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Vitamins Status Following Solid Organ Transplantation

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Abstract

Solid organ transplantation is a popular solution for many end stage organ failures. The functional evaluation of these transplanted organs is multi-factorial and involves many aspects involving organ function, overall patient well-being and quality of life. Literature reports on vitamin status following transplantation had been collected together in this review article. This review summarizes the current status of research in this area with focus on reported deficiencies in vitamins following solid organ transplantation. The deficiencies in either fat-soluble vitamins like vitamin D, vitamin A and vitamin K as well as water soluble vitamins like vitamin B6, vitamin B12 and thiamine have been summarized. The reported deficiencies are noteworthy and necessitate a critical evaluation and interventions in many transplantation programs

Keywords: Vitamins; Deficiency; Transplantation

Introduction

Alterations in vitamin status following solid organ transplantation have been reported. A wide range of alteration can occur and may include both fat soluble vitamins (A, D, E and K) as well as water soluble vitamins (B1, B2, B6, niacin, B12). Vitamin status may be affected following transplantation by inadequate intake or supplementation, disturbed activation by different organ systems, or by immunosuppression. The extent and severity of vitamin level alteration varies considerably depending on the type of organ transplanted and the perioperative nutrition support supplied. Table 1 lists vitamin alterations associated with the type of organ transplantation. Often, vitamin deficiencies associated with organ dysfunction are corrected once a new allograft is received. The purpose of this review is to explore clinical issues in vitamin status following solid transplantation.

Vitamin	Organ
Vitamin A	liver
Vitamin D	Kidney, liver
Vitamin K	liver
Vitamin B6	Small bowel, heart, liver, kidney
Vitamin B12	heart
Thiamine	Kidney, liver

Table 1: Vitamin deficiencies reported following solid organ transplantation.

There is considerable variation in the incidence of fat soluble vitamin deficiency depending on the organ which is transplanted. Renal transplant recipients have a higher prevalence of vitamin D deficiency as the kidney is the site of activation of vitamin D into 25-hydroxyvitamin D [1]. The prevalence of deficiency and insufficiency in this population is approximately 70-80% [2]. The deficiency has been associated with secondary hyperthyroidism and hypocalcaemia [3]. Although, the deficiency prevalence is high regardless of transplant status (recent or long-term), it has been reported to occur in most of the African American kidney recipients [4]. Interestingly, a recent study reported severe vitamin D deficiency among heart and liver transplant recipients despite the supplementation [5]. Likewise, vitamin A, a fat-soluble vitamin which is predominantly stored and metabolized in liver, was higher post liver transplantation. This was hypothetically attributed to increased liver protein synthesis [6]. Studies reported that both vitamin A and vitamin E levels are lower in patients with cirrhosis before transplantation [7,8]. Increased levels of both fat soluble vitamins (vitamin A and vitamin E) have been reported in adult cystic fibrosis patients after lung transplantation [9]. The exact requirements for fat soluble vitamins may differ depending on the type of organ transplantation. So while vitamin K is important for the biosynthesis of procoagulant serum protein factors in the liver [10], vitamin E may have beneficial effects in heart transplantation.

Deficiency of water soluble vitamins has been reported in patients undergoing various forms of transplantation. Vitamin B6 deficiency was significant following intestinal transplantation and to lesser extent in kidney, liver and cardiac transplantation. [11,12]. Similarly, acute folic acid deficiency was observed after bone marrow transplantation [13]. However, there are reports of normal levels of B-group vitamins after renal transplantation [14]. The purpose of this review is to summarize literature reports regarding vitamin status following solid organ transplantations.

Methods

The databases EMBASE including MEDLINE were used to search for articles associated with vitamin status post solid organ transplantation. The keywords used included vitamin, status, deficiency, transplantation. The data within articles were extracted, specifically information relating to vitamin status following transplantation. The articles were reviewed by two faculties for

relevance and content. Only articles that measure vitamin status post solid organ transplantation were included. MEDELEY the reference managing software was utilized to make a library of the selected articles.

Results

The full text articles that include vitamin status evaluated following transplantation were included in the review. This summary is a narrative review of published reports regarding various vitamin status following solid organ transplantation.

Vitamin status following solid organ transplantation

Fat soluble vitamins

Vitamin A: Vitamin A and its metabolites are important for cellular growth and play important role in differentiation. The naturally occurring ester form of vitamin A is usually hydrolyzed to retinol that is taken up by the intestinal mucosa, re-esterified back, coupled with chylomicrons, and finally released via the thoracic duct to the circulation. The remnants of the carrier – containing most of the ester form- are taken by the liver and stored after hydrolysis into retinol. The serum level of vitamin A is maintained through homeostatic regulation from the liver stores. Liver retinol is bound to retinol-binding protein (RBP) before being released and further coupled to transthyretin (TTR) to avoid renal clearance. Finally, in the cells, retinol will be bound to cellular RBP, oxidized to retinoic acid, or re-esterified again. The ester form is stored in different tissues in addition to liver where 50-80% is stored [15]. Cytochrome P450 26 hydroxylation as well as glucuronidation are involved in this process. A plasma retinol level of less than 0.35 μmol/L is utilized to identify the deficiency [16].

Vitamin A deficiency defined as plasma retinol levels less than 1 μM, was reported in patients with end-stage liver disease awaiting transplantation. Both plasma retinol (normal level 1.6-2.3 μM) and serum retinol binding protein RBP (normal level 1.4-2.9 μM) were lower than normal levels in 100 and 95% of the patients respectively. Similarly, 82% (n=77) of pretransplant patients with primary sclerosing cholangitis had serum vitamin A levels that were below the normal range [17]. Ukleja and co-workers reported significantly lower levels of serum and hepatic vitamin A levels as well as the RBP in fifty patients with cirrhosis than matching liver donor's controls [7]. Dark adaptation resulted from vitamin A deficiency in patients waiting for liver transplantation and was improved by intramuscular vitamin A treatment [18].

Following liver transplantation, a beneficial effect on restoring the nutritional status of patient with cystic fibrosis was noted. Both vitamin A and vitamin E increased ($P<0.05$) versus non-transplanted patients) [19]. In addition, a case report of a patient with severe visual field restriction that failed vitamin A supplementation showed improvement following liver transplantation [20]. However, in another patient a case of night blindness secondary to vitamin A deficiency developed after transplantation. This patient likely developed biliary strictures as a complication of the transplantation procedure [21]. Serum vitamin A and retinol binding protein were significantly reduced in the post-transplant period, however did return back to normal several years after transplantation [22].

Vitamin D: The two forms of vitamin D (D2 and D3) need successive hydroxylation in the liver and kidney to form active 1, 25-dihydroxyvitamin D. Vitamin D is absorbed from the intestine into the circulation where it binds to vitamin D-binding protein (DBP). The bound form is transported to liver where it is hydroxylated to 25-hydroxy vitamin D by microsomal CYP450 (CYP2R1) and/or mitochondrial CYP450 (CYP27A1). In kidneys, 25-hydroxyvitamin D3-1α-hydroxylase (CYP27B) will ultimately add another hydroxyl group at position 1 to the active form. The normal vitamin D status, usually measured by 25-hydroxy vitamin D levels, is considered to be at least than 50 nmol/L or 20 ng/ml. New assays are able to measure the di-hydroxy vitamin D metabolite and the normal range is between 16 and 60 pg/ml [16,23].

Vitamin D deficiency was reported in transplant candidates with congestive heart failure, end-stage pulmonary disease, liver failure and most commonly, chronic kidney disease (24). Transplantation unfortunately will not restore vitamin D status regardless of the transplanted organ. Estimates of prevalence of vitamin D deficiency following transplantation were variable according to patient populations, type of transplanted organ, and, probably, the measurement assay of 25-hydroxy metabolite. The vitamin D insufficiency is not uncommon and an estimated 26-33% developed severe deficiency [24]. Low vitamin D levels were suggested to be utilized as a predictor of worsening of graft function and increasing proteinuria [1]. About 40-50% of patients develop vitamin D deficiency post-renal transplantation and almost 90% develop deficiency after liver and/or heart transplantation. The etiology varies and can range from malnutrition, lack of sun exposure, steroid therapy, and alterations in metabolism by the liver [2,3,5].

Vitamin E: Vitamin E, known as α-tocopherol, is poorly absorbed through the intestinal tract and transported via lipoproteins and chylomicrons to liver and other tissues. Vitamin E forms are metabolized by cytochrome P450's then conjugated and excreted in urine or bile. Hepatic CYP4F2 is primarily involved; in addition CYP3A may also be involved. Vitamin E deficiency is defined as α-tocopherol plasma concentration of less than 12 μmol/L [16].

Vitamin E deficiency had been reported in patients with alcohol-related liver disease, viral hepatitis, and hepatocellular carcinoma [8]. Forty three percent of pretransplant patients with primary sclerosing cholangitis had vitamin E levels below normal [17]. The levels of vitamin E were increased significantly ($p<0.05$) in cystic fibrosis patients following liver transplantation when compared with non-transplanted patients [19]. Similar findings with lung transplantation had been reported [25].

Vitamin K: Vitamin K, found mainly in green plants and known as phytonadione, is absorbed from the intestine via the lymphatic system. The normal plasma concentration is estimated to be 1.0 nmol/L (0.45 ng/ml). Tissue carboxylation as well as hepatic reductases have a role in conversion of vitamin K to epoxide active form. The deficiency is rare; however it has serious consequences [16].

Vitamin K has a crucial role in the biosynthesis of procoagulant serum protein factors in the liver [10]. Chronic liver diseases usually require vitamin K supplementation to restore haemostatic abnormalities [26]. Few studies evaluate vitamin K status prior to transplantation as the deficiency can occur due to many different reasons. These reasons include: drug antagonism, liver dysfunction, inadequate intake and/or malabsorption. About 30% of pediatric patients (8/26) pre-bone marrow transplantation had vitamin K deficiency [27].

Vitamin K deficiency after transplantation was reported in a series of case reports after kidney and combined kidney-pancreas transplantation. Four patients from a total of 146 transplant patients developed vitamin K deficiency induced coagulopathy and bleeding 1-week after transplantation [28]. Haemostatic abnormalities associated with liver transplantation are rather inherently related to different surgical phase of the transplantation and no available data about the vitamin K status post transplantation [26].

Water soluble vitamins

Vitamin B6: Vitamin B6 – known as pyridoxine- is composed of three naturally occurring three distinct chemical forms free pyridoxamine and phosphorylated pyridoxal and pyridoxal. Pyridoxamine and the other forms that will be hydrolyzed will be absorbed passively in the jejunum where some trapping phosphorylation may occur. The non-phosphorylated forms will cross into circulation. Pyridoxal binds to albumin and erythrocytes where it will bind to hemoglobin. The majority of the absorbed vitamin B6 unphosphorylated form is transported to liver by simple diffusion where metabolism by pyridoxal kinase into the active form pyridoxal-5 phosphate (P5P). The active form P5P either released into plasma or bound to apo-enzymes. The P5P undergoes hydrolysis by non-specific alkaline phosphatase. Most excess pyridoxal in tissues will be oxidized to urinary excreted end product 4-pyridoxic acid by liver and kidney [29].

Vitamin B6 deficiency is not uncommon and has been reported in different pathological states in patients with alcoholism, cirrhosis, malabsorption, uremia, hyperthyroidism and congestive heart failure. Morris and colleagues in a large epidemiological study evaluated the prevalence of vitamin B6 deficiency in U.S population. The results suggested that about 11% who took a daily supplement and 25% who did not take any supplement have a P5P level of less than 20 nmol/L [30]. Recently, Matarese et al. reported a high incidence of vitamin B6 deficiency following small bowel and multivisceral transplantation ~96% [11]. Variable degrees of deficiencies have also been reported in liver transplantation (60%) [31], renal transplantation 50% [32], and cardiac transplantation 20% in [12]. Vitamin B6 deficiency occurred in about 59% of renal transplant recipients after more than 28 months [33]. Vitamin B6 levels were lower in cardiac transplant patients than controls and the deficiency was seen in about 17.9% of the transplant patients in comparison to 2.2% in controls [33]. However, the mechanism for this deficiency was not investigated.

Vitamin B12: Vitamin B12 – known as cyanocobalamin- is actively absorbed through a highly specific mechanism in the ileum that depends on intrinsic factor and its receptors. The liver and the kidneys are the richest repositories of cobalamin in the body. Vitamin B12 is metabolically active as coenzyme B12 and as methylcobalamin. However, three soluble B12 binding proteins (intrinsic factor, transcobalamin, and haptocorrin) are known to be involved in the uptake and transport of cobalamins in human [34]. In addition, there is a sizable biliary excretion; however, about 70% is normally re-absorbed. The normal serum cobalamin value ranges between 200 and 250 ng/L. The deficiency usually is due to either inadequate intake, gastrointestinal malabsorption, or metabolic disorders such as nitrous oxide toxicity [16]. In addition to serum cobalamin levels, serum methylmalonic acid concentrations had been utilized as an index of tissue cobalamin status [35].

Gupta et al studied 189 orthotropic cardiac transplant recipients and found that cobalamin deficiency was present in 4.3% of their patients and in 5.3% of controls [33]. Vitamin B12 deficiency was not significantly different between heart transplant patients with and without cardiovascular complications and furthermore, vitamin B12 concentrations failed to predict complications or death [34]. Similarly, in renal transplant (n=55) there were no difference in mean vitamin B12 from the matched control group (n=32) [35].

Thiamine: Thiamine is a water soluble B-vitamin known as vitamin B1. Tissue thiamine deficiency was suggested as a potential cause of delayed graft function after kidney transplantation which was improved by thiamine supplementation to donors [36]. Thiamine supplementation improved signs and symptoms of a liver transplant patient who developed hemorrhagic Wernicke's encephalopathy [37]. Wernicke's encephalopathy is a metabolic disorder that is mainly caused by thiamine deficiency and frequently associated with chronic alcoholism and some forms of malnutrition or malabsorption. Few cases of this disorder were similarly reported after allogenic peripheral blood stem cell transplantation [38,39].

Niacin: Niacin -known as vitamin B3- is obtained from the diet from (add food sources here) in the form of tryptophan, nicotinic acid and nicotinamide. It is utilized in the synthesis of NAD which mediates many biochemical redox reactions. Pellagra, which results from a deficiency of niacin, can lead to severe consequences and eventually death. Nicotinic acid is converted in the intestine into nicotinamide which is the predominant form in the circulation. Many cellular transporters were identified to transfer both chemical forms into various cells. However, nicotineamide is also the degradation product of the pyridine nucleotides [40]. There were no reported alterations in niacin following transplantation, however it is very likely as niacin metabolism is largely dependent on vitamin B6 as an essential co-factor.

Discussion

Various vitamin deficiencies had been reported following different solid organ transplantations. The underlying causes had been attributed to organ specific function associated with that specific vitamin. Dietary intake, change in metabolism and other biochemical processes attributed to transplantation or immunosuppression were stated without adequate evidence. Depending on the organ, transplantation requires variable levels of immune suppression that may affect the overall well-being and the long term rehabilitation of the recipient. Different transplantations may experience variable degrees of deficiencies in certain vitamins. Renal transplants are more likely to develop vitamin D deficiency, while liver transplants are more prone to develop vitamin K deficiency. The mechanisms underlying each deficiency also can be variable and unforeseen in many cases. This review may draw attention to further mechanistic analysis of these deficiencies for better understanding. Micronutrient status following transplantation becomes a main stay in the practice and most of the after transplantation protocols mandate a nutritional follow-up. There are no defined clinical practice protocols that give recommendations for these micronutrient deficiencies in solid organ transplant population.

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