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Research Article

Association of Vitamin D and Sodium Levels in Manual Labor

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Abstract: Hyponatremia and vitamin D deficiency are frequent disorders, and both have been associated with gait disturbances, falls and fractures. The aim of this study was to evaluate the existence of an association between serum sodium and vitamin D serum levels. We performed a retrospective investigation to establish whether hyponatremia and vitamin D deficiency may be associated in a general population of unselected outpatients. An electronic search was performed in the laboratory information systems of the Hospital of Govt. Medical College, Amritsar, to retrieve combined results for total vitamin D and sodium obtained in all outpatients referred for health check-up in the year 2013. Combined results of vitamin D and sodium could be retrieved for 509 outpatients (377 females and 232 males; mean age 64±17 years). Vitamin D deficient subjects displayed significantly lower levels of serum sodium (140 versus 141 mmol/L; p<0.001), along with a significantly higher rate of hyponatremia (6.3% versus 5.1%; p=0.037). Accordingly, hyponatremic subjects had significantly lower levels of serum vitamin D (55 versus 60 nmol/L; p=0.015), along with a significantly higher rate of vitamin D deficiency (41.8% versus 36.1%; p=0.030). A highly significant correlation was found between sodium and total vitamin D after adjustment for age and gender (p<0.001). The results of this study demonstrate for the first time the existence of a significant correlation between the serum levels of sodium and total vitamin D in a general population of unselected outpatients.

Keywords: hyponatremia, osteoporosis, sodium, vitamin D, elderly.

INTRODUCTION

Hyponatremia generally defined as a serum sodium concentration < 136 mmol/L (Adrogué, H. J., & Madias, N. E. 2000) has been recently associated with gait disturbances, falls and fractures in the elderly (Hoorn, E. J. *et al.,* 2011). Recent data also show that hyponatremia may directly influence bone metabolism and can hence represent an important predisposing factor for osteoporosis and skeletal frailty (Verbalis, J. G. *et al.,* 2010). Therefore, this electrolyte disorder should be regarded as a direct contributor of osteoporosis and also as an important risk factor for impaired gait, finally leading to falls. In animal studies, sustained hyponatremia was effective to induce progressive reduction of bone mineral density and decreased bone ash calcium, along with reduced phosphate and sodium contents at the tibia and lumbar vertebrae. In these animals, the administration of vitamin D compensated for the reduction in bone formation and halted bone loss (Barsony, J. *et al.,* 2013). The hyponatremic animals also developed hypogonadism, and markedly decreased testicular weight with abnormal testicular histology, along with decreased body fat, skeletal muscle sarcopenia, and cardiomyopathy (Barsony, J. *et al.,* 2013). Interestingly, in a similar experiment, the administration of activated

vitamin D was effective to mitigate the development of left ventricular alterations in hypertensive rats (Bodyak, N. *et al.,* 2007). Interestingly, vitamin D deficiency seems to show similar features. Although there is no universal consensus on optimal levels of 25-hydroxyvitamin D (25-OHD, i.e., the main circulating form of the vitamin) as measured in serum, vitamin D deficiency is generally defined as a 25-OHD level of less than 20 ng/mL (50 nmol/L), whereas a level of 21 to 29 ng/mL (52 to 72 nmol/L) indicates a relative insufficiency, and a level of 30 ng/mL (75 nmol/L) or greater can be considered as normal (Dawson-Hughes, B. *et al.,* 2010). Vitamin D insufficiency and deficiency are highly prevalent, and this is mirrored by the fact that more than half of the worldwide population has levels of 25-OHD below 30 ng/mL (van Schoor, N.M., & Lips, P. 2011). Vitamin D is classically known for its role in bone health, playing an essential role in the maintenance of calcium homeostasis by enhancing and regulating physiologic calcium absorption by the gut (12), as well as by exerting its effects directly on bone cells. Most of the bone cell types are capable of metabolizing 25-OHD to 1, 25(OH) 2D3 (i.e., the active form of the hormone), to stimulate their own biological functions, such as cell proliferation, maturation, mineralization and bone resorption (Christodoulou, S. *et*

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al., 2013). It is generally acknowledged that an adequate vitamin D status is important to minimize the risk of falling in elderly people, and positive effects on falls and muscle function have been shown in community dwelling older individuals (Pfeifer, M. *et al.,* 2009). A recent meta-analysis involving eight trials and 2,426 subjects showed that doses of vitamin D up to 600 IU were ineffective for lowering the risk of falling, whereas higher doses (ranging from 700 to 1,000 IU) reduced such risk by approximately 20% (Pfeifer, M. *et al.,* 2009). In the last decades, vitamin D receptors have been demonstrated to be widespread in brain tissue, and the vitamin D active form has shown neuroprotective effects, including the clearance of amyloid plaques, a hallmark of Alzheimer's disease (Škodrić-Trifunović, V. *et al.,* 2014). At least two large prospective studies recently indicated that low vitamin D concentrations may increase the risk of cognitive decline (Holick, F.M. 2013), thus representing an adjunctive risk factor for falls in elderly and vitamin D deficient subjects. Due to the aforementioned similarities between hyponatremia and vitamin D deficiency in increasing the risk of falls, fractures and all-cause mortality, we performed a retrospective, double center investigation to establish whether any association exists between hyponatremia and vitamin D deficiency in the general population.

MATERIAL AND METHODS

Results were finally expressed as median and interquartile range (IQR). Hyponatremia was defined as serum sodium level lower than 136 mmol/L (Adrogué, H. J., & Madias, N. E. 2000), whereas vitamin D deficiency was defined as a 25-OHD level of less than 20 ng/mL (50 nmol/L) (Dawson-Hughes, B. *et al.,* 2010). The association between variables was tested with Spearman's correlation and multivariate regression analysis, in which serum sodium concentrations were entered as dependent variables and age, gender and 25-OHD levels as independent variables. Differences between groups were assessed with Wilcoxon-Mann-Whitney and Pearson's χ^2 test with Yates' correction (for categorical variables), using Analyse-it (Analyse-it Software Ltd, Leeds, UK). The odds ratios (ORs) were calculated using MedCalc Version 12.3.0 (MedCalc Software, Mariakerke, Belgium). The study was performed in accordance with the Declaration of Helsinki, under the terms of relevant local legislation.

Table I Values Of Serum Sodium Stratified According To Vitamin D Status In A Large Population Of Unselected Outpatients.

VITAMIN D	<50 NMOL/L	50 NMOL/L	P	
N	1853	3244		
AGE (YEARS)	65±17	64±17	0.053	AGE (YEARS)
GENDER (F/M)	1363/1853	2496/3244	0.007	GENDER (F/M)
SODIUM VALUES (MMOL/L)	140 (139–141)	141 (139–142)	<0.001	VALUES (MMOL/L)
HYPONATREMIA	117/1853 (6.3%)	165/3244 (5.1%)	0.036	HYPONATREMIA

RESULTS

Combined results of vitamin D and sodium could be retrieved from the laboratory information systems of the two centers for a total of 509 outpatients throughout the study period (2054 from the laboratory of Parma and 3043 from the laboratory of Govt. Medical college, Amritsar 377 females and 232 males; mean age 64±17 years). Significantly lower levels of serum sodium were found in vitamin D deficient subjects (140 versus 141 mmol/L; p<0.001), along with a marginally but significantly higher rate of hyponatremia (6.3% versus 5.1%; p=0.036) (Table I). Accordingly, the Odds Ratio (OR) of hyponatremia in vitamin D deficient subjects was 1.26 (95% CI, 0.99 to 1.61). Interestingly, although the calculated mean percentage difference between groups (i.e., 1.0%) was only marginally higher than the inter-individual biologic variation of serum sodium (i.e., 0.7%), the observed difference (i.e., 1 mmol/L) was much higher than the minimal clinically important difference for serum sodium calculated in both populations (i.e., 0.06 and 0.04 mmol/L in vitamin D deficient subjects and controls, respectively) (Miller, M. 2006). In the univariate regression analysis, a highly significant association was found between the values of sodium and 25-OHD in the entire study population (Spearman's correlation coefficient, 0.11; p<0.001). The association remained statistically significant in the multivariate regression analysis after adjustment for age and gender (beta coefficient, 0.06; p<0.001), as well as in females (Spearman's correlation coefficient, 0.11; p<0.001) and males (Spearman's correlation coefficient, 0.10; p<0.001).

Table II Values of Total Vitamin D Stratified According To Serum Sodium In A Large Population Of Unselected Outpatients

SODIUM	<136 MMOL/L	136 MMOL/L	P
N	282	4815	
AGE (YEARS)	66±19	64±17	0.068
GENDER (F/M)	213/282	3646/4815	0.995
VITAMIN D			
VALUES (NMOL/L)	55 (33–75)	60 (39–82)	0.015
DEFICIENCY	118/282 (41.8%)	1738/4815 (36.1%)	0.030

DISCUSSION

Plasma renin activity (PRA) and salt sensitivity (SS) of blood pressure (BP) have both been linked to 25-OHD concentrations, and it was also demonstrated that the flux of calcium into vascular smooth muscle cells may be facilitated by the active forms of vitamin D (Holick, M. F. *et al.,* 2005). Vitamin D also acts as a proximal inhibitor of the Renin-Angiotensin System (RAS), and higher 1,25 (OH)2D concentrations have been associated with lower plasma renin activity in hypertensive patients (Christodoulou, S. *et al.,* 2013). Interestingly, an inverse correlation between both 25-OHD and 1, 25(OH) D and plasma renin and angiotensin II concentrations has been recently reported in a selected cohort of patients referred for coronary angiography (Holick, M. F. *et al.,* 2005). Finally, dietary salt loading has been associated with an increase in circulating 1,25OHD concentrations, wherein subjects with the greatest salt-induced increases in 1,25OHD levels were those exhibiting the greatest BP response to salt (Christodoulou, S. *et al.,* 2013). Conversely, there is some evidence that calcium supplementation can, at least in part, contribute to a good response to antihypertensive drugs in the elderly (Holick, M. F. *et al.,* 2005; & Adrogué, H. J., & Madias, N. E. 2000). Along with the previous evidence, vitamin D is known to be an important modulator of the haemostatic system (Holick, M. F. *et al.,* 2005; & Upadhyay, A. *et al.,* 2006), and low levels have been associated with a higher prevalence of arterial and cardiovascular disease [11], which both represent additional and well established risk factors for syncope and falls. Nevertheless, it is still uncertain whether hyponatremia and vitamin D deficiency should be considered real pathogenetic factors of falls and fractures or rather simple epiphenomena of these conditions. Further studies are hence needed to elucidate the pathophysiological link between the two parameters, along with the clinical significance of this potential association (i.e., increased risk of falls, fractures and all-cause mortality with the association of the two metabolic abnormalities). Regardless of the causal or casual nature of this biological interplay, the concentration of serum sodium and 25-OHD should be regarded as a part of a complex and multifactorial impairment that increases the risk of gait disturbances and osteoporosis. Accordingly, it seems reasonable to suggest that serum sodium and 25-OHD levels should be assessed and eventually corrected when the value falls below the lower limit of the reference range. Unfortunately, no studies have evaluated bone density or incidence of falls and fractures before and after correction of hyponatremia, nor have any prospective investigations aiming to demonstrate potential improvements of clinical outcomes after correction of hyponatremia been published so far. Nevertheless, since sodium is a simple, inexpensive and rapid biochemical test, clinicians should investigate the possible presence of hyponatremia in all elderly patients undergoing therapies with drugs potentially involved in the pathogenesis of hyponatremia, in particular diuretics, psychotropic drugs, and anticonvulsants. The patients with mild chronic hyponatremia should also probably be examined for bone mineral density (BMD) and for falls risk using the available predictive models.

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