insensitivity during puberty is a common phenomenon in normal children which is exaggerated during adolescence with insulin-dependent diabetes mellitus (IDDM) (142-145). The reduction in insulin sensitivity during puberty is therefore associated with a compensatory increase in insulin secretion (146). Diabetic adolescents often have poor glycemic control during puberty; as a result, an approximate 30% increase in insulin dosage is required for patients with insulin-dependent diabetes at the onset of puberty (142,147).

GH-induced insulin resistance is well documented despite the fact that low doses of GH-treatment in combination with diet restrictions reduce visceral adipose tissue mass, LDL cholesterol levels, triglycerides, free fatty acids and improve insulin sensitivity and muscle mass (99,148). However, molecular fingerprints that can tip the balance in favor of visceral fat loss without causing diabetogenic effects are still under investigation. GH suppresses the anti-lipolytic action of insulin and enhances adipose tissue lipolysis to induce insulin resistance (149). Chronic elevations in GH levels due to pituitary adenoma or other genetic alterations tip the balance in favor of fat catabolism resulting in lipotoxicity that leads to the development of insulin resistance and related metabolic diseases.

Adipose tissue displays significant depot differences with respect to hormonal responsiveness and metabolic activity. Body fat distribution varies between age, race and sex, with males having more visceral adiposity and females having more subcutaneous fat (150). Although both visceral and subcutaneous fat depots respond to lipolytic signals, visceral fat shows an enhanced response due to enhanced beta adrenergic response and reduced alpha adrenergic response (151-153). Additionally, lean subjects are metabolically flexible with respect to the anti-lipolytic effect of insulin compared to the metabolically inflexible subjects that display visceral adiposity (149).

Clinical studies have established that GH treatment reduces visceral fat mass and improves metabolic parameters in GH-deficient patients and patients with visceral obesity (108,154,155). On the contrary, multiple studies have consistently demonstrated that the diabetogenic effects of GH are primarily due to its lipolytic action (12,96,156,157). Additionally, GH-induced lipolysis leads to frequent hyperglycemic episodes in diabetic patients due to the dawn phenomenon (156,158-160). Dawn phenomenon describes a surge of hormones (including growth hormone and glucagon) produced by the body in early morning hours (approximately 4:00-7:00 AM) that results in an increase in glucose levels in healthy as well as diabetic patients. Diabetic patients however, display high levels of fasting blood glucose due to reduced insulin productivity/activity that compromises their ability to suppress GH-mediated lipolysis in response to the dawn phenomenon. Although the dawn phenomenon was originally described in patients with type 1 diabetes mellitus (T1DM), recent studies have demonstrated its occurrence in approximately 50% of patients with both T1DM and Type 2 diabetes mellitus (T2DM) (158-160). Dawn phenomenon increases HbA1c levels significantly and leads to frequent hyperglycemic episodes that can be entirely corrected by acipimox treatment, an anti-lipolytic compound that suppresses GH-induced lipolysis (24,156,161-163). Acromegalic patients have elevated levels of GH and embody clinical manifestations of the diabetogenic effects of GH since they display increased rates of insulin resistance, hyperinsulinemia and type 2 diabetes (164,165). Many studies have suggested that GH impairs insulin's ability to activate insulin signaling in insulin target cells/tissues (166-169) while others have questioned GH-induced impairment of insulin signaling in human subjects (170,171). Overall, these studies provide a solid foundation and framework to support that GH-mediated lipolysis is a critical regulator of insulin resistance in both healthy subjects and diabetic patients.

Concluding Remarks

Understanding the molecular mechanisms that underlie GH-induced insulin resistance is crucial for the development of pharmacological agents and treatment of a wide variety of patients. Although MEK inhibitors, PPARγ agonists (TZDs) and anti-lipolytic agents (Acipimox) are in clinical use, recent studies have uncovered additional molecular targets for potential intervention of GH-induced insulin resistance and therefore, clearly have bench-to-bed side implications (**figure 1**) (27,28).

Acknowledgements

I would like to thank Dr. Vishwajeet Puri and Dr. John Kopchick for advice and critical reading of the manuscript. I sincerely apologize to those whose work although pertinent to this topic was not mentioned due to inadvertent omission.

Disclosure

The author has nothing to disclose.

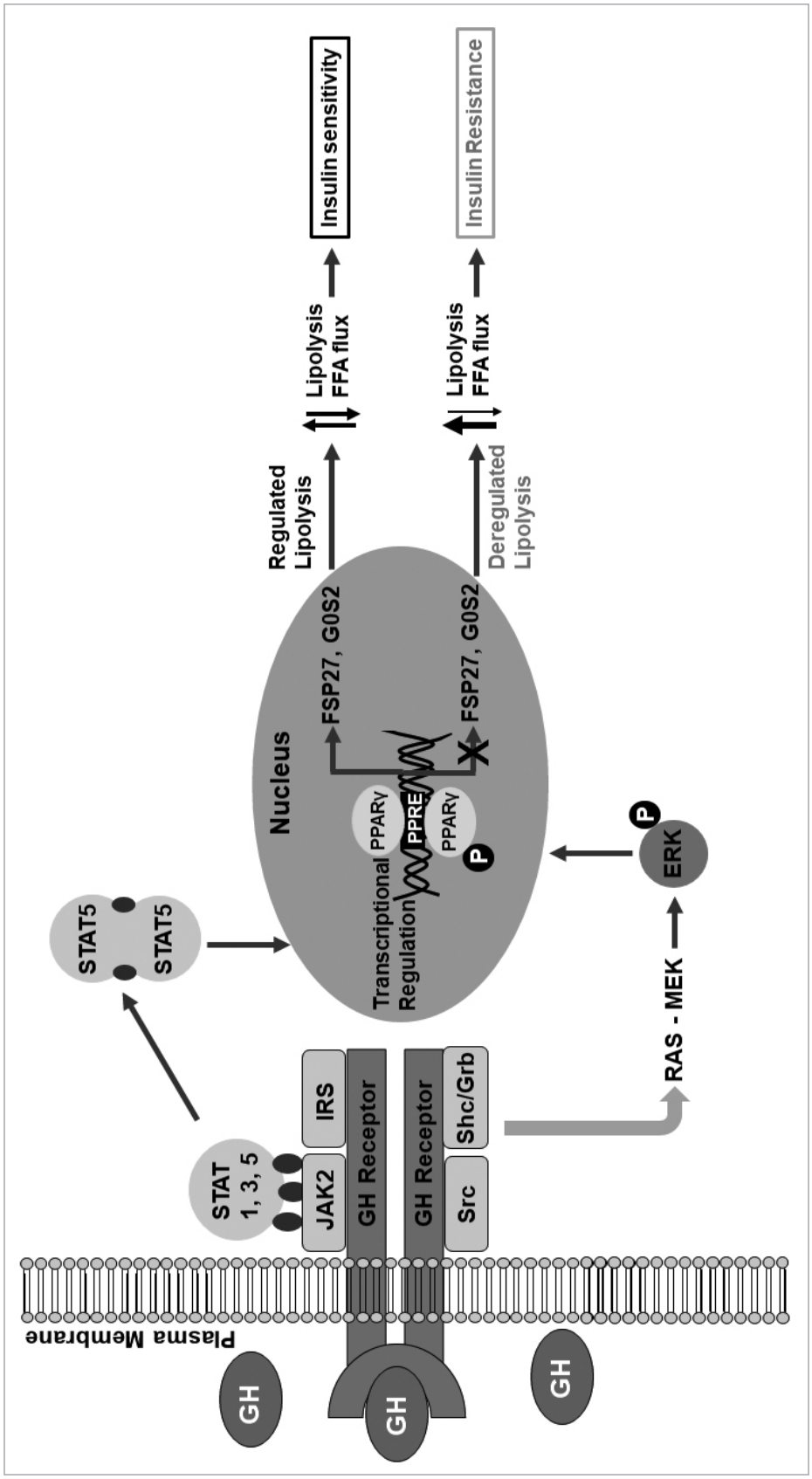


Figure 1. Model of GH signaling under normal and pathological conditions in Human adipocytes

Upon stimulation by GH binding, GHR activates Jak2. Activated Jak2 phosphorylates GHR on tyrosine residues which in turn recruit members of the STAT family of transcription factors. STATs homo/heterodimerize and translocate to nucleus to regulate an array of genes under physiological conditions. Coordinated action of STATs and other signaling pathways lead to a balanced state of lipolysis to provide energy for growth and development under normal as well as under fasting and starvation conditions.

However, chronically elevated GH levels as seen in acromegalic patiens and/or other pathological conditions lead to the activation of multiple signaling pathways including Ras-Raf-MEK-ERK pathway. Phopshorylated ERK translocates to nucleus and phosphorylates PPARγ. Phopshorylated PPARγ is targeted for degradation leading to downregulation of anti-lipolytic genes such as FSP27 causing excessive lipolysis. Sustained levels of systemic FFAs as a result of deregulated lipolysis causes lipotoxicity and pave the way for the development of insulin resistance and related metabolic diseases.

References

1. Evans HM, Long JA. Characteristic Effects upon Growth, Oestrus and Ovulation Induced by the Intraperitoneal Administration of Fresh Anterior Hypophyseal Substance. Proc Natl Acad Sci USA 1922;8(3):38-39 PubMed PMID: 16576618; PMCID: PMC1084981
2. Biasotti A, Houssay BA. Phlorrhizin diabetes in fasting or fed hypophysectomized dogs. J Physiol 1932;77(1):81-91 PubMed PMID: 16994375; PMCID: PMC1394750
3. Young FG. The diabetogenic action of crude anterior pituitary extracts. Biochem J 1938;32(3):513-523 PubMed PMID: 16746649; PMCID: PMC1264060
4. Young FG. "Growth" and the Diabetogenic Action of Anterior Pituitary Preparations. Br Med J 1941;2(4225):897-901 PubMed PMID: 20784024; PMCID: PMC2163715
5. Young FG. Growth and diabetes in normal animals treated with pituitary (anterior lobe) diabetogenic extract. Biochem J 1945;39(5):515-536 PubMed PMID: 16747949; PMCID: PMC1258276
6. Houssay BA, Foglia VG, Smyth FS, Rietti CT, Houssay AB. The Hypophysis and Secretion of Insulin. J Exp Med 1942;75(5):547-566 PubMed PMID: 19871205; PMCID: PMC2135268
7. Li CH, Evans HM. The Isolation of Pituitary Growth Hormone. Science. 1944;99(2566):183-184 doi: 10.1126/science.99.2566.183 PubMed PMID: 17736901
8. Bornstein J, Reid E, Young FG. The hyperglycaemic action of blood from animals treated with growth hormone. Nature 1951;168(4282):903-905 PubMed PMID: 14899520
9. Cotes PM, Reid E, Young FG. Diabetogenic action of pure anterior pituitary growth hormone. Nature 1949;164(4162):209-211 PubMed PMID: 18135939
10. Houssay BA, Rodriguez RR. Diabetogenic action of different preparations of growth hormone. Endocrinology 1953;53(1):114-116 doi: 10.1210/endo-53-1-114 PubMed PMID: 13068337
11. Houssay BA, Rodriguez RR, Cardeza AF. Diabetogenic action of the pituitary growth hormone. CR Seances Soc Biol Fil 1954;148(9-10):910-911 PubMed PMID: 13219834
12. Kastin AJ, Redding TW, Hall R, Besser GM, Schally AV. Lipid mobilizing hormones of the hypothalamus and pituitary. Pharmacol Biochem Behav 1975;3(1 Suppl):121-126 PubMed PMID: 179103
13. Le Roith D, Bondy C, Yakar S, Liu JL, Butler A. The somatomedin hypothesis: 2001 Endocr Rev 2001;22(1):53-74 doi: 10.1210/edrv.22.1.0419 PubMed PMID: 11159816
14. Ohlsson C, Nilsson A, Isaksson O, Lindahl A. Growth hormone induces multiplication of the slowly cycling germinal cells of the rat tibial growth plate. Proc Natl Acad Sci USA 1992;89(20):9826-9830 PubMed PMID: 1409707; PMCID: PMC50226
15. Singhal V, Goh BC, Bouxsein ML, Faugere MC, DiGirolamo DJ. Osteoblast-restricted Disruption of the Growth Hormone Receptor in Mice Results in Sexually Dimorphic Skeletal Phenotypes. Bone Res 2013;1(1):85-97 doi: 10.4248/BR201301006. PubMed PMID: 26273494; PMCID: PMC4472095
16. Nilsson A, Carlsson B, Isgaard J, Isaksson OG, Rymo L. Regulation by GH of insulin-like growth factor-I mRNA expression in rat epiphyseal growth plate as studied with in-situ hybridization. J Endocrinol 1990;125(1):67-74 PubMed PMID: 2187051
17. Nilsson A, Isgaard J, Lindahl A, Dahlstrom A, Skottner A, Isaksson OG. Regulation by growth hormone of number of chondrocytes containing IGF-I in rat growth plate. Science 1986;233(4763):571-574 PubMed PMID: 3523759
18. Nilsson A, Lindahl A, Eden S, Isaksson OG. Demonstration of growth hormone receptors in cultured rat epiphyseal chondrocytes by specific binding of growth hormone and immunohistochemistry. J Endocrinol 1989;122(1):69-77 PubMed PMID: 2769163
19. Yakar S, Isaksson O. Regulation of skeletal growth and mineral acquisition by the GH/IGF-1 axis: Lessons from mouse models. Growth Horm IGF Res 2016;28:26-42 doi: 10.1016/j.ghir.2015.09.004. PubMed PMID: 26432542; PMCID: PMC4809789
20. Kaplan SA, Cohen P. The somatomedin hypothesis 2007: 50 years later. J Clin Endocrinol Metab 2007;92(12):4529-4535 doi: 10.1210/jc.2007-0526 PubMed PMID: 17986643
21. Ohlsson C, Bengtsson BA, Isaksson OG, Andreassen TT, Slootweg MC. Growth hormone and bone. Endocr Rev 1998;19(1):55-79 doi: 10.1210/edrv.19.1.0324 PubMed PMID: 9494780
22. Bengtsson BA, Brummer RJ, Eden S, Bosaeus I, Lindstedt G. Body composition in acromegaly: the effect of treatment. Clin Endocrinol (Oxf) 1989;31(4):481-490 PubMed PMID: 2627748
23. Lin S, Li C, Li C, Zhang X. Growth Hormone Receptor Mutations Related to Individual Dwarfism. Int J Mol Sci 2018;19(5) doi: 10.3390/ijms19051433 PubMed PMID: 29748515; PMCID: PMC5983672
24. Moller N, Jorgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev 2009;30(2):152-177 doi: 10.1210/er.2008-0027. PubMed PMID: 19240267
25. Olarescu NC, Bollerslev J. The Impact of Adipose Tissue on Insulin Resistance in Acromegaly. Trends Endocrinol Metab 2016;27(4):226-237 doi: 10.1016/j.tem.2016.02.005. PubMed PMID: 26948712
26. Veldhuis JD, Roemmich JN, Richmond EJ, Rogol AD, Lovejoy JC, Sheffield-Moore M, Mauras N, Bowers CY. Endocrine control of body composition in infancy, childhood, and puberty. Endocr Rev 2005;26(1):114-146 doi: 10.1210/er.2003-0038 PubMed PMID: 15689575
27. Sharma R, Luong Q, Sharma VM, Harberson M, Harper B, Colborn A, Berryman DE, Jessen N, Jorgensen JOL, Kopchick JJ, Puri V, Lee KY. Growth hormone controls lipolysis by regulation of FSP27 expression. J Endocrinol 2018;239(3):289-301 doi: 10.1530/JOE-18-0282. PubMed PMID: 30400015; PMCID: PMC6226059
28. Sharma VM, Vestergaard ET, Jessen N, Kolind-Thomsen P, Nellemann B, Nielsen TS, Vendelbo MH, Moller N, Sharma R, Lee KY, Kopchick JJ, Jorgensen JOL, Puri V. Growth hormone acts along the PPARgamma-FSP27 axis to stimulate lipolysis in human adipocytes. Am J Physiol Endocrinol Metab 2019;316(1):E34-E42 doi: 10.1152/ajpendo.00129.2018. PubMed PMID: 30325658
29. Reaven G. Insulin resistance and coronary heart disease in nondiabetic individuals. Arterioscler Thromb Vasc Biol 2012;32(8):1754-1759 doi: 10.1161/ATVBAHA.111.241885. PubMed PMID: 22815340
30. Roberts CK, Hevener AL, Barnard RJ. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. Compr Physiol 2013;3(1):1-58 doi: 10.1002/cphy.c110062 PubMed PMID: 23720280; PMCID: PMC4129661
31. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell 2012;148(5):852-871 doi: 10.1016/j.cell.2012.02.017. PubMed PMID: 22385956; PMCID: PMC3294420
32. Yazici D, Sezer H. Insulin Resistance, Obesity and Lipotoxicity. Adv Exp Med Biol 2017;960:277-304 doi: 10.1007/978-3-319-48382-5_12. PubMed PMID: 28585204
33. Salmon WD, Jr, Daughaday WH. A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. J Lab Clin Med 1957;49(6):825-836 PubMed PMID: 13429201
34. Wang J, Zhou J, Bondy CA. Igf1 promotes longitudinal bone growth by insulin-like actions augmenting chondrocyte hypertrophy. FASEB J 1999;13(14):1985-1990 PubMed PMID: 10544181
35. Wang J, Zhou J, Powell-Braxton L, Bondy C. Effects of Igf1 gene deletion on postnatal growth patterns. Endocrinology 1999;140(7):3391-3394 doi: 10.1210/endo.140.7.7045. PubMed PMID: 10385438
36. Brameld JM, Atkinson JL, Saunders JC, Pell JM, Buttery PJ, Gilmour RS. Effects of growth hormone administration and dietary protein intake on insulin-like growth factor I and growth hormone receptor mRNA Expression in porcine liver, skeletal muscle, and adipose tissue. J Anim Sci 1996;74(8):1832-1841 PubMed PMID: 8856437

37. Martini JF, Villares SM, Nagano M, Delehaye-Zervas MC, Eymard B, Kelly PA, Postel-Vinay MC. Quantitative analysis by polymerase chain reaction of growth hormone receptor gene expression in human liver and muscle. Endocrinology 1995;136(4):1355-1360 doi: 10.1210/endo.136.4.7534696. PubMed PMID: 7534696
38. Theyse LF, Oosterlaken-Dijksterhuis MA, van Doorn J, Terlou M, Mol JA, Voorhout G, Hazewinkel HA. Expression of osteotropic growth factors and growth hormone receptor in a canine distraction osteogenesis model. J Bone Miner Metab 2006;24(4):266-273 doi: 10.1007/s00774-006-0683-2 PubMed PMID: 16816920
39. Ram PA, Park SH, Choi HK, Waxman DJ. Growth hormone activation of Stat 1, Stat 3, and Stat 5 in rat liver. Differential kinetics of hormone desensitization and growth hormone stimulation of both tyrosine phosphorylation and serine/threonine phosphorylation. J Biol Chem 1996;271(10):5929-5940 PubMed PMID: 8621467
40. Smit LS, Meyer DJ, Billestrup N, Norstedt G, Schwartz J, Carter-Su C. The role of the growth hormone (GH) receptor and JAK1 and JAK2 kinases in the activation of Stats 1, 3, and 5 by GH. Mol Endocrinol 1996;10(5):519-533 doi: 10.1210/mend.10.5.8732683. PubMed PMID: 8732683
41. Ranke MB, Wit JM. Growth hormone - past, present and future. Nat Rev Endocrinol 2018;14(5):285-300 doi: 10.1038/nrendo.2018.22 PubMed PMID: 29546874
42. Hansen JA, Lindberg K, Hilton DJ, Nielsen JH, Billestrup N. Mechanism of inhibition of growth hormone receptor signaling by suppressor of cytokine signaling proteins. Mol Endocrinol 1999;13(11):1832-1843 doi: 10.1210/mend.13.11.0368 PubMed PMID: 10551777
43. Brooks AJ, Waters MJ. The growth hormone receptor: mechanism of activation and clinical implications. Nat Rev Endocrinol 2010;6(9):515-525 doi: 10.1038/nrendo.2010.123 PubMed PMID: 20664532
44. Dinerstein-Cali H, Ferrag F, Kayser C, Kelly PA, Postel-Vinay M. Growth hormone (GH) induces the formation of protein complexes involving Stat5, Erk2, Shc and serine phosphorylated proteins. Mol Cell Endocrinol 2000;166(2):89-99 PubMed PMID: 10996427
45. Lanning NJ, Carter-Su C. Recent advances in growth hormone signaling. Rev Endocr Metab Disord 2006;7(4):225-235 doi: 10.1007/s11154-007-9025-5 PubMed PMID: 17308965
46. Love DW, Whatmore AJ, Clayton PE, Silva CM. Growth hormone stimulation of the mitogen-activated protein kinase pathway is cell type specific. Endocrinology 1998;139(4):1965-1971 doi: 10.1210/endo.139.4.5884 PubMed PMID: 9528983
47. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001;414(6865):799-806 doi: 10.1038/414799a. PubMed PMID: 11742412
48. Thirone AC, Carvalho CR, Saad MJ. Growth hormone stimulates the tyrosine kinase activity of JAK2 and induces tyrosine phosphorylation of insulin receptor substrates and Shc in rat tissues. Endocrinology 1999;140(1):55-62 doi: 10.1210/endo.140.1.6417 PubMed PMID: 9886807
49. Zhu T, Ling L, Lobie PE. Identification of a JAK2-independent pathway regulating growth hormone (GH)-stimulated p44/42 mitogen-activated protein kinase activity. GH activation of Ral and phospholipase D is Src-dependent. J Biol Chem 2002;277(47):45592-603 doi: 10.1074/jbc.M201385200 PubMed PMID: 12218045
50. Eshet R, Laron Z, Pertzelan A, Arnon R, Dintzman M. Defect of human growth hormone receptors in the liver of two patients with Laron-type dwarfism. Isr J Med Sci 1984;20(1):8-11 PubMed PMID: 6321400
51. Godowski PJ, Leung DW, Meacham LR, Galgani JP, Hellmiss R, Keret R, Rotwein PS, Parks JS, Laron Z, Wood WI. Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron-type dwarfism. Proc Natl Acad Sci USA 1989;86(20):8083-8087 PubMed PMID: 2813379; PMCID: PMC298219
52. Janecka A, Kolodziej-Rzepa M, Biesaga B. Clinical and Molecular Features of Laron Syndrome, A Genetic Disorder Protecting from Cancer. In Vivo 2016;30(4):375-381 PubMed PMID: 27381597
53. Laron Z, Pertzelan A, Mannheimer S. Genetic pituitary dwarfism with high serum concentation of growth hormone--a new inborn error of metabolism? Isr J Med Sci 1966;2(2):152-155 PubMed PMID: 5916640
54. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, Cheng CW, Hwang D, Martin-Montalvo A, Saavedra J, Ingles S, de Cabo R, Cohen P, Longo VD. Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. Sci Transl Med 2011;3(70):70ra13 doi: 10.1126/scitranslmed.3001845. PubMed PMID: 21325617; PMCID: PMC3357623
55. Guevara-Aguirre J, Rosenbloom AL, Balasubramanian P, Teran E, Guevara-Aguirre M, Guevara C, Procel P, Alfaras I, De Cabo R, Di Biase S, Narvaez L, Saavedra J, Longo VD. GH receptor deficiency in ecuadorian adults is associated with obesity and enhanced insulin sensitivity. J Clin Endocrinol Metab 2015;100(7):2589-2596 doi: 10.1210/jc.2015-1678 PubMed PMID: 25985182; PMCID: PMC4490304
56. Laron Z, Kauli R. Fifty seven years of follow-up of the Israeli cohort of Laron Syndrome patients-From discovery to treatment. Growth Horm IGF Res 2016;28:53-56 doi: 10.1016/j.ghir.2015.08.004 PubMed PMID: 26307357
57. Shevah O, Laron Z. Patients with congenital deficiency of IGF-I seem protected from the development of malignancies: a preliminary report. Growth Horm IGF Res 2007;17(1):54-57 doi: 10.1016/j.ghir.2006.10.007 PubMed PMID: 17166755
58. Steuerman R, Shevah O, Laron Z. Congenital IGF1 deficiency tends to confer protection against post-natal development of malignancies. Eur J Endocrinol 2011;164(4):485-489 doi: 10.1530/EJE-10-0859 PubMed PMID: 21292919
59. Hannah-Shmouni F, Trivellin G, Stratakis CA. Genetics of gigantism and acromegaly. Growth Horm IGF Res 2016;30-31:37-41 doi: 10.1016/j.ghir.2016.08.002 PubMed PMID: 27657986; PMCID: PMC5154831
60. Berryman DE, List EO. Growth Hormone's Effect on Adipose Tissue: Quality versus Quantity. Int J Mol Sci 2017;18(8) doi: 10.3390/ijms18081621 PubMed PMID: 28933734; PMCID: PMC5578013
61. Frara S, Maffezzoni F, Mazziotti G, Giustina A. Current and Emerging Aspects of Diabetes Mellitus in Acromegaly. Trends Endocrinol Metab 2016;27(7):470-483 doi: 10.1016/j.tem.2016.04.014 PubMed PMID: 27229934
62. Hannon AM, Thompson CJ, Sherlock M. Diabetes in Patients With Acromegaly. Curr Diab Rep 2017;17(2):8 doi: 10.1007/s11892-017-0838-7 PubMed PMID: 28150161
63. Liu C, Wang J, Li J, Zeng M, Luo R, Shen J, Sun X, Han W, Wang L. Synthesis of N-doped hollow-structured mesoporous carbon nanospheres for high-performance supercapacitors. ACS Appl Mater Interfaces 2016;8(11):7194-204 doi: 10.1021/acsami.6b02404 PubMed PMID: 26942712
64. Argente J, Chowen JA, Zeitler P, Clifton DK, Steiner RA. Sexual dimorphism of growth hormone-releasing hormone and somatostatin gene expression in the hypothalamus of the rat during development. Endocrinology 1991;128(5):2369-2375 doi: 10.1210/endo-128-5-2369 PubMed PMID: 1673430
65. Chowen JA, Garcia-Segura LM, Gonzalez-Parra S, Argente J. Sex steroid effects on the development and functioning of the growth hormone axis. Cell Mol Neurobiol 1996;16(3):297-310 PubMed PMID: 8818398
66. Painson JC, Tannenbaum GS. Sexual dimorphism of somatostatin and growth hormone-releasing factor signaling in the control of pulsatile growth hormone secretion in the rat. Endocrinology 1991;128(6):2858-2866 doi: 10.1210/endo-128-6-2858 PubMed PMID: 1674685
67. Jansson JO, Eden S, Isaksson O. Sexual dimorphism in the control of growth hormone secretion. Endocr Rev 1985;6(2):128-150 doi: 10.1210/edrv-6-2-128 PubMed PMID: 2861084
68. Jansson JO, Frohman LA. Differential effects of neonatal and adult androgen exposure on the growth hormone secretory pattern in male rats. Endocrinology 1987;120(4):1551-1557 doi: 10.1210/endo-120-4-1551 PubMed PMID: 3830058
69. Pincus SM, Gevers EF, Robinson IC, van den Berg G, Roelfsema F, Hartman ML, Veldhuis JD. Females secrete growth hormone with more process irregularity than males in both humans and rats. Am J Physiol 1996;270(1 Pt 1):E107-E115 doi: 10.1152/ajpendo.1996.270.1.E107 PubMed PMID: 8772482

70. Hindmarsh PC, Dennison E, Pincus SM, Cooper C, Fall CH, Matthews DR, Pringle PJ, Brook CG. A sexually dimorphic pattern of growth hormone secretion in the elderly. J Clin Endocrinol Metab 1999;84(8):2679-2685 doi: 10.1210/jcem.84.8.5915 PubMed PMID: 10443659
71. Winer LM, Shaw MA, Baumann G. Basal plasma growth hormone levels in man: new evidence for rhythmicity of growth hormone secretion. J Clin Endocrinol Metab 1990;70(6):1678-1686 doi: 10.1210/jcem-70-6-1678 PubMed PMID: 2347901
72. Arner P. Regional adipocity in man. J Endocrinol 1997;155(2):191-192 PubMed PMID: 9415044
73. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev 2010;11(1):11-18 doi: 10.1111/j.1467-789X.2009.00623.x PubMed PMID: 19656312
74. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR. Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009;360(15):1509-1517 doi: 10.1056/NEJMoa0810780. PubMed PMID: 19357406; PMCID: PMC2859951
75. Kozak LP, Koza RA, Anunciado-Koza R. Brown fat thermogenesis and body weight regulation in mice: relevance to humans. Int J Obes (Lond) 2010;34(Suppl 1:S23-S27 doi: 10.1038/ijo.2010.179 PubMed PMID: 20935661
76. Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. Am J Physiol Endocrinol Metab 2007;293(2):E444-E452 doi: 10.1152/ajpendo.00691.2006 PubMed PMID: 17473055
77. Saito M, Okamatsu-Ogura Y, Matsushita M, Watanabe K, Yoneshiro T, Nio-Kobayashi J, Iwanaga T, Miyagawa M, Kameya T, Nakada K, Kawai Y, Tsujisaki M. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. Diabetes 2009;58(7):1526-1531 doi: 10.2337/db09-0530. PubMed PMID: 19401428; PMCID: PMC2699872
78. Zechner R, Kienesberger PC, Haemmerle G, Zimmermann R, Lass A. Adipose triglyceride lipase and the lipolytic catabolism of cellular fat stores. J Lipid Res 2009;50(1):3-21 doi: 10.1194/jlr.R800031-JLR200 PubMed PMID: 18952573
79. Flint DJ, Gardner MJ. Influence of growth hormone deficiency on growth and body composition in rats: site-specific effects upon adipose tissue development. J Endocrinol 1993;137(2):203-211 PubMed PMID: 8326248
80. Freda PU, Shen W, Heymsfield SB, Reyes-Vidal CM, Geer EB, Bruce JN, Gallagher D. Lower visceral and subcutaneous but higher intermuscular adipose tissue depots in patients with growth hormone and insulin-like growth factor I excess due to acromegaly. J Clin Endocrinol Metab 2008;93(6):2334-2343 doi: 10.1210/jc.2007-2780 PubMed PMID: 18349062; PMCID: PMC2435633
81. Berryman DE, List EO, Coschigano KT, Behar K, Kim JK, Kopchick JJ. Comparing adiposity profiles in three mouse models with altered GH signaling. Growth Horm IGF Res 2004;14(4):309-318 doi: 10.1016/j.ghir.2004.02.005. PubMed PMID: 15231300
82. List EO, Palmer AJ, Berryman DE, Bower B, Kelder B, Kopchick JJ. Growth hormone improves body composition, fasting blood glucose, glucose tolerance and liver triacylglycerol in a mouse model of diet-induced obesity and type 2 diabetes. Diabetologia 2009;52(8):1647-1655 doi: 10.1007/s00125-009-1402-z PubMed PMID: 19468705
83. Laron Z, Ginsberg S, Lilos P, Arbiv M, Vaisman N. Body composition in untreated adult patients with Laron syndrome (primary GH insensitivity). Clin Endocrinol (Oxf) 2006;65(1):114-117 doi: 10.1111/j.1365-2265.2006.02558.x PubMed PMID: 16817829
84. Bartke A, Westbrook R. Metabolic characteristics of long-lived mice. Front Genet 2012;3:288 doi: 10.3389/fgene.2012.00288 PubMed PMID: 23248643; PMCID: PMC3521393
85. Berryman DE, List EO, Palmer AJ, Chung MY, Wright-Piekarski J, Lubbers E, O'Connor P, Okada S, Kopchick JJ. Two-year body composition analyses of long-lived GHR null mice. J Gerontol A Biol Sci Med Sci 2010;65(1):31-40 doi: 10.1093/gerona/glp175. PubMed PMID: 19901018; PMCID: PMC2796884
86. Berryman DE, Lubbers ER, Magon V, List EO, Kopchick JJ. A dwarf mouse model with decreased GH/IGF-1 activity that does not experience life-span extension: potential impact of increased adiposity, leptin, and insulin with advancing age. J Gerontol A Biol Sci Med Sci 2014;69(2):131-141 doi: 10.1093/gerona/glt069. PubMed PMID: 23695394; PMCID: PMC4038240
87. Heiman ML, Tinsley FC, Mattison JA, Hauck S, Bartke A. Body composition of prolactin, growth hormone, and thyrotropin-deficient Ames dwarf mice. Endocrine 2003;20(1-2):149-154 doi: 10.1385/ENDO:20:1-2:149 PubMed PMID: 12668880
88. Hill CM, Fang Y, Miquet JG, Sun LY, Masternak MM, Bartke A. Long-lived hypopituitary Ames dwarf mice are resistant to the detrimental effects of high-fat diet on metabolic function and energy expenditure. Aging Cell 2016;15(3):509-521 doi: 10.1111/acel.12467 PubMed PMID: 26990883; PMCID: PMC4854906
89. Junnila RK, Duran-Ortiz S, Suer O, Sustarsic EG, Berryman DE, List EO, Kopchick JJ. Disruption of the GH Receptor Gene in Adult Mice Increases Maximal Lifespan in Females. Endocrinology 2016;157(12):4502-4513 doi: 10.1210/en.2016-1649 PubMed PMID: 27732088
90. Luque RM, Lin Q, Cordoba-Chacon J, Subbaiah PV, Buch T, Waisman A, Vankelecom H, Kineman RD. Metabolic impact of adult-onset, isolated, growth hormone deficiency (AOiGHD) due to destruction of pituitary somatotropes. PLoS One. 2011;6(1):e15767 doi: 10.1371/journal.pone.0015767 PubMed PMID: 21283519; PMCID: PMC3023710
91. Bergan HE, Kittilson JD, Sheridan MA. Nutritional state modulates growth hormone-stimulated lipolysis. Gen Comp Endocrinol 2015;217-218:1-9 doi: 10.1016/j.ygcen.2015.04.017 PubMed PMID: 25957918
92. Bergan-Roller HE, Sheridan MA. The growth hormone signaling system: Insights into coordinating the anabolic and catabolic actions of growth hormone. Gen Comp Endocrinol 2018;258:119-133 doi: 10.1016/j.ygcen.2017.07.028 PubMed PMID: 28760716
93. Norrelund H, Moller N, Nair KS, Christiansen JS, Jorgensen JO. Continuation of growth hormone (GH) substitution during fasting in GH-deficient patients decreases urea excretion and conserves protein synthesis. J Clin Endocrinol Metab 2001;86(7):3120-3129 doi: 10.1210/jcem.86.7.7618 PubMed PMID: 11443176
94. Norrelund H, Nair KS, Nielsen S, Frystyk J, Ivarsen P, Jorgensen JO, Christiansen JS, Moller N. The decisive role of free fatty acids for protein conservation during fasting in humans with and without growth hormone. J Clin Endocrinol Metab 2003;88(9):4371-4378 doi: 10.1210/jc.2003-030267 PubMed PMID: 12970312
95. Vendelbo MH, Jorgensen JO, Pedersen SB, Gormsen LC, Lund S, Schmitz O, Jessen N, Moller N. Exercise and fasting activate growth hormone-dependent myocellular signal transducer and activator of transcription-5b phosphorylation and insulin-like growth factor-I messenger ribonucleic acid expression in humans. J Clin Endocrinol Metab 2010;95(9):E64-E68 doi: 10.1210/jc.2010-0689 PubMed PMID: 20534752
96. Moller L, Dalman L, Norrelund H, Billestrup N, Frystyk J, Moller N, Jorgensen JO. Impact of fasting on growth hormone signaling and action in muscle and fat. J Clin Endocrinol Metab 2009;94(3):965-972 doi: 10.1210/jc.2008-1385 PubMed PMID: 19066303
97. Jorgensen JO, Moller N, Lauritzen T, Alberti KG, Orskov H, Christiansen JS. Evening versus morning injections of growth hormone (GH) in GH-deficient patients: effects on 24-hour patterns of circulating hormones and metabolites. J Clin Endocrinol Metab 1990;70(1):207-214 doi: 10.1210/jcem-70-1-207 PubMed PMID: 2294131
98. Nielsen TS, Vendelbo MH, Jessen N, Pedersen SB, Jorgensen JO, Lund S, Moller N. Fasting, but not exercise, increases adipose triglyceride lipase (ATGL) protein and reduces G(0)/G(1) switch gene 2 (G0S2) protein and mRNA content in human adipose tissue. J Clin Endocrinol Metab 2011;96(8):E1293-E1297 doi: 10.1210/jc.2011-0149. PubMed PMID: 21613358

99. Nam SY, Kim KR, Cha BS, Song YD, Lim SK, Lee HC, Huh KB. Low-dose growth hormone treatment combined with diet restriction decreases insulin resistance by reducing visceral fat and increasing muscle mass in obese type 2 diabetic patients. Int J Obes Relat Metab Disord 2001;25(8):1101-1107 doi: 10.1038/sj.ijo.0801636 PubMed PMID: 11477493
100. Nam SY, Lobie PE. The mechanism of effect of growth hormone on preadipocyte and adipocyte function. Obes Rev 2000;1(2):73-86 PubMed PMID: 12119989
101. Pasarica M, Zachwieja JJ, Dejonge L, Redman S, Smith SR. Effect of growth hormone on body composition and visceral adiposity in middle-aged men with visceral obesity. J Clin Endocrinol Metab 2007;92(11):4265-4270 doi: 10.1210/jc.2007-0786 PubMed PMID: 17785361
102. Plockinger U, Reuter T. Pegvisomant increases intra-abdominal fat in patients with acromegaly: a pilot study. Eur J Endocrinol 2008;158(4):467-471 doi: 10.1530/EJE-07-0637 PubMed PMID: 18362292
103. Chen XL, Lee K, Hartzell DL, Dean RG, Hausman GJ, McGraw RA, Della-Fera MA, Baile CA. Adipocyte insensitivity to insulin in growth hormone-transgenic mice. Biochem Biophys Res Commun 2001;283(4):933-937 doi: 10.1006/bbrc.2001.4882 PubMed PMID: 11350075
104. Mercado M, Ramirez-Renteria C. Metabolic Complications of Acromegaly. Front Horm Res 2018;49:20-28 doi: 10.1159/000486001 PubMed PMID: 29895013
105. Unal A, Sahin Y, Kelestimur F. Acromegaly with polycystic ovaries, hyperandrogenism, hirsutism, insulin resistance and acanthosis nigricans: a case report. Endocr J 1993;40(2):207-211 PubMed PMID: 7951506
106. Coates RJ, Kolor K, Stewart SL, Richardson LC. Diagnostic markers for ovarian cancer screening: not ready for routine clinical use. Clin Cancer Res 2008;14(22):7575-7576; author reply 7-9 doi: 10.1158/1078-0432.CCR-08-2296 PubMed PMID: 18948387
107. Olsson B, Bohlooly YM, Fitzgerald SM, Frick F, Ljungberg A, Ahren B, Tornell J, Bergstrom G, Oscarsson J. Bovine growth hormone transgenic mice are resistant to diet-induced obesity but develop hyperphagia, dyslipidemia, and diabetes on a high-fat diet. Endocrinology 2005;146(2):920-930 doi: 10.1210/en.2004-1232 PubMed PMID: 15539551
108. Rosenbaum M, Gertner JM, Leibel RL. Effects of systemic growth hormone (GH) administration on regional adipose tissue distribution and metabolism in GH-deficient children. J Clin Endocrinol Metab 1989;69(6):1274-1281 doi: 10.1210/jcem-69-6-1274 PubMed PMID: 2685009
109. Hansen TK, Gravholt CH, Orskov H, Rasmussen MH, Christiansen JS, Jorgensen JO. Dose dependency of the pharmacokinetics and acute lipolytic actions of growth hormone. J Clin Endocrinol Metab 2002;87(10):4691-4698 doi: 10.1210/jc.2002-020563 PubMed PMID: 12364460
110. Richelsen B. Action of growth hormone in adipose tissue. Horm Res 1997;48(Suppl 5):105-110 PubMed PMID: 9434054
111. Fain JN, Cheema P, Tichansky DS, Madan AK. Stimulation of human omental adipose tissue lipolysis by growth hormone plus dexamethasone. Mol Cell Endocrinol 2008;295(1-2):101-105 doi: 10.1016/j.mce.2008.05.014 PubMed PMID: 18640775
112. Johansen T, Richelsen B, Hansen HS, Din N, Malmlof K. Growth hormone-mediated breakdown of body fat: effects of GH on lipases in adipose tissue and skeletal muscle of old rats fed different diets. Horm Metab Res 2003;35(4):243-250 doi: 10.1055/s-2003-39481 PubMed PMID: 12778368
113. Ng FM, Jiang WJ, Gianello R, Pitt S, Roupas P. Molecular and cellular actions of a structural domain of human growth hormone (AOD9401) on lipid metabolism in Zucker fatty rats. J Mol Endocrinol 2000;25(3):287-298 PubMed PMID: 11116208
114. Richelsen B, Pedersen SB, Kristensen K, Borglum JD, Norrelund H, Christiansen JS, Jorgensen JO. Regulation of lipoprotein lipase and hormone-sensitive lipase activity and gene expression in adipose and muscle tissue by growth hormone treatment during weight loss in obese patients. Metabolism 2000;49(7):906-911 doi: 10.1053/meta.2000.6738 PubMed PMID: 10910003
115. Berryman DE, List EO, Kohn DT, Coschigano KT, Seeley RJ, Kopchick JJ. Effect of growth hormone on susceptibility to diet-induced obesity. Endocrinology. 2006;147(6):2801-2808 doi: 10.1210/en.2006-0086 PubMed PMID: 16556764
116. Brasaemle DL, Dolios G, Shapiro L, Wang R. Proteomic analysis of proteins associated with lipid droplets of basal and lipolytically stimulated 3T3-L1 adipocytes. J Biol Chem 2004;279(45):46835-46842 doi: 10.1074/jbc.M409340200 PubMed PMID: 15337753
117. de la Rosa Rodriguez MA, Kersten S. Regulation of lipid droplet-associated proteins by peroxisome proliferator-activated receptors. Biochim Biophys Acta Mol Cell Biol Lipids. 2017;1862(10 Pt B):1212-1220 doi: 10.1016/j.bbalip.2017.07.007 PubMed PMID: 28735095
118. Varga T, Czimmerer Z, Nagy L. PPARs are a unique set of fatty acid regulated transcription factors controlling both lipid metabolism and inflammation. Biochim Biophys Acta 2011;1812(8):1007-1022 doi: 10.1016/j.bbadis.2011.02.014 PubMed PMID: 21382489; PMCID: PMC3117990
119. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schutz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, Evans RM. The nuclear receptor superfamily: the second decade. Cell 1995;83(6):835-839 PubMed PMID: 8521507; PMCID: PMC6159888
120. Georgiadi A, Kersten S. Mechanisms of gene regulation by fatty acids. Adv Nutr 2012;3(2):127-134 doi: 10.3945/an.111.001602. PubMed PMID: 22516720; PMCID: PMC3648713
121. Keller P, Petrie JT, De Rose P, Gerin I, Wright WS, Chiang SH, Nielsen AR, Fischer CP, Pedersen BK, MacDougald OA. Fat-specific protein 27 regulates storage of triacylglycerol. J Biol Chem 2008;283(21):14355-14365 doi: 10.1074/jbc.M708323200 PubMed PMID: 18334488; PMCID: PMC2386939
122. Puri V, Konda S, Ranjit S, Aouadi M, Chawla A, Chouinard M, Chakladar A, Czech MP. Fat-specific protein 27, a novel lipid droplet protein that enhances triglyceride storage. J Biol Chem 2007;282(47):34213-34218 doi: 10.1074/jbc.M707404200. PubMed PMID: 17884815
123. Puri V, Ranjit S, Konda S, Nicoloro SM, Straubhaar J, Chawla A, Chouinard M, Lin C, Burkart A, Corvera S, Perugini RA, Czech MP. Cidea is associated with lipid droplets and insulin sensitivity in humans. Proc Natl Acad Sci USA 2008;105(22):7833-7838 doi: 10.1073/pnas.0802063105 PubMed PMID: 18509062; PMCID: PMC2409392
124. Gong J, Sun Z, Wu L, Xu W, Schieber N, Xu D, Shui G, Yang H, Parton RG, Li P. Fsp27 promotes lipid droplet growth by lipid exchange and transfer at lipid droplet contact sites. J Cell Biol 2011;195(6):953-963 doi: 10.1083/jcb.201104142 PubMed PMID: 22144693; PMCID: PMC3241734
125. Jambunathan S, Yin J, Khan W, Tamori Y, Puri V. FSP27 promotes lipid droplet clustering and then fusion to regulate triglyceride accumulation. PLoS One. 2011;6(12):e28614 doi: 10.1371/journal.pone.0028614 PubMed PMID: 22194867; PMCID: PMC3237475
126. Grahn TH, Kaur R, Yin J, Schweiger M, Sharma VM, Lee MJ, Ido Y, Smas CM, Zechner R, Lass A, Puri V. Fat-specific protein 27 (FSP27) interacts with adipose triglyceride lipase (ATGL) to regulate lipolysis and insulin sensitivity in human adipocytes. J Biol Chem 2014;289(17):12029-12039 doi: 10.1074/jbc.M113.539890 PubMed PMID: 24627478; PMCID: PMC4002109
127. Grahn TH, Zhang Y, Lee MJ, Sommer AG, Mostoslavsky G, Fried SK, Greenberg AS, Puri V. FSP27 and PLIN1 interaction promotes the formation of large lipid droplets in human adipocytes. Biochem Biophys Res Commun 2013;432(2):296-301 doi: 10.1016/j.bbrc.2013.01.113 PubMed PMID: 23399566; PMCID: PMC3595328

128. Nishino N, Tamori Y, Tateya S, Kawaguchi T, Shibakusa T, Mizunoya W, Inoue K, Kitazawa R, Kitazawa S, Matsuki Y, Hiramatsu R, Masubuchi S, Omachi A, Kimura K, Saito M, Amo T, Ohta S, Yamaguchi T, Osumi T, Cheng J, Fujimoto T, Nakao H, Nakao K, Aiba A, Okamura H, Fushiki T, Kasuga M. FSP27 contributes to efficient energy storage in murine white adipocytes by promoting the formation of unilocular lipid droplets. J Clin Invest 2008;118(8):2808-2821 doi: 10.1172/JCI34090 PubMed PMID: 18654663; PMCID: PMC2483680

129. Kim YJ, Cho SY, Yun CH, Moon YS, Lee TR, Kim SH. Transcriptional activation of Cidec by PPARgamma2 in adipocyte. Biochem Biophys Res Commun 2008;377(1):297-302. doi: 10.1016/j.bbrc.2008.09.129 PubMed PMID: 18845124

130. Bergan-Roller HE, Ickstadt AT, Kittilson JD, Sheridan MA. Insulin and insulin-like growth factor-1 modulate the lipolytic action of growth hormone by altering signal pathway linkages. Gen Comp Endocrinol 2017;248:40-48 doi: 10.1016/j.ygcen.2017.04.005 PubMed PMID: 28410970

131. Carter-Su C, Schwartz J, Argetsinger LS. Growth hormone signaling pathways. Growth Horm IGF Res 2016;28:11-15 doi: 10.1016/j.ghir.2015.09.002 PubMed PMID: 26421979

132. Burgermeister E, Chuderland D, Hanoch T, Meyer M, Liscovitch M, Seger R. Interaction with MEK causes nuclear export and downregulation of peroxisome proliferator-activated receptor gamma. Mol Cell Biol 2007;27(3):803-817 doi: 10.1128/MCB.00601-06. PubMed PMID: 17101779; PMCID: PMC1800691

133. Tan X, Cao Z, Li M, Xu E, Wang J, Xiao Y. TNF-alpha downregulates CIDEC via MEK/ERK pathway in human adipocytes. Obesity (Silver Spring) 2016;24(5):1070-1080 doi: 10.1002/oby.21436 PubMed PMID: 27062372

134. Frayn KN. Visceral fat and insulin resistance-causative or correlative? Br J Nutr 2000;83(Suppl 1):S71-S77 PubMed PMID: 10889795

135. Gabriely I, Ma XH, Yang XM, Atzmon G, Rajala MW, Berg AH, Scherer P, Rossetti L, Barzilai N. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? Diabetes 2002;51(10):2951-2958 doi: 10.2337/diabetes.51.10.2951 PubMed PMID: 12351432

136. Janochova K, Haluzik M, Buzga M. Visceral fat and insulin resistance - what we know? Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2019;163(1):19-27 doi: 10.5507/bp.2018.062 PubMed PMID: 30398218

137. Kuk JL, Katzmarzyk PT, Nichaman MZ, Church TS, Blair SN, Ross R. Visceral fat is an independent predictor of all-cause mortality in men. Obesity (Silver Spring) 2006;14(2):336-341 doi: 10.1038/oby.2006.43 PubMed PMID: 16571861

138. Lebovitz HE, Banerji MA. Point: visceral adiposity is causally related to insulin resistance. Diabetes Care. 2005;28(9):2322-2325 doi: 10.2337/diacare.28.9.2322 PubMed PMID: 16123512

139. McCarty MF. A paradox resolved: the postprandial model of insulin resistance explains why gynoid adiposity appears to be protective. Med Hypotheses 2003;61(2):173-176 PubMed PMID: 12888298

140. Porter SA, Massaro JM, Hoffmann U, Vasan RS, O'Donnel CJ, Fox CS. Abdominal subcutaneous adipose tissue: a protective fat depot? Diabetes Care 2009;32(6):1068-1075 doi: 10.2337/dc08-2280 PubMed PMID: 19244087; PMCID: PMC2681034

141. Moran A, Jacobs DR Jr, Steinberger J, Cohen P, Hong CP, Prineas R, Sinaiko AR. Association between the insulin resistance of puberty and the insulin-like growth factor-I/growth hormone axis. J Clin Endocrinol Metab 2002;87(10):4817-4820 doi: 10.1210/jc.2002-020517 PubMed PMID: 12364479

142. Bloch CA, Clemons P, Sperling MA. Puberty decreases insulin sensitivity. J Pediatr 1987;110(3):481-487 PubMed PMID: 2950219

143. Caprio S, Cline G, Boulware S, Permanente C, Shulman GI, Sherwin RS, Tamborlane WV. Effects of puberty and diabetes on metabolism of insulin-sensitive fuels. Am J Physiol 1994;266(6 Pt 1):E885-E891 doi: 10.1152/ajpendo.1994.266.6.E885 PubMed PMID: 8023918

144. Goran MI, Gower BA. Longitudinal study on pubertal insulin resistance. Diabetes 2001;50(11):2444-2450 doi: 10.2337/diabetes.50.11.2444 PubMed PMID: 11679420

145. Moran A, Jacobs DR, Jr, Steinberger J, Hong CP, Prineas R, Luepker R, Sinaiko AR. Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes 1999;48(10):2039-2044 doi: 10.2337/diabetes.48.10.2039. PubMed PMID: 10512371

146. Caprio S, Plewe G, Diamond MP, Simonson DC, Boulware SD, Sherwin RS, Tamborlane WV. Increased insulin secretion in puberty: a compensatory response to reductions in insulin sensitivity. J Pediatr 1989;114(6):963-967 PubMed PMID: 2524556

147. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. N Engl J Med 1986;315(4):215-219 doi: 10.1056/NEJM198607243150402 PubMed PMID: 3523245

148. Ahn CW, Kim CS, Nam JH, Kim HJ, Nam JS, Park JS, Kang ES, Cha BS, Lim SK, Kim KR, Lee HC, Huh KB. Effects of growth hormone on insulin resistance and atherosclerotic risk factors in obese type 2 diabetic patients with poor glycaemic control. Clin Endocrinol (Oxf) 2006;64(4):444-449 doi: 10.1111/j.1365-2265.2006.02490.x PubMed PMID: 16584518

149. Nellemann B, Gormsen LC, Sorensen LP, Christiansen JS, Nielsen S. Impaired insulin-mediated antilipolysis and lactate release in adipose tissue of upper-body obese women. Obesity (Silver Spring) 2012;20(1):57-64 doi: 10.1038/oby.2011.290 PubMed PMID: 21959346

150. Demerath EW, Sun SS, Rogers N, Lee M, Reed D, Choh AC, Couch W, Czerwinski SA, Chumlea WC, Siervogel RM, Towne B. Anatomical patterning of visceral adipose tissue: race, sex, and age variation. Obesity (Silver Spring) 2007;15(12):2984-2993 doi: 10.1038/oby.2007.356 PubMed PMID: 18198307; PMCID: PMC2883307

151. Gjedsted J, Gormsen LC, Nielsen S, Schmitz O, Djurhuus CB, Keiding S, Orskov H, Tonnesen E, Moller N. Effects of a 3-day fast on regional lipid and glucose metabolism in human skeletal muscle and adipose tissue. Acta Physiol (Oxf) 2007;191(3):205-216 doi: 10.1111/j.1748-1716.2007.01740.x PubMed PMID: 17784905

152. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. Int J Obes (Lond). 2010;34(6):949-959 doi: 10.1038/ijo.2009.286 PubMed PMID: 20065965

153. Nielsen TS, Jessen N, Jorgensen JO, Moller N, Lund S. Dissecting adipose tissue lipolysis: molecular regulation and implications for metabolic disease. J Mol Endocrinol 2014;52(3):R199-R222 doi: 10.1530/JME-13-0277 PubMed PMID: 24577718

154. Beauregard C, Utz AL, Schaub AE, Nachtigall L, Biller BM, Miller KK, Klibanski A. Growth hormone decreases visceral fat and improves cardiovascular risk markers in women with hypopituitarism: a randomized, placebo-controlled study. J Clin Endocrinol Metab 2008;93(6):2063-2071 doi: 10.1210/jc.2007-2371 PubMed PMID: 18381581; PMCID: PMC2435650

155. Bredella MA, Gerweck AV, Lin E, Landa MG, Torriani M, Schoenfeld DA, Hemphill LC, Miller KK. Effects of GH on body composition and cardiovascular risk markers in young men with abdominal obesity. J Clin Endocrinol Metab 2013;98(9):3864-3872 doi: 10.1210/jc.2013-2063 PubMed PMID: 23824419; PMCID: PMC3763970

156. Salgin B, Marcovecchio ML, Williams RM, Jackson SJ, Bluck LJ, Humphreys SM, Acerini CL, Dunger DB. Effects of growth hormone and free fatty acids on insulin sensitivity in patients with type 1 diabetes. J Clin Endocrinol Metab 2009;94(9):3297-3305 doi: 10.1210/jc.2009-0378 PubMed PMID: 19567515; PMCID: PMC2846959

157. Segerlantz M, Bramnert M, Manhem P, Laurila E, Groop LC. Inhibition of lipolysis during acute GH exposure increases insulin sensitivity in previously untreated GH-deficient adults. Eur J Endocrinol 2003;149(6):511-519 PubMed PMID: 14640991

158. Bouchonville M, Jaghab J, Duran-Valdez E, Schrader R, Schade D. The Effectiveness and Risks of Programming an Insulin Pump to Counteract the Dawn Phenomenon in Type 1 Diabetes. Endocr Pract 2014:1-25 doi: 10.4158/EP14198.OR PubMed PMID: 25100389

159. Monnier L, Colette C, Dejager S, Owens D. Magnitude of the dawn phenomenon and its impact on the overall glucose exposure in type 2 diabetes: is this of concern? Diabetes Care 2013;36(12):4057-4062 doi: 10.2337/dc12-2127 PubMed PMID: 24170753; PMCID: PMC3836163

160. Monnier L, Colette C, Sardinoux M, Baptista G, Regnier-Zerbib A, Owens D. Frequency and severity of the dawn phenomenon in type 2 diabetes: relationship to age. Diabetes Care 2012;35(12):2597-2599 doi: 10.2337/dc12-0385 PubMed PMID: 22991448; PMCID: PMC3507613

161. Campbell PJ, Bolli GB, Cryer PE, Gerich JE. Pathogenesis of the dawn phenomenon in patients with insulin-dependent diabetes mellitus. Accelerated glucose production and impaired glucose utilization due to nocturnal surges in growth hormone secretion. N Engl J Med 1985;312(23):1473-1479 doi: 10.1056/NEJM198506063122302. PubMed PMID: 2859524

162. Davidson MB, Harris MD, Ziel FH, Rosenberg CS. Suppression of sleep-induced growth hormone secretion by anticholinergic agent abolishes dawn phenomenon. Diabetes 1988;37(2):166-171 PubMed PMID: 3391341

163. Nielsen S, Moller N, Christiansen JS, Jorgensen JO. Pharmacological antilipolysis restores insulin sensitivity during growth hormone exposure. Diabetes 2001;50(10):2301-2308 PubMed PMID: 11574412

164. Hansen I, Tsalikian E, Beaufrere B, Gerich J, Haymond M, Rizza R. Insulin resistance in acromegaly: defects in both hepatic and extrahepatic insulin action. Am J Physiol 1986;250(3 Pt 1):E269-E273 doi: 10.1152/ajpendo.1986.250.3.E269 PubMed PMID: 3513613

165. Rizza RA, Mandarino LJ, Gerich JE. Effects of growth hormone on insulin action in man. Mechanisms of insulin resistance, impaired suppression of glucose production, and impaired stimulation of glucose utilization. Diabetes 1982;31(8 Pt 1):663-669 PubMed PMID: 6761205

166. del Rincon JP, Iida K, Gaylinn BD, McCurdy CE, Leitner JW, Barbour LA, Kopchick JJ, Friedman JE, Draznin B, Thorner MO. Growth hormone regulation of p85alpha expression and phosphoinositide 3-kinase activity in adipose tissue: mechanism for growth hormone-mediated insulin resistance. Diabetes 2007;56(6):1638-1646 doi: 10.2337/db06-0299 PubMed PMID: 17363744

167. Dominici FP, Argentino DP, Munoz MC, Miquet JG, Sotelo AI, Turyn D. Influence of the crosstalk between growth hormone and insulin signalling on the modulation of insulin sensitivity. Growth Horm IGF Res 2005;15(5):324-336 doi: 10.1016/j.ghir.2005.07.001. PubMed PMID: 16112592

168. Krusenstjerna-Hafstrom T, Clasen BF, Moller N, Jessen N, Pedersen SB, Christiansen JS, Jorgensen JO. Growth hormone (GH)-induced insulin resistance is rapidly reversible: an experimental study in GH-deficient adults. J Clin Endocrinol Metab. 2011;96(8):2548-2557 doi: 10.1210/jc.2011-0273 PubMed PMID: 21613350

169. Krusenstjerna-Hafstrom T, Madsen M, Vendelbo MH, Pedersen SB, Christiansen JS, Moller N, Jessen N, Jorgensen JO. Insulin and GH signaling in human skeletal muscle in vivo following exogenous GH exposure: impact of an oral glucose load. PLoS One 2011;6(5):e19392 doi: 10.1371/journal.pone.0019392 PubMed PMID: 21559284; PMCID: PMC3086909

170. Jessen N, Djurhuus CB, Jorgensen JO, Jensen LS, Moller N, Lund S, Schmitz O. Evidence against a role for insulin-signaling proteins PI 3-kinase and Akt in insulin resistance in human skeletal muscle induced by short-term GH infusion. Am J Physiol Endocrinol Metab 2005;288(1):E194-E199 doi: 10.1152/ajpendo.00149.2004 PubMed PMID: 15339744

171. Nielsen C, Gormsen LC, Jessen N, Pedersen SB, Moller N, Lund S, Jorgensen JO. Growth hormone signaling in vivo in human muscle and adipose tissue: impact of insulin, substrate background, and growth hormone receptor blockade. J Clin Endocrinol Metab 2008;93(7):2842-2850 doi: 10.1210/jc.2007-2414 PubMed PMID: 18460563

FGF23 and Associated Disorders of Phosphate Wasting

Anisha Gohil[1], DO, Erik A. Imel[2], MD

[1]Indiana University School of Medicine, Riley Hospital for Children Fellow, Endocrinology & Diabetes, 705 Riley Hospital Drive, Room 5960,Indianapolis, IN 46202, USA, [2]Indiana University School of Medicine, Riley Hospital for Children, Associate Professor of Medicine and Pediatrics, 1120 West Michigan Street, CL 459, Indianapolis, IN 46202, USA

Corresponding author: Anisha Gohil, DO, Indiana University School of Medicine, Riley Hospital for Children, Fellow, Endocrinology & Diabetes, 705 Riley Hospital Drive, Room 5960, Indianapolis, IN 46202, USA, Tel: 317-944-3889, Fax: 317-944-3882, E-mail: agohil@iu.edu

Abstract

Fibroblast growth factor 23 (FGF23), one of the endocrine fibroblast growth factors, is a principal regulator in the maintenance of serum phosphorus concentration. Binding to its cofactor aKlotho and a fibroblast growth factor receptor is essential for its activity. Its regulation and interaction with other factors in the bone-parathyroid-kidney axis is complex. FGF23 reduces serum phosphorus concentration through decreased reabsorption of phosphorus in the kidney and by decreasing 1,25 dihydroxyvitamin D (1,25(OH)2D) concentrations. Various FGF23-mediated disorders of renal phosphate wasting share similar clinical and biochemical features. The most common of these is X-linked hypophosphatemia (XLH). Additional disorders of FGF23 excess include autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, fibrous dysplasia, and tumor-induced osteomalacia. Treatment is challenging, requiring careful monitoring and titration of dosages to optimize effectiveness and to balance side effects. Conventional therapy for XLH and other disorders of FGF23-mediated hypophosphatemia involves multiple daily doses of oral phosphate salts and active vitamin D analogs, such as calcitriol or alfacalcidol. Additional treatments may be used to help address side effects of conventional therapy such as thiazides to address hypercalciuria or nephrocalcinosis, and calcimimetics to manage hyperparathyroidism. The recent development and approval of an anti-FGF23 antibody, burosumab, for use in XLH provides a novel treatment option.

Ref: *Ped. Endocrinol. Rev. 2019;17(1):17-34*
doi: *10.17458/per.vol17.2019.gi.fgf23anddisordersphosphate*
Key words: *FGF23, Klotho, Phosphorus, 1,25(OH)2D, XLH, Burosumab, Rickets*

Introduction

Fibroblast growth factor 23 (FGF23) is part of a family of fibroblast growth factors (FGFs) which are secreted signaling proteins (1). Found in several tissues, they serve essential functions in development and metabolism through all stages of life, beginning in the embryo and continuing through adulthood (2). There are three types of FGFs, categorized based on their mechanism of action: autocrine, paracrine, and endocrine (1). FGFs require heparin sulfate for receptor binding and signaling, enabling autocrine and paracrine functions (3). However, the endocrine FGFs are distinguished by their poor affinity for heparin sulfate, allowing release from the local extracellular matrix to circulate as endocrine hormones and bind receptors on distant cells (4). The endocrine FGFs play an important part in bile acid (FGF19), carbohydrate (FGF21), lipid (FGF21), and phosphate metabolism (FGF23) (2).

The FGF23 gene is located on human chromosome 12 (5). FGF23 is primarily produced in bone by osteocytes and is a 32 kDa protein containing 251 amino acids (5). The N-terminus contains a FGF homology region which binds to the FGF receptor and the C-terminus binds to the co-receptor αKlotho, ultimately creating a FGF receptor complex necessary for signaling at the FGF receptor (6).

In 1989, Meyer et al. suggested the presence of a phosphaturic factor (referred to as a "phosphatonin") in Hyp mice, a mouse model of X-linked hypophosphatemic rickets (XLH) (7). Hyp mice produced this phosphaturic factor which could be transferred to normal mice through parabiosis experiments, resulting in an XLH phenotype (7). FGF23 was discovered in 2000 due to mutations in the FGF23 gene found in a kindred with autosomal dominant hypophosphatemic rickets (ADHR) (8), and was later identified as elevated in XLH and several other renal phosphate wasting disorders as the responsible phosphaturic factor. In our review, we explore the biological function and regulation of FGF23 and discuss hypophosphatemic disorders resulting from a state of FGF23 excess.

Cofactor and Receptors

The endocrine FGFs require a cofactor, αKlotho or ßKlotho, in order to bind their respective receptors and provide tissue specificity (1). αKlotho or ßKlotho are structurally related proteins consisting of approximately 1000 amino acids (2). FGF19 and FGF21 activate their receptor via ßKlotho (1), while FGF23 activates its receptor via αKlotho (9). αKlotho binds to multiple fibroblast growth factor receptors (FGFR), forming a complex with greater affinity for FGF23 than αKlotho or the FGF receptor alone (10). Since many tissues express FGFR, the presence of klotho determines the target organs for the endocrine FGFs (11,12). The primary tissues expressing αklotho are the kidney's proximal and distal tubules, the parathyroid glands, and the brain's choroid plexus (13).

FGFRs are tyrosine kinases (2). Four of them are considered to be high-affinity receptors: FGFR1, FGFR2, FGFR3, and FGFR4. However, αKlotho does not bind strongly to FGFR2 (9,10). Alternative splicing creates different 'b' and 'c' isoforms of FGFR and αKlotho binds best to the 'c' isoform leading to signaling of FGF23 through FGFR1c, FGFR3c, or FGFR4c (9,10). FGF23 has the highest affinity for FGFR1c (9).

Regulation of FGF23

The regulation of FGF23 is complex, involving multiple components in the bone-parathyroid-kidney axis, including phosphorus, 1,25(OH)2D, parathyroid hormone (PTH), and calcium. FGF23 concentrations are increased by 1,25(OH)2D in humans and in animal models (14-20). In cell culture studies, 1,25(OH)2D increased FGF23 gene expression (17). Even in XLH, therapeutic treatment with phosphate and calcitriol led to a further significant increase in already elevated FGF23 levels despite persistent hypophosphatemia (19). In 30 adult dialysis patients with baseline elevated levels of FGF23 and secondary hyperparathyroidisim, FGF23 levels increased further after intravenous calcitriol (15). While phosphorus and 1,25(OH)2D both independently regulate FGF23 (17,18), phosphate binders may be able to block 1,25(OH)2D-induced FGF23 increases (16).

Phosphate intake increases FGF23 levels in studies of healthy adults and animal models (17,21-24). Dietary phosphate was shown to be a key regulator of serum FGF23 in healthy men and women (21,24). Oral phosphate loading significantly increased FGF23, while phosphate restriction led to a significant decrease (21,24). In healthy adult subjects, a diet high in both phosphate and calcium also significantly increased FGF23 levels (23).

The effect of PTH on FGF23 is not entirely clear. Animal models and cell culture studies indicate that PTH directly stimulates FGF23 production via the PTH/PTHrP receptor (25-29). However, human studies are conflicting. One study in healthy adults indicated after PTH (1-34) infusion, that FGF23 and phosphorus levels significantly decreased over 6 hours (30). In contrast, another study in healthy adult men receiving a PTH (1-34) infusion, found FGF23 increased significantly during an 18 hour period (31). In both studies, PTH (1-34) infusion increased 1,25(OH)2D.

Low serum calcium may act as a "brake" on FGF23 production, which may be an adaptive response to prevent further hypocalcemia. Low calcium levels have been shown to decrease FGF23 levels, which subsequently removes FGF23 suppression of 1,25(OH)2D (32,33). Using mutant mouse models, PTH and 1,25(OH)2D were unable to stimulate FGF23 in the setting of hypocalcemia (33). This may also explain why it is often difficult to normalize serum phosphorus in hypoparathyroidism, despite elevated FGF23 (34). In adult patients with hypoparathyroidism, treatment with 1,25(OH)2D increased serum calcium and FGF23 levels (20).

Additional regulation of FGF23 occurs through post-translational mechanisms. Proprotein convertases cleave FGF23 at the C-terminus between amino acids 179 and 180 (35). Mutations affecting this cleavage site result in excess FGF23 (36). FGF23 also requires O-glycosylation within the proprotein convertase cleavage site in order to secrete biologically active intact FGF23 (37). O-glycosylation is directed by the polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) (37). Deficiency of GALNT3 activity prevents O-glycosylation, leading to increased cleavage and inactivation of FGF23 (37). Loss-of-function mutations in GALNT3 result in a deficiency of intact FGF23, and the resulting

phenotype of hyperphosphatemic familial tumoral calcinosis (38). A kinase from the family with sequence similarity 20, member C (FAM20C) phosphorylates FGF23, preventing O-glycosylation, allowing for cleavage by proprotein convertases, such as furin (39). Deficiency of FAM20C leads to FGF23 excess and hypophosphatemia. FGF23 cleavage may be regulated specifically to maintain appropriate concentrations and normophosphatemia. Gene expression increases in the setting of iron deficiency (40), but generally intact FGF23 concentrations remain normal unless a mutation specifically impairs FGF23 cleavage (41). Phosphate regulating endopeptidase homolog X-linked (PHEX) and dentin matrix protein 1 (DMP1) are genes whose deficiency results in upregulation of FGF23 (42, 43). FGFR signaling pathways also regulate FGF23 through Ras-mitogen-activated protein kinase (MAPK), extracellular signal related kinase (ERK), and tyrosine kinase activity (44). **Figure 1** lists positive and negative regulators of FGF23.

FGF23 Regulation of 1,25(OH)2D, Phosphorus and PTH

FGF23 is the principal regulator in the maintenance of serum phosphorus levels (**figure 2**). Administration of FGF23 in animal models decreases serum phosphorus due to a combination of effects on renal phosphate transport and vitamin D metabolism (45-48). Phosphorus is filtered by the glomerulus, but the vast majority is reabsorbed in the proximal convoluted tubule by renal sodium phosphate cotransporters type IIa (NaPi-IIa) and type IIc (NaPi-IIc) (49). FGF23 administration results in reduced brush border expression of the NaPi-IIa and NaPi-IIc (50,51). NaPi-IIa and NaPi-IIc are also down-regulated by PTH (52).

FGF23 decreases serum 1,25(OH)2D levels via suppressed expression of CYP27B1, limiting protein expression of 1α-hydroxylase (45,53), an enzyme necessary to convert 25-hydroxyvitamin D (25(OH)D) to its active form 1,25(OH)2D (53). FGF23 also increases expression of CYP24A1, increasing vitamin D 24-hydroxylase (45), which catabolizes 25(OH)D and 1,25(OH)2D into inactive metabolites (53). Since 1,25(OH)2D upregulates intestinal phosphate transport, decreasing 1,25(OH)2D also contributes to FGF23-mediated hypophosphatemia (50,51).

Conditions of FGF23 excess or deficiencies have expected effects on phosphorus and vitamin D metabolism. Transgenic mice expressing human FGF23 have reduced expression of NaPi-IIa, phosphaturia, and decreased serum 1,25(OH)2D with resultant hypophosphatemia and rachitic bone (50). FGF23 null mice had the opposite biochemical findings with elevated serum phosphorus levels, elevated serum 1,25(OH)2D, and increased renal phosphorus reabsorption (54). These

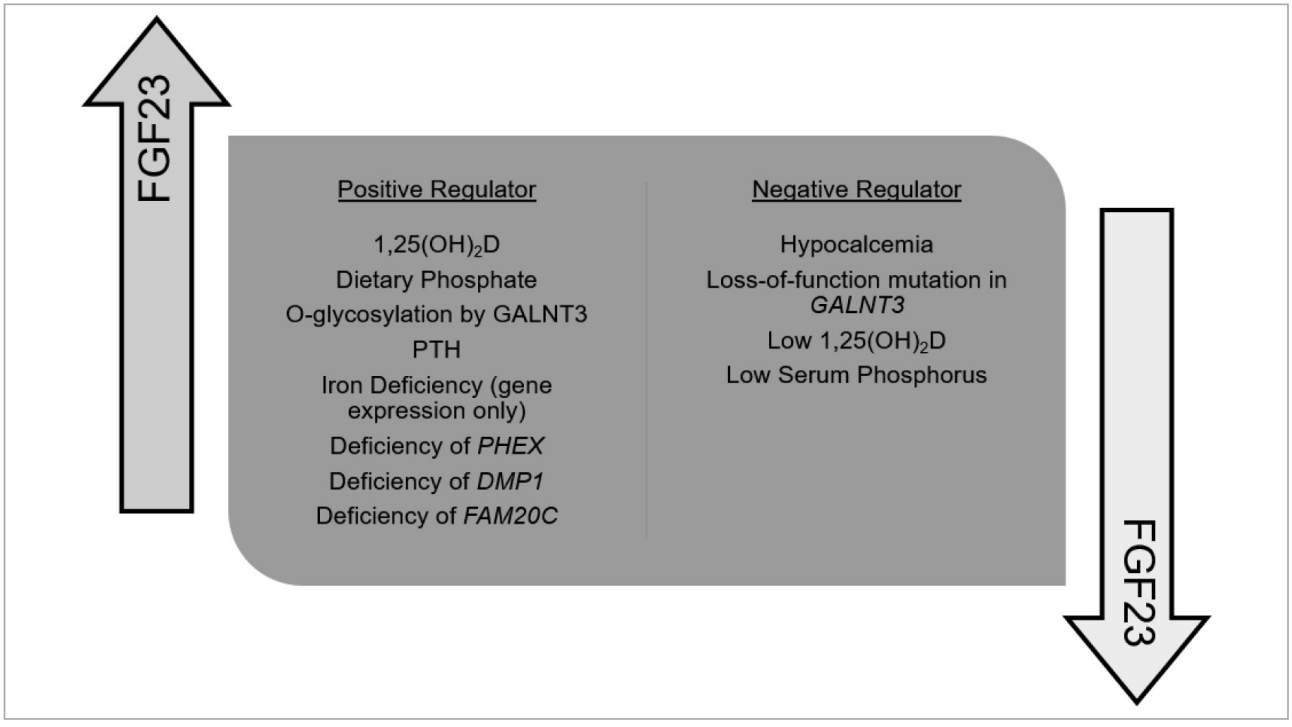


Figure 1. List of positive and negative regulators of FGF23

phenotypes are recapitulated in the human diseases of XLH and hyperphosphatemic tumoral calcinosis, respectively.

The effect of FGF23 on PTH is not well understood. Evidence in vitro and from animal models suggests that FGF23 has an inhibitory effect on PTH, at least during short-term studies (11,55). FGF23 suppressed PTH in rats, but in the setting of hypocalcemia, the inhibition of PTH is lost (56). However, in human diseases or animal models of chronic FGF23 excess, hyperparathyroidism is common (51,57).

Effect of Age and Gender on FGF23

Multiple enzyme linked immunosorbent assays are available for measuring FGF23 in serum or plasma. An assay targeting the C-terminal end of FGF23 (cFGF23) will detect both C-terminal fragments and full length FGF23 (58). However only the intact form is biologically active. Intact FGF23 assays measure only the full-length intact FGF23 (iFGF23) (59). The cFGF23 is best measured in plasma, as serum values will be systematically lower (60). However, the Kainos iFGF23 assay provides similar results in plasma and serum (60).

Table 1 describes reported ranges of FGF23 in healthy populations. In general studies indicate higher values of cFGF23 in newborns and young children than in adults (58,61-67). However, reported iFGF23 ranges are generally similar across studies at different ages in healthy children and adults, though one study suggested lower iFGF23 in cord blood (59,61-63,65-67). While cFGF23 were mostly similar between boys and girls, some studies suggested higher iFGF23 in girls (62,63).

In a study of 180 healthy adults, cFGF23 had lower intra-individual variability, but higher inter-individual variability (66). Since iFGF23 had less inter-individual variability, it may be more clinically useful for diagnostic purposes (66), though currently the cFGF23 assay is more clinically available. Intact FGF23 levels >30 pg/mL using the Kainos intact assay (approximately the normal mean with this assay in some studies) during hypophosphatemia have been proposed as a cutoff for identifying FGF23-mediated hypophosphatemia (68). However, an analogous threshold with cFGF23 has not been determined.

FGF23-Mediated Disorders of Phosphate Wasting

The differential diagnosis for hypophosphatemia is quite broad, but etiologies largely include increased renal excretion (both FGF23-mediated and non-FGF23-mediated), impaired intake or intestinal absorption of phosphate, and transcellular shifts of phosphorus (69). This review concentrates on the FGF23-mediated causes, which include autosomal dominant hypophosphatemic rickets (ADHR), X-linked hypophosphatemic rickets (XLH), autosomal recessive hypophosphatemic rickets (ARHR), fibrous dysplasia (FD), and tumor-induced osteomalacia (TIO) (**table 2**). These FGF23-mediated hypophosphatemic disorders share common features which may include rickets or osteomalacia, bony deformities, short stature, and bone pain (8). Biochemically these conditions are characterized by low serum phosphorus, increased urinary phosphorus excretion [or decreased ratio of the maximum rate of tubular phosphate reabsorption to glomerular filtration rate (TmP/GFR)], normal serum and urine calcium, high alkaline phosphatase (ALP), normal PTH, normal 25(OH)D, decreased or inappropriately normal 1,25(OH)2D, and increased FGF23 (69).

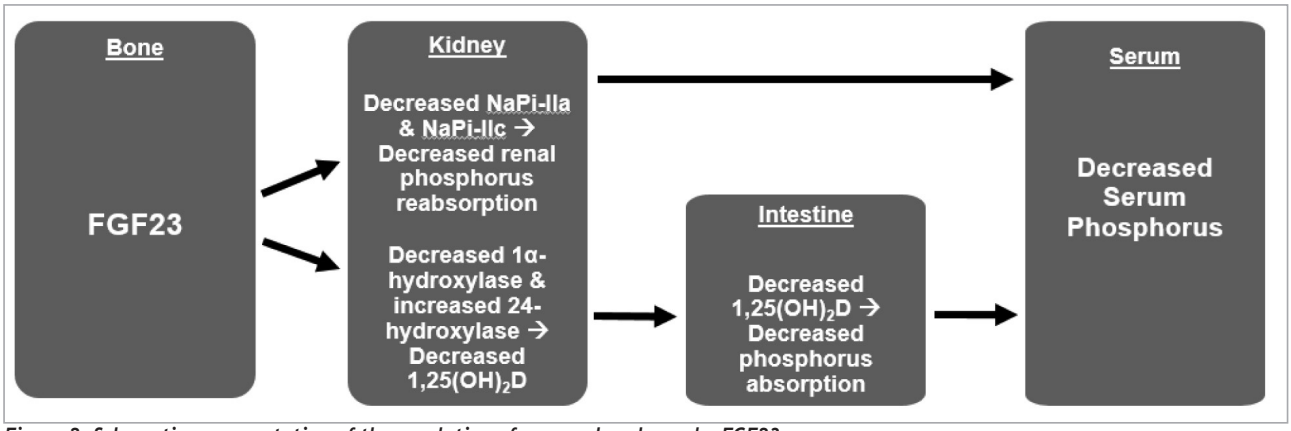


Figure 2. Schematic representation of the regulation of serum phosphorus by FGF23

Table 1. Reference values for cFGF23 and iFGF23 among age groups

Age	Study Sample	Plasma or Serum	cFGF23	cFGF23 Assay	iFGF23	iFGF23 Assay	Study/Year
Neonate	64-full term neonates	Plasma	Median 824 RU/mL (108-7508) Mean 1678 RU/mL (±1857)	Immunotopics	Median <8.5 pg/mL (<8.5-135.4) Mean 16.7 pg/mL (±24.2)	Immuno-topics	Ali et al., 2016 (61)
	113 healthy infants	Cord blood serum at birth	Median Girls 536.2 RU/mL [731.7] Median Boys 605.9 RU/mL [842.9]	Immunotopics	Median Girls 3.0 pg/mL [10.7] Median Boys 3.0 pg/mL [2.3]	Kainos	Holmlund-Suila et al., 2016 (62)
3 months old	113 healthy infants	Serum	Mean Girls 106.9 RU/mL (±64.0) Mean Boys 105.4 RU/mL (±52.1)	Immunotopics	Median Girls 51.4 pg/mL [30.0] Median Boys 25.9 pg/mL [48]	Kainos	Holmlund-Suila et al., 2016 (62)
1 year old	721 healthy children	Plasma	Median Girls 2.9 pmol/L [2.2-3.7] Median Boys 2.8 pmol/L [2.1-3.7]	Biomedica Medizin-produkte GmbH & Co KG	Median Girls 44.4 pg/mL [36.8-51.9] Median Boys 40.9 pg/mL [34.5-49.0]	Kainos	Holmlund-Suila et al., 2017 (63)
Childhood	424 healthy youth and young adults (ages 0.1-21 years)	Plasma	Age ≤ 1 Median 105 RU/mL [75-153] Age 5 Median 68 RU/mL [53-89] Age 10 Median 71 RU/mL [56-88] Age 15 Median 76 RU/mL [59-95] Age ≥ 19 Median 50 RU/mL [39-61]	Immunotopics			Fischer et al., 2012 (64)
	159 healthy children (mean age 8.78 ± 3.47 years)	Serum	Mean 51.14 RU/mL (±12.79)	Immunotopics	Median 35 pg/mL (8.8-120)	Kainos	Gkentzi et al., 2014 (65)
Adulthood	180 healthy adults	Plasma	Median 53.7 RU/mL (range not provided)	Immunotopics	Median 24.7 pg/mL (range not provided)	Immuno-topics	Smith et al., 2012 (66)
	147 healthy adults	Plasma or serum	Mean Women 52.9 RU/mL (±20.8) Mean Men 42.0 RU/mL (±15.8)	Immunotopics			Jonsson et al., 2003 (58)
	55 healthy adults	Plasma	Mean 61.0 RU/mL (±28.6)	Immunotopics	Mean 44.7 pg/mL (±14.9)	Kainos	Imel et al., 2007 (67)
	104 healthy adults	Serum			Mean 28.9 ng/L (8.2-54.3)	Kainos	Yamazaki et al., 2002 (59)

Table 2. Summary of FGF23-Mediated disorders of phosphate wasting and associated genetic & somatic mutations

Disorder	Genetic Mutation
X-linked Hypophosphatemic Rickets	PHEX
Autosomal Recessive Hypophosphatemic Rickets	DMP1, ENPP1, FAM20C
Autosomal Dominant Hypophosphatemic Rickets	FGF23
Fibrous Dysplasia (FD)/McCune-Albright Syndrome	GNAS
Tumor Induced Osteomalacia	FN1-FGFR1 fusion gene
Linear Nevus Sebaceous Syndrome	HRAS, KRAS, NRAS somatic mutations
Jansen's Metaphyseal Chondrodysplasia	PTH/PTHrP receptor
Osteoglophonic Dysplasia	FGFR1

FGF23 Effect on Bone

FGF23 has both direct and indirect effects (through hypophosphatemia) on bone. Hypophosphatemia, secondary to excess FGF23, causes rickets due to arrested apoptosis of the hypertrophic chondrocytes of the growth plate and osteomalacia due to delayed mineral apposition rate of osteoid (70). In growing youth, prior to epiphyseal fusion, rickets and osteomalacia both occur, while in the adult, only osteomalacia occurs (70).

In mouse models, Murali et al. has recently shown that increased FGF23 also has direct autocrine and paracrine effects on the osteocyte, which occur independently of klotho and lead to suppression of osteocyte tissue nonspecific alkaline phosphatase (TNAP), contributing to impaired bone mineralization (71,72). Bone specific alkaline phosphatase hydrolyzes inorganic pyrophosphate (an inhibitor of mineralization) releasing inorganic phosphate, subsequently allowing for synthesis of hydroxyapatite (73). Its deficiency leads to impaired mineralization as seen in hypophosphatasia, while conversely, insufficient inorganic phosphate at the mineralization surface tends to increase alkaline phosphatase activity. In the Hyp mouse model of XLH, while the TNAP activity in the Hyp osteocyte is impaired secondary to increased FGF23 secretion, osteoblast TNAP is increased sufficient to lead to elevated serum ALP (72). ALP activity is also increased within growth plate cartilage during chondrocyte differentiation (74). Increased serum ALP activity is generally seen in human disease states of FGF23-mediated hypophosphatemia (69).

Autosomal Dominant Hypophosphatemic Rickets (ADHR)

In the year 2000, FGF23 was discovered due to the presence of missense mutations in kindreds with ADHR (8). These missense mutations decrease FGF23's susceptibility to proteolytic cleavage, preventing its degradation, hence resulting in elevated circulating levels and hypophosphatemia (75). ADHR is a rare hypophosphatemic disorder with autosomal dominant inheritance pattern, but incomplete penetrance (76).

In fact, disease activity fluctuates according to FGF23 levels in this condition, and there is waxing and waning of the biochemical and symptomatic phenotypes (36). Those with an onset in childhood develop hypophosphatemia, phosphate wasting, rickets, and lower extremity deformities. However, a large subgroup of patients has documented normal phosphate values for age in childhood, grows normally without rickets or leg deformities, and only later as adolescents or adults develops elevated iFGF23 and hypophosphatemia (36,41,76,77).

Those with late-onset of disease in adolescence or adulthood developed significant bone pain, weakness, and insufficiency fractures. Some of those with childhood-onset disease achieve spontaneous resolution of their renal phosphate-wasting defect. Similarly some with late-onset hypophosphatemia also spontaneously normalize their FGF23 and serum phosphorus concentrations, with associated resolution of symptoms (36,41).

Interestingly the FGF23 phenotype of ADHR appears to be driven by the consequences of iron deficiency. In the

setting of iron deficiency, FGF23 gene expression increases (40). In healthy controls or wild type mice, this leads to elevated circulating concentrations of fragments (cFGF23), but biologically active iFGF23 remains normal, with normophosphatemia (40,41). However, in the setting of ADHR mutations, iFGF23 concentrations also become elevated during iron deficiency due to the effect of impaired FGF23 cleavage, and hypophosphatemia results (40,41). The observed waxing and waning of the ADHR biochemical phenotype corresponded to changes in iron status (41). We would propose that if a patient never became iron deficient, clinical features of ADHR might never manifest. In contrast, in XLH patients, iFGF23 is not related to serum iron (78).

The iron story is made somewhat more complicated by adverse effects of intravenous iron administration. In the setting of iron deficiency, patients without ADHR can sometimes be triggered by certain forms of intravenous iron to undergo sudden acute increases in iFGF23, even while their cFGF23 is normalizing (79, 80). This phenomenon can be severe enough to cause hypophosphatemia, and if repeated doses are necessary due to persistent iron deficiency, osteomalacia and insufficiency fractures may result. The mechanism is not certain but appears to involve a transient inability to effectively cleave iFGF23, even in patients without ADHR. This has been mainly reported with intravenous iron carboxymaltose and iron polymaltose (79-81). Thus, patients undergoing iron infusions should have serum phosphorus monitored.

X-Linked Hypophosphatemic Rickets (XLH)

The most common heritable form of rickets is XLH, with an estimated prevalence of 1 in 20,000 and accounting for about 80% of familial cases of hypophosphatemia (57). The inheritance pattern is X-linked dominant, indicating that a single allele will cause phenotypic expression in both males and females. Careful family history should identify the inheritance pattern and guide assessment of a genetic cause, as there are autosomal dominant and recessive disorders that clinically mimic XLH. A mutation in the PHEX gene causes XLH in humans (82), and in the Hyp mouse model as well (83). The PHEX gene is expressed in bone (osteocyte) and teeth (odontoblasts) (57). PHEX deficiency results in increased expression of FGF23, and consequent hypophosphatemia.

XLH has high penetrance, but clinical findings and severity vary widely among individuals, even within a kindred. Clinical features include short stature, lower-extremity deformities, osteomalacia, rickets, and bone pain (57). Features typically manifest around the time of walking, after age 1 to 2 years, when short stature and limb deformities become apparent (57). Frequent limb deformities include genu varum or valgum, tibial torsion, bowing of the tibia and femur, or windswept deformity (84). While rickets is a classic and common feature, its location and presence are variable among individuals (85). A distinctive histologic feature is hypomineralized periosteocytic lesions in cortical bone (86). In XLH, FGF23 is generally elevated. However, some patients may have high-normal levels which are still indicative of an FGF23-mediated cause of their hypophosphatemia (58,59,68).

Dental disease is very common including dental abscesses, caries, periodontal disease, and tooth loss (87-89). Phex and FGF23 are expressed in teeth, and patients with XLH have impaired mineralization of dentin and cementum layers (90-93). Osteopontin is involved in the intrinsic dental abnormalities(91), however hypophosphatemia likely plays a role as well, since treatment with calcitriol and phosphate is associated with fewer tooth abscesses, though they remain common despite treatment (88,89,92).

Osteoarthritis, enthesopathies, and residual lower-extremity long bone curvature are common in adults with XLH (94). Enthesopathies occur in several locations and are commonly found in the hands, feet, spine, hips, and sacroiliac joints and can become quite severe (95,96). These features greatly limit mobility and quality of life. Adults with PHEX mutations often need orthopedic procedures including joint replacement and spinal surgeries (87). With a mean age of 50 at the time of surgery, total knee and hip arthroplasties may benefit adult XLH patients with degenerative osteoarthritis (97). Up to half of adult patients may have pseudofractures (98-100), which are also a source of pain and decreased mobility, which often result in orthopedic procedures for stabilization.

Monitoring for neurologic symptoms is necessary throughout life as patients with XLH can develop neurologic complications due to several disease features. Skull malformations are common in patients with rickets which may sometimes be associated with neurologic consequences. In a study of 44 children with XLH, craniosynostosis, especially sagittal suture fusion, occurred in 59%, and Chiari type 1 malformation was found in 25%, 2 of which had neurological symptoms, and 4 required neurosurgical intervention (101). Hearing loss has been reported in 28.6% of XLH patients compared to 9.8% of unaffected family members (102), in 9% of children and in 48-82% of adults (103,104). Hearing loss is often sensorineural (104). The etiology may involve osteomalacia of the otic capsule bone, but in the Phex mutant mouse model, treatment with calcitriol and phosphate improved mineralization of the capsule bone, but did not prevent sensorineural hearing loss (105).

One study indicated that 12% of adults experience spinal complications including spinal stenosis, cord compression, and myelopathy (87), although lifetime rates may be higher, given the prominent involvement of the spine in enthesopathy,

both at the anterior and posterior longitudinal ligament. Decompressive laminectomy may be needed. These features can contribute to disability. It is important to note that none of the medical treatments discussed below have ever been shown to alter the course of enthesopathy.

Autosomal Recessive Hypophosphatemic Rickets (ARHR)

Autosomal recessive hypophosphatemic rickets (ARHR) is another rare FGF23-mediated condition of renal phosphate wasting with multiple genetic causes. DMP1 mutations cause ARHR type 1 and FGF23 levels are elevated in these individuals and in the DMP1 null mouse (106,107), resulting in hypophosphatemia, severe rickets, and diffuse osteomalacia (43). Mutations in ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) cause ARHR type 2 (108). ENPP1 mutations are also known to cause generalized arterial calcification of infancy (GACI) which causes calcification and stenosis of medium and large-sized arteries (109,110) and is frequently lethal (111). In some individuals with GACI, hypophosphatemia due to renal phosphate wasting developed and was associated with survival past infancy (111), suggesting hypophosphatemia as a protective mechanism seen in milder phenotypes (109). However, in three individuals in a family with ARHR, ENPP1 mutations may also cause ARHR, without GACI (112). Rafaelsen et al. identified a nonlethal variant of Raine syndrome caused by a FAM20C mutation in 2 siblings with elevated FGF23 levels and hypophosphatemia, representing a third genetic form of ARHR (113).

Case reports of individuals with ARHR caused by DMP1 or ENPP1 mutations show a clinical phenotype of short stature, and skeletal deformities starting in early childhood, dental abnormalities such as hypoplasia, caries, and early tooth loss, bone and joint pain, contractures, ligamental calcification, enthesopathies, rickets, and osteomalacia similar to XLH (112,114-118). The siblings with a FAM20C mutation developed tooth decay, osteosclerosis of the long bones, ectopic brain calcifications, and mild facial and acral dysmorphic features (113).

Fibrous Dysplasia (FD)/McCune-Albright Syndrome (MAS)

Fibrous dysplasia (FD) of bone is characterized by replacement of normal bone and bone marrow by abnormal fibro-osseous tissue (119,120). Its occurrence is seen in individuals with McCune-Albright Syndrome (MAS), classically defined as the triad of fibrous dysplasia, café-au-lait macules, and precocious puberty, but can include other endocrinopathies such as hyperthyroidism, growth hormone excess, and Cushing syndrome (121). MAS is rare with an estimated prevalence between 1 in 100,000 and 1 in 1,000,000 (121). It is caused by a post-zygotic mutation in the guanine nucleotide binding protein, alpha stimulating (GNAS) gene, resulting in constitutive activation of the adenylyl cyclase system in affected cells (121,122). FD may also occur in individuals without other features of MAS.

Approximately 50% of individuals with MAS and FD have renal phosphate wasting (120,123), which correlates significantly with the degree of bone involvement (120). However, hypophosphatemic rickets is not common (124). FD lesions locally produce FGF23 and blood cFGF23 levels are increased in FD/MAS compared to normal controls and are significantly higher in FD/MAS with renal phosphate wasting compared to FD/MAS without renal phosphate wasting (123,125). Bone marrow stromal cells with the GNAS mutation have lower GALNT3, but higher furin activity, which ultimately leads to increased FGF23 cleavage causing a larger proportion of the increased FGF23 level being cFGF23, the non-biologically active form, which may explain why classic hypophosphatemic rickets may be less common in FD (126).

Tumor Induced Osteomalacia (TIO)

Tumor induced osteomalacia (TIO) is a rare, sporadic disorder that occurs in children and adults. The tumors are often small and slow growing, of mesenchymal origin, and located in the bone or soft tissue (127). They abundantly express FGF23 (48,128) resulting in elevated blood levels (58,59). Other factors, such as secreted frizzled-related-protein-4 (sFRP-4), fibroblast growth factor 7 (FGF7), and matrix extracellular phosphoglycoprotein (MEPE) are also produced by TIO-associated tumors (129-131), but have not clearly been linked to phosphate pathology. An FN1-FGFR1 fusion gene appears to cause some of these tumors (132). However, as ADHR can also cause late-onset hypophosphatemia, it should be considered in the differential diagnosis of TIO.

Patients often present with vague and long-standing symptoms of bone pain, muscle weakness, fractures, and fatigue (133). Localization of the tumor can be quite difficult, and multiple imaging modalities may need to be employed including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) (133), ^{111}In-octreotide scan, and fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) (134). More recently, Dotatate PET/CT has been used. Selective venous sampling can sometimes detect local elevations in serum FGF-23 levels, allowing for localization of the responsible tumor (135-138). Complete tumor resection is the most effective approach (139)

resulting in resolution of hypophosphatemia and a good prognosis in most (140). Post-operative recurrence can occur even many years later, especially when complete resection is not possible, so ongoing surveillance is necessary (139,140).

Other FGF23-Mediated Disorders of Phosphate Wasting

Other extremely rare causes of FGF23-mediated phosphate wasting include linear nevus sebaceous syndrome (or epidermal nevus syndrome), Jansen's metaphyseal chondrodysplasia, and osteoglophonic dysplasia. Linear nevus sebaceous syndrome (LNSS) is a neurocutaneous disorder affecting multiple organ systems, but mainly the skeletal and central nervous systems (141,142). Postzygotic somatic mutations in HRAS, KRAS, and NRAS are described in LNSS (143,144). Hypophosphatemic rickets may occur with elevated FGF23 levels (145,146). Although some early reports suggested that excision of the nevus corrected the hypophosphatemia (145,147), there is growing evidence that the source is actually the skeleton and that excising these lesions is not beneficial (148,149).

Jansen's metaphyseal chondrodysplasia is a rare form of short limbed dwarfism due to severe growth plate abnormalities with biochemical features similar to primary hyperparathyroidism with hypercalcemia and hypophosphatemia, however PTH is low or undetectable (150). This dysplasia occurs secondary to an activating mutation in the receptor for PTH and PTH-related peptide (PTHrP) (151). Elevated serum FGF23 levels were described in a case report of Jansen's metaphyseal dysplasia and osteocyte expression of this mutation causes elevating FGF23 levels (29,152).

Osteoglophonic dysplasia (OD) is a rare skeletal dysplasia with findings of disproportionate dwarfism, craniofacial defects, and non-ossifying bone lesions caused by an activating mutation in the FGFR1 receptor (153-155). Hypophosphatemia can be seen associated with an elevated FGF23 level, perhaps from local production within bone lesions (155).

Treatment

Conventional therapy for XLH involves multiple daily dosing of oral phosphate supplementation and active vitamin D analogs, such as calcitriol or alfacalcidol (156). Phosphate salts should never be given without an active form of Vitamin D in XLH both because of a lack of effectiveness as monotherapy and due to the effect of phosphate to induce development of secondary and tertiary hyperparathyroidism (157). Conversely some patients can be managed with calcitriol alone (158).

There is no consensus on the optimal doses, and given the extreme variability between patients with XLH, doses need to be individualized (159). Typically published dose recommendations range from 20-60 mg/kg/day of oral phosphate divided into three to five doses per day, and either calcitriol 20-30 ng/kg/day divided into two to three doses per day or alfacalcidol 40-60 ng/kg/day (57,156,160,161). Doses up to 80 mg/kg/day of phosphate and 60 ng/kg/day of calcitriol or higher have also been described in various studies (57,160-162). To our knowledge no systematic study has compared different doses to define an optimal dose level, and most trials typically just report the doses that were administered and are underpowered to compare magnitude of effectiveness of different dose regimens. However, given variability in response, with some patients responding well to lower doses, while others requiring higher doses to achieve effect, it is important to individualize therapy.

Laboratory monitoring, especially of calcium, phosphorus, creatinine, alkaline phosphatase and PTH, as well as of urine calcium and urine creatinine, should be conducted every 3-6 months. Overall, doses should be carefully titrated to achieve a decrease in serum ALP activity while paying careful attention to serum and urine calcium concentrations and serum PTH (160). It is important to know that the primary goal of conventional therapy is not to normalize the serum phosphorus, but rather to improve skeletal outcomes including growth and deformity. In this regard, normalizing the alkaline phosphatase as a marker of osteomalacia is an important goal of therapy and failure to normalize alkaline phosphatase indicates a need to modify therapy and confirm compliance.

However, careful monitoring is also necessary to avoid or manage the clinically important complications of therapy. Gastrointestinal symptoms from the laxative effects of phosphate can often be managed by titrating the dose slowly, but these can be limiting for some patients and complicate adherence. Other clinical complications of conventional therapy include hypercalciuria, nephrocalcinosis, and secondary (or often tertiary) hyperparathyroidism (57,163), which may be related to higher doses (164-166). Consequently, limiting doses or adding adjunctive therapies may be required in some individuals to minimize risk or address occurrence of complications. In particular high doses of phosphate >100 mg/kg/day are associated with higher risk for tertiary hyperparathyroidism (164), though this also is observed with lower doses, especially if accompanied by insufficient dosing of active form of vitamin D.

PTH should be monitored every 3-6 months in children and every 6 months in adults receiving therapy for XLH (57,159). Increasing doses of the active form of vitamin D can ameliorate or normalize the PTH in secondary hyperparathyroidism, though lowering phosphate doses can sometimes be necessary (57,159). Secondary hyperparathyroidism is common, occurring in 83.3% of patients with XLH, leading to tertiary hyperparathyroidism in 16.7%,

including some adolescents (167). There is little data on the outcomes of treatment for tertiary hyperparathyroidism in XLH, which is mostly based on case reports and series. In a recent case series, 75% of XLH patients having parathyroidectomy had recurrence or persistence of tertiary hyperparathyroidism (167).

In a well done study in children with XLH, short term treatment with cinacalcet increased TmP/GFR and serum phosphate, while decreasing PTH levels (168). In an interesting case report, a single patient with XLH was managed with cinacalcet, calcitriol, and hydrochlorothiazide without phosphate salts, demonstrating improvement of rickets (169). Of note cinacalcet use in children is off-label. Several authors have reported success managing the secondary or tertiary hyperparathyroidism of XLH patients with the calcimimetic, cinacalcet (167,170-172). However the responses are variable and patients often still require parathyroidectomy (167).

Nephrocalcinosis is very common on conventional therapy. At baseline, prior to randomization, nephrocalcinosis was present in 23% of the children and 54% of the adults recruited into the recent burosumab clinical trials (98,162). Some studies have found associations of nephrocalcinosis with higher doses of conventional therapy (165,166), while others did not (173). However, these studies also indicated that episodes of hypercalciuria may be associated with nephrocalcinosis risk in XLH. Thus, monitoring urine calcium excretion is important. The long-term consequences of nephrocalcinosis in XLH are uncertain regarding renal function, though CKD is reported in about 8-9 % of patients with XLH (167,174), and end stage renal disease has been reported (167). Renal ultrasounds are recommended every 1-2 years during treatment of XLH with either conventional therapy or burosumab (159).

Thiazides have been used to decrease urinary calcium excretion in XLH patients with hypercalciuria or nephrocalcinosis. In 11 children with XLH on therapy with calcitriol and phosphate, adding the thiazide diuretic, hydrochlorothiazide decreased urinary calcium excretion and while nephrocalcinosis did not resolve, further progression was prevented (175). In another series, the use of thiazides resulted in resolution of nephrocalcinosis in two patients with XLH (176).

Treatment of XLH is required in children to allow for growth and adequate bone mineralization (156), and outcomes are improved when initiated in infancy as opposed to later in childhood (177). However, despite treatment, and even with good adherence, many children have suboptimal growth, and persistent leg deformities with need for surgical correction (177). In particular, Zivicnjak et al. highlight the growth deficits that worsen during puberty even during conventional therapy (178). Therapy has often been stopped at the end of growth in an attempt to balance risks versus benefits of ongoing therapy. During this time period many XLH patients are lost to follow-up until a time when symptoms lead to seeking additional care. However, in adult patients, therapy is typically restarted or continued in symptomatic adults having bone pain or fractures due to osteomalacia. ADHR and ARHR, like XLH, are also treated with oral phosphate and active vitamin D analogs. However, emerging evidence suggests ADHR could be treated with oral iron (41,179) instead of with phosphate and vitamin D, though this approach would be ineffective for XLH (78).

Several studies have evaluated the use of recombinant human growth hormone (GH) in XLH. Uncontrolled studies noted improvement in linear growth in children with short stature and XLH (180-182). Two years of treatment with growth hormone (GH) improved height SDS, with a better response in prepubertal compared to pubertal children (181). GH monotherapy also improved the serum phosphate and 1,25(OH)2D while normalizing PTH in a study of 10 children with XLH (180). A randomized controlled trial in children with XLH and short stature suggested benefit of adding GH to conventional therapy as linear growth significantly improved, although mean height SDS did not differ compared to controls at 3 years (183). However, when these same subjects were followed to final adult height, there was no difference in height between GH-treated patients and controls with XLH, although the sample size was small (184). Another important finding of the controlled study was that GH did not appear to worsen the body disproportion that is seen in XLH.

Recent advances in XLH therapy include regulatory approval of burosumab, an anti-FGF23 antibody, as monotherapy by the Food and Drug Administration and European Medicines Agency. Anti-FGF23 antibodies corrected hypophosphatemia and improved rickets and bone length in Hyp mice (185). Burosumab (previously termed KRN23) is a human anti-FGF23 monoclonal antibody and has been shown to significantly increase serum phosphorus, TmP/GFR, and 1,25(OH)2D in adults and children (186-189). The biochemical pattern after injections results in peak and trough effects over a 4-week dosing cycle in adults, with peak 1,25(OH)2D about 3-7 days after injection and peak phosphorus about 7 days after injection (186). In an adult randomized controlled trial, 134 adults randomized to burosumab every 4 weeks for 24 weeks, demonstrated clear improvements in serum phosphorus versus placebo (98). In this trial the burosumab group demonstrated greater healing of fractures/pseudofractures (43.1% vs 7.7%) during this time period, and improved stiffness scores.

Open label dose-finding phase 2 clinical trials also demonstrated improvements in phosphorus, alkaline phosphatase and rickets severity in 52 children ages 5-12 years (188) and in 13 children ages 1-4 years (189). Children age 5-12 years demonstrated improvements in physical

function as well (188). Modest improvements in height Z-score (+0.15 ± 0.04) were noted (188).

Only one randomized controlled trial has directly compared conventional therapy to burosumab. This phase 3 open-label randomized controlled trial was conducted in 61 children ages 1-12 years with XLH (162). Children who had persistent rickets despite a mean of 3.3-4.3 years of prior conventional therapy were randomized to switch to burosumab (0.8 mg/kg every 2 weeks) or continue conventional therapy (oral phosphate 20-60 mg/kg/day, and calcitriol 20-30 ng/kg/day or alfacalcidiol 40-60 ng/kg/day, titrated based on clinical parameters). By the end of the study most burosumab patients were still receiving 0.8 mg/kg burosumab, though some increased to 1.2 mg/kg, while the control group's mean phosphate dose was 46 mg/kg/day, calcitriol 27 mg/kg/day and alfacalcidiol 86.5 ng/kg/day (162) Clinical improvements in rickets were seen in both groups as rated by radiologists blinded to treatment group using a radiographic global impression of change scale (190), where negative scores indicated worsening, 0 indicated no change +1 minimal healing +2 substantial healing and + 3 complete healing. This study demonstrated superior improvements with burosumab. At the primary outcome of 40 weeks (72.4% of those in the burosumab group achieved substantial healing of rickets by RGI-C of ≥+2 versus only 6.3% in the conventional therapy group). At 64 weeks the mean RGI-C score after burosumab was +2.1 compared to a compared to +1 in the conventional therapy arm. Other statistically significant improvements were seen in serum phosphorus, TmP/GFR, alkaline phosphatase, linear growth, and mobility in the burosumab group compared to the conventional therapy group.

These trials also show a favorable safety profile, with the most common side effects being transient injection site reactions (186-188). There were no signals of increased risk for nephrocalcinosis. However, some subjects in the adult burosumab trial did require dose reductions due to hyperphosphatemia. Consequently, monitoring serum phosphorus remains important to avoid hyperphosphatemia, which could carry a risk of nephrocalcinosis or other ectopic calcifications. Tooth abscesses were numerically higher in the burosumab group for the controlled trials. It is not clear what the long-term impact of burosumab on tooth abscesses, nephrocalcinosis or hyperparathyroidism will be.

Burosumab was approved as monotherapy with dosing in adults of 1 mg/kg every 4 weeks subcutaneously and in children 0.8 to 1.2 mg/kg every 2 weeks, with a maximum dose of 90 mg. Serum phosphorus is targeted within the low-normal range at trough, and we would recommend avoiding high or high-normal values anywhere in the dose cycle. However, clinical monitoring for safety remains important, including monitoring phosphorus, calcium, creatinine, PTH, urine calcium excretion, and renal ultrasounds. Monitoring for efficacy includes measures of ALP and radiographic imaging to monitor rachitic changes and lower limb deformities, or to monitor healing of pseudofractures. It is as yet unknown what the impact of burosumab will be on the need for corrective leg surgeries, final adult height, enthesopathy, or other long-term XLH complications.

Children in the randomized controlled trial were those that had persistent evidence of significant rickets despite prior conventional therapy. Out of 122 screened, 55 (45%) were ineligible due to lesser rickets severity, consistent with the known benefits of conventional therapy. Persistent rickets in these patients could be due to prior compliance or dosing or inherent underlying resistance of their disease to therapy (191,192). Compliance is challenging for patients with multiple daily dosing of medications and patients often find conventional therapy burdensome (192). Furthermore, compliant patients are highly variable in the response to conventional therapy, with some recovering completely and some persisting with severe deformities. These concerns also highlight the difficulties and challenges managing patients with conventional therapy (191). Thus, patients who are responding well to conventional therapy may continue to do well on conventional therapy, while patients with persistent rickets clearly benefited from switching to burosumab.

One commentary raised a concern that patients on higher doses of conventional therapy might have responded better, acknowledging that higher doses of phosphate might also lead to elevated PTH levels which can also contribute to phosphaturia (191). The recent guideline has recommended a somewhat higher dose range for conventional therapy, as cited above (159). A subanalysis of the responses by either pre-trial or on-trial dose range has not been conducted, but patients in the upper quartile of dosing during the trial were within ranges similar to these new guidelines, and in some individuals much higher. However, it is not clear that the very large magnitude of differences in rickets responses in this randomized controlled trial can be explained solely by differences in the conventional therapy dose (at week 40: 72% burosumab vs 6 % conventional therapy having substantial healing or greater with RGI-C of ≥+2; and at week 64: 87% vs 19%).

While a Hyp mouse study comparing a different FGF23 antibody to enormous doses of calcitriol monotherapy found greater improvements in bone parameters with calcitriol (193,194), we would recommend caution in this comparison. That mouse study used doses of calcitriol that were several fold higher than the highest doses recommended in humans even from recent guidelines (159), raising concern for risks of hypercalciuria and nephrocalcinosis. However, a clinical trial is underway (ClinicalTrials.gov Identifier: NCT03748966) which will provide useful information on calcitriol monotherapy but does not include comparison with other treatment regimens.

One proposed approach, given the expense of burosumab is to initiate patients on conventional therapy and advance to burosumab if inadequate skeletal outcomes are seen (191,192). However, there may also be benefit to initiating burosumab early in severely affected patients (191), while the randomized controlled trial would indicate that patients who have been on conventional therapy for years with insufficient improvement are less likely to improve further remaining on conventional therapy (162). Those with pseudofractures, especially while on conventional therapy are also likely to benefit from burosumab (98). As with conventional therapy, decisions regarding burosumab treatment for children and adults should be individualized, taking into account the risks and benefits of therapy, and both approaches require careful monitoring.

Corrective Surgery

Conventional therapy improves limb deformities in most patients, though not necessarily with complete correction. The benefits of therapy on skeletal deformities are likely greatest when therapy is started early (177). Children do frequently still require orthopedic surgery to correct long bone deformities to straighten the lower limbs. Such procedures include osteotomies with internal fixation or external fixation to address bowing and torsional abnormalities, and guided growth procedures using plate across the medial or lateral physis (of the distal femur for example) to limit growth on that side of the physis, while allowing the opposite side to grow, to straighten the deformity (159,195). The timing of surgery is variable. One retrospective study found that patients having initial surgery at younger ages had more total surgeries than those having their first surgery later (195). Though this may have been confounded by severity of the initial deformity, it remains an important consideration and supports that osteotomies may be better performed at later ages when growth is complete or near complete. However, guided growth procedures must be completed while the patient still has at least 2 years of growth remaining in order for the desired effect (159). The optimal timing of surgery must be individualized based on several factors including the severity of the deformity and its functional impact on the developing child, which may indicate earlier surgery. Prior to elective skeletal surgery, medical therapy should be optimized. There is also a risk of overcorrection of a deformity after surgery, or of recurrence of the original deformity, thus patients require continued monitoring. Continued medical therapy is important to promote bone healing after surgery and with a goal of decreasing risk for new additional deformities and optimizing growth. It should be noted that whether burosumab will alter the need for corrective surgery or not has not yet been established in clinical trials.

Conclusion

FGF23 functions as an endocrine factor with its cofactor αKlotho and is a principal regulator in phosphorus homeostasis, its primary action being reduction of phosphorus levels and regulation of vitamin D metabolism. It is one of multiple factors involved in the bone-parathyroid-kidney axis and its interaction with these factors is quite complex. FGF23-mediated disorders of phosphate wasting share similar clinical and biochemical features. Conventional treatment involves multiple daily doses of oral phosphate salts and active vitamin D analogs. Recent development of an anti-FGF23 antibody, burosumab, for use in XLH has shown promising results, but more research is needed, especially regarding long-term outcomes.

Disclosure

This work was supported by NIH grants T32DK065549 and by P30AR072581. EAI has received research funding from Ultragenyx Pharmaceuticals and participated in advisory boards.

References

1. Itoh N, Ohta H, Konishi M. Endocrine FGFs: evolution, physiology, pathophysiology, and pharmacotherapy. Frontiers in endocrinology 2015;6:154
2. Ornitz DM, Itoh N. The fibroblast growth factor signaling pathway. Wiley Interdisciplinary Reviews: Developmental Biology 2015;4(3):215-266
3. Yayon A, Klagsbrun M, Esko JD, Leder P, Ornitz DM. Cell surface, heparin-like molecules are required for binding of basic fibroblast growth factor to its high affinity receptor. Cell 1991;64(4):841-848
4. Goetz R, Beenken A, Ibrahimi OA, Kalinina J, Olsen SK, Eliseenkova AV, Xu C, Neubert TA, Zhang F, Linhardt RJ. Molecular insights into the klotho-dependent, endocrine mode of action of fibroblast growth factor 19 subfamily members. Molecular and cellular biology 2007;27(9):3417-3428
5. Liu S, Quarles LD. How fibroblast growth factor 23 works. Journal of the American Society of Nephrology 2007;18(6):1637-1647
6. Yamazaki Y, Tamada T, Kasai N, Urakawa I, Aono Y, Hasegawa H, Fujita T, Kuroki R, Yamashita T, Fukumoto S. Anti-FGF23 neutralizing antibodies show the physiological role and structural features of FGF23. Journal of Bone and Mineral Research 2008;23(9):1509-1518
7. Meyer Jr RA, Meyer MH, Gray RW. Parabiosis suggests a humoral factor is involved in X-linked hypophosphatemia in mice. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 1989;4(4):493-500
8. White KE, Evans WE, O'Riordan JL, Speer MC, Econs MJ, Lorenz-Depiereux B, Grabowski M, Meitinger T, Strom TM. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nature genetics 2000;26(3):345
9. Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, Yamashita T. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 2006;444(7120):770

10. Kurosu H, Ogawa Y, Miyoshi M, Yamamoto M, Nandi A, Rosenblatt KP, Baum MG, Schiavi S, Hu MC, Moe OW. Regulation of fibroblast growth factor-23 signaling by klotho. Journal of Biological Chemistry 2006
11. Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, Goetz R, Kuro-o M, Mohammadi M, Sirkis R, Naveh-Many T, Silver J. The parathyroid is a target organ for FGF23 in rats. The Journal of clinical investigation 2007;117(12):4003-4008
12. Martin A, David V, Quarles LD. Regulation and function of the FGF23/klotho endocrine pathways. Physiological reviews 2012;92(1):131-155
13. Erben RG, Andrukhova O. FGF23-Klotho signaling axis in the kidney. Bone 2017;100:62-68
14. Kolek OI, Hines ER, Jones MD, LeSueur LK, Lipko MA, Kiela PR, Collins JF, Haussler MR, Ghishan FK. 1α, 25-Dihydroxyvitamin D3 upregulates FGF23 gene expression in bone: the final link in a renal-gastrointestinal-skeletal axis that controls phosphate transport. American Journal of Physiology-Gastrointestinal and Liver Physiology 2005;289(6):G1036-G1042
15. Nishi H, Nii-Kono T, Nakanishi S, Yamazaki Y, Yamashita T, Fukumoto S, Ikeda K, Fujimori A, Fukagawa M. Intravenous calcitriol therapy increases serum concentrations of fibroblast growth factor-23 in dialysis patients with secondary hyperparathyroidism. Nephron Clinical Practice 2005;101(2):c94-c99
16. Georgiadou E, Marketou H, Trovas G, Dontas I, Papaioannou N, Makris K, Galanos A, Papavassiliou AG. Effect of calcitriol on FGF23 level in healthy adults and its dependence on phosphate level. in vivo 2017;31(1):145-150
17. Saito H, Maeda A, Ohtomo SI, Hirata M, Kusano K, Kato S, Ogata E, Segawa H, Miyamoto KI, Fukushima N. Circulating FGF-23 is regulated by 1α, 25-dihydroxyvitamin D3 and phosphorus in vivo. Journal of Biological Chemistry 2005;280(4):2543-2549
18. Yu X, Sabbagh Y, Davis SI, Demay MB, White KE. Genetic dissection of phosphate-and vitamin D-mediated regulation of circulating Fgf23 concentrations. Bone 2005;36(6):971-977
19. Imel EA, DiMeglio LA, Hui SL, Carpenter TO, Econs MJ. Treatment of X-linked hypophosphatemia with calcitriol and phosphate increases circulating fibroblast growth factor 23 concentrations. The Journal of Clinical Endocrinology & Metabolism 2010;95(4):1846-1850
20. Collins MT, Lindsay JR, Jain A, Kelly MH, Cutler CM, Weinstein LS, Liu J, Fedarko NS, Winer KK. Fibroblast Growth Factor-23 Is Regulated by 1α, 25-Dihydroxyvitamin D. Journal of bone and mineral research 2005;20(11):1944-1950
21. Ferrari SL, Bonjour JP, Rizzoli R. Fibroblast growth factor-23 relationship to dietary phosphate and renal phosphate handling in healthy young men. The Journal of Clinical Endocrinology & Metabolism 2005;90(3):1519-1524
22. Antoniucci DM, Yamashita T, Portale AA. Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. The Journal of Clinical Endocrinology & Metabolism 2006;91(8):3144-3149
23. Vervloet MG, van Ittersum FJ, Büttler RM, Heijboer AC, Blankenstein MA, ter Wee PM. Effects of dietary phosphate and calcium intake on fibroblast growth factor-23. Clinical Journal of the American Society of Nephrology 2011;6(2):383-389
24. Burnett SAM, Gunawardene SC, Bringhurst FR, Jüppner H, Lee H, Finkelstein JS. Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women. Journal of Bone and Mineral Research 2006;21(8):1187-1196
25. Kawata T, Imanishi Y, Kobayashi K, Miki T, Arnold A, Inaba M, Nishizawa Y. Parathyroid hormone regulates fibroblast growth factor-23 in a mouse model of primary hyperparathyroidism. Journal of the American Society of Nephrology 2007;18(10):2683-2688
26. Meir T, Durlacher K, Pan Z, Amir G, Richards WG, Silver J, Naveh-Many T. Parathyroid hormone activates the orphan nuclear receptor Nurr1 to induce FGF23 transcription. Kidney international 2014;86(6):1106-1115
27. López I, Rodríguez-Ortiz ME, Almadén Y, Guerrero F, De Oca AM, Pineda C, Shalhoub V, Rodríguez M, Aguilera-Tejero E. Direct and indirect effects of parathyroid hormone on circulating levels of fibroblast growth factor 23 in vivo. Kidney international 2011;80(5):475-482
28. Lavi-Moshayoff V, Wasserman G, Meir T, Silver J, Naveh-Many T. PTH increases FGF23 gene expression and mediates the high-FGF23 levels of experimental kidney failure: a bone parathyroid feedback loop. American Journal of Physiology-Renal Physiology 2010;299(4):F882-F889
29. Rhee Y, Bivi N, Farrow E, Lezcano V, Plotkin LI, White KE, Bellido T. Parathyroid hormone receptor signaling in osteocytes increases the expression of fibroblast growth factor-23 in vitro and in vivo. Bone 2011;49(4):636-643
30. Gutiérrez OM, Smith KT, Barchi-Chung A, Patel NM, Isakova T, Wolf M. (1-34) Parathyroid hormone infusion acutely lowers fibroblast growth factor 23 concentrations in adult volunteers. Clinical Journal of the American Society of Nephrology 2012;7(1):139-145
31. Burnett-Bowie SAM, Henao MP, Dere ME, Lee H, Leder BZ. Effects of hPTH (1-34) infusion on circulating serum phosphate, 1, 25-dihydroxyvitamin D, and FGF23 levels in healthy men. Journal of bone and mineral research 2009;24(10):1681-1685
32. Rodriguez-Ortiz ME, Lopez I, Muñoz-Castañeda JR, Martinez-Moreno JM, Ramírez AP, Pineda C, Canalejo A, Jaeger P, Aguilera-Tejero E, Rodriguez M. Calcium deficiency reduces circulating levels of FGF23. Journal of the American Society of Nephrology 2012:ASN. 2011101006
33. David V, Dai B, Martin A, Huang J, Han X, Quarles LD. Calcium regulates FGF-23 expression in bone. Endocrinology 2013;154(12):4469-4482
34. Gupta A, Winer K, Econs M, Marx S, Collins M. FGF-23 is elevated by chronic hyperphosphatemia. The Journal of Clinical Endocrinology & Metabolism 2004;89(9):4489-4492
35. Benet-Pagès A, Lorenz-Depiereux B, Zischka H, White KE, Econs MJ, Strom TM. FGF23 is processed by proprotein convertases but not by PHEX. Bone 2004;35(2):455-462
36. Imel EA, Hui SL, Econs MJ. FGF23 concentrations vary with disease status in autosomal dominant hypophosphatemic rickets. Journal of Bone and Mineral Research 2007;22(4):520-526
37. Kato K, Jeanneau C, Tarp MA, Benet-Pagès A, Lorenz-Depiereux B, Bennett EP, Mandel U, Strom TM, Clausen H. Polypeptide GalNAc-transferase T3 and familial tumoral calcinosis Secretion of fibroblast growth factor 23 requires O-glycosylation. Journal of Biological Chemistry 2006;281(27):18370-18377
38. Bergwitz C, Banerjee S, Abu-Zahra H, Kaji H, Miyauchi A, Sugimoto T, Jüppner H. Defective O-glycosylation due to a novel homozygous S129P mutation is associated with lack of fibroblast growth factor 23 secretion and tumoral calcinosis. The Journal of Clinical Endocrinology & Metabolism 2009;94(11):4267-4274
39. Tagliabracci VS, Engel JL, Wiley SE, Xiao J, Gonzalez DJ, Appaiah HN, Koller A, Nizet V, White KE, Dixon JE. Dynamic regulation of FGF23 by Fam20C phosphorylation, GalNAc-T3 glycosylation, and furin proteolysis. Proceedings of the National Academy of Sciences 2014:201402218
40. Farrow EG, Yu X, Summers LJ, Davis SI, Fleet JC, Allen MR, Robling AG, Stayrook KR, Jideonwo V, Magers MJ. Iron deficiency drives an autosomal dominant hypophosphatemic rickets (ADHR) phenotype in fibroblast growth factor-23 (Fgf23) knock-in mice. Proceedings of the National Academy of Sciences 2011:201110905
41. Imel EA, Peacock M, Gray AK, Padgett LR, Hui SL, Econs MJ. Iron modifies plasma FGF23 differently in autosomal dominant hypophosphatemic rickets and healthy humans. The Journal of Clinical Endocrinology & Metabolism 2011;96(11):3541-3549
42. Liu S, Zhou J, Tang W, Jiang X, Rowe DW, Quarles LD. Pathogenic role of Fgf23 in Hyp mice. American Journal of Physiology-Endocrinology and Metabolism 2006;291(1):E38-E49
43. Liu S, Zhou J, Tang W, Menard R, Feng JQ, Quarles LD. Pathogenic role of Fgf23 in Dmp1-null mice. American Journal of Physiology-Endocrinology and Metabolism 2008;295(2):E254-E261

44. Yu X, White KE. Fibroblast growth factor 23 and its receptors. Therapeutic Apheresis and Dialysis 2005;9(4):308-312
45. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukumoto S, Yamashita T. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. Journal of Bone and Mineral Research 2004;19(3):429-435
46. Baum M, Schiavi S, Dwarakanath V, Quigley R. Effect of fibroblast growth factor-23 on phosphate transport in proximal tubules. Kidney international 2005;68(3):1148-1153
47. Perwad F, Zhang MY, Tenenhouse HS, Portale AA. Fibroblast growth factor 23 impairs phosphorus and vitamin D metabolism in vivo and suppresses 25-hydroxyvitamin D-1α-hydroxylase expression in vitro. American Journal of Physiology-Renal Physiology 2007;293(5):F1577-F1583
48. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, Takeuchi Y, Fujita T, Fukumoto S, Yamashita T. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proceedings of the National Academy of Sciences 2001;98(11):6500-6505
49. Murer H, Forster I, Biber J. The sodium phosphate cotransporter family SLC34. Pflügers Archiv 2004;447(5):763-767
50. Shimada T, Urakawa I, Yamazaki Y, Hasegawa H, Hino R, Yoneya T, Takeuchi Y, Fujita T, Fukumoto S, Yamashita T. FGF-23 transgenic mice demonstrate hypophosphatemic rickets with reduced expression of sodium phosphate cotransporter type IIa. Biochemical and biophysical research communications 2004;314(2):409-414
51. Larsson T, Marsell R, Schipani E, Ohlsson C, Ljunggren Os, Tenenhouse HS, Jüppner H, Jonsson KB. Transgenic mice expressing fibroblast growth factor 23 under the control of the α1 (I) collagen promoter exhibit growth retardation, osteomalacia, and disturbed phosphate homeostasis. Endocrinology 2004;145(7):3087-3094
52. Kempson SA, Lotscher M, Kaissling B, Biber J, Murer H, Levi M. Parathyroid hormone action on phosphate transporter mRNA and protein in rat renal proximal tubules. American Journal of Physiology-Renal Physiology 1995;268(4):F784-F791
53. Chanakul A, Zhang MY, Louw A, Armbrecht HJ, Miller WL, Portale AA, Perwad F. FGF-23 regulates CYP27B1 transcription in the kidney and in extra-renal tissues. PloS one 2013;8(9):e72816
54. Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, Fukumoto S, Tomizuka K, Yamashita T. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. The Journal of clinical investigation 2004;113(4):561-568
55. Krajisnik T, Björklund P, Marsell R, Ljunggren Ö, Åkerström G, Jonsson KB, Westin G, Larsson TE. Fibroblast growth factor-23 regulates parathyroid hormone and 1α-hydroxylase expression in cultured bovine parathyroid cells. Journal of Endocrinology 2007;195(1):125-131
56. Mace ML, Gravesen E, Nordholm A, Olgaard K, Lewin E. Fibroblast Growth Factor (FGF) 23 Regulates the Plasma Levels of Parathyroid Hormone In Vivo Through the FGF Receptor in Normocalcemia, But Not in Hypocalcemia. Calcified tissue international 2018;102(1):85-92
57. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. Journal of Bone and Mineral Research 2011;26(7):1381-1388
58. Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, Imanishi Y, Yamamoto T, Hampson G, Koshiyama H, Ljunggren Ö. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. New England Journal of Medicine 2003;348(17):1656-1663
59. Yamazaki Y, Okazaki R, Shibata M, Hasegawa Y, Satoh K, Tajima T, Takeuchi Y, Fujita T, Nakahara K, Yamashita T. Increased circulatory level of biologically active full-length FGF-23 in patients with hypophosphatemic rickets/osteomalacia. The Journal of Clinical Endocrinology & Metabolism 2002;87(11):4957-4960
60. El-Maouche D, Dumitrescu C, Andreopoulou P, Gafni R, Brillante B, Bhattacharyya N, Fedarko NS, Collins M. Stability and degradation of fibroblast growth factor 23 (FGF23): the effect of time and temperature and assay type. Osteoporosis International 2016;27(7):2345-2353
61. Ali FN, Josefson J, Mendez AJ, Mestan K, Wolf M. Cord blood ferritin and fibroblast growth factor-23 levels in neonates. The Journal of Clinical Endocrinology & Metabolism 2016;101(4):1673-1679
62. Holmlund-Suila E, Viljakainen H, Ljunggren Ö, Hytinantti T, Andersson S, Mäkitie O. Fibroblast growth factor 23 concentrations reflect sex differences in mineral metabolism and growth in early infancy. Hormone research in paediatrics 2016;85(4):232-241
63. Holmlund-Suila E, Enlund-Cerullo M, Valkama S, Hauta-alus H, Rosendahl J, Helve O, Hytinantti T, Viljakainen H, Andersson S, Mäkitie O. Sex and Iron Modify Fibroblast Growth Factor 23 Concentration in 1-Year-Old Children. The Journal of Clinical Endocrinology & Metabolism 2017;102(12):4526-4533
64. Fischer DC, Mischek A, Wolf S, Rahn A, Salweski B, Kundt G, Haffner D. Paediatric reference values for the C-terminal fragment of fibroblast-growth factor-23, sclerostin, bone-specific alkaline phosphatase and isoform 5b of tartrate-resistant acid phosphatase. Annals of clinical biochemistry 2012;49(6):546-553
65. Gkentzi D, Efthymiadou A, Kritikou D, Chrysis D. Fibroblast growth factor 23 and Klotho serum levels in healthy children. Bone 2014;66:8-14
66. Smith ER, Cai MM, McMahon LP, Holt SG. Biological variability of plasma intact and C-terminal FGF23 measurements. The Journal of Clinical Endocrinology & Metabolism 2012;97(9):3357-3365
67. Imel EA, Hui SL, Ecibs MJ. FGF23 concentrations vary with disease status in autosomal dominant hypophosphatemic rickets. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2007;22(4):520-526
68. Endo I, Fukumoto S, Ozono K, Namba N, Tanaka H, Inoue D, Minagawa M, Sugimoto T, Yamauchi M, Michigami T. Clinical usefulness of measurement of fibroblast growth factor 23 (FGF23) in hypophosphatemic patients: proposal of diagnostic criteria using FGF23 measurement. Bone 2008;42(6):1235-1239
69. Imel EA, Econs MJ. Approach to the hypophosphatemic patient. The Journal of Clinical Endocrinology & Metabolism 2012;97(3):696-706
70. Tiosano D, Hochberg Ze. Hypophosphatemia: the common denominator of all rickets. Journal of bone and mineral metabolism 2009;27(4):392-401
71. Murali SK, Roschger P, Zeitz U, Klaushofer K, Andrukhova O, Erben RG. FGF23 Regulates Bone Mineralization in a 1, 25 (OH) 2D3 and Klotho-Independent Manner. Journal of Bone and Mineral Research 2016;31(1):129-142
72. Murali SK, Andrukhova O, Clinkenbeard EL, White KE, Erben RG. Excessive osteocytic Fgf23 secretion contributes to pyrophosphate accumulation and mineralization defect in Hyp mice. PLoS biology 2016;14(4):e1002427
73. Sharma U, Pal D, Prasad R. Alkaline phosphatase: an overview. Indian journal of clinical biochemistry: IJCB 2014;29(3):269-278
74. Ishikawa Y, Valhmu WB, Wuthier RE. Induction of alkaline phosphatase in primary cultures of epiphyseal growth plate chondrocytes by a serum-derived factor. Journal of cellular physiology 1987;133(2):344-350
75. White KE, Carn G, Lorenz-Depiereux B, Benet-Pages A, Strom TM, Econs MJ. Autosomal-dominant hypophosphatemic rickets (ADHR) mutations stabilize FGF-23. Kidney international 2001;60(6):2079-2086
76. Econs MJ, McEnery PT. Autosomal dominant hypophosphatemic rickets/osteomalacia: clinical characterization of a novel renal phosphate-wasting disorder. The Journal of Clinical Endocrinology & Metabolism 1997;82(2):674-681
77. Sun Y, Wang O, Xia W, Jiang Y, Li M, Xing X, Hu Y, Liu H, Meng X, Zhou X. FGF23 analysis of a Chinese family with autosomal dominant hypophosphatemic rickets. Journal of bone and mineral metabolism 2012;30(1):78-84

78. Imel EA, Gray AK, Padgett LR, Econs MJ. Iron and fibroblast growth factor 23 in X-linked hypophosphatemia. Bone 2014;60:87-92
79. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. Journal of Bone and Mineral Research 2013;28(8):1793-1803
80. Schouten BJ, Hunt PJ, Livesey JH, Frampton CM, Soule SG. FGF23 elevation and hypophosphatemia after intravenous iron polymaltose: a prospective study. The Journal of Clinical Endocrinology & Metabolism 2009;94(7):2332-2337
81. Schaefer B, Würtinger P, Finkenstedt A, Braithwaite V, Viveiros A, Effenberger M, Sulzbacher I, Moschen A, Griesmacher A, Tilg H. Choice of high-dose intravenous iron preparation determines hypophosphatemia risk. PLoS One 2016;11(12):e0167146
82. Francis F, Hennig S, Korn B, Reinhardt R, De Jong P, Poustka A, Lehrach H, Rowe P, Goulding J, Summerfield T. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. Nature genetics 1995;11(2):130
83. Beck L, Soumounou Y, Martel J, Krishnamurthy G, Gauthier C, Goodyer CG, Tenenhouse HS. Pex/PEX tissue distribution and evidence for a deletion in the 3'region of the Pex gene in X-linked hypophosphatemic mice. The Journal of clinical investigation 1997;99(6):1200-1209
84. Pavone V, Testa G, Iachino SG, Evola FR, Avondo S, Sessa G. Hypophosphatemic rickets: etiology, clinical features and treatment. European Journal of Orthopaedic Surgery & Traumatology 2015;25(2):221-226
85. Econs MJ, Feussner JR, Samsa GP, Effman EL, Vogler JB, Martinez S, Friedman NE, Quarles LD, Drezner MK. X-linked hypophosphatemic rickets without "rickets". Skeletal radiology 1991;20(2):109-114
86. Marie PJ, Glorieux FH. Relation between hypomineralized periosteocytic lesions and bone mineralization in vitamin D-resistant rickets. Calcified tissue international 1983;35(1):443-448
87. Chesher D, Oddy M, Darbar U, Sayal P, Casey A, Ryan A, Sechi A, Simister C, Waters A, Wedatilake Y, Lachmann RH, Murphy E. Outcome of adult patients with X-linked hypophosphatemia caused by PHEX gene mutations. J Inherit Metab Dis 2018;41(5):865-876
88. Connor J, Olear EA, Insogna KL, Katz L, Baker S, Kaur R, Simpson CA, Sterpka J, Dubrow R, Zhang JH, Carpenter TO. Conventional Therapy in Adults With X-Linked Hypophosphatemia: Effects on Enthesopathy and Dental Disease. J Clin Endocrinol Metab 2015;100(10):3625-3632
89. Biosse Duplan M, Coyac BR, Bardet C, Zadikian C, Rothenbuhler A, Kamenicky P, Briot K, Linglart A, Chaussain C. Phosphate and Vitamin D Prevent Periodontitis in X-Linked Hypophosphatemia. J Dent Res 2017;96(4):388-395
90. Onishi T, Umemura S, Shintani S, Ooshima T. Phex mutation causes overexpression of FGF23 in teeth. Arch Oral Biol 2008;53(2):99-104
91. Boukpessi T, Hoac B, Coyac BR, Leger T, Garcia C, Wicart P, Whyte MP, Glorieux FH, Linglart A, Chaussain C, McKee MD. Osteopontin and the dento-osseous pathobiology of X-linked hypophosphatemia. Bone 2017;95:151-161
92. Chaussain-Miller C, Sinding C, Wolikow M, Lasfargues JJ, Godeau G, Garabedian M. Dental abnormalities in patients with familial hypophosphatemic vitamin D-resistant rickets: prevention by early treatment with 1-hydroxyvitamin D. J Pediatr 2003;142(3):324-331
93. Fong H, Chu EY, Tompkins KA, Foster BL, Sitara D, Lanske B, Somerman MJ. Aberrant cementum phenotype associated with the hypophosphatemic hyp mouse. J Periodontol 2009;80(8):1348-1354
94. Hardy D, Murphy W, Siegel B, Reid I, Whyte M. X-linked hypophosphatemia in adults: prevalence of skeletal radiographic and scintigraphic features. Radiology 1989;171(2):403-414
95. Polisson RP, Martinez S, Khoury M, Harrell RM, Lyles KW, Friedman N, Harrelson JM, Reisner E, Drezner MK. Calcification of entheses associated with X-linked hypophosphatemic osteomalacia. New England Journal of Medicine 1985;313(1):1-6
96. Liang G, Katz LD, Insogna KL, Carpenter TO, Macica CM. Survey of the enthesopathy of X-linked hypophosphatemia and its characterization in Hyp mice. Calcified tissue international 2009;85(3):235-246
97. Mills ES, Iorio L, Feinn RS, Duignan KM, Macica CM. Joint replacement in X-linked hypophosphatemia. Journal of orthopaedics 2019;16(1):55-60
98. Insogna KL, Briot K, Imel EA, Kamenický P, Ruppe MD, Portale AA, Weber T, Pitukcheewanont P, Cheong HI, Jan de Beur S. A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2018;33(8):1383-1393
99. Beck-Nielsen SS, Brusgaard K, Rasmussen LM, Brixen K, Brock-Jacobsen B, Poulsen MR, Vestergaard P, Ralston SH, Albagha OM, Poulsen S, Haubek D, Gjorup H, Hintze H, Andersen MG, Heickendorff L, Hjelmborg J, Gram J. Phenotype presentation of hypophosphatemic rickets in adults. Calcified tissue international 2010;87(2):108-119
100. Reid IR, Hardy DC, Murphy WA, Teitelbaum SL, Bergfeld MA, Whyte MP. X-linked hypophosphatemia: a clinical, biochemical, and histopathologic assessment of morbidity in adults. Medicine (Baltimore) 1989;68(6):336-352
101. Rothenbuhler A, Fadel N, Debza Y, Bacchetta J, Diallo MT, Adamsbaum C, Linglart A, Di Rocco F. High Incidence of Cranial Synostosis and Chiari I Malformation in Children With X-Linked Hypophosphatemic Rickets (XLHR). Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2019;34(3):490-496
102. Econs MJ, Samsa GP, Monger M, Drezner MK, Feussner JR. X-Linked Hypophosphatemic Rickets - a Disease Often Unknown to Affected Patients. Bone and mineral 1994;24(1):17-24
103. Davies M, Kane R, Valentine J. Impaired hearing in X-linked hypophosphataemic (vitamin-D-resistant) osteomalacia. Ann Intern Med 1984;100(2):230-232
104. Fishman G, Miller-Hansen D, Jacobsen C, Singhal VK, Alon US. Hearing impairment in familial X-linked hypophosphatemic rickets. European journal of pediatrics 2004;163(10):622-623
105. Wick CC, Lin SJ, Yu H, Megerian CA, Zheng QY. Treatment of ear and bone disease in the Phex mouse mutant with dietary supplementation. American journal of otolaryngology 2017;38(1):44-51
106. Feng JQ, Ward LM, Liu S, Lu Y, Xie Y, Yuan B, Yu X, Rauch F, Davis SI, Zhang S. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. Nature genetics 2006;38(11):1310
107. Lorenz-Depiereux B, Bastepe M, Benet-Pagès A, Amyere M, Wagenstaller J, Müller-Barth U, Badenhoop K, Kaiser SM, Rittmaster RS, Shlossberg AH. DMP1 mutations in autosomal recessive hypophosphatemia implicate a bone matrix protein in the regulation of phosphate homeostasis. Nature genetics 2006;38(11):1248
108. Lorenz-Depiereux B, Schnabel D, Tiosano D, Häusler G, Strom TM. Loss-of-function ENPP1 mutations cause both generalized arterial calcification of infancy and autosomal-recessive hypophosphatemic rickets. The American Journal of Human Genetics 2010;86(2):267-272
109. Ruf N, Uhlenberg B, Terkeltaub R, Nürnberg P, Rutsch F. The mutational spectrum of ENPP1 as arising after the analysis of 23 unrelated patients with generalized arterial calcification of infancy (GACI). Human mutation 2005;25(1):98
110. Rutsch F, Ruf N, Vaingankar S, Toliat MR, Suk A, Höhne W, Schauer G, Lehmann M, Roscioli T, Schnabel D. Mutations in ENPP1 are associated with'idiopathic'infantile arterial calcification. Nature genetics 2003;34(4):379
111. Rutsch F, Böyer P, Nitschke Y, Ruf N, Lorenz-Depierieux B, Wittkampf T, Weissen-Plenz G, Fischer RJ, Mughal Z, Gregory JW. Hypophosphatemia, hyperphosphaturia, and bisphosphonate treatment are associated with survival beyond infancy in generalized arterial calcification of infancy. Circulation: Genomic and Precision Medicine 2008;1(2):133-140

112. Levy-Litan V, Hershkovitz E, Avizov L, Leventhal N, Bercovich D, Chalifa-Caspi V, Manor E, Buriakovsky S, Hadad Y, Goding J. Autosomal-recessive hypophosphatemic rickets is associated with an inactivation mutation in the ENPP1 gene. The American Journal of Human Genetics 2010;86(2):273-278
113. Rafaelsen SH, Ræder H, Fagerheim AK, Knappskog P, Carpenter TO, Johansson S, Bjerknes R. Exome sequencing reveals FAM20c mutations associated with fibroblast growth factor 23–related hypophosphatemia, dental anomalies, and ectopic calcification. Journal of Bone and Mineral Research 2013;28(6):1378-1385
114. Saito T, Shimizu Y, Hori M, Taguchi M, Igarashi T, Fukumoto S, Fujitab T. A patient with hypophosphatemic rickets and ossification of posterior longitudinal ligament caused by a novel homozygous mutation in ENPP1 gene. Bone. 2011;49(4):913-916
115. Mehta P, Mitchell A, Tysoe C, Caswell R, Owens M, Vincent T. Novel compound heterozygous mutations in ENPP1 cause hypophosphataemic rickets with anterior spinal ligament ossification. Rheumatology 2012;51(10):1919-1921
116. Turan S, Aydin C, Bereket A, Akcay T, Güran T, Yaralioglu BA, Bastepe M, Jüppner H. Identification of a novel dentin matrix protein-1 (DMP-1) mutation and dental anomalies in a kindred with autosomal recessive hypophosphatemia. Bone 2010;46(2):402-409
117. Mäkitie O, Pereira RC, Kaitila I, Turan S, Bastepe M, Laine T, Kröger H, Cole WG, Jüppner H. Long-term clinical outcome and carrier phenotype in autosomal recessive hypophosphatemia caused by a novel DMP1 mutation. Journal of Bone and Mineral Research 2010;25(10):2165-2174
118. Koshida R, Yamaguchi H, Yamasaki K, Tsuchimochi W, Yonekawa T, Nakazato M. A novel nonsense mutation in the DMP1 gene in a Japanese family with autosomal recessive hypophosphatemic rickets. Journal of bone and mineral metabolism 2010;28(5):585-590
119. Hart ES, Kelly MH, Brillante B, Chen CC, Ziran N, Lee JS, Feuillan P, Leet AI, Kushner H, Robey PG. Onset, progression, and plateau of skeletal lesions in fibrous dysplasia and the relationship to functional outcome. Journal of bone and mineral research 2007;22(9):1468-1474
120. Collins MT, Chebli C, Jones J, Kushner H, Consugar M, Rinaldo P, Wientroub S, Bianco P, Robey PG. Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. Journal of Bone and Mineral Research 2001;16(5):806-813
121. Dumitrescu CE, Collins MT. McCune-Albright syndrome. Orphanet journal of rare diseases 2008;3(1):12
122. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune–Albright syndrome. New England Journal of Medicine 1991;325(24):1688-1695
123. Riminucci M, Collins MT, Fedarko NS, Cherman N, Corsi A, White KE, Waguespack S, Gupta A, Hannon T, Econs MJ. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. The Journal of clinical investigation 2003;112(5):683-692
124. Imel EA, Econs MJ. Fibrous dysplasia, phosphate wasting and fibroblast growth factor 23. PER 2007;4:434-439
125. Kobayashi K, Imanishi Y, Koshiyama H, Miyauchi A, Wakasa K, Kawata T, Goto H, Ohashi H, Koyano HM, Mochizuki R. Expression of FGF23 is correlated with serum phosphate level in isolated fibrous dysplasia. Life sciences 2006;78(20):2295-2301
126. Bhattacharyya N, Wiench M, Dumitrescu C, Connolly BM, Bugge TH, Patel HV, Gafni RI, Cherman N, Cho M, Hager GL. Mechanism of FGF23 processing in fibrous dysplasia. Journal of bone and mineral research 2012;27(5):1132-1141
127. Drezner MK. Tumor-induced osteomalacia. Reviews in Endocrine and Metabolic disorders 2001;2(2):175-186
128. White KE, Jonsson KB, Carn G, Hampson G, Spector TD, Mannstadt M, Lorenz-Depiereux B, Miyauchi A, Yang IM, Ljunggren Os. The autosomal dominant hypophosphatemic rickets (ADHR) gene is a secreted polypeptide overexpressed by tumors that cause phosphate wasting. The Journal of Clinical Endocrinology & Metabolism 2001;86(2):497-500
129. Berndt T, Craig TA, Bowe AE, Vassiliadis J, Reczek D, Finnegan R, De Beur SMJ, Schiavi SC, Kumar R. Secreted frizzled-related protein 4 is a potent tumor-derived phosphaturic agent. The Journal of clinical investigation 2003;112(5):785-794
130. Carpenter TO, Ellis BK, Insogna KL, Philbrick WM, Sterpka J, Shimkets R. Fibroblast growth factor 7: an inhibitor of phosphate transport derived from oncogenic osteomalacia-causing tumors. The Journal of Clinical Endocrinology & Metabolism 2005;90(2):1012-1020
131. Rowe PS, De Zoysa PA, Dong R, Wang HR, White KE, Econs MJ, Oudet CL. MEPE, a new gene expressed in bone marrow and tumors causing osteomalacia. Genomics 2000;67(1):54-68
132. Lee JC, Jeng YM, Su SY, Wu CT, Tsai KS, Lee CH, Lin CY, Carter JM, Huang JW, Chen SH. Identification of a novel FN1-FGFR1 genetic fusion as a frequent event in phosphaturic mesenchymal tumour. The Journal of pathology 2015;235(4):539-545
133. Jiang Y, Xia Wb, Xing Xp, Silva BC, Li M, Wang O, Zhang Hb, Li F, Jing Hl, Zhong Dr. Tumor-induced osteomalacia: An important cause of adult-onset hypophosphatemic osteomalacia in China: Report of 39 cases and review of the literature. Journal of Bone and Mineral Research 2012;27(9):1967-1975
134. Chong WH, Yavuz S, Patel SM, Chen CC, Collins MT. The importance of whole body imaging in tumor-induced osteomalacia. The Journal of Clinical Endocrinology & Metabolism 2011;96(12):3599-3600
135. Andreopoulou P, Dumitrescu CE, Kelly MH, Brillante BA, Cutler Peck CM, Wodajo FM, Chang R, Collins MT. Selective venous catheterization for the localization of phosphaturic mesenchymal tumors. Journal of Bone and Mineral Research 2011;26(6):1295-1302
136. Nasu T, Kurisu S, Matsuno S, Tatsumi K, Kakimoto T, Kobayashi M, Nakano Y, Wakasaki H, Furuta H, Nishi M. Tumor-induced hypophosphatemic osteomalacia diagnosed by the combinatory procedures of magnetic resonance imaging and venous sampling for FGF23. Internal Medicine 2008;47(10):957-961
137. Takeuchi Y, Suzuki H, Ogura S, Imai R, Yamazaki Y, Yamashita T, Miyamoto Y, Okazaki H, Nakamura K, Nakahara K. Venous sampling for fibroblast growth factor-23 confirms preoperative diagnosis of tumor-induced osteomalacia. The Journal of Clinical Endocrinology & Metabolism 2004;89(8):3979-3982
138. Westerberg PA, Olauson H, Toss G, Wikström B, Morales O, Linde T, Jonsson K, Ljunggren Ö, Larsson T. Preoperative tumor localization by means of venous sampling for fibroblast growth factor-23 in a patient with tumor-induced osteomalacia. Endocrine Practice 2008;14(3):362-367
139. Sun Zj, Jin J, Qiu Gx, Gao P, Liu Y. Surgical treatment of tumor-induced osteomalacia: a retrospective review of 40 cases with extremity tumors. BMC musculoskeletal disorders 2015;16(1):43
140. Zuo Qy, Wang H, Li W, Niu Xh, Huang Yh, Chen J, You Yh, Liu By, Cui Am, Deng W. Treatment and outcomes of tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors: retrospective review of 12 patients. BMC musculoskeletal disorders 2017;18(1):403
141. Grebe TA, Rimsza ME, Richter SF, Hansen RC, Hoyme HE. Further delineation of the epidermal nevus syndrome: two cases with new findings and literature review. American journal of medical genetics 1993;47(1):24-30
142. Menascu S, Donner EJ. Linear nevus sebaceous syndrome: case reports and review of the literature. Pediatric neurology 2008;38(3):207-210
143. Groesser L, Herschberger E, Ruetten A, Ruivenkamp C, Lopriore E, Zutt M, Langmann T, Singer S, Klingseisen L, Schneider-Brachert W. Postzygotic HRAS and KRAS mutations cause nevus sebaceous and Schimmelpenning syndrome. Nature genetics 2012;44(7):783

144. Lim YH, Ovejero D, Sugarman JS, DeKlotz CM, Maruri A, Eichenfield LF, Kelley PK, Jüppner H, Gottschalk M, Tifft CJ. Multilineage somatic activating mutations in HRAS and NRAS cause mosaic cutaneous and skeletal lesions, elevated FGF23 and hypophosphatemia. Human molecular genetics 2013;23(2):397-407
145. Hoffman WH, Jueppner HW, DeYoung BR, O'Dorisio MS, Given KS. Elevated fibroblast growth factor-23 in hypophosphatemic linear nevus sebaceous syndrome. American Journal of Medical Genetics Part A 2005;134(3):233-236
146. Skovby F, Svejgaard E, Møller J. Hypophosphatemic rickets in linear sebaceous nevus sequence. The Journal of pediatrics 1987;111(6):855-857
147. Sethi SK, Hari P, Bagga A. Elevated FGF-23 and parathormone in linear nevus sebaceous syndrome with resistant rickets. Pediatric Nephrology 2010;25(8):1577-1578
148. Heike CL, Cunningham ML, Steiner RD, Wenkert D, Hornung RL, Gruss JS, Gannon FH, McAlister WH, Mumm S, Whyte MP. Skeletal changes in epidermal nevus syndrome: does focal bone disease harbor clues concerning pathogenesis? American Journal of Medical Genetics Part A 2005;139(2):67-77
149. Ovejero D, Lim Y, Boyce A, Gafni R, McCarthy E, Nguyen T, Eichenfield L, DeKlotz C, Guthrie L, Tosi LL. Cutaneous skeletal hypophosphatemia syndrome: clinical spectrum, natural history, and treatment. Osteoporosis International 2016;27(12):3615-3626
150. Jüppner H. Jansen's metaphyseal chondrodysplasia: a disorder due to a PTH/PTHrP receptor gene mutation. Trends in Endocrinology & Metabolism 1996;7(5):157-162
151. Schipani E, Langman C, Parfitt A, Jensen G, Kikuchi S, Kooh S, Cole W, Jüppner H. Constitutively activated receptors for parathyroid hormone and parathyroid hormone-related peptide in Jansen's metaphyseal chondrodysplasia. New England Journal of Medicine 1996;335(10):708-714
152. Brown WW, Jüppner H, Langman CB, Price H, Farrow EG, White KE, McCormick KL. Hypophosphatemia with elevations in serum fibroblast growth factor 23 in a child with Jansen's metaphyseal chondrodysplasia. The Journal of Clinical Endocrinology & Metabolism 2009;94(1):17-20
153. Kuthiroly S, Yesodharan D, Ghosh A, White KE, Nampoothiri S. Osteoglophonic Dysplasia: Phenotypic and Radiological Clues. Journal of pediatric genetics 2017;6(04):247-251
154. Brooks SS, Kassner G, Qazi Q, Keogh M, Gorlin R. Osteoglophonic dysplasia: review and further delineation of the syndrome. American journal of medical genetics 1996;66(2):154-162
155. White KE, Cabral JM, Davis SI, Fishburn T, Evans WE, Ichikawa S, Fields J, Yu X, Shaw NJ, McLellan NJ. Mutations that cause osteoglophonic dysplasia define novel roles for FGFR1 in bone elongation. The American Journal of Human Genetics 2005;76(2):361-367
156. Linglart A, Biosse-Duplan M, Briot K, Chaussain C, Esterle L, Guillaume-Czitrom S, Kamenicky P, Nevoux J, Prié D, Rothenbuhler A. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocrine connections 2014;3(1):R13-R30
157. Penido MG, Alon US. Hypophosphatemic rickets due to perturbations in renal tubular function. Pediatric nephrology (Berlin, Germany) 2014;29(3):361-373
158. Drezner MK, Lyles KW, Haussler MR, Harrelson JM. Evaluation of a role for 1,25-dihydroxyvitamin D3 in the pathogenesis and treatment of X-linked hypophosphatemic rickets and osteomalacia. J Clin Invest 1980;66(5):1020-1032
159. Haffner D, Emma F, Eastwood DM, Duplan MB, Bacchetta J, Schnabel D, Wicart P, Bockenhauer D, Santos F, Levtchenko E, Harvengt P, Kirchhoff M, Di Rocco F, Chaussain C, Brandi ML, Savendahl L, Briot K, Kamenicky P, Rejnmark L, Linglart A. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nature reviews Nephrology 2019;15(7):435-455
160. Haffner D, Emma F, Eastwood DM, Duplan MB, Bacchetta J, Schnabel D, Wicart P, Bockenhauer D, Santos F, Levtchenko E, Harvengt P, Kirchhoff M, Di Rocco F, Chaussain C, Brandi ML, Savendahl L, Briot K, Kamenicky P, Rejnmark L, Linglart A. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nature reviews Nephrology 2019;15(7):435-455
161. Wilson DM, Alon U. Renal Hypophosphatemia. In: Alon U, Chan JC, editors. Phosphate in Pediatric Health and Disease: CRC Press 1993; pp. 160-192
162. Imel EA, Glorieux FH, Whyte MP, Munns CF, Ward LM, Nilsson O, Simmons JH, Padidela R, Namba N, Cheong HI, Pitukcheewanont P, Sochett E, Hogler W, Muroya K, Tanaka H, Gottesman GS, Biggin A, Perwad F, Mao M, Chen CY, Skrinar A, San Martin J, Portale AA. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. Lancet (London, England) 2019;393(10189):2416-2427
163. Verge CF, Lam A, Simpson JM, Cowell CT, Howard NJ, Silink M. Effects of therapy in X-linked hypophosphatemic rickets. New England Journal of Medicine 1991;325(26):1843-1848
164. Makitie O, Kooh SW, Sochett E. Prolonged high-dose phosphate treatment: a risk factor for tertiary hyperparathyroidism in X-linked hypophosphatemic rickets. Clin Endocrinol (Oxf) 2003;58(2):163-168
165. Goodyer PR, Kronick JB, Jequier S, Reade TM, Scriver CR. Nephrocalcinosis and its relationship to treatment of hereditary rickets. J Pediatr 1987;111(5):700-704
166. Reusz GS, Hoyer PF, Lucas M, Krohn HP, Ehrich JH, Brodehl J. X linked hypophosphataemia: treatment, height gain, and nephrocalcinosis. Archives of disease in childhood 1990;65(10):1125-1128
167. DeLacey S, Liu Z, Broyles A, El-Azab SA, Guandique CF, James BC, Imel EA. Hyperparathyroidism and parathyroidectomy in X-linked hypophosphatemia patients. Bone 2019;127:386-392
168. Alon US, Levy-Olomucki R, Moore WV, Stubbs J, Liu S, Quarles LD. Calcimimetics as an adjuvant treatment for familial hypophosphatemic rickets. Clinical journal of the American Society of Nephrology. CJASN 2008;3(3):658-664
169. Alon US, Jarka D, Monachino PJ, Sebestyen VanSickle J, Srivastava T. Cinacalcet as an alternative to phosphate therapy in X-linked hypophosphataemic rickets. Clin Endocrinol (Oxf) 2017;87(1):114-116
170. Grove-Laugesen D, Rejnmark L. Three-year successful cinacalcet treatment of secondary hyperparathyroidism in a patient with x-linked dominant hypophosphatemic rickets: a case report. Case reports in endocrinology 2014;2014:479641
171. Yavropoulou MP, Kotsa K, Gotzamani Psarrakou A, Papazisi A, Tranga T, Ventis S, Yovos JG. Cinacalcet in hyperparathyroidism secondary to X-linked hypophosphatemic rickets: case report and brief literature review. Hormones (Athens, Greece) 2010;9(3):274-278
172. Raeder H, Shaw N, Netelenbos C, Bjerknes R. A case of X-linked hypophosphatemic rickets: complications and the therapeutic use of cinacalcet. Eur J Endocrinol 2008;159(Suppl 1):S101-S105
173. Kooh SW, Binet A, Daneman A. Nephrocalcinosis in X-linked hypophosphataemic rickets: its relationship to treatment, kidney function, and growth. Clin Invest Med 1994;17(2):123-130
174. Nakamura Y, Takagi M, Takeda R, Miyai K, Hasegawa Y. Hypertension is a characteristic complication of X-linked hypophosphatemia. Endocr J 2017;64(3):283-289
175. Seikaly MG, Baum M. Thiazide diuretics arrest the progression of nephrocalcinosis in children with X-linked hypophosphatemia. Pediatrics 2001;108(1):E6
176. Auron A, Alon US. Resolution of medullary nephrocalcinosis in children with metabolic bone disorders. Pediatric nephrology (Berlin, Germany) 2005;20(8):1143-1145
177. Makitie O, Doria A, Kooh S, Cole W, Daneman A, Sochett E. Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets. The Journal of Clinical Endocrinology & Metabolism 2003;88(8):3591-3597

178. Zivicnjak M, Schnabel D, Billing H, Staude H, Filler G, Querfeld U, Schumacher M, Pyper A, Schroder C, Bramswig J, Haffner D, Hypophosphatemic Rickets Study Group of Arbeitsgemeinschaft fur Padiatrische E, Gesellschaft fur Padiatrische N. Age-related stature and linear body segments in children with X-linked hypophosphatemic rickets. Pediatr Nephrol 2011;26(2):223-231
179. Imel. Erik A., Liu Z, Coffman M, Acton D, Econs MJ. Oral Iron Therapy Normalizes Fibroblast Growth Factor 23 (FGF23) in Patients with Autosomal Dominant Hypophosphatemic Rickets. J Bone Miner Res 2018;33(S1):S56(LB-1170)
180. Makitie O, Toiviainen-Salo S, Marttinen E, Kaitila I, Sochett E, Sipila I. Metabolic control and growth during exclusive growth hormone treatment in X-linked hypophosphatemic rickets. Hormone research 2008;69(4):212-220
181. Rothenbuhler A, Esterle L, Gueorguieva I, Salles JP, Mignot B, Colle M, Linglart A. Two-year recombinant human growth hormone (rhGH) treatment is more effective in pre-pubertal compared to pubertal short children with X-linked hypophosphatemic rickets (XLHR). Growth hormone & IGF research: official journal of the Growth Hormone Research Society and the International IGF Research Society 2017;36:11-15
182. Seikaly MG, Brown R, Baum M. The effect of recombinant human growth hormone in children with X-linked hypophosphatemia. Pediatrics 1997;100(5):879-884
183. Zivicnjak M, Schnabel D, Staude H, Even G, Marx M, Beetz R, Holder M, Billing H, Fischer DC, Rabl W, Schumacher M, Hiort O, Haffner D. Three-year growth hormone treatment in short children with X-linked hypophosphatemic rickets: effects on linear growth and body disproportion. The Journal of clinical endocrinology and metabolism 2011;96(12):E2097-E2105
184. Meyerhoff N, Haffner D, Staude H, Wuhl E, Marx M, Beetz R, Querfeld U, Holder M, Billing H, Rabl W, Schroder C, Hiort O, Bramswig JH, Richter-Unruh A, Schnabel D, Zivicnjak M, Hypophosphatemic Rickets Study Group of the "Deutsche Gesellschaft fur Kinderendokrinologie und d, Gesellschaft fur Padiatrische N. Effects of growth hormone treatment on adult height in severely short children with X-linked hypophosphatemic rickets. Pediatr Nephrol 2018;33(3):447-456
185. Aono Y, Yamazaki Y, Yasutake J, Kawata T, Hasegawa H, Urakawa I, Fujita T, Wada M, Yamashita T, Fukumoto S. Therapeutic effects of anti-FGF23 antibodies in hypophosphatemic rickets/osteomalacia. Journal of Bone and Mineral Research 2009;24(11):1879-1888
186. Imel EA, Zhang X, Ruppe MD, Weber TJ, Klausner MA, Ito T, Vergeire M, Humphrey JS, Glorieux FH, Portale AA. Prolonged correction of serum phosphorus in adults with X-linked hypophosphatemia using monthly doses of KRN23. The Journal of Clinical Endocrinology & Metabolism 2015;100(7):2565-2573
187. Carpenter TO, Imel EA, Ruppe MD, Weber TJ, Klausner MA, Wooddell MM, Kawakami T, Ito T, Zhang X, Humphrey J. Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia. The Journal of clinical investigation 2014;124(4):1587-1597
188. Carpenter TO, Whyte MP, Imel EA, Boot AM, Högler W, Linglart A, Padidela R, van't Hoff W, Mao M, Chen CY. burosumab Therapy in Children with X-linked Hypophosphatemia. New England Journal of Medicine 2018;378(21):1987-1998
189. Whyte MP, Carpenter TO, Gottesman GS, Mao M, Skrinar A, San Martin J, Imel EA. Efficacy and safety of burosumab in children aged 1-4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial. The Lancet Diabetes & Endocrinology 2019;7(3):189-199
190. Whyte MP, Fujita KP, Moseley S, Thompson DD, McAlister WH. Validation of a Novel Scoring System for Changes in Skeletal Manifestations of Hypophosphatasia in Newborns, Infants, and Children: The Radiographic Global Impression of Change Scale. J Bone Miner Res 2018
191. Gordon RJ, Levine MA. Burosumab treatment of children with X-linked hypophosphataemic rickets. The Lancet 2019;393(10189):2364-2366
192. Collins M. Burosumab: At Long Last, an Effective Treatment for FGF23-Associated Hypophosphatemia. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2018;33(8):1381-1382
193. Liu ES, Martins JS, Raimann A, Chae BT, Brooks DJ, Jorgetti V, Bouxsein ML, Demay MB. 1,25-Dihydroxyvitamin D Alone Improves Skeletal Growth, Microarchitecture, and Strength in a Murine Model of XLH, Despite Enhanced FGF23 Expression. J Bone Miner Res 2016;31(5):929-939
194. Ovejero D, Gafni RI, Collins MT. 1,25-Dihydroxyvitamin D as Monotherapy for XLH: Back to the Future? Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2016;31(5):925-928
195. Gizard A, Rothenbuhler A, Pejin Z, Finidori G, Glorion C, de Billy B, Linglart A, Wicart P. Outcomes of orthopedic surgery in a cohort of 49 patients with X-linked hypophosphatemic rickets (XLHR). Endocr Connect 2017;6(8):566-573

Are We Aware that Hyperphosphatemia Affects Mortality and Morbidity as much as Hypophosphatemia in Pediatric Intensive Care Patients?

Yılmaz Akbaş[1], MD, Alper Koker[2], MD, Nilgün Erkek[3], MD

[1]Hatay State Hospital, Department of Pediatrics, Hatay, Turkey, [2]Hatay State Hospital, Department of Pediatrics, Pediatric Intensive Care Unit, Hatay, Turkey, [3]Akdeniz University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Emergency Care, Antalya, Turkey

Corresponding author: Alper Koker, MD, Hatay State Hospital, Department of Pediatrics, Pediatric Intensive Care Unit Hatay, Turkey, Tel: 0090 3262294400, Fax: 0090 3262294440, E-mail: kokeralper@gmail.com

Abstract

Objective

Hypophosphatemia was previously shown to affect the duration of admission, mechanical ventilator requirements, mortality and morbidity during pediatric intensive care. Different from previous studies, our study was planned with the aim of showing whether hyperphosphatemia affects morbidity and mortality in pediatric intensive care patients as much as hypophosphatemia.

Method

Patients' ages, genders, reason for admission, underlying diseases, phosphorus levels examined on admission and on the 1-4th and 5-10th-days, duration on mechanical ventilation, duration of admission, final status and PRISM and PELOD scores calculated in the first 24 hours of admission were recorded.

Results

Mortality was distinctly higher for those who were hypophosphatemic and hyperphosphatemic compared to those who were normophosphatemic. The highest mortality was identified in those who were hyperphosphatemic on the 5-10th-days. PELOD scores were only significantly different according to admission phosphorus levels (p:0.04).

Conclusion

In our study, we identified that hyperphosphatemia is a serious problem as hypophosphatemia for patients who admitted to the PICU. Patients identified to be hyperphosphatemic on admission had a significantly higher PELOD score. The significant difference of hyperphosphatemia in terms of PELOD score is one of the important points shown in our study. It should not be forgotten that like hypophosphatemia, hyperphosphatemia may cause serious problems in pediatric intensive care patients.

Ref: *Ped. Endocrinol. Rev. 2019;17(1):35-40*
doi: *10.17458/per.vol17.2019.ake.hyperphosphatemiaaffectsmortality*
Key words: *Pediatric intensive care, Hyperphosphatemia, Hypophosphatemia, PELOD, Mortality*

Introduction

Phosphorus is an essential mineral generally found combined with oxygen in phosphate form in the body. Compounds containing phosphorus function in cell structures, cell metabolism, ensuring intercell regulation and maintaining the acid-base balance.

Though hypophosphatemia is commonly observed, diagnosis is rarely placed due to patients being generally asymptomatic. The incidence of hypophosphatemia among patients applying to the hospital for any reason is 1-5% but reaches 80% among those treated in intensive care units (1-3). The tendency toward hypophosphatemic increases in situations like malnutrition, refeeding syndrome, total parenteral nutrition, insufficient phosphorus intake, sepsis, burns, in the period after surgical operations, and with antiacid, diuretic or steroid use (4). Severe clinical findings are generally observed when serum phosphorus levels are below 1 mg/dl (5). It may cause problems related to the central nervous system (paresthesia, convulsions), respiratory system (acute respiratory failure, insufficient diaphragm spasm), muscle and skeletal system (osteomalacia, rhabdomyolysis), and hematologic system (hemolysis, platelet function disorder) (2). Hypophosphatemia in patients with mechanical ventilation may cause difficulty weaning from the mechanical ventilator, and lengthened duration on mechanical ventilation and in the intensive care unit (6). Finally, it negatively affects morbidity and mortality.

In clinical practice, the most common cause of hyperphosphatemia is renal failure. In mild or moderate renal failure, increasing parathormone levels and reducing tubular phosphorus reabsorption may prevent the development of hyperphosphatemia. In severe renal failure, this compensation mechanism cannot prevent the development of hyperphosphatemia. Hyperphosphatemia affects the nervous system and cardiovascular system most. Central nervous system findings occur with disrupted mental status, delirium, coma, convulsion, muscle cramps or tetany, and paresthesia, while hypotension and lengthened QT may be observed in the cardiovascular system.

This study, different from previous studies, was planned with the aim of showing whether hyperphosphatemia affects morbidity and mortality in pediatric intensive care patients as much as hypophosphatemia.

Patients and Methods

This study was approved by Ankara Dr. Sami Ulus Maternity and Children's Training and Research Hospital Ethical Committee, and all parents signed the informed consent prior to enrollment.

Our study included patients admitted to the pediatric intensive care unit of an education and research hospital from 01/01/2008-31/12/2010. Data were collected from patient archive files and monitoring and treatment records of PICU patients.

The study included patients aged from 1 month to 18 years admitted to the PICU for at least 72 hours. Patients with chronic disease affecting phosphorus metabolism (primary hyperparathyroidism, X linked hypophosphatemia, rickets linked to vitamin D deficiency, chronic renal disease), with anorexia nervosa, with diabetic ketoacidosis coma, admitted for less than 72 hours, and re-admitted patients were excluded from the study.

Patient ages, gender, disease-causing admission (primary), underlying diseases (secondary), phosphorus levels on admission to PICU and on the 1-4th and 5-10th days if known, admission examination findings, clinical status (respiratory failure, heart failure, sepsis and septic shock) on the first day of PICU admission, weight on admission and age-adapted weight z-scores, laboratory findings (arterial blood gases, serum calcium, alkaline phosphatase, magnesium, potassium, total protein, albumin, creatine kinase (CK), CK-MB, lactate dehydrogenase, hemoglobin levels, white blood cell and platelet counts) on admission, day patients began feeding, day patients reached calculated target calories, days they reached calculated target protein intake, use of antacids, diuretics, steroids and inotrope, duration on mechanical ventilation (MV) in PICU, duration of PICU admission, final status, and PRISM (Pediatric Risk of Mortality) and PELOD (Pediatric Logistic Organ Dysfunction) scores calculated in the first 24 hours of admission were recorded (7,8). Reasons for admission to PICU were classified as respiratory system diseases, cardiovascular system diseases, central nervous system diseases, intoxication, sepsis and metabolic diseases.

Serum phosphorus levels examined on admission to PICU and on the 1-4th and 5-10th days if known were recorded in mg/dl form. Definition of hypophosphatemia and hyperphosphatemia were determined according to age based on normal serum phosphorus level limits (1 month-3 yrs: 3.8-6.5 mg/dl, 3-11 yrs:3.7-5.6 mg/dl, 11-15 yrs:2.9-5.4 mg/dl, 15-19 yrs:2.7- 4.7 mg/dl) (9). Patients were divided into two groups based on days feeding was begun as the first three days and after the first three days. Those beginning nutrition in the first three days formed the early nutrition group, while those beginning nutrition after the 3rd day formed the late nutrition group. Times to reach target calorie and target protein intake were examined in 2 groups as early (0-5 days) and late (after 5 days).

Statistical Assessment

Statistical analyses were performed with the SPSS for Windows Version 15.0 program. Numerical variables are shown as mean±standard deviation (SD) or median (min-max) values.

Qualitative variables are given as number and percentage. For differences between groups in terms of numerical variables, one-way analysis of variance was used for those abiding by parametric test assumptions and with the Kruskal Wallis test used for those not abiding by parametric test assumptions. The chi-square test was used to determine whether there were differences in terms of qualitative variables. Correlations between numerical variables were examined with the Pearson correlation coefficient. Whether variation in mean serum phosphorus levels was significant or not was examined with the repeated measures variance analysis. The McNemar test was used to investigate whether the variation in patient numbers when grouped according to serum phosphorus levels were significant or not. The significance level was taken as $p<0.05$.

Results

Patient information from files of 277 patients admitted to the PICU from 01/01/2008-31/12/2010 that could be accessed was evaluated. Of these, 103 were admitted for less than 3 days, 7 patients had repeated admission, 20 patients had insufficient data, 8 patients had chronic renal disease and 23 patients had diabetic ketoacidosis and were removed from the study. Thus, the study included 117 patients. When admission diagnoses are investigated, more than half (52.1%, 61/117 patients) were observed to be respiratory system diseases and intoxication.

Mean age was 5.13 years (1 month-18 years) with 61 females (52.1%) and 56 males (47.9%) out of 117 patients. Of patients, 51.3% (60) were under the age of 2. With the aim of assessing malnutrition, the weight z-score calculation was performed according to age for 114 patients with data accessible. Of patients, 64% (73/114) were within -2 SD and normal limits, while 36% (44/114) were malnourished below -2 SD. The distribution of phosphorus level groups according to calculated weight z-scores based on admission weights found no significant difference in phosphorus level group distribution when examined for those who were malnourished on admission.

Time of beginning feeding information was reached for 107 of 117 patients. Of patients, 93/107 (86.9%) began feeding in the early period and 14/107 (13.1%) began in the late period. When group distributions according to phosphorus levels are examined in terms of beginning nutrition, there was a statistically significant difference between the early nutrition group and the 1-4th day patient rates (p:0.003) with no difference for the group beginning nutrition late (p:0.135). This difference appeared to be primarily due to patients with hyperphosphatemic status.

The phosphorus levels of all 117 patients were examined on admission to PICU and from 1-4th days, while the levels of 56 patients were examined from 5-10th days. The mean phosphorus levels of patients were 4.97±1.61 mg/dl on admission, 4.57±1.11 mg/dl on 1-4th days and 4.65±1.41 mg/dl on the 5-10th days. When the variation in mean phosphorus levels are compared according to repeated phosphorus measurements, there was a significant difference between admission and 1-4th day mean phosphorus levels with no statistically significant differences between admission and 5-10th day and between 1-4th and 5-10th day mean phosphorus levels.

Data about the antiacid, diuretic, steroid or catecholamine use were reached for 86 patients. Of patients, 40.6% (35/86) used antiacids, 47.6% (41/86) used diuretics, 24.4% (21/86) used steroids and 58.1% (50/86) used catecholamine. There was no significant difference between patients using antiacid, diuretics or steroid treatment in terms of admission, 1-4th day and 5-10th day mean phosphorus levels or patient rates according to phosphorus levels. Patients receiving catecholamine treatment had a significant difference in patient rates according to 5-10th day phosphorus levels (p:0.025). Patients receiving catecholamine treatment had higher rates in the hypophosphatemic group based on 5-10th day values.

Of patients, 37.6% (44/117) used a mechanical ventilator. There was a significant difference in patients requiring mechanical ventilator according to admission phosphorus levels (**table 1**) (p:0.023). Those with hypophosphatemic and hyperphosphatemic admission phosphorus levels required more mechanical ventilation than those who were normophosphatemic; however, there was no statistically significant difference between duration on mechanical ventilator based on admission, 1-4th day and 5-10th day phosphorus levels.

Table 1. Distribution of serum phosphorus levels according to mechanical ventilation requirements of PICU patients

Serum Phosphorus Levels On Admission		Hypophosphatemia N (%)	Normophosphatemia N (%)	Hyperphosphatemia N (%)
Mechanical Ventilator Requirements	Needs mechanical ventilator (N:43)	10(23.2)	20(46.5)	13(30.3)
***p:0.023**	No need of mechanical ventilator (N:73)	10(13.6)	53(72.6)	10(13.8)

Mean admission duration of patients was significantly different according to phosphorus levels examined on the 1-4th days (p:0.024). Those who were hypophosphatemic on the 1-4th day had longer mean admission durations (**table 2**); however, there was no significant difference in mean admission durations according to admission and 5-10th day phosphorus levels.

There was a statistically significant difference for mortality according to admission, 1-4th day and 5-10th day phosphorus levels. Mortality was distinctly higher for those who were hypophosphatemic and hyperphosphatemic compared to those who were normophosphatemic. The highest mortality (75%) was identified in patients who were hyperphosphatemic on the 5-10th days (**table 3**).

PRISM and PELOD scores were calculated to assess the seriousness of the patient's clinical status. Mean PRISM score was 10.7±13.2 (min-max:0-75, median:5) and mean PELOD score was 9.9±14 (min-max:0-50, median:3). When PRISM and PELOD scores calculated in the first 24 hours were compared according to admission phosphorus levels, only PELOD scores were significantly different according to admission phosphorus levels (p:0.04). Patients who were hypophosphatemic and hyperphosphatemic had higher PELOD scores compared to those who were normophosphatemic (**table 4**).

When patient admission phosphorus levels are compared according to the presence of heart, respiratory failure and sepsis in the clinical tableau on admission, there was a significant difference identified for the presence of sepsis and cardiac failure with admission phosphorus levels with no difference identified for respiratory failure. The presence of sepsis and cardiac failure was higher in those who were hyperphosphatemic (**table 5**).

Table 2. Distribution of serum phosphorus levels according to mean admission duration to the PICU

Serum Phosphorus Levels	Admission N (%)			1-4th day N (%)			5-10th day N (%)		
	Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph
Mean Admission Duration (day,mean±SD)	11,05± 7,22	9,75± 19,86	14,56± 18,13	12,24± 11,56	10,55± 19,21	10,66± 22,38	15,25± 10,96	18,72± 24,96	22,25± 31,85
p	**0.08**			**0.024**			**0.5**		

Table 3. Distribution of serum phosphorus levels according to final status of PICU patients

Serum Phosphorus Levels		Admission N (%)			1-4th day N (%)			5-10th day N (%)		
		Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph
Final Status	Died N:18	4(22,2)	7(38,9)	7(38,9)	5(27,8)	9(50)	4(22,2)	4(30,8)	6(46,2)	3(23,1)
	Alive N:98	16(16,3)	67(68,4)	15(15,3)	20(20,4)	73(74,5)	5(5,1)	4(9,5)	37(88,1)	1(2,4)
P		**0.04**			**0.05**			**0.007**		

Table 4. Distribution of serum phosphorus levels according to PELOD scores of PICU patients

Serum Phosphorus Levels	Admission N (%)			1-4th day N (%)			5-10th day N (%)		
	Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph
PELOD scores (mean±SD)	11,5± 16	7,6± 12,1	7,6± 12,1	10,9± 15,1	9,1± 13,2	14,6± 15,9	17,3± 18,2	8,2± 10,4	18,1± 14,3
p	**0.04**			**0,22**			**0,4**		

Table 5. Distribution of serum phosphorus levels according to presence of sepsis, cardiac and respiratory failure in PICU patients

Serum Phosphorus Levels on admission		Hypophosphatemia N (%)	Normophosphatemia N (%)	Hyperphosphatemia N (%)	p
Clinical Status	Sepsis N:30	5(16.7)	13(43.3)	12(40)	**0,02**
	Respiratory Failure N:62	14(22.6)	37(59.7)	11(17.7)	0,26
	Cardiac Failure N: 33	7(21.2)	13(39.4)	13(39.4)	**0,01**

Discussion

Variations in phosphorus levels, especially hypophosphatemia, do not have clear or specific symptoms and findings reflecting the clinical tableau making it difficult to monitor the clinical importance of phosphorus. Literature scans observed very few studies about phosphorus levels in pediatric intensive care units, with assessments only of single phosphorus level measured during admission or assessment of a classification of whether patients are hypophosphatemic are not (1,10,11). This study was performed in pediatric patients and has the feature of multipurpose assessment in terms of progression and hypo-normo-hyperphosphatemic formation with admission and repeated measurements during monitoring. When PRISM and PELOD scores are examined, they appear to be a heterogeneous group.

According to repeated phosphorus measurements of patients, phosphorus levels fell on the 1-4th day and increased again on the 5-10th days. When mean phosphorus levels are compared, a statistically significant difference was only found between admission (4.97±1,61 mg/dl) and 1-4th day (4.57±1,11 mg/dl) (p:0.034).

A study published by Menezes in 2009 prospectively observed 82 children under the age of 7, and reported no significant difference in mean phosphorus values in 3 measurements repeated within the first 10 days (12). During measurements during the admission duration, with any value, 26.4% of our patients were hypophosphatemic and 22.2% were hyperphosphatemic. The study published by Menezes in 2006 identified that 76% of patients were hypophosphatemic. The reason for this rate is higher than our study is that in Menezes' study a single phosphorus value was examined on the 3rd day and the age groups were different. Additionally, children assessed in this study had distinctly higher rates of malnutrition (83% <-2SD) compared to our study group (36%), which may have affected results as it is a significant risk factor for hypophosphatemia. Menezes reported they found a significant correlation between malnutrition and hypophosphatemia in this study (13). The prospective study by Menezes in 2009 found a positive correlation between weight z-scores of patients on admission and phosphorus levels and showed that mean phosphorus levels of malnourished patients were significantly low (12). In our study, malnourished patients with weight z-score (<-2SD) had higher hypophosphatemia on admission compared to those who were not malnourished (31.1% compared to 12.3%). Additionally, this difference was not statistically significant (p:0.09).

The use of antiacid, steroids and diuretics which can affect phosphorus levels in patients did not affect mean admission, 1-4th day and 5-10th-day phosphorus levels (p:0.73,0.38,0.49, respectively). The 2006 study by Menezes did not show a significant correlation between steroid and diuretic use with hypophosphatemia, which appears to comply with our study results (13). The 2009 Menezes study showed a correlation between diuretic use above 2 mg/kg and any dose of dopamine with hypophosphatemia (12). In our study, patients receiving catecholamine support appeared to have significantly high hypophosphatemia rates in the 5-10th day values (p:0.025).

Phosphorus levels may be associated with hunger and time beginning feeding. It is known that with the increased anabolic activity at cellular levels with the beginning of the feeding and ATP synthesis and the intake of phosphorus into cells, especially in malnourished patients, may cause falls in phosphorus levels leading to serious outcomes (12,14). The majority of our patients began early feeding in the first three days. When early feeding patients are compared with admission, the 1-4th day hyperphosphatemic group clearly reduced and the hypophosphatemic group increased and this was statistically significant (p:0.003).

In our study when the difference in phosphorus levels are compared with scores showing the severity of clinical disease and organ dysfunction status of patients, mean PELOD scores were observed to differ according to admission phosphorus levels (p:0.04). The PELOD scores of patients who were hyperphosphatemic on admission were higher. A retrospective study in Turkey by Kılıç *et al.* in 2008 reported being hypophosphatemic did not cause a significant difference in terms of PELOD scores. However, this study only assessed patients as being hypophosphatemic or not (15). The

significant difference in PELOD score with hyperphosphatemia is one of the important points shown in our study.

Patients with sepsis and cardiac failure on admission were found to have significantly high rates of hyperphosphatemia (p:0.02 and 0.01). Patients with respiratory failure did not show different patient rates according to serum phosphorus levels (p:0.26). Hyperphosphatemia may have developed due to organ dysfunction that may accompany sepsis and cardiac failure. However, though the mechanism is not clear, studies of septic adults and animal studies reported hyperphosphatemia development linked to sepsis-associated multiple organ failure and increased parathormone (16-18).

Of our patients, 37.6% received MV support and hypophosphatemic and hyperphosphatemic patients according to admission values had significantly high rates of MV requirements. However, the duration on mechanical ventilator did not differ according to phosphorus levels. The 2009 study by Menezes reported 13 of 16 patients requiring mechanical ventilation were hypophosphatemic (12). However, patients in this study were only classified as hypophosphatemic and normophosphatemic. The significantly higher rates of mechanical ventilation requirements in hyperphosphatemic patients is associated with more pronounced accompanying organ dysfunctions.

The mean admission duration of patients in our study was 10.9±17.9 days, with durations significantly longer for patients who were hypophosphatemic on 1-4th day values. Hypophosphatemia developing in patients admitted to the PICU lengthens the duration of stay. In our study group, 15.4% of 117 patients died. Mortality was significantly high in patients who were hyperphosphatemic and hypophosphatemic on admission, 1-4th day and 5-10th day values (p: 0.04,0.05,0.007). The highest mortality (75%) occurred among patients who were hyperphosphatemic on the 5-10th days. Though hypophosphatemia did not reach serious levels in patients admitted to the PICU, it increased MV requirements, morbidity and mortality.

In our study, like hypophosphatemia, hyperphosphatemia was identified to be a severe problem for patients admitted to the PICU. Patients identified to have hyperphosphatemia on admission had a higher PELOD score. Additionally, the hyperphosphatemic rates in patients with sepsis and cardiac failure were significantly high. Especially the higher mortality in patients who were hyperphosphatemic on the 5-10th day may be linked to this.

Just like hypophosphatemia, it should not be forgotten that hyperphosphatemia may cause severe problems in pediatric intensive care patients.

Disclosure

The authors have nothing to disclose

References

1. Barak V, Schwartz A, Kalickman I, Nisman B, Gurman G, Shoenfeld Y. Prevalence of hypophosphatemia in sepsis and infection: the role of cytokines. Am J Med 1988;104:40–47
2. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus, Lancet 1988;352:391–396
3. Miller DW, Slovis CM. Hypophosphatemia in the emergency department therapeutics, Am J Emerg Med 2000;18:457-461
4. Subramanian R, Khardori R. Severe hypophosphatemia. Pathophysiologic implications, clinical presentations and treatment, Medicine 2000;79(1):1-8
5. Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. Am J Med 2005;118(10):1098
6. Gustavsson CG, Eriksson L. Acute respiratory failure in anorexia nervosa with hypophosphataemia, J Intern Med 1989;225:63–64
7. http://www.sfar.org/scores2/prism2.html
8. http://www.sfar.org/scores2/pelod2.html
9. Larry A. Greenbaum: Pathophysiology of Body Fluids and Fluid Therapy. In: Behrman RE, Kliegman RM, Jenson HB (eds), Textbook of Pediatrics. 17th ed, Saunders, Philadelphia 2004; p. 220
10. Pomposelli JJ, Pomfret EA, Burns DL, Lally A, Sorcini A, Gordon FD, Lewis WD, Jenkins R. Life-threatening hypophosphatemia after right hepatic lobectomy for live donor adult liver transplantation. Liver Transpl 2001;7:637–642
11. Zazzo JF, Troche G, Ruel P, Maintenant J. High incidence of hypophosphatemia in surgical intensive care patients: efficacy of phosphorus therapy on myocardial function. Intensive Care Med 1995;21:826–831
12. Santana e Meneses JF, Leite HP, de Carvalho WB, Lopes E Jr. Hypophosphatemia in critically ill children: prevalence and associated risk factors. Pediatr Crit Care Med 2009;10(2):235
13. de Menezes FS, Leite HP, Fernandez J, Benzecry SG, de Carvalho WB. Hypophosphatemia in children hospitalized within an intensive care unit. J Intensive Care Med 2006;21(4):236
14. Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. Am J Med 2005;118(10):1094
15. Kilic O, Demirkol D, Ucsel R, Citak A, Karabocuoglu M. Hypophosphatemia and its clinical implications in critically ill children: a retrospective study. J Crit Care 2012;27(5):474-479
16. Lucas CE, Ledgerwood AM, Jeffries CC, Vernier P. Late association of hyperparathyroidism in septic patients with multiple organ failure. Surgery 2010;148(1):135-139
17. Hurcombe SD, Toribio RE, Slovis NM, Saville WJ, Mudge MC, Macgillivray K, Frazer ML. Calcium regulating hormones and serum calcium and magnesium concentrations in septic and critically ill foals and their association with survival. J Vet Intern Med 2009;23(2):335-343
18. Ruiz Magro P, Aparicio López C, López-Herce Cid J, Martínez Campos M, Sancho Pérez L. Metabolic changes in critically ill children. An Esp Pediatr 1999;51(2):143-148

Growth Hormone Deficiency and Excessive Sleepiness: A Case Report and Review of the Literature

Anisha Gohil, DO, Erica Eugster, MD

Indiana University School of Medicine, Riley Hospital for Children, Endocrinology & Diabetes, 705 Riley Hospital Drive, Room 5960, Indianapolis, IN 46202, USA

Corresponding author: Anisha Gohil, DO, Indiana University School of Medicine, Riley Hospital for Children, Fellow, Endocrinology & Diabetes, 705 Riley Hospital Drive, Room 5960, Indianapolis, IN 46202, USA, Tel: +1-317-944-3889, Fax: 317-944-3882, E-mail: agohil@iu.edu

Abstract

The somatotropic axis is intricately involved in normal sleep, as evidenced by the fact that hypothalamic growth hormone-releasing hormone (GHRH) has sleep promoting effects and pituitary growth hormone (GH) release is strongly associated with slow-wave sleep (SWS). Abnormalities in the somatotropic axis, such as GH deficiency of hypothalamic or pituitary origin, result in an alteration of normal sleep patterns which may explain the fatigue reported in these individuals. Sleep disorders such as narcolepsy, in which individuals abnormally enter rapid eye movement (REM) sleep at sleep onset are also associated with an altered GHRH circadian rhythm and abnormal GH secretion. While few studies are available, this review explores what is known about sleep abnormalities in GH deficiency, the effect of treatment on sleep in patients with GH deficiency, and GH secretion in narcolepsy. Emerging evidence suggests a hypothalamic link between narcolepsy and GH secretion. We also describe the unique constellation of isolated idiopathic GH deficiency and severe excessive sleepiness in adopted Nicaraguan siblings, one of which has narcolepsy and the other idiopathic hypersomnia.

***Ref**: Ped. Endocrinol. Rev. 2019;17(1):41-46*
***doi**: 10.17458/per.vol17.2019.ge.ghdeficiencyandsleepiness*
***Key words**: Growth Hormone Deficiency, Narcolepsy, Idiopathic Hypersomnia, Slow-wave Sleep*

Background: Somatotropic Axis and Sleep

Normal sleep consists of two stages: REM and non-REM sleep which alternate cyclically (1). Non-REM sleep consists of stages 1, 2, 3, and 4, each of which has its own unique brain activity (2). Stages 3 and 4, which predominantly happen during the first third of nightly sleep, are known as SWS and are considered the deep stages of sleep (3). Non-REM begins first, progresses through its stages, and subsequently REM sleep occurs (1).

It is well known that pituitary GH is secreted in a pulsatile fashion primarily during sleep and reaches its highest amplitude during SWS (4-6). This release occurs secondary to stimulation by hypothalamic GHRH which results in significantly increased GH secretion (7). GHRH given during SWS, as opposed to during REM sleep or an awakened state, results in a larger GH response (8). GHRH itself has sleep promoting effects (9) and in healthy young adult males its episodic rather than continuous administration increases SWS duration (7,10). In the rodent model, this sleep promoting effect has been shown to occur independent of GH (11). While GHRH's effect on GH release and promotion of SWS occur through distinct hypothalamic neurons, these processes are not completely independent, but instead are quite interconnected (12,13).

Some have hypothesized that in pituitary GH deficiency, the lack of negative feedback inhibition of GH on GHRH leads to increased activity of GHRH and the subsequent promotion of excessive SWS (14). In contrast, patients with a hypothalamic origin may have deficient SWS and REM sleep due to the combination of GHRH and GH deficiencies (15).

Indeed, subjects with isolated GH deficiency have been shown to have decreased duration of SWS (16) and REM sleep (17) which corrects with appropriate GH replacement (18,19). In a study with 18 healthy young adults, GH administration decreased SWS, but increased REM sleep (20).

These studies suggest that since the somatotropic axis is intricately involved in normal sleep, abnormalities may contribute to the fatigue reported in individuals with GH deficiency (21,22). With the paucity of data, further studies are needed to clarify this potential relationship.

Case Report

An 8 4/12 year old Hispanic boy and his 6 6/12 year old sister were referred for pediatric endocrinology evaluation due to poor growth. Both had been adopted from a Nicaraguan orphanage 2 years earlier where they had been placed due to emotional and physical neglect. Both had a history of severe malnutrition which had resolved by the time of our evaluation. Additional history consisted of debilitating fatigue and a pattern of sleeping ~18 hours a day, rendering it impossible for them to attend school or have a normal life.

On physical exam, heights were at -2.17 SD (boy) and -3.25 SD (girl) with BMIs at -1.38 SD (boy) and -1.04 SD (girl). Evaluation revealed low serum IGF-1 levels of 20 ng/ml and 15 ng/ml and stimulation testing demonstrated peak GH levels of 2.39 ng/dl and 4.31 ng/dl in the boy and girl, respectively. Pituitary MRIs were normal. Bone age xrays were delayed at ~-3 SD in the boy and -4 SD in the girl. Thyroid function tests and AM cortisol were normal. GH therapy was started at 0.3 mg/kg/wk and growth velocity improved from 0 to 7.92 cm/yr (boy), and from 2 to 5.56 cm/yr (girl) during the first 6 months of therapy. IGF-1 levels normalized in both.

Both entered puberty spontaneously at age 11 11/12 years (boy) and 10 8/12 years (girl). GH therapy was weight-adjusted and most recent growth parameters have improved with height -1.33 SD, BMI of -0.12 SD, growth velocity of 11.2 cm/yr, and bone age consistent with chronological age at -0.25 SD in the boy and height -1.02 SD, BMI of -0.05 SD, growth velocity of 14.8 cm/yr, and a delayed bone age of -3SD in the girl. The children's growth charts are shown in **figure 1**.

While on GH therapy, the mother reported worsening hypersomnia prompting referral to sleep medicine where the boy was diagnosed with narcolepsy and the girl with idiopathic hypersomnia. Both were started on modafinil, transitioned to armodafinil, and finally sodium oxybate due to poor response. With this most recent regimen, their excessive sleepiness has improved.

Genetic testing has been inconclusive. Whole exome sequencing revealed a previously unreported variant in one of two copies of the CPA1 gene [c.497 G>T (p.G166V)] of uncertain significance in both siblings. Other variants in this gene have been associated with pancreatic disease, but there is no evidence of pancreatic issues in these siblings. Mitochondrial DNA sequencing and metabolic evaluation were negative. Interestingly, testing did reveal that they are half-siblings.

Discussion

Sleep Abnormalities in GH Deficiency

There are few human studies that have examined sleep quality in individuals with GH deficiency. In one, 30 untreated adult subjects with GH deficiency were compared to 30 matched controls (14). Compared with controls, subjects with GH deficiency had poorer sleep quality determined by the Pittsburgh Sleep Quality Index and also had lower quality of life scores. Those with pituitary GH deficiency had a longer duration and more intense SWS, while those with hypothalamic GH deficiency had lower intensity SWS. A sleep study using wrist actigraphy and polysomnography in 9 adults with GH deficiency showed decreased sleep duration and increased sleep fragmentation compared to 9 healthy controls (13). Children with GH deficiency also have different sleep characteristics. In a study of 10 children with GH deficiency compared with 20 matched controls, those with GH deficiency had abnormal sleep macrostructure (decreased sleep duration, sleep efficiency, movement time, stage 2 non-REM sleep, and percent REM sleep) and altered sleep microstructure (reduced arousal instability) (23).

Effect of Treatment on Sleep in GH Deficiency

In 13 adults with GH deficiency of confirmed or likely pituitary origin, after 4 months of GH replacement therapy, there was a significant decrease in sleep duration primarily due to decreased SWS intensity and an earlier wake time (24). Several had panhypopituitarism with and without surgery or radiotherapy and etiologies of GH deficiency varied among subjects and included idiopathic, as well as organic causes. A significant decrease in stage 3 of SWS was also seen after GH therapy in 6 of 7 children with GH deficiency (25). Five of these children had idiopathic, isolated GH deficiency, one had septo-optic dysplasia, and one developed hypopituitarism after resection and radiation therapy for craniopharyngioma. Both of these studies suggest that GH replacement deceases SWS, adding support for the hypothesis that in pituitary

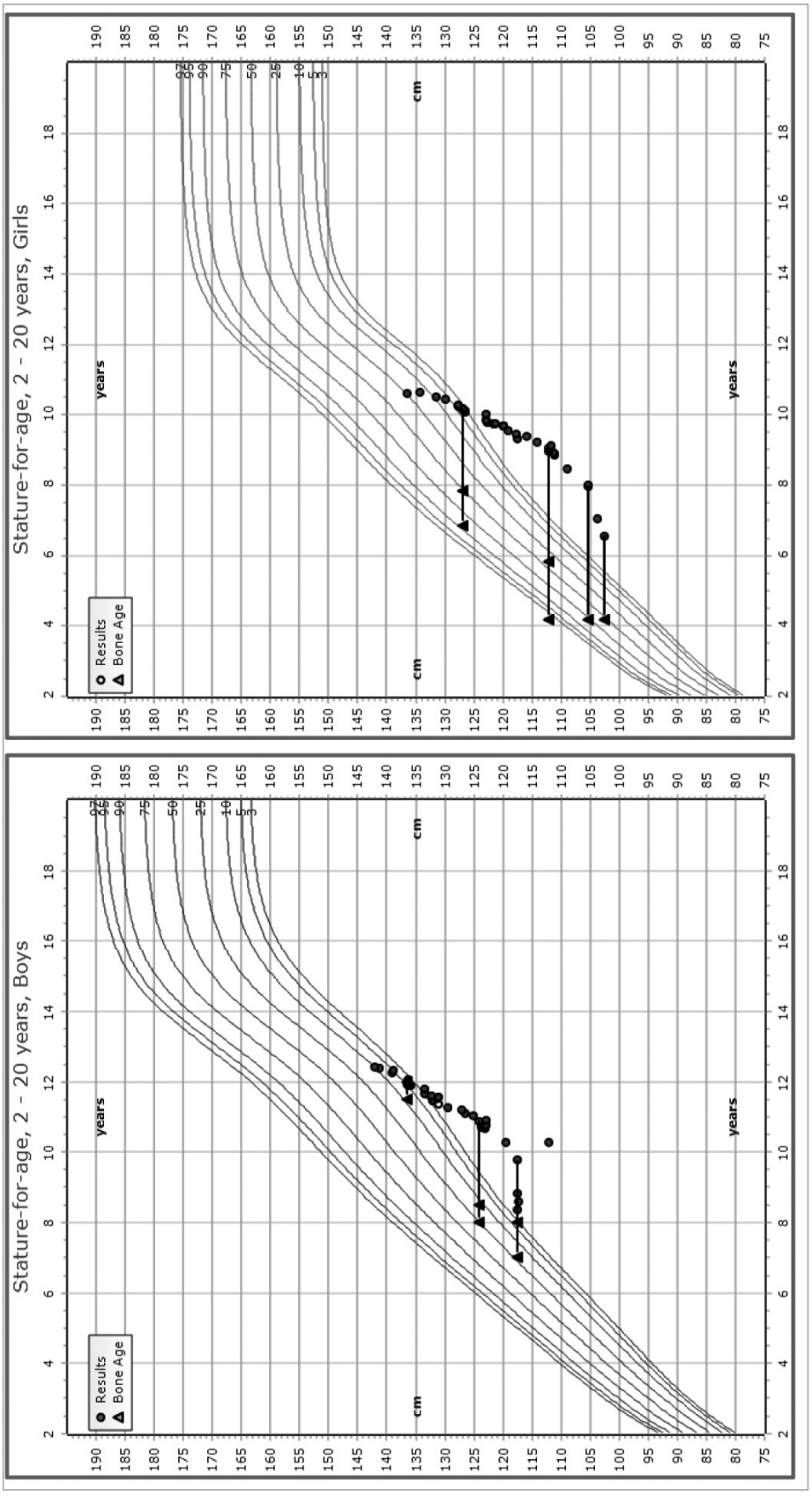


Figure 1. Growth charts for boy (left) and girl (right)
Δ indicates bone ages

GH deficiency, lack of negative feedback of GH results in unopposed GHRH with consequent SWS excess.

However, other studies have found no difference in sleep in treated subjects with GH deficiency (26,27). In a randomized double-blinded placebo controlled trial over 6 months, day and nighttime sleep EEG recordings and a multiple sleep latency test were performed at baseline and after 6 months of GH therapy in 17 adults with GH deficiency and no sleep effect of therapy was found (26). The etiology in the majority of subjects was a pituitary adenoma with subsequent pituitary surgery and occasionally radiation therapy. Thus, it is difficult to draw clear conclusions regarding the impact of GH treatment on sleep.

Narcolepsy and Growth Hormone Secretion

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, abnormal REM sleep including episodes with loss of muscle tone (cataplexy), sleep paralysis, and hypnagogic hallucinations (28). Type 1 narcolepsy is defined by cataplexy and results from extensive loss of the hypothalamic neurons that secrete the neurotransmitter hypocretin (also known as orexin) (29-31). Type 2 lacks cataplexy and the cause is unknown (28). While non-REM sleep normally occurs first, those with narcolepsy enter directly into REM sleep at sleep onset (32). Idiopathic hypersomnia is considered a diagnosis of exclusion once other causes of excessive daytime sleepiness have been ruled out (33). Features of idiopathic hypersomnia include extreme fatigue after awakening from sleep, high sleep efficiency (time spent in bed asleep), and shortened sleep latency (length of time from awakened state to sleep onset) (33,34).

While the presence of GH deficiency in narcolepsy has not been investigated, there are a few small studies that have explored 24-hour GH secretion in this condition. In 4 adult subjects with narcolepsy, the GH peak during SWS was absent or greatly decreased (35) compared with the substantial GH peak within 60 minutes of sleep onset that was observed in 4 healthy controls. Other studies have demonstrated that people with narcolepsy do not have deficient, but rather dysregulated GH secretion that is not clearly linked with sleep stages (36). GH secretion and sleep patterns were assessed over 24 hours in 7 adult individuals with narcolepsy with confirmed hypocretin deficiency and compared to matched controls (37). Basal and pulsatile GH secretion and GHRH-induced GH secretion were similar between subjects with narcolepsy and controls, but those with narcolepsy secreted about 50% of their total daily GH during the day vs only 25% in the controls.

Short stature and GH deficiency are not known features of narcolepsy. One study has described anthropometric and endocrine data in 72 pediatric subjects with type 1 narcolepsy over a 1-year follow up period (38). In the 39 subjects who underwent GH stimulation testing with arginine and clondinine, 23 had a blunted GH concentration defined by a peak level below 8 ng/mL on at least one of the two provocative tests. All had normal IGF-1 z-scores and all children were of normal height (mean z-score 0.72 +/- 1.07) and appropriate for their genetic potential, suggesting a normal functioning GH axis. Growth velocity was low only in the subgroup close to completion of puberty which is expected for this pubertal stage. While linear growth appears normal, other endocrinopathies that have been reported in the setting of narcolepsy are precocious puberty and obesity (38,39).

Table 1 summarizes features of the somatotropic axis as it relates to GH deficiency, narcolepsy, and the normal state.

Hypothalamic Link

While there appears to be a link between abnormalities in the somatotropic axis and sleep regulation, evidence supporting a hypothalamic link between narcolepsy and GH deficiency is beginning to emerge. The hypocretin, orexin-A, was shown in rat models of GH deficiency (hypophysectomized and Lewis dwarf rat) to decrease GHRH expression in the paraventricular nuclei (40). Another study using adult male rats demonstrated that administration of orexin-A decreased spontaneous GH secretion (41). Hypothalamic somatostatin is well-known to inhibit GH release as part of normal physiology (42) and orexin-A stimulated somatostatin release in male rats (43). These studies may explain the disrupted circadian rhythm of GHRH (37) and abnormal GH secretion in humans with narcolepsy (35,44). Considering the complexity of the GH system, additional cross-connections involving hypocretins or other modulators of the somatotropic axis likely exist.

Conclusion

To the best of our knowledge, our siblings represent the first report of GH deficiency in the setting of narcolepsy

Table 1. Established and proposed relationships between the somatotropic axis and sleep in normal physiology, GH deficiency, and narcolepsy

Normal Sleep	GH Deficiency	Narcolepsy
•GHRH increases SWS duration •GH primarily secreted during SWS (Stages 3 & 4)	•Hypothalamic origin •Deficient SWS and REM sleep •Pituitary origin •Lack of negative feedback of GH on GHRH ➞ increased GHRH ➞ promotion of SWS	•GH peak during SWS absent or decreased •24-hour secretion not deficient •Not clearly linked with sleep stages •Greater percentage of secretion during daytime than controls

and idiopathic hypersomnia. We propose that hypothalamic dysfunction may be the link between GH deficiency and sleep disorders in these children. It is unclear why the siblings developed increased sleepiness following initiation of GH therapy as existing reports have found no effect or an improvement in sleep in subjects receiving GH treatment, albeit none of these studies included cases of narcolepsy or idiopathic hypersomnia. Further studies, particularly in humans are needed to clarify the relationship between GH, narcolepsy, and sleep disorders.

Disclosure

This work was supported by NIH grant T32DK065549.

References

1. Carskadon MA, Dement WC. Normal human sleep: an overview. Principles and practice of sleep medicine 2005;4:13-23
2. Altevogt BM, Colten HR. Sleep disorders and sleep deprivation: an unmet public health problem: National Academies Press 2006;pp.33-53
3. Roth T. Slow wave sleep: does it matter? Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine 2009;5(2 Suppl):S4-S5
4. Takahashi Y, Kipnis D, Daughaday W. Growth hormone secretion during sleep. The Journal of clinical investigation 1968;47(9):2079-2090
5. Honda Y, Takahashi K, Takahashi S, Azumi K, Irie M, Sakuma M, Tsushima T, Shizume K. Growth hormone secretion during nocturnal sleep in normal subjects. The Journal of Clinical Endocrinology & Metabolism 1969;29(1):20-29
6. Sassin J, Parker D, Mace J, Gotlin R, Johnson L, Rossman L. Human growth hormone release: relation to slow-wave sleep and sleep-waking cycles. Science 1969;165(3892):513-515
7. Steiger A, Guldner J, Hemmeter U, Rothe B, Wiedemann K, Holsboer F. Effects of growth hormone-releasing hormone and somatostatin on sleep EEG and nocturnal hormone secretion in male controls. Neuroendocrinology 1992;56(4):566-573
8. Van Cauter E, Caufriez A, Kerkhofs M, Van Onderbergen A, Thorner M, Copinschi G. Sleep, awakenings, and insulin-like growth factor-I modulate the growth hormone (GH) secretory response to GH-releasing hormone. The Journal of Clinical Endocrinology & Metabolism 1992;74(6):1451-1459
9. Kerkhofs M, Van Cauter E, Van Onderbergen A, Caufriez A, Thorner MO, Copinschi G. Sleep-promoting effects of growth hormone-releasing hormone in normal men. American Journal of Physiology-Endocrinology And Metabolism 1993;264(4):E594-E598
10. Marshall L, Mölle M, Böschen G, Steiger A, Fehm H, Born J. Greater efficacy of episodic than continuous growth hormone-releasing hormone (GHRH) administration in promoting slow-wave sleep (SWS). The Journal of Clinical Endocrinology & Metabolism 1996;81(3):1009-1013
11. Obal F Jr, Floyd R, Kapas L, Bodosi B, Krueger JM. Effects of systemic GHRH on sleep in intact and hypophysectomized rats. The American journal of physiology 1996;270(2 Pt 1):E230-E237
12. Cauter EV, Plat L, Copinschi G. Interrelations between sleep and the somatotropic axis. Sleep 1998;21(6):553-566
13. Van Cauter E, Latta F, Nedeltcheva A, Spiegel K, Leproult R, Vandenbril C, Weiss R, Mockel J, Legros JJ, Copinschi G. Reciprocal interactions between the GH axis and sleep. Growth hormone & IGF research 2004;14:10-17
14. Copinschi G, Nedeltcheva A, Leproult R, Morselli LL, Spiegel K, Martino E, Legros JJ, Weiss RE, Mockel J, Van Cauter E. Sleep disturbances, daytime sleepiness, and quality of life in adults with growth hormone deficiency. The Journal of clinical endocrinology and metabolism 2010;95(5):2195-2202
15. Tanriverdi F, Karaca Z, Unluhizarci K, Kelestimur F. Unusual effects of GH deficiency in adults: a review about the effects of GH on skin, sleep, and coagulation. Endocrine 2014;47(3):679-689
16. Astrom C, Jochumsen PL. Decrease in delta sleep in growth hormone deficiency assessed by a new power spectrum analysis. Sleep 1989;12(6):508-515
17. Astrom C, Lindholm J. Growth hormone-deficient young adults have decreased deep sleep. Neuroendocrinology 1990;51(1):82-84
18. Astrom C. Interaction between sleep and growth hormone. Evaluated by manual polysomnography and automatic power spectrum analysis. Acta neurologica Scandinavica 1995;92(4):281-296
19. Hayashi M, Shimohira M, Saisho S, Shimozawa K, Iwakawa Y. Sleep disturbance in children with growth hormone deficiency. Brain & development 1992;14(3):170-174
20. Mendelson WB, Slater S, Gold P, Gillin JC. The effect of growth hormone administration on human sleep: a dose-response study. Biological psychiatry 1980;15(4):613-618
21. Brod M, Alolga SL, Beck JF, Wilkinson L, Hojbjerre L, Rasmussen MH. Understanding burden of illness for child growth hormone deficiency. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2017;26(7):1673-1686
22. Brod M, Pohlman B, Hojbjerre L, Adalsteinsson JE, Rasmussen MH. Impact of adult growth hormone deficiency on daily functioning and well-being. BMC research notes 2014;7:813
23. Verrillo E, Bizzarri C, Cappa M, Bruni O, Pavone M, Ferri R, Cutrera R. Sleep characteristics in children with growth hormone deficiency. Neuroendocrinology 2011;94(1):66-74
24. Morselli LL, Nedeltcheva A, Leproult R, Spiegel K, Martino E, Legros JJ, Weiss RE, Mockel J, Van Cauter E, Copinschi G. Impact of GH replacement therapy on sleep in adult patients with GH deficiency of pituitary origin. Eur J Endocrinol 2013;168(5):763-770
25. Wu RH, Thorpy MJ. Effect of growth hormone treatment on sleep EEGs in growth hormone-deficient children. Sleep 1988;11(5):425-429
26. Schneider HJ, Oertel H, Murck H, Pollmacher T, Stalla GK, Steiger A. Night sleep EEG and daytime sleep propensity in adult hypopituitary patients with growth hormone deficiency before and after six months of growth hormone replacement. Psychoneuroendocrinology 2005;30(1):29-37
27. Peker Y, Svensson J, Hedner J, Grote L, Johannsson G. Sleep apnoea and quality of life in growth hormone (GH)-deficient adults before and after 6 months of GH replacement therapy. Clin Endocrinol (Oxf) 2006;65(1):98-105
28. Scammell TE. Narcolepsy. The New England journal of medicine 2015;373(27):2654-2662
29. Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, Nevsimalova S, Aldrich M, Reynolds D, Albin R, Li R, Hungs M, Pedrazzoli M, Padigaru M, Kucherlapati M, Fan J, Maki R, Lammers GJ, Bouras C, Kucherlapati R, Nishino S, Mignot E. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nature medicine 2000;6(9):991-997
30. Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, Cornford M, Siegel JM. Reduced number of hypocretin neurons in human narcolepsy. Neuron 2000;27(3):469-474
31. Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, Vankova J, Black J, Harsh J, Bassetti C, Schrader H, Nishino S. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Archives of neurology 2002;59(10):1553-1562

32. Rechtschaffen A, Wolpert EA, Dement WC, Mitchell SA, Fisher C. NOCTURNAL SLEEP OF NARCOLEPTICS. Electroencephalography and clinical neurophysiology 1963;15:599-609
33. Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. Sleep 2007;30(10):1274-1281
34. Roth B. Narcolepsy and hypersomnia: review and classification of 642 personally observed cases. Schweizer Archiv fur Neurologie, Neurochirurgie und Psychiatrie = Archives suisses de neurologie, neurochirurgie et de psychiatrie 1976;119(1):31-41
35. Higuchi T, Takahashi Y, Takahashi K, Niimi Y, Miyasita A. Twenty-four-hour secretory patterns of growth hormone, prolactin, and cortisol in narcolepsy. The Journal of clinical endocrinology and metabolism 1979;49(2):197-204
36. Besset A, Bonardet A, Billiard M, Descomps B, de Paulet AC, Passouant P. Circadian patterns of growth hormone and cortisol secretions in narcoleptic patients. Chronobiologia 1979;6(1):19-31
37. Overeem S, Kok SW, Lammers GJ, Vein AA, Frolich M, Meinders AE, Roelfsema F, Pijl H. Somatotropic axis in hypocretin-deficient narcoleptic humans: altered circadian distribution of GH-secretory events. American journal of physiology Endocrinology and metabolism 2003;284(3):E641-E647
38. Ponziani V, Gennari M, Pizza F, Balsamo A, Bernardi F, Plazzi G. Growing Up with Type 1 Narcolepsy: Its Anthropometric and Endocrine Features. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine 2016;12(12):1649-1657
39. Maia AP, Kim LJ, Moreira GA, Santos FC, Tufik S, Levy MA. Narcolepsy, Precocious Puberty and Obesity in the Pediatric Population: a Literature Review. Pediatric endocrinology reviews: PER 2018;16(2):266-274
40. Lopez M, Seoane LM, Tovar S, Nogueiras R, Dieguez C, Senaris R. Orexin-A regulates growth hormone-releasing hormone mRNA content in a nucleus-specific manner and somatostatin mRNA content in a growth hormone-dependent fashion in the rat hypothalamus. The European journal of neuroscience 2004;19(8):2080-2088
41. Seoane LM, Tovar SA, Perez D, Mallo F, Lopez M, Senaris R, Casanueva FF, Dieguez C. Orexin A suppresses in vivo GH secretion. Eur J Endocrinol 2004;150(5):731-736
42. Hartman ML, Veldhuis JD, Thorner MO. Normal control of growth hormone secretion. Hormone Research in Paediatrics 1993;40(1-3):37-47
43. Russell S, Kim M, Small C, Abbott C, Morgan D, Taheri S, Murphy K, Todd J, Ghatei M, Bloom S. Central administration of orexin A suppresses basal and domperidone stimulated plasma prolactin. Journal of neuroendocrinology 2000;12(12):1213-1218
44. Clark RW, Schmidt HS, Malarkey WB. Disordered growth hormone and prolactin secretion in primary disorders of sleep. Neurology 1979;29(6):855-861

Central Nervous System Complications in Diabetic Ketoacidosis

Marta Baszyńska-Wilk[1], MD, Marta Wysocka-Mincewicz[1], MD, PhD, Małgorzata Wajda-Cuszlag[1], MD, Anna Świercz[1], MD, Mieczysław Szalecki[1,2], MD, PhD

[1]Department of Endocrinology and Diabetology, The Children's Memorial Health Institute, Warsaw, Poland,
[2]The Faculty of Medicine and Health Sciences, Jan Kochanowski University, Kielce, Poland

Corresponding author: Marta Baszyńska-Wilk, MD, Department of Endocrinology and Diabetology, The Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04-730 Warsaw, Poland, E-mail: mbasz@wp.pl

Commentary to: Paediatric T1DM: DKA is Still a Problem by Martinez E. et al, PER 16(2):233-239

Ref: *Ped. Endocrinol. Rev. 2019;17(1):47-49*
doi: *10.17458/per.vol17.2019.le.bwwmwc.nervouscomplicationsdiabetic*
Key words: *Neurological complications, Diabetic ketoacidosis, Diabetes type 1*

Dear Editor,

We have read the article entitled "Paediatric T1DM: DKA is Still a Problem" by Martinez E. et al published in Pediatric Endocrinology Reviews. We want to congratulate the authors for this successful article, and make some contributions about neurological complications of diabetic ketoacidosis.

It is estimated that approximately 30% of new onset diabetes mellitus type 1 cases are diagnosed with a concomitant ketoacidosis (DKA) (1-3). Its neurological complications are not very frequent, however they can have a serious consequences.

Cerebral edema is the most common neurological complication of DKA. It is estimated that it occurs in 0,5-1% of DKA cases (4,5). It is a serious and life-threatening condition with the approximate 20% mortality rate. The pathomechanism of brain edema remains unknown however several hypotheses are considered. One of them is a change in the osmotic gradient that occurs between the brain cells and the extracellular fluid. As a result of the high level of glucose in the blood, the water moves from the intracellular to the extracellular fluid. After initiating inadequate DKA treatment (too rapid glucose level reduction, intensive hydratation, therapy with bicarbonates) the osmotic gradient changes excessively. Decrease in extracellular osmolality results in a shift of fluid into brain cells and causes osmotic brain edema. Nevertheless clinical studies do not confirm that sudden changes in the osmolarity are the main cause of cerebral edema (5-7). The hypothesis is also questioned by the fact that radiological tests performed in children before the DKA treatment can also show the presence of cerebral edema (6). Another potential cause of this complication is a brain hypoperfusion. Hipocapnia-induced cerebral vasoconstriction and coexisting large dehydration lead to hypoxia followed by cytotoxic edema at presentation. Cerebral hypoperfusion results also in releasing vasoactive substances and inflammatory mediators. This causes the blood-brain barrier impairment and development of vasogenic edema (6). Clinical research indicate that initially low partial pressure of carbon dioxide, low pH, high concentration of serum urea nitrogen, and a therapy with bicarbonates are the potential risk factors for cerebral edema (7,8). Alarm symptoms that may suggest the development of cerebral edema are headache, reduction in heart rate and increase in

blood pressure. Other signs include a change in the patient's neurological status, e.g. anxiety, irritability, increased drowsiness, urinary and fecal incontinence and the presence of specific neurological symptoms, e.g. cranial nerve palsy (9). The treatment of choice is an intravenous infusion of mannitol in a dose of 0,5-1 g / kg within 20 minutes (10). In addition, the volume of fluid infusion should be reduced by about 1/3 as well as the elevation of the patient's head is advisable.

Ischemic and haemorrhagic strokes account for approximately 10% of intracranial complications of DKA (11). It is worth noting that not all of them coexist with cerebral edema. However, it is not excluded that its presence predisposes to the development of other neurological complications (11). DKA is a procoagulant state in which reduction of protein C, increase in von Willebrand factor, disruption of fibrinolytic mechanisms associated with increase in plasminogen activator inhibitor (PAI- 1) are seen (12). DKA is also a pro-inflammatory condition, and oxidative stress induced by hyperglycemia contributes to the growth of CRP, IL-1 beta, IL-6 or TNF alpha (13). The procoagulant, and proinflammatory status may lead to the development of multifocal thrombotic or hemorrhagic lesions in the CNS. Clinically, a stroke may be manifested by focal signs, but the symptoms can also be nonspecific (like in the brain edema or resulting from ketoacidosis itself) which makes differential diagnosis difficult. When a stroke is diagnosed one should strive for a quick and effective treatment of possibly occurring conditions such as fever, infection, seizures. Due to the insufficient amount of evidence for the safety and efficacy of thrombolysis in the treatment of an ischemic stroke in the pediatric population, most international guidelines do not recommend such treatment. However, a few cases of a good therapeutic effect of this method were described in children (14,15). There is also a case report of a successful thrombolysis in a 10-year-old female patient with DKA and cerebral venous sinus thrombosis (16). Early start-up and rehabilitation are recommended in every type of a stroke (13).

In our clinical practice we experienced several neurological complications of DKA in our patients such as brain edema or vasogenic brain lesions (**figure 1**).

In the end we would like to highlight that patients with DKA require careful monitoring of neurological functions and early diagnosis and treatment can improve the patient's outcomes.

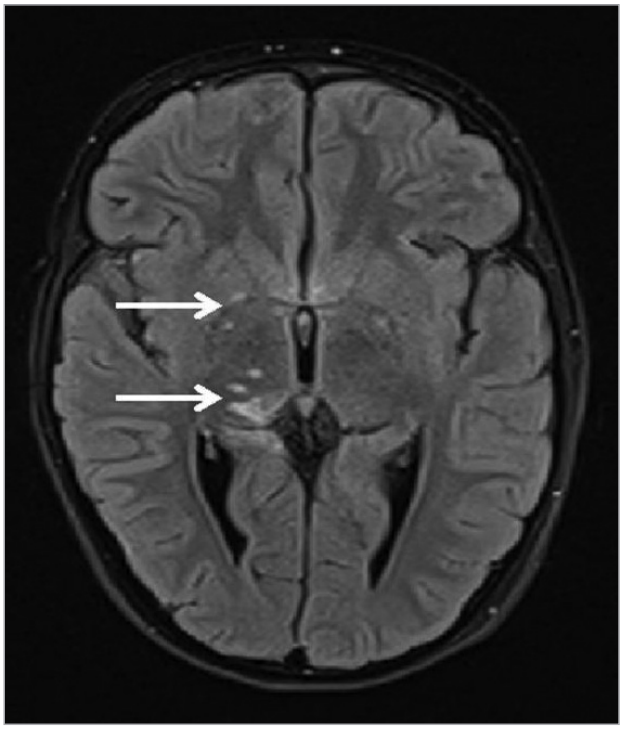


Figure 1. Brain MRI, FLAIR seq. Vasogenic lesions in the right thalamus and lenticular nuclei

Disclosure

All authors have nothing to disclose.

References

1. Martínez E, Portillo N, Lizarralde E, Grau G, Vela A, Rodríguez A, Rica I. For Debate: Paediatric T1DM: DKA is Still a Problem. Pediatr Endocrinol Rev 2018 Dec;16(2):233-239
2. Szypowska A, Dżygało K, Wysocka-Mincewicz M, Mazur A, Lisowicz L, Ben-Skowronek I, Sieniawska J, Klonowska B, Charemska D, Nawrotek J, Jałowiec I, Bossowski A, Jamiołkowska M, Pyrżak B, Rogozińska I, Szalecki M. High incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes among Polish children aged 10-12 and under 5 years of age: A multicenter study. Pediatr Diabetes 2017;18(8):722-728
3. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, Imperatore G, D'Agostino RB Jr, Mayer-Davis EJ, Pihoker C. SEARCH for Diabetes in Youth Study Group. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics 2014;133:e938–e945
4. Edge JA, Hawkins MM, Winter DL. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. Arch Dis Child 2001;85:16–22
5. Levin DL. Cerebral edema in diabetic ketoacidosis. PediatrCrit Care Med 2008;9:320–329
6. Bialo SR, Agrawal S, Boney CM, Quintos JB. Rare complications of pediatric diabetic ketoacidosis. World J Diabetes 2015;15;6(1):167–174
7. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M, Malley R, Kuppermann N. Risk Factors for Cerebral Edema in Children with Diabetic Ketoacidosis. N Engl J Med 2001;344:264-269
8. Lawrence SE, Cummings EA, Gaboury I, Daneman D. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. J Pediatr 2005;146(5):688-692
9. Wolfsdorf JI, Allgrove J, Craig ME. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatric Diabetes 2014:15(Suppl. 20):154–179

10. Aleksandra Araszkiewicz, Elżbieta Bandurska-Stankiewicz, Andrzej Budzyński, Katarzyna Cypryk, Anna Czech, Leszek Czupryniak, Józef Drzewoski, Grzegorz Dzida, Tomasz Dziedzic, Edward Franek, Danuta Gajewska, Maria Górska, Władysław Grzeszczak, Janusz Gumprecht, Barbara Idzior-Waluś, Przemysława Jarosz-Chobot, Zbigniew Kalarus, Tomasz Klupa, Teresa Koblik, Andrzej Kokoszka, Anna Korzon-Burakowska, Irina Kowalska, Adam Krętowski, Lilianna Majkowska, Maciej Małecki, Artur Mamcarz, Barbara Mirkiewicz-Sieradzka, Wojciech Młynarski, Dariusz Moczulski, Małgorzata Myśliwiec, Krzysztof Narkiewicz, Anna Noczyńska, Paweł Piątkiewicz, Joanna Rymaszewska, Jacek Sieradzki, Bogdan Solnica, Marek Strączkowski, Krzysztof Strojek, Agnieszka Szadkowska, Małgorzata Szelachowska, Ewa Wender-Ożegowska, Bogna Wierusz-Wysocka, Bogumił Wolnik, Mariusz Wyleżoł, Edward Wylęgała, Dorota Zozulińska-Ziółkiewicz. 2018 Guidelines on the management of diabetic patients A position of Diabetes Poland. Clinical Diabetology 2018;7(1):1-90
11. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990;13:22–33
12. Carr ME. Diabetes mellitus: a hypercoagulable state. J Diabetes Complications 2001;15(1):44-54
13. Foster JR, Morrison G, Fraser DD. Diabetic ketoacidosis-associated stroke in children and youth. Stroke Res Treat 2011;2011:219706
14. Belvís R. Thrombolysis for acute stroke in pediatrics. Stroke 2007;38(6):1722-1723
15. Benedict SL, Ni OK, Schloesser P, Bale JF. Intra-arterial thrombolysis in a 2-year-old with cardioembolic stroke. J Child Neurol 2007;22(2):225-227
16. Zerah M, Patterson R, Hansen I, Brione M, Dion J, Renfroe B, Resolution of severe sinus vein thrombosis with super selective thrombolysis in a pre-adolescent with diabetic ketoacidosis and a prothrombin gene mutation. Journal of Pediatric Endocrinology and Metabolism 2007;20(6):725–731

2019 Annual Meeting of the Pediatric Endocrine Society: Selected Highlights Baltimore, MD (April 26-29, 2019)

Danielle Guiffre[1], MD, Grace Kim[2], MD, Meenal B. Gupta[2], MD

[1]Children's Hospital Los Angeles, 4650 Sunset Blvd, MS #61, Los Angeles, CA 90027, USA,
[2]Texas Children's Hospital, Baylor College of Medicine, 6701 Fannin St, Suite 1020, Houston, TX 77030, USA

Corresponding author: Danielle Guiffre, MD, Children's Hospital Los Angeles, 4650 Sunset Blvd, MS #61, Los Angeles, CA 90027, USA, E-mail: dgiuffre@chla.usc.edu

Ref: *Ped. Endocrinol. Rev. 2019;17(1):50-62*
doi: *10.17458/per.vol17.2019.gkg.mr.2019annualmeetingbaltimore*
Key words: *Hypothyroidism, Thyromimetics, Hypertriglyceridemia, Hyperchylomicronemia, Familial hypercholesterolemia, Mixed dyslipidemia, Turner syndrome*

The Hot Topic/Topic Symposium entitled: "Alternative Therapies for Hypothyroidism and Thyromimetics" was presented by Jacqueline Jonklaas, MD (Georgetown University, Washington DC, USA). Dr. Jonklaas reviewed the standard-of-care treatment for hypothyroidism, and discussed the knowledge gap remaining in therapies for hypothyroidism as well as potential roles for thyromimetics.

Standard-of-Care Treatment for Hypothyroidism

Dr. Jonklaas began by describing the history of treatment of hypothyroidism, including that prior to the 1980s, when thyroid extract was largely used followed by the increasing use of synthetic levothyroxine. She highlighted that, currently, levothyroxine prescriptions in the US have reached over 120 million per year, overtaking many other commonly prescribed medications, including acetaminophen/hydrocodone, Lisinopril, and atorvastatin. The preference for levothyroxine monotherapy has been based on its efficacy, favorable side-effect profile, ease of administration, good intestinal absorption, long half-life, and low cost.

Dr. Jonklaas then pointed out that, despite all of these supporting reasons to use levothyroxine monotherapy, there is a continued struggle to maintain TSH within the normal range in many patients. Each individual person may have a slightly different TSH set-point at which normal T4/T3 levels are maintained. As evidenced by multiple studies conducted between 1990-2009, only between 40-60% of patients on levothyroxine therapy achieve a TSH level in the desired range.

Knowledge Gaps

Dr. Jonklaas then touched on the current knowledge gaps in treatment of hypothyroidism that could lead to the difficulties in maintaining the serum TSH within the desired

range. She highlighted a study done in 2002 by Saravanan *et al* (1), who distributed satisfaction surveys to patients taking levothyroxine comparing those on levothyroxine with well-controlled TSH levels to euthyroid controls. The survey results suggested that patients on levothyroxine replacement even with a normal TSH report more dissatisfaction than the controls. A second study by Peterson *et al*. in 2016 (2) used the NHANES database to examine levothyroxine users compared to matched controls for age, sex, race, and TSH level. Those on levothyroxine treatment had significantly higher body mass index, beta-blocker use, statin use, and anti-depressant use. She particularly noted that these differences were not associated with T3/FT4 ratios, removing any possible confounder effect. She further described a study done in 2015 by Jorgensen *et al* (3) that surveyed hypothyroid individuals on self-reported health status. She highlighted a specific difference between those that knew that they were diagnosed with hypothyroidism at baseline versus those who did not know they had hypothyroidism at baseline (those that did not report having the diagnosis, but had laboratory results consistent with hypothyroidism). The majority of those that had no knowledge of their condition reported good baseline health (83%), compared to 49% that were aware. Dr. Jonklaas used this example to illustrate that self-reported patient measures can be difficult to interpret. She used another study done by Boesen *et al* in 2018 (4) to help confirm this. They used a survey to assess quality of life in patients with hyperthyroidism. In respect to measures of anxiety and tiredness, retrospective scores were both higher than momentary (present) scores. Of note, all of these surveys carry an inherent reporter bias, as those who feel unwell are more likely to participate in surveys. To begin to investigate a possible etiology for why patients with normal TSH levels on levothyroxine still do not feel well, she conducted a study in 2008 (5) of 50 euthyroid patients who underwent thyroidectomy (for diagnoses of euthyroid goiter, benign nodular disease, or suspected thyroid cancer) and required levothyroxine placement afterwards. As compared to when they had native euthyroidism, both the free T4 and free T4/T3 ratio were significantly higher on treatment with levothyroxine to maintain the same TSH. A similar cross-sectional study in 2011 (6) showed that 15% of patients on levothyroxine post-thyroidectomy with TSH levels that were similar to their prior (native euthyroid) level, had low free T3 levels.

Alternative Therapies: Combination Therapy

Dr. Jonklaas then attempted to summarize the current evidence for and against "combination" T4/T3-containing products. Relevant studies [14 in total (7-16)] on this topic are very different in terms of types of patients, study design, dosing regimens, outcomes measures, and durations of treatment. This makes it difficult for an accurate meta-analysis to be performed. Additionally, the studies took place between 1999-2016. Most of them used TSH, free T4, and T3 as endpoints; however, in some studies, the TSH achieved in the combination group was lower than normal and in some higher than normal, further highlighting the variability between the different studies. Additionally, quality of life was a measure in the majority of the 14 studies; however, only two of the 14 studies showed superiority of the combination therapy compared to monotherapy in this regard. A similar heterogeneity was found for neurocognitive functioning. One trial showed superior neurocognitive functioning on combination therapy, while the rest did not. Finally, Dr. Jonnklaas highlighted the fact that patient preference was studied in five of the cross-over trials and in two of the parallel trials. Combination therapy was actually the preferred treatment in four of the five cross-over trials and in one of the two parallel trials.

Alternative Therapies: Thyroid Extract

Dr. Jonklaas next reviewed a randomized controlled cross-over trial performed by Hoang *et al* in 2013 (17) over 16 weeks comparing levothyroxine to thyroid extract therapy. Using thyroid extract did not result in any significant improvement in quality of life; however, it was associated with a very modest weight loss, which resulted in a greater patient preference for its use.

Alternative Therapies: T3 Monotherapy

Dr. Jonklaas next described a double-blind, cross-over, randomized, controlled trial (RCT) reported in 2010 by Celi *et al* (18) in which T3 monotherapy was compared to T4 monotherapy. The study showed comparable maintenance of TSH levels, but with a small decrease in weight and LDL in the group on T3 monotherapy. As part of the study, both treatments were given thrice daily, which Dr. Jonklaas suggested is less feasible for many patients. Despite the possible benefits found in the studies described above, there remain many risks of combination therapy including T3 thyrotoxicosis, cardiac arrhythmias, and decreased bone mineral density. The full degree of risk is not known, as long-term trials have not been performed. There also is insufficient information about the use of combination therapy in the elderly and pediatric populations. In fact, it is known that endogenous serum T3 levels are fairly consistent throughout the day, without large peaks or troughs, compared to the levels achieved through daily or twice-daily dosing of T3,

which yields high peaks not seen with endogenous secretion, possibly increasing the risk for the above complications.

Alternative Therapies: Combination Therapy with Sustained-Release T3

Dr. Jonklaas next reviewed another alternative therapy, sustained-release T3, which is still under development. She reviewed a study from 2004 (19) that tested an early-phase preparation of a sustained-release formulation of T3 combined with T4. The group that received the combination showed a steadier secretion of T3 compared to that seen with T4 monotherapy and the current T3/T4 combination therapy. However, no further development has occurred to bring this preparation to the market. In 2014, Santini *et al* (20) used a sustained-release T3 sulfate preparation and measured T3 concentrations over 48 hours. The serum levels showed a fairly extended duration of the serum T3 concentration, peaking at an average of 25 ng/dL ~5 hours after ingestion and remaining above 20 ng/dL for 48 hours. Although this preparation showed promise, there has been no further development.

Combination Therapy: Physician Consideration Towards Prescription

One unique consideration that could influence physicians to prescribe combination therapy is whether or not there is a polymorphism present in the genes that alter thyroid hormone synthesis. The presence of one specific polymorphism, called the Thr92Ala polymorphism, has been hypothesized to influence the enzymatic function of the deiodinase-2 gene (D2). This gene encodes the enzyme that converts the prohormone T4 to active T3. A retrospective study done in 2009 (21) of 552 patients on thyroid hormone replacement therapy with known genotyping information, found that 16% of patients had the Thr92A1a polymorphism. While this did not impact circulating thyroid hormone levels, this polymorphism conferred significantly worse health questionnaire scores compared to those without the polymorphism, as well as a better response to combination therapy. The results of this study showed marginal statistical significance and should be interpreted with caution given that these findings have not been replicated prospectively. In fact, a study in 2017 by Wouters *et al* (22) looked at how the presence of the Thr92Ala polymorphism of D2 affects health-related quality of life and cognitive function by comparing levothyroxine users to the general population. They found no difference in either measure or thyroid function parameters between those on levothyroxine therapy and the general population. A third study in 2017 by Castagna *et al* (23) compared Free T3, Free T4, and TSH, and D2 (Thr92A1a) polymorphism status in patients who underwent thyroidectomy. They did not find any difference in either baseline or post-thyroidectomy TSH, Free T4, or T3/T4 levels between those without and without the D2 polymorphism. However, they did find a significantly lower Free T3 in those with the polymorphism, which they hypothesize, could indicate an area of opportunity for use of combination therapy. As part of a study that Dr. Jonklaas conducted in 2017 (24), a survey was distributed to members of the American Thyroid Association (ATA) to assess their willingness to prescribe combination therapy based on various patient factors. A case was presented which described a 29-year old female with Hashimoto thyroiditis receiving 100 mcg/day of Levothyroxine. The patient requested combination therapy despite being clinically and biochemically euthyroid. The survey revealed that about half of the respondents would add T3 to her regimen. A similar case was presented in which the patient also had participated in a study that revealed a genetic polymorphism "that showed she had a genetic problem converting T4 to T3" and even more ATA members were willing to add T3 therapy to her regimen (70%).

Combination Therapy: Pediatrics

Dr. Jonklaas next summarized studies of the use of T3 in children. Only one was an RCT that included patients with congenital hypothyroidism treated with levothyroxine monotherapy and a comparator group receiving combination therapy [Cassio, *et al* 2003 (25)]. Fourteen patients were enrolled, without any significant difference in thyroid hormone analytes or psychomotor outcomes between the treatment and control group after study completion. Another study done by Paone *et al* in 2016 (26) compared patients with congenital hypothyroidism treated with levothyroxine monotherapy to those with T3 added due to persistent TSH elevation. They were able to show that combination therapy is able to lower the TSH effectively and raise T3 levels in the treatment group, suggesting that combination therapy may be beneficial in cases of apparent TSH resistance to T4.

Combination Therapy: Future Trials

Dr. Jonklaas suggested that all of the factors discussed in this symposium may need to be taken into account when developing future trials assessing the validity of combination therapy.

Thyromimetics

Dr. Jonklaas lastly touched on the current and potential future uses of thyromimetics in clinical application. She reviewed the concept of tissue-specific thyroid hormone action including

thyroid hormone-alpha receptors located in the brain, heart, and skeletal muscle versus thyroid hormone-beta receptors in the liver and brain. Given their predominance in the liver, potential uses of thyroid hormone-beta receptor agonists include treatment of hyperlipidemia, atherosclerosis, weight reduction, diabetes, NASH/NAFLD, and pre-neoplastic liver lesions. She listed the medications currently being studied, including Sobetirome and Eprotirome, two thyroid hormone-beta receptor agonists that have gone through phase 1 trials with some improvements seen in body fat percentage and LDL (27). However, both trials were terminated due to adverse effects in animal models. Two other compounds (MGL-3196 and VK2809) are currently in phase 2 trials and show promising reductions in liver fibrosis, LDL, and liver fat by MRI without any major side effects.

The Meet-the-Professor session entitled: "Lipid Disorders in Children - Complex Cases" was presented by Ambika Ashraf, MD (University of Alabama, Birmingham, AL USA). Dr. Ashraf presented various cases of complex lipid disorders in pediatric patients and discussed how to approach and manage the different types.

Approach to Hypertriglyceridemia

Dr. Ashraf's first objective was to explain how to approach elevated serum triglycerides (TG). She began with a published case presentation of a 10-year-old female, with a body mass index (BMI) of 13.7 kg/m^2 and a history of three episodes of pancreatitis in the previous year, with a waxing-and-waning course of hypertriglyceridemia (28). The patient did not have hepatosplenomegaly or xanthomata. The family history was positive for lupus and multiple sclerosis. The child's total cholesterol (TC) was 209 mg/dL and TG were 4,784 mg/dL. The patient's blood sample was lipemic and, after sitting out overnight, had a creamy floating chylomicron layer on top, diagnostic of hyperchylomicronemia.

Dr. Ashraf then went through the differential diagnosis of hyperchylomicronemia. Monogenic mutations in the gene encoding lipoprotein lipase (LPL), the main clearance mechanism for TG, or in those encoding cofactors for LPL should be considered as the basis for severe hypertriglyceridemia that presents in the pediatric population. At least five monogenic gene mutations have been identified: LPL, APOC2, APOA5, LMF1, and GPIHBP1 (29). These mutations typically present in infancy, although some (APOC2, APOA5, and LMF1) may rarely present later in life (30). Other causes considered were polygenic mutations, namely a group of several minor gene variations that collectively lead to hypertriglyceridemia. However, they tend to manifest in the setting of secondary factors such as obesity, weight gain, or diabetes, or are drug-induced. Lipodystrophy and von Gierke disease were also mentioned as possible causes, each with specific phenotypic characteristics. The last etiology examined was autoantibodies to components or cofactors of LPL (31). Two autoantibodies are known to inhibit LPL activity: LPL and GPIHBP1 antibodies (28,32,33). Older patients can present with an oscillating course and may have a family history of autoimmune disease, consistent with that of the presented patient. Autoantibodies against LPL can be associated with other systemic diseases (e.g. lupus, Sjogren syndrome, or Hodgkin lymphoma) and may require immunosuppressive therapy. Also noted was that hypertriglyceridemia may be the first autoimmune clinical manifestation. The presented clinical patient was found to have LPL autoantibodies.

She then reviewed TG metabolism and how to identify the predominantly elevated TG-rich lipoprotein, which facilitates the treatment plan. The serum TG concentration is determined by its rates of synthesis and clearance. TG are synthesized either in response to dietary fat absorption and packaged into chylomicrons or endogenously produced in the liver and packaged into very-low-density lipoproteins (VLDL). Accordingly, postprandial concentrations of TG are transported mostly by chylomicrons, and fasting TG (for at least 8-12 hours) concentrations are represented by VLDL. Moreover, the liver generally produces <500 mg/dL of VLDL. If the serum TG is >500 mg/dL, most likely dietary fat is being transported by chylomicrons and, thus, it is important to repeat the testing with fasting levels. Next, the clearance of TG is primarily mediated via LPL. LPL is stimulated by apolipoprotein C-II and insulin. In states of insulin resistance or deficiency, the clearance activity of LPL will be decreased, leading to elevated levels of chylomicrons and TG. If LPL is temporarily defective, such as with diabetes, insulin can be given to activate the LPL, whereas, if it is completely defective, such as occurs with some genetic mutations, insulin or other medications will not be effective. Therefore, if TG is >500 mg/dL, any additional dietary fat will exponentially increase TG. Hence, fasting is the primary way to initially decrease elevated levels of TG caused by elevated chylomicrons. There are other emerging targeted therapies, including inhibition of the APOC3, ANGPTL3, ANGPTL4, MTTP and DGAT-1 proteins, directed at improving the activity of LPL for clearance or targeting TG-rich lipoprotein synthesis (34).

The management of a patient with very severe hypertriglyceridemia (>2000 mg/dL) was then reviewed (30). First-line treatment is fasting for at least the first 48-72 hours, as it is likely that much of the elevated TG is composed of chylomicrons. Patients with severe cases presenting with end-organ damage, shock, or severe pancreatitis may need plasmapheresis. Insulin can be used if there is residual LPL activity, such as occurs in diabetes, to help stimulate clearance of TG. Fibrates and omega-3 fatty acids will not work acutely in the absence of LPL activity, but can be

considered when TG levels are lower. It is also essential is to exclude secondary causes and to control metabolic risk factors. If TG remain elevated after fasting, the next step is to initiate a stringent dietary restriction of fat to <10-15% of the total daily energy intake. Patients need to be educated about the strict low-fat diet as a vital part of long-term management. For genetic causes of hypertriglyceridemia, the TG target is <500 mg/dL in order to decrease the risk of developing pancreatitis. For secondary causes of hypertriglyceridemia, if the TG is <1000 mg/dL, the initially recommended significant restriction of fat may be relaxed slowly to less stringent criteria to maintain target TG levels. For rare autoimmune etiologies, immunosuppressive therapy may be needed.

To further expand upon management of more common forms of hypertriglyceridemia, a second case was presented, i.e. that of a 16-year-old obese female with a BMI of 44 kg/m2 and type 2 diabetes who presented in diabetic ketoacidosis. Lab testing showed: HbA1c 11.4%, glucose 343 mg/dL, and bicarbonate 14 mmol/L. TC was 545 mg/dL, TG 7,200 mg/dL, and high-density lipoprotein cholesterol (HDL-C) 26 mg/dL. In the blood sample tube, there was a creamy top layer of chylomicrons and, just below it, was a more dense brown layer of VLDL lipoproteins. VLDL contains many atherogenic particles. Due to having high levels of chylomicrons, the patient was made NPO and started on an insulin drip. Afterwards, her TC level decreased to 318 mg/dL, TG decreased to 1985 mg/dL, and HDL-C increased to 34 mg/dL. The next step was deciding which medication to add.

Before considering further management, Dr. Ashraf suggested another means to determine if there are more TG or VLDL present in the blood. TG are present in four lipoproteins (chylomicrons, chylomicron remnant, VLDL, and VLDL remnants). The most TG-rich lipoprotein are chylomicrons, for which the TG/TC ratio is >8:1. This is followed by chylomicron remnants, VLDL with a TG/TC ratio of 5:1, and finally VLDL remnants for which the TG/TC ratio is close to 1:1. Therefore, the ratio of TG to TC can be calculated to determine the predominant lipoprotein. Dr. Ashraf again stressed the importance of repeating fasting lipid profiles once patients are euglycemic. If there are mostly chylomicrons present (i.e., ratio TG/TC is >8:1), treatment should start with being made NPO. If there are more VLDL, (i.e., ratio of TG /TC is <8:1), then one should treat with a fibrate or a statin (30).

Another important factor to consider in evaluating lipid profiles is the non-HDL-C concentration. Non-HDL-C is TC minus HDL-C. As a result, non-HDL-C represents all atherogenic particles [low-density lipoprotein (LDL), intermediate-density lipoproteins (IDL), VLDL, and chylomicron remnants]. Most of these particles contain apoliprotein-B100 (apoB-100). Accordingly, apoB-100 is a non-HDL-C substitute. VLDL and IDL are TG-rich lipoproteins with a substantial content of cholesterol. If TG is >200 mg/dL, one can use non-HDL-C as an alternate therapeutic target as per national guidelines (35,36).

Dr. Ashraf then discussed the long-term medical management of hypertriglyceridemia. In general, data on management of hypertriglyceridemia in children are sparse (29,30). Data on adults show that fibrates may decrease TG by 40-60% (34). Fibrates activate PPAR-α, reduce synthesis of VLDL, and augment the activity of LPL (if not completely defective or saturated). However, there are side effects from fibrates that include dyspepsia, diarrhea, cholelithiasis, and transaminitis. Additionally, fibrates should be used with caution in patients with renal dysfunction and gall bladder disease.

Another triglyceride-lowering medication is omega-3 fatty acids. This effect depends on the content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). This approach also largely reduces the production of VLDL and, to some extent, activates LPL. It additionally prevents lipolysis of adipose tissue. Data in adults have shown that four prescription-strength capsules daily (465 mg/375 mg of EPA/DHA per capsule = 3360 mg) reduces TG by 20-30% (37,38) However, over-the-counter omega-3 fatty acids have much less EPA and DHA (39). Data in children have failed to show a significant lowering effect by omega-3 fatty acids on TG.

In summary, the management of chronic hypertriglyceridemia includes reducing the intake of dietary fat, eating low-glycemic foods, eliminating sugar-sweetened beverages (as dietary glucose can be converted to acetyl CoA, which can be used to make free fatty acids and then TG), restricting the intake of excess calories, and incorporating one hour per day of moderate-to-vigorous physical activity. Weight loss is critical, as it improves insulin sensitivity, reduces release of free fatty acids from adipose tissue, and enhances activity of LPL. Medications, such as fibrates, omega-3 fatty acids, and statins, may also be needed to reduce overall production of VLDL.

Approach to Elevated LDL-C

The next case presentation was that of an 18-year-old female with numerous tendinous and tuberous xanthomata in her antecubital and popliteal fossae, axillae, elbows, knees, hands, and feet, since 6 years of age. The family history was significant for early coronary artery disease (CAD) in the father at 34 years of age, in a maternal aunt in her 40's, and in the maternal grandmother who died suddenly at 45 years of age. The lipid profile in this patient showed TC 694 mg/dL, LDL-C 542 mg/dL, TG 80 mg/dL, and HDL-C 40 mg/dL. The patient had homozygous familial hypercholesterolemia (HoFH), the hallmark being LDL-C >400 mg/dL and development of tendinous xanthomata prior to age 10 years.

Dr. Ashraf then compared the differences between HoFH and heterozygous familial hypercholesterolemia (HeFH). HoFH is

rare, with a prevalence of 1:1,000,000, and characterized by extremely high levels of TC and LDL-C. Commonly LDL-C is >400 mg/dL, with presence of tendon xanthomata prior to age 10 years of age. Early diagnosis and treatment for HoFH is critical because it is associated with very early CAD within the first two decades of life. Management is aggressive and involves administration of several medications and adjuvants. HeFH is relatively common, with a prevalence of 1:250-500. It is associated with LDL-C >160 mg/dL and non-HDL-C >190 mg/dL, and may have no physical examination findings in childhood. CAD is not seen until the 4th or 5th decade of life, which is why universal screening in children is recommended as per the Expert Panel Guidelines (35). Treatment involves diet, lifestyle changes, and usually statin therapy, with or without other medications.

She then reviewed uptake and metabolism of LDL. LDL attaches to the LDL receptor (LDLR) on hepatic cells, which then undergoes endocytosis via clathrin-coated pits and the LDL-adaptor protein. Then there is LDLR-ligand dissociation, LDL is degraded, cholesterol is metabolized, and LDLR is recycled to the cell surface to undergo further uptake of LDL from the blood stream. Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates degradation of LDLR. Uptake of LDL by hepatic cells decreases HMG CoA reductase activity, leading to decreased synthesis of endogenous hepatic cholesterol. Dr. Ashraf stated that the LDL clearance system is normally very efficient and protects against very high levels of LDL-C. Even with a high-fat diet and obesity, LDL-C levels are generally <160 mg/dL.

Familial hypercholesterolemia (FH) is composed of a group of conditions with elevated LDL-C caused by defects in the uptake and metabolism of LDL, clinically presents starting in childhood, and is associated with premature cardiovascular disease (CVD). There are three autosomal dominantly inherited etiologies for FH: deleterious mutations in the LDLR, mutations in APOB gene (resulting in a defective apo-B100 protein that poorly recognizes LDLR for clearance), and gain-of-function mutations of PCSK9 (which degrades and reduces LDLR). An autosomal recessive form also exists and involves mutations in LDLRAP1 (which leads to a defective adaptor protein).

Treatment involves administration of various lipid-lowering medications that have different sites of action. Statins are classically first-line medications and inhibit production of endogenous cholesterol. Ezetimibe inhibits intestinal absorption of dietary cholesterol. Bile-acid sequestrants also inhibit absorption of dietary fat. PCSK9 inhibitors, a newer class of medications, inhibit the degradation of LDLR, thus increasing LDLR for increased clearance of LDL.

Genetic testing is not needed to distinguish HoFH from HeFH, as clinical management is not changed by knowing this information. The probability of FH is 80% if LDL >190 mg/dL. Also, negative testing does not exclude FH, as a mutation may not be found in up to 20% of cases. FH should be considered in a patient with LDL-C >160 mg/dL or non-HDL-C >190 mg/dL, and a positive family history (two or more affected first-degree relatives) of increased LDL-C/premature CVD.

To treat children with elevated LDL-C, it is necessary to evaluate the risk factors for CVD and the family history in relation to the LDL-C concentrations as per Expert Panel Guidelines (35). Treatment starts with the CHILD-2 diet and lifestyle intervention with or without statin therapy, depending on levels and risk factors.

Approach to Mixed Dyslipidemia

The final case was a 10-year-old obese male with BMI in the 99th percentile, who had been trying to diet and exercise. He had fluctuating lipid panels since 7 years of age. His TG concentrations ranged from 196 to 277 mg/dL, LDL-C 133 to 154 mg/dL, and non-HDL-C 178 to 192 mg/dL. At 10 years of age, he had lost weight and his lipid panel improved, with TG 91 mg/dL, LDL-C 103 mg/dL, and non-HDL 132 mg/dL. He had not met any criteria to start medication therapy. However, when he had repeat levels performed at 13 years of age, his TG increased to 384 mg/dL, LDL-C increased to 163 mg/dL, and non-HDL-C increased to 240 mg/dL.

His laboratory results before age 10 years, along with an improved lipid profile with weight loss, were consistent with metabolic syndrome at that time. However, lab results in subsequent years showed significantly elevated non-HDL >190 mg/dL and LDL-C >160 mg/dL, plus one risk factor (obesity), meeting criteria to start statin therapy (35). Dr. Ashraf pointed out that there is a normal physiological 10-20% reduction in levels of lipids in early puberty, and that lifestyle changes can contribute potentially to another 10% reduction. These results can give false reassurance if not continually monitored.

This clinical picture of mixed dyslipidemia (elevated LDL-C, non-HDL-C, and/or TG) can be acquired or genetic. Causes of the acquired form include metabolic syndrome, type 1 or type 2 diabetes, or secondary dyslipidemia (drugs, systemic disorders, etc.). Genetic causes include familial combined hyperlipidemia (FCHL), dysbetalipoproteinemia (which is rare, usually both TC and TG are elevated to 300-500 mg/dL and presents with palmar xanthomata as adults), and lysosomal acid lipase deficiency (which is associated with elevated transaminases).

FCHL is the most common genetic hyperlipidemia, with a prevalence of 1:100. It is autosomal dominant, with incomplete penetrance (may have several defects from several genes). The pathophysiology involves uncontrolled overproduction of apoB-100 relative to LDL-C. Consequently, non-HDL-C is elevated and the apoB-100/LDL-C ratio is >1.

This finding frequently is not manifested until after physiologic pubertal insulin resistance occurs. Diagnosis of FCHL is important, as it leads to premature CVD; FCHL has been reported in 40% of all survivors of myocardial infarctions (40). Patients and relatives have marked variability in lipid profiles, as well as increased levels of cholesterol (LDL-C/non-HDL-C), TG, or both. Additionally, the affected lipoproteins may shift from only one abnormality to the other over time. Manifestation of FCHL commonly requires secondary factors (metabolic syndrome, insulin resistance, diabetes, drugs, etc.), as the gene-environment interaction triggers clinical expression. There is considerable overlap between the lipid profiles of FCHL and metabolic syndrome, and differences were distinguished. In metabolic syndrome, LDL-C typically does not exceed 160 mg/dL, and lipid profiles tend to improve with lifestyle and weight changes. In FCHL, non-HDL-C will be increased, and there is frequently a family history of dyslipidemia and premature CVD.

Dr. Ashraf concluded with a simplified overview of dyslipidemia in pediatrics (**table 1**, 35,41,42). She emphasized that medical nutritional therapy and lifestyle changes are integral components of treatment of all causes of dyslipidemia.

Overall dyslipidemia in pediatrics requires a systematic approach; one must take into account genetics, underlying conditions, diet, and lifestyle, and treat this young generation of patients for life to potentially prevent CVD. Pharmacological options may be instituted after all the factors that can lead to dyslipidemia have been addressed, taking into account that pharmacological interventions will likely be lifelong.

The PES Meet the Professor session entitled: "Update on Turner Syndrome" was presented by Karen Klein, MD (Rady Children's Hospital/University of California San Diego, San Diego, CA, USA). The objectives of this interactive presentation included discussions on growth, puberty induction, fertility options, cardiac monitoring, and general screening recommendations for patients with Turner Syndrome (TS) based on the most recent clinical practice guidelines (43). Dr. Klein began by thanking the committee members of the 2016 International Turner Syndrome consensus meeting and subcommittee members who were co-authors on her paper on estrogen replacement in TS published in 2018 (44). She also highlighted the 'family-friendly' version of these guidelines available on the Turner Syndrome Society website for patients and families (45).

Describing the classic phenotype of patients with TS including a list of characteristic features, Dr. Klein emphasized the importance of care by a multi-disciplinary team. She then discussed the type and frequency of chromosomal abnormalities in TS with 45,X being the most common-40-50%. She also pointed out that, although karyotypes, 46,XXdel(q24), 46,Xidic(X) (q24) are not considered TS, they are associated with premature ovarian failure (POF) (43).

Growth Hormone Therapy

Starting with the section on growth hormone (GH) therapy in patients with TS, Dr. Klein explained that, if the patient is short, treatment should be initiated by 4 years of age or at diagnosis (when diagnosed after 4 years age). She also highlighted the importance of initiating GH prior to estrogen therapy whenever possible. The starting dose for GH is 0.35 mg/kg/week. Oxandrolone, at a dose of 0.03 mg/kg/day, should be added to therapy after 10 years of age only when the patient is extremely short or if GH therapy is delayed without enough time for catch-up growth. It is not routinely recommended in all patients due to the risks of delayed breast development and virilization. The adult height of untreated TS patients is, on average, 8 inches (20 cm) shorter compared to the average female population. This unfavorable outcome

Table 1. Summary of Management of Pediatric Dyslipidemia

Diagnosis	Treatment
Low-density lipoprotein cholesterol (LDL)	LDL >190 mg/dL ➞ statin LDL 160-189 mg/dL + risk factor ➞ statin
Mixed dyslipidemia	TG 200-499 mg/dL 1st target: LDL-C to <130 mg/dL 2nd target: Non-HDL-C > 145 mg/dL ➞ statin
Triglycerides (TG)	TG >500 mg/dL ➞ Fibrate/omega-3 fatty acid TG >2000 mg/dL ➞ NPO, insulin (if diabetes)
Type 1 or type 2 diabetes mellitus	Type 1 diabetes LDL > 160 mg/dL ➞ statin LDL > 130 mg/dL + 1 risk factor ➞ statin Type 2 diabetes LDL > 130 mg/dL ➞ statin TG > 400 mg/dL ➞ fibrate
For all	Medical nutrition therapy and lifestyle changes are integral components

underscores the need for early GH therapy initiation in these patients. Dr. Klein cautioned that height varies widely among individual patients and current TS percentiles give us the best prediction of adult height without treatment. The main factors affecting predicted adult height (PAH) are pre-treatment height; mid-parental height (MPH); age and pubertal status at treatment initiation; dose, frequency, and duration of GH therapy; and timing of initiation of estrogen therapy. The consequences of delaying GH treatment include shorter height in childhood, limited time for treatment, failure to reach adult height potential, and postponement of estrogen therapy which can have negative psychosocial impact.

Dr. Klein then proceeded to present case-based discussions regarding GH therapy. Case 1 was a 4-year-old female with mosaic TS. She was on the 3rd percentile on the CDC growth chart with her MPH being on the shorter side. The audience was asked whether they would start GH therapy for this patient. Being short at 4 years of age, she met criteria for GH treatment. However, with her family being short, her genetic potential for growth was less and family's expectation of final adult height was also lower. Her mosaic genotype made it was difficult to predict her growth trajectory. Although outcomes are improved with early initiation of GH, in this case, both starting treatment and watchful waiting were reasonable options. Case 2 was a 5-year-old female with a 45,X karyotype whose height had declined by 2 percentile curves over the last year and who came from a tall family. Audience response indicated that 100% would start this patient on GH. Dr. Klein confirmed that, with the girl being greater than 4 years of age and having slowing growth and greater genetic potential, starting treatment was warranted.

Hormone Replacement Therapy and Induction of Puberty

The next section focused on optimal timing for estrogen replacement. Most girls with TS have hypergonadotropic hypogonadism so they need female hormone replacement therapy (HRT). HRT is initially administered for induction of puberty and subsequently for maintenance of secondary sexual characteristics, attaining peak bone mass, and normalizing uterine growth (for possible pregnancy later). Up to 1/3 of the girls with TS have spontaneous pubertal onset which is more common with a mosaic Turner karyotype that includes a 46,XX line. Menstrual cycles remain regular in only 6% indicating that spontaneous puberty and menarche are not predictors of long-term normal ovarian function. Dr. Klein then described luteinizing hormone (LH) and follicle-stimulating hormone (FSH) trends in patients with TS. She pointed out that, compared to the general population, a rise in LH occurred at an earlier age depending on the karyotype (46). The goal of estrogen therapy is to mimic normal puberty while maximizing height growth with minimal risk. Delaying estrogen therapy would be deleterious to bone health, uterine growth, and psychosocial health.

The discussion then turned to the importance of understanding the different forms estrogen. Estradiol is the natural form that binds to the estrogen receptor. Ethinyl estradiol is an analog; it is not metabolized to estradiol and consequently retained in target tissues longer. Conjugated estrogens, such as Premarin, are not estrogen precursors and the guidelines recommend against their use due to an increased risk of thromboembolic and cardiovascular risks compared to native estradiol. Regarding the route of delivery, Dr. Klein explained that the systemic route, which includes transdermal, depot and transvaginal routes, is more physiological as it avoids first-pass metabolism in liver. Accumulation of non-physiological forms of estrogen in the liver observed after oral dosing is associated with a pro-coagulable state and, therefore, increased risk of stroke. Currently, transdermal is the preferred route. The depot forms work very well, but, addition of an extra injectable medication for patients already on GH therapy, needs careful consideration. Transvaginal route is not used in young girls.

Dr. Klein emphasized that estrogen should be initiated at a low dose. She then referred to a table from the guidelines listing equivalent doses of low-dose estrogen formulations for pubertal induction (45). Based on individual growth and pubertal progression, the dose should be increased about every 6 months until an adult dose is achieved. For the transdermal route, the starting dose is 3-7 mcg/day. Currently, the lowest available dose in an estradiol patch (Menostar) is 14 mcg/day and the patch is replaced weekly. Therefore, the starting dose in a girl with TS would require the use of half of a patch weekly. In contrast, the lowest dose delivered by the Vivelle Dot patch is 25 mcg/day necessitating use of a quarter patch weekly. The key factors in choosing the right preparation include dose of estradiol delivered, dosing frequency, and acceptability of patch-cutting. The matrix patch can be cut; however, cutting a reservoir form would cause the active drug to leak out. Gel formulations are available in sufficiently low concentrations in some countries, but not in the United States. The cheapest option is Estrace, an oral formulation not typically used due to aforementioned risks. However, it may be a good alternative when transdermal forms are unavailable or per patient preference.

Dr. Klein then described the study of Ross *et al* (47), which investigated the concurrent use of ultra-low-dose estrogen with GH in pre-pubertal patients with TS. Th intent of this dual therapy was to improve height growth without affecting puberty. She explained that, while using ultra-low-dose estrogen therapy in this age group seemed reasonable physiologically, the study did not show sufficient advantage

in growth to risk premature thelarche. Moreover, long-term safety concerns and the exact estrogen dose needed remain unknown, so the guidelines committee would not recommend using it except for research.

The optimal timing of pubertal induction was then reviewed. Dr. Klein noted that induction should be initiated between 11 and 12 years of age, if gonadotropins are elevated or anti-Müllerian hormone (AMH) is low, with the goal of estrogen initiation being to mimic normal physical and social development. Contrastingly, if the gonadotropins are normal, patients should be observed for spontaneous puberty. It is crucial to start with a low dose of estrogen to optimize growth. With a 25-100% dose increment every 6 months based on response, breast buds develop, on average, in 6 months and overall progression to Tanner 4 breasts occurs in approximately 2.25 years similar to timing observed in the general population. Therapy must be individualized based on response and growth potential. Lower doses of estrogen may be continued longer if linear growth is good; alternatively, the time between dose increments can be shortened in an older patient with less growth potential remaining.

Case-based discussions on pubertal induction started with Case 3, an 11-year-old mosaic TS patient on GH therapy since age 4. She demonstrated catch-up growth, but had a slight drop on the last data point for height. She had no breast development yet and serum LH and FSH levels were 2 IU/L each. The audience was asked if this was the appropriate time to start estrogen therapy. Several audience members answered no. Dr. Klein explained that it was important to evaluate whether the drop in her height was a variation in measurement versus actual slowing of growth, and optimize her GH dose if not adequate. She emphasized the need to educate families that initiating estrogen therapy did not automatically signal the end of GH therapy. When LH and FSH levels are normal, it is appropriate to monitor for spontaneous puberty every 6 months. Additionally, this would be a good time to discuss fertility preservation with the family.

Case 4 was a 12-year-old patient with a 45,X karyotype who was started on GH therapy at 10 years of age with a good response. She had no breast development and her serum FSH was 40 IU/L. This high FSH indicated the need for estrogen therapy so she was started on low-dose estrogen. To allow more time for growth, the low-dose estrogen should be continued for at least 12 months prior to dose increment. In response to an audience question regarding the addition of oxandrolone to her treatment regimen, Dr. Klein clarified that, since the patient had a good response to GH, it would likely suffice to optimize her GH dose, and simply monitor serum IGF-I levels and height velocity in response to low-dose estrogen atop the GH.

Routine monitoring of LH and FSH levels is not recommended because very high estradiol levels are needed to normalize gonadotropins in these patients. Sensitive estrogen assays that use tandem mass spectrometry could guide dose titration; however, studies correlating the rise in estrogen levels with pubertal progression are lacking. Therefore, decisions to raise the estradiol dose should depend on physiological progression, clinical response, patient preference (growth versus breast development), and growth potential.

Since patients with TS typically have a normal uterus, progestins must be added once breakthrough bleeding occurs or after 2 years of estradiol treatment without breakthrough bleeding. This decreases the risks of irregular bleeding and endometrial cancer associated with unopposed estrogen action. The combined sequential approach, e.g. oral contraceptive pills, involves adding progestin for 10 days each month for withdrawal bleeding. The combined continuous approach involves giving estrogen and progestin continuously transdermally or orally, and typically does not result in menstruation; this is often preferred by older women.

Oral contraceptive pills (OCPs) are not used to induce puberty because the high amount of estrogen contained in OCPs may affect growth potential and lead to tubular breast development. OCPs may be useful in patients who undergo spontaneous puberty and breast development, but subsequently develop secondary amenorrhea. Ease of use also makes them preferable once adult dosing is achieved. However, OCPs increase the risk of thrombotic episodes; this risk is lower with micronized progesterone. Some studies have also shown unfavorable effects on bone density and blood pressure (BP), so the risk-benefit ratio of different formulations must be considered. Dr. Klein emphasized that compliance is more important than the preparation used because it is a very common to see patients going untreated in their 20's. The focus, therefore, should be to educate patients and to offer the simplest regimen.

For adult dosing, the preparation and dose of HRT depend on patient preference, size of uterus (possibility of future pregnancy via oöcyte donation), bone and body composition, quality of life, and blood pressure. However, most of the currently available information is based on treating other forms of hypogonadism or post-menopausal women; there are limited studies in patients with TS. Once adult dosing is reached, treatment should be continued until menopausal age to mimic normal physiology. Therapy should be individualized to minimize risks of breast cancer and mortality associated with long-term use. The dose, route, age of initiation, and duration of treatment are factors that affect uterine health and, therefore, prospect of future pregnancy. Other outcomes to consider include metabolic health, risk of thrombosis, and neurocognitive and socialization functions.

Fertility

Dr. Klein then proceeded to discuss a key outcome in patients with TS - fertility. According to several studies, the rate of

spontaneous pregnancies in patients with TS ranges from 4-8%, including in those with a 45,X karyotype. Compared to the general population, patients with TS have a higher risk of miscarriages, cesarean sections, and pre-eclampsia. Furthermore, the most important risk to discuss with patients and families is the risk of aortic dissection with pregnancy. Women with TS have a rapidly decreasing ovarian reserve. Studies assessing anti-Müllerian hormone (AMH) as a marker of ovarian function have proposed that levels of <2 or <4 pmol/L indicate no ovarian function (48). However, AMH levels are not an absolute predictor and should be used in conjunction with other variables. For the majority of patients with TS, oöcyte donation is the only way to achieve a viable pregnancy. It is important to point out to families that, per *in vitro* fertilization (IVF) cycle, the clinical pregnancy rate is about 8% and the live-birth rate is 5.7%.

Next, Dr. Klein explained the importance of talking to patients about fertility preservation and making timely referrals to a reproductive endocrinologist/gynecologist. Oöcyte cryopreservation is possible when ovarian function is intact. To date, no pregnancies from thawed oöcytes have been reported in patients with TS, but studies have been limited. Ovarian tissue cryopreservation is still considered experimental. Routine oöcyte retrieval, though not recommended, is available; appropriate timing of oöcyte retrieval remains a topic of debate. An earlier retrieval increases the chances of finding viable oöcytes, but performing ovarian stimulation in a patient just starting puberty would be hard to justify. However, if a patient is around 11-12 years of age with reasonable height and progression of puberty, oöcyte retrieval can be considered and should be discussed.

The next section of the talk focused on pregnancy cautions related to increased cardiovascular risk in patients with TS. The risk of aortic dissection (AoD) is 3-4%, and 75% of those AoD end in death (49). There is also 2-3-fold increased risk of hypertension. Dr. Klein stressed that every patient needs cardiac magnetic resonance imaging (CMR) prior to pregnancy. Ongoing cardiac monitoring is crucial during pregnancy; however, currently only about 50% of these patients are being followed from a cardiac perspective. When aortic dilation is present, based on an aortic size index (ASI) >2.5 cm/m^2, the guidelines recommend against pregnancy. Alternative options for motherhood such as adoption and gestational carriers should be discussed.

Cardiovascular Health Issues in TS

Overall cardiac monitoring in TS was discussed next. Cardiac abnormalities are the most frequent cause of early mortality. Dr. Klein noted that the new recommendation to perform CMR for closer monitoring was based on the fact that not all defects are visualized on transthoracic echocardiography (TTE). To emphasize this point, she then described a couple of real-life cases; both were patients of the cardiologist, Michael Silberbach, MD, who is an expert on TS. The first patient had a non-obstructive bicuspid aortic valve (BAV), coarctation of aorta that had been repaired in infancy, and well-controlled ulcerative colitis. She complained of chest pain on a Sunday and was prescribed antacids by her PCP. On the following Monday, her pediatric cardiologist endorsed the diagnosis of reflux. Then on Wednesday, she died suddenly from an aortic dissection. She was not exercising at the time of death. The second patient had BAV and mild aortic enlargement. A computerized tomography (CT) scan showed a striking aneurysm of left subclavian artery at age 18 years, but it had been overlooked by her internist cardiologist. At age 28 years, her fertility specialist referred her to a cardiologist who, unaware of the aneurysm, told her that assisted reproductive therapy (ART) was an acceptable option and wondered why there was a concern given her mild cardiac disease. Two embryos were implanted; no cardiac imaging was performed during her pregnancy. At 36 weeks, she had chest pain and was diagnosed with aortic dissection. Healthy twins were delivered, but she died 24 hours later. In light of these and other similar cases, Dr. Klein re-iterated the importance of regular cardiac monitoring and evaluations by a cardiologist experienced in assessing patients with TS.

Referring to the cardiac monitoring protocol from the guidelines, Dr. Klein explained that all newly diagnosed patients with TS should be evaluated by a cardiologist and have a TTE. A baseline CMR should be obtained once the patient is old enough to not require anesthesia. CMR should be repeated every 5 years in children with known heart disease and more frequently in patients at high risk, every 5-10 years in adults, during transition of care, and prior to anticipated pregnancy. Serial monitoring of aortic diameter helps guide medical management and timing of elective heart surgery. A resting electrocardiogram (ECG) with QTc measurement should also be obtained and further cardiac evaluation is warranted if the QTc interval is prolonged.

Health Surveillance for Comorbidities in TS

Other screening tests at diagnosis include a karyotype, a renal ultrasound (US), audiology evaluation, and thyroid function tests (TFTs). TFTs, a fasting lipid panel, and a fasting plasma glucose (starting at age 10 years) should be repeated annually. Serum LH and FSH should also be monitored, starting at age 10 years, if there are no signs of puberty. Starting at age 2-3 years, a celiac screen should be obtained every 2-3 years. An audiology evaluation should be conducted every 2-5 years.

Future Directions

Dr. Klein concluded by delineating future research areas including optimization of protocols for pubertal induction with corresponding optimum levels of circulating estradiol during each phase; optimizing dosing, preparation type, and timing of progestins; determining the appropriate formulations and duration for estrogen therapy based on their effects on bone and reproductive health. Moreover, studies are needed to determine optimal OCP preparations with particular focus on ascertaining the long-term effects of a week of placebo therapy in patients with TS, who inherently do not produce enough estrogen.

Audience Q&A

Dr. Klein then answered questions from the audience. In response to a question about the need for TTE, CMR, and EKG studies, Dr. Klein clarified that each of these modalities assessed different aspects of cardiovascular health, and were, therefore, all recommended. Regarding the criteria that children should be 4 years old before starting GH therapy, Dr. Klein explained that studies, albeit of a limited number, did not show significant benefit in adult height when therapy was started before age 4 years. However, GH could be started sooner in patients that are clearly falling off the growth curve. Another audience member brought up a case of a 4-year-old female with antenatal diagnosis of TS, who was short, but had a normal height velocity. The family was asking for GH therapy, but hesitant to optimize calorie intake first for fear of her becoming overweight. Dr. Klein discussed that patients with TS are often at the top on the TS growth chart at around 4 years age, but at the bottom on the regular growth chart. So, in this patient, GH could be considered, but optimizing nutrition was also important. The next question was whether combined contraceptive patches could be used in patients with TS. To this, Dr. Klein and another audience member responded that the lower doses of estrogen contained in those patches would not adequately provide the dose needed in patients with TS. When questioned about the value of obtaining serum AMH levels along with gonadotropins to guide the timing of pubertal induction, Dr. Klein explained that all three levels, in conjunction, would be helpful to ascertain an individual patient's fertility potential rather than the timing of pubertal induction. Lastly, an audience member asked about hesitancy of continuing GH therapy for patients with TS who had IGF-I levels persistently > 2 standard deviations and if low-dose estradiol causes any rise in IGF-I levels. Dr. Klein replied that, while those were valid concerns, there are no data available to determine the appropriate duration of GH therapy in these patients or for assessing the effect of estradiol on IGF-I levels.

Acknowledgments

The authors thank Dr. Mitchell Geffner, Pediatric Endocrinology, Children's Hospital Los Angeles and Dr. Lefkothea Karaviti, Pediatric Endocrinology, Baylor College of Medicine, for reviewing and editing the article. The authors also thank Dr. B. Lee Ligon of the Department of Pediatrics, Baylor College of Medicine, for editorial assistance.

Disclosure

All of the authors have no conflict of interest

References

1. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on "adequate" doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf) 2002;57:577-585
2. Peterson SJ, McAninch EA, Bianco AC. Is a normal TSH synonymous with "euthyroidism" in levothyroxine monotherapy? J Clin Endocrinol Metab 2016;101:4964-4973
3. Jørgensen P, Langhammer A, Krokstad S, Forsmo S. Diagnostic labelling influences self-rated health. A prospective cohort study: The HUNT study, Norway. Fam Pract 2015;32:492-499
4. Boesen VB, Feldt-Rasmussen U, Bjorner JB, Cramon P, Groenvold M, Nygaard B, Rasmussen ÅK, Vilsbøll T, Watt T. How should thyroid-related quality of life be assessed? Recalled patient-reported outcomes compared to here-and-now measures. Thyroid 2018;28:1561-1570
5. Jonklaas J, Davidson B, Bhagat S, Soldin SJ. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy. JAMA 2008;29:769-777
6. Gullo D, Latina A, Frasca F, Moli R, Pellegriti G, Vigneri R. Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. PLoS One 2011;6:4-10
7. Appelhof BC, Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JG, Endert E, van Weert HC, Wiersinga WM. Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: A double-blind, randomized, controlled clinical trial. J Clin Endocrinol Metab 2005;90:2666-2674
8. Bunevicius R, Jakubonien N, Jurkevicius R, Cernicat J, Laas L, Prange AJ. Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease. Endocrine 2002;18:129-133
9. Clyde PW, Harari AE, Getka EJ, Shakir KMM. Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism. A randomized controlled trial. JAMA 2003;290:2952-2958
10. Escobar-Morreale HF, Botella-Carretero JL, Gomez-Bueno M, Galan JM, Barrios V, Sancho J. Thyroid hormone replacement therapy in primary hypothyroidism: A randomized trial comparing l -thyroxine plus liothyronine with l-thyroxine alone. Ann Intern Med 2005;142:412-424

11. Kaminski J, Miasaki FY, Paz-Filho G, Graf H, Carvalho GA. Treatment of hypothyroidism with levothyroxine plus liothyronine: a randomized, double-blind, crossover study. Arch Endocrinol Metab 2016;60:562-572
12. Rodriguez T, Lavis VR, Meininger JC, Kapadia AS, Stafford LF. substitution of liothyronine at a 1:5 ratio for a portion of levothyroxine: Effect on fatigue, symptoms of depression, and working memory versus treatment with levothyroxine alone. Endocr Pract 2013;11:223-233
13. Saravanan P, Simmons DJ, Greenwood R, Peters TJ, Dayan CM. Partial substitution of thyroxine (T4) with tri-iodothyronine in patients on T4 replacement therapy: Results of a large community-based randomized controlled trial. J Clin Endocrinol Metab 2005;90:805-812
14. Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT. Does a combination regimen of thyroxine (T4) and 3,5,3′-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. J Clin Endocrinol Metab 2003;88:4551-4555
15. Siegmund W, Spieker K, Weike AI, Giessmann T, Modess C, Dabers T, Kirsch G, Sänger E, Engel G, Hamm AO, Nauck M, Meng W. Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14:1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. Clin Endocrinol (Oxf) 2004;60:750-757
16. Valizadeh M, Seyyed-Majidi MR, Hajibeigloo H, Momtazi S, Musavinasab N, Hayatbakhsh MR. Efficacy of combined levothyroxine and liothyronine as compared with levothyroxine monotherapy in primary hypothyroidism: A randomized controlled trial. Endocr Res 2009;34:80-89
17. Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MKM. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: A randomized, double-blind, crossover study. J Clin Endocrinol Metab 2013;98:1982-1990
18. Celi F, Zemskova M, Linderman J, abar NI, Skarulis MC, Csako G, Wesley R, Costello R, Penzak SR, Pucino F. The pharmacodynamic equivalence of levothyroxine and liothyronine. A randomized, double blind, cross-over study in thyroidectomized patients. Clin Endocrinol (Oxf) 2010;72:709-715
19. Hennemann G, Docter R, Visser TJ, Postema PT, Krenning EP. Thyroxine plus low-dose, slow-release triiodothyronine. Replacement in hypothyroidism: Proof of principle. Thyroid 2004;14:1-6
20. Santini F, Giannetti M, Ricco L, Querci G, Saponati G, Bokor D, Rivolta G, Bussi S, Braverman LE, Vitti P, Pinchera A. Steady-state serum T3 concentrations for 48 hours following the oral administration of a single dose of 3,5,3'-triiodothyronine sulfate (T3S). Endocr Pract 2014;20:680-689
21. Panicker V, Saravanan P, Vaidya B, Evans J, Hattersley AT, Frayling TM, Dayan CM. Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. J Clin Endocrinol Metab 2009;94:1623-1629
22. Wouters HJCM, van Loon HCM, van der Klauw MM, Elderson MF, Slagter SN, Kobold AM, Kema IP, Links TP, van Vliet-Ostaptchouk JV, Wolffenbuttel BH. No effect of the thr92ala polymorphism of deiodinase-2 on thyroid hormone parameters, health-related quality of life, and cognitive functioning in a large population-based cohort study. Thyroid 2016;27:147-155
23. Castagna MG, Dentice M, Cantara S, Ambrosio R, Maino F, Porcelli T, Marzocchi C, Garbi C, Pacini F, Salvatore D. DIO2 Thr92Ala reduces deiodinase-2 activity and serum-T3 levels in thyroid-deficient patients. J Clin Endocrinol Metab 2017;102:1623-1630
24. Jonklaas J, Tefera E, Shara N. Physician choice of hypothyroidism therapy: Influence of patient characteristics. Thyroid 2018;28:1416-1424
25. Cassio A, Cacciari E, Cicognani A, Damiani G, Missiroli G, Corbelli E, Balsamo A, Bal M, Gualandi S. Treatment for congenital hypothyroidism: Thyroxine alone or thyroxine plus triiodothyronine? Pediatrics 2004;111:1055-1060
26. Paone L, Fleisch AF, Feldmen HA, Brown RS, Wassner AJ. Liothyronine improves biochemical control of congenital hypothyroidism in patients with central resistance to thyroid hormone. J Pediatr 2016;175:167-172
27. Lindemann JAL, Webb P. Sobetirome: The past, present and questions about the future. Expert Opin Ther Targets 2015;20:1-5
28. Ashraf A, Beukelman T, VP D, Kelly D, Garg A. Type 1 hyperlipoproteinemia and recurrent acute pancreatitis due to lipoprotein lipase antibody in a younger girl with Sjogren's syndrome. J Clin Endocrinol Metab 2011;96:3302-3307
29. Valaiyapathi B, Sunil B, Ashraf AP. Approach to hypertriglyceridemia in the pediatric population. Pediatr Rev 2017;38:424-434
30. Valaiyapathi B, Ashraf AP. Hospital management of severe hypertriglyceridemia in children. Curr Pediatr Rev 2018;13:225-231
31. Kihara S, Matsuzawa Y, Kubo M, Nozaki S, Funahashi T, Yamashita S, Sho N, Tarui S. Autoimmune hyperchylomicronemia. N Engl J Med 1989;320:1255-1259
32. Beigneux AP, Miyashita K, Ploug M, lom DJ, Ai M, Linton MF, Khovidhunkit W, Dufour R, Garg A, McMahon MA, Pullinger CR, Sandoval NP, Hu X, Allan CM, Larsson M, Machida T, Murakami M, Reue K, Tontonoz P, Goldberg IJ, Moulin P, Charrière S, Fong LG, Nakajima K, Young SG. Autoantibodies against GPIHBP1 as a cause of hypertriglyceridemia. N Engl J Med 2017;376:1647-1658
33. Lilley JS, Linton MF, Kelley JC, Graham TB, Fazio S, Tavori H. A case of severe acquired hypertriglyceridemia in a 7-year-old girl. J Clin Lipidol 2017;11:1480-1484
34. Bell DA, Watts GF. Contemporary and novel therapeutic options for hypertriglyceridemia. Clin Ther 2015;37:2732-2750
35. Science AS for CL. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics 2011;128(Suppl):S213-S256
36. NCEP. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-3421
37. Harris W, Ginsberg H, Arunakul N, Shachter NS, Windsor SL, Adams M, Berglund L, Osmundsen K. Safety and efficacy of Omacor in severe hypertriglyceridemia. J Cardiovasc Risk 1997;4:385-391
38. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: Its etiology, effects and treatment. CMAJ 2007;176:1113-1120
39. Fialkow J. Omega-3 fatty acid formulations in cardiovascular disease: Dietary supplements are not substitutes for prescription products. Am J Cardiovasc Drugs 2016;16:229-239
40. Gaddi A, Cicero AFG, Odoo FO, Poli AA, Paoletti R. Practical guidelines for familial combined hyperlipidemia diagnosis: An up-date. Vasc Health Risk Manag 2007;3:877-886
41. ADA. 13. Children and adolescents: Standards of medical care in diabetes-2019. Diabetes Care 2019;42:S148-S164
42. Donaghue KC, Marcovecchio ML, Wadwa RP, Chew EY, Wong TY, Calliari LE, Zabeen B, Salem MA, Craig ME. ISPAD Clinical Practice Consensus Guidelines 2018: Microvascular and macrovascular complications in children and adolescents. Pediatr Diabetes 2018;19:262-274
43. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, Lin AE, Mauras N, Quigley CA, Rubin K, Sandberg DE, Sas TCJ, Silberbach M, Söderström-Anttila V, Stochholm K, van Alfen-van derVelden JA, Woelfle J, Backeljauw PF, International Turner Syndrome Consensus Group. Clinical practice guidelines for the care of girls and women with Turner syndrome: Proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol 2017;177:G1-G70
44. Klein KO, Rosenfield RL, Santen RJ, Gawlik AM, Backeljauw PF, Gravholt CH, Sas TCJ, Mauras N. Estrogen replacement in Turner syndrome: Literature review and practical considerations. J Clin Endocrinol Metab 2018;103:1790-1803

45. Rieser P, Davenport M. Turner syndrome: A guide for families. Available at: https://www.turnersyndrome.org/guidelines-and-checklists
46. Hagen CP, Main KM, Kjaergaard S, Juul A. FSH, LH, inhibin B and estradiol levels in Turner syndrome depend on age and karyotype: Longitudinal study of 70 Turner girls with or without spontaneous puberty. Hum Reprod 2010;25:3134-3141
47. Ross JL, Quigley CA, Cao D, Feuillan P, Kowal K, Chipman JJ, Cutler GB Jr. Growth hormone plus childhood low-dose estrogen in Turner syndrome. Obstet Gynecol Surv 2011;66:486-487
48. Lunding SA, Aksglaede L, Anderson RA, Main KM, Juul A, Hagen CP, Pedersen AT. AMH as predictor of premature ovarian insufficiency: A longitudinal study of 120 turner syndrome patients. J Clin Endocrinol Metab 2015;100:E1030-E1038
49. Chevalier N, Letur H, Lelannou D. Maternofetal cardiovascular complications in turner syndrome after oocyte donation: Insufficient prepregnancy screening and pregnancy follow-up are associated with poor outcome. Obstet Gynecol Surv 2011;66:275-277

Meetings of Interest

2019

September

2-3 **12th Edition of International Conference on Endocrinology & Diabetology**
Berlin, Germany
Email: endocrinology@conferencesguide.org
Web: https://endocrinology.euroscicon.com/

5-6 **Updates in Diagnosis and Management of Hyperinsulinism and Neonatal Hypoglycemia Conference**
Children's Hospital of Philadelphia, USA
Email: CMEOFFICE@email.chop.edu
Web: https://congenitalhi.org/chop-symposium/

17-19 **2019 Clinical Endocrinology Update (CEU)**
Seattle, Washington, USA
Web: www.endocrine.org/ceu

17-21 **3rd JENS Meetings**
MAASTRICHT, The Netherlands
Email: info@mcascientificevents.eu
Web: https://www.mcascientificevents.eu/jens/

19-20 **2nd World Congress on Gynecology and Obstetrics**
Miami, USA
Email: wcgo-2019@scientificfederation.org
Web: https://www.scientificfederation.com/wcgo-2019/

19-21 **58th ESPE Meeting**
Vienna, Austria
Email: peter.clayton@manchester.ac.uk
Web: www.eurospe.org/meetings/

27-28 **International Conference and Exhibition on Nursing Nursing USA 2019**
Houston, USA
Email: angela_b@nursingintconf.com

October

14-15 **World Congress on Nursing, Healthcare and Hospital Management (WCNHHM-2019)**
Paris, France
Email: info@ijeert.com
Web: https://nursing.conferenceera.com/

14-15 **World Congress on Diabetes and Endocrinology (WCDE-2019)**
Paris, France
Email: diabetes@conferenceera.com
Web: http://diabetes.conferenceera.com/

17-19 **Frontiers in Biosimilars and Biologics Congress**
Rome, Italy
Email: biosimilars@frontiermeetings.com
Web: www.emedevents.com/c/medical-conferences-2019/global-experts-meeting-on-frontiers-in-biosimilars-and-biologics-congress

21-22 **World Congress on Gynecology and Obesity**
Switzerland
Email: gynecology@conferenceera.com
Web: http://gynecology.conferenceera.com/

24-25 **2nd International Conference on Obesity and Diabetes**
Valencia, Spain
Email: catherineparker@globalobesityconferences.org
Web: https://www.colloquiumonline.com/conference/2nd-international-conference-on-obesity-and-diabetes

24-27 **The Seventh Annual EndoBridge**
Antalya, Turkey
Web: www.endobridge.org/?p=meeting

25-27 **9th Annual World Congress of Molecular& Cell Biology (CMCB-2019)**
Singapore
Email: judy_du@mol-cell.com
Web: http://www.bitcongress.com/cmcb2019/programlayout.asp

28-30 **Global Forum on Nursing and Nurse Education**
Miami, USA
Email: nursingusa@globalhealthcareconferences.com
Web: http://nursing-conferences.com

October-November

30-2 **ISPAD 2019**
45th Annual Conference (International Society for Pediatric and Adolescent Diabetes)
Boston, USA
Web: https://2019.ispad.org/

November

1-3 **13th World Congress of Regenerative Medicine& Stem Cell-2019 (RMSC-2019)**
Dalian, China
Email: emma@rmsccongress.com
Web: http://www.bitcongress.com/rmsc2019/ContactUs.asp

4-5 **The 2nd World Congress on Pediatrics & Child Care Meeting**
Porto, Portugal
Email: contact@pediatrics2019.org
Web: https://www.pediatricsconference.org/

14-15 **European Neonatal Ethics Conference 2019**
UK
Email: mproveonline@gmail.com
Web: www.bapm.org/events/european-neonatal-ethics-conference-2019

15-17 **The 17th Annual Congress of International Drug Discovery Science and Technology-2019 (IDDST-China 2019)**
Nanjing, China
Email: jessica@iddst-china.com
Web: http://www.iddst.com/IDDSTCHINA2019/welcomemessage.asp

2020

January

29-30 **13th International Conference on Diabetes, Endocrinology and Metabolism**
Sydney, Australia
Email: worlddiabetes@eurosessions.com
Web: www.diabetes.euroscicon.com

March

28-31 **The Annual Meeting 2020 of the Endocrine Society**
San Francisco, CA, USA
Email: media@endocrine.org
Web: https://www.endocrine.org/endo2020

April

15-17 **13th Annual World Protein & Peptide Conference (PepCon-2020)**
Osaka, Japan
E-mail: Barbara@food-congress2019.com

23-27 **PES 2020**
TX, USA
Email: info@pedsendo.org
Web: www.pedsendo.org/education_training/annual_meetings/

25-26 **PCS 5th Annual Health Care Congress (HCC-2020) and PCS 5th Annual Mental Health Forum (MHF-2020)**
Moscow, Russia
Email: William@pcszhang.com
Web: www.pcscongress.com/hcc2020

June

18-19 **2nd International Conference on Diabetes and Endocrinology**
Berlin, Germany
Email: info@scitechconferences.com
Web: www.diabetes.scitechconferences.com

September

5-8 **OI 2020 (14th International Conference on Osteogenesis Imperfecta)**
Sheffield , UK
Email: n.j.bishop@sheffield.ac.uk
Web: https://events.time.ly/qhzk1lk?event=20383885

10-12 **59th Annual ESPE Meeting**
Liverpool, UK
Email: peter.clayton@manchester.ac.uk
Web: www.eurospe.org/meetings/

Volume 16 SUBJECT INDEX

Volume 16 SUBJECT INDEX

Volume 16 SUBJECT INDEX

Volume 16 AUTHOR INDEX

Volume 16 AUTHOR INDEX

Volume 16 AUTHOR INDEX

International and Regional Presidents and Secretaries of Pediatric Endocrine Societies

SOCIETY	PRESIDENTS	SECRETARIES
APPES Asia Pacific Paediatric Endocrine Society www.appes.org	A/Prof Suttipong Wacharasindhu PO Box 180 Morisset NSW 2264 Australia Tel: +61 2 49736573 Fax: +61 2 4973 6609 Email: appes@willorganise.com.au	Dr. Jun Fen Fu PO Box 180 Morisset NSW 2264 Australia Tel: +61 2 49736573 Fax: +61 2 4973 6609 Email: appes@willorganise.com.au
ESPE European Society for Paediatric Endocrinology www.eurospe.org	Prof. Gabriele Häusler Medical University of Vienna Währinger Gürtel 18-20, A-1090 Vienna, Austria Tel: +43 (0)1 40400 - 32320 Fax: +43 (0)1 40400 - 79830 Email: gabriele.haeusler@meduniwien.ac.at	Prof. Peter Clayton ESPE Team, Bioscientifica, Euro House 22 Apex Court, Woodlands, BS32 4JT Bristol, UK Tel: + 44 (0) 1454 642246 Fax: + 44 (0) 1454 642222 Email: espe@eurospe.org
ISPAD International Society for Pediatric and Adolescent Diabetes www.ispad.org	Kim C Donaghue, MB BS, PhD, FRACP Sydney Medical School, University of Sydney The Children's Hospital at Westmead Locked Bag 4001 Westmead, NSW 2145, Sydney, Australia Tel: +49 (0)30 24603-210 Fax: +49 (0)30 24603-200 Email: kim.donaghue@health.nsw.gov.au	David Maahs, MD, PhD Lucile Packard Children's Hospital Stanford University, School of Medicine 300 Pasteur Drive, Room-313 Stanford, CA 94305 Tel: +49 (0)30 24603-210 Fax: +49 (0)30 24603-200 Email: dmaahs@stanford.edu
PES Pediatric Endocrine Society www.pedsendo.org	Erica Eugster, MD Riley Hospital, Pediatric Endocrinology 702 Barnhill Drive, Room 5960 Indianapolis, IN 46202, USA Tel: (317) 274-3889 Fax: (317) 274-3882 Email: eeugster@iupui.edu	Mitchell Geffner, MD Children's Hospital Los Angeles 4650 Sunset Blvd., MS #61 Los Angeles, CA 90027 USA Tel: 323-361-5678 Fax: 323-361-1301 E-mail: mgeffner@chla.usc.edu
SLEP Sociedade Latino Americana de Endocrinologia Pediátrica www.slep.com.br	Dr. Rodolfo Rey Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CEDIE) CONICET - FEI - División de Endocrinología, Hospital de Niños R. Gutiérrez Gallo 1330 - C1425EFD Buenos Aires, Argentina Tel: +54-11-4963-5931 int. 133 Email: rodolforey@cedie.org.ar Web: www.cedie.org.ar	Dr. Germán Iñíguez Instituto de Investigaciones Materno Infantil (IDIMI) Facultad de Medicina, Universidad de Chile Hospital San Borja Arriarán Avenida Santa Rosa Nº 1234, Santiago, Chile Tel: +56-2-2977 0850 Email: giniguez@med.uchile.cl Web: www.idimi.cl
APEG Australasian Paediatric Endocrine Group www.apeg.org.au	Dr Esko Wiltshire PO Box 180 Morisset NSW 2264, Australia Tel: +61 2 4973 6673 Fax: +61 2 4973 6609 Email: info@apeg.org.au	Dr Helen Woodhead PO Box 180 Morisset NSW 2264, Australia Tel: +61 2 4973 6673 Fax: +61 2 4973 6609 Email: info@apeg.org.au
CPEG Canadian Pediatric Endocrine Group www.cpeg-gcep.net	Dr. Elizabeth Sellers Email: esellers@hsc.mb.ca	Ms. Eileen Pyra Email: eileen.pyra@albertahealthservices.ca
JSPE The Japanese Society for Pediatric Endocrinology www.jspe.umin.jp/eng	Keiichi Ozono, MD, PhD Osaka University School of Medicine 1-1 Yamadaoka, Suita, Osaka 565-0871, Japan	Academic Square Co. Ltd. 2-348 Ryogae-cho Fushimi-ku, Kyoto 612-8082, Japan Tel: +81-75-468-8772 Fax: +81-75-468-8773 Email: jspe@ac-square.co.jp
SEEP Sociedad Española de Endocrinología Pediátrica www.seep.es	Beatriz Garcia Cuartero Head Pediatric Department Ramon y Cajal University Hospital Carretera Colmenar Viejo 9, 28034 Madrid, Spain Email: bgcuartero@salud.madrid.org	Marta Ferrer Lozano Calle Castelló, 128 - 7ª planta 28006 Madrid, Spain Email: mferrer@salud.aragon.es; seep@seep.es

SOCIETY	PRESIDENTS	SECRETARIES
BSPED British Society for Paediatric Endocrinology and Diabetes www.bsped.org.uk	Dr. Justin Davies Tel: +44 (0)1454 642258 Fax: +44 (0)1454 642222 Email: bsped@endocrinology.org	Dr. Joanne Blair Tel: +44 (0)1454 642258 Fax: +44 (0)1454 642222 Email: bsped@endocrinology.org
ICET-A International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine www.endothalassemia.org.	Vincenzo de Sanctis, MD Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital 44121 Ferrara (Italy) Tel: (532) 770243 Email: vdesanctis@libero.it	Prof. Heba Elsedfy Professor of Pediatrics Ain Shams University, Egypt Tel: +201005189166 Email: hebased@yahoo.com
ASPAE African Society for Paediatrics and Adolescent Endocrinology www.aspae2015.com	Dr. Renson Mukhwana Email: info@aspae.co.za	Dr. Iroro Yahere, Nigeria The Secretariat Paediatric Endocrinology Training Centre, Gertrudes Children Hospital, Nairobi, Kenya Tel: +254-020-2702600 / +254-722898948 Cell: 0726-161590 Email: info@aspae.co.za
SFEDP French Society of endocrinology and diabetology pediatric 67 rue Saint Jacques 75005 Paris www.sfedp.org	Rachel Reynaud MD, PhD Service de pédiatrie multidisciplinaire CHU Timone Enfants 264 rue Saint Pierre 13385 Marseille cedex 05, France Email: rachel.reynaud@univ-amu.fr	Isabelle Oliver MD Service de Pédiatrie - Endocrinologie, génétique et gynécologie médicale Pôle enfants , Hôpital des enfants , 330, avenue de Grande Bretagne - TSA 70034 - 31059 Toulouse cedex 9, France Email: secretariat.sfedp@gmail.com
ISPAE The Indian Society for Pediatric and Adolescent Endocrinology www.ispae.org.in	Dr. Vijayalakshmi Bhatia Email: vbhatia@sgpgi.ac.in	Dr. M Vijayakumar E-mail: ravikarnam@doctors.net.uk
ISPED The Italian Society of Pediatric Endocrinology and Diabetology www.ispae.org.in	Prof. Stefano Cianfarani Professor of Pediatrics, Department of Systems Medicine, University of Rome 'Tor Vergata', Chief of Diabetology Unit, 'Bambino Gesù ' Children's Hospital, Rome Piazza S. Onofrio 4, 00165-Rome, Italy Tel: +39 06 6859 3074 (Hosp.) / +39 06 72596178 (Lab.) Fax: +39 06 6859 2508 (Hosp.) / +39 06 72596172 (Lab.) E-mail: stefano.cianfarani@uniroma2.it; stefano.cianfarani@opbg.net	Prof Giuliana Valerio Department of Movement Sciences and Wellbeing, University of Naples Parthenope via Medina 40, 80133 Naples, Italy Tel: +39 081 547 4663 Fax: +39 081 547 4668 E-mail: giuliana.valerio@uniparthenope.it
FOPO Federation of Pediatric Organizations www.fopo.org	Theodore C. Sectish, MD Email: Theodore.Sectish@childrens.harvard.edu	Thomas P. Shanley Email: tshanley@med.umich.edu
SGA-ER Study Group for Integral Adolescent Health Care-Emilia Romagna www.sga-er-sga.blogspot.com	Prof. Vincenzo de Sanctis Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital 44121 Ferrara, Italy Tel: (532) 770243 Email: vdesanctis@libero.it	Andrea Zucchini, MD Consultant, Pediatric Endocrinology Azienda USL della Romagna Presidi Ospedalieri di Ravenna, Faenza e Lugo, Italy Tel: 3382641617 Email: andrea.zucchini@auslromagna.it
PIES Pediatric Israel Endocrine Society www.ies.org.il	Prof. Naomi Weintraub Email: weintrob@netvision.net.il	Dr. Tali Ben-Ari Wolfson Medical Center Email: tali@benari.com

SI and Metric Units for Plasma, Serum, or Blood

	Metric unit	Conversion factor	SI unit
Acetoacetate	mg/dl	97.95	μmol/l
Acetone	mg/dl	172.2	μmol/l
Adrenocorticotropin	pg/ml	0.2202	pmol/l
Aldosterone	ng/dl	27.74	pmo/l
Amino acids			
• Alanine	mg/dl	112.2	μmol/l
• α-Aminobutyric acid	mg/dl	96.97	μmol/l
• Arginine	mg/dl	57.40	μmol/l
• Asparagine	mg/dl	75.69	μmol/l
• Aspartic acid	mg/dl	75.13	μmol/l
• Citrulline	mg/dl	57.08	μmol/l
• Cystine	mg/dl	41.61	μmol/l
• Glutamic acid	mg/dl	67.97	μmol/l
• Glutamine	mg/dl	68.42	μmol/l
• Glycine	mg/dl	133.2	μmol/l
• Histidine	mg/dl	64.45	μmol/l
• Hydroxyproline	mg/dl	76.26	μmol/l
• Isoleucine	mg/dl	76.24	μmol/l
• Leucine	mg/dl	76.24	μmol/l
• Lysine	mg/dl	68.40	μmol/l
• Methionine	mg/dl	67.02	μmol/l
• Ornithine	mg/dl	75.67	μmol/l
• Phenylalanine	mg/dl	60.54	μmol/l
• Proline	mg/dl	86.86	μmol/l
• Serine	mg/dl	95.16	μmol/l
• Taurine	mg/dl	79.91	μmol/l
• Threonine	mg/dl	83.95	μmol/l
• Tryptophan	mg/dl	48.97	μmol/l
• Tyrosine	mg/dl	55.19	μmol/l
• Valine	mg/dl	85.36	μmol/l
Amino acid nitrogen	mg/dl	0.7139	mmol/l
Amylase	units/l	1.0	units/l
Androstenedione	μg/l	3.492	nmol/l
Calcitonine	pg/ml	1.0	ng/l
Calcium	mg/dl	0.2495	mmol/l
Calcium ion	meq/l	0.500	mmol/l
Carbone dioxide content	meq/l	1.00	nmol/l
Cholesterol	mg/dl	0.02586	mmol/l
Citrate (as citric acid)	mg/dl	52.05	μmol/l
Cortisol	μg/dl	27.59	nmol/l
C-peptide	ng/ml	0.331	nmol/l
Creatinine	mg/dl	88.40	μmol/l
Creatinine clearance	ml/min	0.01667	ml/s
Cyclic AMP	μg/l	3.038	nmol/l
Cyclic GMP	μg/l	2.897	nmol/l
Dehydroepiandrosterone	μg/l	3.467	nmol/l
Dehydroepiandrosterone sulfate	ng/ml	0.002714	μmol/l
11-Deoxycortisol	μg/dl	28.86	nmol/l
Epinephrine	pg/ml	5.458	pmol/l

	Metric unit	Conversion factor	SI unit
Estradiol	pg/ml	3.671	pmol/l
Estrone	pg/ml	3.699	pmol/l
Fatty acids,nonesterified	mg/dl	0.01	g/l
Follicle-stimulaing hormone	mIU/ml	1.00	IU/l
Fructose	mg/dl	0.05551	mmol/l
Galactose	mg/dl	0.05551	mmol/l
Gases			
• Po_2	mmHg	0.1333	kpa
• Pco_2	mmHg	0.1333	kpa
Gastrin	pg/ml	1.0	ng/l
Gastroinhibitory polypeptide	pg/ml	0.201	pmol/l
Glucagon	pg/ml	1.0	ng/l
Glucose	mg/dl	0.05551	mmol/l
Glycerol,free	mg/dl	0.1086	mmol/l
Growth hormone	ng/ml	1.0	μg/l
β-Hydroxybutyrate (as β-Hydroxybutyric acid)	mg/dl	96.05	μmol/l
17α-Hydroxyprogesterone	μg/l	3.026	nmol/l
Insuline	μU/ml	6.0	pmol/l
Lactate (as lactic acid)	mEq/l	1.0	mmol/l
Lipase	units/l	1.0	units/l
Lipoproteins			
• LDL (as cholesterol)	mg/dl	0.02586	mmol/l
• HDL (as cholesterol)	mg/dl	0.02586	mmol/l
Luteinizing hormone	mIU/ml	1.0	IU/l
Norepinephrine	pg/ml	0.005911	nmol/l
Osmolality	mOsm/kg	1.0	mnol/kg
Pancreatic polypeptide	pg/ml	0.239	pmol/l
Phosphate (as inorganic phosphorus)	mg/dl	0.3229	mmol/l
Phospholipid phosphorus	mg/dl	0.3229	mmol/l
Progesterone	ng/ml	3.180	nmol/l
Prolactine	ng/ml	1.0	μg/l
Protein,total	g/dl	10.0	g/l
Pyruvate(as pyruvic acid)	mg/dl	113.6	μmol/l
Renin	$ng \cdot ml^{-1} \cdot h^{-1}$	0.2778	$ng \cdot l^{-1} \cdot s^{-1}$
Serotonin	μg/dl	0.05675	μmol/l
Somatostatin	pg/ml	0.611	pmol/l
Testosterone	ng/ml	3.467	nmol/l
Thyroid-stimulating hormone	μU/ml	1.0	mU/l
Thyroxine	μg/dl	12.87	nmol/l
Triglycerides	mg/dl	0.0112	mmol/l
Triiodothyronine	ng/dl	0.01536	nmol/l
Urea nitrogen	mg/dl	0.3570	mmol/l
Vasoactive intestinal polypeptide	pg/ml	0.331	pmol/l

Acknowledgement to Referees of Articles in PER Volume 16

U. Alon
A. Biason
C. Blunden
H. Claahsen
J. Dahlgren
V. De Sanctis
H. Domene
E. Eugster
J. Fuqua
M. Geffner
A. Grimberg
C. Hampe
S. Izraeli
O. Konen
P. Lee
V. Mericq
B. Nambam
D. Schatz
D. Styne
D. Tiosano
H. Werner

Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism

Volume 15 • No. 2 • December 2017

Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism

Volume 15 • No. 3 • March 2017

Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism

Volume 15 • No. 4 • June 2018

Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism

Volume 16 • Supplement 1 • September 2018

Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism

Volume 16 • No. 1 • September 2018

Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism

Volume 16 • No. 2 • December 2018

Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism

Volume 16 • No. 3 • March 2019

Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism

Volume 16 • Supplement 2 • May 2019

Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism

Volume 16 • No. 4 • June 2019

PER Pediatric Endocrinology Reviews
Diabetes Nutrition Metabolism

Affiliated Journal of the Pediatric Endocrine Society (PES-USA)
Affiliated Journal of the Japanese Society of Pediatric Endocrinology (JSPE)

Subscription to Volume 17

☐ Renewal ☐ New

Date: *September 2019*

Name_____ ***Address***_____

City_____ ***Country***_____

Tel_____ ***Email***_____

Price: $180	**PER Renewal Volume 17 (2019-2020) - Printed version**
Price: $160	**PER Renewal Volume 17 (2019-2020) - Electronical version**

**The rate is for individual subscriptions*

We accept the following credit cards: ☐ VISA ☐ MASTERCARD

Credit Card details: _____ _____ _____
Name Card no. Expiry

Bank Details:
Union Bank of Israel
Beneficiary Name: Y.S. Medical Media
LTD Account no. 51820009
Netanya no.091
SWIFT: UNBKILIT
IBAN: IL330130910000051820012
Address: 17 Stamper St, Netanya
Tel: 972-9-860-8622

Email: per@medmedia.co.il, Fax:+ 972-3-5217462, Web: www.pediatricendoreviews.com