Endocrinology & Metabolic Syndrome

Godala et al., Endocrinol Metab Syndr 2016, 5:5
DOI: 10.4172/2161-1017.1000254

Research Article Open Access

Metabolic Syndrome Increases the Risk of Plasma Vitamin A, C, E and D Deficiency

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Received date: January 04 2016; **Accepted date:** October 10, 2016; **Published date:** October 31, 2016

Abstract

The increasing incidence of metabolic diseases such as obesity or diabetes made them a major public health problem. Increasing oxidative stress induced by reactive oxygen species, which initiate the oxidative adverse changes in the cell, is mentioned, among other risk factors, to underlie these diseases. Vitamin A, C and E are listed among non-enzymatic mechanisms counteracting this phenomenon. Vitamin D deficiency is also associated with cardiovascular diseases.

Objectives: The aim of the study was to assess the risk of vitamin A, C, E and D deficit in plasma of metabolic syndrome (MS) patients.

Material and methods: The study included 191 patients with MS and 98 subjects without MS. Log-linear analysis was used in the assessment of mutual interactions between the vitamin concentration and the analysis of classification by ROC curves to predict the frequency of vitamin deficiency in MS patients.

Results: A correlation was found between the plasma level of vitamins in the group of MS patients. Vitamin A concentration correlated with that of vitamin C (r=0.51, p=0.0000), vitamin D (r=0.49, p=0.0000) and E (r=0.32, p=0.0001). The plasma level of vitamin D correlated with the level of vitamin E (r=0.46, p=0.00000) and vitamin C (r=0.37, p=0.0000). Regression analysis showed a correlation between the concentration of the tested vitamins in patients with MS. Interactions were observed between vitamins C-A and C-D. HDL cholesterol level was lower in patients with vitamin A deficiency compared to patients with its normal level.

Conclusions: The plasma levels of vitamin A, C, E and D were significantly lower in patients with MS than in healthy subjects and they mutually correlated with each other. The normalization of glucose and HDL level may contribute to the regulation of the concentration of vitamin A in patients with MS.

Keywords: Metabolic syndrome; Antioxidant vitamins; Vitamin D deficiency

Introduction

The increasing incidence of metabolic diseases such as obesity or diabetes made them a major public health problem. Accumulation of metabolic risk factors for atherosclerosis, known as metabolic syndrome (MS), has been known for a long time. Increasing oxidative stress induced by reactive oxygen species (ROS), which initiate the oxidative adverse changes in the cell, is mentioned, among other risk factors, to underlie these diseases. Free radicals damage the structure and function of nucleic acids, lipids, proteins and sugars, which in turn leads to changes in the genetic material and to the incidence of cancer, cardiovascular , respiratory and eye diseases and may accelerate the aging process. To defend itself against ROS the body uses its own antioxidant system as well as antioxidants consumed in the diet. Vitamin A, C and E are listed among non-enzymatic mechanisms counteracting this phenomenon [1,2].

Vitamin D deficiency is associated with cardiovascular diseases. Its receptors are located in many organs and tissues and numerous studies have shown that there is an inverse correlation between serum 25 (OH) Dlevel and the occurrence of MS. Vitamin D is involved in the regulation of blood pressure and it is thought to influence lipid metabolism and insulin secretion. Furthermore, numerous studies have shown that its concentration in obese individuals, especially those with abdominal obesity, is significantly lower than among those of normal body composition. Thus, the plasma 25 (OH) D level has a significant impact on all components of MS. Supplementation of vitamin D: alone or in combination with Ca: as a strategy for the prevention of cardiovascular diseases raises considerable debate [3,4].

The aim of the study was to assess the risk of vitamin A, C, E and D deficit in plasma of MS patients.

Subjects and Methods

Study population

The study included 191 patients with MS recruited from the Department of Internal Medicine and Nephrodiabetology, Medical University of Lodz, 101 men and 90 women, aged 30-65 years (mean 56.73 ± 7.51 years).

The control group comprised 98 subjects, 54 men and 44 women, aged 41-65 years (mean 57.45 ± 5.24 years), clinically healthy, without MS.

All of them were nonsmokers and in the last year they did not take any dietary supplements.

Metabolic syndrome (definition)

The MS diagnosis was based on IDF (International Diabetes Federation) criteria, stating the type of central obesity (waist circumference in women ≥ 80 cm, in men ≥ 94 cm) and two of the following risk factors: triglycerides ≥ 1.7 mmol/l or treatment of this disorder, low HDL cholesterol (in women <1.3 mmol/l, in men <1.0 mmo/l) or treatment of the disorder, fasting glucose level ≥ 6.1 mmol/l or treated type 2 diabetes, blood pressure ≥ 130/85 mmHg or treatment of hypertension [5].

Biochemical analyses

The mean of three blood pressure readings (systolic and diastolic) were measured using a mercury sphygmomanometer.

Fasting blood glucose was determined with a reaction between glucose and ATP catalyzed by hexokinase; TG concentration was enzymatically measured with coupled reactions in which TG was hydrolyzed to produce glycerol; TC was measured with reactions using cholesteryl ester hydrolase, cholesterol oxidase, and peroxidase; HDL was measured using a heparin-manganese precipitation method; LDL was assessed using Friedewald rule.

The concentration of 25-hydroxy vitamin D (25-OH-D) was assessed with the application of the LIAISON® test using chemiluminescent immunoassay (CLIA) technology. The plasma level of 25(OH) D above 30 ng/ml was considered normal, between 20 ng/ml and 30 ng/ml suboptimal (hipovitaminosis) and below 20 ng/ml insufficient (deficiency) [3].

In all patients, the determinations of the serum level of vitamin A, C and E were performed by spectrophotometric method using a spectrophotometer T60V (PG Instruments) according to the modified Rutkowski et al. method [6-8]. Plasma levels of the investigated vitamins were given in µmol/l. Plasma vitamin deficiency was stated for vitamin A <0.9 µmol/l, for vitamin C <36.1 µmol/l and for vitamin E<12 µmol/l [6-8].

Anthropometry analyses

Height was measured using a fixed stadiometer and weight was taken with individuals wearing light clothes and no shoes on a digital scale with a capacity of 200 kg and accurate to the nearest 100 g. Body mass index (BMI) was calculated as weight (kilograms) divided by height in meters squared. Waist circumference was measured at the midpoint between the bottom of the rib cage and above the top of the iliac crest during minimal respiration.

Statistical analyses

Statistical analysis was performed using Statistica 7.1 PL and Office 2010 software. The normal distribution was determined using the Shapiro-Wilk test. The variables not normally distributed underwent logarithmic transformation (log10) before statistical analysis. The comparison between the means of two independent groups was performed using Student's t test and Mann-Whitney U test for continuous variables, chi-square test was applied for dichotomic ones. Correlations were assessed by Pearson's coefficient (r).

Log-linear analysis was used in the assessment of mutual interactions between the vitamin concentration and the analysis of classification by ROC curves (Receiver Operating Characteristic) to predict the frequency of vitamin deficiency in MS patients

Logistic regression analysis with the estimation of the odds ratio was applied in the assessment of the effect of MS parameters on the risk of vitamin A, C, E and D deficiency. $p < 0.05$ was considered as statistically significant.

The study was approved by the Bioethics Committee of the Medical University in Lodz (No:RNN/556/10/KB).

Results

The study included 191 patients with MS and 98 controls without MS. Table 1 presents characteristics of the tested subjects. As expected, BMI, waist circumference, systolic and diastolic blood pressure, the level of blood glucose, TG and LDL cholesterol were higher in MS patients, whereas HDL level was lower than in subjects without MS. There were no significant differences in total cholesterol concentration in MS patients and controls. Gender and age of the tested subjects did not differentiate significantly the investigated parameters. Mean concentrations of all studied vitamins were significantly lower in patients with MS than in the control group. Deficiency of the tested vitamins was observed significantly more frequently among the MS patients (Table 1). Gender and age did not affect either the mean concentrations of the tested vitamins or the incidence of their deficiency.

Characteristics	MS (n=191)	Without MS (n=98)	p-value
	Mean ± SD/%(n)	Mean ± SD/%(n)	
Age [years]	56.73 ± 7.51	57.45 ± 5.24	0.5347[a]
Sex [% women]	47.12 (90)	44.90 (44)	0.3187[a]
BMI [kg/m^2]	35.16 ± 5.91	28.04 ± 2.52	<0.0001[a]
Waist [cm]	114.34 ± 10.78	95.96 ± 11.21	<0.0001[a]
SBP [mmHg]	145.98 ± 17.45	127.87 ± 11.65	<0.0001[b]

DBP [mmHg]	88.72 ± 9.25	81.52 ± 7.47	<0.0001[b]
Glc [mmol/l]	7.68 ± 2.28	5.12 ± 0.57	<0.0001[b]
TG [mmol/l]	1.98 ± 0.72	1.45 ± 0.16	<0.0001[b]
TC [mmol/l]	4.39 ± 1.16	4.49 ± 0.79	0.8171[a]
HDL [mmol/l]	1.07 ± 0.21	1.32 ± 0.31	<0.0001[a]
LDL [mmol/l]	2.93 ± 0.84	2.76 ± 0.72	<0.0001[a]
25(OH)D [ng/ml]	13.54 ± 7.91	27.71 ± 10.26	<0.0001[a]
Vitamin A [µmol/l]	1.368 ± 0.35	1.821 ± 0.575	<0.0001[a]
Vitamin C [µmol/l]	31.14 ± 8.91	57.83 ± 17.85	<0.0001[a]
Vitamin E [µmol/l]	12.69 ± 2.46	25.61 ± 2.98	<0.0001[a]
25(OH)D deficiency [%]	81.15 (155)	23.47 (23)	<0.0001[c]
Vitamin A deficiency [%]	15.71 (30)	1.02 (10	<0.0001[c]
Vitamin C deficiency [%]	79.58 (152)	8.16 (8)	<0.0001[c]
Vitamin E deficiency [%]	40.31 (77)	1.02 (1)	<0.0001[c]
[a]Student's t test, [b]Mann-Whitney U test, [c]χ^2 test			

Table 1: Characteristics of study participants.

A correlation was found between the plasma level of vitamins in the group of MS patients. Vitamin A concentration correlated with that of vitamin C (r=0.51, p=0.0000), vitamin D (r=0.49, p=0.0000) and E (r=0.32, p=0.0001). The plasma level of vitamin D correlated with the level of vitamin E (r=0.46, p=0.00000) and vitamin C (r=0.37, p=0.0000). No correlation was observed between plasma level of vitamin C and E.

Regression analysis showed a correlation between the concentration of the tested vitamins in patients with MS. Interactions were observed between vitamins C-A and C-D (Figure 1).

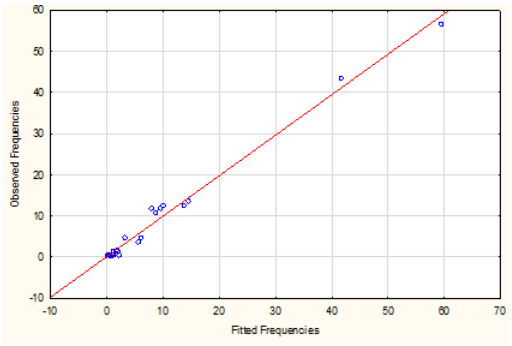

Figure 1: Log-linear correlation between the level of vitamin A, C, E and D in the plasma of MS patients.

Moreover, on the basis of the data on vitamin A, C, E and D deficiency/normal plasma levels there was determined the predicted incidence of their deficiency in patients with MS. The highest predictive value was obtained for vitamin E, then for vitamin C and D and the lowest - for vitamin A (Figure 2).

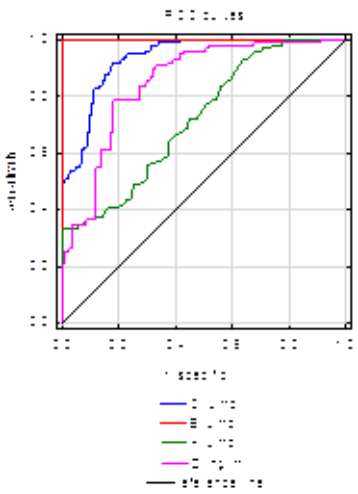

Figure 2: Predicted prevalence of vitamin A, C, E and D deficiency in MS patients.

The vitamin C level was lower in patients with vitamin A deficiency in relation to patients with normal vitamin A level (22.20 ± 3.60 µmol/l *vs.* 32.88 ± 10.99 µmol/l, p=0.0003) and the concentration of vitamin A was lower in patients with vitamin C deficiency compared to patients with its normal level (1.34 ± 0.42 µmol/L *vs.* 1.77 ± 0.29 µmol/L,

p=0.009). It has been demonstrated that vitamin C deficiency increased 3.5-fold the risk of vitamin A deficiency in patients with MS.

HDL cholesterol level was lower in patients with vitamin A deficiency compared to patients with its normal level (0.76 ± 0.41 mmol/L *vs.* 1.10 ± 0.29 mmol/L, p=0.03). It was also found that individuals with vitamin A deficiency have higher glucose concentration than MS patients with normal vitamin A level (8.91 ± 3.58 mmol/l *vs.* 6.75 ± 5.56 mmol/l, p=0.04) and hyperglycemia increased 6-fold the risk of vitamin A deficiency.

Discussion

Reactive oxygen species (ROS), natural product of cellular metabolism, may have a beneficial effect on cell function (help fight infections, as secondary transmitters stimulate cellular signal transduction pathways) or can be the etiological factor of metabolic disorders.

Adverse effects are associated with excessive lipid peroxidation, protein and DNA damage which disrupts cell proper functioning. The effect of ROS ctivity depends on the efficiency of antioxidant mechanisms in the cell. In addition to the enzymatic mechanisms, such as superoxide dismutase, glutathione peroxidase and catalase, there are non-enzymatic mechanisms, which include vitamins A, C and E.

Antioxidant vitamins are an important element of the body non-enzymatic antioxidant barrier and their proper concentration determines the protection against ROS. It results from our previous studies and the studies by other authors that the concentrations of vitamins A, C and E are lower in patients with cardiovascular diseases than in healthy subjects, even with their appropriate intake from the diet [1,2,9]. Cardiovascular and metabolic diseases are also thought to be associated with vitamin D deficiency. Although vitamin D is not included into antioxidant vitamins, it results from the research studies carried out in different countries that it has an impact on the components of MS and its concentration in patients with metabolic disorders is significantly lower than in the group of healthy individuals [4,10]. In our study, we attempted to assess the risk of deficiency of these vitamins in patients with MS.

We found among MS patients a significant deficiency of all investigated vitamins, both as regards their mean concentrations (significantly lower compared to healthy subjects) and the frequency of their deficiency levels. Low levels of vitamin A, C and E in patients with cardiovascular diseases were observed by other authors [11-14], but there have been no studies that would assess the scale of the phenomenon, that is the prevalence of the deficiency of antioxidant vitamins in the population of healthy subjects and those with MS. Vitamin D has been discussed in literature more often. Its low levels in MS patients have been demonstrated in numerous studies [15-17] and the prevalence of its deficiency is defined as common not only among patients with cardiovascular diseases, but also in the healthy population [18-20].

The problem of simultaneous occurrence of the deficiency of antioxidant vitamins in MS patients requires further research. In our study we have shown a correlation between vitamin A, C, E and D level in patients with MS. The strongest correlations were observed between the plasma level of vitamin A and D, D and E and A and C. We have also evaluated the risk of the deficiency of the tested vitamins in patients with MS and the highest prediction value of deficiency level was obtained for vitamin E, whereas the lowest - for vitamin A. Moreover, we have shown that the concentration of vitamin C was lower in patients with deficiency of vitamin A and vitamin C deficiency 3.5-fold increased the risk of vitamin A deficiency.

In the available literature there are studies on the interactions that occur between antioxidant vitamins to prevent mutual degradation or promote regeneration. Vitamin C is an essential cofactor in many processes of systemic biosynthesis. It participates in metabolic processes as a substance transferring electrons, interacts in the synthesis of collagen, is involved in the metabolism of fats, cholesterol and bile acids. Vitamin C has proven to be one of the most potent antioxidants. Coupled pair of its forms - the oxidized and reduced - creates a redox system capable of reducing ROS that are toxic to cells [1,9]. Furthermore, it has been shown that ascorbic acid is involved in the regeneration of hydrophobic antioxidants, such as α-tocopherol and β-carotene from the radical form. It is assumed that this reaction takes place on the surface of cell membranes. Ascorbate reduces tocopherol radical creating ascorbyl radical. This reaction is possible because of chroman rings in tocopherol molecules which face the outside of the cell membrane and can react with ascorbate found in an aqueous medium. Also, vitamin E protects retinol esters from oxidation, which is conducive to maintaining its proper concentration [21]. In our study, we found no correlation between the concentration of vitamin C and vitamin E. It can result from the fact that in MS patients ascorbic acid regenerating α-tocopherol undergoes degradation [22].

Among the components of MS the level of glucose and HDL-cholesterol affected the concentration of vitamin A. Thus, subjects with vitamin A deficiency had lower HDL-cholesterol levels and higher glucose concentration. It was also shown that hyperglycemia increased up to 6-fold the risk of vitamin A deficiency in these patients. Vitamin A is a set of compounds that includes retinol, retinal and carotenoids. Vitamin A antioxidant properties have been frequently reported in vivo and in vitro [23,24]. They are exhibited at low (physiological) oxygen partial pressure. Retinol can react with peroxide radicals (ROO •), thereby it interrupts the chain reaction of lipid peroxidation to form hydroperoxides (ROOH). Furthermore, vitamin A is capable of directly reacting with ROS to form a 5,6-epoxide retinoid [24]. Carotenoids also exhibit potent antioxidant properties. In addition to their capacity to scavenge peroxyl radicals (ROO •) they are effective singlet oxygen quenchers [23]. An inverse correlation between vitamin A and E level and the risk of cardiovascular diseases was found in many case-control and prospective observational studies [1,9,12]. This protective effect was attributed to their antioxidant properties. However, clinical trials that evaluated interventions designed to confirm the cause-effective nature of these correlations failed to confirm the results of observational studies [25]. There appeared reports of New York researchers from Weill Cornell Medical College, who showed that low level of vitamin A can lead to degradation of pancreatic β cells producing insulin in patients with type 2 diabetes. This means faster progressive development of the disease and a higher risk of complications [26]. The research was conducted on laboratory animals diagnosed with pancreatic β-cell atrophy after elimination of vitamin A from the diet. After its reintroduction into the diet, pancreatic β cells began to regenerate. Numerous clinical studies have demonstrated the important role of vitamin A in the production of pancreatic cells in fetal life, but there are no studies that would confirm this relationship in adults. Still, it has not been clarified whether vitamin A deficiency results from its participation in the pathogenesis of diabetes, inadequate intake from the diet or from the metabolic defect. The question of the possible involvement of vitamin A

deficiency in the pathogenesis of diabetes mellitus type 1 and 2 will require further studies.

Further research is also needed to assess the validity and effectiveness of possible implementation of antioxidant vitamin supplements in these patients. Although our studies suggest such a need, the results of studies available in the literature on the effect of vitamin supplements on cardiovascular complications are contradictory. Some authors showed reduction in oxidative stress, decrease of the risk of cancer and cardiovascular diseases and reduced overall mortality after application of antioxidant vitamin (A,C,E) supplements [22,27,28]. Other studies demonstrated that the effect of vitamins depends on many factors, such as smoking, exposure to environmental chemicals, rate of the deficiency of supplemented vitamins or a dose of vitamin preparations and their type [29,30]. Uncontrolled - excessive use of antioxidant vitamin supplements, especially in patients with corrected deficiency, often results in different effect, i.e. the intensification of oxidative stress and increased risk of cardiovascular complications. Exceptionally frequently this type of adverse effects is attributed to vitamin C and E [28-30]. Thus, the key issue when planning vitamin supplementation in patients with MS seems to be the dosage and preparation composition determined on individual basis.

Conclusions

The plasma levels of vitamin A, C, E and D were significantly lower in patients with MS than in healthy subjects and they mutually correlated with each other. Particular correlation was found between vitamin A and C, at the same time vitamin C deficiency increased 3.5-fold the risk of vitamin A deficiency in these patients. Moreover, we have shown that hyperglycemia increased the risk of vitamin A deficiency and the concentration of HDL cholesterol was significantly lower in patients with this vitamin deficiency. Thus, the normalization of glucose and HDL level may contribute to the regulation of the concentration of vitamin A in patients with MS.

Acknowledgement

The study financed by the Medical University in Lodz (research task No: 502-03/6-024-02/502-64-050).

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