Scholars LITERATURE

La Prensa Medica Argentina

Research Article

DOI: https://doi.org/10.47275/0032-745X-311
Volume 107 Issue 1

Vitamins Disturbance in Cancerous Patients: A Prospective Comparison Study

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Abstract

Cancers are a complex disease that involve abnormal cell growth pattern and it is the leading cause of morbidity and mortality worldwide. The chemotherapy is one of the most common treatments for cancer. Cancer cause malnutrition and deficiencies of vitamins, in addition chemotherapy causes those deficiencies by induced anorexia, stomatitis, and alimentary tract disturbances. The study aims to determined and assessed the levels of serum vitamins (A, B12, B6, B9, E, D, and K) before and after chemotherapy administration. A prospective study carried out on newly diagnosed cancerous patients whom receiving chemotherapy. Fifty patients enrolling and recruited. Follow up will be recorded after the first, third, and sixth cycles of chemotherapy. The panel used for evaluation of vitamins concentration included the following six kits: Human Vitamin AV, E, VB6, B12, VD3 DIY, VK and FOLR3 ELISA kits. 38 females and 12 males included, with mean age was 48.35±15.28 years. The mostly distributed age group was belonging to fifth decades. The mean body mass index (BMI) was 33.12±5.51 m2/Kg. The majority of the sample treated were breast cancers females about 26 (52%). Regarding chemotherapy regimens, the AC+Taxen protocol was mostly used. The mean level of vitamin A found to be declined to the half from (69.23±24.66 µg/dL) at C0 to (35.73±18.89 µg/dL) at C6. Normal mean value of vitamin B12 level was presented in the most of patients pre- and post- chemotherapy. Vitamin B6 concentrations in the most of patients risen by double post-chemotherapy. Vitamin D concentration not changed in pre- and post- chemotherapy. We observed a statistically significant differences among vitamin E concentration pre- and post- chemotherapy (ANOVA=3.213, P=0.033). In this study, most of patients pre-chemotherapy period had normal folate level, whereas it to decreased from (6.23±3.12 ng/mL) to reached (3.33±2.72 ng/mL) after anti-cancer, with strong statistically significant differences (ANOVA=6.56, P=0.012). In addition, vitamin K concentration was unchanged throughout chemotherapy cycles. Many factors in cancerous participants lead to vitamins deficiencies. Several vitamins remained within normal concentration throughout anti-cancer course might be due to vitamins supplement taken by persons during their regimens. Almost always vitamins concentration dropped during cycles, but still within normal value, except vitamin E, which was deficient in last cycle of chemotherapy. Vitamins replacement are mandatory for substitution dropping level because off those are essential for many body processes and regulation.

Keywords: Vitamins; Cancer, Chemotherapy; Hypovitaminosis; Hypervitaminosis

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Citation: Aimutori DMK, Alsaymaree SMR, Al-Jassani HMA, et al. (2021) Vitamins Disturbance in Cancerous Patients: A Prospective Comparison Study, Prensa Med Argent, Volume 107:1. 311. DOI: https://doi.org/10.47275/0032-745X-311.

Received: October 04, 2020; **Accepted:** October 19, 2020; **Published:** October 24, 2020; **Journal Issue:** February, 2021

Introduction

Cancers are a large entity of complex diseases that involve abnormal cell growth pattern with the potential to invasion or metastasis to other parts of the body [1,2]. It is the leading cause of deaths worldwide, accounting for 9.6 million deaths in 2018. Lung, breast, stomach, and colon cancer cause the most deaths every year [1]. GLOBOCAN reported 18.1 million newly cancer cases diagnosed in 2018 [3]. In Iraq, the newly registered cancer cases were more than 25 thousand that are estimated by the latest Iraqi Cancer Registry report [4]. Chemotherapy is a type of cancer treatment that utilize one or more anti-cancer drugs or agents as part of regimens [5]. The traditional chemotherapeutic agents are almost always cytotoxic, are interfering with cell division (mitosis), beside that the chemotherapy destroy cells whether cancerous or healthy, which may then lead to cell death [5]. Chemotherapy side effects traced to destroy normal cells that divide rapidly and thus include cells in the bone marrow, digestive tract and hair follicles [5,6]. All chemotherapy regimens require that the recipient be capable of undergoing the treatment and comfortable [7,8].

Hypovitaminosis A may cause night blindness whereas hypervitaminosis A lead to increased intracranial pressure, headache, irritability, drowsiness, dizziness, lethargy, vomiting, diarrhea, bulging of fontanels in infants, diplopia, papilledema [9].

Hypovitaminosis E is associated with ß lipo-proteinemia, premature, very low birth weight infants, cystic fibrosis, and cholestasis and severe liver disease [10]. Peh et al, mention that the low levels of vitamin E have been linked to increased incidence of breast and colon cancer [11].

Hypovitaminosis D can occur from a combination of insufficient exposure to sunlight, inadequate dietary intake of vitamin D, genetic defects with endogenous vitamin D receptor, or even severe liver or kidney disease [12].

Vitamin B6 is essential nutrients required for normal functioning of many biological systems within the body. More specifically, pyridoxine is converted to pyridoxal 5-phosphate in the body, which is an important coenzyme for synthesis of amino acids, neurotransmitters (serotonin, dopamine, norepinephrine and gamma-aminobutyric acid (GABA)), sphingolipids, and aminolevulinic acid [13,14].

Cyanocobalamin is a highly complex, essential vitamin, owing its name to the fact that it contains the mineral, cobalt. This vitamin is produced naturally by bacteria, and is necessary for DNA synthesis and cellular energy production [15,16]. Vitamin B12 is generally non-toxic, even at higher doses. Mild, transient diarrhea, polycythemia vera, peripheral vascular thrombosis, itching, transitory exanthema, a feeling of swelling of entire body, pulmonary edema and congestive heart failure in early treatment stages may occur [17].

Folic acid is a water-soluble B-complex vitamin found in foods such as liver, kidney, yeast, and leafy, green vegetables. Also known as folate or Vitamin B9, is a member of the B vitamin family and an essential co-factor for enzymes involved in DNA and RNA synthesis [9]. More specifically, is required by the body for the synthesis of purines, pyrimidines, and methionine before incorporation into DNA or protein. Folic acid is particularly important during phases of rapid cell division, such as infancy, pregnancy, and erythropoiesis, and plays a protective factor in the development of cancer [9,10].

Most diets contain an adequate amount of vitamin K [18]. Vitamin K transport across the placenta is poor, increasing the risk of vitamin K deficiency in newborn babies [18]. During the first few weeks of life, vitamin K deficiency can cause vitamin K deficiency bleeding (VKDB), a condition formerly known as "classic hemorrhagic disease of the newborn." VKDB is associated with bleeding in the umbilicus, gastrointestinal tract, skin, nose, or other sites [18].

Here we assessed and evaluated concentration of essential vitamins before and after chemotherapy course to figure the level of vitamins in each cycle of anti-cancer.

Methods

Study Design and Setting

A prospective study will be carried out on newly diagnosed cancerous patients before and after receive chemotherapy treatment for a period of four months from February 2020 to June 2020. Assessments of the studied samples will be conducted as a baseline before receiving chemotherapy, designated as C0, while the period after administration of the first, third, and sixth cycle of chemotherapy will be termed as C1, C3, and C6.

Participants

Fifty newly diagnosed cancerous patients enrolling and recruited at their first visit to the center. Each patient attending our center meeting the inclusion criteria were invited to be including in our study after which written informed consent was obtained. Demographic characters of patients like age, and gender were collected from medical records of the participants. Follow up will be recorded after the first, third, and sixth cycles of chemotherapy.

Inclusion Criteria

- Patients who will in the first cycle of chemotherapy.
- Those who have the physical, and cognitive ability to respond to the data collection.

Exclusion Criteria

- Anticancer treatment that did not include chemotherapy.
- Patients in the second cycle of chemotherapy.
- Bad performance status.

The Kits

The panel used for evaluation of vitamins concentration included the following six kits: Human Vitamin AV ELISA Kit (CUSABIO TECHNOLOGY LLC, Catalogue No.: CSB-E07889h), Human Vitamin E Elisa kit (MyBioSource, Catalogue No.: MBS269047), Vitamin B6 (VB6) ELISA Kit (MyBioSource.com, Catalogue No.: MBS453092), Human Vitamin B12 ELISA Kit (Aviva Systems Biology Corp., Catalogue No.: OKEH02574), Vitamin D3 (VD3) DIY ELISA Kit (MyBioSource, Catalogue No.: MBS2088931), VK Elisa kit (MyBioSource, Catalogue No.: MBS746981) and Human FOLR3 ELISA kit (RayBiotech, Catalogue No.: ELH-FOLR3-1).

Data Sources/Measurement

In EDTA anti-coagulated tubes (ATACO / China, Catalogue No.:753134), the blood samples were collected (2-3 ml). We put the collected whole blood in refrigerator at 4°C for the night. Then centrifuge it for 10min at 1000-3000rpm. Then take supernatant tested immediately or put samples at -20°C (for 1-3 months) or -80°C (for 1-3 months) for storage. Bring all kits and all components and samples to room temperature (20-25 °C) before use. Get the Elisa Kit out of refrigerator 20 minutes in advance and take test when it balances to room temperature. We diluted the concentrated washing solution with double distilled water (1:25). Each kit has its directions and steps as mention in the leaflets.

Statistical

We use mean and standard deviation to represent the data, while describing variables presented using their numbers and parentage. One way ANOVA for variables were used. SPSS version 20 was used for data entry and analysis. P-value was considered significant if <0.05.

Results

Generally

We enrolled 50 patients, 38 (76%) were females and 12 (24%) were males, with mean age was 48.35±15.28 years. The mostly distributed age group was belonging to fifth decades 20 (40%) patients. 21 (42%) of women were housewife. The mean body mass index (BMI) was 33.12±5.51 m^2/Kg. The most patients belonged to overweight 25 (50%), whereas the normal BMI figured in 46% patients. The majority of the sample treated were breast cancers females about 26 (52%). Regarding chemotherapy regimens, the AC+Taxen protocol was mostly used as 50%, followed by 20% Carboplatin+Taxen and Xelox (Table 1).

Vitamins

The mean level of vitamin A found to be within normal throughout course of chemotherapy, but the value was decline to the half from (69.23±24.66 µg/dL) at C0 to (35.73±18.89 µg/dL) at C6, with statistically significant differences between pre- and post-chemotherapy (ANOVA=10.955, *P*=0.023) (Table 2) (Figure 1).

Normal mean value of vitamin B12 level was presented in the most of patients pre- chemotherapy and post- chemotherapy. At beginning, the mean was (349.2±100.54 pg/mL), whereas after C6, it was (300.63±90.1

Table 1: General characters of the study (n=50).

		No.	%
Gender	Male	12	24
	Female	38	76
Age (years)	20-30	2	4
	31-40	8	16
	41-50	12	24
	51-60	20	40
	61-70	8	16
Occupation	Employer	12	24
	Housewife	21	42
	Non- employer	19	38
	Student	3	6
BMI (m^2/Kg)	Underweight	2	4
	Normal	23	46
	Overweight	25	50
Cancer types	Bladder	1	2
	Breast	26	52
	Cervix	2	4
	Colorectal	6	12
	Lung	10	20
	Lymphoma	2	4
	Ovary	2	4
	Prostate	1	2
Chemotherapy protocols	5FU+Cisplatin	2	4
	ABVD	2	4
	AC+Taxen	25	50
	Carboplatin+Taxen	10	20
	FOLFIRINOX	1	2
	Xelox	10	20

**ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine; Taxen: Paclitaxel or Docetaxel; AC: Adriamycin and Cyclophosphamide; FOLFIRINOX: Folinic acid, 5FU, Irinotecan, Oxaliplatin; Xelox: Oxaliplatin and Capecitabine.

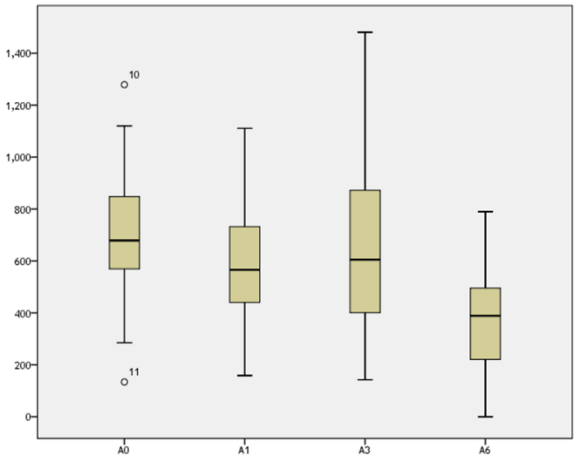

Figure 1: Box plot of vitamin A concentration pre- and post- chemotherapy.

pg/mL). These results were non-significant (ANOVA=2.93, *P*=0.089) (Table 2) (Figure 2).

Vitamin B6 concentrations in the most of patients risen by double post-chemotherapy. The mean level was (4.16±1.75 pg/mL) at C0 and became (8±4.93 pg/mL) at C6, with no significant between vitamin B6 levels pre- and post- chemotherapy (ANOVA=1.379, *P*=0.236) (Table 2) (Figure 3).

Regarding vitamin D concentration, the level not changed in pre-chemotherapy, and post- chemotherapy. The normal level found in all cycles of chemotherapy, except after 1st cycle, which was deficient. The variation in concentration between pre- and post- chemotherapy

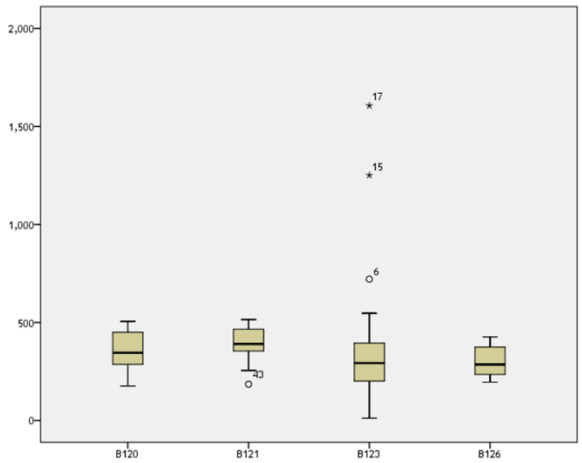

Figure 2: Box plot of vitamin B12 concentration pre- and post- chemotherapy.

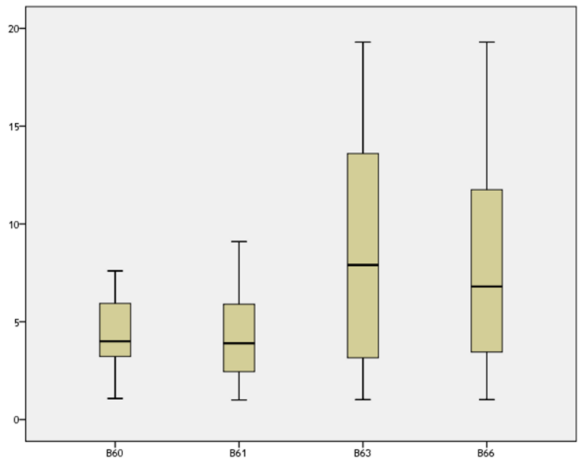

Figure 3: Box plot of vitamin B6 concentration pre- and post- chemotherapy.

Table 2: Vitamins concentration pre- and post- chemotherapy.

Vitamins	C0	C1	C3	C6	ANOVA	P- value
	(Mean±SD)					
A (20-100 µg/dL)	69.23±24.66	59.17±20.87	62.3±30.71	35.73±18.89	10.955	0.023
B12 (279-996 pg/mL)	349.2±100.54	384.2±88.18	355.6±30.53	300.63±90.1	2.93	0.089
B6 (5-30 ng/mL)	4.16±1.75	4.22±2.13	8.45±5.85	8±4.93	1.379	0.236
D (25-45 pg/mL)	23.58±8.46	18.73±4.75	26±12.8	27±17.33	1.062	0.054
E (12-42 µmol/L)	23.2±15.6	20.25±7.3	15.83±5.4	11.51±5.1	3.213	0.033
FOLATE (5.4-18 ng/mL)	6.23±3.12	6±2.84	4.4±2.6	3.33±2.72	6.56	0.012
K (12-42 µmol/L)	23.97±3.55	23.8±4.25	22.6±4.1	21.7±3.42	0.468	0.95

was not statistically significant (ANOVA=1.062, *P*=0.054). All these variations in concentration may be due to most patients received vitamin D supplements during the chemotherapy courses or cycles (Table 2) (Figure 4).

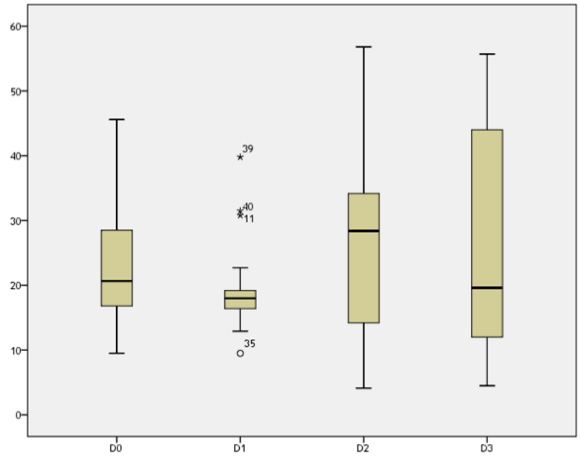

Figure 4: Box plot of vitamin D concentration pre- and post- chemotherapy.

We observed a statistically significant differences among vitamin E concentration pre- and post- chemotherapy (ANOVA=3.213, *P*=0.033). At baseline setting, the deficient not presented (23.2±15.6 µmol/L), whereas it dropped to (11.51±5.1 µmol/L) at C6 (Table 2) (Figure 5).

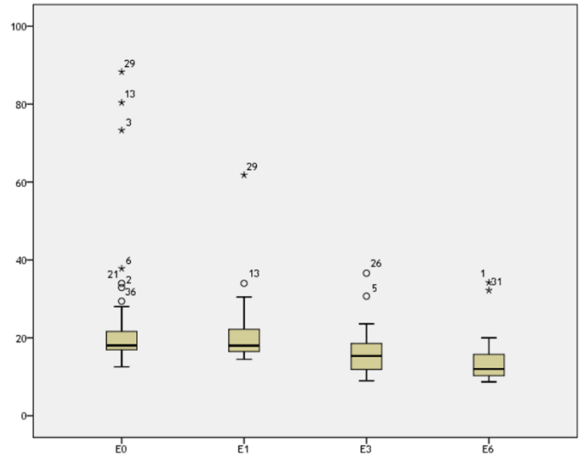

Figure 5: Box plot of vitamin E concentration pre- and post- chemotherapy.

In this study, most of patients pre-chemotherapy period had normal folate level. Post- chemotherapy the level started to decreased from (6.23±3.12 ng/mL) to reached (3.33±2.72 ng/mL). These results were strong statistically significant differences (ANOVA=6.56, *P*=0.012) (Table 2) (Figure 6).

In addition, vitamin K concentration was unchanged throughout chemotherapy cycles, with no relation (ANOVA=0.468, *P*=0.95) (Table 2) (Figure 7).

Discussion

Cancer can cause malnutrition of specific vitamins. In addition, chemotherapy causes those deficiencies by pressed anorexia, stomatitis, and alimentary tract disturbances [19,20]. Cytotoxic drugs inhibit synthesis of essential vitamins, purines, and pyrimidines. Because of

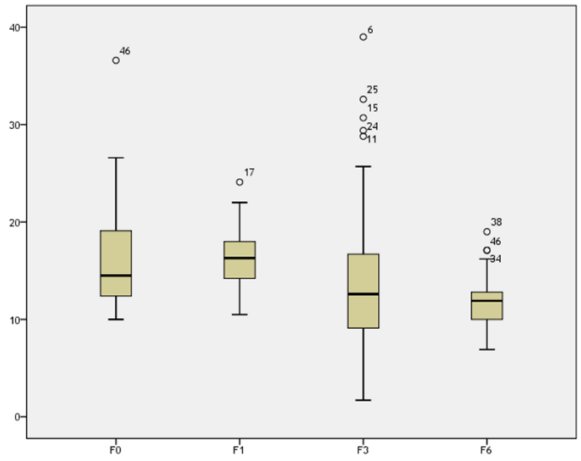

Figure 6: Box plot of folate concentration pre- and post- chemotherapy.

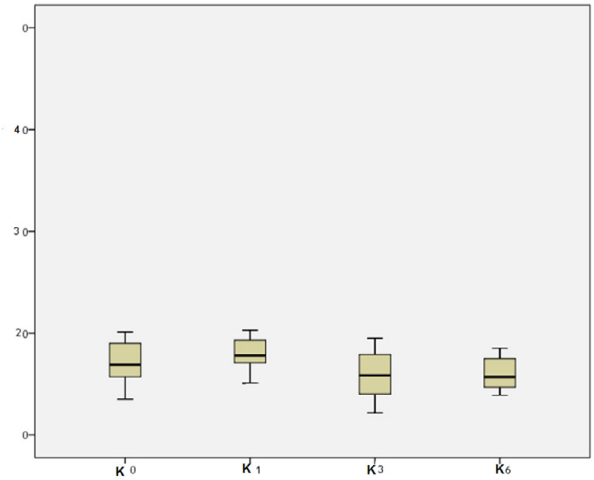

Figure 7: Box plot of vitamin K concentration pre- and post- chemotherapy.

the vitamin levels in the blood are often non-diagnostic, nutritional deficiency is identified almost based on clinical signs and symptoms and the patient's response to therapy. Deficiencies of vitamins B1, B2, and K and of niacin, folic acid, and thymine also may result from chemotherapy [19]. Nutritional deficiencies are chemically correctable; however, the tumor must be eradicated to relieve cachexia, which is may be reoccur due to usable of chemotherapy in the process of eradication [19]. Lukaski HC (2004) found the evidence of inadequate dietary vitamins and minerals intake among physically active individuals, but not in a cancer patient [21].

Retinol and derivatives play an essential role in metabolic functioning of the retina, the growth of and differentiation of epithelial tissue, the growth of bone, reproduction, and the immune response. Dietary vitamin A is derived from a variety of carotenoids found in plants. It is enriched in the liver, egg yolks, and the fat component of dairy products. Vitamin A refers to a group of fat-soluble substances that are structurally related to and possess the biological activity of the parent substance of the group called all-*trans* retinol or retinol [22]. The role of Vitamin A in epithelial differentiation, as well as in other physiological processes, involves the binding of Vitamin A to two families of nuclear retinoid receptors (retinoic acid receptors, RARs; and retinoid-X receptors, RXRs). These receptors function as ligand-activated transcription factors that modulate gene transcription. When

there is not enough Vitamin A to bind these receptors, natural cell differentiation and growth are interrupted. Peeling of skin around mouth may be observed from 1 to several days after ingestion and may spread to the rest of the body. Chronic, excessive ingestion may produce symptoms of pseudotumor cerebri, anorexia, weakness, arthralgias, bone pain, bone demineralization, dry skin, cracked lips, brittle nails, hair loss, splenomegaly, hepatomegaly, hypoplastic anemia, leukopenia, optic neuropathy, and blindness [9]. Because of these roles in regulating cell growth and differentiation, several studies have examined the association between vitamin A and various types of cancer. However, the relationship risk is unclear. Several prospective and retrospective observational studies in current and former smokers, as well as in people who have never smoked, found that higher intakes of carotenoids, fruits and vegetables, or both are associated with a lower risk of lung cancer [23,24]. However, clinical trials have not shown that supplemental beta-carotene and/or vitamin A helps prevent lung cancer [25-27], in all three of these studies, taking very high doses of beta-carotene, with or without 7,500 mcg RAE (25,000 IU) retinyl palmitate or 325 mg aspirin, did not prevent lung cancer. The evidence on the relationship between beta-carotene and prostate cancer is mixed. CARET study participants who took daily supplements of beta-carotene and retinyl palmitate had a 35% lower risk of nonaggressive prostate cancer than men not taking the supplements [28]. However, the ATBC study found that baseline serum beta-carotene and retinol levels and supplemental beta-carotene had no effect on survival [29]. Moreover, men in the highest quintile of baseline serum retinol levels were 20% more likely to develop prostate cancer than men in the lowest quintile [30].

Vitamin B12 has many forms, including the cyano-, methyl-, deoxyadenosyl- and hydroxy-cobalamin forms. The cyano form, is the most widely used form in supplements and prescription drugs. This drug was initially approved by the FDA in 1942 [10]. Vitamin B12 supplements are widely available and indicated in patients who require supplementation for various reasons. Dose requirements for vitamin B12 which are higher than normal (caused by pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, malignancy, hepatic and renal disease) [17]. Vitamin B12 deficiency is characterized by megaloblastic anemia, fatigue, weakness, constipation, loss of appetite, and weight loss [31]. Neurological changes, such as numbness and tingling in the hands and feet, can also occur [18]. Additional symptoms of vitamin B12 deficiency include difficulty maintaining balance, depression, confusion, dementia, poor memory, and soreness of the mouth or tongue [18]. The neurological symptoms of vitamin B12 deficiency can occur without anemia, so early diagnosis and intervention is important to avoid irreversible damage [32]. During infancy, signs of a vitamin B12 deficiency include failure to thrive, movement disorders, developmental delays, and megaloblastic anemia [33]. Many of these symptoms are general and can result from a variety of medical conditions other than vitamin B12 deficiency like cancer. In many cases we supplied our patients with vitamin B12.

Pyridoxine is the 4-methanol form of vitamin B6, which is an important water-soluble vitamin that is naturally present in many foods [9]. More specifically, pyridoxine is converted to pyridoxal 5-phosphate in the body, which is an important coenzyme for synthesis of amino acids, neurotransmitters (serotonin, dopamine, norepinephrine and gamma-aminobutyric acid (GABA)), sphingolipids, and aminolevulinic acid [9]. Pyridoxine is indicated for the treatment of vitamin B6 deficiency and for the prophylaxis of Isoniazid-induced peripheral neuropathy. Hypervitaminosis B6 effects include convulsions, dyspnea, hypermotility, diarrhea, ataxia and muscle weakness [13,14]. Vitamin B6 deficiency is associated with microcytic anemia, electroencephalographic abnormalities, dermatitis with cheilosis (scaling on the lips and cracks at the corners of the mouth) and glossitis (swollen tongue), depression and confusion, and weakened immune function [34]. End-stage renal diseases, chronic renal insufficiency, and other kidney diseases can cause vitamin B6 deficiency, which were seen post chemotherapy agents [34]. In addition, vitamin B6 deficiency can result from malabsorption syndromes, such as celiac disease, Crohn's disease, and ulcerative colitis. Certain genetic diseases, such as homocystinuria, can also cause vitamin B6 deficiency [18]. A meta-analysis of prospective studies found that people with a vitamin B6 intake in the highest quintile had a 20% lower risk of colorectal cancer than those with an intake in the lowest quintile [35]. However, the small number of clinical trials completed to date has not shown that vitamin B6 supplementation can help prevent cancer or reduce its impact on mortality. For example, an analysis of data from two large randomized, double-blind, placebo-controlled trials in Norway found no association between vitamin B6 supplementation and cancer incidence, mortality, or all-cause mortality [36].

Vitamin D ultimately comprises a group of lipid-soluble seco-steroids responsible for a variety of biological effects, some of which include increasing the intestinal absorption of calcium, magnesium, and phosphate [12]. Vitamin D play an essential physiological role in maintaining calcium homeostasis and metabolism [10]. Laboratory and animal studies suggest that vitamin D might inhibit carcinogenesis and slow tumor progression by, for example, promoting cell differentiation and inhibiting metastasis. Vitamin D might also have anti-inflammatory, immunomodulatory, proapoptotic, and antiangiogenic effects [37]. Observational studies and clinical trials provide mixed evidence on whether vitamin D intakes or serum levels affect cancer incidence, progression, or mortality risk [18]. In a meta-analysis of 16 prospective cohort studies in a total of 137,567 participants who had 8,345 diagnoses of cancer, 5,755 participants died from cancer [38]. A 50 nmol/L (20 ng/mL) increase in 25(OH)D levels was associated with an 11% reduction in total cancer incidence rates and, in women but not men, a 24% reduction in cancer mortality rates. A meta-analysis of prospective studies that evaluated the association between serum 25(OH)D levels and cancer incidence (8 studies) or cancer mortality (16 studies) found that cancer risk decreased by 7% and cancer mortality rates decreased by 2% with each 20 nmol/L (8 ng/mL) increase in serum 25(OH)D levels [39]. Some observational studies support an inverse association between 25(OH)D levels and breast cancer risk and mortality, but others do not [40]. The Women's Health Initiative clinical trial randomized 36,282 postmenopausal women to receive 400 IU vitamin D3 plus 1,000 mg calcium daily or a placebo for a mean of 7 years [41]. The vitamin D3 and calcium supplements did not reduce breast cancer incidence, and 25(OH)D levels at the start of the study were not associated with breast cancer risk [42]. A large case-control study included 5,706 individuals who developed colorectal cancer and whose 25(OH)D levels were assessed a median of 5.5 years from blood draw to cancer diagnosis and 7,105 matched controls [43]. The results showed an association between 25(OH)D levels lower than 30 nmol/L (12 ng/mL) and a 31% higher colorectal cancer risk. Levels of 75 to less than 87.5 nmol/L (30 to less than 35 ng/mL) and 87.5 to less than 100 nmol/L (35 to less than 40 ng/mL) were associated with a 19% and 27% lower risk, respectively. The association was substantially stronger in women. Another study included 2,259 healthy individuals aged 45 to 75 years who had had one or more serrated polyps (precursor lesions to colorectal cancer) that

had been removed [44]. These participants were randomized to take 25 mcg (1,000 IU) vitamin D3, 1,200 mg calcium, both supplements, or a placebo daily for 3-5 years, followed by an additional 3-5 years of observation after participants stopped the treatment. Vitamin D alone did not significantly affect the development of new serrated polyps, but the combination of vitamin D with calcium increased the risk almost fourfold. The VITAL trial found no association between vitamin D supplementation and the risk of colorectal adenomas or serrated polyps [45]. A study of cohorts that included 5,313 participants who developed lung cancer and 5,313 matched controls found no association between serum 25(OH)D levels and risk of subsequent lung cancer, even when the investigators analyzed the data by sex, age, race and ethnicity, and smoking status [46]. Several studies published in 2014 suggested that high levels of 25(OH)D might increase the risk of prostate cancer. For example, a meta-analysis of 21 studies that included 11,941 men with prostate cancer and 13,870 controls found a 17% higher risk of prostate cancer for participants with higher levels of 25(OH)D. What constituted a "higher" level varied by study but was typically at least 75 nmol/L (30 ng/mL). In a cohort of 4,733 men, of which 1,731 had prostate cancer, those with 25(OH)D levels of 45-70 nmol/L (18-28 ng/mL) had a significantly lower risk of the disease than men with either lower or higher values [47,48]. This U-shaped association was most pronounced for men with the most aggressive forms of prostate cancer. A case-control analysis of 1,695 cases of prostate cancer and 1,682 controls found no associations between 25(OH)D levels and prostate cancer risk [49]. However, higher serum 25(OH)D levels (at a cut point of 75 nmol/L [30 ng/mL]) were linked to a modestly higher risk of slow-growth prostate cancer and a more substantial lower risk of aggressive disease.

In 1922, vitamin E was demonstrated to be an essential nutrient [10]. It is a term used to describe 8 different fat soluble tocopherols and tocotrienols, alpha-tocopherol being the most biologically active, and it act as an antioxidant, protecting cell membranes from oxidative damage [10]. The antioxidant effects are currently being researched for use in the treatment of diseases causing bone loss, cardiovascular diseases, diabetes mellitus and associated comorbidities, eye diseases, inflammatory diseases (including skin conditions), lipid disorders, neurological diseases, and radiation damage [11]. Vitamin E supplementation is indicated for treatment of vitamin E deficiency which can occur in cystic fibrosis, cholestasis and severe liver disease, a beta lipo-proteinemia or simply poor diet [9]. Low levels of vitamin E have been linked to increased incidence of breast and colon cancer [11]. Antioxidant nutrients like vitamin E protect cell constituents from the damaging effects of free radicals that, if unchecked, might contribute to cancer development [31]. Vitamin E might also block the formation of carcinogenic nitrosamines formed in the stomach from nitrites in foods and protect against cancer by enhancing immune function [50]. In a clinical trial involving 29,133 male smokers, men randomly assigned to take daily supplements of 111 IU of synthetic vitamin E (50 mg, as *dl*-alpha-tocopheryl acetate) for 5–8 years had 32% fewer prostate cancers compared to subjects who did not take the supplements [51]. One study of women in Iowa provides evidence that higher intakes of vitamin E from foods and supplements could decrease the risk of colon cancer, especially in women <65 years of age [52]. The overall relative risk for the highest quintile of intake (>35.7 IU/day, form not specified) compared to the lowest quintile (<5.7 IU/day, form not specified) was 0.32. However, prospective cohort studies of 87,998 women in the Nurses' Health Study and 47,344 men in the Health Professionals Follow-up Study failed to replicate these results [53].

Folic acid is a water-soluble B-complex vitamin found in foods such as liver, kidney, yeast, and leafy, green vegetables. Also known as folate or Vitamin B9, is a member of the B vitamin family and an essential cofactor for enzymes involved in DNA and RNA synthesis [9]. More specifically, is required by the body for the synthesis of purines, pyrimidines, and methionine before incorporation into DNA or protein. Folic acid is particularly important during phases of rapid cell division, such as infancy, pregnancy, and erythropoiesis, and plays a protective factor in the development of cancer [18]. Several epidemiological studies have suggested an inverse association between folate intakes and status and the risk of colorectal, lung, pancreatic, esophageal, stomach, cervical, ovarian, breast, bladder, and other cancers [54,55]. Research has not established the precise nature of folate's effect on carcinogenesis, but scientists hypothesize that folate might influence cancer development through its role in one-carbon metabolism and subsequent effects on DNA replication and cell division [56]. Results from clinical trials involving folic acid supplementation have been mixed. In addition, most trials have included other B-vitamins (frequently at doses well above RDA levels) and sometimes other nutrients, making it difficult to disentangle the effects, if any, of folic acid alone. For example, in a trial in France, 2,501 people with a history of cardiovascular disease received daily supplements of 560 mcg folic acid, 3 mg vitamin B6, and 20 mcg vitamin B12 for 5 years [56]. The researchers found no association between B-vitamin supplementation and cancer outcomes. In a combined analysis of two trials in Norway (where foods are not fortified with folic acid), supplementation with 800 mcg/day folic acid plus 400 mcg/day vitamin B12 for a median of 39 months in 3,411 people with ischemic heart disease increased cancer incidence rates by 21% and cancer mortality rates by 38% compared with no supplementation [36]. Findings from these Norwegian trials have raised concerns about folic acid supplementation's potential to raise cancer risk. In a randomized clinical trial investigating osteoporotic fracture incidence in 2,919 participants aged 65 years or older with elevated homocysteine levels, those who received 400 mcg folic acid plus 500 mcg vitamin B12 and 600 IU vitamin D3 for 2 years reported a significantly higher cancer incidence, especially of colorectal and other gastrointestinal cancers, than those who received only 600 IU vitamin D3 [57]. In addition, a 2018 prospective study found that folic acid intake from fortified foods and supplements was positively associated with a risk of cancer recurrence among 619 patients with non–muscle-invasive bladder cancer, whereas natural folate intakes showed no significant association [58]. Higher plasma folate concentrations have also been associated with an increased risk of breast cancer in women with a *BRCA1* or *BRCA2* mutation [59]. A secondary analysis of the study by Cole and colleagues [60] found that folic acid supplementation significantly increased the risk of prostate cancer [18]. Subsequent research has shown an association between increased cancer cell proliferation and higher serum folate concentrations in men with prostate cancer [18]. A meta-analysis of six randomized controlled trials that included a total of 25,738 men found that the risk of prostate cancer was 24% higher in men receiving folic acid supplements than those taking a placebo [61]. The mixed findings from clinical trials, combined with evidence from laboratory and animal studies indicating that high folate status promotes tumor progression, suggest that folate might play dual roles in cancer risk, depending on the dosage and timing of the exposure. Modest doses of folic acid taken before preneoplastic lesions are established might suppress cancer development in healthy tissues, whereas high doses taken after the establishment of preneoplastic lesions might promote cancer development and progression [18].

In this study vitamin K level not affected by chemotherapy agents, but deficiency is only considered clinically relevant when prothrombin time increases significantly due to a decrease in the prothrombin activity of blood [62]. Thus, bleeding and hemorrhage are the classic signs of vitamin K deficiency, although these effects occur only in severe cases. Because vitamin K is required for the carboxylation of osteocalcin in bone, vitamin K deficiency could also reduce bone mineralization and contribute to osteoporosis [63]. Vitamin K deficiency can occur during the first few weeks of infancy due to low placental transfer of phylloquinone, low clotting factor levels, and low vitamin K content of breast milk [62]. Clinically significant vitamin K deficiency in adults is very rare and is usually limited to people with malabsorption disorders or those taking drugs that interfere with vitamin K metabolism [18]. In healthy people consuming a varied diet, achieving a vitamin K intake low enough to alter standard clinical measures of blood coagulation is almost impossible [18].

Conclusion

Many factors in cancerous participants lead to vitamins deficiencies, some related to the cancer itself, cytotoxic chemotherapy, stress, management, anti-side effect of chemotherapy, and others related to the patients like diet, comorbidity diseases, malnutrition, and mal-absorption. Several vitamins remained within normal concentration throughout anti-cancer course might be due to vitamins supplement taken by persons during their regimens. Almost always vitamins concentration dropped during cycles, but still within normal value, except vitamin E, which was deficient in last cycle of chemotherapy. Vitamins replacement are mandatory for substitution dropping level because off those are essential for many body processes and regulation.

Conflict of Interest

NONE.

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