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Monitoring vitamin D in the melanoma patient – impact of sun avoidance on vitamin D levels of melanoma patients at a tertiary UK referral melanoma service

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Clinicians across specialties are increasingly aware of health risks associated with vitamin D deficiency (VitD-). The link to bone health is obvious, but there is mounting evidence of associations with disorders including autoimmune and cardiovascular, diabetes, and various cancers (1). Vitamin D is endogenously synthesised in the skin by ultraviolet radiation or orally ingested (2). In the UK, few foods are supplemented with vitamin D, therefore, the main source is sun exposure. Unfortunately, patients in much of the UK are exposed to a UV index <3 for almost

half the year, significantly limiting their ability to obtain vitamin D from this modality.

Patients diagnosed with melanoma are advised to avoid sun exposure to reduce further melanoma risk; thus at danger of rendering them VitD- with long-term health consequences. Data from the Leeds melanoma cohort suggested that sub-optimal vitamin D may be associated with poorer survival (2). Vitamin D has anti-proliferative effects on melanoma cell lines in-vitro, which have been linked to the vitamin D signalling pathway (3). Vitamin D metabolites can inhibit proliferation and induce differentiation in melanoma cells (4). Furthermore, vitamin D receptors are found on all immune cells (5), though precise association with immune-competence and cancer progression/regression is unclear.

We established a vitamin D (25-hydroxyvitamin D2/3) testing service for melanoma patients according to previous protocols (2,6). Patients are tested at:

- Primary diagnosis
- Routine follow-up (two years after primary diagnosis, annually thereafter)
- At recurrence

We aimed to determine the effects of sun avoidance advice on vitamin D levels in these cohorts, thereby auditing the feasibility and utility of offering this service at our centre.

A prospectively-planned audit was registered and undertaken one year after establishing our testing service. We identified all melanoma patients who underwent vitamin D testing from May 2013-April 2014. Normal serum vitamin D level ranged from 50-120nmol/L according to local guidelines. Accordingly, for the purpose of this audit, we classified levels <50 nmol/L as deficient (regardless of terminology use in other references) since this indicated the level at which we would recommend supplementation. Parameters examined included patient demographics, tumour characteristics and vitamin D levels. Statistical analysis was performed using two-tailed Mann-Whitney U-test and Chi^2 analysis for comparing between patients at diagnosis and routine follow-up.

407 melanoma patients who underwent vitamin D testing were identified. 102 patients were tested at primary melanoma diagnosis; 289 at follow-up and 16 at recurrence. Median age was 66 years (21-90 years). Female to male distribution was equal (153:154).

Table 1 summarizes the results. Key findings were:

- Overall incidence of vitamin D deficiency was 9% greater in the follow-up cohort compared to the primary diagnosis cohort (55% versus 46%, respectively; Mann-Whitney: p=0.017)
- Vitamin D deficiency was significantly associated with ulcerated primary tumours (p=0.06) and those with a higher mitotic index (median 4/mm^2 versus median 1/mm^2, Mann-Whitney: p=0.012)
- Age was linked to vitamin D deficiency in the primary and follow-up groups; patients aged ≥65 years were more likely to be VitD- (p<0.000, P<0.001)
- We found no seasonal variation in the vitamin D levels in all groups.

Our audit has revealed a significant trend towards increasing vitamin D deficiency in melanoma patients in long-term follow-up, though initial incidence in melanoma patients at diagnosis was also high (46%). Older patients and those with higher-risk primaries were more likely to be VitD- and should be specifically targeted. Primary tumours in the VitD- cohort were associated with higher mitotic rate and ulceration; both characteristics have well-known-associations with lower survival probability (7). VitD- is common in the UK melanoma patient and is associated with risk of melanoma relapse (2). Currently, evidence is lacking regarding direct therapeutic value of vitamin D supplementation in melanoma patients and the need for further research in this area has been highlighted (8).

At our centre, baseline vitamin D is measured at time of melanoma diagnosis. When levels are within normal range, dietary advice is given. If levels are <50nmol/L, vitamin D3 supplementation of 1200IU (30micrograms) is commenced once daily for at least 6 months. If severe deficiency is detected (<20nmol/L), then supplementation

is increased. Calcium levels are monitored six weeks after to ensure no unmasking of hyperparathyroidism. Vitamin D levels are re-checked at 6 months. If levels have moved into normal range, supplementation of 400IU (10micrograms) is advised during the winter months. There remains debate to ideal levels of vitamin D. Our local range is 50-120nmol/L, though higher level (60-85nmol/L), depending on the season, has been suggested as at this level, parathyroid hormone reach a basal level and is not reduced with vitamin D supplementation (6,9)

Our data suggests that measuring vitamin D levels may be of benefit in melanoma patients, with appropriate supplementation prescribed according to local/NICE guidance (8,10). In future, as vitamin D testing becomes more widely available and the correction of deficiency more commonplace, this service is likely to be undertaken in primary care.

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	Vitamin D levels		**<50 nmol/L**	**≥50 nmol/L**
Primary diagnosis (n = 102)	Total		47	55
	Age	≤65 years	18	28
		>65 years	29	27
	Ulcerated primary tumour		17	11
	Unknown ulceration		2	4
	Median mitotic index (/mm^2)		4	2
Post-primary diagnosis (n = 289)	Total		162	129
	Age	≤65 years	83	61
		>65 years	79	66
	Ulcerated primary tumour		26	26
	Unknown ulceration		13	13
	Median mitotic index (/mm^2)		3	3
At recurrence (n = 16)	Total		6	10
	Age	≤65 years	3	2
		>65 years	3	8
	Ulcerated primary tumour		2	4
	Unknown ulceration		2	5
	Median mitotic index (/mm^2)		8	8

Table 1: Result summary.