Serum Vitamin D Levels in Kidney Transplant Recipients: the Importance of an Immunosuppression Regimen and Sun Exposure

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ABSTRACT: **Background:** Vitamin D deficiency was shown to be prevalent among renal transplant recipients in northern countries, but little is known regarding risk factors.

Objectives: To test vitamin D levels in kidney transplant recipients residing closer to the equator, compare them to levels in liver transplant recipients and hemodialysis patients, and identify possible risk factors.

Methods: In a cross-sectional study 103 kidney transplant recipients, 27 liver transplant recipients and 50 hemodialysis patients followed at our institute were tested for vitamin D levels. Demographic data, medical history and current treatment were recorded from the medical files.

Results: Inadequate vitamin D levels (< 30 ng/ml) were found in 75% of all patients and 75% of all kidney transplant recipients. Vitamin D levels were higher among dialysis patients than transplant recipients, though deficiency rates were similar. No association was found between kidney function and vitamin deficiency. Deficiency was associated with higher prednisone doses, use of mycophenolate sodium, tacrolimus, and iron supplements, or lower doses of vitamin D supplementation.

Conclusions: Despite potential higher ultraviolet B exposure, inadequate vitamin D levels were prevalent in our study group. Importantly, some immunosuppressive medications were associated with vitamin D deficiency and high doses of vitamin D were associated with less deficiency.

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KEY WORDS: vitamin D, kidney transplant, liver transplant

Vitamin D deficiency results in rickets in children and in osteomalacia and increased risk for osteoporosis in adults. Also, deficiency is associated with myopathies, autoimmune and cardiovascular diseases, and an increased prevalence of various cancers [1]. Vitamin D is produced de novo following sun exposure, and 10–20% of the recommended daily intake is typically obtained from dietary sources [2]. Vitamin D deficiency is prevalent worldwide, particularly among patients with chronic kidney disease [1,3,4]. Multiple causes contribute to the deficiency prevalence, including low vitamin D intake, sedentary lifestyle leading to reduced sun exposure, and reduction in dermal synthesis secondary to chronic kidney disease. Cholecalciferol deficiency aggravates the development of renal osteodystrophy [4,5]. Moreover, already at early stages of chronic kidney disease, fibroblast growth factor 23 inhibits the production of renal calcitriol [6].

It is difficult to predict vitamin D levels in the kidney recipient population. Deficiency can be expected for several reasons. Some degree of chronic kidney disease exists in most of the recipients [7], and patients are advised to avoid sun exposure because of increased skin cancer risk [8]. Also, corticosteroids, commonly used against rejection, increase vitamin D catabolism [9]. However, compared to chronic kidney disease patients, transplant recipients can maintain an active lifestyle with possibly more sun exposure and can consume a more diverse diet that could be richer in vitamin D [2].

Several studies examined vitamin D deficiency prevalence in kidney transplant recipients, mostly finding it to be common. Inadequately low levels were found in 80–97% of kidney recipients examined in Germany, Spain, Denmark and England [10-13]. However, since most of these studies were performed in northern latitudes where solar ultraviolet B exposure is low, generalizing these findings to more southern regions is questionable. Importantly, these studies did not consistently identify risk factors associated with vitamin D deficiency. The aim of the present study was therefore to explore, in a cross-sectional design, the prevalence of vitamin D deficiency in kidney recipients in Israel, a country closer to the Equator, and to identify possible associated factors.

PATIENTS AND METHODS

The study was carried out at the Hadassah University Hospital in Jerusalem, Israel, situated at a latitude of 31°47'N. It was approved by the hospital's ethics committee. Kidney transplant, hemodialysis and liver transplant patients were recruited at the respective follow-up clinics during August–September 2010, with additional recruitment to the control groups in January–February 2011. The only exclusion criterion was refusal or inability of the patient to sign the informed consent.

QUESTIONNAIRE

Each patient was asked to complete a questionnaire on demographic details, the cause of end-stage kidney or liver disease, transplant type and date of transplantation, or when hemodialysis was begun. The questionnaire also included items regarding sun exposure habits, such as average daily exposure of < 1 or ≥ 1 hour, occupational sun exposure, and wearing of short or long-sleeved shirts and trousers. Also included were questions on patients' consumption of vitamin supplements, food additives and "natural" supplements.

PATIENTS' RECORDS

Patients' records were used to complete the reported data and the prescribed treatment. The immunosuppressive regimen, vitamin supplements and cinacalcet were recorded by dose, whereas other medications were documented as taken or not.

VITAMIN D LEVELS AND BLOOD AND URINE TESTS

Serum calcidiol levels were tested [5,10] using an electrochemiluminescence immunoassay on Elecsys (Roche Diagnostics, Mannheim, Germany). Vitamin D status was defined according to the K/DOQI guidelines for kidney disease patients [14], considering serum concentrations ≥ 30 ng/ml as adequacy, 16–30 ng/ml as insufficiency, and ≤15 as deficiency. Serum urea, creatinine, calcium, phosphate and uric acid, and urine for 24 hours protein and creatinine secretion were measured using a Cobas system (Roche Diagnostics). Serum calcineurin or mTOR inhibitor trough levels were measured: tacrolimus, cyclosporine and sirolimus using CMIA assays on an Architect i1000SR system (Abbott Diagnostics, Abbott Park, IL, USA) and everolimus using an LC-MS/MS assay (Waters Corp., Milford, MA).

STATISTICAL ANALYSIS

Analyses were performed using the three abovementioned categories of vitamin D sufficiency state as well as a two-category set contrasting patients with proper deficiency from patients with insufficiency or adequacy pooled together. Statistical analyses were performed using SPSS 18 for windows. Analysis of variance or Student's *t*-test were performed for normally distributed variables, and Mann-Whitney or Kruskal-Wallis tests for variables that were not. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, as appropriate. Correlations between continuous variables were assessed using Pearson's correlation or Spearman's rho. All tests were two sided, and *P* values < 0.05 were considered significant.

RESULTS

The study population comprised 182 patients: 103 kidney transplant patients, 50 dialysis patients and 29 liver transplant patients. Their characteristics are detailed in Table 1. No significant differences in gender, ethnicity or average daily sun exposure were found between the three groups (data on the latter two are not shown). Dialysis patients were significantly older than the transplant patients.

Table 1. All patients: demographics and vitamin D levels (n=182)

	All patients (%)	Kidney transplant recipients (%)	Dialysis patients (%)	Liver transplant recipients (%)	*P*†‡
No. of patients	182 (100)	103 (56.6)	50 (27.5)	29 (15.9)	
Gender (Male/Female)	128 (70.3)/ 54 (29.7)	67 (65)/36 (35)	38 (76)/ 12 (24)	23 (79)/6 (21)	0.195§
Age	56.2 ± 15.4	54.0 ± 14.0	62.5 ± 17.0	53.1 ± 15.0	0.002#
Vitamin D levels					
Mean	26.16 ± 15.28	23.49 ± 9.88*	30.29 ± 19.09**	28.52 ± 21.33◊	–
Median	24.00	22.00	27.00	21.00	–
Interquartile range	17.21–31.00	16.09–30.70	20.20–33.18	17.00–27.50	–
Sufficiency state categories					0.230§
Patients with deficiency	34 (18.7)	23 (22.3)	5 (10.0)	6 (20.7)	
Patients with insufficiency	97 (53.9)	54 (52.4)	26 (52.0)	17 (58.6)	
Patients with adequacy	51 (28.0)	26 (25.2)	19 (38.0)	(20.7)	

†Two-sided *P* values for comparisons between the three patient groups

‡*P* values < 0.05 were considered significant

§Tested using Pearson's chi-square test

#Tested using analysis of variance

*Mann-Whitney comparison of the kidney transplant recipients and hemodialysis groups revealed a *P* value of 0.021

**Mann-Whitney comparison of the hemodialysis and liver transplant recipient groups revealed a *P* value of 0.09

◊Mann-Whitney comparison of the kidney transplant recipients and liver transplant recipient groups revealed a P value of 0.94

Since recruitment to both control groups took place in two separate periods, we compared vitamin D levels between periods within each group. No significant difference was found in either group (data not shown).

SERUM VITAMIN D LEVELS IN TRANSPLANTED PATIENTS

In all three groups mean vitamin D levels were mostly within the insufficiency range [Table 1]. No difference was found when comparing the groups in terms of sufficiency state. However, a non-parametric comparison of vitamin D levels between the kidney transplant and hemodialysis groups showed significantly higher levels among dialysis patients. Similar comparisons of the kidney and liver transplant and of the hemodialysis and liver transplant groups failed to find a significant difference, although the latter could be attributed to the smaller sample size. When all the transplant patients together were compared with the hemodialysis group, a significant difference was found, with lower levels in transplanted patients.

Table 2. Kidney transplant patients: demographics and sun exposure (n=103)

	Entire group	Vitamin D deficiency (%)	Vitamin D insufficiency (%)	Vitamin D adequacy (%)	*P*†‡
Age (yr)	54.0 ± 14.0	53.8 ± 14.1	51.3 ± 14.3	59.9 ± 11.8	0.035§
Gender (Male/Female)	67/36	12 (17.9)/ 11 (30.6)	39 (58.2)/ 15 (41.7)	16 (23.9)/ 10 (27.8)	0.219#
Average daily sun exposure less than 1 hour	81 (79)	18 (22.2)	41 (50.6)	22 (27.2)	0.734*
Occupational sun exposure					0.763*
Unemployed	61 (59)	14 (23.0)	30 (49.2)	17 (27.9)	
Indoors work	39 (38)	9 (23.1)	21 (53.8)	9 (23.1)	
Outdoors work	3 (3)	0 (0)	3 (100)	0 (0)	
Wearing of long sleeves and trousers	28 (27)	7 (25.0)	14 (50.0)	7 (25.0)	0.920#

†Two-sided *P* values for comparisons between the three categories of vitamin D sufficiency state
‡*P* values < 0.05 were considered significant
§Tested using analysis of variance
#Tested using Pearson's chi-square test
*Tested using Fisher's exact test

Table 3. Kidney transplant patients: transplantation characteristics and immunosuppression regimen (n=103)

	Entire group	Vitamin D deficiency (%)	Vitamin D insufficiency (%)	Vitamin D adequacy (%)	*P*†‡
Time elapsed from transplantation (yr)	7.53 ± 6.22	4.73 ± 4.43	7.61 ± 0.91	9.85 ± 5.70	0.014§
Prednisone daily dose (mg)	6.1 ± 5.8	8.0 ± 9.3	6.0 ± 4.8	4.6 ± 1.8	0.004#
Using/Not using prednisone	101 (98)/ 2 (2)	23 (22.8)/ 0 (0.0)	54 (53.5)/ 0 (0.0)	24 (23.8)/ 2 (100.0)	0.110*
Using/Not using azathioprine	14 (14)/ 89 (86)	3 (21.4)/ 20 (22.5)	7 (50.0)/ 47 (52.8)	4 (28.6)/ 22 (24.7)	0.930*
Using/Not using mycophenolate mofetil	71 (69)/ 32 (31)	13 (18.3)/ 10 (31.3)	39 (54.9)/ 5 (46.9)	19 (26.8)/ 7 (21.9)	0.344**
Using/Not using mycophenolate sodium	16 (16)/ 87 (84)	7 (43.8)/ 16 (18.4)	8 (50.0)/ 46 (52.9)	1 (6.3)/ 25 (28.7)	0.042*
Using/Not using mycophenolate	87 (84)/ 16 (16)	20 (23.0)/ 3 (18.8)	47 (54.0)/ 7 (43.8)	20 (23.0)/ 6 (37.5)	0.513*
Using/not using tacrolimus	66 (64)/ 37 (36)	20 (30.3)/ 3 (8.1)	33 (50.0)/ 21 (56.8)	13 (19.7)/ 13 (35.1)	0.022**
Using/Not using cyclosporine	24 (23)/ 79 (77)	3 (12.5)/ 20 (25.3)	12 (50.0)/ 42 (53.2)	9 (37.5)/ 17 (21.5)	0.197**
Using/Not using sirolimus	2 (2)/ 101 (98)	0 (0.0)/ 23 (22.8)	2 (100.0)/ 52 (51.5)	0 (0.0)/ 26 (25.7)	1.000*
Using/Not using everolimus	10 (10)/ 93 (90)	0 (0.0)/ 23 (24.7)	6 (60.0)/ 48 (51.6)	4 (40.0)/ 22 (23.7)	0.160*
Tacrolimus trough level (ng/ml)	5.7 ± 1.9	5.2 ± 1.2	5.7 ± 1.6	6.7 ± 3.0	0.239#
Cyclospoirne trough level (ng/ml)	69 ± 19	60 ± 16	69 ± 19	70 ± 21	0.654#
Sirolimus trough level (ng/ml)	12.4 ± 5.1	–	12.4 ± 5.1	–	–
Everolimus trough level (ng/ml)	4.5 ± 1.4	–	5.4 ± 1.1	3.5 ± 0.8	0.014#

†Two-sided *P* values for comparisons between the three categories of vitamin D sufficiency state
‡*P* values < 0.05 were considered significant
§Tested using analysis of variance
#Tested using the Kruskal-Wallis test
*Tested using Fisher's exact test
**Tested using Pearson's chi-square test

VITAMIN D DEFICIENCY AND DEMOGRAPHIC CHARACTERISTICS

We looked for correlations between vitamin D levels and demographic characteristics of the kidney transplant group [Table 2]. Vitamin D deficiency was significantly associated with younger age. No association was found with regard to gender, daily sun exposure, or ethnicity (not shown).

Since vitamin D deficiency was more prevalent among kidney recipients than dialysis patients, we tested whether the time elapsed from the transplantation was associated with vitamin D deficiency [Table 3]. Interestingly, deficiency was strongly associated with shorter time from transplantation. Moreover, dialysis time prior to transplantation was not associated with vitamin D levels or deficiency. Vitamin D deficiency was not associated with the type of transplantation, history of previous kidney transplantations, or cause of the kidney failure (data not shown).

CORRELATION OF VITAMIN D LEVELS WITH IMMUNOSUPPRESSIVE MEDICATIONS

Most of the kidney recipients at our clinic are treated with a combination of a corticosteroid, an anti-metabolite and a calcineurin or mTOR inhibitor. We explored the effect of prescribed doses of these medications on the serum vitamin D levels [Table 3]. Increasing prednisone doses were associated with lower vitamin D levels, both by correlation to measured levels ($P = 0.003$, correlation coefficient -0.287) and by association to deficiency state categories ($P = 0.004$). Use of mycophenolate sodium irrespective of dosing was significantly associated with vitamin D deficiency. Interestingly, no correlation was found between dosing of mycophenolate sodium and vitamin D levels, although each variable correlated with time elapsed from transplantation (for dosing $P = 0.001$, correlation coefficient -0.76). When considered irrespective of preparation (as sodium or mofetyl), mycophenolate dose was significantly inversely correlated with vitamin D levels ($P = 0.042$, correlation coefficient -0.201), but was not associated with deficiency. Higher doses of tacrolimus were associated with a tendency towards vitamin D deficiency in the two-category set only, and use of tacrolimus irrespective of dosing was also associated with vitamin D deficiency. No association was found between vitamin D levels and use or dosage of other agents.

When blood levels of the relevant drugs were measured [Table 3], no association was found between vitamin D deficiency or serum vitamin D levels and tacrolimus, cyclosporine or sirolimus levels. In contrast, none of the patients for whom blood everolimus levels were known (nine patients) had vitamin D deficiency. In conclusion, low vitamin D levels were associated with higher prescribed doses of corticosteroids, mycophenolate and tacrolimus. In comparison, for everolimus the serum levels and not the prescribed dose were associated with vitamin D deficiency.

VITAMIN D SUPPLEMENTATION AND SERUM VITAMIN D LEVELS

We tested for associations of the different drug groups with vitamin D deficiency or serum levels [Table 4]. As expected, vitamin D levels were significantly directly correlated with vitamin D supplementation dosage, though only weakly ($P = 0.014$, correlation coefficient 0.242). Association between vitamin D dose and deficiency was highly significant in the two-category set. Importantly, vitamin D dosage was not correlated with age. Higher alfacalcidol doses were associated with a tendency towards vitamin D deficiency in the two-category set only. Patients taking iron supplements were also prone to deficiency.

TRANSPLANTED KIDNEY FUNCTION AND VITAMIN D SERUM LEVELS

We evaluated the importance of kidney function in relation to vitamin D levels [Table 4]. No association was found between vitamin D deficiency and blood levels of urea, creatinine, calcium, phosphate or uric acid, or with creatinine clearance or proteinuria as measured by 24 hour urine collection (only data on kidney function are shown).

MULTIVARIATE ANALYSIS

Some of the variables described above are potentially related. To assess confounding of the various variables and validate the previous findings, we performed multivariate analyses. A general linear multivariable model was designed taking vitamin D deficiency in the three-category set as a dependent variable, and the variables found associated with it independently as independent variables. Age, vitamin D, prednisone dosage, and use of mycophenolate sodium or tacrolimus all remained significantly associated with deficiency, while time from transplantation was not ($P < 0.0001$ for the model). A stepwise logistic regression model for vitamin D deficiency in the two-category set as a dependent variable, taking as independent variables the variables found associated independently with deficiency in this set, revealed that use of tacrolimus, mycophenolate sodium or iron supplements as well as lower vitamin D dosages were all associated with vitamin D deficiency, quasi-R^2 being 39%. This model allows quantification of each factor's contribution to the odds ratio of having vitamin D deficiency, demonstrating that each 1 IU/day of vitamin D supplementation was associated with a 0.3% reduction in the odds ratio of vitamin D deficiency. Hence, both multivariate analyses enforced the correlation found between prescribed immunosuppression, vitamin D and iron supplementation and vitamin D deficiency state.

Table 4. Kidney transplant patients: general medications and kidney function (n=103)

	Entire group	Vitamin D deficiency (%)	Vitamin D insufficiency (%)	Vitamin D adequacy (%)	P†‡
Using/Not using anti-hypertension medication	88 (85)/ 15 (15)	20 (22.7)/ 3 (20.0)	46 (52.3)/ 8 (53.3)	22 (25.0)/ 4 (26.7)	1.000§
Using/Not using statins	64 (62)/ 39 (78)	14 (21.9)/ 9 (23.1)	30 (46.9)/ 24 (61.5)	20 (31.3)/ 6 (15.4)	0.180#
Using/Not using other medications	87 (84)/ 16 (16)	20 (23.0)/ 3 (18.8)	42 (48.3)/ 12 (75.0)	25 (28.7)/ 1 (6.3)	0.096§
Vitamin D daily dose (IU)	397 ± 646	148 ± 243	454 ± 625	500 ± 865	0.051*
Alfacalcidol daily dose (mg)	0.06 ± 0.18	0.14 ± 0.29	0.03 ± 0.09	0.06 ± 0.20	0.085*
Using/Not using iron supplements	23 (22)/ 80 (78)	9 (39.1)/ 14 (17.5)	6 (26.1)/ 48 (60.0)	8 (34.8)/ 18 (22.5)	0.013#
Blood urea (mmol/L)	9.4 ± 5.5	10.0 ± 6.4	8.8 ± 5.0	10.3 ± 5.6	0.380*
Creatinine (μmol/L)	139 ± 86	146 ± 109	143 ± 89	126 ± 50	0.477*
Creatinine clearance by 24 hr urine collection (ml/min)	76 ± 34	69 ± 30	79 ± 35	75 ± 35	0.554*
Urine protein by 24 hr urine collection (g/24 hr)	0.52 ± 0.84	0.84 ± 1.35	0.45 ± 0.61	0.38 ± 0.53	0.602*

†Two-sided *P* values for comparisons between the three categories of vitamin D sufficiency state
‡*P* values < 0.05 were considered significant
§Tested using Fisher's exact test
#Tested using Pearson's chi-square test
*Tested using the Kruskal Wallis test

DISCUSSION

This study was undertaken to explore the prevalence of vitamin D deficiency in the kidney transplant community in Israel, and to assess possible factors affecting the vitamin D status of these patients. Serum vitamin D levels were tested in kidney recipients and compared to those of hemodialysis patients and liver recipients. The main findings were:

- ~75% of patients tested had some degree of vitamin D deficiency
- Transplanted patients had lower levels of vitamin D than hemodialysis patients
- A direct correlation was found between age and vitamin D levels
- Patients receiving higher doses of immunosuppression had lower vitamin D levels
- No correlation was found between kidney function and vitamin D levels
- Large doses of vitamin D supplementation were associated with higher vitamin D levels.

Adequate vitamin D levels were found in 26% of the kidney recipients, 52.4% had insufficient levels and 23% showed definite deficiency. This distribution is substantially better than demonstrated in most previous studies of kidney transplant patients [11-13]. This could be explained by the lower latitude of the region where this study was performed, leading to greater UVB exposure. Additionally, while we tested vitamin D levels during the summer to identify the prevalence of deficiency when it is least expected, these previous studies do not

UVB = ultraviolet B

note when testing took place. While in our study no difference was found between subjects tested during summertime and wintertime, in more northern latitudes the season might have a significant impact on vitamin D levels. Interestingly, results similar to ours were reported from Denmark, even though that study was performed during wintertime [10]. Therefore, it is possible that other characteristics such as vitamin D supplementation or genetic variations are responsible for the higher vitamin D levels we found.

Prevalence rates of vitamin D deficiency and insufficiency found in this study were similar to those of the general Israeli population [15,16]. This might be explained by the intensity of medical follow-up of the transplant patients, counteracting their multifactorial stronger predisposition toward hypovitaminosis D. Despite limitations of the comparison, the lack of difference between kidney and liver transplant patients suggests that the type of organ transplanted is not of paramount importance to the risk of deficiency. The lack of difference in deficiency prevalence between kidney transplant and hemodialysis patients, and the higher vitamin D levels among hemodialysis patients, imply that kidney function is not a major risk factor for deficiency in this population, concurring with our finding of no association between creatinine clearance and vitamin D deficiency within the kidney and liver transplant groups (data not shown)

Vitamin D deficiency was associated with several aspects of the immunosuppressive treatment, partially contrasting with the results of previous studies of these agents in autoimmune diseases [17,18]. Higher prednisone doses were associated with lower vitamin D concentrations and a greater tendency towards deficiency. This might be explained by the stimulatory effect of glucocorticoids on vitamin D catabolism [9], or related to the reason necessitating the higher steroid dose. Use of mycophenolate sodium, irrespective of dose, was found to be associated with vitamin D deficiency. Importantly, in our institution the choice between mycophenolate preparations is arbitrary; hence, a confounding factor related to the choice of preparation seems less plausible. Patients using higher doses of tacrolimus were more prone to develop vitamin D deficiency, yet no association was found between tacrolimus serum levels and serum vitamin D levels. This suggests that the association reported here might result from a factor associated with both vitamin D levels and the need for greater tacrolimus doses to reach goal concentrations, such as metabolism rates or intestinal lipid absorption [1,19].

Serum levels of vitamin D were directly correlated with vitamin D supplementation, though only weakly, and vitamin D deficiency was associated with lower vitamin D supplementation doses. Vitamin D supplementation at doses of 400 IU/day led to no significant change in vitamin D levels of kidney recipients, while supplementation doses in the order of 7000 IU/day produced a dramatic increase [11,20]. Supplementation doses in our study were low, which might account for the partial observed effect of supplementation. We found no association between vitamin D and kidney function, calcium levels or proteinuria, agreeing with previous reports [11,13].

For the two-category set of deficiency (vitamin D deficiency versus higher vitamin D levels) a stepwise logistic regression model was created using the factors found to be significant independently in that set. According to this model, the reduction in odds ratio for having vitamin D deficiency is 0.3% per 1 IU/day of vitamin D supplementation. While our study design does not allow discussion of causality, this finding reinforces the notion that in order to prevent deficiency the supplementation dose should be above the daily recommended dose of 400 IU. While it examines the risk only for vitamin D deficiency and not for insufficiency, this regression model accounts for almost 40% of the observed variation in vitamin D status, a rate exceeding that of a previously suggested model for vitamin D levels in this patient population [11].

CONCLUSIONS

Vitamin D deficiency is quite prevalent among kidney transplant recipients even in a geographic area with high UVB exposure. Vitamin D levels are not related to graft function. Higher doses of immunosuppression are associated with lower vitamin D levels, as is the use of tacrolimus and mycophenolate sodium. Importantly, vitamin D supplementation is associated with less deficiency, and in order to significantly decrease the risk for deficiency, higher doses than the recommended daily intake should be prescribed.

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Capsule

Safety and efficacy of RNAi therapy for transthyretin amyloidosis

Transthyretin amyloidosis is caused by the deposition of hepatocyte-derived transthyretin amyloid in peripheral nerves and the heart. A therapeutic approach mediated by RNA interference (RNAi) could reduce the production of transthyretin. Coelho et al. identified a potent anti-transthyretin small interfering RNA, which was encapsulated in two distinct first- and second-generation formulations of lipid nanoparticles, generating ALN-TTR01 and ALN-TTR02, respectively. Each formulation was studied in a single-dose, placebo-controlled phase 1 trial to assess safety and effect on transthyretin levels. The authors first evaluated ALN-TTR01 (at doses of 0.01 to 1.0 mg/kg of body weight) in 32 patients with transthyretin amyloidosis and then evaluated ALN-TTR02 (at doses of 0.01 to 0.5 mg/kg) in 17 healthy volunteers. Rapid, dose-dependent and durable lowering of transthyretin levels was observed in the two trials. At a dose of 1.0 mg/kg, ALN-TTR01 suppressed transthyretin, with a mean reduction at day 7 of 38%, as compared with placebo ($P = 0.01$); levels of mutant and non-mutant forms of transthyretin were lowered to a similar extent. For ALN-TTR02, the mean reductions in transthyretin levels at doses of 0.15–0.3 mg/kg ranged from 82.3 to 86.8%, with reductions of 56.6–67.1% at 28 days ($P < 0.001$ for all comparisons). These reductions were shown to be RNAi-mediated. Mild-to-moderate infusion-related reactions occurred in 20.8% and 7.7% of participants receiving ALN-TTR01 and ALN-TTR02, respectively.

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Eitan Israeli

Capsule

Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality

Optimal vitamin D intake and its status are important not only for bone and calcium-phosphate metabolism, but also for overall health and well-being. Vitamin D deficiency and insufficiency as a global health problem are likely to be a risk for a wide spectrum of acute and chronic illnesses. Reviewing randomized controlled trials, meta-analyses, and other evidence of vitamin D action on various health outcomes, Pludowski and colleagues found that adequate vitamin D status seems to be protective against musculoskeletal disorders (muscle weakness, falls, fractures), infectious diseases, autoimmune diseases, cardiovascular disease, type 1 and type 2 diabetes mellitus, several types of cancer, neurocognitive dysfunction and mental illness, and other diseases, as well as infertility and adverse pregnancy and birth outcomes. Vitamin D deficiency/insufficiency is associated with all-cause mortality. They concluded that adequate vitamin D supplementation and sensible sunlight exposure to reach optimal vitamin D status are among the front-line factors of prophylaxis for the spectrum of disorders. Supplementation guidance and population strategies for the eradication of vitamin D deficiency must be included in the priorities of physicians, medical professionals and healthcare policy-makers.

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