Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 113; No. 2; P23

Does Vitamin D Deficiency Predispose to Post Stroke Fatigue?

K. Njoku[1,2], E. Iveson[2]

1. University of Manchester, School of Medical Sciences, Faculty of Biology, Medicine and Health, 5th Floor Research, St Mary's Hospital, Oxford Road, Manchester M13 9WL, United Kingdom
2. Acute stroke unit, York Teaching Hospital NHS Foundation Trust, York, YO31 8HE, United Kingdom

Abstract

Aim
This study is aimed at assessing the prevalence and associates of vitamin D deficiency amongst stroke survivors with fatigue and the impact of vitamin D supplementation on fatigue symptoms.

Methods
This was a retrospective observational study in which records of 58 consecutive stroke survivors with fatigue who had their vitamin D levels checked at presentation were reviewed and analysed. Comparison between groups was assessed using Pearson Chi Square and Fishers Exact tests.

Results
A total of 58 survivors (mean age 75.8, range 37-94 years) were included, the majority of which were females (56.9%), aged over 75 years (65.5%), lived with a partner (72.4%), were ambulant at presentation (53.4%) and had modified rankin scores (MRS) of <4(79.3%). The over-all prevalence of vitamin D insufficiency was 74.5% while the prevalence amongst ambulant survivors was 77.4%. There was significant improvement in fatigue symptoms in 100%of those treated.

Conclusion
Our results indicate a high prevalence of vitamin D deficiency especially amongst ambulant survivors where such deficiencies are unexpected; as well as improvement in symptoms following correction. If replicated in a longitudinal randomised study, this can open treatment options and possibly improve the quality of life of stroke survivors with fatigue.

Keywords: Stroke, fatigue, survivors, vitamin D deficiency

Introduction

Post stroke fatigue (PSF) is increasingly recognised as a common and long term problem after a stroke[1]. Not only is it distressing to patients[2], it is known to predict mortality[3]. Prevalence estimates of fatigue after stroke range between 16% -70%[3] and is reportedly more common in women and in those with a premorbid history of fatigue. PSF has been defined as persistent tiredness and lack of energy in the post stroke period, unrelated to previous levels of exertion[4]. While the aetiology of PSF remains unclear, several factors have been suggested as likely predisposing factors including depression, sleep disturbances and physical deconditioning among others[5, 15, 16]. There have been conflicting findings on the association between PSF and brain infarct size or location[6] while vitamin B12 deficiency has been shown to be associated with severe fatigue symptoms amongst lacunar stroke survivors independent of age[13].

Given the negative impact of PSF on the neurological recovery, quality of life and work capacity of stroke survivors, identifying likely predisposing risk factors for PSF is crucial in facilitating the development of effective preventive and therapeutic strategies for this real and complex phenomenon[4, 6].

Previously tried pharmacological interventions such as the use of Fluoxetine and Modafinil have been largely ineffective[5, 7] while non-pharmacological strategies including sleep and stress managements have been met with limited success[4]. Malnutrition, vitamin D deficiency and co-morbid medical conditions are factors known to increase fatigue in the general population[4]. The exact role of Vitamin D deficiency in PSF is however yet to be fully elucidated. Identification of effective treatment modalities for this common but frequently neglected sequelae after stroke is critical in optimizing recovery and rehabilitation of survivors [4]. The aim of this observational study is to assess the prevalence of vitamin D deficiency amongst stroke survivors with PSF and the impact of vitamin D supplementation on PSF. This study also aims to identify possible associates of vitamin D deficiency in the post stroke period.

Methods

Records of 58 stroke survivors who had their vitamin D levels checked at presentation were retrospectively reviewed and analysed. Both ischaemic and haemorrhagic stroke survivors of both sexes and all age groups were included in the analysis. York teaching hospital serves a population of over 500,000 in north Yorkshire, mostly Caucasians. The study was approved by the research committee of the York Teaching Hospital NHS Foundation Trust. Fatigue was mainly self-reported at presentation and follow up. Post stroke fatigue, necessitating the assessment of vitamin D levels in our patients, was defined as a state of persistent and excessive physical tiredness and lack of energy in the post-stroke period[4]. Information on the Modified Rankin Scores (MRS) of participants were retrieved and used to assess the functional status of the study cohort. Mobility at presentation was classified as either normal (fully ambulant) or reduced (mobilising with Zimmers etc). Type of stroke was categorised into ischaemic and haemorrhagic with transient ischaemic attacks (TIA) included as a third category. Other variables of interest were age, sex and living conditions. Vitamin D levels were measured using a Siemen DVIA Centaur automated immunoassay analyser. Vitamin D levels below 30nmol/l were considered vitamin D deficient, values between 30-50nmol/l vitamin D insufficient and values above 50nmol/l vitamin D replete. Combined deficiency/insufficiency was therefore defined as vitamin D levels below 50nmol/l.These cut-off values are universally used in defining vitamin D levels, hence their usage in this study. Vitamin D deficient patients were treated with a loading dose of cholecalciferol (pro D 100,000 units) daily for a month followed by maintenance course of calcium and vitamin D. Statistical analysis was performed using the statistical package STATA (version 10.0).Comparisons between proportions were computed using the Pearson Chi Square and Fishers Exact tests. All categorical variables included in the analysis were dichotomised. Vitamin D level was the primary variable of interest while other variables included in the analysis were age, sex, type of stroke, MRS scores, mobility status and living condition.

Results

A total of 58 stroke survivors were included in this study of which 33(56.9%) were females and 25(43.1%) were males. The age of the patients ranged from 37 years to 94 years with a mean age of 76years [SD 12.5 years]. Majority of the patients were aged 75 and above (65.5%), lived with either a partner/relative (72.4%), were fully ambulant at presentation(53.4%) and had MRS scores less than 4(79.3%).

While majority (77.6%) had an ischaemic stroke, only 5.2% had a haemorrhagic stroke. TIAs were observed in 17.2%. MRS scores ranged from 0 to 4 with a median MRS score of 2. Time between 1st and 2nd fatigue assessments ranged between 4 weeks and 6 months.

Vitamin D levels ranged from <30nmol/l to 105nmol/l. Vitamin D deficiency was found in 26(44.8%) of our cohort while 16(31.0%) were vitamin D insufficient. Another 16(31.0%) were vitamin D replete. Combined Vitamin D deficiency and insufficiency defined as Vitamin D levels less than 50nmol/L was therefore found amongst 42(72.4%) of the stroke survivors with fatigue.

Table 1 presents the results of the differences in proportions between groups using Chi-square/Fischers exact test. There were no statistically significant differences in the proportion of patients with low vitamin D levels by age group, gender, mobility status, living condition or MRS. Figures 1, 2 and 3 depict the frequencies of survivors with

low and normal vitamin D levels by MRS scores, stroke type and age group respectively. All patients treated with cholecalciferol reported significant improvement in fatigue symptoms at their follow up clinics.

Table 1: Characteristics of survivors and vitamin D levels

Variable	All patients (n=58)	Normal vitamin D (n=16)	Low vitamin D (n=42)	P value
Age group				
<75years	21(34.5%)	5(23.8%)	16(76.2%)	0.76
>75years	37(65.5%)	11(29.7%)	26(70.3%)	
Gender				
Female	33(56.9%)	10(30.3%)	23(69.7%)	0.77
Male	25(43.1%)	6(24.0%)	19(76.0%)	
Stroke severity				
TIA	10(17.2%)	5(50.0%)	5(50.0%)	0.12
Stroke	48(82.8%)	11(22.9%)	37(77.1%)	
Stroke Type				
Ischaemic	45(77.6%)	10(22.2%)	35(77.8%)	0.22
Haemorrhagic	3(5.2%)	1(33.3%)	2(66.7%)	
TIA	10(17.2%)	5(50%)	5(50%)	
Mobility				
Normal	31(53.4%)	7(22.6%)	24(77.4%)	0.40
Reduced	27(46.6%)	9(33.3%)	18(66.7%)	
MRS				
<4	46(79.3%)	14(30.4%)	32(69.6%)	0.48
>4	12(20.7%)	2(16.7%)	10(83.3%)	
Living condition				
Alone	16(27.6%)	2(12.5%)	14(87.5%)	0.19
Family/spouse	42(72.4%)	14(33.3%)	28(66.7%)	

Figure 1: Frequency of low (<50nmol/l) and normal vitamin D levels by MRS scores

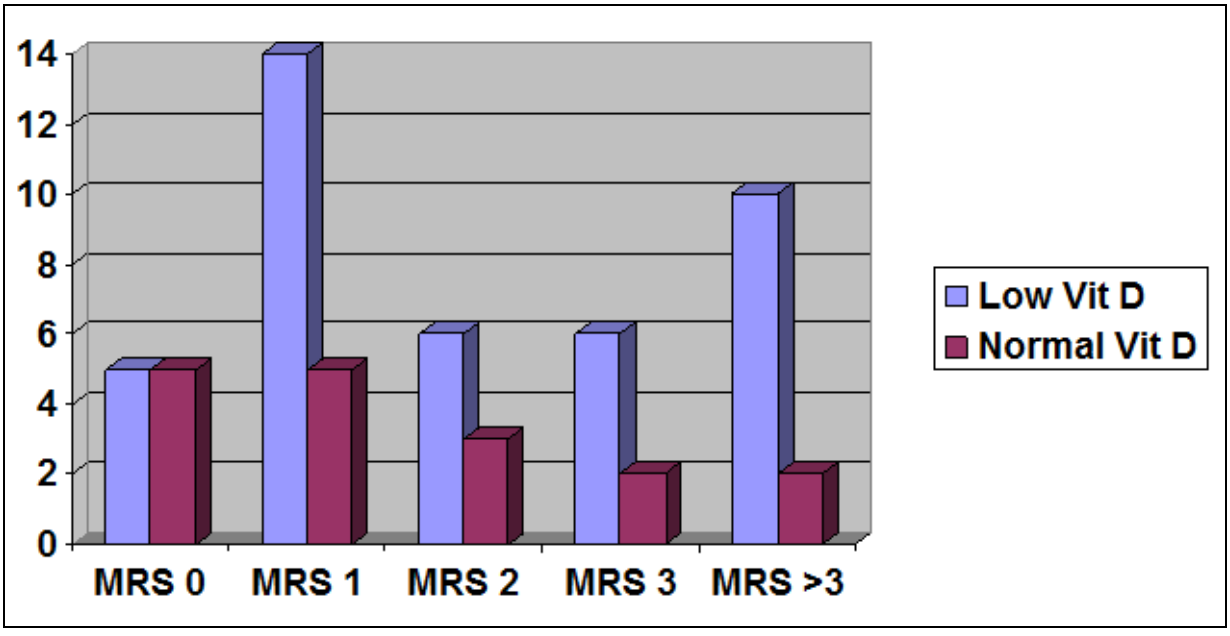


Figure 2: Frequency of low (<50nmol/l) and normal vitamin D levels by stroke type

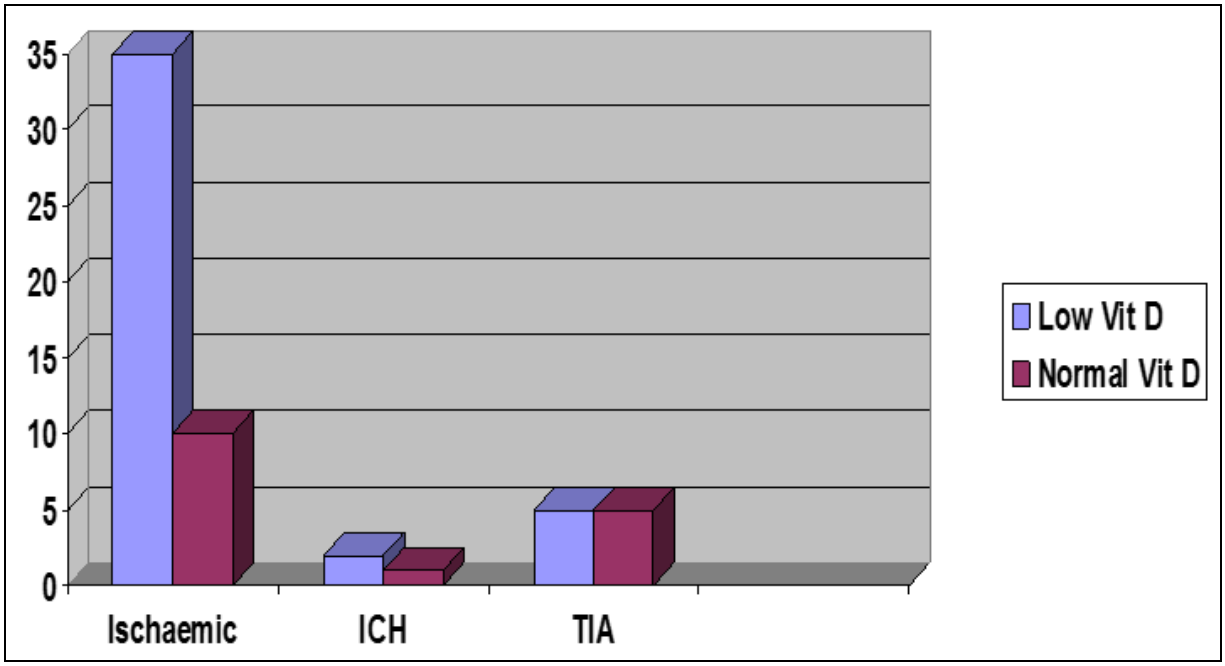
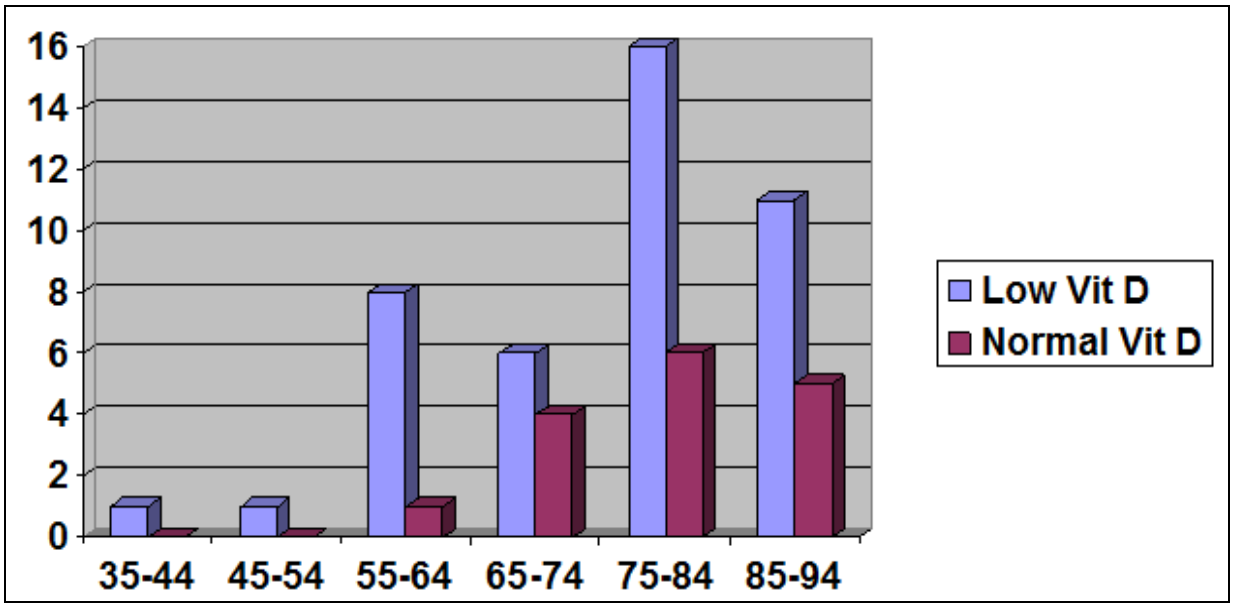


Figure 3: Frequency of low (<50nmol/l) and normal vitamin D levels by age group



Discussion

This retrospective observational study of vitamin D deficiency and post stroke fatigue demonstrated two important findings: First, a high prevalence of low vitamin D amongst stroke survivors with fatigue and especially amongst ambulant survivors where such deficiencies are unexpected. Second, improvement in fatigue symptoms following correction amongst survivors for whom data was available. This study therefore adds to the accumulating body of evidence linking vitamin D deficiency to fatigue after stroke, and of the potential role of Vitamin D supplementation in alleviating these symptoms.

While low vitamin D levels are common in the elderly, the prevalence of vitamin D deficiency/insufficiency in our cohort was greater than that reported in general medical inpatients without a stroke[8] but similar to the prevalence amongst ambulatory patients with stable chronic medical conditions presenting with fatigue[9].

Interestingly, a higher prevalence of vitamin D deficiency was found amongst our ambulant survivors in comparison to those that are relatively non ambulant at presentation. With good mobility in the post stroke period, it is difficult to attribute the observed vitamin D deficiencies in the ambulant cohort to reduced sun exposure from lack of mobility in the post stroke period. It is however plausible that these deficiencies might have preceded the stroke from poor dietary intake or limited exposure to sunlight[10]. With lack of data on the premorbid vitamin D status of our patients, we were unable to explore this possibility. It is also possible that these deficiencies are due to an acute reduction in vitamin D levels in the post stroke period from a decline in hormone synthesis or existing stores [10] or from reduced dietary intake related to stroke complications such as swallowing difficulties.

The lack of an association between mobility status, MRS functional status, living condition and vitamin D deficiency (table 1, figure 1) is in keeping with the possibility that mechanisms other than sun exposure might be contributory. While the prevalence of PSF was higher in those with ischaemic strokes (figure 2), the small numbers of survivors with haemorrhagic strokes and TIAs makes direct comparisons difficult. PSF prevalence was also higher in the older survivors (figure 3), and is consistent with the literature. Our findings are in keeping with a recent prospective non-randomised therapeutic study[9] which not only showed a high prevalence of vitamin D deficiency amongst stable ambulatory patients with chronic medical conditions presenting with fatigue; but also revealed significant improvement in fatigue symptoms following normalisation of vitamin D levels. Kim and colleagues, in a small retrospective case control analysis of 51 stroke patients reported a decrease in serum vitamin D levels that was more pronounced in the chronic group (12.3 vs. 16.3 ng/mL; $p<0.05$) in comparison to the subacute group, and aggravated by the use of total parenteral nutrition[17]. This study was however limited by the lack of adjustment for confounding variables.

Comparison with other relevant studies showed similar observations in different settings in which correction of vitamin D deficiency improved fatigue symptoms amongst patients with myasthenia gravis and breast cancer[11, 12]. Recently, there has been growing interest in the role of vitamin D deficiency in the incidence and severity of stroke with studies suggesting that patients with low vitamin D levels have more brain tissue damage from their strokes compared to those with normal vitamin D levels[14]. These studies have also suggested that patients with low vitamin D were less likely to have good outcomes from their stroke when compared to those who are vitamin D replete[14]. These findings may explain the link between PSF and poor outcomes in stroke survivors.

Our findings of older female patients with ischaemic strokes having a higher prevalence of PSF are in keeping with previous studies[3].However, although other studies suggest a higher fatigue prevalence amongst survivors living alone or in an institution[3], the lower prevalence amongst our subjects is probably related to the smaller cohort size and case mix of our patients. Further studies are needed to clarify the mechanisms underlying the presumed link between vitamin D deficiency and PSF.

This study is limited by its it's retrospective cross-sectional study design, which makes it difficult to infer a temporal relationship or direct causality between vitamin D deficiency and PSF, and between vitamin D correction and improvement in fatigue symptoms. Another limitation is the small sample size and the attendant reduction in the power of the study in detecting significant differences between groups. Finally, the non-usage of a validated fatigue assessment tool is another limitation as this would have provided insight into the relationship between fatigue severity and vitamin D deficiency in the post stroke period. A longitudinal randomised study with a larger sample size and use of a validated fatigue assessment tool is therefore needed to provide robust evidence on the association between vitamin D deficiency and PSF and importantly, to confirm causality.

Within the limitations of this study, we posit that vitamin D deficiency is a possible predisposing factor to PSF and should be actively sought for in stroke survivors presenting with fatigue. Well-designed longitudinal studies are now needed to fully elucidate the relationship between PSF and vitamin D deficiency. With post stroke fatigue increasingly affecting the quality of life of stroke survivors, identification of survivors with concomitant vitamin D deficiency and correction may improve the quality of life of survivors.

Acknowledgments:
Njoku K is supported by a Cancer Research UK Manchester Cancer Research Centre Clinical Research Fellowship.

Presentations:
Abstract of this study was presented at the annual autumn meeting of the British Geriatrics Society, Brighton, United Kingdom.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

Corresponding Author:
Dr Kelechi Njoku,
University of Manchester,
School of Medical Sciences,
Faculty of Biology,
Medicine and Health,
5th Floor Research,
St Mary's Hospital,
Oxford Road,
Manchester M13 9PL.
Email: Kelechi.njoku@manchester.ac.uk

References:

1. Ingles JL, Eskes GA, Phillips SJ (1999) Fatigue after stroke. Arch Phys Med Rehabil 80: 173–178
2. van der Werf SP, van den Broek HL, Anten HW, Bleijenberg G (2001) Experience of Severe Fatigue long after stroke and its relation to depressive symptoms and disease characteristics. Eur Neurol 45: 28–33
3. Glader E-L, Stegmayr B, Asplund K (2002) Post-stroke fatigue. A 2 year follow-up study of stroke patients in Sweden. Stroke 33: 1327–1333.
4. De Groot MH, Phillips SJ, Eskes GA. Fatigue associated with stroke and neurologic conditions: implications for stroke rehabilitation. Arch Phys Med Rehabil 2003; 84:1714–20
5. Annoni JM, Staub F, Bogousslavsky J, Brioschi A (2008) Frequency, characterization and therapies of fatigue after stroke. Neurol Sci 29: S244–246. doi: 10.1007/s10072-008-0951-0
6. A. W. Barrit and D. G. Smithard, "Targeting fatigue in stroke patients," *ISRN Neurology*, vol. 2011, Article ID 805646, 6pages, 2011.
7. 7.S. Choi-Kwon, J. Choi, S. U. Kwon,D.W. Kang, and J. S. Kim,"Fluoxetine is not effective in the treatment of poststroke fatigue: a double-blind, placebo-controlled study," *CerebrovascularDiseases*, vol. 23, no. 2-3, pp. 103–108, 2007.
8. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS. Hypovitaminosis D in medical inpatients. *N Engl J Med*. 1998;338:777–783.
9. Roy S, Sherman A, Monari-Sparks MJ, Schweiker O, Hunter K. Correction of Low Vitamin D Improves Fatigue: Effect of Correction of Low Vitamin D in Fatigue Study (EViDiF Study).N Am J Med Sci. 2014 Aug;6(8):396-402.
10. Poole KE, Loveridge N, Barker PJ, Halsall DJ, Rose C, Reeve J, Warburton EA. Reduced vitamin D in acute stroke. *Stroke*. 2006; 37:243–245.
11. Dev R, DelFabbro E, Schwartz GG, Hui D, Palla SL, Gutierrez N, *et al*. Preliminary Report: Vitamin D deficiency in advanced cancer patients with symptoms of fatigue or anorexia. Oncologist 2011; 16:1637-41.
12. Askmark H, Haggård L, Nygren I, Punga AR. Vitamin D deficiency in patients with myasthenia gravis and improvement of fatigue after supplementation of vitamin D3: A pilot study. Eur J Neurol 2012; 19:1554-60.
13. Huijts M, Duits A, Staals J, van Oostenbrugge RJ (2012) Association of Vitamin B12 Deficiency with Fatigue and Depression after Lacunar Stroke. PLoS ONE 7(1): e30519. doi:10.1371/journal.pone.003051
14. Turetsky A, Goddeau RP, Henninger N. Low serum vitamin D is independently associated with larger lesion volumes after ischemic stroke. J Stroke Cerebrovasc Dis 2015; 24(7):15555-63.
15. Wang S-S, Wang J-J, Wang P-X, Chen R (2014) Determinants of Fatigue after First-Ever Ischemic Stroke during Acute Phase. PLoS ONE 9(10): e110037. doi:10.1371/journal.pone.0110037
16. Choi-Kwan S, Han SW, Kwon SU, Kim JS (2005) Post-stroke fatigue: Characteristics and Related factors. Cerebrovasc Dis 19: 84–90.
17. Kim K, Cho KH, Im SH, Choi J, Yu J, Kim M. Decrement of serum vitamin D level after stroke. Annals of rehabilitation medicine. 2017;41(6):944.