

Does Vitamin D Deficiency Affect Diabetic Retinopathy?: A Primary Care Survey and Literature Review

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Received: August 30, 2016; **Published:** October 20, 2016

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Introduction: The objective of this paper is to review the literature on the relationship between VD deficiency (VDD) and DR, and assess current practice at a primary care level with the aim to increase awareness of the impact vitamin D levels can have on eye disease.

Methods: A cross sectional survey was conducted with a web-based, self-completion questionnaire. Information regarding awareness of the effect of VDD in diabetic patients as well as current prescribing habits of vitamin D supplements amongst general practitioners (GP) within West Midlands, was collated. The results of 63 respondents were analysed using Microsoft Excel.

Results: 81.2 % of GPs did not check serum 25 hydroxyvitamin D levels in DR patients. Only 3.45% of GPs commenced patients with background diabetic retinopathy on Vitamin D supplements.

A qualitative analysis revealed 41.4% of GPs believe Vitamin D supplements are not indicated in patients with DR. 13.8% were not aware this was indicated.

Discussion: VDD has been implicated in the development of diabetic retinopathy (DR). The evidence suggests serum 25(OH)D are low in diabetics, and is inversely related to the severity of retinopathy.

Our survey looked at current practice amongst GPs in the West Midlands where there is a high percentage of ethnic minorities who are predisposed to VDD as well as being diabetics. Clinicians need to be aware of the relationship between VDD and DR, with a view to tackling both where possible. We recommend investigating VD levels and commencing treatment early, in the light of the literature reviewed.

Keywords: *Vitamin D Deficiency; Diabetic Retinopathy; Type 1 Diabetes; Type 2 Diabetes; Primary Care*

Introduction:

Diabetic Retinopathy is a leading cause of preventable sight loss within the working age population in the United Kingdom (UK) [1]. The prevalence of any diabetic retinopathy (DR) and sight-threatening DR in those with type 1 diabetes has been reported to be as high as 56.0% and 11.2%, respectively, and in type 2 diabetics 30.3% and 2.9%, respectively [2].

There are numerous publications on the significant role Vitamin D (VD) plays in the biochemical processes of diabetic retinopathy (DR).

In addition to its classical role of bone and mineral homeostasis, VD has modulatory effects on inflammation and endothelial cell proliferation as well as angiogenesis, all of which are involved in the development of DR [3].

Recent studies have shown high prevalence of vitamin D deficiency (VDD) in both type 1 and type 2 diabetics compared to non-diabetics [4,5]. Some suggest a link between VDD and the severity of DR [5].

The objective of this paper is to review the literature on the relationship between VDD and DR, and assess current practice at a primary care level with the aim to increase awareness of the impact vitamin D levels can have on eye disease.

Methods:

A cross sectional survey was conducted, and information regarding awareness of the effect of VDD in diabetic patients as well as current prescribing habits of vitamin D supplements amongst general practitioners (GP), was collated within the West Midlands region in the United Kingdom.

GPs were contacted by email using a regional database. A web-based, self-completion questionnaire (Figure 1) was circulated for a period 3 months between April 2015 and June 2015.

- 1) Do you check serum 25 hydroxyvitaminD levels in patients with diabetic retinopathy?
Yes NO
- 2) When do you start patients on vitamin D supplements?
If they have a diagnosis of osteoporosis
If they have musculoskeletal symptoms indicating osteoporosis
If they have intestinal malabsorption (ed. Coeliac disease, Crohn’s disease, gastrectomy)
If they have liver disease
If they have renal disease
When taking certain medications such as anticonvulsants, cholestyramine, rifampicin, antiretrovirals
If they have diabetic retinopathy
- 3) Do you routinely start patients with diabetic retinopathy on vitamin D supplements?
Yes NO
- 4) At what stage of retinopathy do you start patients on vitamin D supplements?
R1 (background diabetic retinopathy)
R2 (non-proliferative retinopathy)
R3 (proliferative retinopathy)
R3P (stable treated proliferative retinopathy)
M1 (maculopathy)
MIP (stable treated maculopathy)
- 5) Why do you start patient with diabetic retinopathy on vitamin D supplements?
Not indicated
When advised by ophthalmologist
When vitamin D levels are low
Not aware this is indicated
Non applicable.

Figure 1: Online Questionnaire.

63 GPs responded and the results of the survey were analysed using Microsoft Excel.

Results:

In patients with DR 81.2 % of GPs who participated in the survey did not check serum 25 hydroxyvitamin D levels whilst only 18.8 % did (Figure2) (Graph 1). The most common reason for starting VD supplements was osteoporosis, with 79.31% of GPs commencing treatment in such patients. Followed by 51.72 % starting in those with musculoskeletal disorders, 41.38% in patients with intestinal malabsorption, 27.59% in patients with renal disease, 10.34% started supplements if patients where on certain medications such as anticonvulsants, cholestyramine, rifampicin and/or antiretrovirals. Only 3.45% of GPs commenced patients with background diabetic retinopathy (digital staging R1) on Vitamin D supplements (Figure 2) (Graph 2). None of the GPs in our survey routinely started patients with DR on Vitamin D supplements (Figure 2) (Graph 3).

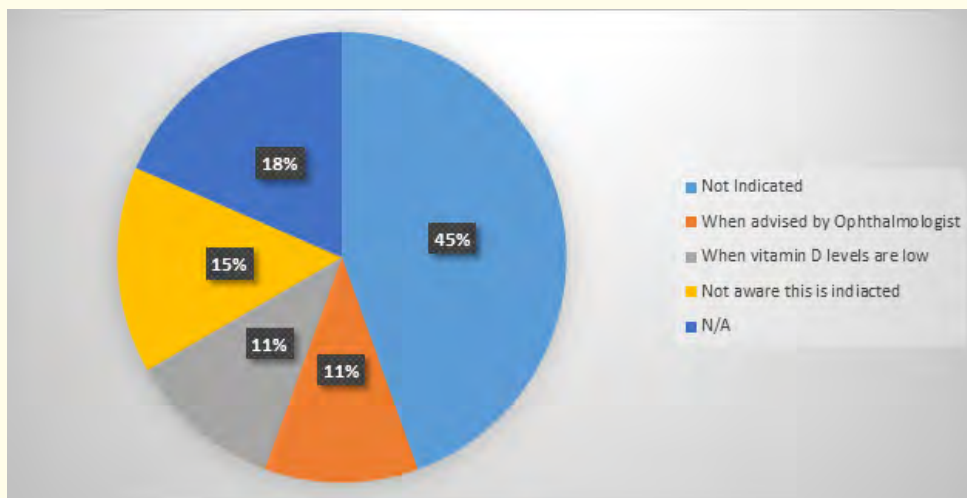
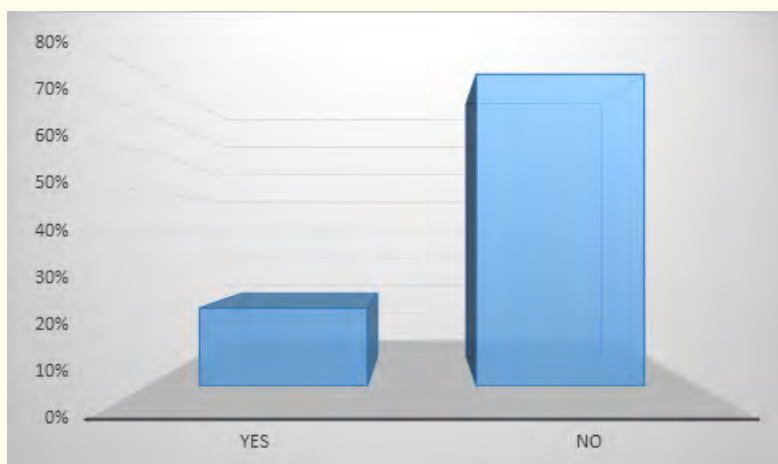
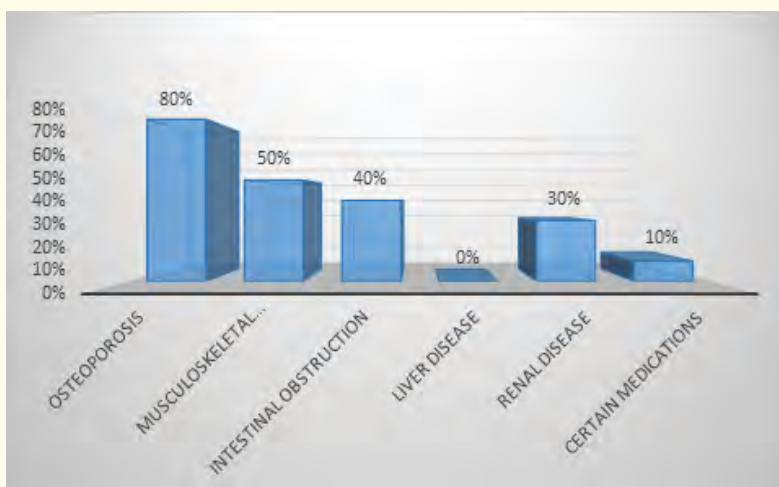


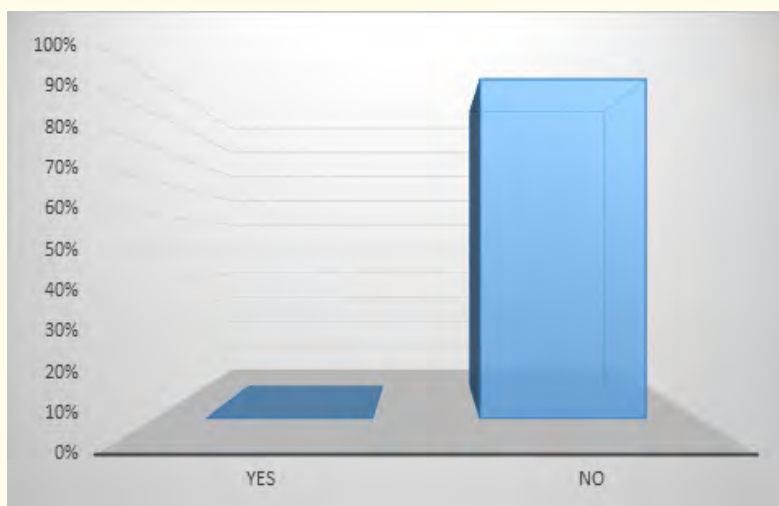
Figure 2: Why do you start patients with diabetic retinopathy on Vitamin D supplements?



Graph 1: Do you check serum 25 Hydroxyvitamin D levels in patients with diabetic retinopathy.

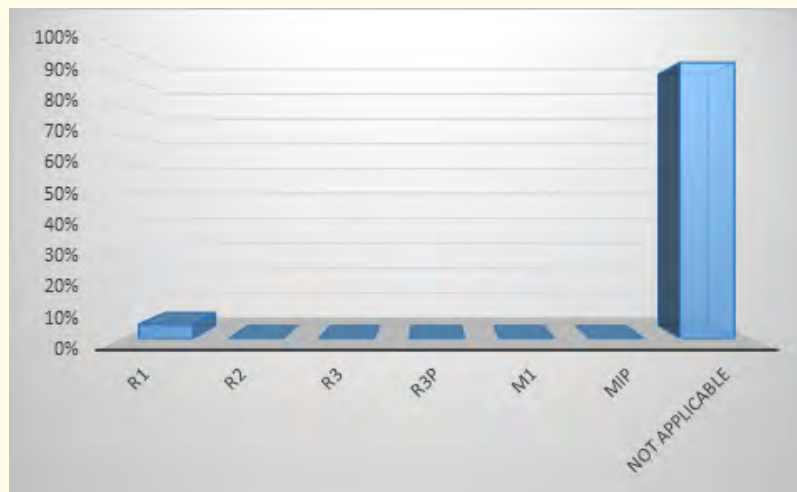


Graph 2: When do you start patients on Vitamin D supplements?



Graph 3: Do you routinely start patients with diabetic retinopathy on Vitamin D supplements?

A qualitative analysis revealed 41.4% of GPs believe Vitamin D supplements are not indicated in patients with DR. 17.2% felt the question was not applicable. 13.8% were not aware this was indicated and 10.3% started medication either when advised by ophthalmologists or if vitamin D levels were low (Figure 2) (Graph 4).



Graph 4: At what stage of retinopathy do you start patients on Vitamin D supplements?

Discussion:

Vitamin D deficiency (VDD) has been implicated in the development of diabetes complications, specifically diabetic retinopathy (DR) [6-11].

It has a number of metabolites the 2 most important of which are 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) and 25 vitamin hydroxyapatite {25(OH)D}. The serum concentrations of both have been used to quantify vitamin D deficiency and study its relationship with diabetic retinopathy.

In a mouse model of Ischaemic retinopathy, 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) has been shown to inhibit retinal neovascularization [10] and in cell cultures it inhibited endothelial cell proliferation [11], most likely due to its interaction with vascular endothelial growth factor (VEGF).

Genetic studies have revealed that vitamin D receptor (VDR) is present in the human retina, and polymorphisms of VDR are related to retinopathy risk in type 1 diabetes. For example, the Fok 1 single nucleotide polymorphism of the VDR gene has been associated with increased transcriptional activity of the VDR gene and less severe diabetic retinopathy [12] and Taq 1 polymorphism of VDR gene with decreased incidence of retinopathy [13].

This protective role vitamin D may have on the diabetic retina has been further explored by several studies in recent years, which have investigated the epidemiological evidence in humans.

A large American study looked at 1790 diabetics in United States of America (USA), and the percentage of individuals with vitamin D deficiency increased with severity of retinopathy. However, the study did not demonstrate a statistically significant relationship between severity of retinopathy and serum 25(OH)D concentration [14].

A Turkish study carried out in 2000 compared serum 25(OH)D between 66 diabetic patients and 20 non diabetics and found it to be significantly lower in diabetics. The study also found an inverse relationship between the severity of retinopathy and serum 25(OH)D concentrations which was lowest in patients with proliferative diabetic retinopathy (PDR). The authors suggested that measurement of serum 25(OH)D maybe helpful in predicting severity of DR in diabetic patients [15] Suzuki, *et al.* studied this relationship in Japanese type 2 diabetics and found patients with proliferative retinopathy had lower serum 25(OH)D [16]. This was further confirmed by a cross

sectional study constituting 221 patients in USA, where patients with diabetes and specifically proliferative diabetic retinopathy had significantly lower serum 25(OH)D levels compared to non-diabetics [5].

Hala, *et al.* found this to be true in 136 Lebanese type 2 diabetics with retinopathy, and vitamin D levels were an independent predictor of retinopathy [17]. In China 1520 type 2 diabetics with retinopathy had low serum 25(OH)D concentrations and this link was more significant in those with sight-threatening retinopathy [12]. This study found a two-fold increase in sight-threatening retinopathy among subjects with serum 25(OH)D below 15.57 ng/ml (normal range 20 - 50ng/ml). A Korean cross-sectional study also found 25(OH)D concentrations are lower in type 2 diabetics with any stage of retinopathy [13].

Gungor, *et al.* studied retinal nerve fibre layer (RNFL) thickness in type 2 diabetics with early diabetic retinopathy with and without VDD, and found low serum 25 (OH)D concentrations contribute to RNFL thinning. It is well known that in addition to vascular changes, the earliest stages of DR feature neurodegenerative processes such as loss of ganglion cells and thinning of retinal layers [18]. The study indicates that vitamin D has a neuroprotective component [19].

Interestingly, this relationship is also evident in type 1 diabetes both in adults as well as children and adolescents [3,20].

Because of the cross-sectional and/or observational nature of the majority of these studies, we cannot assume a causal relationship between VDD and retinopathy. However, the evidence is compelling in animal models, and the epidemiological evidence continues to grow with evolving research about a possible relationship between decreased levels of 25(OH)D and increasing severity of diabetic retinopathy.

This suggests the need for clinicians to be aware of the relationship between VDD and DR, with a view to tackling both where possible.

Our survey looked specifically at current practice amongst GPs in the West Midlands where there is a high percentage of ethnic minorities who are predisposed to VDD as well as being type 2 diabetics. The results show that 81.2% of clinicians surveyed do not check vitamin D levels in patients with diabetic retinopathy with only 3.45% commencing treatment in this patient population. A qualitative analysis of their rationale revealed 41.4% do not feel this indicated and 13.8 % were not aware of an indication. In a population with a high incidence of diabetic retinopathy and VDD, as in the West Midlands, investigating vitamin D levels and commencing treatment early needs to be considered, in the light of the literature reviewed.

In summary although the evidence available to date has its limitations, it remains strongly suggestive that VDD deficiency is present in higher proportions in both type 1 and type 2 diabetics compared to non- diabetics. Some studies have shown that an inverse relationship exists between serum 25(OH)D and severity of retinopathy with significantly low levels in patients with proliferative diabetic retinopathy. Our survey aims to analyse current literature on the topic in relation to current practice at a primary care level. Our survey reports that patients with diabetic retinopathy of any stage do not routinely have their vitamin D levels checked in the West Midlands. We suggest that diabetics with retinopathy should be tested for VDD and started on supplements if serum 25(OH)D or $1,25(\text{OH})_2\text{D}_3$ are low, at the discretion of their treating clinician, but with the evidence base reviewed in mind.

There are, of course, limitations to this study, the foremost of which is the representativeness and size of the sample. A challenge of any survey research is finding and recruiting participants from the target population, which is compounded by an online survey with its distribution limitations and survey bias. Although selection bias was minimized by contacting all registered practices in the region, the small sample size reflects non-response bias.

Further research is necessary to ascertain prescribing habits on a national level in order to standardize the care delivered to patients with vitamin D deficiency and Diabetic Retinopathy.

Declarations:

- The authors do not have any proprietary interest in any product mentioned.

- Funding was not required for the study
- Ethical approval was not required for the study

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Volume 4 Issue 1 October 2016

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