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The interaction between neuroendocrine and immune systems in infants and children during under nutrition

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Abstract

Malnutrition remains an international concern because it represents a major cause of childhood morbidity and mortality. In infants and children malnutrition significant metabolic, hormonal, and immune changes occur with short- and long-term effects and outcomes. Thus, studies which contribute to the prevention, amelioration, or rehabilitation of the detrimental effect of malnutrition are necessary. Investigations on endocrine, metabolic, and immune changes related to severe malnutrition started a long time ago. However, recently there has been little work on these important changes, their mechanism/s of action and interactions, and their effect on different systems. The neuroendocrine system is the initial response to stress, so it is reasonable to assume that this system also plays a key role in the pathophysiological changes during nutritional deprivation. However, many of the newly identified functions/changes are better explained by the action of conventional neurotransmitters (e.g., glutamate and GABA) that constitute a neuronal circuit. In addition, the mechanistic Target of Rapamycin (mTOR) is an evolutionarily conserved serine/threonine kinase has emerged as a sensor for nutrients that has a central joint in cellular metabolism, cell growth, and differentiation. Its functions during malnutrition in the central nervous system, endocrine system, and different end organs and tissues (liver, pancreas, muscle, and adipose tissue) need elucidation. This article presents a brief review of neuroendocrine changes during malnutrition and their effects on the modulation of metabolism, growth, and immune functions. The pros and cons of these endocrine changes are discussed as well as their reversibility on nutritional rehabilitation.

Keywords: Neuroendocrine; Hormones; Immune system; Growth; Infection; Inflammation; Enteropathy

1. Introduction

About 8 million of the world's children under the age of 5 years die every year; undernutrition is the underlying factor in 35% of these cases (1–3). The consequences of chronic malnutrition in children are both immediate and long-term and include increased morbidity and mortality, poor child growth and development, impaired learning capacity, and increased risk of infections. In addition, they have an increased risk of developing non-communicable diseases including obesity, diabetes, hypertension, and dyslipidemia. During their adulthood, they have lowered working capacity and unfavorable maternal reproductive outcomes. (3-7) However, obesity, as a form of malnutrition, is not a part of this review.

The neuroendocrine system including the hypothalamus, and pituitary gland, and their network connections represent a major regulatory system. The hypothalamic hormones control the secretion of the anterior pituitary hormones which are necessary for adaptation to internal and external stresses, growth, reproduction, and metabolism. Body homeostasis

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including linear growth and weight gain is predominantly controlled by hormones secreted by endocrine organs. In addition, the neuroendocrine system also cooperates with the immune system in regulating body responses to various forms of stress and in modulating responses to stimuli provoking immunologic responses. (8,9)

Conventionally, neurohormones released by the hypothalamus and the pituitary gland have received much consideration owing to the distinctive roles of the end hormones released by their target peripheral organs (e.g., glucocorticoids, growth hormone, thyroxine). (10)

Recent advances have revealed several important metabolic functions of hypothalamic neurohormone-expressing cells, many of which are not readily explained by the action of the corresponding classical downstream hormones. These newly identified functions are better explained by the action of conventional neurotransmitters (e.g., glutamate and GABA) that constitute a neuronal circuit. For example, leptin (secreted by adipose cells) plays an important role in regulating energy balance largely through acting on γ-aminobutyric acid (GABA)ergic neurons in the brain. Ghrelin is an orexigenic hormone primarily produced in the stomach and increases appetite as well as growth hormone (GH) release. Ghrelin antagonizes leptin by reducing the firing of proopiomelanocortin (POMC) neurons by raising the frequency of spontaneous synaptic γ-aminobutyric acid (GABA) release onto them. (11-12)

In addition, the mechanistic Target of Rapamycin (mTOR) is an evolutionarily conserved serine/threonine kinase which is a member of the PI3K related kinase (PIKK) family, has emerged as a sensor for nutrients that has a central joint in cellular metabolism, cell growth, and differentiation, in the central nervous system as well in different tissues (liver, pancreas, muscle, and adipose tissue). (13)

The malnutrition-related immune suppression increases susceptibility to infection and is characterized by recurrent infections and chronic inflammation. Both infection and inflammation aggressively contribute to malnutrition which causes and perpetuates a vicious cycle. Death rates from diarrhea, pneumonia, measles, and malaria are increased considerably in undernourished children. (14) Malnutrition causes immunosuppression through a variety of peripheral and central mechanisms, including the involvement of the central nervous system and endocrine system.

Investigating the possible relation/s between changes in the neuroendocrine system and immune system represents an important step to understand the pathophysiologic mechanisms that contributes to lowered systemic and local immunity during chronic malnutrition. (15,16)

Classical studies analyzed the levels of selected hormones and metabolites in undernourished infants and young children and healthy adults subjected to prolonged fasting. Yet link between these hormonal changes and the pathogenesis of malnutrition remains inadequately recognized. In this review, we studied the changes of the neuroendocrine system reported by different investigators and discussed their possible effects (pros and cons) on body homeostasis (metabolic, growth and immune functions) in infants and children during severe malnutrition as well as the effect of nutritional rehabilitation on these changes. (17-21)

2. Discussion

2.1. General perspectives

The neuroendocrine system is the initial response to stress, so it is reasonable to assume that this system also plays a key role in the pathophysiological changes during nutritional deprivation. In addition to their metabolic effects, recent research suggested and proposed an important role of hormonal changes in the control of growth, musculoskeletal system, immunity, inflammation, and response to infection. (9) Activation of the HPA axis provides a slower, sustained, and amplified physiological response to stress including starvation. Stressor perception is communicated to neurons in the PVN which in turn release corticotropin-releasing hormone (CRH) and other releasing factors, from in the median eminence. CRH passes through the hypothalamic-pituitary portal circulation to the pituitary and stimulates the release of adrenocorticotropic hormone (ACTH) from corticotropes into the systemic circulation. Subsequently, ACTH stimulates the adrenal cortex to produce and secrete cortisol. Glucocorticoids act on their receptors throughout the brain and body to exert numerous effects, including mobilization of stored energy. Glucocorticoids mobilize fuel from the liver via increased gluconeogenesis and from white adipose tissue by increased lipolysis. The net effect is to increase the availability of fuel, facilitating a physiological response to the (starvation) threat. (22-24)

The central nervous system and the autonomic system combine and integrate multiple peripheral signals to control appetite. Peripheral hormonal messages indicative of long-term energy whole-body status are produced by adipose tissue including leptin, and adiponectin. On the other hand, acute orexigenic (+) ghrelin signal (produced in the gut) and

anorexigenic (−) signals such as the gut hormones peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and cholecystokinin (CCK), and the pancreatic hormones [insulin, glucagon, amylin, and pancreatic polypeptide (PP)] indicate long-term energy status. Proopiomelanocortin (POMC) neurons mainly located in the arcuate nucleus of the hypothalamus and the nucleus tractus solitarius of the brainstem are the site of this control. POMC neurons are inhibited by energy deficits. During fasting (starvation), for instance, when both glucose and insulin levels drop, certain POMC neuronal subsets could either be activated or inhibited, working towards the same goal of increasing plasma blood glucose or reducing glucose uptake into peripheral organs, to maintain constant systemic glucose levels. (25-26)

The functions of the mechanistic mTOR system during malnutrition. In addition to the central mechanisms regulating endocrine, growth, and immunological changes during nutritional deprivation stress, control through the Target of Rapamycin (mTOR) represents a major cellular control mechanism. The mechanistic mTOR is an evolutionarily conserved serine/threonine kinase that is a member of the PI3 K-related kinase (PIKK) family. mTOR emerged as a central joint in cellular metabolism, cell growth, and differentiation. It senses the nutrients, energy, insulin, growth factors (GH and IGF1), and environmental signals and transmits signals to downstream targets to downregulate nutrient and energy use and helps cells survive periods of starvation and intermittent fasting. During malnutrition shortage of nutrients (amino acids, glucose) and lower insulin and IGF1 decrease, the mTOR activity which decreases the mTOR medicated cellular protein synthesis and lipogenesis and epiphyseal cartilage growth. Notably, mTOR has been also implicated in the regulation of both the innate and adaptive immune responses. (27-29)

In the liver, this inhibition of mTOR is required for inhibiting lipogenesis and activation of ketogenesis and it regulates the hepatic glucose output and peripheral lipid metabolism. In skeletal muscle, mTORC1 activity exerts a significant effect on muscle mass by affecting protein synthesis and degradation (autophagy process). mTOR inhibition increases the rate of protein degradation and decreases protein synthesis. (Muscle wasting) and decreases skeletal muscle insulin sensitivity. In addition, glucocorticoids may regulate mTOR by modulating the level of both BCAT2 and myostatin to regulate catabolism in skeletal muscle. (30-32)

In the brain, within the hypothalamus, mTOR functions as a cellular signaling hub that integrates internal and external cues (which is associated with changes in energy status) to control the central or peripheral tissue functions. mTOR plays a critical role in the regulation of food intake and body weight. mTOR combines and coordinates signals from various "energy controlling " hormones such as leptin, insulin, IGF-I, and ghrelin. This regulatory mechanism occurs in the arcuate nucleus (ARC) of the hypothalamus. Peripheral hormones such as ghrelin and leptin act on 2 types of neurons that can analyze the metabolic status of the periphery: 1. The orectic neurons [neuropeptide Y (NPY)/agouti-related peptide (AgRP) containing neurons and 2. The anorectic neurons [POMC and cocaine- and amphetamine-regulated transcript (CART)-containing neurons]. (32-34) On the other hand, inhibition of mTOR negatively affects immunity because mTOR plays a central role in the differentiation of T-cell subsets, and controls aspects of B-cell and antigen-presenting cell (APC) development. (32-36)

There are bi-directional circuits linking CNS and immune systems. The CNS can connect with the immune system to regulate its activity, through the autonomic nervous system, the catecholaminergic pathway, or the neuropeptides, and through controlling anterior pituitary hormone release. In this perspective, GH and IGF1, corticosteroids, insulin, and leptin can modulate the immune system by different mechanisms. (9)

3. Hormonal changes and their effect on metabolism, growth, and immunity during malnutrition: (figure 2)

3.1. Adipocyte Hormones

3.1.1. Leptin

Leptin secretion and its level in blood are low in all forms of malnutrition (mild, moderate, and severe) due to lower or depleted fat mass. (36-38) The leptin level serves as a measure of energy reserves (adipose tissue) and instructs the central nervous system to manipulate food consumption and energy spending accordingly. In response to fasting and starvation, leptin levels fall rapidly before and out of proportion to any changes in fat mass. Low leptin levels have been documented in all studies of children with malnutrition despite the lack of standardization of the timing of the collection of samples. (39) The fall in serum leptin concentration leads to neurohumoral and behavioral changes, trying to preserve energy reserves for vital functions. Emerging evidence suggests that starvation hypo-leptinemia increase the activity of the hypothalamic-pituitary-adrenal axis, promoting white adipose tissue (WAT) lipolysis, increasing hepatic acetyl-CoA concentrations, and maintaining euglycemia. In addition, leptin is also responsible for facilitating the shift from a dependence upon glucose metabolism (absorption and glycogenolysis) to fat metabolism (lipolysis increasing

gluconeogenesis). This function sustains the supply of energy substrates to the brain, heart, and other vital organs. In this way, a leptin-mediated glucose-fatty acid cycle appears to maintain glycemia and permit survival in starvation. (37-40)

Leptin promotes IFN-γ secretion by memory T cells, inhibits Th2 responses, and induces activation markers (CD69, CD25, and CD71). In addition to inducing lymphopoiesis, leptin seems to deliver survival signals to T cells (94) In innate immunity, leptin enhances the activity of neutrophils by the release of oxygen free radicals. It stimulates the migration of immune cells at the sites of inflammation through increasing intercellular adhesion molecule-1 (ICAM-1). Moreover, leptin activates the monocytes and dendrite cells (DCs) that in turn leads to the production of pro-inflammatory cytokines such as TNF-α, and IL-6 along with IL-12, a key cytokine that facilitates the shifting of T-cells toward the Th1 phenotype. Leptin also promotes DCs survival by triggering the activation of nuclear factor-kappa B (NF-kappa B) (41-44)

These important functions explain how leptin deficiency negatively influences cellular immunity and predisposes to infection. Leptin deficiency in both mice and humans results in severe immune defects characterized by a decrease in total lymphocytes, CD4+ helper T cell number, increased thymocyte apoptosis, and a shift from the Th1 toward Th2 phenotype. These changes increase susceptibility to intracellular infections. The systemic leptin deficiency in malnutrition correlates with several bacterial, viral, and parasitic infections due to defective cytokine production. These include tuberculosis, pneumonia, sepsis, colitis, viral infection, leishmaniasis, trypanosomiasis, amoebiasis, and malaria. (44) In 77 edematous and non-edematous undernourished children a diminished leptin level was the most reliable biochemical predictor of mortality. (45,47)

3.1.2. Adiponectin

Bartz et al reported decreased Adiponectin in their undernourished children which increased significantly on nutritional rehabilitation. (46) Adiponectin is one of the key adipocyte-derived hormones that regulate systemic or tissue lipid and glucose metabolism. Contrary to the action of other adipocyte-derived hormones, adiponectin improves insulin sensitivity and enhances lipid and glucose metabolism. It increases fatty acid oxidation in the liver and muscle. It promotes insulin-sensitizing and fat-burning which can be useful during malnutrition. Adiponectin plays a role in insulin sensitivity by impacting insulin sensitivity in skeletal muscle and liver and increasing insulin release from beta cells. Low adiponectin (secreted by adipocytes) may lead to impaired insulin secretion and decreased insulin sensitivity in these children. (48-51) The anti-inflammatory properties of Adiponectin are due to its suppression of M1 macrophage activation and supporting M2 macrophage proliferation. It decreases inflammation, apoptosis, and oxidative injury in muscle, heart, and brain. Its decrease during malnutrition may encourage the inflammation process and increase oxidative tissue injury. (52)

3.2. Gut hormones

The gastrointestinal (GI) tract is the body's largest endocrine organ producing hormones that have important sensing and signaling roles in the regulation of energy homeostasis. (53) Ghrelin is a multifaceted gut hormone with many functions including stimulating food intake, fat deposition, and growth hormone release. Ghrelin regulates glucose hemostasis by inhibiting insulin secretion and regulating gluconeogenesis/glycogenolysis. Ghrelin shares in maintaining glucose homeostasis during starvation through increasing glucose synthesis and release by activating gluconeogenesis and/or increasing growth hormone. Bartz et al reported hyper-ghrelinemia in undernourished children. (46) The high Ghrelin stimulates GH secretion which promotes lipolysis and maintains blood glucose through stimulating hepatic gluconeogenesis. The lipolytic and gluconeogenic effects of GH are independent of IGF-I. (53-56) GLP-1 is secreted in the small intestine in response to nutrients. It promotes glucose-dependent insulin secretion, decelerates gastric emptying, and reduces food intake.

On the other hand, intraluminal nutrients, particularly fats stimulate the secretion of PYY by enteroendocrine cells. PYY inhibits gastric emptying and induces satiety. Levels of GLP-1 and PYY at baseline were found to be considerably higher in undernourished infants compared to normal infants and children and declined sharply during outpatient RUTF treatment. The significant increase of these GI hormones during malnutrition helps to delay gastric emptying and give longer time for nutrient absorption. Low levels of leptin and adiponectin and high levels of PYY were correlated with mortality in these children. (57)

Many undernourished children living in low-income countries (LICs) suffer from environmental enteric dysfunction (EED). EED refers to a subclinical enteropathy characterized by mucosal inflammation and villus blunting mediated by T cell activation. Exposure to intestinal pathogens and intestinal dysbiosis (an imbalance of the microorganisms within the intestine), as a consequence of poor sanitation and possibly specific micronutrient deficiencies (e.g., zinc, vitamin D,

vitamin A, and protein), lead to intestinal inflammation and disruption of intestinal barrier function. The damaged barrier function permits the translocation of pathogens (bacteria and bacterial products from the intestine to the mesenteric and systemic circulation. This exposure activates innate immune cells in the mesenteric lymph nodes, liver, and systemic circulation to generate proinflammatory cytokines. (58,59)

Zonulin is a hormone secreted mainly from the liver, but also from enterocytes, adipose tissue, brain, heart, immune cells, lungs, kidney, and skin. It is a master modulator of the intercellular tight junctions, important in antigen trafficking, and is a key player in regulation of the mucosal immune response. Zonulin is a marker of intestinal permeability. Its concentrations correlate significantly with total calorie-, protein-, carbohydrate intake. Zonulin plays a role in the pathogenesis of malabsorption in two forms of malnutrition (anorexia nervosa and celiac disease) and probably has an important role in the pathogenesis of wasting. During malnutrition, Zonulin levels may increase due to inflammation, infection, injury, or poor diet and enhance intestinal permeability which leads to paracellular passage of non-self-antigens (D) into the lamina propria (loose connective tissue in the mucosa), where these foreign antigens interact with the immune system. It has been shown that serum zonulin levels and other markers of barrier dysfunction is correlated with stunted growth in EED patients. (60)

In mice, it has been demonstrated that vitamin D deficiency (VDD), a common association in undernourished children, could lead to a significant upregulation in mRNA expression of the jejunum zonulin level with increase of serum level of zonulin. (60) Directly blocking zonulin by larazotide acetate (AT-1001), a first-in-class TJ regulator, is currently used in phase III clinical trials for celiac disease to improve intestinal barrier function. (61) The first randomized controlled phase IIb trial of an anti-inflammatory drug for environmental enteric dysfunction (EED) using aminosalicylate mesalazine proved its safety with modest reductions in several inflammatory markers compared to placebo. Before mesalazine treatment the IGF-1 concentration was negatively correlated with several inflammatory markers. With mesalazine treatment for 56 days, there was an increase in the IGF-1 level and decreases in the inflammatory marker concentrations that correlated with linear growth. (62)

3.3. Insulin and glucose homeostasis

Severe malnutrition predisposes children to develop either hypo- or hyperglycemia. During severe malnutrition, depleted glycogen stores and adipose tissue reserves have been correlated to hypoglycemia. In severely undernourished children, especially edematous forms hepatic glucose synthesis has been observed to be low. Hormonal changes with impaired insulin responses have been reported in severely undernourished children. Insulin responses to oral glucose and to a meal are strongly impaired in both kwashiorkor and marasmus, with low glucose clearance. Low insulin state decreases tissue and fat anabolism and permits the catabolic activity of other hormones to break down glycogen and fat to assure energy supply for vital organs and prevent hypoglycemia. Plasma insulin increases significantly during catch-up growth with nutritional rehabilitation. (63- 66) In addition, severe malnutrition, especially the edematous form, is associated with an impaired glucose absorption and decreased glucose absorption correlates with oxidative stress (infection and inflammation) in these children. (67,68)

In a meta-analysis review of 16 studies, Ledger et al reported that the prevalence of hypoglycemia in severely undernourished infants across studies based on of proportions was 9%. Meta-analysis results showed that hypoglycemia was associated with a higher chance of mortality during hospitalization in children with SAM (dys-adaptation). According to the GRADE evaluation, the certainty of the evidence for the prevalence of hypoglycemia was low and for hyperglycemia was very low. (68)

Recent findings have shown an important role for insulin in shaping the immune response during an infection. This includes the ability of insulin to modulate immune cell differentiation and polarization as well as the modulation of effector functions such as biocidal ROS production. On the other hand, both through a direct and indirect effects inflammatory mediators can control serum insulin levels. Therefore, low insulin status in severely undernourished children may adversely affect their immune response during an infection. (69)

3.4. Hypothalamic Pituitary adrenal (HPA) and GH (HPG) axes:

HPA Axis Cortisol increases markedly in children with malnutrition, especially those with infection. Hypercortisolemia causes muscle wasting both in vivo and in vitro by increasing protein breakdown and reducing protein synthesis. Metabolically, raised cortisol levels increase the availability of all fuel substrates by mobilization of glucose, free fatty acids, and amino acids from endogenous stores which reduces muscle mass and may enhance energy expenditure. The release of amino acids from muscle provides good substrate for gluconeogenesis during malnutrition which guards against hypoglycemia. (70) On the other hand, cortisol excess can adversely arrest bone growth in these children. (this spares energy for the major metabolic processes during malnutrition) (71,72)

In addition, glucocorticoids inhibit many of the initial events in inflammatory and immune responses. High cortisol inhibits the vasodilation and vascular permeability that occurs following inflammatory insult and decreases leukocyte emigration into inflamed sites, effects that require new protein synthesis. High cortisol represses transcription of many genes encoding pro-inflammatory cytokines and chemokines, cell adhesion molecules and key enzymes involved in the initiation and/or maintenance of the host inflammatory response. High cortisol can alter leukocyte distribution/trafficking, death/survival and, significantly, alter cellular differentiation programs, thus shaping the subsequent response. These different effects can be shared in the compromised immune and inflammation responses in undernourished infants. In fact, serum cortisol concentration was shown to be associated with severity and mortality in patients with pneumonia. (72-74)

3.5. Hypothalamic pituitary- growth hormone -IGF1 axis

An appropriate balance between the immune and GH-IGF systems is necessary for normal growth and immunity. In humans, GH is a critical factor to increase the rate of lipolysis during fasting. Growth hormone levels are high in children with malnutrition and represent an important means of mobilizing fat stores and maintaining euglycemia in states of under-nutrition. Yet, if the GH-IGF-I axis remained intact during states of nutritional deprivation, the elevated levels of GH would result in elevated IGF-I levels, leading to increased energy expenditure which is a clear disadvantage that compromises survival during malnutrition. Therefore, GH resistance, with an inability of GH to appropriately generate IGF-I production, is likely an adaptive mechanism to preserve calories during periods of under-nutrition. Protein deficiency not only results in GH resistance but also likely results in a state of end-organ resistance to IGF-I, with the result inhibiting growth. There appears to be a good adaptive mechanism where growth arrest spares energy necessary for survival. (72, 76) Zinc, magnesium, and vitamin B6 deficiencies that occur in many children with malnutrition have been associated with GH resistance and reduced IGF-I levels, although the mechanisms of each are unknown. (77)

Growth hormone and IGF-1 have important immunoregulatory effects. In a large cohort of undernourished children, infection and inflammation were associated with GH resistance, a low level of IGF-1, as well as with growth impairment. (78) In addition, GH and IGF-1may act to protect the host from lethal bacterial infection by promoting the maturation of myeloid cells, stimulating phagocyte migration, priming them to produce superoxide anions and cytokines, and enhancing opsonic activity. Therefore, GH resistance and low IGF1 may compromise these immunoregulatory functions during malnutrition and infection. (72,78,79) Moreover, IGF-I plays an essential role in the growth, stimulation, proliferation, and function of T cells. IGF-I regulates various aspects of T-cell, B-cell, and monocyte function through its interactions with IGF-IR. IGF-I can prolong lymphocyte survival through activation of T cell Akt. (80)

IGFs depress proinflammatory cytokine signaling by increasing IL-10 secretion and via JNK and NF-κB pathways. Therefore, in malnutrition IGF1 deficiency may negatively affect the functions of lymphocytes and predispose to infection as well as inflammation. Patients with inflammatory bowel disease (IBD) with low IGF1 have associated high inflammatory activity (ESR, CRP, and IL6). Suppression of inflammation by prednisolone or infliximab increased the IGF-1 levels and suppressed the inflammatory process. (80,81,82)

On the other hand, pro-inflammatory cytokines, which increase in severe forms of malnutrition especially those with infection, induce a dysregulation in GH–IGF axis and IGF system, both at central and peripheral levels. In the brain, inflammation/infection determines a dysregulation of GH secretion. (83)

In the liver, TNF-α, a pro-inflammatory cytokine can cause GH resistance mainly through downregulation of liver GH receptor expression. Additionally, the predominance of proinflammatory cytokines decreases IGF sensitivity by enhancing IGFBP production and by decreasing signaling through the (insulin receptor signaling) IRS/ Akt pathway. (83,84) During malnutrition, GH and IGF-1 resistance are also present in the growth plate. In these children and infants' abnormalities in IGF binding proteins (IGFBPs), with low IGFBP 3 levels, lead to a decline in IGF bioavailability. MicroRNAs (miRNAs) genes are known to regulate GH, IGF1, IGF2, and IGF1R in the context of body growth. During malnutrition, miRNAs targeting genes within the GH–IGF axis and IGF system are dysregulated. (83) The increase in local muscle cytokines produced during inflammation makes the muscle GH-resistant and reduces its own IGF-I production. Both decreased IGF-I production by muscle, and lower muscle sensitivity to the anabolic effects of IGF-I, may contribute to muscle wasting observed in response to severe malnutrition. (83,84) Myokines secreted by the skeletal muscle itself in response to inflammation have been implicated as autocrine and paracrine mediators of cachexia, as well as potential modulators of this debilitating condition. (85)

The first randomized controlled in the initial management of severely acutely undernourished children with environmental enteric dysfunction (EED) using aminosalicylate mesalazine proved its safety with modest reductions in several inflammatory markers compared to placebo. Before mesalazine treatment, the IGF-1 concentration was

negatively correlated with several inflammatory markers. With mesalazine treatment for 56 days, there was an increase in the IGF-1 level and decreases in the inflammatory marker concentrations that correlated with linear growth. (86)

3.6. Effect of Nutrition rehabilitation on hormonal changes and inflammatory markers

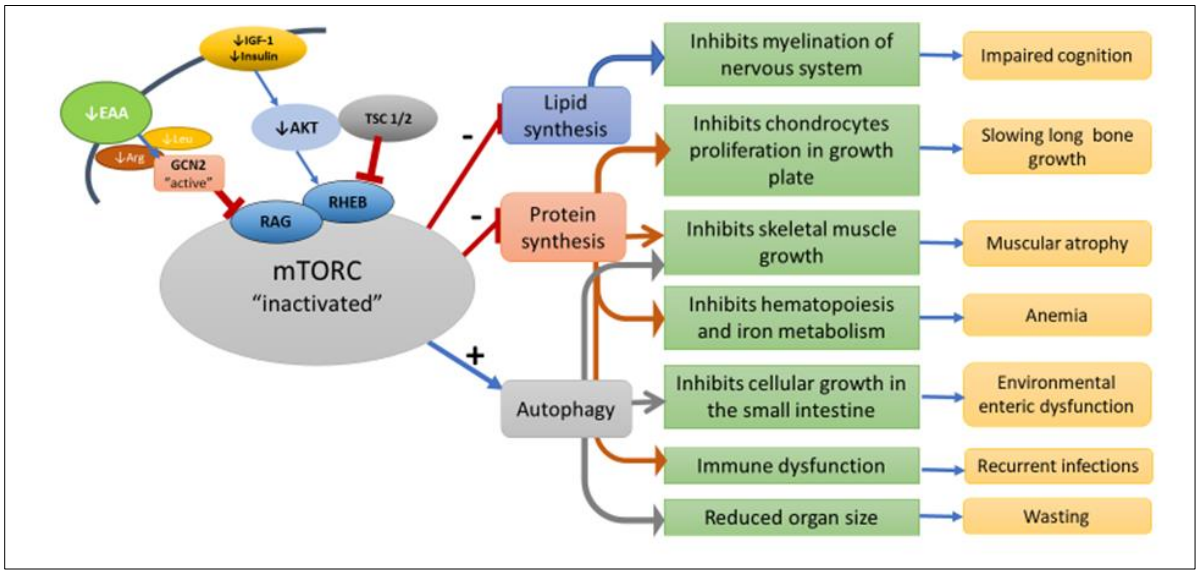

Figure 1 mTOR complex role in the pathogenesis of nutritional stunting and wasting in children.

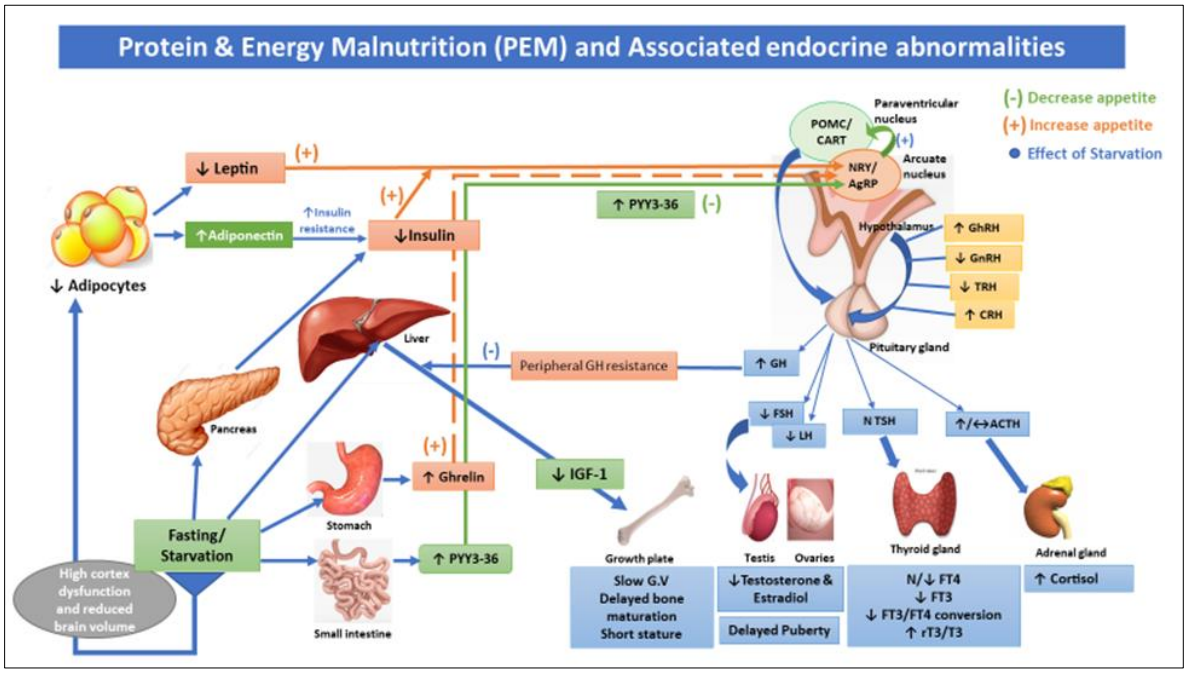

Figure 2 The interaction between malnutrition, central (hypothalamic pituitary) and peripheral (IGF1, FT4, insulin) endocrine organs

Nutritional replacement in children with severe malnutrition can normalize the GH/IGF-I axis. Within two weeks of refeeding, IGF-I concentrations can double or triple and after 50 days of intensive inpatient nutritional therapy, basal GH and IGF-I levels are indistinguishable from controls. (57, 72, 87) Nutritional interventions are associated with early increases in IGF-I levels, even before changes in anthropometric measures are observed. In addition, the blunted increase in GH concentrations following arginine stimulation testing also resolves with treatment. In one study on undernourished infants and toddlers, insulin levels rose 50% during formula feeding, whereas leptin and IGF-I levels

increased nearly 3-fold. GH fell by 21% and cortisol levels also declined. In addition, after 2 weeks of formula feeding, leptin, and insulin levels increase significantly with refeeding while ghrelin, cortisol, and PYY decrease significantly. There were downward trends in almost all inflammatory cytokines. (57, 72, 87. 88) Therefore, it is understandable that all the consequences of low IGF1 (Metabolic – immune and growth) are correctable when proper nutrition restores the normal IGF1 level necessary for catch-up growth during rehabilitation.

4. Conclusion

In summary, it appears that in infants and children. the endocrine changes in response to malnutrition mediate an adaptation process that secures energy substrates to vital organs and prevents hypoglycemia through a catabolic process (high GH, high cortisol, and low insulin, IGF1, and leptin) involving lipolysis, gluconeogenesis, and muscle wasting. Meanwhile, this process impairs/stops linear growth (low IGF1) to spare energy. These endocrine changes however may have a negative effect on systemic immune and inflammatory responses to infections (high cortisol, low IGF1, and low insulin) which are commonly associated with malnutrition. However, on nutritional rehabilitation, all these endocrine changes are easily reverted to normal even before any change occurs in the anthropometric data. (Weight gain).

Compliance with ethical standards

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Author's Contribution

- Ashraf Tawfik Soliman, MD, Ph.D. FRCP: design of the work: Data collection. analysis and interpretation and drafting the article.
- Nada Mwafak Alaaraj, MD: Data collection, analysis and drawing the figures.
- Doaa Khater MD: shared in the drafting and revision of the article.
- Alan D. Rogol, MD Ph. D.: Data interpretation and critical revision from the endocrine point of view

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