The impact of Middle Eastern Origin, HIV, HCV, and HIV/HCV co-infection in the development of hypovitaminosis D in adults

Saad Warraich1 | Aven Sidhu1 | Michelle Hou1 | Osamah Alenezi1,2

1Vancouver Virology Centre, Vancouver, BC, Canada
2CIHR HIV Clinical Trials Network, Vancouver, BC, Canada

Correspondence
Saad Warraich, Vancouver Virology Centre, Vancouver, BC, Canada.
Email: saad_warraich@hotmail.com

Abstract

Background: A relationship between hypovitaminosis D and infection with HIV and HCV has been established in the scientific literature. Studies comparing these illnesses to other risk factors for development of hypovitaminosis D, such as being of Middle Eastern origin, have been lacking. The goals of this study were: (a) to document vitamin D levels in groups of individuals at high risk of developing its deficiency, (b) analyze the data collected to numerically determine which group had the lowest average vitamin D levels, and (c) discuss the impact of the findings and offer possible explanations.

Methods: This retrospective observational study involved reviewing medical charts and documenting recent vitamin D levels. Our subgroups were: (a) individuals infected with HIV, (b) individuals infected with HCV, (c) individuals co-infected with HIV/HCV, and (d) people of Middle Eastern origin. The gathered data was subsequently subjected to statistical analysis.

Results: People of Middle Eastern origin were found more likely to be vitamin D deficient as compared to those infected with HIV, HCV, or co-infected with both HIV and HCV.

Conclusion: This suggests that genetic and environmental factors unique to otherwise healthy Middle Eastern people are more detrimental, in terms of developing hypovitaminosis D, than being chronically infected with the aforementioned illnesses.

KEYWORDS
adults, Hepatitis C Virus, Human Immunodeficiency Virus, hypovitaminosis D, Middle East

1 INTRODUCTION

Vitamin D is a fat-soluble vitamin involved mainly in calcium homeostasis in the body. Relatively recently, vitamin D has also been shown to have immunomodulatory effects; its receptors have been found on monocytes, macrophages, as well as B and T lymphocytes (Holick, 2007). Synthesis of vitamin D begins in the skin with the conversion of 7-dehydrocholesterol to cholecalciferol under the influence of Ultraviolet B radiation. This molecule is hydroxylated to 25-hydroxycholecalciferol in the liver, which itself consequently gets hydroxylated, mostly in the kidneys, to 1,25-dihydroxycholecalciferol. In addition to this, vitamin D is also acquired through diet.

The Endocrine Society (ENDO) and the International Osteoporosis Foundation (IOF) recommends that levels of
et al. (2011) found 85% of HIV cirrhosis cohort had vitamin D deficiency. Whereas, Terrier (2010) found that 95.3% of patients from their hepatitis C of HIV dorfer et al., 2013). Dao et al. (2011) discovered that 70.3% of HIV-HCV (Arteh, Narra, & Nair, 2010; Dao et al., 2011; Mandorfer et al., 2013). Dao et al. (2011) discovered that 70.3% of HIV-infected individuals were found to have low vitamin D levels in their selected sample of patients. Arteh et al. (2010) found that 95.3% of patients from their hepatitis C cirrhosis cohort had vitamin D deficiency. Whereas, Terrier et al. (2011) found 85% of HIV-HCV co-infected patients to be deficient. Vitamin D deficiency has shown to play a key role in the course of these illnesses (Lange et al., 2011; Mandorfer et al., 2013). For instance, low vitamin D levels have been associated with poor response to therapy with pegylated interferon-alfa plus ribavirin in patients infected with HCV genotype 2 and 3; 50% versus 81% sustained virologic response was observed for patients with and without severe vitamin D deficiency, respectively (Lange et al., 2011). Another well-known group of people that are found to be deficient are individuals of Middle Eastern origin (van Schoor & Lips, 2011). In a study, vitamin D levels in Saudi Arabian students and older people was found on average to be around 10 nmol/L (Sedrani, Elidrissy, & El Arabi, 1983).

In general, deficiency can be attributed to certain factors such as lifestyle choices, diet, some disease states, and intake of certain medications. Genetic causes of developing hypovitaminosis D have also been identified. In their study involving exclusively Caucasian individuals, Wang et al. (2010) found that variants near genes concerned with cholesterol synthesis, hydroxylation, and vitamin D transport lead to a significantly increased risk of developing vitamin D insufficiency.

The aim of this study was to rank four factors that are known to be implicated in the development of hypovitaminosis D. Namely, these four factors are: (a) HIV infection, (b) HCV infection, (c) HIV-HCV co-infection, and (d) Middle Eastern origin. By setting out to accomplish this task, the hope was to highlight the relative contribution of each of these factors in developing vitamin D deficiency and thereby facilitate discourse about the course of action moving forward. Knowing which factor is most dominant will enable discussion on policy change considerations where applicable, such as those related to vitamin D screening, and also it will spark enthusiasm for research exploring that factor further.

### METHODS

This retrospective observational study looked at vitamin D levels in people attending an infectious diseases clinic in Vancouver, BC. The medical charts of 266 patients were anonymized and reviewed to tabulate vitamin D levels. Individuals were divided into the following four categories: (a) infected with HIV, (b) infected with HCV, (c) co-infected with HIV and HCV, and (d) individuals of Middle Eastern background without HIV or HCV. The respective number of people in each category was as follows: (a) 26, (b) 46, (c) 38, and (d) 156.

When determining vitamin D levels, the bone marker 25-hydroxyvitamin D was used. The total amount of 25-hydroxyvitamin D is represented by the sum of 25-hydroxylated vitamin D2 and vitamin D3 species. The values indicating low, normal, high, and toxic were determined by local lab services. Consequently, we defined vitamin D levels <75 nmol/L as low, 75–149 nmol/L as normal, 150–200 nmol/L as high, and above 200 nmol/L as toxic. The collected data was then subjected to statistical analysis; the software used for this purpose was Microsoft Excel version 14.0.7015.1000. The average vitamin D level was calculated for people in each category; the corresponding confidence interval and p value was also computed. The resultant values for the HIV, HCV, and co-infected subgroups were then compared against the Middle Eastern subgroup.

| Subgroups                  | HIV  | HCV  | Co-infected | Middle Eastern |
|----------------------------|------|------|-------------|----------------|
| Proportion found to be deficient (%) | 7.7  | 6.5  | 2.6         | 35.3           |
| Mean Vitamin D (nmol/L)    | 64.81| 72.83| 65.18       | 43.02          |
| Sample size                | 26   | 46   | 38          | 156            |
| 95% confidence Interval (nmol/L) | 54.58–75.03 | 59.67–85.98 | 54.08–76.29 | 38.08–47.96 |
RESULTS

Our results showed that people of Middle Eastern background had, on average, lower levels of vitamin D than those infected with HIV, HCV, or those co-infected with both HIV and HCV. It was found that 7.7% of HIV, 6.5% of HCV, and 2.6% of co-infected individuals were vitamin D deficient, as compared to 35.3% of Middle Eastern individuals. The mean value of vitamin D in each of our subgroups was as follows: 64.81 nmol/L (CI = 54.58–75.03; p < 0.05) in the HIV subgroup, 72.83 nmol/L (CI = 59.67–85.98; p < 0.05) in the HCV subgroup, 65.18 nmol/L (CI = 54.08–76.29; p < 0.05) in the co-infected subgroup, and 43.02 nmol/L (CI = 38.08–47.96) in the Middle Eastern subgroup. These findings are presented in Table 1 and depicted graphically in Figure 1. Females in the HIV, co-infected, and Middle Eastern subcategories had on average lower vitamin D levels than their male counterparts (see Table 2). There were only three individuals with toxic levels of vitamin D; one person was from the Middle Eastern subgroup, and the other two belonged to the HCV subgroup. There were no females with hypovitaminosis D in HIV and HCV subcategories.

DISCUSSION

Hypovitaminosis D among individuals afflicted with HIV is a widely discussed topic in the scientific literature (Adeyemi et al., 2011; Allavena et al., 2012; Dao et al., 2011; Mehta et al., 2010; Mueller et al., 2010; Vescini et al., 2011; Viard et al., 2011). Chronic hepatitis C infection, particularly which progresses to liver cirrhosis, is also associated with the development of vitamin D deficiency (Arteh et al., 2010). Interestingly, another group of individuals that are stricken by hypovitaminosis D are otherwise healthy Middle Eastern people (van Schoor & Lips, 2011). One of the more prevalent problems faced by persons from the Middle East due to vitamin D deficiency, and subsequent osteomalacia, is chronic low back pain (Al Faraj & Al Mutairi, 2003).

Our study showed that a greater percentage of healthy Middle Eastern people have vitamin D deficiency as compared to persons infected with HIV, HCV, and those co-infected with these two illnesses. Also, we discovered that the mean vitamin D levels are lower in this group than the other three. These results suggest that factors unique to healthy Middle Eastern people are more influential, in the development of vitamin D deficiency, than chronic infection with HIV, HCV or co-infection with HIV/HCV. We believe possible reasons for this increased vulnerability can broadly be attributed to environmental and genetic causes specific to the Middle Eastern group.

Environmental factors could include daytime outdoor exposure, clothing, and diet. It is well known that people in the Middle Eastern region avoid daytime outdoor exposure due to the intense heat. Clothing that covers most of the body is also used to protect against the sunlight. Moreover, culture and religion also dictate clothing choices; for instance, many women in Middle East can be seen wearing hijab or niqab (face veil). It was found that the vitamin D level of Turkish women with Western-style clothing was on average 56 nmol/L; for those who wore hijab it was

| TABLE 2 Distribution of average vitamin D levels according to gender among the sample populations |
|-----------------------------------------------|
| HIV (nmol/L) | HCV (nmol/L) | Co-infected (nmol/L) | Middle Eastern (nmol/L) |
| Males | Females | Males | Females | Males | Females | Males | Females |
| 68.14 | 50.80 | 65.94 | 88.57 | 69.39 | 46.57 | 41.63 | 33.99 |
32 nmol/L, whereas for those who wore the niqab, it was only 9 nmol/L (Alagöl et al., 2000; Atli, Gullu, Uysal, & Erdogan, 2005). Similar pattern was found in Jordan with the values being 37 nmol/L, 28 nmol/L, and 24 nmol/L in women who wore Western-style clothing, the hijab, and the niqab, respectively (Mishal, 2001). Additionally, dietary precaution in order to offset these influences is usually not taken. In Qatar, food is not currently fortified with vitamin D (Hamilton, Grantham, Racinais, & Chalabi, 2009). Having mentioned this, data regarding this matter for other countries within the Middle East is presently sparse.

Genetic factors leading to low levels of vitamin D in the Middle Eastern population could be presumed to include individual or combinations of genes involved in synthesis, reabsorption, or utilization of vitamin D or its precursors. Although studies exploring genetic causes of vitamin D deficiency in Middle Eastern people have not been conducted, studies involving individuals of Caucasian descent are available. In one study, it was found that variations in genes involved in cholesterol synthesis, hydroxylation, and vitamin D transport predispose to vitamin D insufficiency (Wang et al., 2010). It is on the basis of such findings that we postulate that similar genetic mechanisms might be at play in Middle Easterners as well.

In conclusion, the findings and the associated discussion presented by this preliminary work yearns further research focused on quantifying and ranking factors unique to Middle Eastern individuals that lead to hypovitaminosis D. Due to the important association of vitamin D with bone health, immunomodulation, cardiovascular disease, and malignancy, it is hoped that our study shifted some attention to the Middle Eastern population—a privilege traditionally apportioned to other high-risk groups such as those infected with HIV and HCV.

ACKNOWLEDGMENTS

This work was supported by the CIHR Canadian HIV Clinical Trials Network. We would also like to acknowledge the efforts of Yadhavan Thiruchselvam, Sunny Bui, Tony Zhou, and Jasper Gao.

ETHICAL STATEMENT

This project was exempt from Research Ethics Board (REB) review as per Tri-Council Policy Statement 2: Ethical Conduct for Research involving Humans (TCPS 2) 2014, Article 2.4.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES

Adeyemi, O. M., Agniel, D., French, A. L., Tien, P., Weber, K., Glesby, M. J., … Cohen, M. (2011). Vitamin D deficiency in HIV-infected and un-infected women in the US. Journal of Acquired Immune Deficiency Syndromes, 57, 197–204. https://doi.org/10.1097/QAI.0b013e31821ae418
Al Faraj, S., & Al Mutairi, K. (2003). Vitamin D deficiency and chronic low back pain in Saudi Arabia. Spine, 28, 177–179. https://doi.org/10.1097/01.BRS.0000041252.55870.7F
Alagöl, F., Shihadeh, Y., Boztepe, H., Tanakol, R., Yarman, S., Azizlerli, H., & Sandalci, O. (2000). Sunlight exposure and vitamin D deficiency in Turkish women. Journal of Endocrinological Investigation, 23, 173–177. https://doi.org/10.1007/BF03343702
Allavena, C., Delpierre, C., Cuzin, L., Rey, D., Viget, N., Bernard, J., … Raffi, F. (2012). High frequency of vitamin D deficiency in HIV-infected patients: Effects of HIV related factors and antiretroviral drugs. Journal of Antimicrobial Chemotherapy, 67, 2222–2230. https://doi.org/10.1093/jac/dks176
Arteh, S., Narra, S., & Nair, S. (2010). Prevalence of vitamin D deficiency in chronic liver disease. Digestive Diseases and Sciences, 55, 2624–2628. https://doi.org/10.1007/s10620-009-1069-9
Atli, T., Gullu, S., Uysal, A. R., & Erdogan, G. (2005). The prevalence of vitamin D deficiency and effects of ultraviolet light on vitamin D levels in elderly Turkish population. Archives of Gerontology and Geriatrics, 40, 53–60. https://doi.org/10.1016/j.archger.2004.05.006
Dao, C. N., Patel, P., Overton, E. T., Rham, F., Pals, S. L., Johnson, C., … the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN) Investigators (2011). Low vitamin D among HIV-infected adults: Prevalence of and risk factors for low vitamin D levels in a cohort of HIV-infected adults and comparison to prevalence among adults in the US general population. Clinical Infectious Diseases, 52, 396–405. https://doi.org/10.1093/cid/ciq158
Dawson-Hughes, B., Heaney, R. P., Holick, M. F., Lips, P., Meunier, P. J., & Vieth, R. (2005). Estimates of optimal vitamin D status. Osteoporosis International, 16, 713–716. https://doi.org/10.1007/s00198-005-1867-7
Dawson-Hughes, B., Mithal, A., Bonjour, J. P., Boonen, S., Burckhardt, P., Fuleihan, G. E., … Yoshimura, N. (2010). IOF position statement: Vitamin D recommendations for older adults. Osteoporosis International, 21, 1151–1154. https://doi.org/10.1007/s00198-010-1285-3
Hamilton, B., Grantham, J., Racinais, S., & Chalabi, H. (2009). Vitamin D deficiency is endemic in Middle Eastern sportsmen. Public Health Nutrition, 13, 1528–1534. https://doi.org/10.1017/ S136898000999320X
Holick, M. F. (2007). Vitamin D deficiency. The New England Journal of Medicine, 357, 266–281. https://doi.org/10.1056/NEJMra070553
Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., … Endocrine Society (2011). Evaluation, treatment, and prevention of vitamin D deficiency: An

ORCID

Saad Warraich http://orcid.org/0000-0001-5070-5242
Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism, 96, 1911–1930. https://doi.org/10.1210/jc.2011-0385

Lange, C. M., Bojunga, J., Ramos-Lopez, E., vonWagner, M., Hassler, A., Vermehren, J., … Sarrazin, C. (2011). Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy. Journal of Hepatology, 54, 887–893. https://doi.org/10.1016/j.jhep.2010.08.036

Mandorfer, M., Reiberger, T., Payer, B. A., Ferlitsch, A., Breitbart, F., Aichelburg, M. C., … the Vienna HIV & Liver Study Group (2013). Low vitamin D levels are associated with impaired virologic response to PEGIFN + RBV therapy in HIV–hepatitis C virus coinfected patients. Aids, 27, 227–232. https://doi.org/10.1016/j.aids.2013.02.041

Mehta, S., Giovannucci, E., Mugusi, F. M., Spiegelman, D., Aboud, S., Hertzmark, E., … Fawzi, W. W. (2010). Vitamin D status of HIV-infected women and its association with HIV disease progression, anemia, and morality. PLoS One, 5, e8770. https://doi.org/10.1371/journal.pone.0008770

Mishal, A. A. (2001). Effects of different dress styles on vitamin D levels in healthy young Jordanian women. Osteoporosis International, 12, 931–935. https://doi.org/10.1007/s001980170021

Mueller, N. J., Fux, C. A., Ledergerber, B., Elzi, L., Schmid, P., Dang, T., … the Swiss HIV Cohort Study (2010). High prevalence of severe vitamin D deficiency in combined antiretroviral therapy-naïve and successfully treated Swiss HIV patients. AIDS, 24, 1127–1134. https://doi.org/10.1097/QAD.0b013e328337b161

Palacios, C., & Gonzalez, L. (2014). Is vitamin D deficiency a major global public health problem? Journal of Steroid Biochemistry & Molecular Biology, 144, 138–145. https://doi.org/10.1016/j.jsmb.2013.11.003

Sedrani, S. H., Eledrisy, A. W., & El Arabi, K. M. (1983). Sunlight exposure and vitamin D status in normal Saudi subjects. The American Journal of Clinical Nutrition, 38, 129–132. https://doi.org/10.1093/ajcn/38.1.129

Souberbielle, J. C., Body, J. J., Lappe, J. M., Plebani, M., Shoenfeld, Y., Wang, T. J., … Zittermann, A. (2011). Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Autoimmunity Reviews, 9, 709–715. https://doi.org/10.1016/j.autrev.2010.06.009

Terrier, B., Carrat, F., Geri, G., Pol, S., Piroth, L., Halfon, P., … Cacoub, P. (2011). Low 25-OH vitamin D serum levels correlate with severe fibrosis in HIV-HCV co-infected patients with chronic hepatitis. Journal of Hepatology, 55, 756–761. https://doi.org/10.1016/j.jhep.2011.01.041

van Schoor, N. M., & Lips, P. (2011). Worldwide vitamin D status. Best Practice & Research Clinical Endocrinology & Metabolism, 25, 671–680. https://doi.org/10.1016/j.beem.2011.06.007

Vescini, F., Cozzi-Lepri, A., Boderi, M., Carla Re, M., Maggiolo, F., Luca, D. E., … Monforte, A. A. (2011). Prevalence of hypovitaminosis D and factors associated with vitamin D deficiency and morbidity among HIV-infected patients enrolled in a large Italian cohort. Journal of Acquired Immune Deficiency Syndromes, 58, 163–172. https://doi.org/10.1097/QAI.0b013e31822e57e9

Viard, J., Souberbielle, J., Kirk, O., Reekie, J., Knysz, B., Losso, M., … Mocroft, A. (2011). Vitamin D and clinical disease progression in HIV infection: Results from the EuroSIDA study. Aids, 25, 1305–1315. https://doi.org/10.1097/QAD.0b013e328347f6f7

Wang, T. J., Zhang, F., Richards, J. B., Kestenbaum, B., van Meurs, J. B., Berry, D., … Spector, T. D. (2010). Common genetic determinants of vitamin D insufficiency: A genome-wide association study. Lancet, 376, 180–188. https://doi.org/10.1016/S0140-6736(10)60588-0

How to cite this article: Warraich S, Sidhu A, Hou M, Alenezi O. The impact of Middle Eastern Origin, HIV, HCV, and HIV/HCV co-infection in the development of hypovitaminosis D in adults. Mol Genet Genomic Med. 2018;6:1010–1014. https://doi.org/10.1002/mgg3.475