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ROLE OF INFLAMMATORY CYTOKINES IN THE DEVELOPMENT OF PROTEIN ENERGY MALNUTRITION

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Abstract

Protein-energy malnutrition (PEM) is a major public health concern, particularly in developing countries where it contributes significantly to childhood morbidity and mortality. Evidence increasingly highlights the role of inflammatory cytokines as critical mediators in PEM, linking immune dysfunction with metabolic imbalance and impaired growth. The objective of this review is to examine the role of inflammatory cytokines in the development and progression of PEM, focusing on their effects on appetite regulation, nutrient metabolism, immune function, and growth outcomes. By synthesizing findings from clinical studies, experimental models, and epidemiological data, the review aims to provide a comprehensive understanding of cytokine-driven mechanisms in malnutrition. Methodologically, a structured search of peer-reviewed literature was conducted across PubMed, Scopus, and Web of Science, prioritizing studies published in the last two decades. Keywords included "protein-energy malnutrition," "cytokines," "inflammation," "immune response," and "child nutrition." Relevant articles were critically analyzed to identify consistent patterns, mechanistic insights, and areas of divergence in current knowledge. Results indicate that elevated pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β are associated with anorexia, muscle wasting, impaired intestinal absorption, and increased susceptibility to infections. These cytokines interfere with insulin-like growth factor signaling, impair protein synthesis, and compromise gut integrity, thereby perpetuating nutritional deficits and worsening PEM outcomes. In conclusion, inflammatory cytokines are active drivers in the progression of PEM. Their influence on metabolic imbalance, appetite suppression, and immune dysfunction underscores the need for integrated interventions that combine nutritional rehabilitation with immunomodulatory strategies. Addressing cytokine dysregulation may provide a pathway to breaking the cycle of malnutrition and infection, ultimately improving survival and growth outcomes in vulnerable populations.

Keywords: *Protein-energy malnutrition, Inflammatory cytokines, Immune dysfunction, Child nutrition, TNF-α.*

INTRODUCTION

Childhood malnutrition is still a major disabler and serious public health problem in low-income countries (WHO, 2013; Yusuf *et al*., 2026). It can be best viewed as a syndrome of developmental impairment characterized by growth faltering, delayed motor, cognitive, and behavioural development; decrease immunity, increased morbidity and mortality, suboptimal adult work capacity and even increased risk of disease in adulthood (Helen and Demewez, 2017; Shashidhar, 2018). One such form of malnutrition is protein energy malnutrition (PEM).

The two main clinical syndromes of the extreme forms of PEM are marasmus and kwashiorkor, although a mixed picture is also seen frequently. In marasmus, there is progressive weight loss, wasting of both muscle and fat tissues, and a reduction of serum proteins such as albumin, pre-albumin, and transferrin. Muscle wasting appears to be the strongest and most consistent pathophysiological anomalies associated with this subgroup of PEM (Shashdhar, 2018). While both increased protein breakdown and decreased muscle protein synthesis are likely to contribute to this condition, the mechanisms leading to wasting are not yet fully elucidated.

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In kwashiorkor, the presence of edema is one of the hallmarks of this subgroup of PEM. The fluid retention (edema) usually starts in the feet and legs and spreads in more advanced cases to the hands and face. The pathogenesis of edema in PEM is currently unresolved and most likely multifactorial. Hypoalbuminemia and electrolyte imbalance have been put forward as possible causes (Waterlow, 1992; Ahmed *et al*., 2009). Even though low serum albumin is probably a necessary condition, it is certainly not always a sufficient explanation.

For instance, in an animal model, some features of kwashiorkor, such as hypoalbuminaemia, were induced by a diet low in protein and high in monosaccharides and disaccharides but oedema was rarely observed (Bhutta *et al*., 2017). In addition, the degree of hypoalbuminaemia and recovery upon nutritional management in children with kwashiorkor correlates poorly with the degree of oedema or the speed of its resolution (Ahmed *et al*., 2009; Kazeem *et al*., 2009). Thus, controversy remains regarding the contribution of factors other than hypoalbuminaemia to the development of oedema in individuals with kwashiorkor.

It is imperative to note that despite longstanding knowledge of kwashiorkor, the underlying pathophysiological mechanisms remain enigmatic. Kazeem *et al*. (2009) reported that edema in kwashiorkor may clear during nutritional rehabilitation without any change in serum albumin concentration. Therefore, there may be other underlying factors that precipitate the extracellular fluid retention.

Cytokines act as pleiotropic polypeptides regulating inflammatory and immune responses through actions on cells. They provide important signals in the pathophysiology of a range of diseases. The recognition of these molecules as significant pathogenic mediators leaves open the possibility of new potential therapeutic targets. Therefore, this article seeks to bring together current information concerning the role of inflammatory cytokines in the development and progression of PEM.

CAUSAL FRAMEWORK OF CHILDHOOD MALNUTRITION

Malnutrition among preschool children is determined by a complex interaction between illness and lack of food. In the conventional and widely accepted conceptual framework, the basic causes of malnutrition are social-political and economic factors that operate at societal level. The underlying causes include poverty, which results in household food insecurity, inadequate care, and an unhealthy household environment. The immediate causes include suboptimal nutrient intake and disease, which ultimately lead to malnutrition (UNICEF, 2013). Further from the conventional framework, literature report suggest that cytokine release, especially the release of tumour necrosis factor, IL-1 and IL-6, can negatively influence body composition through a reduction in appetite and food intake, as well as direct catabolic effects on skeletal muscle and adipose tissue (Bhutta *et al*., 2017).

INFLAMMATORY CYTOKINES

Cytokines are a large group of glycoproteins that modulate functional activity of individual cells under both physiological and pathological conditions. These polypeptides mediate and regulate the innate and adaptive immunological responses and act as inflammatory mediators or modulatory molecules during an infectious process. The production of cytokines is transitory and is usually limited to the duration of the stimulus.

Cytokines play important role in coordinating inflammatory response of the body to various external and internal stimuli (Savino, 2002). Based on their action, they may be categorized into pro-inflammatory and anti-inflammatory cytokines. The pro-inflammatory cytokines are essential for initiation of defense against various pathogens. The anti-inflammatory cytokines down regulate the inflammatory process by suppressing production of the pro-inflammatory cytokines when there is overproduction.

Pro-Inflammatory Cytokines

The pro-inflammatory cytokines are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions. This group of inflammatory cytokines play crucial role in the pathogenesis of PEM. They stimulate acute phase response (APR) and promote major changes in protein and amino acid metabolism (Phillips *et al*., 2005). Amino acids released from muscle and other tissues may be inadequate for synthesis of the acute phase proteins (APP) and other proteins. In particular, requirements for specific amino acids such as arginine, cysteine and methionine may be increased.

Tissue repair after an inflammatory process also may increase the requirement for non essential amino acid glycine, which is an important component of collagen (Savino, 2002). Present evidence suggests that cytokines, as intercellular mediators, play a key role in the nutrition-infection complex (Rhodus *et al*., 2005). Infections increase pro-inflammatory cytokine production thereby interfering with nutritional status by impairing metabolic activity and inducing anorexia (Delgado *et al*., 2008).

Anti-Inflammatory Cytokines

The anti-inflammatory cytokines are a series of immunoregulatory molecules that suppress the pro-inflammatory cytokine response. These cytokines act in concert with specific cytokine inhibitors and soluble cytokine receptors to regulate the human immune response. Their physiologic role in inflammation and pathologic role in systemic inflammatory states are increasingly recognized. Major anti-inflammatory cytokines include IL-4, IL-10, IL-11, and IL-13 (Piotr *et al*., 2014).

Among all the anti-inflammatory cytokines, IL-10 is the cytokine with the most potent anti-inflammatory properties, repressing the expression of inflammatory cytokines such as TNF-α, IL-6 and IL-1 by activated macrophages. In addition, IL-10 can up-regulate endogenous anti-cytokines and down-regulate pro-inflammatory cytokine receptors (Jun and

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Jianxiong, 2007). Thus, it can counter-regulate production and function of pro-inflammatory cytokines at multiple levels (Piotr *et al*., 2014).

Inflammatory Cytokines in etiology of PEM

Cytokines are a group of pharmacologically active, low molecular weight polypeptides that possess autocrine, paracrine, and juxtacrine effects with characteristic features. Cytokines are produced by a wide variety of cells in the body, playing an important role in many physiological responses that have a therapeutic potential. When considering the role of cytokines in pathophysiological processes underlying disease, it is necessary to take into account the fact that the activities of these molecules are very complex, as reflected by important features, including their pleiotropic actions.

The association between PEM and inflammatory response may be an explanation for morbidity and mortality associated with childhood malnutrition (Qureshi *et al*., 2002). Thus, chronic inflammation may be the missing link that causally ties PEM to morbidity and mortality in early life. Therefore, the following arguments have been proposed to indicate the possible role of cytokines in the development of PEM:

- Pro-inflammatory cytokines precipitate inflammation in malnourished children which lead to progressive weight loss and a negative protein balance, because there may be a shift in the protein synthesis from the muscle to the acute phase proteins (Kaizu *et al*., 1998).
- The proinflammatory cytokines such as the tumour necrosis factor-α (TNF-α), not only promote the catabolic processes, engendering both protein degradation and suppression of the protein synthesis, but they also induce anorexia (McCarthy, 2000). A low appetite has been associated with increased levels of inflammatory markers in children with PEM.
- Elevated serum CRP in children with PEM suppresses albumin synthesis (Kaysen *et al*., 2000).
- Cytokines and other inflammatory mediators induce gaps between endothelial cells by causing disassembly of intracellular junctions and/or alterations in the cytoskeletal structure or by directly damaging the cell monolayer. This creation of gaps can result in micro vascular leakage and tissue edema.
- It has also been suggested that acute phase response and pro-inflammatory cytokines directly affect the bone remodelling required for longitudinal growth (Stephensen, 1999).

Mechanisms by which Inflammation can lead to Muscle wasting

Muscle nitrogen balance is finely modulated by several agents such as nutrient and energy availability, mechanical stress, hormones and cytokines. Protein breakdown in the skeletal muscle is mediated by two main degradation systems, the ubiquitin-proteasome and the autophagy pathways. The proteasome system preferentially targets short-lived proteins, and several reports considered the proteasome as the degradation machinery mostly involved in wasting processes (Costelli and Baccino, 2003).

The autophagy system is in charge of degrading long-lived proteins and organelles (mitophagy, pexophagy, etc.), and recent observations suggest that, beyond the proteasome, even autophagy plays a crucial role in muscle wasting (Penna *et al*., 2014). In addition to proteasome and autophagy dependent proteolysis, intact myofilaments were postulated to undergo a preliminary cleavage in order to be released from the myofibrils for the subsequent ubiquitin dependent degradation, and such activity was proposed to be carried out by calpains or by caspase-3 (Hasselgren *et al*., 2002; Du *et al*., 2004).

Muscle protein degradation systems are modulated by a coordinated network of signaling pathways activated or suppressed by hormones and cytokines. On one hand, anabolic signals are activated by insulin, IGF-1, GH, and androgens, while catabolism is stimulated by a variety of proinflammatory cytokines as well as glucocorticoids and ROS. IGF-1 promotes muscle hypertrophy, while low IGF-1 circulating levels have been associated with several muscle atrophy conditions (Vinciguerra *et al*., 2010). IGF-1, and similarly insulin, activates the PI3K/Akt pathway, which promotes protein synthesis through mTOR and its downstream effectors, mTORC1/2 complexes, not to mention that mTOR activation in the skeletal muscle results in autophagy inhibition (Castets and Rüegg, 2013), thus determining at the same time both protein synthesis activation and inhibition of protein degradation.

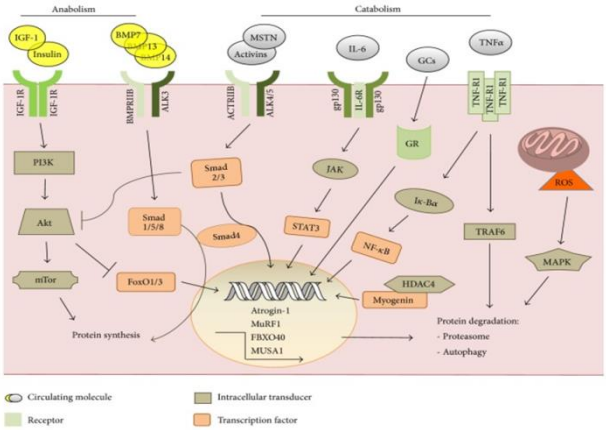

Figure 1: Mediators that drive anabolic and catabolic responses in the skeletal muscle (Source: Domiziana *et al*., 2015; *Mediators Inflamm*., 80:51-72).

Proinflammatory cytokines, together with altered homeostasis of classical hormones, put on complex network that result in inhibition of anabolic and/or anticatabolic signals in favor of lipolysis and proteolysis (Domiziana *et al*., 2015). In particular, proinflammatory cytokines are well known to impinge on muscle protein metabolism. In this regard, data obtained in both experimental models and human pathology have demonstrated that systemic inflammation is associated with reduced rates of protein synthesis paralleled by enhanced protein breakdown, both accounting for the loss of muscle

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mass. However, the precise mechanism by which inflammation modulates protein turnover rates is still poorly investigated (Domiziana *et al*., 2015).

The regulation of muscle protein metabolism by humoral factors is widely accepted. In this regard, the activity of both proteasome and lysosomes, the two proteolytic systems mainly involved in muscle depletion, is known to be affected by the hormonal and cytokine milieu. As an example, healthy animals exposed to proinflammatory cytokines such as TNF-*α*, IL-1, or IL-6 develop muscle wasting associated with increase of both ubiquitin expression and proteasome enzymatic activity (Tisdale, 2008).

Consistently, few studies demonstrated in the past that cytokines play a crucial role in the onset of muscle wasting. Indeed, muscle depletion, enhanced protein breakdown, and increased ubiquitin can be prevented by treating tumor-bearing animals with antibodies directed against IL-6, TNF-*α*, or IFN-*γ* (Costelli *et al*., 1993). Proinflammatory cytokines contribute to muscle wasting also in chronic diseases of noncancer origin. Indeed, increased circulating levels of TNF-*α*, IL-1, and IL-6 in sepsis appear to be correlated with disease severity and lethality.

The effects exerted by proinflammatory cytokines on muscle mass are mediated, partially at least, by activating the transcription factor NF-*κ*B. The transcriptional activity is regulated by the phosphorylation and consequent degradation of the inhibitor I*κ*-B*α*, allowing the positive regulation of MuRF1 (Cai *et al*., 2004) and other atrophy related genes, including the inducible nitric oxide synthase (Di Marco et al., 2005). Another protein related to the TNF-*α* cascade, TRAF6, was shown to coordinate the activation of both proteasome and autophagy (Paul *et al*., 2010).

Among proinflammatory cytokines, tumor necrosis factor-like weak inducer of apoptosis (TWEAK) has been shown to induce muscle wasting mainly by stimulating proteasome-dependent proteolysis (Mittal *et al*., 2010). TWEAK-induced down regulation of both PGC-1*α* expression and mitochondrial biogenesis has been proposed to mediate the effects on muscle mass. Indeed, PGC1*α* hyperexpression protects against TWEAK-induced effects such as NF-*κ*B activation, increased ubiquitin ligase levels, and muscle wasting (Hindi *et al*., 2014). In addition, several cytokines act on the JAK/STAT pathway, and muscle STAT3 was demonstrated to induce atrogin-1 and to block autophagy, leading to muscle degeneration (Mittal *et al*., 2010).

Proinflammatory cytokines act on muscle protein metabolism not only by activating catabolic pathways, but also by downregulating the anabolic ones. As an example, lipopolysaccharide-induced muscle wasting is associated with increased circulating levels of TNF-*α* and IL-1 that lead to inhibition of the Akt/mTOR signal transduction pathway (Frost and Lang, 2008). In this regard, treatments able to restore Akt physiological activity appear to counteract TNF*α*-induced wasting (Liu *et al*., 2013).

The antianabolic action of proinflammatory cytokines is partially exerted through interactions with the IGF-1-dependent signaling pathway. Indeed, TNF-*α* leads to serine phosphorylation of IRS-1, inhibits its recruitment to the insulin/IGF-1 receptor (Domiziana *et al*., 2015). TNF-*α* can impinge on the insulin/IGF-1 signaling via direct interaction between the IKK complexes and IRS-1. Alternatively, TNF*α*-induced activation of JNK may play a role, as shown by the observation that the downregulation of the IGF-1-dependent signaling exerted by the cytokine does not occur in the presence of a JNK inhibitor (Grounds *et al*., 2008). Finally, proinflammatory cytokines may modulate anabolism also by inducing leucine-resistance, resulting in decreased mTOR phosphorylation and reduced protein synthesis (Domiziana *et al*., 2015).

Ubiquitin proteasome pathway

Pro-inflammatory cytokines may lead to stimulation of protein breakdown and subsequent muscle wasting via stimulation of the ATP-ubiquitin-proteasome pathway (Sartori *et al*., 2013). As TNF-*α* modulates at least in part the ATP-ubiquitin-proteasome proteolytic pathway; inflammation may contribute to wasting by affecting this pathway. Indeed, it has been shown that TNF-*α* administration to rats resulted in increased skeletal muscle proteolysis, augmentation of ubiquitin, and increased gene expression of ubiquitin (Vinciguerra et al., 2010). Also other cytokines, such as IL-1 and INF-*γ*, upregulate ubiquitin gene expression (Vinciguerra *et al*., 2010). However, while cytokines have the potential to enforce the acceleration of muscle protein breakdown, it is largely unknown how the proteolytic pathways involved are activated (Domiziana *et al*., 2015).

Anorexia

The cause(s) of anorexia are multifactorial, and include the release of neurotransmitters such as, serotonin; neuropeptides like neuropeptide Y, orexin; cholecystokinin, and cytokines (Walston *et al*., 2008). Inflammatory cytokines interact with several pathways in the central nervous system to affect specific brain areas related to the appetite regulation.

Literature report shows associations between the loss of appetite and higher levels of inflammatory markers (Domiziana *et al*., 2015). Thus, PEM patients with anorexia and vomiting showed higher plasma levels of TNF-*α* than patients without these symptoms (Wang *et al*., 2014). In accordance, levels of IL-6 and TNF-*α* progressively increased as appetite scores got worse in PEM patients (Domiziana *et al*., 2015). Moreover, PEM patients with the worse appetite had the worst nutritional status and the worst clinical outcome, suggesting a link between inflammation, decreased appetite, nutritional status, and outcome (Durham and Dillon, 2009).

Edema in PEM

There are two principal theories regarding the etiology of kwashiorkor; the classical theory of protein deficiency and the theory of free radical damage. Both theories emphasize different aspects of the environment; in the classical theory,

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nutrients, and in the free radical theory, oxidative stresses. The classical theory of protein deficiency was supported by Williams' original description of kwashiorkor developing in children who were weaned onto starchy gruels after being deposed from the breast and being cured by milk.

The free radical theory of kwashiorkor proposes that kwashiorkor results from an imbalance between the production of toxic free radicals and their safe disposal. The free radical theory attempts to explain the entire spectrum of clinical findings in kwashiorkor by implicating a wide range of nutritional deficiencies, as well as environmental oxidative stressors (noxae). Important noxae include infections and exogenous toxins such as aflatoxin and its metabolites. Inadequate diet leads to a state of impaired antioxidant defense.

Besides the classical and free radical theory, literature report suggest that cytokine and other inflammatory mediators induce gaps between endothelial cells by causing the disassembly of intracellular junctions and/or alterations the cellular cytoskeletal structure or by directly damaging cell monolayer. This creation of gaps can result in micro vascular leakage and tissue edema (Raman and Peter, 2013).

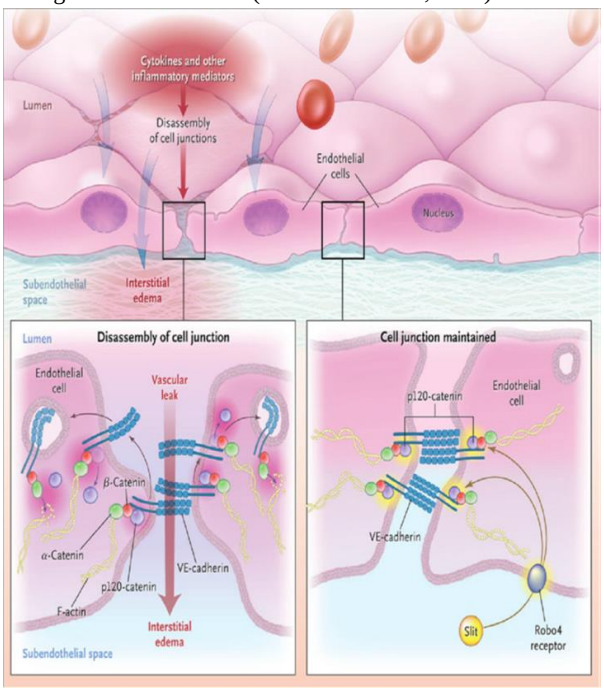

Figure 5: Micro vascular leakage and tissue edema induced by inflammatory cytokines (Source: Raman and Peter, 2013; *Pediatr Nephrol*).

CONCLUSION

The global impact of childhood malnutrition is staggering. The synergism between malnutrition and inflammation contributes substantially to childhood morbidity and mortality. There are several altered biochemical parameters which may serve as indicators of PEM. There are increases in pro-inflammatory cytokines such as IL-6, tumor necrosis factor-α and C-reactive protein in malnourished children. The higher levels of pro-inflammatory cytokines and depletion of albumin in children with kwashiorkor suggest that these inflammatory mediators could be critical biomarkers during clinical phases of kwashiorkor.

Furthermore, multiple factors link inflammation to malnutrition, anorexia and wasting in children with PEM. Research focusing on plausible link between inflammation and PEM; as well as how to improve metabolic abnormalities and reduce negative cytokine signaling could lead to new preventive and therapeutic strategies that may contribute to reduce the incidence of muscle wasting and improve survival of children with PEM. Such strategies may include appetite stimulants, anti-inflammatory nutritional supplements, and anti-inflammatory pharmacologic agents that may be tested alone, or in combination with nutritional support programs.

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Conflicts of Interest

The authors hereby declare no conflict of interest.

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