Endocrine Changes in Undernutrition, Metabolic Programming, and Nutritional Recovery

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Vinicius José Baccin Martins, Maria Paula de Albuquerque, and Ana Lydia Sawaya

Contents

V. J. B. Martins (✉)
Department of Physiology and Pathology, Federal University of Paraíba, Health Sciences Center, João Pessoa, PB, Brazil
e-mail: vifisio@yahoo.com.br; viniciusjbmartins@gmail.com

M. P. de Albuquerque
Department of Physiology, Federal University of São Paulo, Center for Nutritional Recovery and Education (CREN), São Paulo, SP, Brazil
e-mail: saude_vm@cren.org.br; mariapauladealbuquerque@gmail.com

A. L. Sawaya
Department of Physiology, Federal University of São Paulo, São Paulo, SP, Brazil
e-mail: alsawaya@unifesp.br; al.sawaya@yahoo.com.br

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Abstract

Undernutrition is a consequence of an unbalance between supply of nutrients/energy and the demand of the body to ensure its functions and growth. It has deleterious effects on the development of organs and growth, generating stunting and underweight in childhood. Globally, about 159 million children (<5 years of age) have stunting, and more than 50 million are underweight.

Undernutrition undermines economic growth, perpetuates poverty, and is associated with the development of noncommunicable diseases in the long term. Several studies have demonstrated that fetuses and infants under a limited supply of nutrients program their metabolism to ensure their survival by sparing energy and selectively preserving tissues and organs. This strategical programming results in specific metabolic and endocrine changes that remain throughout the life span and in the next generations. The aim of this chapter is to describe the major endocrine changes in undernutrition and, in addition, to present some results of an adequate recovery in height and weight in the first 5 years of life.

Keywords

Cortisol · IGF-1 · Thyroid hormones · Insulin · Leptin · Reproductive hormones · Undernutrition · Stunting · Low birth weight · Metabolic programming · Nutritional recovery

List of Abbreviations

ACTH	Adrenocorticotropic hormone
α-MSH	Alpha-melanocyte stimulating hormone
CART	Cocaine amphetamine-regulated transcript
CREN	Center for nutrition education and recovery
CRH	Corticotrophin-releasing hormone
FSH	Follicle stimulating hormone
GH	Growth hormone
GnRH	Gonadotropin-Releasing Hormone
GR	Glucocorticoid receptor
HOMA	Homeostasis model assessment
HPA	Hypothalamus-pituitary-adrenal
HPT	Hypothalamus-pituitary-thyroid
IGF	Insulin-like growth factor
LH	Luteinizing hormone
POMC	Proopiomelanocortin
T3	3,5,3′-Triiodothyronine
T4	3,5,3′,5′-Tetraiodothyronine (or thyroxine)

TNF	Tumor necrosis factor
TRH	Thyrotropin-releasing hormone
TSH	Thyroid stimulating hormone

Introduction

Undernutrition in the critical windows of body development promotes endocrine and metabolic changes to guarantee immediate survival that seems to have long-term deleterious effects (Martins et al. 2011). Some of these adaptations have programming effects that are being progressively clarified. Undernourished children and adolescents, for example, show metabolic and endocrine alterations that increase the risk of noncommunicable diseases (Reynolds 2013). Moreover, studies in short stature adults have demonstrated higher prevalence of diabetes, cardiovascular diseases, and obesity; and significantly lower labor capacity (Florêncio et al. 2008).

The aim of this chapter is to describe the major endocrine changes in undernutrition and, in addition, to present some results of an adequate recovery in height and weight in the first 5 years of life.

Hypothalamus-Pituitary-Thyroid Axis

3,5,3′-triiodothyronine (T3) and 3,5,3′,5′-tetraiodothyronine (T4) are the major hormones produced by the thyroid gland and have a significant role in several physiological processes such as linear growth, neural development, metabolic rate, and body temperature (McAninch and Bianco 2014). The thyroid produces T4 in higher concentrations than T3, but in peripheral tissues, T4 can be converted to T3, by deiodinases. T3 is the major active thyroid hormone. The production of these hormones is controlled by the hypothalamus-pituitary-thyroid (HPT) axis.

The hypothalamic arcuate nucleus integrates signals that originate in peripheral tissues, such as the hormones ghrelin, leptin, insulin, and the metabolites glucose and fatty acids. It responds to different conditions such as hunger or satiety by activating orexigenic neurohormones such as neuropeptide Y and agouti-related peptide, or anorexigenic hormones such as proopiomelanocortin (POMC), alpha-melanocyte stimulating hormone (α-MSH), and cocaine amphetamine-regulated transcript (CART), respectively (Joseph-Bravo et al. 2015). When orexigenic neurons are active, there is a decrease in TRH expression, while anorexigenic neurons activate TRH expression. In animals submitted to fasting, the central administration of α-MSH or CART avoids inhibition of TRH gene expression and can maintain or increase TRH release (Fekete and Lechan 2014). Fasting can also accelerate the inactivation of T4 and T3 by conjugation with glucuronic acid (McAninch and Bianco 2014). Lower concentrations of T4 and T3, such as observed in severe hypothyroidism, can decrease the total energy expenditure about 50% (McAninch

and Bianco 2014). These data together show the importance of the HPT axis in response to energy deficits.

Children with kwashiorkor, a severe form of undernutrition, show a decrease in circulating concentrations of T4 and T3 due to the decrease in the carrier proteins, thyroid hormone binding globulin and thyroid hormone binding prealbumin and albumin (Kumar et al. 2009).

The duration of undernutrition appears to be important in determining alterations in the HPT axis (Brown and Brasel 1990). In acute undernutrition, there is a reduction in total T3 and T4 concentrations secondary to the reduction on plasma proteins, with maintained euthyroid status, whereas prolonged and severe undernutrition damage the adaptive mechanisms resulting in hypothyroidism with low concentrations of free T3 and an increase of reverse T3 (inactive form) (Waterlow et al. 1992). The lower T3 reduces thermogenesis and oxygen consumption, which allows a better conservation of energy across the insufficiency of energy. In addition, the decrease in peripheral level (liver and kidney) of the enzyme activity that converts T4 to T3, 5′- deiodinase (which promotes the hormone action at the target cell) can contribute to the lower concentrations of thyroid hormones in undernutrition (Waterlow et al. 1992). Another physiological adaptation in undernourished children can be the inhibition of the thyroid function caused by higher activity of hypothalamus pituitary adrenal axis (HPA) (Joseph-Bravo et al. 2015).

It has been described that undernutrition during gestation programs thyroid status in adulthood. Women with low birth weight and low stature show increased risk of spontaneous hypothyroidism (Kajantie et al. 2006). One study with offspring rats undernourished during gestation and lactation found normal T4 and TSH but lower T3 at weaning, indicating normal thyroid status but decreased function in target tissues (Ayala-Moreno et al. 2013). The weaning animals then received ad libitum access to food and on the 90th day normal concentrations of T3, but lower free T4 and higher concentration of TSH were found compared to controls, indicating persistent thyroid impairment.

Stunting in less severely undernourished children promotes changes in thyroid status as well. Normal concentrations of TSH and free T3, but lower free T4, were found in stunted children when compared to nonstunted controls (Martins et al. 2016). Similar findings were observed in short stature Brazilian women (but not men) with overweight/obesity, since it was found lower T3 concentrations in these short stature women in comparison to overweight/obese women with normal stature (Sawaya et al. 2009).

Hypothalamus-Pituitary-Adrenal Axis

The adrenal gland produces the stress hormone cortisol through stimulation of HPA axis. Undernourished individuals have higher cortisol concentration (Romero et al. 2009). The production of cortisol depends on the release of corticotrophin-releasing hormone (CRH) by paraventricular nucleus in hypophyseal portal system that stimulates synthesis and secretion of adrenocorticotropic hormone (ACTH) by

adenohypophysis. ACTH then acts in the zona fasciculata of adrenal gland stimulating cortisol production (Gunnar and Quevedo 2007).

Cortisol has catabolic effects that are important during undernutrition, as it promotes the increase of gluconeogenic activity, proteolysis, and lipolysis. These effects are responsible to maintain normal glycemia and to ensure energy supply to the brain. Glucose is the major energetic substrate of the nervous system. Cortisol interacts with glucocorticoid receptors (GR) located in the cytosol and nucleus of the target cells to promote its effects. Marasmic children without infection show higher nuclear GR in leukocytes in comparison to well-nourished children with infection (Manary et al. 2006). However, cortisol concentrations in these children were lower than in those with marasmus and infection. This is important because it demonstrates that infection is a strong stimulus to increase cortisol concentrations. Moreover, the higher number of GR demonstrates that nutritional status modulates glucocorticoid receptor action, in addition to the increase in circulating glucocorticoid concentrations (Manary et al. 2006).

Changes in the epigenetic status of the GR were found in the liver of offspring rats that were fed a protein-restricted diet during the intrauterine period (Stevens et al. 2011). These animals showed a decreased GR methylation, with a 200% increase in GR expression in comparison to controls. Furthermore, these changes persisted in the offspring even though the dietary restriction had stopped, suggesting that the methylation status of genes is potentially permanent.

Epigenetic effects in cortisol response have also been described in human fetus that suffered intrauterine undernutrition (Weaver 2009). Children born at term but with low birth weight, for example, show higher cortisol concentration at 10 years of age (Cianfarani et al. 2002). Another example of the reprogramming of HPA axis is the change in the activity of the 11 Beta-hydroxysteroid dehydrogenase type 2 enzyme. This enzyme converts cortisol to cortisone and constitutes a placental barrier that protects the baby from the higher maternal cortisol concentration during stress conditions. Undernutrition promotes a down regulation of this enzyme and a fetal overexposure to maternal cortisol (Draper and Stewart 2005).

Higher maternal cortisol concentrations present in undernourished pregnant animals in the latter half of pregnancy contribute to change the set point of HPA axis in the offspring, making this axis more reactive to stress (Reynolds 2013). Thereafter, many studies have pointed out cortisol as one of those hormones responsible for the higher risk of noncommunicable diseases in adult life among undernourished individuals (Reynolds 2013).

Growth Hormone and Insulin-like Growth Factor-1 Axis

One of the most evident consequences of undernutrition is the restriction on linear growth. This is mainly a result of a disruption on the growth hormone (GH) –insulin-like growth factor-1 (IGF-1 or somatomedin C) axis. Children with marasmus or kwashiorkor have higher GH concentration, whereas the hepatic IGF-1 production is reduced when compared to normal children (Kilic et al. 2004). This can be explained

by a decreased negative feedback at the pituitary level due the lower concentration of IGF-1. IGF-1 acts in hypothalamus and pituitary decreasing secretion of growth hormone releasing hormone and GH, respectively. In addition, the lower IGF-1 concentrations, despite of higher GH, seem to be due to three factors: (1) lower expression of the hepatic GH receptor or defect in intracellular mechanisms postreceptor such as found in animal models of starvation and protein deficiency, respectively; (2) lower blood insulin and T3 concentrations (Fazeli and Klibanski 2014); and (3) lower essential amino acid concentrations (Thissen et al. 1999). This GH resistance allows the increase of lipolysis and gluconeogenesis and, consequently, brain energy availability (Fazeli and Klibanski 2014). The lower IGF-1 concentration, on the other hand, is an important determinant for the decrease in linear growth. For this reason, IGF-1 is considered a biomarker of nutritional status in children (Hawkes and Grimberg 2015).

Insulin and Glucose Metabolism

Changes in insulin concentration are common in undernourished individuals. Severe hypoglycemia is a signal commonly found in terminal cases, but in general, undernourished individuals show low or normal fasting glycemia concentrations accompanied by low insulin. The production of insulin by the pancreas appears to be particularly affected. Lower insulin release following oral glucose tolerance test was observed among undernourished children (Das et al. 1998). In addition, a decreased activity of beta-cell function was found in stunted adolescents (Martins and Sawaya 2006) (Fig. 1).

The alterations in glucose and insulin metabolism seem to have a programming effect as well. Higher insulin sensitivity was observed in small for gestational age newborns (Soto et al. 2003). A study in Brazilian stunted adolescents found higher insulin sensitivity (HOMA-S) as well as lower insulin production (HOMA-B) (Fig. 1). Other studies found that undernutrition in the first year of life independent of the birth weight was associated with higher insulin concentration and lower insulin sensitivity, which worsened as BMI increased in adult life (González-Barranco et al. 2003). Brazilian adult women with short stature and obesity showed higher insulin resistance, together with altered glycemic and lipid profile, in relation to obese normal height women (Florêncio et al. 2007). Although an increase in total body mass was associated with a moderate decline in peripheral insulin sensitivity, abdominal obesity showed a much steeper decline in insulin sensitivity and was accompanied by reduced peripheral glucose stimulation and insulin production. In addition, compared to women of medium height, women with short stature had higher concentrations of glycated hemoglobin, total cholesterol, and LDL, whereas HDL cholesterol concentrations were significantly lower. Stature was identified as the main factor associated with insulin resistance. These findings demonstrate that undernutrition when associated with overweight generates worst metabolic consequences in comparison to normal height individuals with overweight.

Changes in the metabolism of glucose and insulin may also be observed in subjects with mild stunting (height for age between −2 and −1 Z score). Overweight

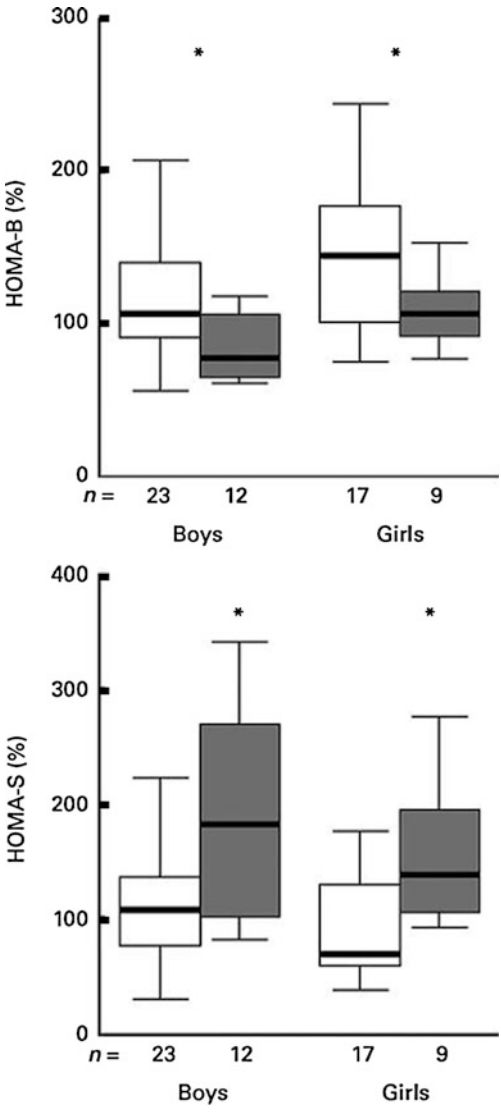

Fig. 1 Insulin production and sensitivity in stunted and well-nourished children. Homeostasis model assessment for pancreatic beta-cell function (*HOMA-B*) and for insulin sensitivity (*HOMA-S*) values of stunted (*black box*) and nonstunted (*white box*) boys and girls. The box represents the interquartile range which contains 50% of the values, the vertical bars indicate the highest and lowest values (excluding outliers) and the line across the box indicates the median. Significant difference between groups: $*P < 0.05$. Lower HOMA-B means lower insulin production and higher HOMA-S show higher insulin sensitivity, both in stunted children (Reprinted with permission from British Journal of Nutrition (2006), 95, 996–1001)

Brazilian adolescents with mild stunting showed higher blood glucose, insulin resistance, and lower insulin production (da Luz Santos et al. 2010). Moreover, adolescents with mild stunting presented elevated insulin concentration at a lower waist circumference deciles compared with nonstunted subjects (Fig. 2) (Clemente et al. 2014). The authors suggested that the increase in plasma insulin is one of the primary metabolic deviations that occur in stunted individuals and may be associated with the elevated risk of insulin resistance and diabetes found in short stature adults.

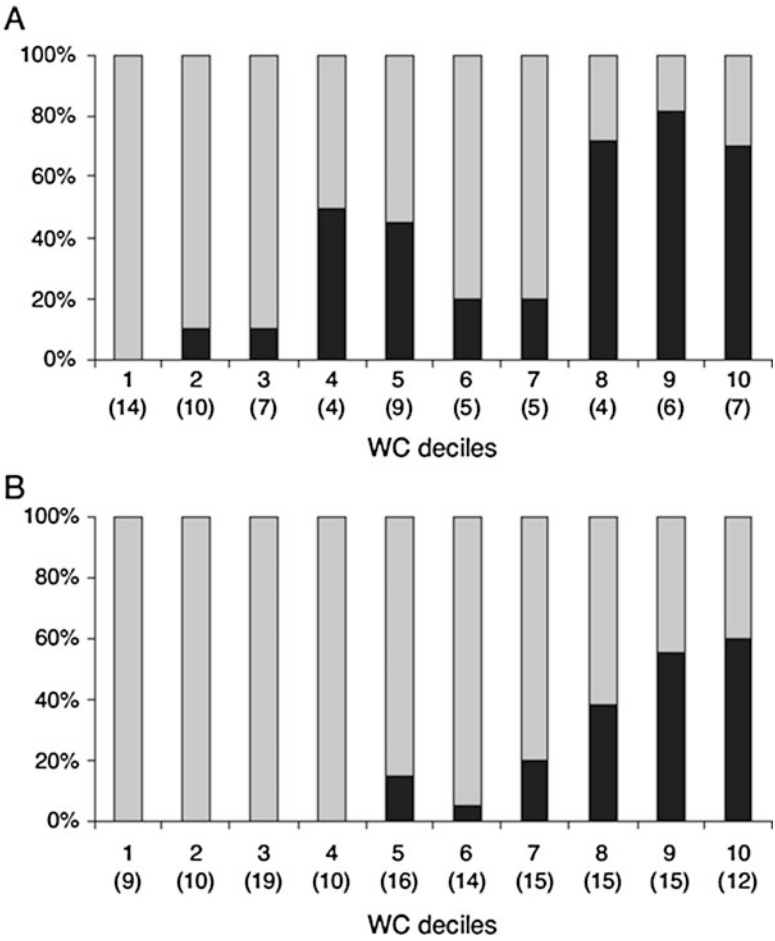

Fig. 2 Relationship between waist circumference and elevated insulin in stunted and well-nourished children. Distribution of stunted (**a**) and nonstunted (**b**) individuals according to waist circumference (*WC*) deciles and their respective prevalences of elevated insulin concentrations: (*black box*) > 75th percentile; (*gray box*) ≤75th percentile. The WC deciles correspond to the following absolute values of stature of studied population: (*1*) 53 cm, (*2*) 55.90 cm, (*3*) 57.50 cm, (*4*) 59.50 cm, (*5*) 62 cm, (*6*) 65 cm, (*7*) 68 cm, (*8*) 71 cm, (*9*) 76.74 cm. The numbers between parentheses represent the number of individuals of the sample in each decile of WC (Reprinted with permission from J Pediatr (Rio J). 2014;90(5):479–485)

Leptin

The use of fat stores is essential in situations of food restriction and undernutrition. Adipose tissue is the local synthesis of many hormones such as leptin, adiponectin, plasminogen activator inhibitor-1 (PAI-1), and others, which are collectively referred

to as adipokines. Leptin is considered an adipostat signal because it provides a good measure of the volume of the adipose tissue (Park and Ahima 2015).

Leptin is regulated by peripheral factors such as insulin, cortisol, estrogens and tumor necrosis factor alpha (TNF-alpha) (Park and Ahima 2015). It acts particularly at the hypothalamic level through binding to the ObRb receptor (Park and Ahima 2015); and its main action is to regulate (stimulatory effect) the expression of the anorexigenic peptides and inhibit orexigenic hormones in the nucleus arcuate. Leptin acts synergistically with the peripheral hormonal signals to influence the release or inhibition of these peptides and, consequently, the regulation of energy expenditure and eating behavior.

Leptin is considered a "starvation hormone" because of its strong signaling action in the central nervous system in energy deficit and the activation of counterregulatory mechanisms to conserve energy as the reduction of thyroid hormones, basal metabolic rate, and protein turnover (Prentice et al. 2002). Leptin also plays an important role in the control of linear growth, pubertal development, cardiovascular and immune function (Soliman et al. 2012).

Studies in children with kwashiorkor or marasmus have demonstrated lower leptin concentrations compared to healthy children (Soliman et al. 2000). Similar findings have also been observed in Brazilian children with mild to moderate undernutrition (Martins et al. 2014).

Reproductive Hormones

Undernourished children have delayed puberty and lower concentrations of FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone) (Iwasa et al. 2015). The decrease in these hormones contributes to a delay in the menarche. It is well established that the organism has to reach a critical weight and body size for the initiation of puberty, regardless of the age at which started the spurt of adolescence growth, and leptin plays a key role in this mechanism (Iwasa et al. 2015). As the leptin concentrations are lower in undernourished individuals, the excitatory effect of leptin in the GnRH expression is impaired. In this condition, the activity of hypothalamus pituitary gonadal axis is decreased, explaining at least in part the delay in pubertal developmental in undernourished adolescents (Iwasa et al. 2015).

The major endocrine changes in undernutrition are summarized in Figs. 3 and 4.

Metabolic Programming

Changes in Body Composition

Undernutrition promotes long-term changes in body composition, by increasing central fat mass, and therefore, ensuring fast availability of energy (Martins et al. 2004; Hoffman et al. 2007). Undernourished children have also lower resting metabolic rate associated with lower lean mass and this decrease in energy expenditure helps the

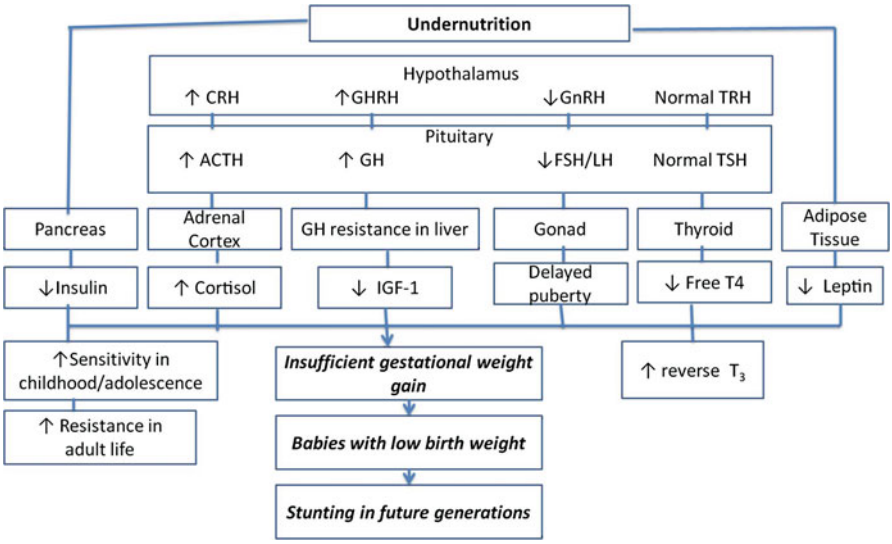

Fig. 3 Major endocrine changes found in undernutrition. These changes are associated with increased risk of development of noncommunicable diseases in adulthood and may impact next generations

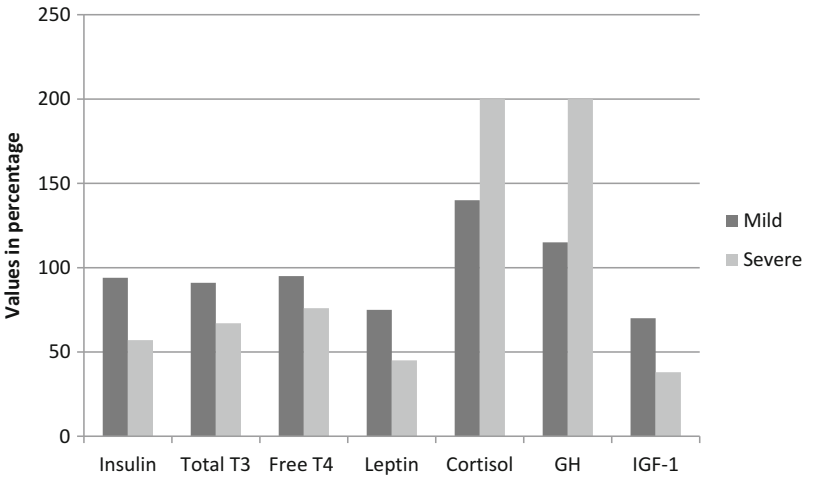

Fig. 4 Changes in hormonal concentrations in children that suffer mild or severe undernutrition. Hormonal concentrations are presented in percentage of normal hormone concentration (100%). Leptin, GH, and IGF-1 concentrations are influenced by age and gender. Cortisol concentration is positively associated to the degree infection. The increase or decrease in hormone concentrations depends of the degree of undernutrition, energy balance and protein intake. For example, acute severe undernutrition (72 h) can promote wide hormonal changes such as 75% decrease in leptin (accompanied by a weight loss). Children with kwashiorkor have high GH concentration and when treated with protein during 3 days show 50% decrease on GH concentration. This decrease does not occur when the children are treated with carbohydrate only

increase in fat mass (Soares-Wynter and Walker 1996; Sawaya et al. 2003). In addition, smaller increments in bone mineral density were described in undernourished adolescents of both sexes during prospective studies (Martins et al. 2011). A decrease in fat oxidation was also identified (Hoffman et al. 2000). These findings demonstrate that in environmental conditions where the consumption of energy and nutrients is insufficient or inadequate, the organism prefers to reduce growth and energy expenditure, while at the same time activating mechanisms of energy conservation.

Hypertension

High prevalence of hypertension has been found in children, adolescents (Fernandes et al. 2003), and adults (Florêncio et al. 2004) that suffer undernutrition. Intrauterine development of the kidney is particularly affected by maternal undernutrition due to the lower number of nephrons formed (Hinchliffe et al. 1992). The renal structure and specifically the number of nephrons are some of the main determinants of blood pressure and renal function, so that individuals with low numbers of nephrons have a predisposition to hypertension.

Maternal short stature is independently associated with obesity, abdominal obesity, and increased blood pressure and is an important determinant of children's health, as it is associated with low birth weight and stunting (Ferreira et al. 2009).

Some mechanisms have been proposed to explain the development of hypertension in this population. A deficit in elastin synthesis of the aortic wall and large vessels was described, and this deficiency may cause changes in the mechanical properties of the vessel (Martyn and Greenwald 2001). Changes in the renin-angiotensin-aldosterone and sympathoadrenal system also have been found. Girls born small for gestational age showed increased noradrenaline concentration when compared to those born with adequate weight for gestational age (Franco et al. 2008). The boys, on the other hand, showed increased activity of the angiotensin-converting enzyme and higher angiotensin II activity.

Diabetes

It is known that poor countries with accelerated urbanization have shown an increase in the prevalence of type 2 diabetes (Yajnik 2004). Diabetes among Ethiopian adults, for example, was shown to be associated with a history of undernutrition and lack of basic sanitation in childhood, reinforcing the importance of adequate postnatal development for long-term health maintenance (Fekadu et al. 2010). Adults who suffered intrauterine growth restriction have also higher risk of development of diabetes (Forsén et al. 2000).

Nutritional Recovery

One of the biological variables that have the greatest impact on the long-term health is stature. Special attention to the quality of the diet is then essential during nutritional recovery, especially in the quality of the protein intake, to allow the

gain in stature without an exaggerated increase in the energy supply. As an example, undernourished school-aged children treated with high-protein diet showed an increase in height directly related to the amount of protein supplementation compared to a group fed an oil-added diet (Kabir et al. 1998). Refeeding these children with normocaloric and normoprotein diet increased IGF-1 concentrations after 5 days by up to 70% of the basal levels before feed restriction, whereas refeeding with isocaloric but hypoprotein diet delayed recovery in IGF-1 for 2 days, and the concentrations of these hormones did not reach 50% of the prerestriction values (Thissen et al. 1999).

One strategy to adequate recovery in height and weight of undernourished children is the investment in the creation of rehabilitation centers with outpatient and day-hospital services. Few decades ago, some rehabilitation centers were established in Brazil in Southeast area in the city of São Paulo, and later in Northeast area, in the city of Maceió, one of the poorest areas of the country. These centers are called Centers for Nutrition Education and Recovery (CREN). They offer treatment to thousands of undernourished children living in urban slums every year. In the box, there is a detailed description of the methodology of the treatment developed at CREN in Brazil, aiming the recovery of height as well as weight.

Policies and Protocols

CREN Treatment Protocol at day Hospital

Active search is an important aspect of the CREN methodology to find undernourished children directly at the community level (Fig. 5). After identifying children with underweight and/or stunting by anthropometric census, families are visited at home and invited to CREN for treatment.

Any child under 5 years of age with weight-for-height and/or height-for-age Z score < -2.00 is eligible for day-hospital treatment. Children that present diseases which potentially could affect linear growth (e.g., hypothyroidism, deficiency of growth hormone, congenital cardiac diseases, genetic syndromes, or cystic fibrosis) are referred to other health services.

The daily follow-up aims at providing an overall improvement of the nutritional, cognitive, motor, psychological, and social status. The children stay at the center, from Mondays to Fridays, from 7:30 to 17:30. During the day, they engage in educational activities and are divided into groups of approximately 15 children, according to their ages. Pediatricians, nurses, dieticians, social workers, psychologists, and teachers participate in the treatment. The intervention included treatment of all diagnosed infections and other conditions, such as anemia and a diet that rotated daily every 11 weeks, as follows:

7:30–8:30: Patients are admitted. Breakfast (one serving of dairy and carbohydrates, such as bread, biscuits, or cake).
9:00: Snack (one serving of fruit).

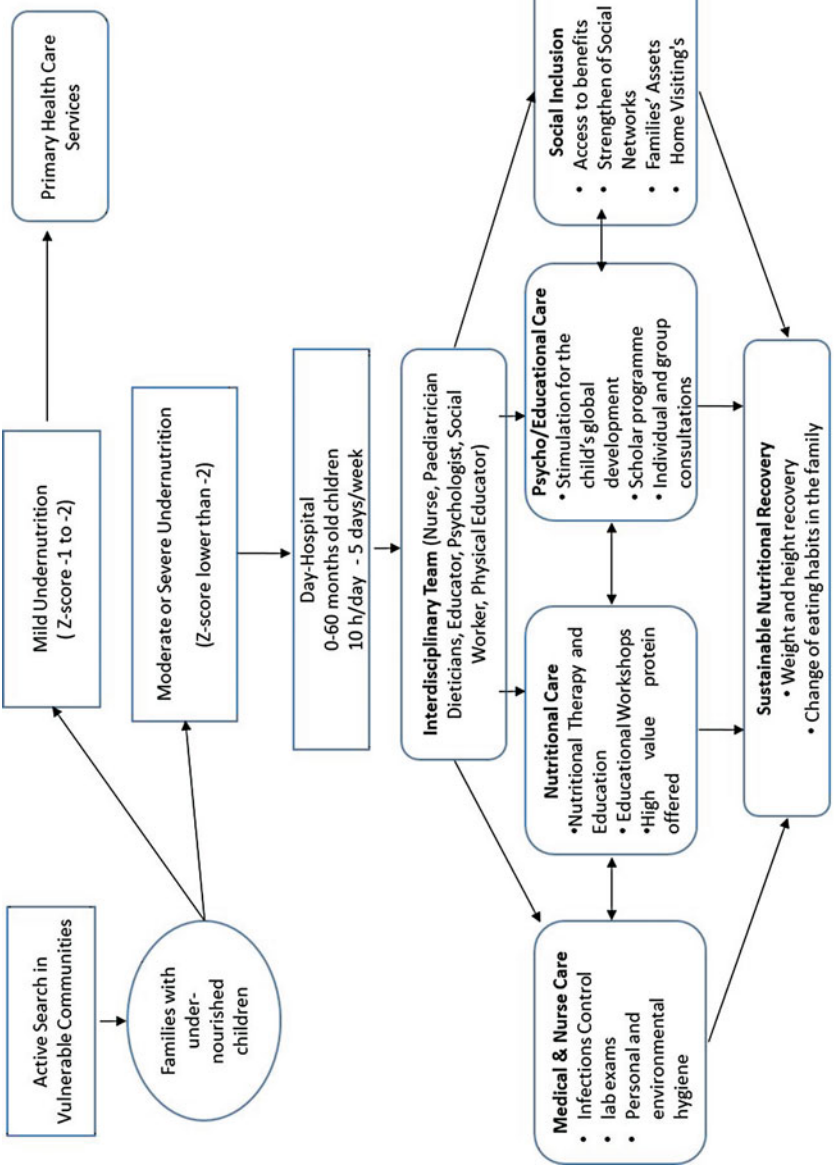

Fig. 5 Flow of day hospital treatment for undernourished children at CREN. For adequate treatment of undernourished children, an interdisciplinary team is necessary

11:30: Lunch: Rice, beans, meat or eggs, salad, and cooked vegetables with a dessert of fruit.
12:00: Nap.
13:30: Afternoon activity period.
14:00: Snack (one serving of dairy).
16:00: Afternoon meal: Rice, beans, protein (fish, beef, chicken, or pork), salad, and cooked vegetables with a dessert of fruit.
17:30: Return to home.

All children receive five meals each weekday using traditional Brazilian food such as: rice, beans, meat, fruit, and vegetables. Ultraprocessed foods are excluded. Meals are provided to meet 70% of daily energy requirements, 100% of daily dietary protein using biological high-value protein (meat, eggs, and milk), and recommended fiber intake according to the Dietary Reference Intake (Trumbo 2002). The meals provided to children supply approximately the following macronutrient composition as percent of total calories for children 6–12 months, 1–3, and 4–8 years of age, respectively: 45% carbohydrates, 15% protein, and 40% fat; 55% carbohydrates, 15% protein, and 20% fat; and 57% carbohydrates, 17% protein, and 18% fat. The family of each child is instructed to offer two more meals at home. Infant formulas are used for children less than 1 year of age who are no longer breastfed. Food supplements or special formulas are not used.

Micronutrient supplements like iron (Wayhs et al. 2012), zinc (Trumbo et al. 2001), and vitamins are used in prophylactic doses. Higher doses are used in cases of deficiency, with clinical or laboratory evidence, according to the recommendations of the Brazilian Pediatric Society (Wayhs et al. 2012; de Paula et al. 2016).

A pediatrician monitored the clinical status, laboratory results, and anthropometric progress of each child on a daily basis during their treatment at CREN as follows:

7:30–8:30: Patients are admitted and undergo a preliminary exam by nurses and are referred to the attending pediatrician for a physical exam. When health problems are detected, antibiotics, bronchodilators, and/or other necessary medications are prescribed.
9:00: Micronutrient supplementation: Vitamin complexes (A, B, C, and D) and Zn are provided to all children. Iron is provided according to age and laboratory test results. Administration of medications to patients as needed.
12:00: Oral hygiene and nap.
13:00: Monitoring of vital signs during sleep (i.e., temperature, pulse, and respiratory rate) and bathroom break (monitoring and recording of bowel movements and urination).
15:00: Administration of medications to patients as needed.
16:45: Oral hygiene and bathroom break (monitoring and recording of bowel movements and urination).
17:15: Consulting period with nurses to determine follow-up of medication protocol and continuation of basic health care at home for patients receiving medications.

Nutritional Education

An important aspect of CREN's intervention is nutritional education. The children participate in nutrition education workshops according to the psychomotor and cognitive readiness with the objective of facing the feeding problems. The contents of these workshops aim at the knowledge of the varieties of fruits and vegetables, to promote the neuropsychomotor development, improving the relationship between child and food, enhancing palatability, and promoting the development of good eating habits. Parents are also involved in treatment in frequent activities through the participation in regular nutrition education workshops for reinforcement of nutrition, for the expansion of its social networks and for health advice. Novel foods are also displayed during these meetings.

Monitoring and Treating Infectious Diseases

Children are monitored for infections on daily basis. Parents and caregivers are required as to the presence of symptoms such as fever, cough, runny nose, dyspnea, vomiting, diarrhea, or presence of worms in the stool. Positive responses are recorded. Diagnosis is recorded along with notation of medications prescribed. Intestinal parasites are confirmed by testing of stool sample or by maternal report of occurrence of intense anal itching or elimination of worms in feces. All children admitted at the Day Hospital receive deworming medication.

Discharge

Discharge from the day-hospital occur when the child reaches the weight and height for age greater than −1.64 Z scores or when they reach the age to enter regular school (6 years). Following discharge, the child continues to receive treatment using an established outpatient regimen.

A description of the nutritional and health outcomes of a sample of children treated at CREN showed that 92.5% of the children recovered at least one anthropometric index and 67.9% recovered weight and height (Alves Vieira et al. 2010). Almost half of the children presented nutritional recovery of more than 0.50 Z score in height for age (46.2%) and about 40% in weight for age (38.7%). The mean age at admission was 23.7 months, with an equal proportion of boys and girls. The mean duration of treatment was 16.4 months for all children, and the longer treatment time was associated with higher weight for age and height for age increases. The mean birth weight was 2563 g, and approximately 40% of the children were classified as low birth weight. The gain in stature was statistically different according to the birth weight, being greater among those who were born smaller. The most prevalent diseases during treatment were upper respiratory infections, and 82% of children showed at least one episode, 44% had diarrhea, and 18% had lower respiratory tract infections.

Recovered children at CREN present increase in height for age greater than weight for age, in general. Past studies showed normalization of body composition

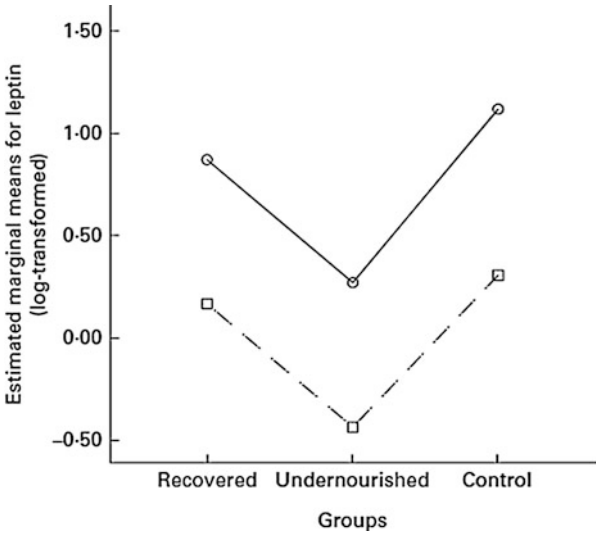

Fig. 6 Serum leptin concentrations in children recovered from undernutrition, undernourished, and well-nourished children. Boys (*dotted line*) have significantly lower leptin concentrations than girls (*continuous line*). Leptin concentrations in both sexes in the undernourished group were significantly lower than those in the other two groups. The scale is in logarithms (Reprinted with permission from British Journal of Nutrition (2014), 112, 937–944)

and bone mass (das Neves et al. 2006). In terms of food consumption, a study found higher protein intake in recovered children, compared to a control nontreated group of children living in the same poor communities, even after 6 years of discharge. Moreover, recovered children demonstrated normalization of insulin and glucose metabolism (Martins et al. 2008), and normal leptin concentrations in both sexes (Fig. 6) (Martins et al. 2014).

A study performed with the objective of determining cortisol activity found lower cortisol response after recovery comparing to undernourished children, but similar to that of well-nourished controls, indicating a normal HPA response after treatment (Martins et al. 2016). The daily cortisol response was also measured after an unpleasant stimulus (immersing the right hand in cold water for 1 min, at 10:00 h) (Fig. 7) and a pleasant stimulus (watching a video with pictures of nature at 14:00 h) (Fig. 8). After the application of the unpleasant stimulus, there was an increase in cortisol for all children (controls, stunting, and underweight) with exception of the recovered ones. No significant differences were found between groups in terms of response to the pleasant stimulus, with exception of a slight elevation in cortisol concentrations among undernourished children.

Another interesting result was lower free T4 concentrations in the recovered children in comparison to controls (Martins et al. 2016). This can indicate a programming effect that may lead to future accumulation of body fat, and this justifies the maintenance of a continuous observation of anthropometric and clinical indicators as well as encouragement for healthy lifestyles in these children.

In conclusion, programs and policies should be designed to prevent undernutrition taking into account the findings on its long-term effects on the health of the world's low-income population.

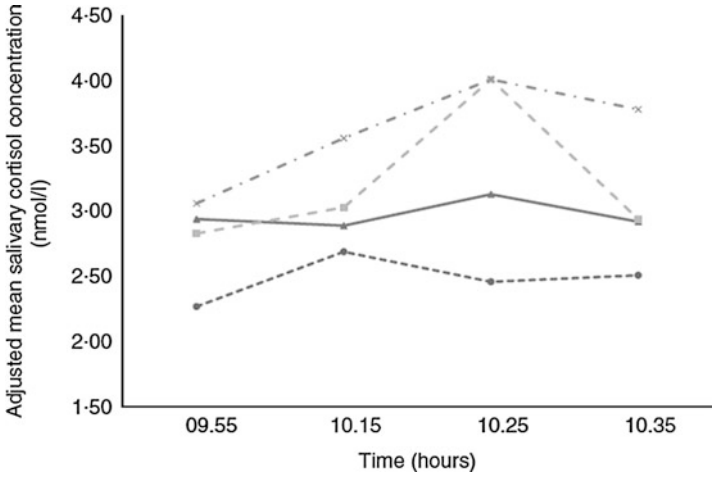

Fig. 7 Salivary cortisol concentrations in children recovered from undernutrition, undernourished, and well-nourished children submitted to unpleasant stimulus (cold pressor test). Salivary cortisol concentrations were similar in all groups before the application of the stimulus and increased after the unpleasant stimulus in the control, stunted, and underweight groups but not in the recovered group. Control; stunted; underweight; recovered (Reprinted with permission from Br J Nutr. 2016 14;115(1):14–23)

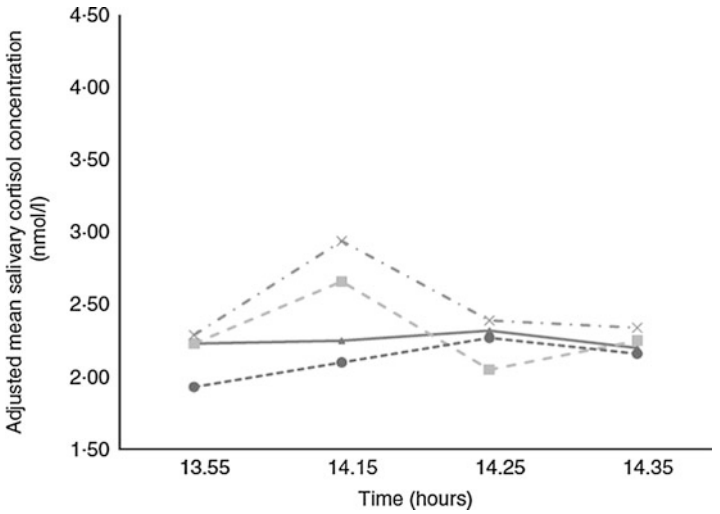

Fig. 8 Salivary cortisol concentrations in children recovered from undernutrition, undernourished, and well-nourished children submitted to pleasant stimulus (pictures of nature). No differences were found between groups in terms of response to the pleasant stimulus; however, the undernourished groups showed an increase of salivary cortisol after the pleasant stimulus in comparison with the recovered and control groups. Control; stunted; underweight; recovered (Reprinted with permission from Br J Nutr. 2016 14;115(1):14–23)

Dictionary of Terms

- **Undernutrition** – Refers to children with low weight for age, short stature for age or stunting.
- **Basal metabolic rate** – Oxygen consumption in total rest, refers to basal energy expenditure (after 12 h of fasting and 8 h of sleep).
- **Resting metabolic rate** – Oxygen consumption measured in recumbent position. This value is higher than basal metabolic rate.
- **Programming** – Adaptation to any kind of biological or psychological insult (low supply of nutrients and energy, for example) that occurs during critical periods of body development (intrauterine or postnatal period). This metabolic adaptation, at one hand, allows the individual to survive, but at the cost of permanent changes in the morphology and physiology of organs.
- **Z-score** – Can be positive or negative, with a positive value indicating the score is above the mean and a negative score indicating it is below the mean. Positive and negative scores reveal the number of standard deviations; the score is either above or below the mean.

Summary Points

- Undernutrition in early life promotes morphological and physiological changes associated with programming effects and noncommunicable diseases in adulthood.
- Undernourished children, adolescents, and adults show lower thyroid hormone activity.
- There is a marked decrease in IGF-1 in undernutrition, although higher GH concentrations can be observed.
- Undernutrition is a major form of stress and, therefore, shows higher cortisol concentrations.
- Undernourished children have normal/low glucose concentrations, lower insulin production, and higher insulin sensibility. This condition is associated with the development of insulin resistance in adulthood and diabetes.
- Lower concentrations of leptin can be observed in undernourished children.
- Undernourished children have delayed puberty and lower concentrations of FSH and LH.
- Undernutrition in early life is associated with the development of hypertension in adult life.
- Undernutrition in children promote changes in body composition. Higher fat mass and lower lean mass can be observed in stunted children.
- Adequate treatment is important to ensure recovery of height and weight. Recovered children show normal insulin, leptin, and cortisol concentrations.

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