Original Communication

Vitamin D Supplementation and Serum Levels of Magnesium and Selenium in Type 2 Diabetes Mellitus Patients: Gender Dimorphic Changes

Nasser M. Al-Daghri[1,2,3], Khalid M. Alkharfy[1,2,4], Nasiruddin Khan[2], Hanan A. Alfawaz[1,5], Abdulrahman S. Al-Ajlan[6], Sobhy M. Yakout[1], and Majed S. Alokail[1,2,3]

[1]Prince Mutaib Chair for Biomarkers of Osteoporosis, Biochemistry Department, College of Science, King Saud University, Riyadh, Saudi Arabia
[2]Biomarkers Research Program, Biochemistry Department, College of Science, King Saud University, Riyadh, Saudi Arabia
[3]Center of Excellence in Biotechnology Research, King Saud University, Riyadh, Saudi Arabia
[4]Clinical Pharmacy Department, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[5]College of Food Science & Agriculture, Department of Food Science & Nutrition, King Saud University, Riyadh, Saudi Arabia
[6]Riyadh College of Health Sciences, King Saud University, Ministry of Higher Education, Riyadh, Saudi Arabia

Received: December 22, 2013; Accepted: May 5, 2014

Abstract: The aim of our study was to evaluate the effects of vitamin D supplementation on circulating levels of magnesium and selenium in patients with type 2 diabetes mellitus (T2DM). A total of 126 adult Saudi patients (55 men and 71 women, mean age 53.6 ± 10.7 years) with controlled T2DM were randomly recruited for the study. All subjects were given vitamin D3 tablets (2000 IU/day) for six months. Follow-up mean concentrations of serum 25-hydroxyvitamin D [25-(OH) vitamin D] significantly increased in both men (34.1 ± 12.4 to 57.8 ± 17.0 nmol/L) and women (35.7 ± 13.5 to 60.1 ± 18.5 nmol/L, $p < 0.001$), while levels of parathyroid hormone (PTH) decreased significantly in both men (1.6 ± 0.17 to 0.96 ± 0.10 pmol/L, $p = 0.003$) and women (1.6 ± 0.17 to 1.0 ± 0.14 pmol/L, $p = 0.02$). In addition, there was a significant increase in serum levels of selenium and magnesium in men and women (p-values < 0.001 and 0.04, respectively) after follow-up. In women, a significant correlation was observed between delta change (variables at six months-variable at baseline) of serum magnesium versus high-density lipoprotein (HDL)-cholesterol ($r = 0.36$, $p = 0.006$) and fasting glucose ($r = -0.33$, $p = 0.01$). In men, there was a significant correlation between serum selenium and triglycerides ($r = 0.32$, $p = 0.04$). Vitamin D supplementation improves serum concentrations of magnesium and selenium in a gender-dependent manner, which in turn could affect several cardiometabolic parameters such as glucose and lipids.

Key words: hypovitaminosis D, magnesium, selenium, diabetes, Saudi Arabia

Introduction

The high prevalence of vitamin D deficiency in the kingdom of Saudi Arabia is ironically exacerbated by summer season in that geographical region [1]. This hypovitaminosis D predisposes the general Saudi population to risk factors associated with osteoporosis, type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome, and cardiovascular diseases [2, 3].

The measurement of 25-(OH) vitamin D concentration in the serum or plasma is considered the best indicator of vitamin D nutritional status [4]. Circulating vitamin D is regulated through the interaction of various factors, including intestinal absorption and renal function, as well as serum calcium and parathyroid hormone (PTH) levels [5, 6], although the latter may not be true for the Saudi population [7].

Serum magnesium has well-established actions in the modulation of calcium transport; sub-optimum levels have been speculated to have a causal link to pathological conditions such as obesity [8], osteoporosis [9], atherosclerosis, hypertension [10], and T2DM [11]. However, controversial results have been reported in showing a positive dose-response [12], as well as an inverse relation [13] between magnesium intake and risk of T2DM, respectively. It has been postulated that vitamin D may play a major role in the regulation of magnesium absorption [14].

Farhanghi and colleagues demonstrated that vitamin D supplementation in obese individuals improved low serum magnesium levels [15], while Rude and colleagues showed that low serum 1,25-(OH)2D concentrations are associated with magnesium deficiency [16]. On the contrary, Wilz and colleagues reported no association between plasma 1,25-(OH)2D concentrations and magnesium absorption [17].

Selenium has known roles in thyroid and immune function [18], while serum levels have been associated with cardiovascular risk [19] and hypertension [20]. Like magnesium, the relation between circulating levels of selenium and T2DM is controversial with mixed findings [21–23]. Mykkanen and colleagues demonstrated an increase in selenite (inorganic form of selenium) uptake by cholecalciferol treatment [24].

We previously demonstrated that oral vitamin D3 supplementation (2000 IU/day) significantly improved the metabolic profile with favorable changes in high-density lipoprotein/low-density lipoprotein (HDL/LDL) ratio in T2DM patients, particularly in women [25], with changes modestly affected by the type of T2DM regimen [26]. Taken from the same cohort, the objective of this present study was to investigate the relation between oral vitamin D supplementation and serum levels of magnesium and selenium and other biochemical variables in men and women with T2DM.

Materials and methods

Study population

A total of 126 adult Saudi patients (55 men and 71 women) with controlled T2DM (HbA1c < 7.0 or T2DM duration < 1 year), were randomly selected from an existing Vitamin D Study database of the Prince Mutaib Chair for Biomarkers of Osteoporosis (PMCO) in King Saud University, Riyadh, Kingdom of Saudi Arabia [25, 26]. In brief, subjects were recruited from several primary health care centers across Riyadh, KSA. Subjects using mineral oil products, taking antacids regularly, receiving glucocorticoids or other steroids, diuretics, weight-loss drugs, phenobarbital and phenytoin, having liver problems, gallbladder disease, or gastrointestinal disorders, and taking vitamin D supplements or multivitamins were excluded from the study. A general questionnaire, including past and present medical history, was administered to subjects followed by a physical examination. All subjects were given a six-month supply of 2000 IU Vitamin D3 tablets (Vigantoletten; Merck Pharma, Germany) to be taken daily, and were instructed to return to their assigned primary care center for repeat assessments. Written and informed consents were taken before inclusion. Ethics approval was obtained from the ethics committee of the College of Medicine Research Center at King Saud University, Riyadh, KSA.

Anthropometry was also measured at baseline and after 6 months and included height (to the nearest 0.5 cm), weight (to the nearest 0.1 kg), waist and hip circumference utilizing a standardized measuring tape in cm, and systolic and diastolic blood pressure measurements. Body mass index (BMI) was calculated as weight in kg divided by height in square meters.

Biochemical analysis

Fasting blood samples were collected at baseline and after 6 months of vitamin D supplementation for quantification of different metabolic parameters. Fasting blood glucose, lipid profile, inorganic phosphate (Pi), and magnesium concentrations were measured routinely using a chemical analyzer (Konelab, Espoo, Finland). Intact PTH and 25(OH)D were measured by specific ELISAs in accordance with the instructions

Table I: General characteristics of the subjects at baseline and after six months of vitamin D supplementation.

	Baseline	6 Months	P
N	126		
Age (years)	53.6 ± 10.7		
BMI (kg/m^2)	30.8 ± 4.8	30.8 ± 4.6	0.81
Hips (cm)	109.5 ± 8.0	111.5 ± 12.8	0.34
Waist (cm)	107.5 ± 10.6	105.4 ± 8.8	0.18
Systolic BP (mmHg)	126.7 ± 14.1	124.8 ± 16.4	0.22
Diastolic BP (mmHg)	80.5 ± 8.3	78.6 ± 8.8	0.05
Total Cholesterol (mmol/L)	5.2 ± 1.0	5.1 ± 1.2	0.41
LDL-cholesterol (mmol/L)	4.1 ± 0.93	3.9 ± 0.96	0.39
HDL-cholesterol (mmol)	1.0 ± 0.29	0.96 ± 0.26	0.28
Triglycerides (mmol/L)	2.1 ± 0.96	1.9 ± 0.96	0.11
Glucose (mmol/L)	10.8 ± 4.1	11.1 ± 4.8	0.48
25 (OH) vitamin D (nmol/L)	35.4 ± 13.0	59.5 ± 17.8	<0.001
PTH (pmol/L)	1.62 ± 0.11	1.0 ± 0.10	<0.001
Ca (mmol/L)	2.4 ± 0.30	2.5 ± 0.28	0.22
Corrected Calcium (mmol/L)	2.3 ± 0.23	2.4 ± 0.19	0.01
Pi (mmol/L)	1.16 ± 0.21	1.15 ± 0.23	0.73
Magnesium (mmol/L)	0.71 ± 0.10	0.74 ± 0.11	0.03
Selenium (ng/mL)	100.8 ± 35.1	102.6 ± 36.2	0.68

Data represented as Mean ± standard deviation. Level of significance is given by $P \leq 0.05$.

BMI – body mass index, BP – blood pressure, LDL – low-density lipoprotein, HDL – high-density lipoprotein, PTH – parathyroid hormone, Pi – inorganic phosphate.

provided by the manufacturer (IDS, Tyne & Wear, UK). The inter- and intra-assay variabilities were 5.8 % and 3.4 % for the intact PTH, and 5.3 % and 4.6 % for the 25(OH)D, respectively. For the purpose of this study, a serum 25(OH)D levels of >40 nm for women and >35 nm for men are considered normal [27].

Determination of Selenium in serum samples

Serum Se level was determined using Shimadzu graphite furnace atomic absorption spectrometry (Shimadzu, Model: AA- 7000 series) equipped with auto sampler [28]. Pyrolytically coated tubes were used as atomizers. The conditions for selenium were: A Shimadzu selenium hollow cathode lamp with wavelength of 196.0 nm, lamp current: 290 mA, slit width: 2.0 nm, matrix modifier was palladium [28]. The detection limit of the method was less than 5 μg/L, precision < 11 %, and inaccuracy < 1 %. Samples were diluted in proportion 1:10 with a special reducing reagent containing ascorbic acid, Triton X-100, and Antifoam B Emulsion in deionized water to improve the sample viscosity and reproducibility of the results. Stock standard solutions for selenium were prepared from the commercial Se standard (1000 mg/L) purchased from Solution Acros Organics (USA). The working standard solutions were prepared weekly by appropriate dilution and kept refrigerated at 4°C. Argon was applied as a protective gas and 10 μL samples were injected into the graphite furnace (GF). All samples were analyzed in duplicate. Human reference serum (Seronorm™Trace Elements in Serum) from Sero AS (Billingstad, Norway) was used to check the entire proposed analytical method reliability. This reference material was supplied in lyophilized form and reconstituted by dissolving the vial total content using high purity deionized water. The results for the reference sample agreed with the certified acceptable range of selenium concentration.

Statistical analyses

Data was analyzed using SSPS for Windows version 16.0 (Chicago, IL, USA). Variables exhibiting non-Gaussian distribution were logarithmically transformed. Paired Student's *t*-tests were performed to compare the baseline and follow-up period variables.

Pearson's correlation was used to compare the delta change of variables (at six months – baseline variables). A two-tailed probability value of 0.05 was considered significant.

Results

The basic characteristics of the subjects are shown in Table I. The mean age was 53.6 ± 10.7 years. The level of 25(OH)D, serum magnesium, and corrected calcium was significantly higher after six months of follow-up, than at baseline (p-values < 0.001, 0.03, < 0.001, and 0.01, respectively). After stratifying by gender, the mean serum 25(OH)D ($p < 0.001$) and magnesium ($p = 0.04$) significantly increased while PTH concentrations ($p = 0.02$) decreased significantly in women after 6 months of vitamin D supplementation. In men, PTH levels significantly decreased ($p = 0.003$) after 6 months, and a significant increase in serum 25-hydroxyvitamin D, corrected calcium, phosphorus, and selenium (p-values < 0.001, 0.01, 0.04, < 0.001, respectively) were also observed (Table II).

Correlation between the changes in magnesium, selenium and biochemical variables

A significant correlation was observed between delta changes of serum magnesium levels with HDL-cholesterol ($r = 0.36$, $p = 0.006$) and fasting glucose ($r = -0.33$, $p = 0.01$) in women. In men, there was a significant correlation between delta changes of serum selenium and triglyceride levels ($r = 0.32$, $p = 0.04$) (Table III). Moreover, a significant correlation between delta changes of serum 25-hydroxyvitamin D and PTH ($r = -0.28$, $p = 0.03$ and $r = -0.26$, $p = 0.03$) were observed for all subjects.

Table II: Gender-based stratification of anthropometric and biochemical variables, and trace elements (magnesium and selenium) at baseline and after six months of oral vitamin D supplementation.

	Women			Men		
	Baseline	6 Months	P	Baseline	6 Months	P
N	71			55		
Age (years)	52.1 ± 10.1			54.2 ± 10.6		
BMI (kg/m^2)	33.1 ± 6.7	33.8 ± 5.7	0.12	30.6 ± 4.9	30.7 ± 5.4	0.60
Hips (cm)	108.4 ± 8.0	112.0 ± 14.3	0.38	110.5 ± 8.3	111.1 ± 12.6	0.43
Waist (cm)	105.8 ± 11.8	104.4 ± 8.9	0.53	109.9 ± 8.7	106.6 ± 9.2	0.19
Systolic BP (mmHg)	129.0 ± 14.5	127.2 ± 16.5	0.42	124.2 ± 13.5	122.3 ± 16.2	0.30
Diastolic BP (mmHg)	81.5 ± 7.7	79.8 ± 9.5	0.17	79.6 ± 9.0	77.3 ± 8.1	0.14
Total Cholesterol (mmol/L)	4.9 ± 1.2	4.5 ± 0.92	0.52	5.2 ± 1.1	5.1 ± 1.3	0.71
LDL-cholesterol (mmol/L)	4.1 ± 0.89	4.1 ± 1.0	0.98	4.0 ± 1.2	3.7 ± 1.0	0.17
HDL-cholesterol (mmol)	1.0 ± 0.26	1.0 ± 0.26	0.52	1.0 ± 0.35	0.97 ± 0.22	0.36
Triglycerides (mmol/L)	1.9 ± 0.13	2.1 ± 0.11	0.19	1.9 ± 0.12	2.1 ± 0.13	0.21
Glucose (mmol/L)	10.8 ± 3.8	11.6 ± 4.3	0.18	10.3 ± 4.5	10.3 ± 4.3	0.93
25 (OH) vitamin D (nmol/L)	35.7 ± 13.5	60.1 ± 18.5	< 0.001	34.1 ± 12.4	57.8 ± 17.0	< 0.001
PTH (pmol/L)	1.6 ± 0.17	1.0 ± 0.14	0.02	1.6 ± 0.17	0.96 ± 0.10	0.003
Ca (mmol/L)	2.4 ± 0.33	2.5 ± 0.23	0.21	2.5 ± 0.26	2.5 ± 0.34	0.50
Corrected Calcium (mmol/L)	2.4 ± 0.23	2.4 ± 0.17	0.10	2.3 ± 0.19	2.4 ± 0.21	0.01
Pi (mmol/L)	1.17 ± 0.15	1.18 ± 0.23	0.59	1.18 ± 0.22	1.09 ± 0.21	0.04
Magnesium (mmol/L)	0.70 ± 0.06	0.74 ± 0.10	0.04	0.74 ± 0.11	0.75 ± 0.11	0.85
Selenium (ng/mL)	75 ± 41.2	87.9 ± 33.0	0.42	86.6 ± 35.0	112.2 ± 37.3	< 0.001

Data represented as mean ± standard deviation. Level of significance is given by $p \leq 0.05$.

Table III: Gender-based Correlations between Delta Change in Trace Elements and Anthropometric and Biochemical Variables.

	Women				Men			
	Δ 25 (OH) vitamin D	ΔMg	Δ Pi	ΔSe	Δ 25 (OH) vitamin D	ΔMg	Δ Pi	ΔSe
	r	r	r	r	r	r	r	r
Δ BMI	−0.31*	−0.22	0.12	0.09	−0.28*	−0.16	0.13	−0.18
Δ Hips (cm)	−0.41**	−0.18	0.11	0.14	−0.24	−0.29	0.19	0.13
Δ Waist (cm)	−0.26*	−0.17	0.15	0.05	−0.29*	−0.12	0.12	0.10
Δ Systolic BP (mmHg)	−0.07	−0.13	0.08	0.15	−0.08	−0.20	−0.10	0.23
Δ Diastolic BP (mmHg)	−0.21	−0.08	0.07	0.07	−0.09	−0.21	−0.21	0.11
Δ Cholesterol (mmol/L)	−0.15	0.16	0.05	−0.13	−0.29*	0.08	0.43**	−0.13
Δ LDL-cholesterol (mmol/L)	−0.11	0.07	−0.23	0.21	−0.18	−0.10	0.28	0.27
Δ HDL-cholesterol (mmol)	0.09	0.36**	0.14	0.17	0.10	0.13	0.38*	−0.24
Δ Triglycerides (mmol/L)	−0.15	−0.13	0.31*	0.22	−0.22	−0.06	0.13	0.32*
Δ Glucose (mmol/L)	−0.11	−0.33*	−0.19	0.27	−0.23	−0.02	−0.22	0.14
Δ PTH (pmol/L)	−0.26*	−0.18	−0.30*	−0.13	−0.28	−0.06	−0.16	−0.12

Δ change: (variables at six months- variables at baseline), *: $p < 0.05$; ** $p < 0.001$.

Discussion

The data collected from this study revealed that serum 25(OH)D and magnesium levels significantly improved in women, and a significant increase in serum 25(OH)D and selenium were observed in men after six months of vitamin D supplementation. Differences between genders were seen in serum magnesium, selenium, HDL-cholesterol, fasting glucose, and triglyceride levels. In addition, increased levels of vitamin D and decreased serum PTH levels were observed for all subjects. The gender differences observed are not in accordance with most of the previous studies that showed contradictory and inconsistent results regarding the role of magnesium and selenium levels in the risk of T2DM [10, 29–31].

In this study, a significant increase in serum magnesium was observed with vitamin D supplementation only in women. Earlier studies, however, did not observe gender-specific differences in serum magnesium in patients with either diabetes type 1 or 2 [11, 32]. Our results do support the findings of Farhangi and colleagues, which showed an increase in the level of serum magnesium in women after vitamin D supplementation [15].

There are controversies regarding the intake of magnesium and risk of T2DM [11, 32, 33]. Patients with unstable T2DM tend to have abnormal lipid profiles that can further decompensate glycemia. Studies have shown that low HDL-cholesterol is directly correlated to serum Mg even in pre-diabetic states, and dietary Mg intake is inversely associated with fasting serum insulin, HDL-cholesterol, systolic and diastolic blood pressure, suggesting that oral magnesium supplementation may be effective in reducing plasma fasting glucose levels and raising HDL cholesterol in patients with T2DM [35, 36]. In the present study, the improved levels of serum magnesium were an after-effect of vitamin D supplementation and were not associated with dietary magnesium intake. Our results showed a negative and positive correlation of serum magnesium levels with fasting plasma glucose and HDL-cholesterol levels, respectively. These findings partially support the study of Song et al., showing that an increase in magnesium supplementation could lead to a decrease in fasting glucose levels and an increase in HDL-cholesterol in patients with T2DM [36].

In men, a significant increase in the serum selenium level was observed after six months of vitamin D supplementation. The relationship between circulating vitamin D and selenium has not been well studied, but low selenium intake has been associated with an increased risk of bone-related diseases [37, 38]. Moreover, it has been shown that a single intravenous dose of 100 IU cholecalciferol, 100 IU ergocalciferol, or 0.1 μg 1,25 dihydroxycholecalciferol could increase selenite uptake, exhibiting an important association with different vitamin D compounds [24].

There are contradictory results regarding serum selenium levels in men and women [39, 40]. A study

performed by Lee et al. demonstrated decreasing selenium levels with age (>40 years) and concluded that the association of selenium status with blood lipid levels is applicable only in young-adult women [41]. The analysis of men and women in NHANES III studies exhibited significantly higher mean serum selenium concentrations in men than with the same age group in women [42].

Apart from gender differences, the level of selenium intake is also influenced by several confounding factors like health-related behaviors and dietary intake of other nutrients. For instance, alcohol consumption was in direct association with serum selenium in women, but not in the men of NHANES III [42], while, an inverse relation was demonstrated between selenium concentration and smoking, which was stronger in men than in women [43]. The present study supports the NHANES III results showing a significant increase in serum selenium concentration in men, but the gender difference regarding selenium increase after vitamin D supplementation is still not clear and needs to be studied further.

Observational studies have shown a positive association of serum selenium levels with triglyceride concentrations in different populations [44, 45]. Yang and colleagues showed a significant increase in the levels of triglycerides with increased serum selenium concentrations in the Taiwanese elderly [46]. Gender-specific analysis of the same study demonstrated that triglycerides increased significantly across the highest selenium quartiles in men, while total HDL- and LDL-cholesterol concentrations increased significantly across the highest selenium quartiles in women [46]. Our findings confirm the study performed by Yang et al. [46], showing a positive correlation of triglycerides with the level of serum selenium in men.

The authors acknowledge some limitations. Several confounders were not included in the study such as dietary information and medications, which can influence magnesium and selenium. Furthermore, the serum levels of the trace elements studied do not reflect the overall magnesium and selenium status of patients and as such, results should be interpreted with caution.

In conclusion, the supplementation of vitamin D for up to six months in T2DM patients favorably modulated the serum levels of magnesium and selenium in a gender-dimorphic manner. These changes in magnesium levels were associated with an increased HDL-cholesterol and decreased fasting glucose level, while selenium levels were associated with increased triglyceride levels. Overall, the vitamin D influence in physiologically important circulating trace elements such as magnesium and selenium could possibly explain how the different risk factors associated with T2DM can be corrected through vitamin D supplementation.

Conflict of interest

The authors have no conflict of interest to disclose related to this study.

Acknowledgements

The present study was financially supported by King Saud University, vice deanship of scientific research chair. We also thank Benjamin Vinodson for the statistical analysis of the data.

References

1. Al-Daghri, N.M., Al-Attas, O.S., Alokail, M.S., Alkharfy, K.M., El-Kholie, E., Yousef, M., Al-Othman, A., Al-Saleh, Y., Sabico, S., Kumar, S. and Chrousos, G.P. (2012) Increased vitamin D supplementation recommended during summer season in the Gulf region: a counterintuitive seasonal effect in vitamin D levels in adult, overweight and obese Middle Eastern residents. Clin. Endocrinol. 76, 346–50.

2. Al-Daghri, N.M, Al-Attas, O.S., Al-Okail, M.S., Alkharfy, K.M., Al-Yousef, M.A., Nadhrah, H.M., Sabico, S.B. and Chrousos, G.P. (2010) Severe hypovitaminosis D is widespread and more common in non-diabetics than diabetics in Saudi adults. Saudi Med. J. 31, 775–80.

3. Al-Daghri, N.M., Al-Attas, O.S., Alokail, M.S., Alkharfy, K.M., Yousef, M., Nadhrah, H.M., Al-Othman, A., Al-Saleh, Y., Sabico, S. and Chrousos, G.P. (2010) Hypovitaminosis D and cardiometabolic risk factors among non-obese youth. Cent. Eur. J. Med. 5, 752–757.

4. Heaney, R.P. (2004) Functional indices of vitamin D status and ramifications of vitamin D deficiency. Am. J. Clin. Nutr. 80, 1706S–9S.

5. Eastell, R., Barton, I., Hannon, R.A., Chines, A., Garnero, P. and Delmas, P.D. (2003) Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J. Bone Miner. Res. 18, 1051–6.

6. Nakamura, K., Tsugawa, N., Saito, T., Ishikawa, M., Tsuchiya, Y. and Hyodo, K. (2008) Vitamin D status, bone mass, and bone metabolism in home-dwelling postmenopausal Japanese women: Yokogoshi study. Bone 42, 271–7.

7. Al-Saleh, Y., Al-Daghri, N.M., Alkharfy, K.M., Al-Attas, O.S., Alokail, M.S., Al-Othman, A., Sabico, S. and Chrousos, G.P. (2013) Normal circulating PTH in Saudi healthy individuals with hypovitaminosis D. Horm. Metab. Res. 45, 43–6.

8. Huerta, M.G., Roemmich, J.N., Kington, M.L., Bovbjerg, V.E., Weltman, A.L., Holmes, V.F., Patrie, J.T., Rogol, A.D. and Nadler, J.L. (2005) Magnesium deficiency is associated with insulin resistance in obese children. Diabetes Care 28, 1175–81.

9. Rude, R.K., Singer, F.R. and Gruber, H.E. (2009) Skeletal and hormonal effects of magnesium deficiency. J. Am. Coll. Nutr. 28, 131–41.

10. Ma, J., Folsom, A.R., Melnick, S.L., Eckfeldt, J.H., Sharrett, A.R., Nabulsi, A.A., Hutchinson, R.G. and Metcalf, P.A. (1995) Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. J. Clin. Epidemiol. 48, 927–40.

11. Barbagallo, M., Dominguez, L.J., Galioto, A., Ferlisi, A., Cani. C., Malfa, L., Pineo, A., Busardo', A. and Paolisso, G. (2003) Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. Mol. Aspects Med. 24, 39–52.

12. Larsson, S.C. and Wolk, A. (2007) Magnesium intake and risk of type 2 diabetes: a meta-analysis. J. Intern. Med. 262, 208–14.

13. Schulze, M.B., Schulz, M., Heidemann, C., Schienkiewitz. A., Hoffmann, K. and Boeing, H. (2007) Fiber and magnesium intake and incidence of type 2 diabetes: a prospective study and meta-analysis. Arch. Intern. Med. 167, 956–65.

14. Hardwick, L.L., Jones, M.R., Brautbar, N. and Lee, D.B. (1991) Magnesium absorption: mechanisms and the influence of vitamin D, calcium and phosphate. J. Nutr. 121, 13–23.

15. Farhanghi, M.A., Mahboob, S. and Ostadrahimi, A. (2009) Obesity induced magnesium deficiency can be treated by vitamin D supplementation. J. Pak. Med. Assoc. 59, 258–61.

16. Rude, R.K., Adams, J.S., Ryzen, E., Endres, D.B., Niimi, H., Horst, R.L., Haddad, J.G. Jr. and Singer, F.R. (1985) Low serum concentrations of 1,25-dihydroxyvitamin D in human magnesium deficiency. J. Clin. Endocrinol. Metab. 61, 933–40.

17. Wilz, D.R., Gray, R.W., Dominguez, J.H. and Lemann, J., Jr. (1979) Plasma 1,25-(OH)2-vitamin D concentrations and net intestinal calcium, phosphate, and magnesium absorption in humans. Am. J. Clin. Nutr. 32, 2052–60.

18. Thomson, C.D. (2004) Assessment of requirements for selenium and adequacy of selenium status: a review. Eur. J. Clin. Nutr. 58, 391–402.

19. Wei, W.Q., Abnet, C.C., Qiao, Y.L., Dawsey, S.M., Dong, Z.W., Sun, X.D., Fan, J.H., Gunter, E.W., Taylor, P.R. and Mark, S.D. (2004) Prospective study of serum selenium concentrations and esophageal and gastric cardia cancer, heart disease, stroke, and total death. Am. J. Clin. Nutr. 9, 80–5.

20. Laclaustra, M., Navas-Acien, A., Stranges, S., Ordovas, J.M. and Guallar, E. (2009) Serum selenium concentrations and hypertension in the US Population. Circ. Cardiovasc. Qual. Outcomes 2, 369–76.

21. Bleys, J., Navas-Acien, A. and Guallar, E. (2007) Serum selenium and diabetes in U.S. adults. Diabetes Care 30, 829–34.

22. Tabar, M.B. (2012) Determination of Serum Selenium in Patients with Type II Diabetes Mellitus. Middle-East Journal of Scientific Research 12, 433–5.

23. Stranges, S., Sieri, S., Vinceti, M., Grioni, S., Guallar, E., Laclaustra, M., Muti, P., Berrino, F. and Krogh, V. (2010) A prospective study of dietary selenium intake and risk of type 2 diabetes. BMC Public Health 10, 564.

24. Mykkanen, H.M. and Wasserman, R.H. (1990) Relationship of membrane-bound sulfhydryl groups to vitamin D-stimulated uptake of [75Se] Selenite by the brush border membrane vesicles from chick duodenum. J. Nutr. 120, 882–8.

25. Al-Daghri, N.M., Alkharfy, K.M., Al-Othman, A., El-Kholie, E., Moharram, O., Alokail, M.S., Al-Saleh, Y., Sabico, S., Kumar, S. and Chrousos, G.P. (2012) Vitamin D supplementation as an adjuvant therapy for patients with T2DM: an 18-month prospective interventional study. Cardiovasc. Diabetol. 11, 85.

26. Alkharfy, K.M., Al-Daghri, N.M., Sabico, S.B., Al-Othman, A., Moharram, O., Alokail, M.S., Al-Saleh, Y., Kumar, S. and Chrousos, G.P. (2013) Vitamin D supplementation in patients with diabetes mellitus type 2 on different therapeutic regimens: a one-year prospective study. Cardiovasc. Diabetol. 12, 113.

27. Al-Daghri, N.M., Al-Attas, O.S., Alokail, M.S., Alkharfy, K.M., Yousef, M., Nadhrah, H.M., Al-Othman, A., Al-Saleh, Y., Sabico, S. and Chrousos, G.P. (2010) Hypovitaminosis D and cardiometabolic risk factors among non-obese youth. Cent. Eur. J. Med. 5, 752–7.

28. Application Note: AN40511_E 10/03C. Atomic Absorption Method Guide Se in blood serum. Thermo ELECTRON CORPORATION, 2008.

29. Kao, W.H., Folsom, A.R., Nieto, F.J., Mo, J.P., Watson, R.L. and Brancati, F.L. (1999) Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. Arch Intern Med 159, 2151–9.

30. Rajpathak, S., Rimm, E., Morris, J.S. and Hu, F. (2005) Toenail selenium and cardiovascular disease in men with diabetes. J. Am. Coll. Nutr. 24, 250–6.

31. Kilinc, M., Guven, M.A., Ezer, M., Ertas, I.E. and Coskun, A. (2008) Evaluation of serum selenium levels in Turkish women with gestational diabetes mellitus, glucose intolerants, and normal controls. Biol. Trace Elem. Res. 123, 35–40.

32. Inoue, S., Akazawa, S., Nakaigawa, Y., Shimizu, R. and Seo, N. (2004) Changes in plasma total and ionized magnesium concentrations and factors affecting magnesium concentrations during cardiac surgery. J. Anesth. 18, 216–9.

33. Lal, J., Vasudev, K., Kela, A.K. and Jain, S.K. (2003) Effect of oral magnesium supplementation on the lipid profile and blood glucose of patients with type 2 diabetes mellitus. J. Assoc. Physicians India 51, 37–42.

34. Humphries, S., Kushner, H. and Falkner, B. (1999) Low dietary magnesium is associated with insulin resistance in a sample of young, nondiabetic Black Americans. Am. J. Hypertens. 12, 747–56.

35. Guerrero-Romero, F. and Rodrı guez-Mora n, M. (2000) Hypomagnesemia is linked to low serum HDL-cholesterol irrespective of serum glucose values. J Diabetes Complicat. 14, 272–6.

36. Song, Y., He, K., Levitan, E.B., Manson, J.E. and Liu, S. (2006) Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. Diabet. Med. 23, 1050–6.

37. Johnson, C.C., Fordyce, F.M., and Rayman, M.P. (2010) Symposium on 'Geographical and geological influences on nutrition': Factors controlling the distribution of selenium in the environment and their impact on health and nutrition. Proc. Nutr. Soc. 69, 119–32.

38. Manolagas, S.C. (2010) From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. Endocr. Rev. 31, 266–300.

39. Huang, J.H., Lu, Y.F., Cheng, F.C., Lee, J.N. and Tsai, L.C. (2012) Correlation of magnesium intake with metabolic parameters, depression and physical activity in elderly type 2 diabetes patients: a cross-sectional study. Nutr. J. 11, 41.

40. Bleys, J., Navas-Acien, A., Stranges, S., Menke, A., Miller, E.R. 3rd and Guallar, E. (2008) Serum selenium and serum lipids in US adults. Am. J. Clin. Nutr. 88, 416–23.

41. Lee, O., Moon, J. and Chung, Y. (2003) The relationship between serum selenium levels and lipid profiles in adult women. J. Nutr. Sci. Vitaminol. 49, 397–404.

42. Kafai, M.R. and Ganji, V. (2003) Sex, age, geographical location, smoking, and alcohol consumption influence serum selenium concentrations in the USA: third National Health and Nutrition Examination Survey, 1988–1994. J. Trace Elem. Med. Biol. 17, 13–8.

43. van den Brandt, P.A., Goldbohm, R.A., van't Veer, P., Bode, P., Hermus, R.J. and Sturmans, F. (1993) Predictors of toenail selenium levels in men and women. Cancer Epidemiol. Biomarkers Prev. 2, 107–12.

44. Obeid, O., Elfakhani, M., Hlais, S., Iskandar, M., Batal, M., Mouneimne, Y., Adra, N. and Hwalla, N. (2008) Plasma Copper, Zinc, and Selenium Levels and Correlates with Metabolic Syndrome Components of Lebanese Adults. Biol. Trace Elem. Res. 123, 58–65.

45. Laclaustra, M., Stranges, S., Navas-Acien, A., Ordovas, J.M. and Guallar, E. Serum selenium and serum lipids in US adults: National Health and Nutrition Examination Survey (NHANES) 2003–2004. (2010) Atherosclerosis 210, 643–8.

46. Yang, K.C., Lee, L.T., Lee, Y.S., Huang, H.Y., Chen, C.Y. and Huang, K.C. (2010) Serum selenium concentration is associated with metabolic factors in the elderly: a cross-sectional study. Nutrition & Metabolism 7, 38.

Nasser M. Al-Daghri, PhD

Prince Mutaib Bin Abdullah Chair for Osteoporosis
Biochemistry Department
College of Science
King Saud University
PO Box, 2455, Riyadh 11451
Saudi Arabia
Tel.: 0096614675939
Fax: 0096614675931
aldaghri2011@gmail.com