Author's response to reviews

Title: Female asylum seekers with musculoskeletal pain: the importance of diagnosis and treatment of hypovitaminosis D3

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Manuscript: Female asylum seekers with musculoskeletal pain: the importance of diagnosis and treatment of hypovitaminosis D3

Dear Editor,

We would like to ask you to consider our revised manuscript for publication in your journal. The manuscript has not been published elsewhere and has been approved by all authors.

We thank you for your comments and we provide here following the point-by-point responses to the two reviewers.

We hope that the changes made are satisfactory and that the manuscript can now be published.

Thank you very much, yours faithfully,

Gabrielle de Torrenté de la Jara, Bernard Favrat
Response to reviewer Dr. Peter Robert M. Ebeling

**Major Compulsory Revisions**

1. “Hypovitaminosis D3” has been removed and replaced by “hypovitaminosis D” throughout the manuscript. In the Participants section, we included (in brackets) the degree of hypovitaminosis D (25-[OH] vitamin D < 21nmol/l) even if we discussed this point more in detail in the Methods and Discussion sections. The treatment intervention is now mentioned in the abstract:

   “Treatment intervention: The patients received either two doses of 300,000 IU intramuscular cholecalciferol as well as 800 IU of cholecalciferol with 1000 mg of calcium orally, or the oral treatment only.”

   We reworded the first line in “Main outcome measures”:

   "Main outcome measures: We recorded the first diagnosis made by the physicians before the correct diagnosis of hypovitaminosis D,...”

2. The term “25OH vitamin D3” has been replaced by ”25-(OH) vitamin D” throughout the manuscript, as well as “hypovitaminosis D3” by “hypovitaminosis D”. SI units are now used in the manuscript. We have included the conversion factor in the Methods section. In Switzerland and maybe other countries, both units are still used. It therefore seems important to give the conversion factor in the manuscript.

3. Concerning “hypovitaminosis D3”, see above. In the Methods section, we added a comment on the levels of hypovitaminosis D. This aspect is extensively developed in the Discussion section.

   “The reference range for 25-(OH) vitamin D is derived from a group of 20 male and 24 female healthy, predominately Caucasian volunteers from the midwestern USA, aged between 23 and 67
years, during the month of October (DiaSorin Inc.). It is well known, however, that this reference range describes a severe hypovitaminosis D, and that levels below 50 nmol/l are considered insufficient (see Discussion section)."

4. See above.

5. This is an interesting consideration. Among patients who did not respond to treatment, there were patients in both treatment groups. Due to the small sample size, it is not possible to compare the oral treatment group with the intramuscular plus oral treatment group. This consideration needs to be readdressed.

Thank you for the additional references. We indeed find them interesting and have included them in the Discussion section.

“Risk factors (reduced exposure to sunlight and strict vegetarian diet) [10, 32, 33] must be minimized to achieve these concentrations. Nevertheless, these risk factors are difficult to modify; even in Australia, the paradox of hypovitaminosis D in a sunny country is emerging as a public health problem.[34]”

“One very interesting study showed the effectiveness of an annual megadose of intramuscular cholecalciferol (600,000 IU) in patients with vitamin D deficiency. This therapy appears to be safe, even if certain concerns, such as hypercalciuria, need to be examined. This treatment could potentially be applied on a large scale.[37]”

6. We draw your attention to our recommendation that the exposure should last only 5 to 15 minutes, not more, and is only for skin types II and III. Therefore, this duration should be acceptable even in Australia, especially around 1000 or 1500 h. Nevertheless, we have added two caveats to the relevant sentence.
“...exposing the hands, arms, and face, if culturally acceptable and with caution in low latitudes, without sunscreen for 5-15 min between 1000 and 1500 h in the spring, summer, and fall for individuals with type II and III skin.”

Concerning your second point, it is true that such an exposure could be unsuitable for certain ethnic groups, meaning that they should certainly be considered to be at-risk groups and probably need supplementation. We address this point a bit further.

“Routine supplementation could be the only effective way of preventing hypovitaminosis D in the population described in our study, since it is not likely that sun exposure habits and diet will change to any meaningful extent.”

7. In the 12 Balkan women in our study, 4 wore a veil (not complete), 7 did not, and no details were obtained for one woman. Nevertheless, it is possible that limited sun exposure (due to housebound status) that is not veil-dependent is an important factor in hypovitaminosis D, but this is only a hypothesis. We have addressed this point in the text, as follows:

“We wish to emphasize the importance of the diagnosis in a female Balkan population, a group in which osteomalacia has not yet been formally described. Only one-third of these patients wore a veil, so there is no direct correlation between these two parameters. It is nevertheless possible that global sun exposure (due to housebound status) is limited, and that dietary factors have an influence in this population.”

**Minor Essential Revisions**

1. This has been corrected.
2. The women are asylum seekers, and come from various countries. In Switzerland, asylum seekers keep this status, sometimes for years (mean stay in Switzerland: 5.27 years), until they receive a decision allowing their permanent stay or a rejection. They are therefore sometimes transitory immigrants, and sometimes permanent. In our canton (state), asylum seekers are necessarily in a double gate-keeping system (nurse practitioner and primary care physicians), which is specific for this health network. This made the follow-up of our patients, by a review of all files, possible.

The two terms are used in the text; the term “asylum seekers” is used more in a political sense, and the term “immigrant” more generally. If necessary, the term “immigrant” can be replaced by “asylum seeker” in the manuscript.
Response to reviewer Dr. Vin Tangpricha

Major Compulsory Revisions

1. No approval was required from a human studies committee for this study. We aimed to detect more cases of hypovitaminosis D in our Outpatient Department and only suggested the treatment to the physicians. The follow-up was left free to each physician and was not modified by our study. We then only reviewed the files.

2. The cut-off is mentioned in the Methods section and is discussed extensively in the Discussion section.

“The reference ranges are 21-131 nmol/l for 25-(OH) vitamin D, 2.15 -2.55 mmol/l for calcium and 0.8 – 1.6 mmol/l for phosphate. (For 25-[OH] vitamin D, 1 µg/l = 2.5 nmol/l). The reference range for 25-(OH) vitamin D is derived from a group of 20 male and 24 female healthy, predominately Caucasian volunteers from the midwestern USA, aged between 23 and 67 years, during the month of October (DiaSorin Inc.). It is well known, however, that this reference range describes a severe hypovitaminosis D, and that levels below 50 nmol/l are considered insufficient (see Discussion section).”

3, 4, 5, 6. The 33 patients were discovered within the general consultation and the emergency department of our primary care clinic. They were reported by the physicians to the main author, after receipt of two circular letters and several informal reminders. As described in the manuscript, we informed the physicians of the possible high prevalence in an asylum seeker population and encouraged them to dose 25OH vitamin D in suspect cases. They were then free to follow the treatment recommendations in the circular letter (intramuscular and oral treatment) or not. We do not know the reasons for prescription of only the oral treatment.
Concerning the prevalence of the disease in this population, we analysed the outpatient clinic’s database over a year. The clinic was consulted by 7610 patients (3664 male, 3946 female), of whom 35 (4 male) were diagnosed with hypovitaminosis D3. There were 20 female asylum seekers presenting with this condition and associated symptoms, and 1 male. The prevalence of hypovitaminosis D3 in the consulting population is 0.46%; in women it is 0.79% and in female asylum seekers it is 6.86%

These points (except the prevalence) are specified in the text as follows. With these changes, we do not think it is necessary to constitute a flow diagram since the recruiting procedure was quite simple and consisted only of self-reporting by the primary care physicians:

“After a certain number of cases of hypovitaminosis D were diagnosed in 2000, the centre’s primary care physicians were informed by two circular letters, in March and April 2001, of the suspected high prevalence of this disease in female asylum seekers, particularly those with a minimal exposure to sunlight and presenting with a history of bone pain, proximal muscular weakness, a change in gait and/or fatigue. In suspected cases seen within the outpatient department (emergencies and follow-ups), we checked serum levels of 25-(OH) vitamin D, while the physician determined other biochemical parameters if judged necessary: calcium, phosphate, alkaline phosphatase, and parathyroid hormone (PTH). We included women with symptoms of hypovitaminosis D and a confirmed deficiency in the study. Only women were included because of their risk factors and histories. There were no exclusion criteria. In our setting, we did not constitute a control group. The physicians were asked several times to report their cases, but we did not revise all files systematically. The physicians were advised to follow treatment recommendations specified in the circular letters (300,000 IU of intramuscular cholecalciferol with an ongoing course of 800 IU of cholecalciferol associated with 1000 mg of calcium), but were free not to do so. Therefore, the decisions to dose 25-(OH) vitamin D, to report the cases, and to treat, if necessary, the patients, were left to the physicians who were directly in charge of the patients. Nevertheless, we discussed the two circular letters extensively with the primary care physicians and had informal discussions as well.”

7. As specified above, we did not constitute a control group for various reasons. We were principally interested in easing our patients’ suffering, which had in some cases
lasted for several years, and therefore found it unethical to create a control group. We also consider our study to be a pragmatic one, and it is certain that the lack of a control group limits the significance of our results. Nevertheless, we think it is possible to consider them pragmatic and preliminary. These limitations are discussed in the manuscript (Discussion section).

“Our results also show a reduction in the use of medical services and the prescription of analgesic drugs. These results should be considered preliminary, because no control group was constituted. Nevertheless, these two facts could be of primary importance.”

“Our study clearly suffers from a number of limitations. First, the study lacks a control group. Second, we do not know the number of patients that were not included in the study because of failure of the physicians to properly record the data. Third, we do not possess the complete biochemical data for all the patients (alkaline phosphatase, PTH, and albumin). Finally, the records can occasionally be imprecise in the descriptions of symptoms and diagnoses.”

8. The other chronic medical illnesses were various, with certain patients suffering from more than one. We provide a list here, but do not think that it should be complete in the manuscript. We added the more frequent one as examples.

“The patients were suffering from a mean of 2.76 chronic illnesses, such as iron deficiency with or without anaemia, obesity, gastritis, tension headache, hypertension (SD 1.97), ”

List:
Iron deficiency with or without anaemia: 10
Obesity: 10
Gastritis/dyspepsia: 8
Tension headache: 8
Hypertension: 5
Irritable bowel syndrome: 4
Osteoarthritis: 4
Varicosis: 3
Hypothyroidism (treated): 2
Diabetes 2: 2
Chronic hepatitis C: 2, Chronic hepatitis B and C: 1
COPD: 2
Plegia secondary to poliomyelitis: 2
Migraine: 1
Pregnancy: 1
Gallbladder stones: 1
Heterozygous alpha thalassemia: 1

9. We determined if the symptoms resolved by chart review only, and did not use a pain questionnaire. We agree that in certain cases it is difficult to know accurately whether a symptom resolved or not. We were severe in judging and only considered symptoms to be resolved when the chart was very clear in this respect, in terms of patients’ comments: “I don’t have anymore pain, especially in the legs”; “This is fantastic, my life has changed”; “I feel much better, I don’t have pain anymore”. In all cases where it seemed unclear, when not all symptoms disappeared, we noted the patients as partial or nonresponders. Subjectively, it seemed more difficult in older patients with more chronic illnesses to achieve a resolution of symptoms, even though this does not appear in the statistical analysis. We have only a small population sample.

“There was no standardized questionnaire designed for the follow-up. The information was retrieved from the files with an extraction sheet only.”

(Methods section)

Another important point is that all our patients have had severe hypovitaminosis D, which justifying treatment even if the symptoms did not disappear.

10. Certain patients received analgesic medication for other chronic illnesses, which we have now listed in the manuscript. As described, these illnesses are chronic and
are not subject to major change in 12 months, our time frame for the analysis of the change in the number of prescribed analgesic medications. We have added this to the Results section.

“Certain patients suffered from chronic medical conditions (tension headache, osteoarthritis, irritable bowel syndrome, migraine) requiring analgesic medication that did not vary significantly over the 12-month period for which we analysed the data.”

11. The changes in both figures are statistically significant. This data is in the manuscript in the Results section. The tests used were two-sample t-tests.

“During the whole period preceding diagnosis, the patients received a mean of 3.27 analgesic drugs (SD 2.28), compared to a mean of 1.67 (SD 1.51) during the 6 months before diagnosis. In the 6 months after diagnosis and initiation of treatment, the number of analgesic drugs fell to 0.85 (SD 1), (P = 0.001).”

“However, the emergency visits fell from 0.88 (SD 1.08) six months before diagnosis to 0.39 (SD 0.83) six months after (P = 0.027).”

12. Unfortunately, we did not check 25-(OH) vitamin D levels after treatment in all patients, principally for economic reasons. Below are the details of the 15 patients who had their 25-(OH) vitamin D controlled. We chose not to add to the manuscript, since the data was incomplete and because the probability of an elevation in 25-(OH) vitamin D level after intramuscular injection is high. We do see that 1 person with a high post-injection 25-(OH) vitamin D level did not respond to treatment.
| Baseline 25OH vitamin D (nmol/l) | Control 25OH vitamin D (nmol/l) | Delay (months) | Treatment | Respond |er |
|--------------------------------|---------------------------------|----------------|-----------|---------|
| 1.6                           | 94                              | 4              | intramuscular and oral | yes |
| 7.75                          | 100.5                           | 6.56           | intramuscular and oral | yes |
| 3.75                          | 45.5                            | 2              | intramuscular and oral | yes |
| 13.5                          | 81.25                           | 8.53           | intramuscular and oral | yes |
| 22.75                         | 102.5                           | 3              | intramuscular and oral | yes |
| 18                            | 24.5                            | 5.83           | intramuscular and oral | yes |
| 4                             | 52                              | 1.37           | intramuscular and oral | yes |
| 9.5                           | 99.5                            | 10             | intramuscular and oral | no  |
| 13.25                         | 9.25                            | 4              | oral then intramuscular | yes |
| 4.5                           | 76.75                           | 4.47           | intramuscular and oral | yes |
| 14.25                         | 117                             | 3.23           | intramuscular and oral | yes |
| 7.5                           | 157.5                           | 2.5            | intramuscular and oral | yes |
| 9.5                           | 21.5                            | 3.5            | oral only            | yes |
| 4.5                           | 16                              | 6.5            | oral then intramuscular | yes |
| 16.25                         | 78.25                           | 6.33           | intramuscular and oral | yes |

**Minor Essential Revisions**

1. We have replaced “25OH vitamin D3” with “25-(OH) vitamin D”.

2. The DiaSorin assay measures both 25-(OH) vitamin D3 and 25-(OH) vitamin D2. We have therefore corrected this in the manuscript.

3. This has been corrected.

“A recent study in the United States showed that of 150 consecutive patients (immigrant and non-immigrant) of a community clinic with persistent, non-specific musculoskeletal pain, 100% had vitamin D3 insufficiency (<50 nmol/l) and 28% had severe deficiency (<20 nmol/l) [8].”
4. We have introduced SI units throughout the paper. Nevertheless, we have included the conversion factor in the Methods section, since, in certain parts of Switzerland and probably other countries, the unit used is µg/l.

5. The paragraphs are now indented.

Conclusions

We understand the general comment of Dr. Tangprisha and agree that our study has limitations. This study was designed as a pragmatic study in a primary care centre, where we were surprised by the number of cases of hypovitaminosis D when we entered it in our differential diagnosis list. We did not constitute a control group principally for ethical reasons. We agree that one of the conclusions of our paper concerning the reduction in emergency room visits and analgesic drugs cannot be certain without a control group. Nevertheless, we suggest considering our results preliminary and of possible importance to the field. We also consider the other findings of our study—diagnosis made before hypovitaminosis D, duration of symptoms before treatment, proportion of patients responding to treatment, and time for response to treatment—relevant, since we have not seen these evaluated in many other papers. It is also important to us that primary care physicians be more aware of hypovitaminosis D and we think we have addressed that point in the manuscript.

NB. We have revised the English.