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Malnutrition and immunity: A review

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Abstract
Malnutrition, which includes both lack and overnutrition, is a major cause of disease and mortality around the world. Malnutrition is caused by dietary absorption problems, but it is also marked by recurring infections and persistent inflammation, signaling an underlying immunological problem. Defects arise in the immunoepigenome of impoverished parents before birth, and these may lead to intergenerational malnutrition cycles. Immune dysfunction is both a cause and a consequence of starvation, according to this review, which includes major recent data from experimental animals, *in vitro* models, and human cohorts. We emphasize gaps in existing understanding of immune- physiological dysfunction in malnutrition, with the goal of therapeutically addressing immunological pathways as a novel strategy to reduce morbidity and death in children.

Keywords: Immunoepigenome, low of protein diet, malnutrition cycles, immune dysfunction, dietary absorption

Introduction

Malnutrition as an Immunodeficiency Syndrome

Malnutrition, which includes both under- and over-nutrition, causes a huge health burden worldwide (Rahman and Adjeroh, 2015; Black *et al.*, 2013) [35, 6]. Nutritional aspects have always found to be very instrumental with the physiological attributes not only that various nutritional changes input various physiological changes projecting the deficiency and sufficiency of the key factors responsible for the particular nutrient markers.

Despite being usually described as poor nutritional digestion, malnutrition is not solely caused by a lack of food intake. Obesity can develop without a poor diet and continue even if a healthy diet is adopted (Clemente *et al.*, 2012; DeBoer *et al.*, 2012; Godfrey *et al.*, 2011; Gregor and Hotamisligil, 2011; van der Klaauw and Farooqi, 2015) [8, 11, 17, 19, 48], while intensive feeding therapies only marginally reduce stunting prevalence (Bhutta, 2008). Despite the fact that under- and overnutrition manifest as separate physical defects, several studies suggest that they share etiological pathways: early-life undernutrition increases the risk of obesity later in life (DeBoer *et al.*, 2012; Roseboom, 2006) [11, 38], altered metabolism (Bartz *et al.*, 2014; Kong *et al.*, 2014; O'Keefe *et al.*, 2015) [3, 24, 29], chronic inflammation (Kong *et al.*, 2014; Prendergast *et al.*, 2014; Kosek *et al.*, 2013) [24, 32, 25], and gut dysfunction (enteropathy) (Kong *et al.*, 2014; O'Keefe *et al.*, 2015; Subramanian *et al.*, 2014) [24, 29, 46], in overweight people, excessive calorie and macronutrient intake is commonly linked to micronutrient deficiencies. Malnutrition is increasingly being recognized as a complex condition with overlapping and poorly understood comorbidities (Humphrey, 2009; Prendergast *et al.*, 2014; Ahmed *et al.*, 2014) [21, 33, 2]. In order to create novel therapeutic diet (Therapeutic diet is a diet which is given to the patient who is suffering from any type of disease condition (Tewari, 2019) [47] to support international aims to increase nutrition, health, and well-being, pathogenesis across the malnutrition spectrum must be characterized.

Malnutrition affects immunity

A primary immunodeficiency is an immune system condition caused by a genetic or developmental defect. Secondary or acquired immunodeficiency is the loss of immunological function caused by a range of external factors. Although infection with the human immunodeficiency virus (HIV) is the most well-known cause of secondary immunodeficiency, acute malnutrition is the most prevalent cause of immunodeficiency worldwide, affecting up to 50% of the population in some underprivileged communities (Geraix *et al.*, 2008) [15]. Both innate and adaptive immunity are affected by immune system abnormalities.

It's impossible to separate the innate and specific arms of immunity in practice since they're so closely linked in the body. But, for the sake of clarity, let's start with some innate systems, or those that act against any pathogen. For example, malnutrition reduces complement component availability and phagocyte activity, directly impacting pathogen clearance. This happens because the complement system can kill bacteria and viruses on its own, or because pathogens are trapped on the phagocyte surface by complement receptors. Sakamoto *et al*. discovered that complement levels were much reduced, notably C3, the major opsonic component (DMSc *et al*., 1998) [12]. Furthermore, phagocytes' ability to ingest and kill bacteria is critical.

Both innate and acquired immune responses require antigen-presenting cells (APC) for activation, regulation, and maintenance (Mellman and Steinman, 2001) [28]. Various studies have found that nutritional deficiencies impair the biological function of many cell types (B lymphocytes, macrophages, and Kupffer cells) (Redmond *et al.*, 1991; Petro *et al.*, 1994; Honda *et al.*, 1995; Stapleton *et al*., 2001) [36, 31, 20, 45].

The most significant immunological changes discovered in humans or experimental fasting models that affect adaptive immunity pathways will be briefly discussed below. Severe protein deficiency is closely connected to reduction of the so-called fundamental lymphoid organs, such as the bone marrow and thymus, in newborns and babies. The results are disastrous since these organs produce B and T cell repertoires. Furthermore, hunger has a clear effect on hematopoiesis, leading in anaemia, leucopenia, and a significant reduction in bone marrow. The production of IL-6 and TNF- is also significantly reduced in starved animals (Fock *et al.*, 2007) [14]. The capacity of malnourished hematopoietic stroma to sustain the formation of hematopoietic stem cells (CD34+) *in vitro* is similarly reduced (Xavier *et al.*, 2007) [50]. This is significant because CD34+ cells can create myeloid, erythroid, and lymphoid lymphohematopoietic lineages (B and T) (Giassi *et al.*, 2008) [16].

Thymus atrophy is caused by severe protein deprivation, which reduces the number of thymus cells and has an adverse effect on the development of peripheral lymphoid organs, particularly in infants and small children (Savino, 2002) [41]. This atrophy causes leucopenia, a decreased CD4/CD8 ratio, and an increase in immature T cells in the peripheral blood. Rats with moderate and severe malnutrition had significantly fewer CD3+ cells in their spleens, according to Cortés *et al.*, (2008) [10]. T cell activation was also found to be significantly reduced, as evidenced by lower CD25 and CD71 expression in these cells.

In starved experimental animals, these thymus anomalies have been examined in greater depth. Patent atrophy, for example, is characterized by a decrease in T cell proliferation and an increase in apoptosis, which affects predominantly young TCD4+ and TCD8+ cells. At least in part, this has been linked to lower leptin levels during famine or starvation (Ahima *et al.*, 1996; Savino, 2002) [1, 41]. Reduced thymic hormone synthesis has been linked to morphological changes in thymic epithelial cells during starvation. A hormonal imbalance comprising a dip in leptin levels and a rise in glucocorticoid hormone levels in the blood appears to be associated to this feature.

Malnutrition has a significant impact on epithelial barrier immune responses. Modifications in the architecture of the gut mucosa, such as flattened hypotrophia microvilli, lower lymphocyte counts in Peyer's patches, and lower immunoglobulin levels, characterize these changes (Beisel, 1996; Souza *et al.*, 2007) [4, 44].

Immune Defects in poor-nourished Children

A recent comprehensive literature analysis (Rytter *et al.*, 2014) [39] found 245 articles documenting immunological parameters in undernourished children (ages 0–5) published between 1957 and 2014. The majority of trials, however, were conducted decades ago using outdated immunological methodologies and focused on hospitalized infants with severe malnutrition and many coinfections, according to the review. The lack of longitudinal research, particularly for mild and moderate malnutrition, made it difficult to characterize immunodeficiency. The specific nature of immunodeficiency in undernutrition is therefore unknown; however, the existing evidence suggests that malnutrition impairs both innate and adaptive immunity. Impaired epithelial barrier function of the skin and gut, diminished granulocyte microbicidal activity, and fewer circulating dendritic cells are all examples of innate immune dysfunction. Reduced levels of soluble IgA in saliva and tears, lymphoid organ atrophy, reduced delayed- type hypersensitivity responses, fewer circulating B cells, a shift from Th1-associated to Th2- associated cytokines, and lymphocyte hyporesponsiveness to phytohemagglutinin are all defects in adaptive immune function, but lymphocyte and immunoglobulin levels in peripheral blood are preserved. Despite this, most malnourished children appear to respond to vaccination satisfactorily, albeit the timing, quality, and longevity of vaccine-specific responses may be affected (Prendergast, 2015; Savy, 2019) [15, 42].

Contemporary investigations of childhood malnutrition using cutting-edge functional immunological approaches in well-characterized longitudinal cohorts of children are clearly needed. Malnutrition must be defined using existing measurements like as stunting, wasting, or both, with appropriate well-nourished comparison groups, and relationships between immunological markers and clinical outcomes must be evaluated. New experimental methodologies to investigate immunological ontogeny and epigenetics (Godfrey *et al.*, 2011; Cooper *et al.*, 2012; Khulan *et al.*, 2012; Dominguez *et al.*, 2014) [17, 9, 23, 13], immunometabolomics (McGettrick *et al.*, 2013) [27], the gut microbiome (Gordon *et al.*, 2012) [18] and virome (Reyes *et al.*, 2015) [37], enteropathy (Brown *et al.*, 2015) [7], and nutrient-sensing (Veldhoen and Ferreira, 2015; Li *et al.*, 2018) [49] additionally, they give unrivalled prospects for translation into immunological studies of childhood malnutrition. Immunodeficiency is also a symptom of malnutrition (Gregor and Hotamisligil, 2011; Huttunen and Syrjänen, 2013) [19], immunological research in overweight and obese children could help researchers better understand the immunopathogenesis of malnutrition.

Conclusion

Malnutrition-related immune-physiological changes in children may contribute to higher mortality. However, the underlying processes, as well as why different types of starvation are linked to diverse immune-physiological changes, are yet unknown. Sudden pathophysiological constraints are too much difficult to conclude the particular

nutrient as a marker so better constructed prospective trials, based on current immunological knowledge and using cutting-edge methodologies, are highly required to draw better hypothesis.

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