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The link between malnutrition, immunity, infection, inflammation and growth: New pathological mechanisms

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Abstract

Primary (acute and chronic) malnutrition is still prevalent in developing countries because of inadequate nutrition and poor sanitation caused by social, economic, and environmental factors. In addition, acute malnutrition can occur secondary to an underlying disease that interferes with the intake, digestion, absorption, or assimilation of different nutrients increases nutrient loss, and/or increases energy expenditure. Immune dysfunction and infection are tightly linked to and actively contribute to the metabolic and hormonal dysregulation as well as to the progression of malnutrition.

An inadequate dietary intake of macro-and micronutrients is proposed to adversely affect local intestinal and systemic immunity, intestinal mucosal integrity, and the interaction between host defense and pathogens. Lowered immunity, mucosal damage, recurrent and prolonged infections, and gut inflammation negatively affect the malnourished child growth in weight and height as well as psycho-mental development in endemic areas. Both infection and inflammation aggressively contribute to malnutrition triggering a vicious cycle. Almost all infantile and childhood malnutrition in endemic settings (unlike anorexia nervosa) results from deficient diet, infection, inflammation, and intestinal dysfunction (most children in endemic areas have environmental enteric dysfunction (EED), often with high fecal inflammatory markers. We highlight gaps in our understanding of the current interaction among immune dysfunction, infection, and inflammation in malnourished children, and evaluate the possible responsibility of pro-inflammatory cytokines in the initiation and progression of severe malnutrition. Breach of the malicious cycle between malnutrition and infection/inflammation requires innovative interferences to recover the immune defense and enforce host defense against pathogens and reduce morbidity and mortality.

Keywords: Malnutrition; Infection; Inflammation; Immunity; T Cells; Cytokines.

1. Introduction

Both acute and chronic forms of malnutrition occur due to inadequate energy and/or protein intake of different duration and severity. The prevalence of primary acute malnutrition is still high in developing countries because of inadequate nutrition and poor sanitation caused by social, economic, and environmental factors. In addition, acute malnutrition can occur secondary to an underlying disease that interfere with intake, digestion, absorption, or assimilation of different nutrients, increases nutrient loss and/or increases energy expenditure. Acute malnutrition produces are associated with many metabolic, immunological, hormonal, and psychological changes [1,2].

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Malnutrition increases vulnerability to infection and is commonly associated with recurring and variable infections (bacterial, viral and parasitic) and chronic inflammation, indicating an underlying defective immune response to pathogens. Immune-system defect. Malnutrition-associated shifts in intestinal microbiota and the occurrence of environmental enteropathy dysfunction correlate significantly with growth faltering, systemic and local immune dysfunction, and inflammation. Both infection and inflammation aggressively contribute to malnutrition which causes and perpetuates a vicious cycle [3].

Most of the malnourished children in endemic areas have environmental enteropathy dysfunction (EED), often with fecal inflammatory markers. The malnutrition-associated immune defect can be a trigger as well as a result of undernourishment and is proposed to be an important cause of recurrent and chronic infections and inflammation in these children. Studying the possible relation/s between inadequate intake of nutrients (macro-and micronutrients) and lowered systemic and local immunity, mucosal injury, invasiveness of different pathogens, and their relation to impaired growth in malnourished children is an essential step for proper management of severe nutritional disorders [4,5].

2. Methods

Here, we update knowledge on the current relations/interactions between immune dysfunction, infection, and systemic and intestinal inflammation in children with malnutrition and we reviewed the role of pro-inflammatory cytokines in the pathogenesis and progression of severe malnutrition. [6,7] The authors extensively searched the literature on using Ovid, EMBASE, the Cochrane Database, PubMed, and Google scholar, including original articles, metanalysis, and review articles on the above-mentioned topics.

Ethical clearance has been approved by the local Pediatric search committee of Hamad General Hospital.

3. Discussion

3.1. Starvation/malnutrition: auxologic evaluation, prevalence, and consequences

Malnutrition can be categorized as acute versus chronic, and its severity can be classified into mild, moderate, and severe. Features of chronic malnutrition include: [8] poor weight gain, [9]mental apathy, [10] stunted growth, and [4] developmental delay.

The two major forms of acute severe protein-energy malnutrition (SAM) are marasmus (more common) and kwashiorkor. However, some patients may have both (marasmic kwashiorkor). Marasmus is characterized by a weight-for-height z score [WHZ] < −3 without edema. Kwashiorkor is distinguished by the presence of pitting pedal edema, independent of weight and length criteria. Patients with marasmic kwashiorkor have both edema and significant wasting. [8-11]

There are 4 described partially distinct sub-types of undernutrition: wasting, stunting, underweight, and deficiencies in vitamins and minerals. [12-14] Despite having different definitions, wasting, and stunting, are closely related and often occur together because they share many of the causal factors. (Table 1) [12-18]

Table 1 Potential causes of nutritional stunting may be caused by

insufficient maternal nutrition,
intrauterine undernutrition,
lack of breastfeeding until 6 months of age,
later introduction of complementary feeding,
inadequate (quantity and quality) complementary feeding, and
impaired absorption of nutrients owing to infectious diseases
insufficient maternal nutrition,

The correlates of childhood stunting are both immediate and longer-term. (Table 2)

Table 2 Short- and long-term correlates of childhood stunting

Lower fat oxidation
Lower energy expenditure
Increased risk of infections and non-communicable diseases
A risk for insulin resistance, and glycemic and metabolic abnormalities
Increased susceptibility to accumulate fat mostly in the central region of the body
Increased morbidity and mortality
Stunted children who experienced rapid weight gain after 2 years have an increased risk of becoming overweight or obese later in life.
Poor child development and learning capacity and low work capacity
Unfavourable maternal reproductive outcomes in adulthood

3.2. The tight link between malnutrition and infection (a vicious cycle)

Globally, malnutrition is believed to be the leading cause of immunodeficiency and until now many investigators aim at clarifying its pathogenesis. [4-6] epidemiologically, acute, and chronic malnutrition greatly increase vulnerability to many infectious diseases particularly in children in poor and developing countries. In children under 5 years, malnutrition is accountable for 54% of the 10.8 million deaths per year and responsible for every second death (53%) associated with infectious diseases in developing countries. [19]. A report from 10 cohorts in different developing countries, revealed that 52.5% of all deaths in young children were attributable to undernutrition, varying from 44.8% for deaths because of measles to 60.7% for deaths because of diarrhea. (20) In this malicious sequence infection results in undernutrition due to nutrient loss (diarrhea), reduced food intake (decreased appetite), and/or increased energy expenditure (fever, hypermetabolic status) [21, 22] On the other hand, undernutrition increases the vulnerability for infection by impairing gut barrier function, altering the intestinal microbiota, releasing inflammatory cytokines, and decreasing the uptake of key micro and macronutrients. [8, 22- 23]

Epidemiologically, apart from protein and energy insufficiency, micronutrient deficiencies (e.g., iron, zinc, vitamin D, Vitamin A) may have profound adverse effects such as higher vulnerability to infection, diminished growth, and impaired intellectual functions, and increased mortality. [22-23]

3.3. Malnutrition and Immune Function

Primary malnutrition is a frequent cause of secondary immune insufficiency termed nutritionally acquired immunodeficiency syndrome. A fundamental link is strongly advocated both in human and animal experiments. [6.7,9] Not only lymphocyte functions are affected but also macrophages and granulocytes are adversely altered. [6,7]

In newborn and small infants' severe malnutrition produces atrophy of the thymus with diminished cell numbers and poor development of lymph nodes and spleen. This nutritional insult leads to long-lasting impairment of the immune characterized by leukopenia and lymphopenia (decreased CD4+ and CD8+ T cell numbers in whole-blood samples). Not only the number of lymphocytes is affected but also the CD4+ to CD8+ ratio decreases and there is the appearance of immature T cells in the periphery. These abnormalities greatly predispose to infection. [6, 7, 24]

Malnourished children have decreased levels of cytokines (IL-12, IL-18, and IL-21) important for Th1 differentiation. They have decreased Th1 cytokines IFN-γ and IL-2 and increased expression of Th2 cytokines IL-4 and IL-10. These changes lead to a significant swing in the balance between the pro-inflammatory Th1 versus anti-inflammatory Th2 cytokines and offer a possible clarification of how malnutrition prompts infection and inflammation. [25]

Malnutrition has been reported to cause more severe viral infections and may decrease markedly the immune response to vaccines. Malnourished mice on a low-protein diet required an extremely lower viral load for having 50% lethality by Sendai virus pneumonia compared to normally fed controls. [26] In addition, undernourished mice suffer significantly higher severity when infected with Dengue virus and those infected with Mycobacterium tuberculosis had

2–3 logs more bacilli in their lungs compared to mice receiving a full protein diet. [27, 28] In support of this view, protein supplementation to mice infected with influenza virus resulted in fast viral clearance and significantly reduced mortality. [29]

In malnourished children, lung infections (pneumonia), gastrointestinal infections (diarrhea), viral infections (e.g., measles), and malaria occur more frequently and have a lingering course. [21] In low-income countries, pneumonia, commonly associated with malnutrition, is considered the major cause of morbidity and death among young children. [30,31] Unfortunately, during severe malnutrition, the reduced inflammatory response to pathogens modifies or silences the clinical presentation of the disease that can markedly delay the diagnosis and management. [32] In addition, malnourished children have distinct varieties and frequency of infective pathogens that differ from those reported in normal children living in the same location. [33]

3.4. Effect of malnutrition on lymphocytes: The serine/threonine kinase mammalian/mechanistic target of rapamycin system (mTOR)

The mammalian target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine kinase that can simultaneously integrate multiple signaling inputs, including nutrients, amino acids, glucose, fat, and growth factors (e.g., IGF-1), and cytokines to regulate cell metabolism, proliferation, and growth. mTOR has a vital role in regulating many fundamental cell processes, from protein synthesis to autophagy, and disturbed mTOR signaling is deranged during nutritional disorders. [34] In addition, mTOR represents an energetic link between immune function and metabolism. It regulates many lymphocytic functions including T cell activation, CD8+ memory cell formation and function, and helper T lineage differentiation. In addition, mTOR has important functions in the hormonal and central control of immunity and inflammation during malnutrition which will be discussed below. Amino acid and glucose deficiency during starvation and malnutrition suppress the mTOR immune and metabolic mediated functions. [35]

3.5. Inflammation, pro-inflammatory markers, immunity, muscle wasting in malnutrition, and response to vaccination

Malnutrition swings the balance between pro-inflammatory Th1 versus anti-inflammatory Th2 cytokines. This leads to higher production of pro-inflammatory (Th1) versus anti-inflammatory Th2 cytokines. Consequently, this imbalance increases inflammatory responses and encourages inflammation, and may contribute to edema formation. [36]

Signals of cellular stress (as occurs during nutritional deprivation) markedly influence the immune system components and their functions. The integrated stress response (ISR) is a coordinated cellular program that permits cells to respond to such microenvironmental stressors. In the case of low amino acid levels, (as occurs in kwashiorkor) the ISR is stimulated by a kinase known as general control nonderepressible 2 (GCN2). The GCN2 is a metabolic sensor that identifies the lack of any amino acids and forms the evolutionarily conserved amino acid starvation response (AAR) pathway. [37]. the amino acid sensor GCN2 can control inflammation through posttranscriptional processes, and autophagy. For example, during Shigella infection, the bacteria invade and damage the host cell membrane which leads to a local lack of amino acids that stimulates the GCN2 kinase-mediated activation of the ISR pathway, and simultaneously reduces mTOR activity. [38]

Proinflammatory cytokines mainly exert their effects by increasing the expression of calpains and E3 ligases as well as of Nf-κB, required for protein breakdown and local inflammation. They act locally to suppress the anabolic effects of IGF-1 and insulin. They stimulate FoxO activation and inhibit Akt activity (the central link of carbohydrate, lipid, and protein metabolism). [39]

In muscles, the pro-inflammatory cytokines are essential to keep the equilibrium between anabolism and catabolism. This keeps normal myogenesis. During malnutrition, enhanced expression of these cytokines can induce the breakdown of skeletal muscle. [40] In marasmic children and those with marasmic kwashiorkor, high inflammatory interleukin levels and low/disturbed amino acid levels/ratio (essential versus non-essential) are associated with varying degrees of muscle wasting. In animals, acute treatment with IL-6 can augment muscle proteolysis. [41]. In the human experiments, IL-6 profoundly modifies amino acid yield and causes a significant reduction in plasma amino acid levels with a consequent decrease in muscle protein turnover and a mild increase in muscle degradation. Moreover, In vivo perfusion studies in human showed that increased TNF-α (as occurs during infection/inflammation) accelerates protein breakdown and directly increase net muscle protein loss. These actions actively contribute to the general protein loss during severe malnutrition that may progress to cachexia. [41]

Dendritic cells (DC), a key member of the innate immune system, are accountable for the innate identification of pathogens through their recognition receptors. In severely malnourished infants with endotoxemia (infection) the extracted DC were defective and can partially explain their immune anergy status. [42]

Failure and attenuated response to vaccination has been observed in malnourished children compared to normal children. This is exemplified by the significantly lower seroprevalence rates of poliomyelitis and measles in these children. In one study, the seroprevalence rates of the polio 1, polio 2, polio 3 antibodies and the measles antibodies in malnourished children (40.5%, 59.5%, 40.5% and 35.1%) compared to the control group (94.1%, 97.1%, 91.2% and 82.4% respectively. [39] Another example is the demonstration of reduced effectiveness of following human rotavirus (HRV) vaccination due to impaired B cell response both mucosal and systemic) in children with a deficient diet. [43]

3.6. The long-term effect of malnutrition and associated enteric infections on child growth and development

Malnourished children suffer from a higher frequency, increased severity, and longer course of diarrheal infections. Studying the growth of children in Guatemala and Brazil who had repeated diarrhea showed that their growth slipped progressively away from their potential height. The collective effect of their diarrheal illnesses led to progressive stunting and markedly attenuated normal growth and development. [44]

It must be noticed that growth attenuation has been documented in many children with asymptomatic enteric infections (without diarrhea). Anthropometric data analyses following a diarrheal illness in Brazil discovered that recurrent diarrhea reduced weight and height gains by 48% and 21%, respectively, when compared with children who did not have recurrent diarrhea. During nutritional rehabilitation, malnourished children who did not experience heavy diarrhea had significant catch-up in weight but those with significant diarrheal burden failed to catch up. [44,45] Other investigators proposed that diarrheal illnesses, including intestinal helminthic infestation, in the first 1–2 years of life may be responsible for an ~8.2 cm deficit in the final adult height in these children. [46]

3.7. Effect of malnutrition on pathogens and their virulence

The frequency and severity of gastrointestinal infections appear to be significantly higher in malnourished children. Both increased incidence and prolonged course of diarrheal illnesses have been documented. [47] A retrospective analysis realized that infection with typical enteropathogenic E Coli (EPEC) and enterotoxigenic E Coli producing heat-stable toxin (ST-ETEC) produced more severe diarrhea among children with acute malnutrition compared to children with better nutritional status. (47) Mortality rate, as another parameter of severity, was significantly higher in children with acute malnutrition following an episode of moderate-to-severe diarrhea and they represented the majority of deaths. [48]

The studies on children in Africa and Asia identified pathogens in 83% of children with diarrhea and 72% of controls. These findings draw attention to the frequency of entero-pathogen carriage in these areas with a high prevalence of undernutrition. [49] These asymptomatic enteric infections can negatively affect linear growth and weight gain. [50] In addition, decreased dietary protein intake impairs intestinal cell turnover, an important host protection factor against certain pathogens like Cryptosporidium as suggested by Liu J, et al. [51]

On the other hand, micronutrient deficiencies, common in malnourished children, can modify the response to diarrheal infections. Zinc deficiency has been shown to prolong Campylobacter shedding, bloody diarrhea, and increase weight loss, and.iron deficiency anemia has been shown to decrease the humoral, nonspecific immunity (phagocytic activity and oxidative burst), and the IL-6 levels. Vitamin D deficiency is reported to increase the susceptibility and severity of acute infections and with unfavorable outcomes. [52, 53]

The link between malnutrition and viral virulence was studied in mice. Nutritionally deficient mice infected with viral quasispecies (mainly avirulent and a few virulent viruses mix) developed severe pathology which did not occur in well-nourished mice. [54]

3.8. Gut microbiota, inflammation due to environmental enteric dysfunction (EED), and gut barrier factors during malnutrition

Diet and microbiota greatly influence postnatal growth, maturation, and development. There is a bidirectional link between the microbiota and gut mucosa. Microbiota can induce mucosal inflammation and in the other direction, the mucosal inflammatory environment can modify and alters the microbiota. Diet is a markedly impacts the structure of the gut microbiota. Microbiota is a sensor of dietary changes, and signals from microbiota are essential for competent mucosal immune development as well as for digestion.

It has been reported that SAM is associated with significant relative microbiota immaturity. Nutritional intervention can ameliorate the composition and function of gut microbiota. [55]

Immaturity of microbiota in less severe forms of malnutrition has been correlated with both impaired growth as well as with defective immune function. [56] In Malawi and Bangladesh investigators found a relation between severe stunting and lower diversity of gut microbiota. They reported that the relative abundance of Acidaminococcus was correlated with decreased linear growth. [57]

These facts raise the possibility of using dietary manipulation of microbial diversity, composition, and stability for therapeutic purposes. [58] The microbiota has an important role in digestion by directly breaking down nutrients that the human gut cannot digest. [59] Innovative gut microbiota-targeted strategies using plant-based and low-protein diets, prebiotic, probiotic, and synbiotic supplementation represent potential conservative therapies for malnourished children. [60, 61]

Exclusive infant Breastfeeding infants has been shown to be protective against diarrhea. Lactobacillus bacteria and other Probiotic bacteria in breast milk have a favorable effect on the formation of the infant's intestinal microbiome. On the other children receiving antibiotics, through changing the gut microbiota, in the first 6 months of life had a 33% increased risk of diarrhea through the following 3 years. [62-65]

3.9. Intestinal barrier function, intestinal dysbiosis, and environmental enteropathy (EED): (figure 1)

Environmental enteric dysfunction (EED) represents a subclinical enteropathy characterized by mucosal inflammation and villus blunting mediated by T cell activation. [66] Children living in low-income countries (LICs) and poor environmental conditions have a high risk to develop EED. Poor hygiene increases exposure to intestinal pathogens and leads to an imbalance of the microorganisms within the intestine (intestinal dysbiosis). Consequently, intestinal inflammation and disruption of intestinal barrier function occur. Attenuation of the barrier function permits the passage of bacteria and their toxic products from the intestine to mesenteric lymph nodes and systemic circulation. Bacteria and their products activate innate immune cells in the mesenteric lymph nodes, liver, and systemic circulation. Immune activation generates proinflammatory cytokines and can explain their high in undernourished children, even without clinical evidence of acute infection. [64]

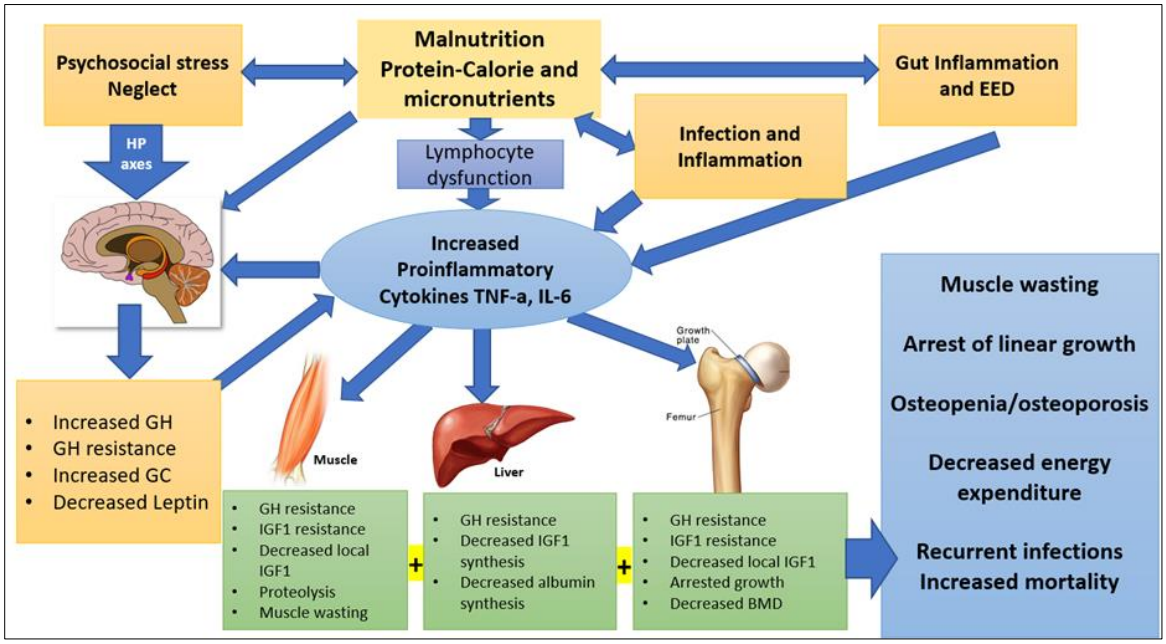

Figure 1 Overview of actions of pro-inflammatory cytokines on the hypothalamic -pituitary axes, and end organs in malnutrition

Environmental enteric dysfunction-associated inflammation deteriorates the nutritional status and immune function of the child through decreasing nutrient absorption, increasing intestinal permeability and systemic translocation of immune-stimulatory PAMPs molecules, such as lipopolysaccharide. Chronic systematic exposure to lipopolysaccharide significantly alters innate cytokine production and impairs T-cell proliferation. The increased systemic and intestinal

inflammation associated with EED and diarrhea impair immune defense and growth and is associated with increased morbidity and mortality. [65.66]

Unfortunately, chronic immune stimulation may result in immune paralysis (persistence of a marked compensatory anti-inflammatory innate immune response) that predisposes to recurrent invasive infections. In Children living in LIC, EED-driven immune paralysis increases their vulnerability to both acute and chronic infections as well as stunting during childhood. [9, 66-68] (Table 3).

Table 3 Possible mechanisms that lead to growth failure in infants with EED

• Intestinal leakiness and heightened permeability.
• Gut inflammation.
• Shifts in the small intestinal microbiota
• Dysbiosis and bacterial translocation.
• Systemic inflammation.
• Nutrient malabsorption

Since EED has multiple causal pathways, approaches to manage it need to be multifaceted. Possible variable interventions to tackle EED are summarized in Table 4:

Table 4 Potential interventions to tackle EED include

1.	Reduction of exposure to feces and contact with animals through programs such as improved water, sanitation, and hygiene
2.	Breastfeeding and enhanced dietary diversity
3.	Probiotics and prebiotics
4.	Nutrient supplements, including zinc, polyunsaturated fatty acids, and amino acids
5.	Anti-inflammatory agents such as 5-aminosalicyclic acid

3.10. The risk of diarrhea in relation to the degree of malnutrition

Malnourished children seem to be at higher risk to develop diarrhea and having a prolonged and /or severe course. Analyses of several cohorts of children during their first two years revealed that children who had >or=5 diarrhoeal episodes before 24 months had a high risk to be stunted (25%). (69). Many studies confirmed the correlation between having frequent episodes of diarrhea and prolonged impairment of linear growth, [69].

Table 5 What is known and what is new about the link between malnutrition, immunity, and inflammation

What is known:
• There is a tight link between malnutrition on the one hand and infection and inflammation on the other hand
• Providing high qualitative and adequately quantitative nutrition, proper and prompt treatment of infection can interrupt the vicious link between infection-inflammation and malnutrition
What is new:
• The presence of environmental enteric dysfunction (EED) deteriorates the nutritional status through inducing local intestinal and systemic inflammatory reactions
• Even asymptomatic infection can adversely affect growth and nutritional status of undernourished children
• Malnutrition is associated with abnormal pattern of intestinal microbiota that share in the pathogenesis of enteropathy

• Possible therapeutic modification of the gut flora can enhance local and systemic immunity

4. Conclusion

Malnutrition increases vulnerability to infection and inflammation through variable pathological mechanisms involving local and systemic immunity. Molecular and clinical studies showed that improving the environmental condition, providing high qualitative and adequately quantitative nutrition, proper and prompt treatment of infection, and possible therapeutic modification of the gut flora can enhance local and systemic immunity and interrupt the vicious circle of infection-inflammation –malnutrition. (table 5)

Compliance with ethical standards

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Contributions

Ashraf Soliman: Substantial contributions to the conception of the work; extensive searching of the literature and drafting the review; and approved the manuscript for publication.

Nada Alaaraj: Shared actively in searching the literature and writing up the review; constructing the tables and drawing the figures; and approved the manuscript for publication.

Alan D Rogol: Contributed to the conception of the work and critically revised the manuscript for accuracy and integrity and approved the manuscript for publication.

Disclosure of conflict of interest

There was no conflict of interest among authors.

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