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Effects of Micronutrient Supplementation on Concentrations of Vitamins and Minerals, Inflammation and Cardiovascular Risk Factors

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Abstract

There is growing interest in the role of micronutrients (essential trace elements and vitamins) in the optimization of health, and prevention and treatment of diseases. As multivitamin –multimineral supplementation (MVMM) is the most commonly reported supplement, it is important to study the health benefits associated with regular intake.

We investigated the use of a particular MVMM supplement, developed by the Pure North Foundation, on blood chemistry parameters and lipid profiles, along with the inflammation marker C - reactive protein, in 100 steel company workers over a one year period of supplementation.

According to our study, participants with lower levels of vitamins D, B2, and C before supplementation tended to show higher levels of inflammation. Vitamin D levels correlated with a variety of lipid profile parameters. Analysis of the data after one year of supplementation demonstrated that participants with blood vitamin D concentrations above 30 ng/ml showed decreases in triglycerides, cholesterol to HDL ratio, and improvement of HDL levels. In addition, higher vitamin C levels were associated with lower triglyceride and VLDL levels.

Blood concentrations of vitamin C, D, and E increased substantially as a result of supplementation, but coenzyme Q10 levels, lutein, lycopene, and vitamin A levels were not greatly affected.

Furthermore, looking into the distinction between smokers and non-smokers, our data indicate that improvements in antioxidant levels during MVMM supplementation are less dramatic in smokers. After one year supplementation, smokers had lower plasma antioxidant concentrations than nonsmokers. The greatest differences were found with lycopene, lutein, and vitamin A, while improvements in vitamin C, vitamin D and vitamin E were practically the same for both groups. Smokers had less improvement of the health score in comparison with non-smokers. For all participants, half year and one year of supplementation eliminated very low health scores, and increased the number of people with high scores.

Keywords: Multivitamin-multimineral supplementation; Inflammation; Lipid profile; Health markers

Introduction

Micronutrients are vitamins or minerals that the human body requires, but in small amounts, for normal growth and development. Deficiencies in the intake of these nutrients are significant public health concerns. The "classic" example is vitamin A deficiency in children, which leads to blindness and immune system compromise, the latter increasing the risk of death due to infectious diseases. Other important micronutrient deficiencies include iron, vitamin D, folate, and vitamin B12 [1]. Many nations have developed recommendations for the daily intake of micronutrients so as to prevent these sorts of deficiency based pathologies [2-4]. As a result, multivitamin and multi-mineral supplementation (MVMM) has become common in children and adults [5-9]. As MVMM has become more popular, interest in the possible health benefits of supplementation over and above the minimum daily requirements to prevent clinical manifestations of deficiency has increased. Since many of these nutrients have antioxidant properties, they are thought to be beneficial in preventing cancer (by reducing oxidation induced DNA mutations). Also, the ability of antioxidants to protect cell membranes and to increase telomere lengths in cellular DNA had led some to suspect they can reduce the effects of aging [10,11].

Epidemiological studies and clinical trials into the effect of MVMM on cancer [12-21], cardiovascular disease [17, 22-25], eye disease [26-31], incidence of infection [32-35] and general health or mortality [12,36-44] have produced ambiguous results. For example, a recent meta-analysis showed no effect of supplementation on total mortality [45], yet a trend toward supplementation reducing mortality can be found across thirteen primary prevention trials [12-14,26-28,32,33,36,46,47]. Studies focused on cancer also yield mixed results, with several reporting a reduction in risk accompanying supplementation [12,16,18,19] with other studies showing no benefit [17]. One study found that multivitamin supplementation led to a small but significant reduction in total cancers, but no significant site specific reduction [14]. Another study indicated a benefit to men, but not women, in cancer reduction with supplementation [43]. A controlled clinical study examining the effects of supplementation on eye disease showed a significant reduction in macular degeneration with supplementation, but no effect on cataracts [30,31]. Data from the Linxian trial [12,37] of MVMM supplementation suggest that selenium, a-tocopherol, retinol, and zinc supplementation may reduce the incidence of stroke, but that other micronutrients studied had no effect. Obviously, the experimental design of these clinical studies is widely variable, making direct comparisons and conclusions difficult. We decided to investigate the use of a particular MVMM supplement, developed by the Pure North Foundation, on blood chemistry parameters and lipid profiles, along with the cardiovascular risk marker C - reactive protein, in a group of steel workers over a one year

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period of supplementation. This allows us to determine if a particular supplement formula (a) actually increases vitamin and mineral levels in the body, (b) is associated with an increase or decrease in inflammation as measured by C-reactive protein, or (c) affects lipid levels associated with cardiovascular risk.

Methods

A multivitamin multi-mineral supplement containing forty-two nutrients was obtained from the Pure North Foundation (Calgary, Canada). The Pure North formulation (Pure Encapsulations) is designed to support and enhance antioxidant activity, boost immune system and support digestion; it includes vitamins, fatty acids, essential metals, probiotics, digestive enzymes, and extracts from green tea and berries. Supplements come in packets, each containing eight capsules that together comprise a single daily dosage. A list of its ingredients is provided in Table 1.

Supplements were provided to one-hundred workers, seventy-five males and twenty-five females, averaging forty eight years old at the start of the study. Blood samples were obtained from subjects at time zero, after six months supplementation, and after one year supplementation. Twenty-six subjects discontinued supplementation after several months, leaving sixty-four subjects who actually completed the study.

The study was conducted under Institutional Review Board Approval of Riordan Clinic. Demographics were limited to ensure confidentiality, and informed consent was obtained from all patients. The tests were performed by the Bio-Center Laboratory at Riordan Clinic, an accredited clinical laboratory, using standard assay procedures and Laboratory Corporation. All identifying data were deleted from the lab results.

Statistics

Data were analyzed by using Kaleidograph and Systat software. Differences between smokers and nonsmokers were analyzed by using one-way ANOVA. Differences between data from before and after supplementation were analyzed by using paired *t* tests. A two tailed *P*-value <0.05 was considered statistically significant. Values are reported as means ± SDs.

Results

Nutrition parameters and supplementation

Average values for various nutrient levels are shown in Table 2. Upon examining the values initially (prior to MVMM), mean vitamin D and C values were outside normal ranges. In fact, 90% of the participants had blood vitamin D levels below the lower limit of the normal range. This was reduced to 40% after one year of MVMM usage. Similarly, 46% of the participants had vitamin C levels below the lower limit of the normal range (0.2 mg/dl). This number was reduced to 17% after one year of supplementation. Our data confirm that vitamin concentrations in blood increased significantly after one year of supplementation, with vitamin D and C levels showing the most dramatic improvements (178% and 85% improvement, respectively).

There were seven parameters that fit the following criterion: (1) their mean values before supplementation were below normal or on the low end of normal, as defined by being one or more standard deviations below the normal range midpoint; and (2) were improved in a statistically significant fashion ($p<0.05$) by supplementation: coenzyme Q10, lutein, lycopene, and vitamins A, D, C, and E. Figure 1 illustrates how the relative levels of these nutrients changed during the course of supplementation.

The most dramatic improvements are seen with vitamin C and D. Figure 1 suggests that these participants were at least somewhat low in nutrient levels prior to supplementation, and that supplementation improved those levels. In most cases, the improvement continued between six months and one year of supplementation.

Participants experienced small but statistically significant ($P<0.05$) decrease in zinc (Zn) and magnesium (Mg) while showing an increase in copper (Cu), as it is shown in Figures 2 and 3. One possible reason for the decreases of magnesium and zinc concentrations after MVMM use was that copper has high binding capacity relative to other metals. As all these three metals are included in supplementation, we suspect that copper binds with organic molecules more readily, and thus substitutes for the other essential minerals (Zn and Mg).

In addition, we examined how supplementation affected nutrient levels in participants by using "health scores". The participant's level of a given nutrient was scored from one to six relative to the nutrient's normal range. The individual values are scored depending on where they fall within the normal range: values more than two standard deviations below the midpoint of the normal range are assigned a value of 1, values between one and two standard deviations below the midpoint of the normal range are assigned a value of 2, etc. The sum of these scores for each vitamin (A, C, D, E, beta-carotene), lutein, lycopene, coenzyme Q10, magnesium, zinc and copper represents the "health score" for a participant. The total health score is the sum of the scaled (1-6) values. Based on studies with healthy volunteers conducted at the Riordan Clinic, the "normal range" for this sum of parameters would be 34 to 50. Prior to treatment, our study group had an average health score of 33 ± 8. The average rose to 44 ± 2 after six months MVMM use and 46 ± 7 after twelve months MVMM use. This represents a statistically significant improvement in health score.

Nutrient	Dose	RDA
Vitamin A (palmitate)	150 mcg	900 mcg
Vitamin B1(Thiamine HCl)	4.2 mg	1.2 mg
Benfotiamine	4.2 mg	NA
Vitamin B2 (Riboflavin 5-phosphate	0.83 mg	1.2 mg
Vitamin B3 (Niacin)	16.7 mg	15 mg
Pantothenic acid (Calcium-d-Pantothenate	16.7 mg	5 mg
Vitamin B6 (Pyridoxal 5-Phosphate)	2.5 mg	1.5 mg
Biotin	50 mcg	30 mcg
Folic Acid(5-Methyltetrahydrofolic acid)	66.7 mcg	NA
Vitamin B12 (Methylcobalamin)	500 mcg	2.4 mcg
Vitamin C (Ascorbic acid)	83 mg	80 mg
Vitamin D3 (Cholecalciferol)	25 mcg (x4)	15 mcg
Vitamin K2 (Menaquinone-7)	13.3 mcg	100 mcg
Choline (Bitartrate)	4.2 mg	500 mg
Inositol	4.2 mg	500 mg
Calcium (Hydrolyzed vegetable protein (HVP) Chelate)	16.7 mg	1000 mg
Magnesium (HVP Chelate)	53.3 mg	370 mg
Manganese (Citrate)	0.42 mg	2 mg
Zinc (Citrate)	2.5 mg	9 mg
Selenium (Selenomethionine)	33.3 mcg	55 mcg
Copper (HVP Chelate)	0.17 mg	900 mcg
Iodine (Ascophyllum nodosum, whole plant)	75 mcg	150 mcg
Chromium (Polynicotinate)	33.3 mcg	30 mcg
Molybdenum (Citrate)	66.7 mcg	45 mcg

Table 1: Pure North Supplement Packet: Selected ingredients, along with recommended daily allowances (RDA) provided for comparison. Other ingredients include potassium, boron, vanadium, ascorbyl palmitate, mixed carotenoids, mixed tocopherols, mixed tocotrienols, lutein, lipoic acid, cinnamon, l-carnosine, taurine, green tea extract, Indian kino tree extract and rosemary extract.

Coenzyme Q10 (Blood) (µg/ml) (0.3– 1.5 norm)	initial	0.51 ± 0.22	
	6 months	0.68 ± 0.28	†
	12 months	0.74 ± 0.31	†
Lutein (Blood) (µg/dl) (7– 28 norm)	initial	8.6 ± 3.4	
	6 months	9.2 ± 5.3	
	12 months	11.0 ± 4.8	†
Lycopene (Blood) (µg/dl) (13– 54 norm)	initial	25.5 ± 8.9	
	6 months	24.9 ± 8.4	
	12 months	28.8 ± 12.2	
Vitamin D (Blood) (ng/ml) (40 – 80 norm)	initial	20.4 ± 9.0	
	6 months	36.7 ± 14.3	†
	12 months	37.9 ± 20.7	†
Vitamin A (Blood) (µg/dl) (24 – 90 norm)	initial	47.8 ± 10.9	
	6 months	48.0 ± 10.6	
	12 months	53.2 ± 13.4	†
Vitamin C (Blood) (mg/dl) (0.4 – 1.5 norm)	initial	0.4 ± 0.3	
	6 months	1.3 ± 0.8	†
	12 months	1.1 ± 0.6	†
Vitamin E (Blood) (mg/dl) (0.6 – 2.7 norm)	initial	1.25 ± 0.40	
	6 months	1.33 ± 0.42	
	12 months	1.49 ± 0.50	†
Copper (RBC) (µg/dl) (46 – 79 norm)	initial	55.5 ± 6.4	
	6 months	61.7 ± 5.9	†
	12 months	59.2 ± 7.3	†
Magnesium (RBC) (mg/dl) (4.0 – 6.4 norm)	initial	5.2 ± 0.5	
	6 months	4.8 ± 0.5	†
	12 months	4.7 ± 0.5	†
Zinc (RBC) (µg/dl) (8.6 – 15.8 norm)	initial	12.3 ± 1.6	
	6 months	11.8 ± 1.4	
	12 months	11.8 ± 1.7	

Table 2: Concentrations of six key antioxidants in blood, along with three minerals in red blood cells (RBC), before and after MVMM supplementation for 64 subjects. Errors are shown as standard deviations. Units and normal ranges (via the clinic laboratory) are given. Crosses indicate values significantly different ($p < 0.05$) from pre-supplementation ("initial").

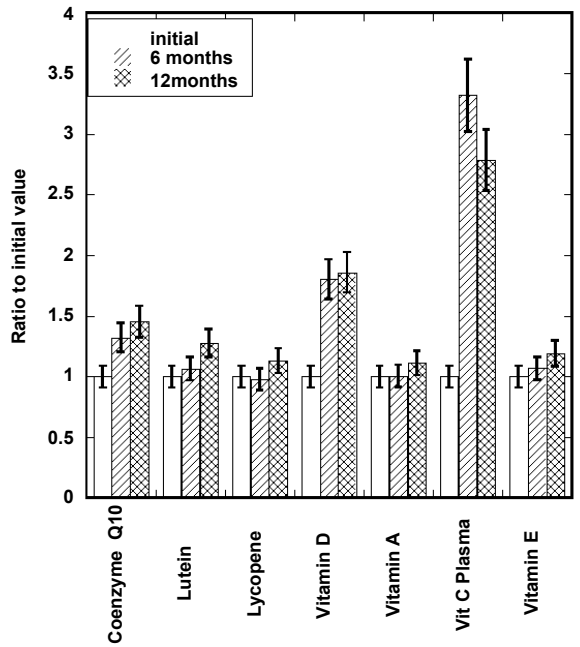

Figure 1: Nutrient concentrations normalized on the initial pre-treatment levels. Data presented as means ± SE.

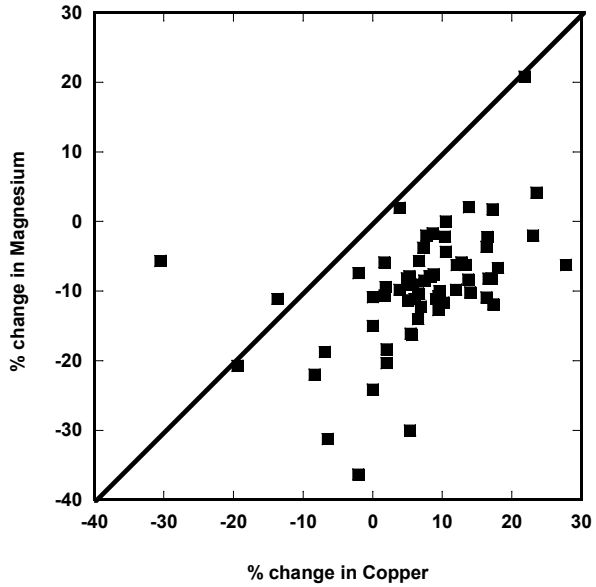

Figure 2: Percentage of changes of magnesium and zinc vs. changes in concentration of copper.

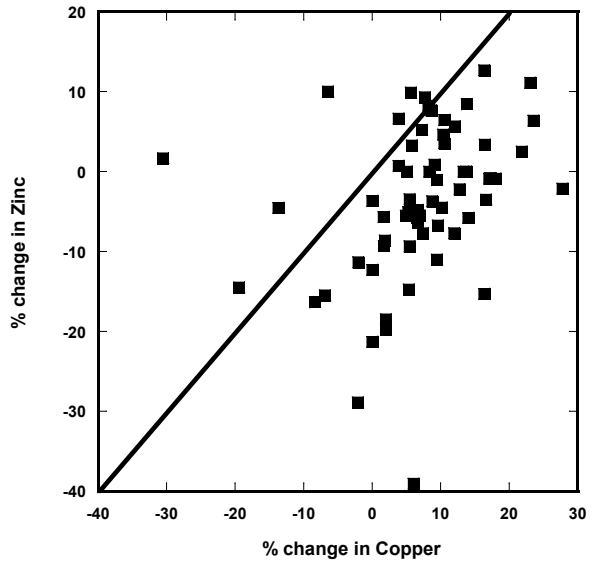

Figure 3: Percentage of changes of magnesium and zinc vs. changes in concentration of copper.

This parameter was used as a general measure of nutritional health, and as a means of allowing participants to set goals for improving their nutrition.

Comparison of Smokers and Non-Smokers

Study subjects (68 total participants) were separated into two groups: smokers (26 subjects) and non-smokers (34 subjects). For eight subjects, we did not have tobacco usage information. Pre-treatment levels, and the degree of improvement with supplementation, are given for seven key nutrients in Table 3. After one year of supplementation, the levels of vitamins in blood were increased but in almost every case there was less improvement in smokers compared to non-smokers. This was most dramatic for lutein, lycopene, and coenzyme Q10. Prior

Parameter	Smoker	Initial	% Δ, p-value
Coenzyme Q10 0.3– 1.5 (μg/ml)	No	0.49 ± 0.20	59% (<0.001)
	Yes	0.53 ± 0.34	33% (<0.001)
Lutein 7– 28 (μg/dl)	No	9.3 ± 3.5	33% (<0.001)
	Yes	8.1 ± 3.2	20% (0.01)
Lycopene 13– 54 (μg/dl)	No	25.0 ± 9.2	24% (<0.01)
	Yes	25.0 ± 7.0	1% (NS)
Vitamin D 40 – 80 (ng/ml)	No	20.8 ± 8.1	86% (<0.001)
	Yes	20.5 ± 10.5	76% (<0.001)
Vitamin A 24 – 90 (μg/dl)	No	49.0 ± 10.0	16%9 (<0.01)
	Yes	47.8 ± 10.7	7% (NS)
Vitamin C 0.4 – 1.5 (mg/dl)	No	0.41 ± 0.35	188% (<0.001)
	Yes	0.38 ± 0.25	164% (<0.001)
Vitamin E 0.6 – 2.7 (mg/dl)	No	1.28 ± 0.46	19%(<0.01)
	Yes	1.24 ± 0.30	17% (<0.01)

Table 3: Key nutrient concentrations in smokers and non-smokers prior to supplementation (Initial), along with percent increase (% Δ) in values after supplementation.

to MVMM usage, 77 % of smokers had low total health scores (≤ 32, based on ranges in healthy volunteers). The pre-MVMM value for non-smokers was 68%. Supplementation reduced the low health score fractions to 48 % among smokers and to 26 % among non-smokers. The smokers seem to see lower level of improvement.

Smokers may require more antioxidants than non-smokers, and this may make it harder for them to accumulate antioxidants in the blood. They may also be subject to higher levels of inflammation. To examine this, and to investigate cardiovascular risk factors, we analyzed the inflammation marker C-reactive protein (CRP) and lipid panels in smokers and non-smokers. CRP is associated with increased mortality and poor prognosis for cardiovascular disease, particularly in younger patients with elevated CRP levels. For the entire study group, the mean CRP level increased from 3.7 mg/L prior to supplementation to values of 4.2 mg/L after six months supplementation and 4.5 mg/L after one year of supplementation, but the difference was not statistically significant at the 95% confidence level.

Figure 4 shows how the pre-treatment distribution of CRP varies between the smokers and non-smokers. There is a greater incidence of high values in the smoker data set. The mean pre-treatment CRP value for non-smokers was 2.6 ± 2.5 mg/L while that for smokers was 5.2 ± 9.1 mg/L.

Interestingly, the increase in CRP observed during the supplementation phase of the study was more dramatic among smokers. After one year of MVMM usage, the mean CRP value for non-smokers was 3.4 ± 4.1 mg/L while that for smokers was 6.6 ± 10.1 mg/L. Despite the high standard deviations, the increase in CRP among smokers after one year was statistically significant (p-value<0.05).

The data in Figure 4 clearly are not "normally distributed": they are skewed by subjects with high (above 5 mg/L) CRP levels. From Figure 4, it appears that there are a higher proportion of smokers with abnormally high CRPs compared to the non-smoker group. We thus decided to break the subjects down into risk groups, with CRP levels below 1.9 mg/L being "low risk", levels above 3.8 mg/L being "high risk", and levels in between being "moderate risk" (www.webmd.com/heart-disease/guide), values are adjusted according to our laboratory measurements of normal range). There are a much greater proportion of "high risk" subjects in the smokers group (50%) in comparison with non-smoker group (21%). The non-smokers do not seem to change much over the course of supplementation, with roughly half of the subjects being "low risk" and the rest approximately evenly split between "moderate" and "high" risk subjects. The smokers, however, seem to gain more "moderate risk" subjects and lose some "low risk" subjects during the course of supplementation. For this group of participants the portion of moderate risk was changed from 6% to 23%, the portion of low risk -from 46% to 37% and the portion of high risk -from 50% to 42%.

We also examined lipid profiles in smokers and non-smokers. Results are shown in Table 4. Cholesterol and key cholesterol ratios tended, on average, to be at the high end of the normal range while average HDL levels were in the middle of the normal range and average LDL levels were above the normal range. On average, smokers had higher levels of "bad" cholesterols (cholesterol, LDL) and lower levels of "good" HDL cholesterol. The ratio of cholesterol to HDL was higher in smokers as compared to non-smokers. Also, LDL levels increased for both groups during MVMM usage.

In analyzing these data, interesting correlations emerge:

CRP concentrations correlate with vitamin B_2 and vitamin D levels. This is shown in Figure 5. In particular, subjects with the highest CRP levels tended to be low in vitamins D and B_2.

Vitamin D levels correlate with a variety of lipid profile parameters (Figure 6). Participants with blood vitamin D concentrations above 30

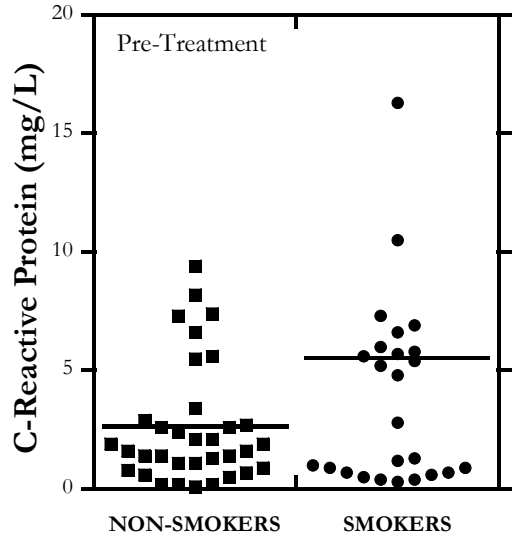

Figure 4: Distributions of C-reactive protein levels in smokers and non-smokers prior to MVMM.

Parameter with normal range	Smoker	Initial	6 months	12 months
Cholesterol/HDL 0 – 5 (ratio)	No	4.0 ± 1.0	4.1 ± 1.0	4.2 ± 0.9
	Yes	4.7 ± 1.3 †	4.6 ± 1.5 †	4.9 ± 1.4 †
Cholesterol 100– 200 (mg/dL)	No	183 ± 36	204 ± 40	210 ± 42
	Yes	192 ± 24	204 ± 25	207 ± 35
HDL 29-90 (mg/dL)	No	47 ± 10	52 ± 11	51 ± 12
	Yes	45 ± 16	49 ± 17	45 ± 15
LDL 50-100 (mg/dL)	No	110 ± 29	121 ± 32	132 ± 31
	Yes	115 ± 28	118 ± 26	126 ± 35
LDL/HDL 0 – 3.6 (ratio)	No	2.4 ± 0.8	2.4 ± 0.8	2.7 ± 0.7
	Yes	2.8 ± 1.0	2.8 ± 1.1	3.0 ± 1.2

Table 4: Lipid profile parameters for smokers and non-smokers prior to supplementation, six months into supplementation, and after one year of supplementation. Cross indicates values significantly different (p < 0.05) from non-smoker values.

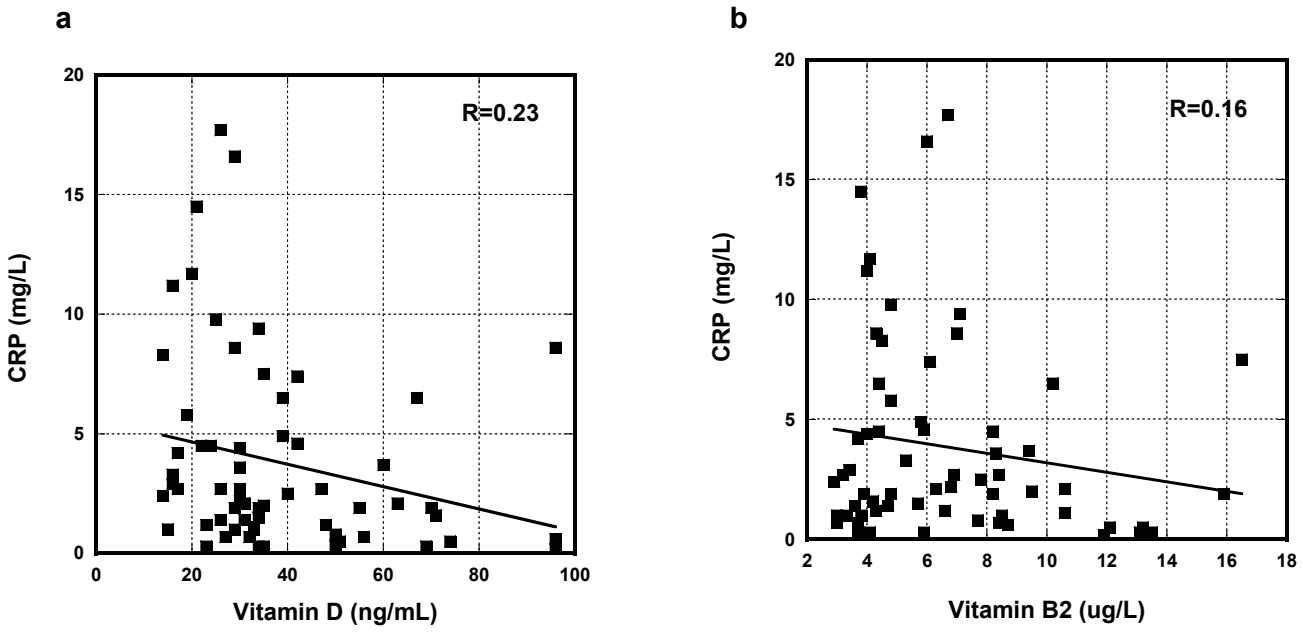

Figure 5a,b: Correlations between vitamin D or B2 and CRP.

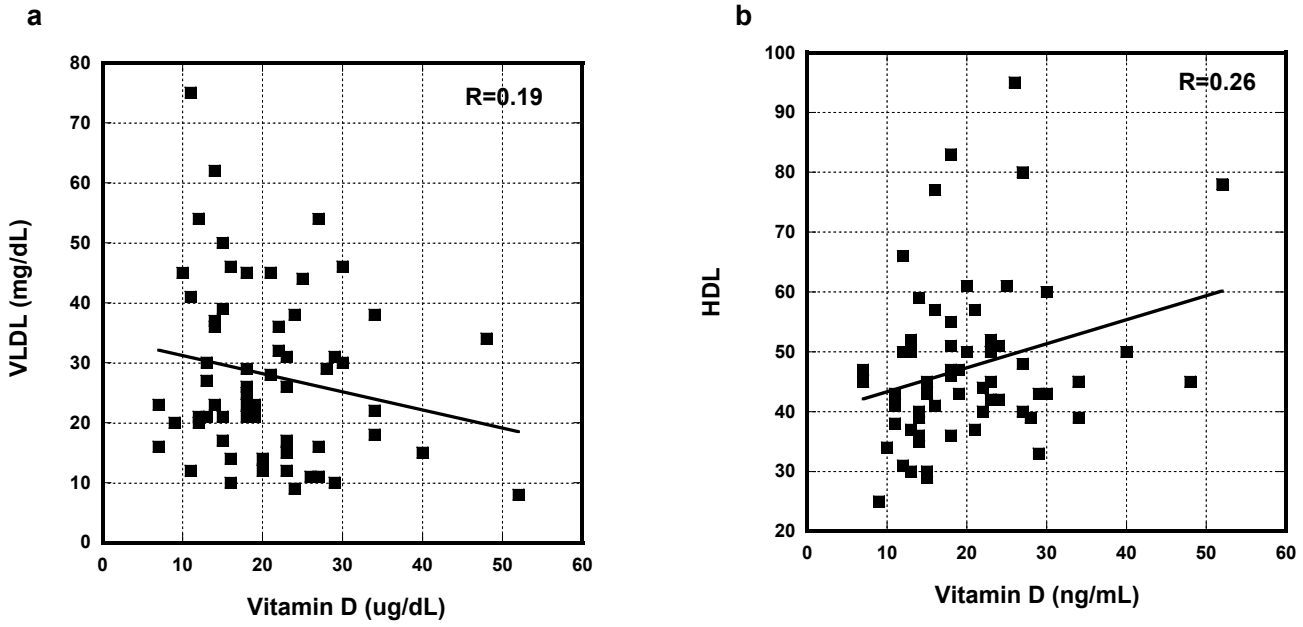

Figure 6a,b: Correlations between vitamin D and triglyceride, HDL and VLDL.

ng/ml showed decreases in triglycerides, cholesterol to HDL ratio, and improvements of HDL levels. This suggests that patients who are low in vitamin D also tend to have unfavorable cholesterol levels. Similar correlations were seen after one year of supplementation. In this case, participants with vitamin D levels above 40 ng/mL had triglyceride levels below 200 mg/dL.

Higher vitamin C levels were associated with lower triglyceride and VLDL levels. Lower vitamin C concentrations are associated with higher triglyceride and VLDL values. Data for triglycerides are shown in Figure 7.

According to these data, the changes in concentration of vitamin C and vitamin D in blood resulted in the improvement of lipids' profile. These changes also have a positive effect on the cardiovascular risk factors. On the basis of epidemiologic data, it is shown that each one percent reduction in LDL cholesterol results in a roughly one percent reduction in the risk of a major cardiovascular event. Similarly, each two percent increase in HDL is associated with a two percent reduction in cardiovascular event risk. If raising the HDL level and lowering the LDL level decreases cardiovascular event risk, and then participants in this study may have reduced their risks as a result of MVMM supplementation.

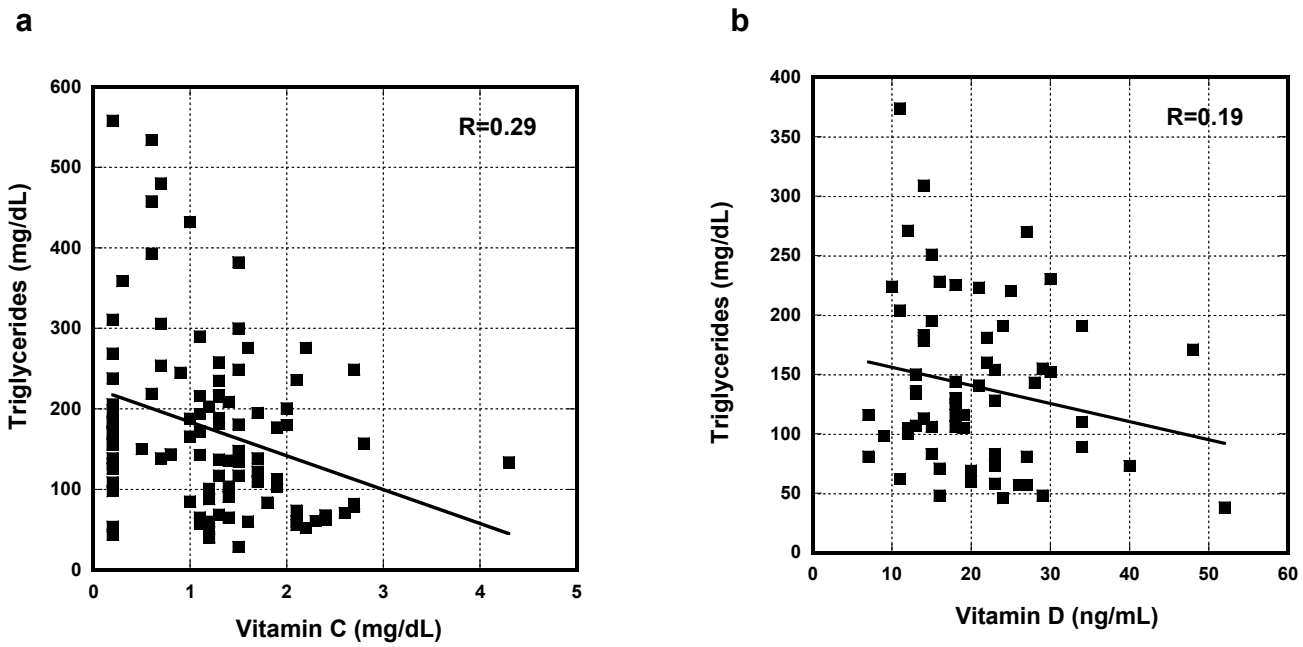

Figure 7a,b: Correlation between vitamins C, D and triglycerides.

Parameter	Normal Range	Initial	Final (12 Mo)	
A/G Ratio	1.1-2.5 (ratio)	1.83 ± 0.32	1.68 ± 0.32	†
Globulin	1.5-4.5 (g/dL)	2.47 ± 0.38	2.70 ± 0.36	†
Albumin	3.5-5.5 (g/dL)	4.41 ± 0.28	4.44 ± 0.36	
Total Prot.	6-8.5 (g/dL)	6.88 ± 0.38	7.13 ± 0.41	†
Bilirubin	0-1.2 (mg/dL)	0.59 ± 0.35	0.57 ± 0.39	
BUN	6-24 (mg/dL)	15.2 ± 5.3	13.8 ± 3.3	
Creatinine	0.57-1.27 (mg/dL)	0.88 ± 0.16	0.84 ± 0.13	
BUN/Creatinine	6-24 (ratio)	17.4 ± 4.6	16.7 ± 3.7	
Uric Acid	2.5-8.6 (mg/dL)	5.84 ± 1.4	5.66 ± 1.3	
Hemoglobin	12-17.3 (mg/dL)	15.4 ± 1.1	15.3 ± 1.3	
Hematocrit	39-55 (%)	44.8 ± 3.2	46.1 ± 3.9	†
MCH	34-36 (g/dL)	30.9 ± 1.4	30.3 ± 1.3	†
MCHC	31-37 (g/L)	34.5 ± 0.8	33.1 ± 0.8	†
MCV	80-100 (fL)	89.6 ± 3.2	91.6 ± 3.6	†
Platelets	140-440 (K/uL)	272 ± 60	290 ± 64	
RBC	4.3-5.9 (M/uL)	5.01 ± 0.41	5.04 ± 0.45	
WBC	4.6-11 (K/uL)	6.38 ± 2.01	6.84 ± 2.05	

Table 5: Concentrations of various blood chemistry and blood count parameters before and after MVMM supplementation. Errors are shown as standard deviations. Units and normal ranges are given. Crosses indicate values significantly different ($p < 0.05$) from pre-supplementation ("initial").

Effects of supplementation on blood chemistry and blood count parameters are shown in Table 5. In most cases, parameters were within the normal range before and after supplementation, with supplementation not appearing to have a dramatic effect.

According to our data there was a small increase in total proteins and globulin levels, which resulted in the decrease of albumin to globulin ratio. We consider that the probable explanation of this effect may be the increase in the level of inflammation in some participants (especially in smoking group). Another possibility is that during the one year of intervention some participants could develop infection, which results in overproduction of globulins. In addition, there were small changes in the average values of hematocrit, mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV). The increase in hematocrit values with improvement of MCV suggests the positive effect of supplementation, as the deficiencies of nutrients such as iron, folate, vitamin B12, and vitamin B6 decrease the hematocrit level.

Discussion

The data presented above provide information on how long term usage of MVMM supplements supplied by Pure North Foundation (Calgary, Canada) affects vitamin, mineral and lipid levels as well as the inflammation marker C - reactive protein. Blood concentrations of vitamin C, D, and E increased substantially as a result of supplementation, as did coenzyme Q10 levels, while lutein, lycopene, and vitamin A levels were not greatly affected. Supplement use yielded an increase in copper levels, along with a slight decrease in magnesium and zinc levels. We suspect that copper binds with organic molecules

more readily, and thus substitutes for the other essential minerals. The balance between "bad" and "good" cholesterol, as defined by the LDL/HDL ratio, slightly increased over the course of MVMM usage.

According to our data, participants with lower levels of vitamins D and C before supplementation tended to show higher levels of CRP, a non-specific inflammation marker. CRP concentrations directly correlate with disease activity and can contribute to disease progression through a range of pro-inflammatory properties [48-50]. Following an acute phase stimulus, CRP values may increase by as much as 10,000-fold by hepatic synthesis regulated by pro-inflammatory cytokines. IL-6 and CRP are related in that the former induces production of the latter by the liver during inflammation [51]. Published studies indicate that increasing CRP concentration from levels below 5mg/L to levels above 80 mg/L increases mortality risk three-fold [52]. Serum CRP concentrations in human subjects are inversely correlated with antioxidant nutrient concentrations [53]. CRP is thus a useful screening tool for organic disease, monitoring treatment responses, and detecting current infection.

Our data indicate that CRP levels, on average, increased slightly during MVMM supplementation. However, when subjects were split into "smoker" and "non-smoker" groups, the proportion of smokers who had CRP concentrations in the high risk category (concentrations above 3.8 mg/L) decreased during the course of the study. Smokers tended to have higher CRP levels prior to supplementation.

Looking into the distinction between smokers and non-smokers further, our data indicate that improvements in antioxidant levels during MVMM supplementation are less dramatic in smokers. Cigarette smoke contains oxidants and toxic derivatives of oxygen metabolism, the reactive oxygen species (ROS), which can induce oxidative stress in tissues [54]. Free radicals in smokers deplete plasma antioxidants in vitro [55,56], and several studies indicate lower plasma antioxidant concentrations in smokers in vivo [57-63]. Our data show that while both smokers and non-smokers were low in some antioxidants at the start of supplementation, and had a sub-optimal overall nutrient supply as indicated by low total health scores, antioxidant levels after MVMM supplementation were lower for smokers. Our results demonstrated that, after supplementation, smokers have lower plasma antioxidant concentrations than do nonsmokers. The greatest differences were found with lycopene, lutein, and vitamin A, while improvements in vitamin C, vitamin D and vitamin E were practically the same for both groups.

Analysis of the blood parameters did not show significant improvement. For chemistry profile, there was improvement in BUN and creatinine levels that may indicate on improvement of kidney functioning. Changes in lipid profiles tended to be correlated with improvements in vitamin D and vitamin C levels.

Finally, we developed the total health score metric in which blood nutrient concentrations are scaled according to where they fall in the observed ranges for healthy adults. The sum of values for vitamins, magnesium, zinc, and copper represent the subject's "Health Score". The results of the scores' statistics for participants before and after half year supplementation showed that percentage of participants with low health score (77%-62%) before supplementation was changed to 35%-26% after supplementation, meaning that more participants improved their nutrient levels. Smokers had less improvement of the health score in comparison with non-smokers. Half year and one year of supplementation eliminated very low scores, and dramatically increased the number of people with high scores.

The strength of the study is the way the group was selected, data were recorded or analysis performed. In our study the testing was performed the same way for three periods of treatment and for treated group and control group. The group of participants was selected by random selection from many industrial companies. We also suggest that the health score metric can be particularly useful in assessing the effect of multi-nutrient supplementation.

The addition of supplements was the only variable we directly manipulated in this study. While it is impossible to be certain in any study of this length that compliance was absolute or that subjects experienced no additional environmental or behavioral changes during the time frame of the study, participants did not report to us any significant changes in confounding variables nor did they indicate any issues with compliance. At the same morbidity and life style profile, the participants took supplementation during the long period of time and the health scores were measured before and after. We consider that the outcomes of the study can provide insights more generally to how other groups or populations might be affected by supplementation.

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Competing Interests

The authors have no direct financial interest in the subject matter discussed in the submitted manuscript.

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