Journal of Clinical Gerontology & Geriatrics 6 (2015) 120–124

Contents lists available at ScienceDirect

Journal of Clinical Gerontology & Geriatrics

journal homepage: www.e-jcgg.com

Original article

Link between vitamin B12, type 2 diabetes mellitus, and bone mineral density in elderly patients

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ARTICLE INFO

Article history:
Received 26 August 2014
Received in revised form
22 March 2015
Accepted 23 March 2015
Available online 6 May 2015

Keywords:
elderly
osteoporosis
type 2 diabetes
vitamin B12

ABSTRACT

Background/Purpose: There have been many conflicting reports on the effects of type 2 diabetes mellitus (DM) and the level of vitamin B12 on bone mineral density (BMD) in elderly patients. Moreover, conflicting data exists regarding the prevalence of vitamin B12 deficiency among elderly diabetics. The aim of this study was to investigate the link between vitamin B12 levels, type 2 DM, and BMD in elderly patients.

Methods: A case–control study was conducted on 61 participants, ≥60 years of age, divided into 31 cases of patients with diabetes and 30 age-matched healthy controls. Patients receiving vitamin B12 supplements were excluded. The relationship between BMD and serum levels of vitamin B12 was examined.

Results: Borderline/deficient serum B12 status was more common in the control group; it was found in 53.33% of the controls and 25.80% of diabetic patients. The mean serum vitamin B12 concentration was 820.65 ± 544.77 pg/mL in patients with diabetes and 677.80 ± 619.89 pg/mL in healthy control participants ($p = 0.34$). Serum vitamin B12 concentration showed no significant difference between osteoporotic patients, osteopenic patients, and normal patients among the diabetic group.

Conclusion: The prevalence of vitamin B12 deficiency was higher in the control group than the diabetic group who did not receive oral B12 supplementation. Low serum vitamin B12 is commonly overlooked in the elderly, with or without diabetes. The presence of diabetes mellitus did not affect BMD in the elderly. Furthermore, there is no significant relationship between serum vitamin B12 levels and BMD among diabetics.

1. Introduction

Diabetes mellitus (DM) is a prevalent disease with multiple alarming complications that represent major threats to one's general health.[1] These complications are often associated with poor prognosis, increased morbidity, and impaired quality of life. Furthermore, the life span of patients with DM is dependent upon the presence/absence of these complications.[2]

One of the most overlooked complications of diabetes is osteoporosis, which has not been listed as a traditional diabetic complication. However, patients with either type 1 DM or type 2 DM are considered to be at an increased risk of developing osteoporotic fractures.[3]

Although there is a strong correlation between the reduction of bone mineral density (BMD) and type 1 DM,[4] there is a lack of data on the occurrence of osteoporosis in type 2 DM. The BMD of patients with type 2 diabetes was found to be lower, equal, or even higher when compared with their healthy counterparts.[5–7]

There are many proposed pathological mechanisms by which type 2 DM can affect bone tissue; these include obesity, hyperinsulinemia, the deposition of advanced glycosylation end-products in collagen fibers, reduced circulating levels of insulin growth factor-1, hypercalciuria, renal affection, microangiopathy, and chronic inflammatory state.[8]

Moreover, a variety of dietary factors have been linked to the occurrence of osteoporosis, e.g., inadequate levels of protein, calcium, and vitamin D. Recently there has been an increased interest

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http://dx.doi.org/10.1016/j.jcgg.2015.03.006

in studying the effects of other nutrients, including vitamin B12, on bone health.[9]

The mechanism by which vitamin B12 deficiency can alter bone health is by inducing hyperhomocysteinemia, which interferes with collagen cross-linking, causing an altered bone matrix resulting in more fragile bones.[10]

Previous studies of the association between vitamin B12 level and BMD showed diverse results. Some researchers linked osteoporosis to low vitamin B12 levels,[11] whereas others did not observe an association between vitamin B12 status and BMD.[12,13]

The relationship between vitamin B12 level and BMD in elderly patients with and without type 2 DM remains inconclusive. Therefore, the aim of this study was to study the link between vitamin B12, type 2 DM, and BMD in elderly patients.

2. Method

2.1. Study population

Sixty-one elderly patients, aged $\geq$ 60 years, attended the outpatient clinic at Ain Shams University Hospital, Cairo, Egypt. Thirty-one patients with type 2 DM and 30 healthy participants were recruited in the study.

Diabetes mellitus, as defined according to the American Diabetes Association criteria (fasting plasma glucose $\geq$ 126 mg/dL; minimum of 8 hours fasting), a random or postload serum glucose level $\geq$ 200 mg/dL after an oral glucose tolerance test, or the use of hypoglycemic medication.[14] All participants underwent comprehensive geriatric assessment that included detailed personal and medical histories, physical examination, and cognitive, functional, and mood assessment tests.

Patients with a history of pernicious anemia, chronic renal insufficiency as defined by a creatinine level $\geq$ 1.5 mg/dL, prior bariatric surgery, gastrectomy, vitamin B12 supplementation of any form, prior ileum resection, and Crohn's disease were excluded from the study. Data regarding the intake of metformin, other antidiabetic drugs, and insulin were collected.

2.2. BMD measurement

Bone densitometry was performed on all patients by dual energy X-ray absorptiometry, using a Lunar DpX MD pencil scanner with software version 1.3 g (Lunar Radiation Corp., Madison, WI, USA), and also using the DPX machine (Lunar Radiation Corp.). Scanning was carried out with the patient in the supine position. The examined areas were the lumbar vertebrae and the left femoral neck. The graph display showed the total BMD in g/cm^2 in relation to age, its age-matched percentage (Z-score), and its peak reference percentage (T-score), taking into consideration the patients' sex, weight, and height.

The World Health Organization defined osteopenia as a BMD T-score between -1 and -2.5, and defined osteoporosis as a T-score of -2.5 or less.[15]

2.3. Laboratory assessment

Vitamin B12 level was estimated using the fully automated UniCel DxI 600 Immunoassay System (access from Beckman and Coulter, Brea, California, USA). This device used a two-step competitive binding technique. The analytical sensitivity of this assay was 50 pg/mL. The analytical measurement range was 50–1500 pg/mL, and a total assay imprecision of 12% was found as the measurement range. Vitamin B12 levels were evaluated as follows[16]; normal range: >350 pg/mL, borderline range: 200–350 pg/mL, and deficient range: < 200 pg/mL.

The researchers notified and gave recommendations for treatment to all vitamin B12-deficient patients identified and to those within the borderline vitamin B12 range.

2.4. Ethical considerations

Informed consent was obtained from all the participants in this study. The study methodology was reviewed and approved by the Research Review Board of the Geriatrics and Gerontology Department, Faculty of Medicine, Ain Shams University.

2.5. Statistical methods

The collected data was coded, tabulated, revised, and statistically analyzed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). Quantitative variables were presented in the form of means and standard deviations. Qualitative variables were presented in the form of frequency tables (number and percent). Comparisons between quantitative variables were done using student *t* test or analysis of variance (ANOVA), and between qualitative variables using Pearson's Chi-square test.

3. Results

The characteristics of the two study groups are shown in Table 1. There was no significant difference between the study groups regarding age, BMI, history of previous fractures, bone health status, lumbar spine BMD, left femur BMD, and physical performance assessed by activities of daily living[17] and instrumental activities of daily living.[18]

The group with DM had more *fallers* than the control group ($p = 0.05$). Borderline/deficient serum B12 status was more common in the control group (16/30 patients; 53.33%) compared with the patients with DM (8/31 patients; 25.80%); this difference was statistically significant ($p = 0.04$). Although not reaching statistical significance, the mean serum vitamin B12 level was higher in the diabetic group.

In the current study, 11 (35.5%) of the diabetic patients had ischemic heart disease, eight (25.80%) patients were hypertensive, five (16.1%) patients had heart failure, two (6.50%) patients had chronic obstructive pulmonary disease, and five (16.13%) cases reported no comorbidity.

Among the cases with DM, the osteoporotic patients were older compared with patients with osteopenia and normal patients ($p = 0.005$). None of the diabetic patients with osteoporosis used metformin, whereas two patients with osteopenia received metformin. There was no significant relationship between the occurrence of osteoporosis and serum B12 level, insulin use, smoking, sex, or BMI (Table 2).

Table 3 showed that there was no significant difference between diabetic females and males in regard to age, serum B12 concentrations, left femoral neck BMD, and lumbar spine BMD. Diabetic females were more obese than males.

There was no linear relationship between serum vitamin B12 concentrations and BMD at the lumbar spine and left femoral neck (Fig. 1).

4. Discussion

In this study, there was no significant difference between the two study groups in regard to the prevalence of osteoporosis or osteopenia. Similarly, no significant difference was found between the two groups regarding the mean BMD at the lumbar spine or left femoral neck; therefore, the occurrence of osteoporosis is not

Table 1
Comparison of variables studied between the study groups.

		Diabetic patients not receiving vitamin B12 supplements $N = 31$	Controls not receiving vitamin B12 supplements $N = 30$	p
Age (y)		65.03 ± 4.9	66.8 ± 8.08	0.36
BMI (kg/m^2)		33.20 ± 9.9	29.20 ± 6.56	0.07
Smoking	Ex-smoker	6 (19.35)	0	0.03
	Nonsmoker	20 (64.5)	22 (73.33)	
	Current	5 (16.12)	8 (26.67)	
History of previous falls		6 (19.35)	1 (3.33)	0.05 *
History of previous fractures		0 (0)	1 (3.33)	0.30
Bone health status	Normal	10 (32.26)	7 (23.33)	0.62
	Osteopenia	10 (32.26)	13 (43.33)	
	Osteoporosis	11 (35.48)	10 (33.33)	
ADL	Assisted	5 (16.12)	2 (6.7)	0.29
	Dependent	1 (3.22)	0	
	Independent	25 (80.64)	28 (93.33)	
IADL	Assisted	9 (29.03)	6 (20)	0.229
	Dependent	2 (6.45)	0	
	Independent	20 (64.51)	24 (80)	
Serum B12 status	Borderline	6 (19.35)	13 (43.3)	0.04 *
	Deficient	2 (6.45)	3 (10)	
	Normal	23 (74.19)	14 (46.67)	
Serum B12 (pg/mL)		820.65 ± 544.77	677.80 ± 619.89	0.34
Lumbar spine BMD (g/cm^2)		0.96 ± 0.18	0.92 ± 0.13	0.31
Left femur BMD (g/cm^2)		0.893 ± 0.17	0.87 ± 0.18	0.62

Data are presented as n (%) or mean ± standard deviation.
*Statistically significant.
ADL = activity of daily living; BMI = body mass index; BMD = bone mineral density; IADL = instrumental activity of daily living.

Table 2
Comparison between different densitometry categories and different variables among the diabetic group.

		Normal $N = 10$	Osteopenia $N = 10$	Osteoporotic $N = 11$	p
Age (y)		65.20 ± 4.9	62.20 ± 1.5	68.43 ± 4.45	0.005 *
Sex	Male	6 (60)	3 (30.0)	7 (63.63)	0.24
	Female	4 (40.0)	7 (70.0)	4 (36.36)	
Body mass index (kg/m^2)		38.83 ± 11.94	30.46 ± 2.09	30.56 ± 2.73	0.09
Smoking	Ex-smoker	1 (10.0)	2 (20.0)	3 (27.27)	0.83
	Nonsmoker	7 (70.0)	7 (70.0)	6 (54.54)	
	Current smoker	2 (20.0)	1 (10.0)	2 (18.18)	
Serum vitamin B12 level (pg/mL)		823.20 ± 530.24	539.50 ± 400.79	1073.9 ± 585.78	0.07
ADL	Assisted	2 (20.0)	0 (0)	3 (27.27)	0.26
	Dependent	0 (0)	0 (0)	1 (9.09)	
	Independent	8 (80.0)	10 (100.0)	7 (63.63)	
IADL	Assisted	4 (40.0)	1 (10.0)	4 (36.36)	0.128
	Dependent	0 (0)	0 (0)	2 (18.18)	
	Independent	6 (60)	9 (90.0)	5 (45.45)	
Left femur BMD (g/cm^2)		1.07 ± 0.15	0.87 ± 0.26	0.743 ± 0.09	0.000 *
Lumbar spine BMD (g/cm^2)		1.33 ± 0.10	1.03 ± 0.09	0.93 ± 0.17	0.000 *
Metformin use		4 (40.0)	2 (20.0)	0 (0)	0.068
Other antidiabetic drugs use		1 (10.0)	2 (20.0)	2 (18.18)	0.076
Insulin use		6 (60)	8 (80.0)	9 (81.81)	0.344

Data are presented as n (%) or mean ± standard deviation.
*Statistically significant.
ADL = activity of daily living; BMD = bone mineral density; IADL = instrumental activity of daily living.

Table 3
The differences between both sexes among diabetics regarding the studied variables.

	Females $N = 15$	Males $N = 16$	p
Age (y)	65.00 ± 4.70	65.42 ± 5.66	0.13
BMI	37.91 ± 8.30	29.31 ± 6.25	0.004 *
Serum B12 concentration (pg/mL)	918.77 ± 492.68	865.39 ± 523.78	0.63
Left femoral BMD (gm/cm^2)	0.840 ± 0.128	0.892 ± 0.175	0.74
Spine BMD (gm/cm2)	0.993 ± 0.135	1.10 ± 0.222	0.19

Data are presented as the mean ± standard deviation.
*Statistically significant.
BMD = bone mineral density; BMI = body mass index.

linked to the presence of diabetes. The same results were found when analyzing males and females, separately.

This agrees with Maghbooli et al[19] who found no significant difference in the prevalence of osteopenia and osteoporosis between patients with type 2 DM and participants without diabetes. Moreover, Al-Elq and Sadat-Ali[20] studied 154 male Saudi Arabian patients and reported that the presence of type 2 DM did not influence the incidence of osteopenia or osteoporosis in males.

Regarding the female sex, Gupta et al[21] reported that premenopausal Arab women with type 2 DM had a higher BMD at the spine than women without diabetes with a matched BMI. This was explained by diffuse osteoarthritis at the vertebral site in diabetic women, which can lead to false elevated values of BMD at this

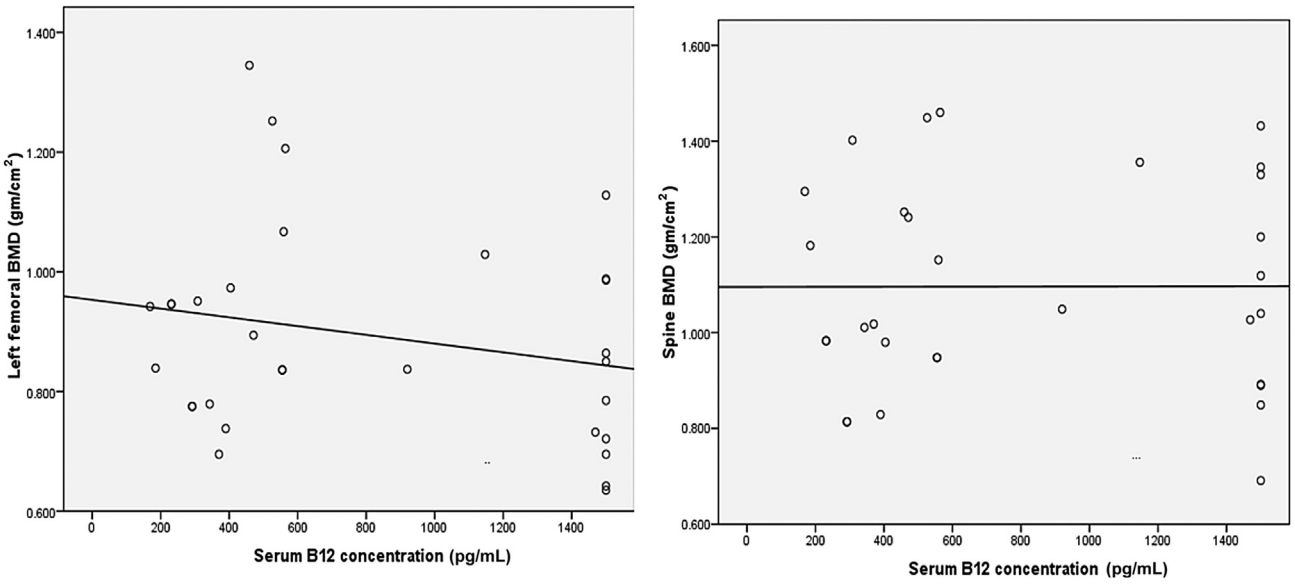

Fig. 1. Relationship between serum vitamin B 12 concentrations and bone mineral density (BMD) at the lumbar spine and left femur neck in diabetics. Among diabetics, there was no linear relationship between serum vitamin B 12 concentrations and BMD at the lumbar spine and left femur neck.

site.[22] Meanwhile, Moghimi et al[23] in 2008, reported that type 2 DM patients have significantly lower T-score values and a greater frequency of osteoporosis than healthy postmenopausal women.

Contradictory results for vitamin B12 levels in diabetic patients have been reported. Furthermore, there is little information, if any, regarding vitamin B12 status in Egyptian elders. In the current study, low serum vitamin B12 concentration was found in a considerable number of the studied patients. Twenty four (39.35%) patients were found to have either deficient or borderline serum vitamin B12 levels.

However, our results showed that borderline/deficient serum vitamin B12 status was more common in the control group (16/30 patients; 53.33%) compared with patients with DM (only 8/31 patients who did not receive oral vitamin B12 supplements; 25.80%), and this difference was found to be statistically significant ($p = 0.04$). The mean serum vitamin B12 concentration was 820.65 ± 544.7 pg/mL in patients with diabetes and 677.80 ± 619.89 pg/mL in healthy participants ($p = 0.34$).

This was similar to a study by Delen et al,[24] who reported that serum vitamin B12 levels were higher in patients with type 2 DM compared with the controls, however, this difference was not statistically significant. El Oudi et al[25] also found that diabetic cases had elevated serum levels of vitamin B12 ($p < 0.001$) compared with the controls. This higher serum level of vitamin B12 in patients with DM was explained by cytosolic metabolic resistance to vitamin B12 in those patients.[26]

Some researchers, however, reported a higher prevalence of vitamin B12 deficiency in patients with DM.[13] In their study, the daily use of >2000 mg of metformin was associated with a higher prevalence of vitamin B12 deficiency.

In the present study, only 19.40% of the patients with diabetes received metformin, with a mean dose of 925.00 ± 442.43 mg/d; it was found that there was no significant difference between patients taking metformin and those who did not take metformin, in regard to their mean serum B12 level or the prevalence of vitamin B12 deficiency.

Another target of our study was to assess the effects of serum vitamin B12 levels on bone mass. Serum vitamin B12 concentration showed no significant difference between osteoporotic, osteopenic, and normal participants in both groups. Regarding the general population, many other studies did not observe the association between vitamin B12 status and BMD.[12,13] By contrast, many studies reported a significant association between low vitamin B12 and osteoporosis.[11,27,28]

Besides the current study, only two other studies have assessed the relationship between vitamin B12 and BMD, specifically in patients with diabetes.[29,30] Both studies found that homocysteine was inversely correlated with BMD; however, there was no significant association between BMD and the serum concentrations of vitamin B12. Furthermore, they concluded that metformin did not have a significant effect on serum vitamin B12 status.[29,30]

The exact mechanisms by which vitamin B12 can affect bone health remains unclear, however, data indicates that vitamin B12 deficiency, when causing hyperhomocysteinemia, may increase osteoclast formation and bone resorption, while higher B12 levels may affect osteoblast maturation.[31] The contradictory results regarding the relationship of vitamin B12 level and BMD, obtained from different studies, may be explained by differences in the mean age and sex distribution of the study populations, genetic differences between different study populations, and the level of adjustment for other confounders affecting bone health.

Our study had several limitations; firstly, due to the small sample size, its statistical power might be insufficient. Secondly, we did not examine multiple confounders that may contribute to mineral-bone metabolism, e.g., the serum levels of calcium, 1,25(OH)2D, dietary phosphorus, and calcium intake. Thirdly, we did not examine plasma homocysteine levels which may play a role in the occurrence of osteoporosis independent of vitamin B12 levels.

5. Conclusion

Surprisingly, we found that BMD was not related to serum vitamin B12 concentration in diabetics as well as in controls. Serum vitamin B12 concentration may be normal or even high in elderly patients with type 2 DM, making the decision of vitamin B12 supplementation a complex one. Vitamin B12 deficiency was more common in elderly nondiabetics than in diabetics. The exact mechanism of higher vitamin B12 levels among diabetics should be studied.

Conflicts of interest

All authors have no conflicts of interest with respect to the authorship and/or publication of this article.

Acknowledgments

This work was supported by Ain Shams Faculty of Medicine Grant's Office, Grant No 2012-10.

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