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A Review on Micronutrient Deficiency and Immune Dysfunction in Anorexia

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Abstract: **The number of adolescents affected by Anorexia Nervosa (AN) has been on the rise during the Covid-19 pandemic. AN hs been proven to be associated with several health complications due to severe energy restriction - including a weakened immune system; however, less is known of the direct impact micronutrient deficiency on immune function in patients with AN. This purpose of this review is to evaluate whether micronutrient deficiency is the main cause for immune dysfunction in patients with AN and analyze the current information available regarding this topic in hopes of opening a new field of research. By conducting secondary research through the usage of google scholars with the keywords "mircronutrient deficiency" "immune dysfunction" and "aorexia nervosa", it was found that several research yielded contradicting results. Thus, a conclusion as to whether micronutrient deficiency is the sole cause of immune dysfunction could not be made due to inconsistent data and lack of information available in regards to this topic.**

Keywords: **Micronutrient Deficiency, Immune Dysfunction, Anorexia Nervos.**

1. INTRODUCTION

The ongoing pandemic has brought stress to people of all ages, bringing about mental health concerns due to social isolation. One concern is the rise in patients affected with Anorexia Nervosa; research conducted in Western Australia[1] found that there was a 104% increase in children with Anorexia Nervosa during the pandemic. Another study in Israel[2] also found that there was a significant increase in the number of adolescents hospitalized for Anorexia Nervosa during this time.

Anorexia nervosa (AN) is an eating disorder that is characterized by a restriction of energy intake relative to requirement[3]. Not only is AN an eating disorder, but it is also a psychological disorder, causing patients to have distorted body image with the inability to recognize the seriousness of their significantly low body weight[3]. Research has shown that, patients with AN often face health complications such as endocrine abnormalities, cardiac problems and weakened immune system due to severe energy restriction[4].

However, less is known about the direct effects micronutrient deficiency has on the immune function in patients with AN.

In the present, it is widely accepted that an adequate micronutrient status is required to maintain a well-functioning immune system. Consequently, micronutrient deficiencies can increase one's susceptibility to infections as deficiencies can result in immunosuppression[5]. With covid-19 still negatively affecting the world, maintaining a healthy immune system is crucial.

This review aims to discuss whether micronutrient deficiency results in immune dysfunction in patients with Anorexia and evaluate the current information available in regards to this topic. Google Scholar was utilized as the main search engine to find studies that were published no more than 5 years back, using the keywords "micronutrient deficiencies" "immune dysfunction" and "anorexia nervosa".

2. STATUS OF IMMUNE FUNCTION IN PATIENTS WITH AN

Patients with AN have been reported to have decreased levels of pro-inflammatory cytokines and elevated levels of interleukin. In a study by Francisco Ruiz Guerrero[6], serum concentration of pro-inflammatory cytokines was measured in 48 young patients with an early diagnosis of an eating disorder and compared to 29 healthy controls. Their results showed

that levels of proinflammatory cytokine IL-1β and IL-6 were significantly lower in ED patients, compared with healthy controls.

However, this contradicts the findings of a study done by Javier R Caso[7] where he found that plasma levels of the pro-inflammatory cytokine IL-1β were significantly increased in 27 AN patients in comparison to 23 healthy controls. Guerrero also reported that elevated levels of IL-10 were found when comparing different groups of females which align with Caso's findings and support the idea of an immunosuppressive status.

In regards to IL-10, Ostojic[8] found that the levels of inflammatory cytokine IL-10 is significantly influenced by BMI, a low BMI results in the overproduction of IL-10 and the down-regulation of pro-inflammatory cytokines. This would explain Guerrero's findings as the majority of AN patients have low BMI; however, recent research has shown that not all AN patients have a low BMI[9].

In 2017, a research done by Elegido[10] with a sample of 66 adolescent females diagnosed with AN found that patients with AN had lower leukocyte numbers as well as lower CD8+, NK, and memory CD8+ counts in comparison to control groups.

A more recent study in 2019 conducted by Gibson[11] also found lower NK cell quantity in patients with AN when compared to controls which support Elegido's findings. Additionally, Gibson also reported that NK cell activity was normal despite the lowered quantity. Regardless, Gibson concluded that the innate in patients with AN did have multiple abnormalities - there was a deficit in neutrophils in chemotaxis and a decrease in neutrophil adherence. Cell-mediated immunity in AN patients was also noted as 'dysregulated,' and the response of cell-mediated cytotoxicity was significantly reduced. However, T cell proliferation seemed to be intact, if not increased and regulatory T cell function remained normal.

This may explain why DeSarbo[12] reported in his article that the rate of infection in patients with AN has neither increased nor decreased and is relatively similar to that of the general population. This aligns with Schmidt's[13] findings, where she reported that the range of immunological parameters assessed in AN subjects wasn't significantly different when compared to healthy controls.

DeSarbo also noted that symptoms of a viral infection can mimic the symptoms of AN which makes the diagnosis of infection in AN patients more complicated.

The latter corresponds with Ostojic's findings where she found that AN has been associated with fewer symptomatic viral infections.

3. MICRONUTRIENT STATUS IN PATIENTS WITH AN

Due to their restrictive intakes, patients with AN are prone to be deficient in micronutrients. In 2017, Achamrah[14] conducted research to assess the micronutrient initial status of 153 AN patients due to conflicting data present in the past. She found that the mean plasma concentrations of zinc, copper, and vitamin B12 were within a normal range whereas the most prevalent deficit was for vitamin B9. She also concluded that at least one vitamin deficiency was found in 45.7% of the patients.

A similar study was conducted 2 years later with a larger population, where Hanachi[15] analyzed the micronutrient status of 374 severely malnourished AN inpatients. She yielded more extreme results in comparison to Achamrah; Hanachi reported that the majority suffered from one or multiple micronutrient deficiencies - only 7.2% had no deficiencies. This is most likely because the subjects were in near-critical conditions. Zinc deficiency was the most common, with 64.3% of the patients suffering from this. 54% of the patients suffered from vitamin D deficiency, 37.1% suffered from selenium deficiency, 20.5% from vitamin B1, 4.7% from vitamin B12, and 8.9% from vitamin B9. Some of Hanachi's findings contradict the findings of Achamrah as vitamin B9 deficiency had the lowest prevalence whereas Achamrah found vitamin B9 deficiency to be most common. Furthermore, several vitamins and minerals which Achmarah found to be within normal ranges, were concluded as deficient in Hanachi's studies.

In Schmidt's[13] more recent study where the micronutrient status of those with a restrictive eating disorder - not specifically diagnosed as AN or hospitalized - were analyzed, results showed that intake of vitamin B1 and zinc were significantly lower than the control group; supporting Hanachi's findings. However, in regards to the intake of vitamin B12, B9, and D, it was reported that no differences were observed when compared to healthy controls despite a significantly lower energy consumption which is what Achmara also found. Schmidt concluded that no difference in vitamin D intake was found most likely due to the high prevalence of vitamin D deficiency in the population.

4. HOW MICRONUTRIENT DEFICIENCY CAUSES IMMUNE DYSFUNCTION

Micronutrients play a crucial role in supporting the immune system - influencing every stage in the immune response. Consequently, being deficient in micronutrients will inevitably result in immunosuppression.

Ali Gorji M.D.[16] reported that Zinc modulates the pro-inflammatory response and contributes to the function of various immune cells. As a result, zinc deficiency enhances the production of proinflammatory cytokines such as IL-1b, IL-6, and TNF-a, reduces the lytic activity of natural killer cells, and decreases the production of antibodies.

Mitra[17] reported that Selenium is an essential component of selenoproteins, which are necessary for NK cells, macrophages, neutrophils, and T lymphocyte functions. On the same note, Selenium deficiency is known to cause impaired functions of neutrophils, T-cells, lymphocytes, NK cells, and thymocytes, weakening the host immune system against viral infections[16]. Poor selenium intake reduces adaptive immunity and exacerbates inflammation[18].

Copper deficiency can lead to a decrease in the levels of IL-2 and a decrease in T cell proliferation. Phagocytic ability is also reduced due to inadequate levels of copper[11] It has been reported that an insufficient amount of copper decreases the number of neutrophils in the peripheral blood, reducing the capacity to produce superoxide anions and destroy ingested bacteria[17]

Energy generation in various immune cells is regulated by different vitamin B's. Vitamin B1 deficiency impairs the maintenance of B cells whilst being deficient in vitamin B12 leads to a reduction in the number of NK cells and levels of IL-6[16]. This is supported by a study conducted by Mikkelsen[19], where he found that an insufficient amount of vitamin B12 affects the production of nucleic acid and protein synthesis, inhibits immune cell activity as well as interferes with several metabolic processes; all of which drastically alters the immune response.

The immune response, in general, is impaired due to vitamin B9 deficiency, this also reduces the blastogenic response of T lymphocytes[16]. Abnormalities likely cause the negative immunological functions in DNA and RNA synthesis or methyl metabolism as these 2 processes are heavily affected by the level of vitamin B9 available in the body[17]

Vitamin D is responsible for inhibiting dendritic cell differentiation and maturation which prevents autoimmunity and promotes self-tolerance[20]. Thus, it can be claimed that vitamin D deficiencies will result in an inefficient immune response. This is supported by findings that claim that vitamin D deficiency was associated with more severe illnesses, multiply organ dysfunction, and higher mortality levels[16].

5. CONCLUSION

Based on the findings, patients with AN reportedly have lower levels of inflammatory cytokine IL-10, leukocytes, CD8+, memory CD8+, and NK cells but they all seem to function fine - independent of the severity of their illness. Additionally, the response of cell-mediated cytotoxicity was decreased and there were lower amounts of neutrophils in chemotaxis yet several studies reported no difference in the rate of infection when comparing AN patients and healthy controls. In regards to micronutrient deficiencies, it can be seen that micronutrient deficiency in patients with AN is dependent on an individual's condition; however, it seems that most are deficient in B vitamins and vitamin D. Even though it is evident that micronutrient deficiency can result in immune dysfunction, the inconsistent reports regarding immune function in patients with AN along with the vitamins patients are deficient in, suggest that it can't be concluded that micronutrient deficiency alone is responsible for immune dysfunction. The significance of micronutrient deficiency as being one of the causes of immune dysfunction in patients with AN still remains unclear due to the other factors that should be taken into consideration when assessing the roots of immune dysfunction. Given the lack of recent information available revolving around micronutrient deficiency in patient with AN, this should be an area medical professions pay more attention to as it's a potential cause of various health complications. By identifying the correct cause, sufficient treatment can be provided to the patients.

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