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Short Communication

# Vitamin A deficiency: experience from a tertiary referral UK hospital; not just a low- and middle-income country issue

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## Abstract

*Objective:* Vitamin A (VA) deficiency, more common in low- and middle-income countries (LMIC) secondary to malnutrition, is associated with increased morbidity and mortality. The prevalence and impact of VA deficiency in high-income countries (HIC) where chronic conditions may predispose is less well understood.

*Design:* Interpretation of serum retinol may be affected by inflammation, so C-reactive protein (CRP) levels were sought. Binary logistic regression and generalised estimating equations were performed to review the relationship between CRP and VA.

*Setting:* We examined the scale of low and deficient VA status in our tertiary University Teaching Hospital (HIC).

*Participants:* Patients undergoing serum retinol concentrations 2012–2016 were identified from laboratory records, and records examined.

*Results:* Totally, 628 assays were requested, with eighty-two patients VA low (0·7–0·99 Umol/l) or deficient (<0·7 Umol/l). Sixteen patients were symptomatic (fifteen deficient), predominantly visual. Only one symptomatic patient's VA deficiency was secondary to poor intake. Other symptomatic patients had chronic illnesses resulting in malabsorption. The incidence of a low VA level increases significantly with a raised CRP.

*Conclusion:* The majority of patients tested either were replete or likely to have abnormal VA levels due to concomitant inflammation. A minority of patients had signs and symptoms of VA deficiency and was a cause of significant morbidity, but aetiology differs from LMIC, overwhelmingly malabsorption, most commonly secondary to surgery or hepatobiliary disease. A correlation between inflammation and low VA levels exists, which raises the possibility that requesting a VA level in an asymptomatic patient with active inflammation may be of questionable benefit.

**Keywords**
Vitamin A
Deficiency
Inflammation
Malnutrition
Night blindness

Vitamin A (VA), retinol, is a fat soluble unsaturated organic compound[1]. It is required for vision, cell function for growth, reproduction, haematopoiesis and immunity[2], both innate and adaptive immune systems[3]. One of its metabolites, retinoic acid, enhances cytotoxicity[4] and T-cell proliferation[5], possibly by enhanced IL-2 production, and influences antigen presentation by modulation of dendritic cell function[6]. VA is required for the production of visual pigments for the two photoreceptor cells, rods (low-light vision) and cones (bright-light and colour), as the precursor to retinal. In rod cells, retinal and opsin combine to create rhodopsin, which is the photosensitive pigment required for dark adaptation[7,8].

VA can only be obtained from the diet, as retinol from animal sources, such as dairy, meat, fish and eggs,

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and/or provitamin A (e.g. β-carotene) from plant sources, such as green leafy vegetables, through food fortification and food supplements, and cannot be synthesised by the human body[1].

VA deficiency is associated with increased morbidity and mortality from infectious diseases, visual disturbance, classically night blindness, anaemia, growth retardation and reduced fertility[9]. VA deficiency is primarily associated as a serious public health problem in low- and middle-income countries (LMIC). In the WHO 2009 report, low VA levels were estimated to affect 190 million preschool children and 19·1 million pregnant women worldwide and remains a significant cause of morbidity and mortality[10]. Night blindness was present in 5·2 million preschool children and 9·8 million pregnant women[10]. VA deficiency is increasingly seen in high-income countries (HIC), often as a result of chronic conditions such as chronic pancreatitis, chronic liver disease[11] and other causes of gastrointestinal malabsorption, for example bariatric surgery or short bowel syndrome and intestinal failure. Identifying VA deficiency may be challenging with just undertaking blood sampling[10] given its complex relationship with inflammation and other micronutrient deficiencies such as Zn, and therefore should be interpreted with caution and preferably with clinical details to corroborate any low readings.

### *Design and setting*

We undertook a clinical service evaluation, registered with the Clinical Audit Department, to review the pattern of testing for low or deficient VA status within the Hospital Trust in the UK and the clinical indications for undertaking the investigation. We aimed to identify if there were clinical symptomatic consequences of severe VA deficiency and whether the presence of inflammation influenced the serum retinol concentration. VA levels were determined as serum retinol concentrations by the City Hospital Vitamin Laboratory, Sandwell and West Birmingham Hospitals NHS Trust, using HPLC.

### *Participants*

All patients undergoing a serum retinol concentration between 2012 and 2016 in a large tertiary centre in a HIC were identified through laboratory records. A serum retinol concentration of <1 Umol/l was considered as low or deficient in keeping with the HPLC assay lower limit of normal utilised at the Vitamin Laboratory, City Hospital. We acknowledge that the WHO use a cut-off of <0·7 Umol/l for deficiency and 0·7–1·05 as low, but this figure is utilised as a population deficiency marker rather than individual cases[10]. All those patients who were low or deficient in VA were reviewed and the following information was collected on standardised data collection forms: (a) indication for the test; (b) patient symptoms; (c) past medical history and (d) and which specialty requested the test. If a patient was symptomatic and treated with VA replacement, the following data were collected: (a) the treatment given and (b) whether there was clinical or biochemical improvement. The possibility of any inflammation was sought by the presence of a CRP within 2–3 months of the VA assay in all of those who were low or deficient and also one in five, selected sequentially, of those with a normal VA level. Binary logistic regression analysis was undertaken to explore whether the probability of an abnormal VA level varied with CRP, and because some patients had several entries, a generalised estimating equation was also undertaken (IBM SPSS Statistics for Windows, Version 22.0. IBM Corp.).

## Results

Of 628 requests for VA levels 2012–2016, 110 serum retinol concentrations were low or deficient in a total of eighty-two patients. Sixty-two patients were deficient by the WHO criteria (<0·7 Umol/l), whilst forty eight were defined as having low serum retinol concentrations (0·7–0·99 Umol/l). There were a further seventeen patients with a serum retinol concentration between 1 and 1·04 Umol/l, who were not defined as abnormally low according to the laboratory assay utilised (and thus not in the current study), but a range that could be considered as low according to international criteria. CRP values were available for all but 8 of the low or deficient serum retinol concentration cases (*n* 102). The majority of patients (*n* 66, 80 %) did not report symptoms and their hypovitaminosis was diagnosed as part of the management of their chronic disease. Serum retinol concentrations were requested by a variety of specialties but most commonly by liver (*n* 36, 45 %), gastroenterology/nutrition (*n* 27, 33·8 %) and ophthalmology (*n* 10, 12·5 %) with neurology (*n* 2) and hepatobiliary surgery (*n* 2) being the larger of the remaining groups.

Sixteen patients were symptomatic (20 % of those with serum retinol levels below the laboratory lower limit of normal), presenting with predominantly visual symptoms: night blindness (*n* 10), blurred vision (*n* 2), night blindness and recurrent miscarriage (*n* 1) reduced/poor vision (*n* 2) and xerophthalmia (*n* 1). All but one were in the deficiency range (<0·7 Umol/l). Serum retinol concentrations ranged from 0·10 to 0·85 Umol/l, mean 0·34 Umol/l, median 0·26 Umol/l and interquartile range 0·34 Umol/l as described by the responsible clinician in the medical notes. Only one symptomatic patient's VA deficiency was primarily due to inadequate dietary intake. All other symptomatic patients had coexisting chronic illnesses resulting in malabsorption, including primary biliary cirrhosis, intestinal failure due to multiple resections for Crohn's disease, small bowel neuroendocrine tumour and malabsorption post gastric bypass (Table 1).

Patients with serum retinol levels below the lower limit of normal were more likely to have abnormal CRP levels

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**Table 1** Distribution of symptoms

| Symptom | No. of patients | Median retinol concentration: Umol/l | IQR |
|---|---|---|---|
| Night blindness | 10 | 0·22 | 0·19 |
| Reduced vision | 2 | 0·45 | |
| Blurred vision | 2 | 0·625 | |
| Xeropthalmia | 1 | 0·14 | |
| Night blindness and recurrent miscarriages | 1 | 0·39 | |
| Total no. of symptomatic patients | 16 | | |

(59 % *v.* 44 %). The higher the abnormal CRP level, the more likely it was that the serum retinol concentration was abnormally low. Figure 1 shows the estimated probabilities based on the logistic regression ($P = 0{\cdot}026$) and the generalised estimating equation ($P = 0{\cdot}031$).

Symptomatic and asymptomatic patients were managed with a variety of VA supplements. Forceval and Dalivit were the most commonly prescribed oral supplementation. Symptomatic patients saw variable responses to VA replacement, some improving clinically, others only biochemically (Table 2).

## Discussion

We have demonstrated those with VA deficiency, or even a low serum retinol concentration as seen in one case, may have significant morbidity in a HIC, and not only in LMIC. Whilst the WHO utilises a lower limit of <0·7 Umol/l to define deficiency and 0·7–1·05 Umol/l as low, this is based on population basis rather than an individual basis. We adopted the lower limit of normal as 1·0 Umol/l in keeping with the serum retinol concentration assay used, but differentiated between low and deficient ranges. However, the overall number of patients low or deficient in VA appears to be small, accepting that many are not considered for testing, with only 628 assays being requested, around 125 per year in a large tertiary academic centre, which is likely to see a higher concentration of more severe hepato-biliary disease than a district general hospital in a HIC. The cause of deficiency is dissimilar to LMIC (poor diet and malnutrition), overwhelmingly due to malabsorption, most commonly secondary to surgery or hepatobiliary disease.

Presenting symptoms amongst the deficient patients (and one symptomatic case with a low level of 0·85 Umol/l) were predominantly visual, with the classical presentation being night blindness, and as such may be underreported by patients. However, from work in LMIC VA deficiency is known to cause immunosuppression with increased mortality from infectious diseases, anaemia, growth retardation and reduced fertility, in addition to visual disturbance[2]. It would seem possible that these complications are unrecognised, particularly as chronic illness may be blamed, especially with normocytic anaemia, which may be attributed to be anaemia of chronic disease rather than VA deficiency.

Given the reported prevalence of VA deficiency found in certain populations, for example 33 % of patients with Primary Biliary Cirrhosis[11], with the mechanism of

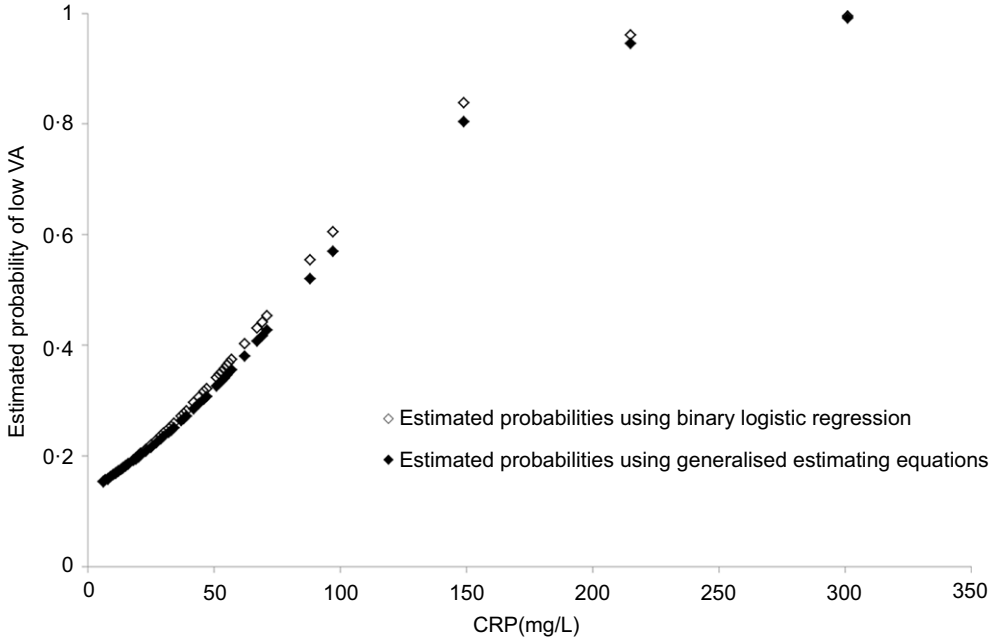


**Fig. 1** The estimated probability of the serum retinol concentration being low plotted against C-reactive protein (CRP) level. Hollow diamonds are from binary logistic regression (i.e. ignoring the fact that some patients have multiple 'serum retinol concentrations-CRP pairs'), $P = 0{\cdot}026$. Shaded diamonds are from generalised estimating equations, $P = 0{\cdot}031$. These probabilities relate to the original sample of 628 assays. (The estimated odds were divided by 5 to adjust for the 1 in 5 sampling of the normal serum retinol concentrations.) Y-axis legend: low VA = low serum retinol concentration

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**Table 2** Symptomatic patients' serum retinol concentration, underlying aetiology/disease, treatment and response to management

| | Aetiology of hypovitaminosis A | Retinol concentration (Umol/l) | Age (years) | Symptoms | Dept. requesting assay | Treatment | Response to treatment |
|---|---|---|---|---|---|---|---|
| 1 | Liver cirrhosis secondary to alcohol and inadequate intake | 0·1 | 60 | Night blindness | Ophthalmology | Forceval | Clinical Response |
| 2 | Crohn's disease | 0·1 | 55 | Night blindness | Gastro/Nutrition | Forceval | Clinical Response |
| 3 | Small bowel bacterial overgrowth | 0·14 | 48 | Xerophthalmia | Ophthalmology | Intravenous vitamin A infusion | Clinical response |
| 4 | Primary sclerosing cholangitis | 0·14 | 72 | Night blindness | Liver | Vitamin A and D capsules | Unknown |
| 5 | Liver cirrhosis secondary to alcohol | 0·15 | 60 | Night blindness | Liver | Underwent liver transplant | N/A |
| 6 | Carcinoid syndrome (small bowel NET) | 0·2 | 67 | Night blindness | Gastro/nutrition | Forceval | Clinical response |
| 7 | Liver cirrhosis secondary to alcohol | 0·24 | 58 | Night blindness | Ophthalmology | Forceval | Unknown |
| 8 | Liver cirrhosis secondary to alcohol | 0·24 | 63 | Reduced vision | Ophthalmology | Oral supplements | Unknown |
| 9 | Coeliac disease | 0·28 | 75 | Night blindness | Ophthalmology | Unknown | N/A (died) |
| 10 | Primary biliary cirrhosis | 0·33 | 63 | Night blindness | Liver | Vitamin A and D capsules | Clinical response |
| 11 | Crohn's disease with multiple resections | 0·35 | 70 | Night blindness | Ophthalmology | Intravenous vitamin A infusion | Clinical response |
| 12 | Roux-en-Y gastric bypass | 0·39 | 33 | Night blindness and recurrent miscarriage | Gastro/Nutrition | Intravenous vitamin A infusion then $\beta$ carotene | Clinical response |
| 13 | Severe pancreatic exocrine insufficiency | 0·57 | 51 | Blurred vision | Neurology | Forceval and Creon | Clinical response |
| 14 | Primary biliary cirrhosis | 0·65 | 42 | Poor vision | Liver | Forceval | Unclear and now post liver transplant |
| 15 | Primary biliary cirrhosis | 0·68 | 79 | Blurred vision | Liver | Oral supplement | No |
| 16 | Aetiology unknown | 0·85 | 71 | Night blindness | Ophthalmology | Oral supplements | No |

malabsorption being reduced concentrations of intraluminal bile, and 39 % of patients following bariatric gastric bypass surgery (*v.* 28 % sleeve gastrectomy) at 6 months[12], we suggest that VA deficiency may be under-recognised in HIC. In our tertiary centre with a large Hepatobiliary and Liver Transplant Unit, one would expect a larger population of patients identified as being VA deficient. One would also expect that even though our hospital is not a specialist centre for bariatric surgery, given the growing population of patients who have previously undergone bariatric surgery, we would see a larger number of these patients being diagnosed and treated. Our hepatology services have a well-established dietetic support team who recommend fat-soluble vitamin oral supplementation empirically, which may reduce the number of VA assays requested.

Among pre-school aged children and pregnant women in LMIC, it is evident that the presence of infection such as malaria[13] and inflammation[13,14], causing a rise in inflammatory markers leads to a lower serum retinol concentration, which is likely to lead to a false interpretation of VA deficiency and unnecessary VA supplementation[15]. Serum retinol levels are known to return to baseline levels once the inflammatory/infective period has resolved, suggesting redistribution between body stores, despite the possibility of decreased intake due to poor appetite, decreased intestinal absorption and urinary losses associated with the inflammatory phase[16]. Indeed correction of VA levels by inflammatory markers has brought the resulted level back to a similar value as the healthy population[17], but this metanalysis was predominant among pre-school children and pregnant women in LMIC. However, using a relative dose response test to estimate liver stores in patients with Crohn's disease, VA deficiency by serum assay was not only confirmed but also shown to underestimate the issue[18]. In our evaluation, there is a clear relationship between inflammation as estimated by the CRP and VA deficiency, although we acknowledge that the CRP half-life of 21 d may not reflect in chronology to the serum retinol concentration, but as this evaluation is dealing with chronic conditions these seems a fair assumption to have taken. Only 16 of the 80 patients with a low retinol concentration developed symptoms of deficiency, and of these particular cases fifteen were defined as deficient (<0·7 Umol/l). This would suggest that the remaining cases may well not be truly deficient, noting that previous research comparing cadaveric plasma VA levels and liver stores did not correlate well but this was in a small study in Thai road accident victims[19] and may not be representative of population data. This must be noted as an example of limitations of utilising an assay for an estimation of deficiency.

We acknowledge that this retrospective service evaluation is limited by the very nature of the study design, with analysis of those in whom clinicians have considered VA deficiency, rather than testing all patients. It is, however, evident that it is common practice in our hepatology

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services to consider supplementing patients with risk of malnutrition and Primary Biliary Cirrhosis with fat-soluble vitamins including A and D as a matter of standard practice, reducing both the number of assays requested and potential morbidity. Furthermore, we have not examined the potential morbidity and mortality from infectious diseases or anaemia, nor the effect on patients' quality of life from infertility. Early recognition and testing/treatment of at risk patients is crucial though as patients could be left with long-term visual impairment, given the symptoms seen in this cohort with VA deficiency.

This evaluation illustrates that the majority of serum retinol concentrations requests either did not yield a low or deficient level or that the low/deficient level is likely to have been influenced by on-going inflammation. It is noted that the WHO do not recommend the use of serum retinol as a marker of VA deficiency, with issues concerning infections, both clinical and subclinical reducing the result by 25 % artificially, zinc deficiency affecting both the result and also retinol-binding protein and finally that VA levels may not be normally distributed[20]. We have thus tried to focus on those with both a deficient serum retinol concentration (<0·7 Umol/l) and clinical signs in this paper to be more robust. A small proportion of individuals had significant deficiency leading to symptoms and signs and clearly warranted intervention. There should be a low threshold for checking VA status in those patients with early symptoms consistent with VA deficiency and chronic diseases which can predispose to malabsorption of fat-soluble vitamins, and monitoring of those in specific situations such as intestinal failure requiring long-term parenteral support. However, routine testing is unlikely to be of meaningful benefit, especially in the presence of active inflammation. In the situation where inflammation is suspected, markers of such (e.g. CRP) should be undertaken at the same time to give the best possible opportunity to allow a more accurate interpretation.

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## Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S1368980021003347

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