

## Embracing cancer immunotherapy with vital micronutrients

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### Abstract

Immunotherapy is now commonly prescribed to cancer patients, but autoimmune-related adverse events are considerable. For severe, life-threatening side effects, cessation of therapy seems unavoidable, let alone intensive medical care required for patching up the adverse events. Even without serious adverse events, the response rates are too low and various combinatory regimens have been tried. However, toxicities are also added on, unless the adjuvant agents have remarkably few side effects. Actually, micronutrients are usually taken by a majority of cancer patients as nutritional support or to boost the immune function, let alone hoping to counteract treatment side effects. Recent studies have shown that combinations of micronutrients exert pleiotropic effects in controlling tumor growth and metastasis by modulating the tumor microenvironment, enhancing gut microbiota immune functions, and providing adjunct nutritional support to micronutrient deficient cancer patients. A higher than recommended dietary allowance micronutrient dose is proposed to reduce the toxic free radicals generated as a result of immunotherapy and tumor metabolism. This is not only helpful for managing treatment side effects but also enhancing treatment efficacy. As micronutrient supplementation is also useful to improve patients' quality of life, prolong survival, and sustain compliance to immunotherapy, further investigations are mandatory.

**Key Words:** Immunotherapy; Micronutrients; Immune-related adverse events; Vitamins; Tumor microenvironment; Immunonutrition

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immunomodulation and minimizing immune-related adverse events, improve acquired immune response through modification of the tumor microenvironment, enhance gut-microbiota immune functions, boost immune-nutrition function, and improve patient outcome.

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## INTRODUCTION

It was estimated that 30% to 90% of cancer patients took some form of supplements and micronutrients for immunity support and reducing treatment side effects upon being diagnosed with cancer. Micronutrients such as various vitamins and minerals, especially selenium, zinc, *etc.*, are often consumed without any discussion with their oncologists for fear of being criticized. After all, the role of micronutrients for cancer patients is not generally accepted. Actually, micronutrients such as vitamin C (usually at high dosages) have been used since its discovery in the 1930s not just as a nutritional supplement but also as an anti-microbial agent when there were no potent anti-microbial agents by then[1,2]. Currently, micronutrients are much more often employed by naturopaths and complementary and integrative medical practitioners with or without other modalities to treat chronic diseases, autoimmune disorders, and even cancers[3]. Even in this era of cancer immunotherapy, various immune-related adverse events (irAEs) constitute a real concern. Nevertheless, micronutrients may well be useful for tackling some of these adverse events and even enhance the efficacy, as is being alluded to in this review.

## CANCER IMMUNOTHERAPY: IRAES

Checkpoint protein inhibitors (CPIs), including cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitors and programmed cell death protein 1 pathway/programmed cell death protein 1 ligand (PD-1/PDL-1) inhibitors, are now commonly employed to treat a progressively wider spectrum of cancers with fewer side effects and much better tolerance than classical chemotherapy[4]. Unfortunately, the response rates are low and the immune-related toxicities are considerable[5]. CPIs act by enhancing the immune function of T cells by blocking the connection between PD-1 and PDL-1 and preventing the inhibition of T cells. T cell cytotoxicity then attacks the tumor cells. CTLA-4 blocks the connection between dendritic cells and T cells related to CTLA-4. CTLA-4 removes the inhibition related to dendritic cells on T cells to achieve a cancer-killing effect. Because checkpoints may also regulate autoreactivity, immune checkpoint inhibitor therapy is complicated by irAEs[6]. The mechanisms leading to irAEs are similar to those promoting anti-tumor responses, which involve T and B cell immune modulation and induce autoantibody production [7]. However, the wide range of irAEs associated with immune checkpoint blockade may be diverse and serious. These may well lead to the suspension of the otherwise effective immunotherapy. The irAEs may affect various organs and patients would have multiple side effects. In a study of 78 patients receiving CPIs, 53% developed irAEs with 15% of patients developing more than one complication[4]. Notably, a small number of side effects are life-threatening or require urgent medical attention [8]. Some serious irAEs are colitis, interstitial pneumonitis, myocarditis, pericarditis, arrhythmia, impaired ventricular function, and vasculitis. Neurological complications such as myasthenia gravis, Guillain-Barrie syndrome or peripheral neuropathy, aseptic meningitis, and encephalitis are also documented. Endocrine side effects such as hypothyroidism, hyperthyroidism, adrenal insufficiency, and type I diabetes mellitus, as well as hepatitis, nephritis, autoimmune hemolytic anemia, thrombocytopenia, skin rashes, and bullous dermatoses are also seen[9]. Since many of these side effects are related to similar immunologic actions for the immunotherapy therapeutic effects, the management of such adverse events constitutes a major challenge. Ideally, an efficient

adjuvant drug should be available to enhance cancer immunity whilst alleviating the irAEs[10]; otherwise, irAEs may preclude the continuation of CPIs[8,11]. Currently, medical management of irAEs may often be limited to symptomatic relief with systemic corticosteroids or immunosuppressants together with specialist care. There is a great need for multidisciplinary guidance from different specialties to establish broad-based perspectives in early recognition and management of organ-specific irAEs and to set up management guidelines[12]. Notably, the Society for Immunotherapy of Cancer has set up such a multidisciplinary Toxicity Management Working Group to develop recommendations and initiate treatment protocols for irAEs[11].

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## ROLE OF VITAL MICRONUTRIENTS IN IMMUNE FUNCTION AND INFECTION

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Micronutrients such as vitamins A, D, C, E, B6, and B12, folate, zinc, iron, copper, and selenium are best tailored according to age-related needs[13]. As adequate amounts of these micronutrients are vital for proper immune functioning[14], a high enough dose is necessary for various kinds of immuno-compromised or even the terminally ill[15, 16]. According to some studies, micronutrients with the strongest evidence for immune support are vitamin C, vitamin D, and zinc[15,17,18].

Patients with micronutrient deficiencies are prone to various infections and even body dysfunctions due to weakened immune responses to pathogens such as viruses like SARS-CoV-2, the virus that causes COVID-19[19]. Strikingly, micronutrient deficiencies affect about two billion people worldwide[20], contribute to low immunity against infections, and constitute a common cause of immunodeficiency in developing countries[21]. On the other hand, micronutrient supplementation could enhance immune functions and help the body to fight against pathogens and cancers[15,22-24].

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## CLINICAL IMPACT OF MICRONUTRITION IN CANCER TREATMENT

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Since the 1980s, there was abundant epidemiologic evidence that high intakes of fruits and vegetables reduced the risks of most cancers. This may support the concept that micronutrients could play a vital role in cancer prevention[24]. Recent systematic reviews on micronutrients and breast cancer[25] have shown that micronutrient consumption may reduce the incidence rates and/or progression of cancers[24]. Epidemiological and experimental studies showed that the percentage of cancer-related deaths attributable to diet and tobacco was as high as 60%-70% worldwide[26]. For micronutrients, *in vitro* and *in vivo* studies on over 50 human cancer cell lines have demonstrated a good anti-cancer effect being achieved in combinations of micronutrients (rather than the individual compounds). It was also well documented that nutrient combinations exert pleiotropic effects in controlling tumor growth, invasion, and metastasis[16,27-29].

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## CONTROVERSY OVER USE OF MICRONUTRIENTS IN CANCER THERAPY

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Since most micronutrients may also act as antioxidants, some physicians are concerned about possible inhibitory effects on chemotherapy killing actions[30]. On the contrary, there are reliable studies on the beneficial effects of antioxidants and micronutrients for patients during radiation therapy[31,32] and chemotherapy[33,34]. A recent extensive review comprising of 174 peer-reviewed articles and 93 clinical trials with a total of 18208 cancer patients showed that antioxidants have superior potentials in reducing chemotherapy-induced toxicity[35]. The conclusion was that antioxidant supplementation during oncology treatments enhanced chemotherapeutic efficacy and even prolonged patient survival. Moreover, in other studies, when antioxidants were given concurrently with chemotherapy, no interference occurred. Rather, they enhanced the chemotherapeutic effects, and even protected normal tissues and increased patient survivals and therapeutic responses[36,37].

## VITAL MICRONUTRIENTS — ROLE IN AMELIORATING IRAES AND ENHANCING IMMUNOTHERAPY

### ***Tumor microenvironment modification***

The tumor microenvironment (TME) is largely composed of mesenchymal stem cells, fibroblasts, endothelial cells, adipocytes, and immune cells with an altered extracellular matrix having an acidic and hypoxic composition. TMEs can promote immune tolerance through the secretion of lactate and competing for nutrients between tumor cells and immune cells[38]. Cancer-associated fibroblasts and solid tumors can promote immunosuppression by inhibiting T cell functions and extracellular matrix remodeling[39]. Recent studies have suggested that nutrients available in the TME can influence immunotherapy response and cancer cell metabolic pathways[38,40]. Micronutrients like vitamin C can enhance immune cell functions by modifying the TME by hypoxia-inducible factors[41]. High-dose vitamin C modulates infiltration of the TME by immune cells and delays cancer cell growth in a T cell-dependent manner. Vitamin C enhances the proliferation and maturation of T cells and natural killer cells[42]. It also reduces the formation of neutrophil extracellular traps in the TME, which are related to irAEs due to checkpoint blockade[43]. The combination of high-dose vitamin C and immune checkpoint therapy may potentially enhance the efficacy of immunotherapy for cancer[44].

Vitamin D supplementation also suppresses tumor angiogenesis, progression, and metastasis *via* targeting components of the TME[45]. The active form of vitamin D, 1,25(OH)<sub>2</sub>D<sub>3</sub>, regulates stromal cells including tumor-associated fibroblasts, tumor-derived endothelial cells, cancer stem cells, and infiltrating immune cells within the TME to facilitate cancer suppression. Vitamin D also has anti-inflammatory effects within the TME. This leads to the inhibition of proliferation, induction of apoptosis and differentiation, suppression of migration, and autophagic cell death of tumor cells [45]. Taken together, these may reaffirm the anti-cancer potential of vitamin D[46].

### ***Enhancing gut microbiota immune functions***

Micronutrient deficiencies have been linked to changes of bacterial species in the human gut microbiota affecting the host regulation of immune responses[47]. The activity of the gut microbiota has significantly contributed to the host immune health and is linked to the development of many diseases including cancer. Therapeutic interventions to optimize microbiota composition to improve immunotherapy outcomes have shown promising results[48,49]. In addition, gut microbiota modulations through micronutrient supplementations could effectively enhance efficacy and relieve or tackle resistance during immunotherapy treatments[50]. Gut microbiota may also activate or repress the host's response to CPIs and potentially modulate resistance to cancer immunotherapy[51]. As vitamin D deficiency has been linked to gut dysbiosis and bowel inflammation, vitamin D may play a significant role in gut microbiome regulation and host immune responses[52]. Moreover, vitamin D supplementation has been shown to increase gut microbial diversity significantly. This is a positive health impact on healthy individuals[53] and cancer patients[54].

### ***Adjunct nutrition support for cancer patients***

It was estimated that about 30%-90% of patients believed that they had inadequate diets leading to nutritional deficiencies and poor immune functions; some cancer patients were obviously cachexic. Micronutrient deficiencies do have negative impacts on immunotherapy as the host's immunocompetence is weakened. There is also an increased risk of developing irAEs and a negative impact on the patient's quality of life. Nutritional deficiencies can be reversed early if adjunct micronutrients are given before and during oncology treatments. Some chemotherapy drugs may have side effects of depleting certain micronutrients. This tends to worsen the nutritional deficiency, *e.g.*, cyclophosphamide and paclitaxel can deplete vitamin D by an increased breakdown of calcidiol and calcitriol[55]. A cohort study from the Mayo Clinic has shown a 26% reduction of non-small cell lung cancer mortality with improved quality of life and prolonged survival through micronutrient supplementation[56]. Apparently, immunonutrition has the potential to modulate the activity of the immune system by interventions with specific nutrients. It may be applied with immunotherapy to improve immune functions, modulate the acquired immune response, decrease treatment toxicity, and enhance patient outcomes[57]. Micronutrients such as selenium, vitamin C, and vitamin D (at high doses) have been found to be effective and safe for patients undergoing oncological intervention[16,55,58,59].

### **Protecting normal healthy cells**

Immunotherapy-associated irAEs include autoimmune reactions, cytokine release syndromes, and vascular leak syndrome. These vary depending on the type of immunotherapy and the specific mechanism of action. Cytokines such as high-dose IL-2 will lead to capillary leakage and a sepsis-like syndrome or multi-organ failure[60]. CPIs disinhibiting T cell anti-tumor action can lead to a distinct constellation of organ-specific inflammatory side effects or irAEs[12].

Vitamin D and zinc have been known for balancing immune functions through the prevention and treatment of autoimmune diseases[61]. Several observational studies have shown that vitamin D deficiencies increased the risk of autoimmune diseases such as type I diabetes, systemic lupus erythematosus, inflammatory bowel disease, Hashimoto's thyroiditis, multiple sclerosis, psoriasis, and rheumatoid arthritis[62,63]. Vitamin D supplementation is found to be beneficial to prostate, breast, and colorectal cancers and melanoma patients during treatment[64].

Vitamin B12 supplements may reduce the direct toxic side effects of immunotherapy as vitamin B12 is required for red blood cell synthesis, neural functions, and reduction of the severity of drug-induced peripheral neuropathy[65]. Vitamin B12 has been added as a supplement to pemetrexed and cisplatin chemotherapy agents, as used in pleural mesothelioma and non-small cell lung cancer. This was allegedly because of its folate similarity and inhibition of purine and pyrimidine synthesis[66]. Vitamin B12 effectively reduced the toxic side effects of the main chemotherapy.

Vitamin C is concentrated in most immune cells which support essential immune functions such as enzyme cofactors for Fe- or Cu- containing oxygenase. This regulates cell metabolism, epigenetics, growth, survival pathways, and even stem cell phenotypes[42]. High-dose intravenous vitamin C has been found to be useful as an adjunct to interleukin-2 immunotherapy to reduce capillary leakage, systemic complement activation, and a non-specific rise in inflammatory mediators such as TNF-alpha and C-reactive proteins by protecting the endothelium from inflammation [67]. High-dose intravenous vitamin C may also reduce cytokines which cause tumor angiogenesis and inflammation in cancer patients[68].

Vitamin D deficiency has been linked to autoimmune diseases[63] such as psoriasis, vitiligo[69,70], autoimmune thyroid diseases, Hashimoto's thyroiditis, and postpartum thyroiditis[71]. Vitamin D decreases the expression of various cytokines that cause vitiligo and other autoimmune disorders by preventing the destruction of melanocytes [69]. Oral vitamin D3 has been reported to be effective for improving the levels of epidermal keratin in psoriatic patients and to improve the treatment outcome with topical dithranol, PUVA (psoralen and ultraviolet A, a light therapy for skin diseases), and oral etretinate and hydroxyurea therapy[72]. A pilot study with prolonged supplementation of high dose vitamin D has improved the clinical course of vitiligo and psoriasis[73]. Melanoma patients often present with cutaneous lesions such as vitiligo, representing an autoimmune disorder with progressive destruction of melanocytes[74]. Dermatologic side effects such as vitiligo and leukoderma are often seen in melanoma patients who are on PD-1 inhibitors (up to 10%, more for ipilimumab)[75]. Notably, irAEs affect all organ systems and most commonly the skin (pruritus, rash, and vitiligo), the gastrointestinal tract (enterocolitis), the liver (hepatitis), and the endocrine system while less commonly involve the neurological system. The gastrointestinal tract, liver, lung, and skin are actually maintained in an immunologically quiescent state, which may explain the vulnerability of these organs for the development of irAEs[6].

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## **MICRONUTRIENTS: VENTURING TO REDUCE AUTOIMMUNE-RELATED IRAES**

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Interestingly, a recent cohort study has shown that vitamin D supplementation could reduce the risks of CPI-induced colitis by as much as 65%[76]. As CPI-induced colitis is an irAE that is basically autoimmune-related, such micronutrients as vitamin D may also reduce the risks of other CPI-induced and autoimmune-related irAEs. As alluded to above, vitamin D deficiency is rather closely linked with autoimmune disorders, let alone vitamin D administration may be beneficial. Hence, it would appear highly worthwhile to look at the prospects of such micronutrients in managing autoimmune-related disorders. There may be a potential role of micronutrients in preventing irAEs induced by CPIs. Currently, CPIs do have considerable autoimmune-related irAEs. For instance, the phase 2 KEYNOTE-224 trial of pembrolizumab for advanced hepatocellular carcinoma patients who have been treated previously with sorafenib saw

considerable adverse events[77]. In that trial, treatment-related adverse events occurred in 73% of 104 patients. Most of the more serious adverse events were immune-related. Naturally, serious adverse events may well lead to dropouts or suspension of the immunotherapy, defeating the whole purpose of such a valuable modality of treatment. Apparently, it would be worthwhile to examine whether vitamin D or zinc really has beneficial effects on the management of autoimmune disorders. If so, it may support the feasibility of using these micronutrients prospectively to reduce the autoimmune-related irAEs of CPIs. If some simple measures could prevent or reduce such adverse events, it would be most helpful. More cancer patients may then be able to benefit from CPIs. Before that could ever happen, one could start by scrutinizing how effective are these micronutrients, especially vitamin D and zinc for the management of autoimmune-related disorders. Table 1[78-85] shows selected trials of zinc and vitamin D on autoimmune-related disorders.

Notably, the 3<sup>rd</sup> study listed in Table 1 involved a combination of zinc and vitamin A supplementation that had been shown to improve serum apoprotein A-1 and apoprotein B levels and the apoprotein B/proprotein A-1 ratio in patients with type 1 diabetes mellitus (T1DM). In fact, the deficiency of vitamin A would mainly involve an impaired transport mechanism of vitamin A from its hepatic storage to the target sites [86]. As insulin therapy would reverse this impairment, the replacement of vitamin A may not be crucial for controlling T1DM. Hence, the beneficial adjuvant effect of the combination of zinc and vitamin A for T1DM was more likely to be due to zinc than vitamin A. Moreover, from Table 1, three studies had involved T1DM cases of recent onset (studies 4, 5, and 6). Apparently, the adjuvant role of micronutrients for T1DM cases of recent onset may be more effective. Possibly, the fact that a vitamin D analog could benefit recent-onset T1DM may suggest that it would be useful to prevent an irAE that involves the beta cells of the pancreas.

Moreover, as micronutrients are but adjunctive treatment modalities, for demonstrating their effectiveness would also depend largely on the main modalities of treatment. In case that there is a significant difference in the effectiveness of those main modalities of treatment between the study groups, then the effectiveness of the adjunctive modalities of treatment would be difficult to demonstrate. Another highly relevant factor is the distribution of genetic predispositions between various groups of the study population. As to balance very evenly the genetic predispositions among the groups is not done easily or not done at all, the effect of such an imbalance between the groups would naturally affect the results[87]. Thus, incidental negative trial findings of micronutrients should not be taken as definitive proof that micronutrients are not useful.

Lastly, even the diet may affect autoimmunity. It was reported that heavy metals like mercury[88] might be incriminated. Chronic exposure to low levels of methylmercury (organic) and inorganic mercury was common among 1352 female subjects 16 to 49 years of age from the US National Health and Nutrition Examination Survey. Probably, the mercury was from consuming fish and even the slow disintegration of dental amalgams. Also, 16% of subjects were antinuclear antibody (ANA) positive. Hair and blood mercury levels were associated with ANA positivity. As ANA is closely related to autoimmune disorders, methylmercury exposure was deemed to be associated with subclinical autoimmunity among subjects and autoantibodies may even predate the onset of clinical diseases by years.

Taken together, several factors may affect the effectiveness of vitamin D and zinc on autoimmune disorders. When trials were performed on such micronutrients, it was challenging to balance evenly all the relevant factors among different arms of those studies. As such, results can be rather variable but may not reflect the true effectiveness of these micronutrients. Thus, negative clinical trial results should not be taken at their face value. After all, all these adjuvants have to act together with other more specific agents before exerting their effects. Moreover, the duration of onset of the autoimmune-related disorders may also be highly relevant. It is also possible that such adjuvant agents are most effective for prevention rather than treatment. In any case, these micronutrients should be further investigated thoroughly for their ability of preventing or reducing early autoimmune-related irAEs induced by CPIs. This is especially so as they have an excellent safety profile, are easily taken and eminently affordable.

Actually, cancer patients who are also suffering concurrently from immune disorders are routinely precluded from receiving any CPI, even if they are already on specific drugs for their autoimmune disorders. This is because of the fear of exacerbating their autoimmune symptoms once CPIs commence. If more studies can be done on vitamin D and zinc on their ability to prevent exacerbation of autoimmune disorder symptoms, one may know how effective these can prevent such autoimmune-related

**Table 1 Selected trials on the effect of zinc and vitamin D on autoimmune related disorders**

No.	Autoimmune disorder	Agent	Dose	Period	Trial type	Benefit	Year
1	MS	Cholecalciferol	50000 IU/wk	12 mo	R, C, DB	Decreased incidence rate of demyelination plaques, reduced progression risk	2013[78]
2	RA	ZnSO <sub>4</sub>	220 mg/3×/d	12 wk + 12 wk	C then O	Decreased joint swelling, stiffness, walking time	1976[79]
3	T1DM	ZnSO <sub>4</sub> + vit A	10 mg/d + vit A 25000 IU	12 wk	R, C, DB	Increased serum apo A1; decreased apo B/Apo A1 ratio	2010[80]
4	T1DM (RO)	Alpha-calcidol	10 IU/1-2×/d	6 mo	R, C, B (prtps)	FCP higher; lower requirement of insulin	2013[81]
5	T1DM (RO)	Cholecalciferol	2000 IU/d	18 mo	R, C, DB	Protective immunologic effect; slow decline of residual β-cell function (serum FCP and SCP levels)	2012[82]
6	T1DM (RO)	Cholecalciferol	70 IU/kg/d	12 mo	R, C, DB	Improved the suppressive capacity of Tregs	2015[83]
7	PS	Zinc pyrithione topical 0.25% in an emollient base	2×/d	3 mo	R, C, DB	Decreased plaques/PASI score	2011[84]
8	SLE	Vit D	50000 IU/wk	24 wk	R, C, DB	Decreased disease activity parameters; reduced fatigue	2016[85]

Apo: Apoprotein; B: Blind; C: Controlled; DB: Double blind; FCP: Fasting C-peptide; MS: Multiple sclerosis; O: Open; PASI: Psoriasis area and severity index; prtps: Participants; PS: Psoriasis; R: Randomized; RA: Rheumatoid arthritis; RO: Recent onset; SCP: Stimulated C-peptide; SLE: Systemic lupus erythematosus; T1DM: Type 1 diabetes mellitus; Treg: Regulatory T cells; Vit: Vitamin.

irAEs of CPIs. Hopefully, these unfortunate cancer patients suffering from two major disorders may then benefit from CPIs. Even those patients without any pre-existing autoimmune disorders may also benefit from reduced autoimmune-related irAEs upon commencing CPIs. Their autoimmune-related irAEs may be reduced by micronutrients and those unplanned suspensions of CPIs are avoided. Even for those who already have such unfortunate suspensions, such micronutrients might still contribute to a more successful rechallenging program. After all, if there are no other realistic options than CPIs, the threat to life is actually higher for uncontrollable cancers than autoimmune-related irAEs.

### ***Immunomodulating micronutrients enhances immunotherapy***

Vitamin A, beta-carotene, folic acid, vitamin B12, vitamin C, vitamin D, riboflavin, iron, zinc, and selenium may all have immunomodulating functions and could enhance the immune response rates of immunotherapy and even reduce irAEs[89]. They play an important role in reducing oxidative stress in diseases and cancers. Vitamin A supplementation improves levels of IgA immunoglobulin and CD40 ligand-activated IgG and reduces inflammatory cytokine levels[90]. Vitamin E as a potent antioxidant would reduce inflammation by modulating T cell function and downmodulating prostaglandin E2 in patients[91]. Vitamin C improves immune functions by supporting natural killer cell activities, lymphocyte proliferation, and chemotaxis, stimulates dendritic cells to secrete interleukin-12, and activates T and B cell functions[42]. High-dose vitamin C not only enhances the cytotoxic activity of CD8 T cells but also enhances immunotherapy by co-operating with immune checkpoint therapy in several cancer types[44]. Vitamin B12 deficiency has been linked to low lymphocyte counts, impaired NK cell function, decreased CD8+ cells, and impaired immune functions. Eventually, the raised CD4/CD8 ratio[92] would be potentially reversible by oral or intramuscular B12 injections. Vitamin D [1,25-(OH)<sub>2</sub>D<sub>3</sub>] binds to the vitamin D receptor of both the antigen-presenting cells (APC), dendritic cells, and T lymphocytes so as to exert its indirect and direct effects on T lymphocytes. The latter effect on the T lymphocytes is a change towards a more tolerogenic (capable of producing immunological tolerance) state with induction of T helper-2 (Th2)-lymphocytes and regulatory T lymphocytes (Tregs), together with a downregulation of the pro-inflammatory Thelper-1 (Th-1)-lymphocytes, Thelper-17 (Th-17)-lymphocytes, and Thelper-9 (Th9)-lymphocytes][93]. Notably, vitamin D suppresses T cell prolifer-

eration and then results in a shift from a Th-1 to a Th-2 development, inhibition of Th-17 cell development, and also facilitation of T regulatory cells with an arrest of cytotoxic T lymphocyte infiltration as well as increased CD4<sup>+</sup>CD25<sup>+</sup> Tregs[94]. Lastly, vitamin D inhibits inflammatory cytokine production by monocytes, and suppresses dendritic cell differentiation and maturation. This helps to maintain tolerance and would also promote protective immunity[95].

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## DISCUSSION

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Micronutrients are closely associated with the body's immune functions; a micronutrient deficient subject will have poor immune status and be prone to infections and even cancer development. Immunotherapy is emerging as an important adjunct oncology modality of treatment. The key to success is dependent on a good host's immune response to tackle cancers. The target of immunotherapy is killing the cancer cells with minimal collateral damages and leaving the body's immune system intact. Even though cancer immunotherapy provides a better option than chemotherapy, achieves higher success rates, and causes less marrow depression, it has considerable limitations. More than half of treated patients develop irAEs[4], let alone only a minority of cancer patients respond well to immunotherapy. Moreover, a minority of irAEs can be serious and even fatal. To overcome these limitations, supplementation of vital micronutrients to immunotherapy patients seems to be the simplest and the most pragmatic way of reducing such irAEs. Micronutrients have been used successfully in conventional oncology to reduce treatment side effects, enhance therapy efficacy, prolong survival, and improve quality of life[25,27,28,59,96]. For immunotherapy, despite less clinical experience, similar biophysiological mechanisms may also work when micronutrients are added to immunotherapy. Realistically, micronutrients may well offer comparable benefits to immunotherapy patients by strengthening the immune cell functions, enhancing tumor-killing effects, and reducing or preventing treatment complications[55].

Notably, micronutrient deficiency in one particular nutrient is rather difficult to diagnose and clinical symptoms may not be obvious, let alone overlapping effects with other clinical conditions. Thus, for best results, micronutrients as an adjunct oncology therapy should be given prospectively and in combination with the main treatment[15, 97].

Unfortunately, there are no standard micronutrient supplementation protocols for immunotherapy patients. Despite some negative findings[37,98], a general consensus could still be built on the effectiveness of known positive trials and the remarkable safety profile of micronutrient therapy. After all, negative trials may well be due to various related factors and the imbalance of trial participants in various arms, as has been discussed in great detail. Moreover, as the antioxidant effect of micronutrients has already been proven to be not a concern, some studies advocate using higher than the recommended dietary allowance doses of micronutrients in combination for cancer patients to achieve optimal benefits[44,59,96,99]. A higher dose of micronutrients offering greater antioxidant effects may better tackle free radicals generated during immunotherapy and also enhance host immune function[15,100]. Importantly, future oncology research should be directed towards investigating the effects of different groups of micronutrients in combination with the main oncology modalities of treatment for different cancer types so as to delineate the optimal micronutrient regimens for immunotherapy.

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## CONCLUSION

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Micronutrients used to play an active role in the past. High-dose vitamin C has been administered for viral infections before the debut of more specific agents; vitamin D has also been used for treating some autoimmune disorders before more specific agents are now available for such disorders. Currently, these and similar micronutrients should be investigated actively to better define their definitive adjuvant role in the era of cancer immunotherapy. Actually, micronutrients play a pivotal role in maintaining good immune cell functions and would also play an integral role in the defense against infectious agents and even cancers. Adequate amounts of micronutrients during immunotherapy have been shown to have the potential of enhancing immunotherapy efficacy, reducing irAEs, improving patients' quality of life, prolonging survivals, and even sustaining the best treatment compliance. As the use of



micronutrients as adjuvants for oncology treatments is still in its infancy, many more studies are required to explore the full potential of such safe, convenient, and affordable agents.

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