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Review Article

Application of Nutritional Support Therapy in Ataxia-Telangiectasia: A Narrative Review

Yayu He[1], Chenhan Luo[1], Yiru Wang[1], Ying Zhang[1], Donglan Wang[1], Canyang Wang[1], Zehui Hu[3*], Xueqiong Yao[1,2*]

[1]School of Public Health, University of South China, Hengyang, China; [2]School of Basic Medical Sciences, University of South China, Hengyang, China; [3]Department of Hospital-Acquired Infection Control, University of South China (Hunan Provincial Veterans Administration Hospital), Hunan, China

ABSTRACT

Ataxia-Telangiectasia (A-T) patients are vulnerable to malnutrition and growth failure, mainly due to recurrent infections, feeding disorders, choking and other swallowing difficulties. As a result, the nutritional intake of A-T patients is insufficient, which affects the development of the disease as well as the prognosis and the quality of life. Previous studies have demonstrated that early and appropriate nutritional support can relieve malnutrition, enhance immunity, improve neurological function as well as reduce the risk of infectious complications. Therefore, optimal nutritional support should be considered as an important part of the treatment of A-T. In this review, we discuss the main nutritional intervention methods for patients with A-T, including micronutrient supplementation, dietary supplement intake, diet management, enteral nutrition, nutritional monitoring, assessment and nutritional education. We emphasize the critical role of nutritional supportive therapy in the treatment of A-T for functional improvement, better prognosis and life quality. Aiming to provide new therapeutic ideas for A-T patients who are currently without effective treatment.

Keywords: Ataxia-telangiectasia; Nutritional support; Micronutrients; Dietary supplement; Enteral nutrition; Nutritional assessment

INTRODUCTION

Ataxia-Telangiectasia (A-T) is a rare autosomal recessive disease caused by mutations in the Ataxia Telangiectasia-Mutated (*ATM*) gene, which encodes a serine/threonine protein kinase [1,2]. By controlling several aspects of cell cycle management and promoting Double-Strand Break (DSB) repair, *ATM* is thought to be responsible for most of the clinical manifestations of A-T [3,4]. The primary characteristics of A-T include progressive cerebellar ataxia, oculocutaneous telangiectasias, recurrent infections due to immunodeficiency, radiosensitivity and a higher risk of malignancy [5-7]. Other abnormalities such as growth failure, poor pubertal development, insulin-resistant diabetes, gonadal atrophy, lung disease, cutaneous abnormality and cardiovascular disease have also been reported in A-T patients [8-11]. Symptoms related to ataxia typically manifest before the age of three and individuals affected by this condition may require the use of a wheelchair between the ages of 10 and 15 [12,13]. However, this congenital disorder has phenotypic heterogeneity, which results in a continuous spectrum from severe classical childhood-onset A-T to a relatively mild adult-onset disorder. The severity of the condition is dependent on the presence of *ATM* protein and kinase activity, as well as other genetic and environmental modifying factors [2,4].

The prevalence of A-T is estimated at 1/100000 to 1/40000 and it has been reported in all regions of the world [14]. Races and ethnicities are affected equally for patients with A-T, but the incidence is significantly higher in populations with high rates of consanguineous marriage rates than in the general population [1,15]. Due to their poor prognosis and severe disability, patients with A-T have a Kaplan-Meier 20-year survival rate of 53.4% and their median survival is estimated to be 25 years [14,16-18]. Fortunately, the life expectancy of patients in America has been prolonged in the past 25 years, which may be related to better medical care. Individuals with the diagnosis may live to be thirty years of age or more [19,20].

Frequent bronchopulmonary infections and an increased risk of malignancy are the main causes of death for A-T patients [10,21]. Despite numerous studies on the mechanisms and pathogenesis of A-T disease, there are few effective therapies available. The backbone

Correspondence to: Xueqiong Yao, School of Public Health, University of South China, Hengyang, China, E-mail: Yxq1212@usc.edu.cn

Zehui Hu, Department of Hospital-Acquired Infection Control, University of South China (Hunan Provincial Veterans Administration Hospital), Hunan, China, E-mail: zehuide@163.com

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of treatment for A-T remains symptomatic and rehabilitative or medicinal measures [20,22]. Given that patients have complex needs and are rarely cured, many scholars believe that a multidisciplinary care model involving both medical and non-medical approaches is essential treatment [12,23,24]. This essay highlights the urgency of finding new strategies for the long-term management of A-T. Proper symptom management can lower morbidity and mortality rates and enhance quality of life by avoiding complications. Except for the application of new drugs, more accessible methods such as nutritional management should be considered so that patients may have a better prognosis. To gain a better understanding of nutritional support in A-T, we conducted a comprehensive review of articles related to nutrition in A-T, ranging from cell and animal experiments to population research and concluded the benefits of nutritional support on A-T patients and mainly interventional methods.

LITERATURE REVIEW

The importance of nutritional support therapy

Several studies have identified malnutrition as a common clinical symptom in individuals with A-T [25-29]. This is typically observed during childhood, as children's weights and heights are usually well below the third percentile [30]. As they grew older, both the Body Mass Index (BMI) Z-score and growth rate gradually decreased [21,25,28,31,32]. A study assessed patients' nutritional status using anthropometric and Body Cell Mass (BCM) calculations. It described the situation of poor oral intake, diet quality, chronic fatigue and the need for caregiver assistance with meals, emphasizing the necessity of early nutritional intervention and family nutritional support for A-T kids [33].

Malnutrition was primarily caused by food aspiration and oropharyngeal dysphagia [34,35]. These factors have been found to increase fatigue and infection-related morbidity and mortality, reduce appetite and intake of food and liquids and result in patients lacking essential macro- and micronutrients [36,37]. Changes in nutrition and metabolism were correlated with the severity of ataxia in A-T patients [38]. Malnutrition can have several negative effects, including weight loss, lung infections and lowered immunity [39-42]. For these reasons, early nutritional intervention is thought to be crucial in the treatment of A-T patients.

The goal of nutritional intervention is to meet nutritional demands and avoid or lessen the impact of problems such as infection, fatigue and poor coordination, in order to promote overall health and well-being. Sufficient nutrition is also necessary to ensure proper growth. Evidence from randomized control trials has proven that nutritional therapy can improve the clinical conditions of patients with lung illness when adequate nutritional supplements are provided [42-44]. Further clinical studies have also shown that nutritional intervention can improve the BMI percentiles of patients with Cystic Fibrosis (CF). Enteral nutrition, a high-fat, high-calorie diet and a comprehensive nutritional plan have all been found to be effective [45-47]. These findings suggest that nutritional support therapy may be vital in the long-term care of patients with AT due to its clinical importance.

However, there are no established guidelines for nutritional therapy. Thus, many patients took a variety of vitamins, trace elements and herbal supplements without their doctor's knowledge. This can not only be costly without providing any benefits but can also lead to adverse effects from excessive vitamin intake [20]. Another study pointed out an inconsistency in the idea that A-T patients with severe growth failure should follow a high-calorie diet, which is usually achieved by taking fat supplements [28]. However, research has already shown that individuals with A-T have an increased risk of diabetes, cardiovascular disease and other liver diseases, as well as a tendency to develop a fatty liver [11,27,29,48-50]. There is still a controversy regarding the nutritional intervention therapy approach. In the absence of clear guidelines, patients may suffer harm or misunderstandings. People's awareness of A-T is restricted to diagnosis and medical care [51,52]. Therefore, it is important to carefully select the best meal supplement to ensure patients receive maximum benefits. To arrive at a comprehensive, effective and practical nutritional support therapy plan, it is necessary to consider when to be concerned, when to conduct tests and how to treat. Answering these questions requires extensive observational and experimental evidence.

Nutritional support therapy

Micronutrients: These include vitamins and trace elements obtained from the diet that are essential for cellular metabolism and optimal tissue function. For A-T patients, micronutrients play an essential role in regulating oxidative stress, supporting immune function, reducing the risk of infections and promoting growth and development. Multiple studies have reported micronutrient deficiencies in A-T patients. Supplementation of micronutrients can improve certain symptoms, such as motor function, senescence, malignancy and neurodegeneration [53-55]. However, research outcomes have been inconsistent, possibly due to insufficient sample sizes leading to accidental results. Nonetheless, these findings provide some guidance for clinical application.

Vitamin A: There is evidence that cells with an *ATM* gene mutation have been exposed to oxidative stress for a prolonged period, resulting in the presence of Reactive Oxygen Species (ROS) [56]. Excessive oxidative stress can lead to neurodegeneration, cell malfunction and other symptoms [57-59]. Under such circumstances, lowering the ROS level and maintaining sufficient levels of free radical scavengers will help alleviate the symptoms associated with A-T [60]. Nutritional therapy is considered reasonable due to the ability of antioxidant micronutrients to eliminate ROS [61,62]. A study measuring plasma levels of Total Antioxidant Capacity (TEAC) in ten A-T patients discovered a decline in TEAC, retinol and tocopherol. This suggests that vitamin E and A therapy may be worth trying for the treatment of A-T [63]. In a cross-sectional study, researchers measured the levels of zinc and vitamin A in A-T patients and a control group. The study concluded that there was no significant difference between the two groups. However, the author repeatedly emphasized the importance of adding antioxidants to the diet to maintain adequate nutrition. In addition, considering the impact of maintaining micronutrient homeostasis on the nervous and immune systems, as well as the correlation between retinol with Malondialdehyde (MDA) and Immunoglobulin A (IgA), appropriate nutritional interventions and monitoring of these factors should be taken into account as part of the treatment plan [64]. Moreover, the association between the *ATM* diplotype and the risk of breast cancer was predominantly among women with low intake of antioxidant vitamins including vitamin A, vitamin C and folic acid. A reduced risk for breast cancer has been linked to vitamin A and α-tocopherol, as well as some water-soluble vitamins like vitamin B2, vitamin C and folic acid intake [61].

Vitamin B3: Nicotinamide Riboside (NR) treatment of animal models with A-T improved their neurological prognosis and survival and it is now approved as a dietary supplement [65]. In an open-label, proof-of-

concept trial, NR was provided to 24 A-T patients for four months. The therapy was well tolerated and linked to improvements in ataxia and serum immunoglobulin levels in A-T patients [66]. Recently, another individual with ataxia and recurrent infections was treated with NR since he was age 3 years and 6 months. During 11 months of follow-up, the ataxia symptoms and motor function were improved significantly and the use of antibiotics and frequency of hospitalizations due to infections were reduced by more than 90%. Given the absence of adverse effects, the author hypothesized that the early treatment would lead to even better outcomes and encouraged to consideration of NR in all individuals with ataxia telangiectasia [67]. The benefits of long-term NR supplementation have been proven. It appeared to be safe and well tolerated and it improved motor coordination and eye movements in patients of A-T [53]. Furthermore, researchers have illustrated that in mice lacking the *ATM* gene, NR therapy not only improves motor performance but also inhibits senescence and neuroinflammation and prevents neurodegeneration. The pathogenesis of aging in A-T caused by mitochondrial malfunction has been discussed. NR can be used as a potential therapeutic intervention to increase intracellular depletion of Nicotinamide Adenine Dinucleotide (NAD^+) levels. This, in turn, can accelerate DNA repair in nerve cells, enhance mitophagy and prevent senescence and neurodegeneration [54,55].

Vitamin E: As an important antioxidant, vitamin E inhibits the oxidation of polyunsaturated lipids in membranes. This protects cells and lipoproteins from oxidative attack and stress-induced lysis [29]. Several studies have recommended supplements of vitamin E to enhance antioxidant ability [63]. Apart from its antioxidant capacities, vitamin E has important immunostimulatory and anti-aging effects. Vitamin E deficiency may contribute to the high susceptibility to neoplastic disorders in patients with immunodeficiency [68,69]. Besides, a number of studies on hereditary ataxias have demonstrated a close association between primary or secondary vitamin E deficiency and severe cerebellar symptoms [70-72]. Patients with A-T may benefit from adequate vitamin E intake due to their increased risk of neurodegeneration and malignancies [73]. However, two studies examining vitamin E levels in A-T patients reached adverse conclusions, possibly due to the small sample size. Despite this, both authors contended that vitamin E supplements may protect A-T patients and will be worth trying in treatment [63,74]. Another study investigated the *in vitro* effect of vitamin E (DL-alpha-tocopherol) on the incidence of chromosomal damage in lymphocytes from patients with A-T. The study found that vitamin E reduces chromosomal damage in lymphocytes from patients with ataxia telangiectasia, which may be helpful in the treatment of A-T. However, there was no significant improvement in their repair activity [75].

Vitamin D: A study of vitamin D levels in a cohort of children with A-T found that vitamin D deficiency was particularly common in the patients, as documented in several studies [76-79]. The absence of a strong correlation between low vitamin D and weight Z score, according to the author, implied that variables other than malnourishment, such as sun exposure, might be involved. Vitamin deficiencies also raised the risk of osteoporosis in A-T patients in addition to immobility [77]. Conversely, a controlled cross-sectional study with 24 individuals discovered a negative correlation between the concentrations of 25-Hydroxyvitamin D (25(OH)D) and the percentage of body fat and BMI [78]. As vitamin D plays a crucial role in preventing osteoporosis, disease mortality and the increased risk of malignancy in A-T patients, it is essential to monitor 25(OH)D levels and supplement them as needed [80]. Furthermore, a meta-analysis found that cancer patients with higher circulating 25(OH)D levels at or around diagnosis have better outcomes [79]. Given that cancer is the second leading cause of death for A-T patients, it is suggested that vitamin D supplementation may improve clinical treatment results [81]. Besides, elderly patients or those who use wheelchairs were at a higher risk of vitamin D insufficiency according to the research, therefore they required further positive monitoring and treatment [18].

Selenium: A Cross-sectional and controlled study described the plasma levels of selenium and erythrocyte glutathione peroxidase activity in A-T patients and related them to oxidative stress and lipid status biomarkers. The results showed that nearly 40% of A-T patients had selenium levels below the reference value and low Glutathione Peroxidase (GPx) activity. The levels of selenium and the indicators for oxidative stress showed a strong, inverse and independent relationship. These findings highlight the significance of checking the patients' selenium nutritional status. The author also assumed that the lower intake in the A-T group may complicate the neurodegeneration [82]. Another study demonstrates the critical function of Selenoprotein H (SelH) in inhibiting oxidative stress and replicative senescence [83].

Dietary supplements

Antioxidants: Several researchers have recommended α-lipoate as an option for reducing total oxidative stress [84-87]. With advances in blood-brain barrier crossing, it can lower ROS concentrations and diminish oxidative stress-induced mitochondrial dysfunction and Interleukin-8 (IL-8) production associated with A-T [88]. Both α-lipoate and especially dihydrolipoate have been shown to be potent antioxidants that can regenerate other antioxidants such as vitamin C and vitamin E and increase intracellular glutathione levels [89]. Therefore, it appears to be an appropriate chemical for treating oxidative brain and neural disorders involving free radical activities. Besides, several studies have investigated the effects of antioxidants in *ATM*-deficient mice, which are used as an animal model of A-T. When examined for their chemo-preventive qualities, N-acetyl-L-cysteine (NAC), EUK-189, tempol and 5-Carboxy-1,1,3,3-tetramethylisoindolin-2-yloxyl (CTMIO) exhibited some beneficial effects [90]. In particular, NAC was found to prolong the lifespan of *ATM*-deficient mice, reduce the incidence and multiplicity of lymphomas and suppress the incidence of oxidative DNA damage [91]. Among the tested antioxidants, NAC has the advantage of a long history of safety and efficacy in clinical settings. Therefore, it has the potential to emerge as a dietary supplement for preventing tumors in humans with cancer-prone syndromes, especially those related to oxidative stress [92,93]. However, patients who choose to pursue high-dose antioxidant therapy should be aware of any possible hepatic or hematopoietic side effects [20].

Superoxide Dismutase (SOD): Experiments on human lymphoblastoid cells have shown that manganese-containing superoxide dismutase mimics have radioprotectant effects on A-T cells. These mimics can protect A-T patients before undergoing radiation therapy or standard diagnostic radiologic procedures such as computed tomography [94]. The use of Copper-Chaperone-for-SOD (CCS) protein to treat the mouse and rat models of Amyotrophic Lateral Sclerosis (ALS) has provided compelling evidence that continued treatment can extend the survival of these mice by an average of 18 months. This advancement in delaying neurodegeneration could be applied to the management of A-T [95].

N-acetyl-DL-leucine: A study assessed the effect of N-acetyl-DL-leucine supplementation on ataxia symptoms in a 9-year-old female with A-T. They found that supplementation with N-acetyl-DL-leucine at a dose of 4 g/day for 16 weeks was well tolerated and significantly improved

ataxia symptoms, handwriting and quality of life in patients with A-T without any serious adverse events [96]. It may also improve ataxia and ocular stability in A-T patients, although the molecular basis remains to be elucidated [97]. N-acetyl-L-leucine is currently under investigation for safety and efficacy in A-T in a multinational, multicenter, open-label, rater-blinded phase II trial (NCT03759678).

Glutamine: With its neuroprotective effects, has been proven to be beneficial in the treatment of Alzheimer's Disease (AD) [98]. The blood glutamine concentrations of *ATM*-deficient mice were 25% lower than those of age-matched control mice. However, after being supplied with glutamine, these *ATM*-deficient male mice gained much faster. Their blood glucose levels were restored to proper and their lifespan was prolonged by nearly one-third to 120 days. Thus, supplementing with glutamine shows potential as a therapeutic option for treating human AD, A-T and other related conditions [99].

Dietary management

According to the guidance on diagnosis and clinical care for A-T children produced by the UK Ataxia-telangiectasia Society, dietetic interventions tend to fall into one of three levels [100].

- General advice for children whose appetite is good and who are growing as expected, including optimal nutrition and adequate hydration as well as a variety of foods based on the main food groups identified in the 'Eat Well Plate'.
- Nutritional support for children having trouble with eating and drinking, including regular monitoring of weight and height, small frequent meals and snacks using nutrient-rich foods such as full-fat dairy products and food fortification and other oral nutritional supplements or prescribable products.
- Enteral feeding using a gastrostomy or jejunostomy tube to supplement or replace oral intake.

In addition to ensuring adequate nourishment, a nutritionist and a speech and language therapist can help address the physical challenges associated with eating and drinking [34,100,101]. Despite regular dietician advice, fortified food and nutritional supplements, a study has found that approximately a quarter of our clinic patients were defined as underweight and/or stunted at some point during the study period [21]. Furthermore, some studies have reported a high prevalence of dyslipidemia and an increased risk of developing atherosclerosis and cardiovascular disease. This highlights the significance of multidisciplinary care, regular monitoring of cardiovascular biomarkers and appropriate dietary recommendations [27,29].

The coordination and other neurological problems that develop over time in A-T can affect the nutrition and hydration of people with A-T in several ways. Dysphagia refers to difficulties with swallowing, eating and drinking [100]. These factors can be worsened by symptoms such as fatigue and recurrent infections leading to reduced appetite, nutritional intake, weight loss and under-nutrition. This, in turn, increases fatigue and vulnerability to infection and other illnesses [34]. Dysphagia is a common occurrence, particularly among elderly individuals who drink thin liquids through straws [35]. Therefore, it is recommended to evaluate the safety and adequacy of dietary intake at least once a year [36]. Also, appropriate interventions should be taken, such as teaching patients how to drink, chew and swallow more safely, removing thin liquids, cutting foods into small pieces, or using a straw or sipper cup to increase oral intake and meet nutritional needs [33-35].

External nutrition

According to the A-T treatment guidelines, external nutrition has advantages as it can lower the risk of infection and aspiration while simultaneously meeting dietary and hydration needs [100]. In a prospective cohort study of 101 children, researchers found that the growth rate of A-T patients declined as they grew up and this trend became more obvious after the age of eight. After conducting a longitudinal study of 12 patients with early gastrostomy tube feeding Percutaneous Endoscopic Gastrostomy (PEG), it was found that their weight ended up improving. This has suggested that growth failure is not an inevitable consequence of A-T, but rather a complication that may be successfully managed with early intervention. For this reason, the author advised proactive consideration of PEG starting at age 8 in case of growth failure [21]. Likewise, another study made the same suggestion, advising that gastrostomy insertion be considered for young A-T patients who begin to experience progressive nutritional insufficiency, respiratory deterioration and aspiration caused by dysphagia that is unresponsive to common conservative measures [36]. Both studies emphasized the benefits of early PEG placement due to evidence suggesting improved safety and easier mealtimes for patients [102-105]. Individuals undergoing gastric tube placement should be re-fed very slowly at first to prevent aspiration from gastroesophageal reflux disease. The general objective should be to maintain weight at the 10^{th} to 25^{th} percentile [34]. A child who is fed through an enteral tube needs to keep in close contact with their local dietetic team for advice and support, including the modification of feeding schedules in response to changing nutritional needs [100]. Research has indicated that some children with A-T syndrome may experience reflux of the stomach, raising the possibility of aspiration, esophagitis and anemia. It is also important to undergo evaluation before inserting a gastrostomy tube [22]. Furthermore, although there was a trend towards lower Forced Vital Capacity (FVC%) among people with gastric tubes, this trend did not reach significance. The trend toward decreased lung function in gastric tube users and its possible association with respiratory pathology and growth failure would require longitudinal research to establish causality [39].

Nutritional evaluation and monitoring

Since a child's growth failure starts in the early stages, using BMI as a measure of malnutrition may have certain drawbacks, as both short and thin children's BMIs fall within the normal range. The majority of the retrieved documents were using BMI as the measurement. However, BCM depletion presented a more accurate representation of nutritional status and has revealed a high prevalence of malnutrition (69%), even among individuals who were considered overweight using conventional techniques [33]. Additionally, other researchers have noted that Bioelectrical Impedance Analysis (BIA) is a low-cost and simple method of analyzing body composition, as it can detect early signs of qualitative malnutrition [18,106]. After reviewing the primary, A-T treatment approach, we found that early intervention and positive monitoring are crucial tactics, as highlighted in numerous other studies. These studies cover a range of topics, including the surveillance of nutritional complications, monitoring of food intake and malnutrition and the results of PEG [18,23,38,39,100]. These check-ups should take place at least once a year, but it is advisable to schedule them more frequently, particularly if your A-T symptoms are changing.

Nutritional education

Nutritional education is essential for the long-term management of A-T patients and their families due to the progressive nature of the condition. It should begin as soon as they are diagnosed. In addition to receiving good care in the hospital, patients should also take advantage of the national A-T center evaluation, which enables them to get long-term nutritional assistance and advice from a professional team of interdisciplinary staff members, including community pediatricians, nurses, physiotherapists and dieticians [100,107]. To ensure an accurate assessment by the medical team, family caregivers should closely monitor the food, drinks and nutritional status of A-T patients [33]. Besides, it is recommended to encourage A-T youngsters to voice their thoughts about the illness [108-110]. A study that examined the dietary intake of patients with AT discovered that a considerable amount of the energy consumed by these individuals came from foods that were chosen casually, such as those high in calories, sugar, or fat density [33]. Dietary advice has been discussed above, but unfortunately, systematic recommendations about nutritional education have not yet been established. Furthermore, numerous investigations have supported the value of PEG as a typical therapy technique. However, some parents may be hesitant to accept PEG, so it is crucial to provide a thorough explanation of the benefits and risks to parents [100].

DISCUSSION

There were the following problems with the study design. Because A-T is a rare disease, there is not enough research on medications and dietary support for it. Experiments and studies in clinical settings are insufficient. Also, the studies that have been published used limited sample sizes and have not been able to conduct randomized control trials due to the low prevalence of A-T. Most of the current literature has a cross-sectional study design. However, a long-term follow-up study would be preferable for A-T as it is a progressive condition, to describe the dynamic change of individuals. Meanwhile, some of the data are not precise enough, with its recalling and reporting bias, the analyst is unable to specifically assess the daily nutrient intakes. It will be challenging to identify the nutritional abnormalities in the early stages since some researchers did not select the most appropriate index or approach for assessing the nutritional status of A-T patients.

In the future, large sample sizes and multicenter, observational or experimental studies are needed to guide the improvement of long-term nutritional status and quality of life. In addition, the material of the intervention can also be expanded from micronutrients to phytochemicals, probiotics and other macronutrients, to explore the function in A-T patients' health management. Given the individual differences in A-T patients, individualized nutritional therapy should be valued in the future. This requires the support of multidisciplinary experts and national A-T centers.

CONCLUSION

To conclude, A-T has no established guidelines for effective treatment and most patients suffer from malnutrition and related complications. To handle these symptoms and provide a practical nutritional interventional strategy for A-T patients, this essay summarizes the relevant literature on nutritional support and therapy in patients with A-T. We discussed disease status, the significance of nutritional therapy and the main methods of nutritional support therapy. Based on a comprehensive analysis of the existing studies, we have determined that the main approaches to nutritional support therapy include micronutrient supplementation, the use of dietary supplements, diet management, enteral nutrition, the assessment and monitoring of nutritional status and nutritional education. Some of them have already shown clinical effectiveness such as improved function, prognosis and better life quality, while others still need more powerful evidence to support. The scope of this essay is not exhaustive due to the limited amount of literature. In the future, more rigorous evidence will be available on nutritional support therapy to provide practical guidelines for A-T patients and improve their quality of life.

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