Austin Journal of Nutrition & Metabolism

Open Access

Austin Publishing Group

Review Article

Optimising Response to Chemotherapy in Colorectal Cancer Patients by Ensuring Adequate Vitamin D Status

Pamela R von Hurst*, Holland S and Coad J
Vitamin D Research Centre, College of Health, Massey University, New Zealand

***Corresponding author:** Pamela von Hurst, Vitamin D Research Centre, College of Health, Massey University, Private Bag 102904, Auckland, New Zealand

Received: July 14, 2015; **Accepted:** August 08, 2015; **Published:** August 11, 2015

Abstract

People with colorectal cancer, especially those receiving chemotherapy, are at increased risk of vitamin D deficiency compared with their healthy peers. This deficiency has the potential to increase the negative consequences of chemotherapy whilst lessening the effectiveness of the treatment. We hypothesize that there are a number of mechanisms by which simple supplementation with vitamin D could optimize response to treatment, reduce side effects and bolster overall health status in cancer patients, especially those receiving chemotherapy.

Keywords: Colorectal cancer; Oxaliplatin; CINV; Neuropathy; Vitamin D

Background

A recently published systematic review and meta-analysis reported significantly higher overall and disease-specific survival rates amongst colorectal and breast cancer patients with high vitamin D status compared to those with lower levels. Colorectal cancer patients had a 35% lower risk of disease-specific mortality if their 25 (OH) D concentrations were above 75 nmol/l. These highly significant results were improved even further when a study of stage IV cancer patients was excluded. Similar results were seen for breast cancer patients with a 43% risk reduction in disease specific mortality [1].

There are a number of potential mechanisms for these, and similar, findings mostly concerned with the antitumor effects of the active form 1α, 25-dihydroxyvitamin D. However, we propose that in addition to the above benefits, there are other means by which vitamin D may improve response to chemotherapy treatment and quality of life by increasing tolerance of side effects, resisting infection and maintaining good psychological health.

Hypotheses

- That colon cancer patients will generally have less than optimum vitamin D status (i.e. serum 25OHD < 75nmol/l or 30ng/ml)

- That optimizing vitamin D status to levels > 75 nmol/l will improve tolerance of treatment, nutritional status and quality of life based on the following:

  o That vitamin D deficiency plays a role in the development and severity of Oxaliplatin-induced peripheral neuropathy, and the perception of chronic pain.

  o That vitamin D deficiency reduces the effectiveness of corticosteroids such as dexamethasone which are used to ameliorate the side effects of chemotherapy.

  o That vitamin D, in its role as a moderator of serotonin, can affect mood and gastro-intestinal disturbances in cancer patients.

  o That vitamin D is a moderator of hepcidin secretion and thus has a potential role in enhancing iron status in chronically ill patients which may affect response to treatment.

  o That in its role as a moderator of the immune system, vitamin D can bolster innate defense systems and reduce risk of infectious disease in cancer patients.

Vitamin D Status in Colon Cancer Patients

Cancer patients receiving chemotherapy have an increased likelihood of being vitamin D deficient as they are instructed to avoid sun exposure due to drug-induced photosensitivity [2]. Fluorouracil, which is one of the most commonly used therapies in colorectal cancer, comes into this category [2]. Within a cohort of Stage IV colorectal cancer patients (n=515) Ng et al (2011) found 50% of participants to be vitamin D deficient (plasma 25(OH)D <20ng/ml [50nmol/l]) and 82% to be vitamin D insufficient (25(OH)D <30ng/ml [75nmol/l]) [3], whilst Fakih et al (2009) found the median 25(OH)D status to be 21.3ng/ml (53nmol/l) within a similar cohort (n=315) [4].

Vitamin D Supplementation in Chemotherapy Patients

It has now been well established that lower baseline 25(OH) D levels correspond with a greater response to supplementation in a range of populations [5,6], and the same has been shown to apply to cancer patients [7]. A retrospective observation of 2198 cancer patients who received 8000IU per day from the start of their cancer treatment indicated that type of cancer was a significant effector of response, with lung and prostate cancer having a better response (in terms of reaching 25(OH)D >32ng/ml by first follow-up, mean duration 14.9 weeks) and colorectal and pancreatic cancer patients having the lowest response [7].

Cancer patients receiving chemotherapy appear to have an attenuated response to vitamin D supplementation, as measured by serum 25(OH) D concentrations, compared with cancer patients not receiving treatment. In 46 colorectal cancer patients (baseline 25(OH)D 17.9 ng/ml) receiving 2000IU per day for three months, those receiving chemotherapy achieved a mean 25(OH)D of 28.7 ±10.3 ng/ml compared with 39.0 ±7.9 ng/ml in those receiving no

Citation: von Hurst PR, Holland S and Coad J. Optimising Response to Chemotherapy in Colorectal Cancer Patients by Ensuring Adequate Vitamin D Status. Austin J Nutr Metab. 2015; 2(4): 1027.

treatment. There was no significant change in concentrations between 3 and 6 months suggesting that levels had plateaued with 50% of the chemotherapy patients failing to achieve >32ng/ml [8].

Oxaliplatin, Neuropathy and Vitamin D

Oxaliplatin is a third generation platinum drug first approved for the treatment of colorectal cancer in 1999. The drug is usually provided in conjunction with 5-fluorouracil (5-FU) and leuvocorin (LV); 5-FU inhibits DNA & RNA synthesis with LV enhancing the overall affect. The combination of oxaliplatin and 5-FU/LV (referred to as FOLFOX) provides a two-fold higher tumour response rate (WHO criteria) when compared to 5-FU/LV alone [9].

Oxaliplatin-based chemotherapy regimens have proven to effectively slow disease progression and increase survival in advanced, metastatic stages of colon cancer. However, the associated peripheral neuropathy which appears to affect approximately 85-95% of patients often results in suspension of treatment, and severely impacts on quality of life [10,11]. Oxaliplatin-induced neuropathy appears in both acute and chronic forms, the first being transitory following treatment and the latter becoming more severe and neurotoxic as cumulative drug dose increases.

The mechanisms of the induction by oxaliplatin of these two distinct forms of neuropathy have yet to be fully elucidated; however is it thought that the acute form is caused by a dysfunction of the calcium-dependent voltage-gated sodium channels [12]. As calcium is rapidly chelated by the oxalates produced by oxaliplatin therapy, a standard prophylactic treatment is the co-administration of bolus doses of intravenous (IV) calcium and magnesium, thus theoretically supporting both extra- and intra-cellular homeostasis [13]. The variability in efficacy of this treatment could, hypothetically, be influenced by vitamin D status as the active hormone is involved in the expression of calcium influx and efflux channel proteins [14-16].

The chronic form is thought to be the result of neurotoxicity in the dorsal root ganglia (DRG) [17]. This is longer-lasting, potentially permanent, and more likely to disrupt treatment. The vitamin D receptor (VDR), together with the vitamin D metabolizing enzymes CYP27B1 and CYP24, is widely distributed throughout the nuclei of DRG neurons of the rat suggesting a range of transcriptional roles, including expression of neurotrophins [18]. The VDR has also been identified in the cytoplasm of nerve cells and could be involved in rapid signaling pathways in sensory neurons such as calcium channel activity. Vitamin D deficiency has been associated with low levels of neurotrophins and impaired neuronal calcium homeostasis in animal studies [19]. These deficiencies leave the neuron vulnerable to toxins, impaired nociceptor function, nerve damage and lowered pain threshold [19].

Vitamin D and Chronic Pain

It is possible that vitamin D may have a direct influence upon the perception of chronic pain, despite not appearing to be an effective treatment for chronic pain in most individuals [20]. Eyles et al [21] found the highest density of VDR receptors within the ventromedial hypothalamus and anterior cingulate cortex (the descending pain inhibitory control centre and modulator of endogenous pain control respectively). This could suggest that pain inhibition is dysfunctional in the vitamin D deficient state and that once the pain signalling pathways are activated, vitamin D repletion may not be sufficient to extinguish chronic pain. Should this theory find research support, it would be advisable to ensure patients have replete vitamin D status prior to the commencement of oxaliplatin therapy.

Diabetic Neuropathy – A Possible Lesson

Over recent years the aetiology of diabetes mellitus has been associated with vitamin D deficiency, resulting in considerable interest in the role of this pleiotropic secosteroid in the development of disease and the amelioration of symptoms. Fifty percent of diabetic patients suffer peripheral diabetic neuropathy caused by the neurotoxic effect of hyperglycaemia [22]. Vitamin D status has been inversely related to diabetic neuropathy in a large, ecological study [22] and in a smaller, observational study where 100% of the patients with neuropathy were vitamin D deficient [23]. Bell (2012) has reported a dramatic reversal of symptoms in a patient with long-term, severe diabetic neuropathy following high-dose vitamin D supplementation prescribed after a low 25(OH)D concentration was observed [24]. Finally, a recent meta-analysis of six studies (n=1484) reported that vitamin D deficiency was significantly associated with risk of neuropathy in diabetic patients (odds ratio 2.88, 95 % CI 1.84-4.50, $P < 0.001$) [25].

Vitamin D and Dexamethasone – A Mutually Beneficial Relationship

Control of chemotherapy-induced nausea and vomiting (CINV) is an essential component in assuring quality of life for cancer patients. Intravenously administered dexamethasone prior to treatment, with or without oral administration for 2-4 days following, has been shown to be an effective treatment for both acute and delayed CINV [26]. Dexamethasone is a powerful corticosteroid which is also a first line response to severe asthma. In asthma patients who appear to be steroid resistant, it has been shown that the anti-inflammatory effects of dexamethasone are greatly enhanced when administered with vitamin D supplementation [27]. It is therefore worth considering that vitamin D deficiency could impair the actions of dexamethasone's role in control of CINV.

Meanwhile, dexamethasone and vitamin D in combination have been shown to have antitumor effects in squamous cell carcinoma due to dexamethasone directly regulating the expression of the vitamin D receptor (VDR) gene. This results in increased *de novo* transcription of the VDR, amplifying the pro-differentiation and pro-apoptotic effects of vitamin D [28].

Vitamin D and Regulation of Serotonin Production

The neurotransmitter Serotonin or 5-hydroxytryptamine (5-HT) is synthesized in two steps from the essential amino acid, tryptophan. The first step involves the action of one of two tryptophan hydroxylases – TPH1 or TPH2 each localized in different tissues. TPH2 is found only in the brain where it is responsible for producing 5-HT. Unlike 5-HT, tryptophan can cross the blood-brain barrier, so the final steps of 5-HT metabolism have to take place *in situ*. TPH1, however, is found in non-brain tissues, especially the enterochromaffin cells in the gut.

Excessive release of 5-HT from the enterochromaffin cells in response to the cytotoxic effects of chemotherapy plays a significant role in CINV. 5-HT stimulates the vagal afferent nerves, initiating vomiting, thus making the 5-HT3 receptor antagonists an effective and popular choice in the treatment of CINV [29].

Vitamin D has been shown to regulate the expression of the genes coding for both TPH1 and TPH2, but with opposing effects; whilst activating and up-regulating transcription of TPH2, it appears that vitamin D represses transcription of TPH1 [30]. As a consequence of this differential regulation, optimal vitamin D status results in decreased expression of 5-HT in the peripheral tissue, especially the gut, and increased expression in the brain where its function is related to improved mood and lowered anxiety.

Vitamin D and Iron Status

Iron deficiency and iron deficiency anemia are very common in patients with colorectal cancer, affecting 30-90% patients [31]. Chronic blood loss associated with the gut lesions, surgery and inflammation predispose to iron deficiency which is exacerbated by chemotherapy and radiotherapy. Furthermore raised levels of inflammatory cytokines, such as interleukins 1 and 6 [32] and tumor necrosis factor [33], drive hepatic production of hepcidin which results in decreased ferroportin-mediated export of iron from the macrophages involved in erythrophagocytosis and from enterocytes absorbing dietary iron. The raised hepcidin concentration therefore results in functional iron deficiency, where the iron is sequestered within cells rather than being available for haemoglobin synthesis despite stores appearing to be adequate; functional iron deficiency is thus resistant to oral iron therapy. Furthermore, inflammatory cytokines also depress erythropoiesis.

The consequence of iron deficiency is associated with compromised response to FOLFOX treatment [34] deleterious effects on quality of life and a decrease in survival [35]. Patients with higher haemoglobin levels have better responses to chemotherapy [36]. Iron deficiency in cancer patients is traditionally treated with blood transfusions, erythropoiesis stimulating agents (ESA) and/or iron therapy. All of these approaches are fraught with complications. Blood transfusions are costly and increase transfusion-related problems [37] and all-cause mortality. The safety concerns about ESA treatment, which is associated with progression of disease and increased mortality [38], have led to recommendations that the lowest effective dose should be used; 30% of patients do not respond to ESA, probably because they have raised hepcidin levels. Oral iron is not well-tolerated and is ineffective in inflammatory states associated with high hepcidin concentrations. Although there are safety concerns about intravenous iron therapy, this is currently considered to be the most effective therapy [39].

Vitamin D is anti-inflammatory; it suppresses hepcidin secretion [40]. Patients with chronic kidney disease have high levels of inflammatory cytokines. Their serum 25(OH)D levels are inversely associated with hypo responsiveness to ESA and positively associated with haemoglobin concentrations [41]. In anemic patients undergoing haemodialysis, vitamin D supplementation results in lower requirements for ESA. We conjecture that optimising vitamin D status prior to chemotherapy, through supplementation strategies, will suppress inflammation and reduce hepcidin concentrations so responses to oral or intra-venous iron therapy will be enhanced. The improved iron status would thus positively affect responses to chemotherapy.

Vitamin D and Innate Immunity

The rapid and effective response of the innate immune system to infectious pathogens is dependent on adequate vitamin D status for a number of functions. The induction of the antimicrobial peptides, cathelicidin and beta-defensin by toll-like receptors is mediated by a vitamin D-dependent signaling pathway, together with vitamin D response elements in the promoter regions of both genes [42]. In the intestine, vitamin D is essential for maintaining the integrity of the epithelial barrier [43], reducing injury from pathogen invasion and mucosal inflammation [44], and enhancing the integrity of intercellular junctions by inducing junction protein expression [45]. These mechanisms are probably common to other mucosal epithelia such as those in the respiratory tract, although at this stage this does not appear to have been investigated. Interventions with supplemental vitamin D have demonstrated improved resistance to respiratory infections in populations of children [46,47] and immune-compromised adults [48].

Summary

The majority of vitamin D supplementation trials currently proposed or underway tend to be concerned with preventing the development of cancer. Such trials are by their very nature difficult, long and expensive.

Research to test the effect of improved vitamin D status on patients undergoing chemotherapy with easily measured outcomes such as tolerance of side effects, improved iron status and resistance to respiratory infections is pragmatic, affordable and manageable. Although there is a lack of consensus regarding optimum 25(OH) D concentrations it does appear that patients with cancer and with diabetic neuropathy are advantaged by levels >32ng/ml (75 nmol/l) [1,22]. Therefore it will be important to establish supplementation protocols which are certain to achieve and maintain these levels in cancer patients regardless of other treatment protocols, baseline levels or the range of other factors known to affect response to supplementation [49].

The findings of such straight-forward studies would have the potential to change clinical practice in a very moderate and inexpensive way, whilst possibly making a considerable difference to quality of life, if not response to treatment and increased survival in patients undergoing cancer treatment.

References

1. Maalmi H, Ordóñez-Mena JM, Schöttker B, Brenner H. Serum 25-hydroxyvitamin D levels and survival in colorectal and breast cancer patients: systematic review and meta-analysis of prospective cohort studies. *Eur J Cancer*. 2014; 50: 1510-1521.

2. Birner AM, Meyer LP. Photosensitivity associated with fluorouracil, prochlorperazine, and topical tretinoin. *Pharmacotherapy*. 2001; 21: 258-260.

3. Ng K, Sargent DJ, Goldberg RM, Meyerhardt JA, Green EM, Pitot HC, et al. Vitamin D status in patients with stage IV colorectal cancer: findings from Intergroup trial N9741. *J Clin Oncol*. 2011; 29: 1599-1606.

4. Fakih MG, Trump DL, Johnson CS, Tian L, Muindi J, Sunga AY. Chemotherapy

is linked to severe vitamin D deficiency in patients with colorectal cancer. *Int J Colorectal Dis*. 2009; 24: 219-224.

5. Mazahery H, Stonehouse W, von Hurst PR. The effect of monthly 50,000 IU or 100,000 IU vitamin D supplements on vitamin D status in premenopausal Middle Eastern women living in Auckland. *Eur J Clin Nutr*. 2015; 69: 367-372.
6. Zittermann A, Prokop S, Gummert JF, Börgermann J. Safety issues of vitamin D supplementation. *Anticancer Agents Med Chem*. 2013; 13: 4-10.
7. Vashi PG, Trukova K, Lammersfeld CA, Braun DP, Gupta D. Impact of oral vitamin D supplementation on serum 25-hydroxyvitamin D levels in oncology. *Nutr J*. 2010; 9: 60.
8. Fakih MG, Andrews C, McMahon J, Muindi JR. A prospective clinical trial of cholecalciferol 2000 IU/day in colorectal cancer patients: evidence of a chemotherapy-response interaction. *Anticancer Res*. 2012; 32: 1333-1338.
9. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000; 18: 2938-2947.
10. Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP. A review on oxaliplatin-induced peripheral nerve damage. *Cancer Treat Rev*. 2008; 34: 368-377.
11. Kweekel DM, Gelderblom H, Guchelaar HJ. Pharmacology of oxaliplatin and the use of pharmacogenomics to individualize therapy. *Cancer Treat Rev*. 2005; 31: 90-105.
12. Grolleau F, Gamelin L, Boisdron-Celle M, Lapied B, Pelhate M, Gamelin E. A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels. *J Neurophysiol*. 2001; 85: 2293-2297.
13. Wen F, Zhou Y, Wang W, Hu QC, Liu YT, Zhang PF, et al. Ca/Mg infusions for the prevention of oxaliplatin-related neurotoxicity in patients with colorectal cancer: a meta-analysis. *Ann Oncol*. 2013; 24: 171-178.
14. Choi KC, Jeung EB. Molecular mechanism of regulation of the calcium-binding protein calbindin-D9k, and its physiological role(s) in mammals: a review of current research. *J Cell Mol Med*. 2008; 12: 409-420.
15. Nijenhuis T, Hoenderop JG, Bindels RJ. TRPV5 and TRPV6 in Ca(2+) (re) absorption: regulating Ca(2+) entry at the gate. *Pflugers Arch*. 2005; 451: 181-192.
16. Pike JW, Zella LA, Meyer MB, Fretz JA, Kim S. Molecular actions of 1,25-dihydroxyvitamin D3 on genes involved in calcium homeostasis. *J Bone Miner Res*. 2007; 22 Suppl 2: V16-19.
17. Holmes J, Stanko J, Varchenko M, Ding H, Madden VJ, Bagnell CR, et al. Comparative neurotoxicity of oxaliplatin, cisplatin, and ormaplatin in a Wistar rat model. *Toxicol Sci*. 1998; 46: 342-351.
18. Tague SE, Smith PG. Vitamin D receptor and enzyme expression in dorsal root ganglia of adult female rats: modulation by ovarian hormones. *J Chem Neuroanat*. 2011; 41: 1-12.
19. Mascarenhas R, Mobarhan S. Hypovitaminosis D-induced pain. *Nutr Rev*. 2004; 62: 354-359.
20. Straube S, Andrew Moore R, Derry S, McQuay HJ. Vitamin D and chronic pain. *Pain*. 2009; 141: 10-13.
21. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J Chem Neuroanat*. 2005; 29: 21-30.
22. Soderstrom LH, Johnson SP, Diaz VA, Mainous AG 3rd. Association between vitamin D and diabetic neuropathy in a nationally representative sample: results from 2001-2004 NHANES. *Diabet Med*. 2012; 29: 50-55.
23. Skalli S, Muller M, Pradines S, Halimi S, Wion-Barbot N. Vitamin D deficiency and peripheral diabetic neuropathy. *Eur J Intern Med.* 2012; 23: e67-68.
24. Bell DS. Reversal of the Symptoms of Diabetic Neuropathy through Correction of Vitamin D Deficiency in a Type 1 Diabetic Patient. *Case Rep Endocrinol*. 2012; 2012: 165056.
25. Lv WS, Zhao WJ, Gong SL, Fang DD, Wang B, Fu ZJ, et al. Serum 25-hydroxyvitamin D levels and peripheral neuropathy in patients with type 2 diabetes: a systematic review and meta-analysis. *J Endocrinol Invest*. 2014; .
26. Ioannidis JP, Hesketh PJ, Lau J. Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. *J Clin Oncol*. 2000; 18: 3409-3422.
27. Xystrakis E, Kusumakar S, Boswell S, Peek E, Urry Z, Richards DF, et al. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. *J Clin Invest*. 2006; 116: 146-155.
28. Hidalgo AA, Deeb KK, Pike JW, Johnson CS, Trump DL. Dexamethasone enhances 1alpha,25-dihydroxyvitamin D3 effects by increasing vitamin D receptor transcription. *J Biol Chem*. 2011; 286: 36228-36237.
29. Smith HS, Cox LR, Smith EJ. 5-HT3 receptor antagonists for the treatment of nausea/vomiting. *Ann Palliat Med*. 2012; 1: 115-120.
30. Patrick RP, Ames BN. Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. *FASEB J*. 2014; 28: 2398-2413.
31. Edna TH, Karlsen V, Jullumstrø E, Lydersen S. Prevalence of anaemia at diagnosis of colorectal cancer: assessment of associated risk factors. *Hepatogastroenterology*. 2012; 59: 713-716.
32. Lee P, Peng H, Gelbart T, Wang L, Beutler E. Regulation of hepcidin transcription by interleukin-1 and interleukin-6. *Proc Natl Acad Sci U S A*. 2005; 102: 1906-1910.
33. Alvarez-Hernández X, Licéaga J, McKay IC, Brock JH. Induction of hypoferremia and modulation of macrophage iron metabolism by tumor necrosis factor. *Lab Invest*. 1989; 61: 319-322.
34. An MS, Yoo JH, Kim KH, Bae KB, Choi CS, Hwang JW, et al. T4 stage and preoperative anemia as prognostic factors for the patients with colon cancer treated with adjuvant FOLFOX chemotherapy. World *J Surg Oncol*. 2015; 13: 64.
35. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer*. 2001; 91: 2214-2221.
36. Tampellini M, Saini A, Alabiso I, Bitossi R, Brizzi MP, Sculli CM, et al. The role of haemoglobin level in predicting the response to first-line chemotherapy in advanced colorectal cancer patients. *Br J Cancer*. 2006; 95: 13-20.
37. Schrijvers D. Management of anemia in cancer patients: transfusions. *Oncologist*. 2011; 16 Suppl 3: 12-18.
38. Patterson SD, Rossi JM, Paweletz KL, Fitzpatrick VD, Begley CG, Busse L, et al. Functional EpoR pathway utilization is not detected in primary tumor cells isolated from human breast, non-small cell lung, colorectal, and ovarian tumor tissues. *PLoS One*. 2015; 10: e0122149.
39. Keeler BD, Simpson JA, Ng S, Tselepis C, Iqbal T, Brookes MJ, et al. The feasibility and clinical efficacy of intravenous iron administration for preoperative anaemia in patients with colorectal cancer. *Colorectal Dis*. 2014; 16: 794-800.
40. Bacchetta J, Zaritsky JJ, Sea JL, Chun RF, Lisse TS, Zavala K, et al. Suppression of iron-regulatory hepcidin by vitamin D. *J Am Soc Nephrol*. 2014; 25: 564-572.
41. Zughaier SM, Alvarez JA, Sloan JH, Konrad RJ, Tangpricha V. The role of vitamin D in regulating the iron-hepcidin-ferroportin axis in monocytes. *J Clin Transl Endocrinol*. 2014; 1: 19-25.
42. Liu PT, Schenk M, Walker VP, Dempsey PW, Kanchanapoomi M, Wheelwright M, et al. Convergence of IL-1beta and VDR activation pathways in human TLR2/1-induced antimicrobial responses. *PLoS One*. 2009; 4: e5810.
43. Assa A, Vong L, Pinnell LJ, Rautava J, Avitzur N, Johnson-Henry KC, et al. Vitamin D deficiency predisposes to adherent-invasive Escherichia coli-induced barrier dysfunction and experimental colonic injury. *Inflamm Bowel Dis*. 2015; 21: 297-306.
44. Li YC, Chen Y, Du J. Critical roles of intestinal epithelial vitamin D receptor signaling in controlling gut mucosal inflammation. *J Steroid Biochem Mol Biol*. 2015; 148: 179-183.

45. Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, et al. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *Am J Physiol Gastrointest Liver Physiol*. 2008; 294: G208-216.

46. Camargo CA Jr, Ganmaa D, Frazier AL, Kirchberg FF, Stuart JJ, Kleinman K, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics*. 2012; 130: e561-567.

47. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr*. 2010; 91: 1255-1260.

48. Bergman P, Norlin AC, Hansen S, Rekha RS, Agerberth B, Björkhem-Bergman L, et al. Vitamin D3 supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study. *BMJ Open*. 2012; 2.

49. Mazahery H, von Hurst PR. Factors Affecting 25-Hydroxyvitamin D Concentration in Response to Vitamin D Supplementation. *Nutrients*. 2015; 7: 5111-5142.

Citation: von Hurst PR, Holland S and Coad J. Optimising Response to Chemotherapy in Colorectal Cancer Patients by Ensuring Adequate Vitamin D Status. Austin J Nutr Metab. 2015; 2(4): 1027.