Supplementation with 80,000 IU vitamin D3/month between November and April corrects vitamin D insufficiency without overdosing: Effect on serum 25-hydroxyvitamin D serum concentrations

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Summary

Introduction > Vitamin D insufficiency, defined by a 25-hydroxyvitamin D (25OHD) serum concentration < 20 ng/mL, is highly frequent in the French general population, especially between November and April. The aim of this study was to evaluate whether 80,000 IU vitamin D3 every month during this period of the year was able to maintain a 25OHD level between 20 and 60 ng/mL in apparently healthy subjects whatever their basal vitamin D status.

Methods > Ninety-eight subjects volunteered to receive an 80,000 IU vitamin D3 dose every month between November 2014 and April 2015. Serum 25OHD, calcemia and calciuria were measured just before the first dose (Month 0), just before the 4th dose (M4), and one month after the 6th dose (M7).

Results > At M0, 25OHD was 17.5 ± 9.5 ng/mL. Sixty subjects (61.2%) had a 25OHD < 20 ng/mL and 25 (25.5%) had a 25OHD < 10 ng/mL. 25OHD increased significantly at M4 (35.3 ± 8.0 ng/mL) and M7 (40.1 ± 8.5) without change in calcemia and calciuria. At M4, 2 subjects had a 25OHD slightly below 20 ng/mL (17.6 and 19.7 ng/mL), and none had a concentration > 60 ng/mL. At M7, all had a serum 25OHD > 20 ng/mL and 2 subjects had a value slightly above 60 ng/mL (62.1 and 63.2 ng/mL).

Conclusion > A monthly supplementation with 80,000 IU vitamin D3 between November and April corrected vitamin D insufficiency in subjects in whom it was initially very frequent, without...
The 25-hydroxyvitamin D (25OHD) serum concentration is the consensual marker of vitamin D status[1,2]. The minimum 25OHD level that defines an optimal vitamin D status remains however highly debated. While all experts agree that a 25OHD concentration below 10–12 ng/mL corresponds to a severe vitamin D deficiency that may cause rickets/osteomalacia and/or diffuse pain, the current tendency to define a less severe deficiency, also called “insufficiency”, is to consider separately the healthy general population for which a 25OHD > 20 ng/mL corresponds to an optimal vitamin D status according to many experts[1], and the patients with bone, renal, digestive or phosphocalcic diseases for whom a concentration > 30 ng/mL is thought to be more appropriate[2].

In France, two large epidemiological studies have described the vitamin D status of the general populations, the SUVIMAX study[3,4] and the “Étude nationale Nutrition Santé” (ENNS, 2006–2007)[5]. The authors of these studies concluded that vitamin D overdosing. This protocol is simple, safe and costless, and can be easily implemented when physicians detect risk factors for hypovitaminosis D in patients for whom a 25OHD measurement is not indicated.

Résumé

Une supplémentation par 80 000 UI de vitamine D3 par mois entre novembre et avril corrige l’insuffisance en vitamine D sans surdosage : effet sur les concentrations sériques de 25-hydroxyvitamine D

Introduction > L’insuffisance en vitamine D, définie par une concentration sérique de 25-hydroxyvitamine D (25OHD) < 20 ng/mL, est très fréquente en population générale en France, en particulier entre novembre et avril. L’objectif de ce travail était d’évaluer si une supplémentation par 80 000 UI de vitamine D3 par mois pendant cette période de l’année pouvait permettre d’atteindre et de maintenir un concentration de 25OHD entre 20 et 60 ng/mL chez des membres du personnel du CEA Saclay, quel que soit leur statut vitaminique D initial.

Méthodes > Quatre-vingt-dix-huit sujets volontaires ont reçu une ampoule de 80 000 UI de vitamine D3 par mois entre novembre 2014 et avril 2015. La 25OHD, la calcémie et la cacluie ont été mesurées juste avant la prise de la première ampoule (mois 0), juste avant la prise de la 4ème (M4) et un mois après la prise de la 6ème ampoule (M7).

Résultats > À M0, la 25OHD était de 17,5 ± 9,5 ng/mL. Soixante sujets (61,2 %) avaient une 25OHD < 20 ng/mL et 25 (25,5 %) avaient une 25OHD < 12 ng/mL. La 25OHD a augmenté significativement à M4 (35,3 ± 8,0 ng/mL) et à M7 (40,1 ± 8,5) sans modification de la calcémie ou de la cacluie. À M4, 2 sujets avaient une 25OHD légèrement < 20 ng/mL (17,6 et 19,7 ng/mL) et aucun n’avait une valeur > 60 ng/mL. À M7, tous avaient une 25OHD > 20 ng/mL et 2 sujets avaient une 25OHD discrètement > 60 ng/mL (62,1 et 63,2 ng/mL).

Conclusion > Un protocole de supplémentation simple, sans risque et peu coûteux, par une ampoule de 80 000 UI de vitamine D3 par mois entre novembre et avril a permis de corriger l’insuffisance en vitamine D initial, très fréquente chez les sujets étudiés, sans induire de surdosage. Ce protocole peut facilement être mis en place par les services de médecine du travail ou par les médecins qui identifient des facteurs de risque d’hypovitaminose D chez des patients dont les pathologies ne relèvent pas d’un dosage sanguin de la 25OHD.

What was known?

Vitamin D insufficiency defined as a 25OHD serum concentration below 20 ng/mL is highly frequent in the French general population, especially during the winter months. 25OHD testing in the general population is not reimbursed in France. How to supplement the general population in winter without prior 25OHD testing so that most subjects have a 25OHD serum level between 20 and 60 ng/mL is currently unknown.

What this study adds

A monthly 80,000 IU vitamin D3 dose between November and April in 98 apparently healthy French subjects with a mean baseline 25OHD of 17.5 ng/mL has corrected vitamin D deficiency in all initially vitamin D deficient participants without overdosing in the non-deficient subjects.
insufficiency was highly frequent in France and that it was important to reduce its prevalence. As the 25OHD measurement is no longer reimbursed in France with the exception of some clinical conditions that have been highly debated [6,7], the challenge is thus to increase the vitamin D intake without prior 25OHD testing so that most individuals have a 25OHD concentration > 20 ng/mL. As the currently acceptable upper limit for an optimal 25OHD concentration is around 60 ng/mL [8], it will be equally important to avoid excessive 25OHD concentration and overdosage.

We previously found a high frequency of vitamin D insufficiency in 164 CEA (Centre de Saclay du Commissariat à l’énergie atomique et aux énergies alternatives) employees who had a 25OHD measurement in 2013-2014. While these subjects may be considered as belonging to the general population, 40 of them (24%) had a 25OHD < 10 ng/mL and 89 (54%) had a 25OHD < 20 ng/mL (unpublished data). The 80,000 IU vitamin D3 dose that we used in the present study is the "smallest" of the high doses available in France. When given at a monthly interval, it may grossly correspond to 2,667 IU/day which, although being much higher than the current recommended dietary intake, is much lower than the 4,000 IU/day that are currently viewed as the upper limit of safety without monitoring [1].

Our main objective was to evaluate whether a vitamin D supplementation with a monthly dose of 80,000 IU vitamin D3 between November and April in employees of the CEA was able to maintain a 25OHD serum concentration between 20 and 60 ng/mL in most participants.

Methods
Participants and methodology
This was an open, prospective, longitudinal study whose aim was to evaluate the effect of a vitamin D supplementation on the 25OHD serum levels of CEA employees. The Saclay CEA centre is situated in the South-West of Paris (latitude 49° N). It employs approximately 5,500 persons who mainly work indoor and has its own clinical laboratory. Employees that are exposed to radiological or chemical risks have a yearly medical follow-up while the other employees have a biannual medical checkup by the Industrial Medicine Department. At each medical visit, a biological evaluation is performed. In 2014, the Industrial Medicine Department have done 3,735 yearly and 1,720 biannual evaluations. Approximately one hundred CEA employees were randomly selected among those who were volunteers to participate to this study whatever their mode of follow-up (annual or biannual). The number of subjects to be included was defined according to the capacity of the Industrial Medicine Department on the one hand, and according to financial constraint on the other hand. Inclusion criteria were (1) being a CEA employee, and (2) having signed an informed consent. Non-inclusion criteria were the use of vitamin D supplements during the 3 months preceding the study (a list of the pharmaceutical forms of vitamin D available in France was given to the volunteers), and having (or having had) sarcoidosis or another granulomatous disease. All the recruited subjects had a morning blood (calcium, creatinine, 25OHD) and urine (calcium, creatinine) sample after an overnight fast in early November 2014 (M0). Then, they had a discussion with a nurse or a doctor of the CEA Industrial Medicine Department during which they signed the informed consent and responded to a questionnaire whose aim was to verify the absence of non-inclusion criteria, and to document some points that may modify the 25OHD serum level. Sex, phototype according to the Fitzpatrick classification, weight and height were recorded and the BMI (Body Mass Index) was calculated. Then, the volunteers took an 80,000 IU vitamin D3 dose (Zymad® 80000) in the presence of a nurse or a doctor. Until April 2015, the participants took a 80,000 IU vitamin D3 dose at the beginning of each following month, again in the presence of a nurse or a doctor, and had a fasting blood (calcium, creatinine, 25OHD) and urine (calcium, creatinine) sample in early February (M4), that is one month after the third vitamin D3 dose, and early May, that is one month after the 6th vitamin D dose. All measurements were done in the clinical laboratory of the CEA centre. Blood and urine creatinine (enzymatic method) and calcium measurements were done on a Cobas 6000 platform (Roche Diagnostics, Meylan, France). The 25OHD serum concentration was assessed by means of an immunochemiluminescent assay on the Liaison XL analyser (DiaSorin, Saluggia, Italy). The limit of quantification of this assay is 3 ng/mL. The study was approved by the CHST (Comité d’hygiène, de sécurité et des conditions de travail) of the CEA Saclay.

Statistics
Continuous data are presented as mean ± SD with the mention of the minimal and the maximal value. The frequency of the nominal data was expressed as the number and percentage of subjects. Paired data were compared by ANOVA for paired values. Unpaired data were compared by ANOVA. Associations between continuous variables were assessed by the Pearson correlation. Percentages were compared with the Chi² test. The Lowess curve was used to smooth the relationship between the 25OHD concentration at M0 and the percent increase in the 25OHD level between M0 and M7.

Results
One hundred and five subjects were initially recruited and 7 did not complete the study and were excluded. The reasons for these exclusions were voluntary discontinuation possibly due to adverse effects for 3 subjects (digestive effects for one subject, skin eruption after the 4th vitamin D dose for a second subject, abnormal gain of weight for a third subject), the prescription of a supplementary vitamin D dose by the general practitioner (GP) for one subject, the diagnosis of an auto-immune disease for
was the only significant risk factor of having a low serum 25OHD at M0: 13.2 ± 7.4 ng/mL (n = 44) versus 21.1 ± 7.9 ng/mL (n = 54) in those who did have sunny holidays (P < 0.001). Age, BMI, phototype, having outdoor activities or consuming fish more or less than twice a week had no significant influence on the 25OHD levels at M0.

The mean 25OHD concentration significantly increased between M0 and M4 or M7 (P < 0.001) but not between M4 and M7, without change in calcemia, calcuria or creatininemia (Table II). The percentage of subjects with a 25OHD concentration < 20 ng/mL significantly decreased (P < 0.001) between M0 and M4 or M7 (Table II). At M4, only 2 subjects had a 25OHD concentration slightly < 20 ng/mL (17.6 and 19.7 ng/mL), 24 had a 25OHD < 30 ng/mL, and none had a 25OHD > 60 ng/mL. At M7, all had a 25OHD > 20 ng/mL, 11 had a 25OHD < 30 ng/mL and 2 subjects had a 25OHD slightly > 60 ng/mL (62.1 and 63.2 ng/mL). The BMI was moderately but significantly and negatively correlated to the increase, expressed in ng/mL, of the 25OHD concentration between M0 and M7 (P = 0.03).

The 25OHD concentration at M0 was strongly and negatively correlated to the percent increase in 25OHD concentration at M4 (P < 0.0001) and at M7 (P < 0.0001). This relationship was not linear and presented a steeper slope for the low 25OHD at M0 (Figure 1). The percent increase of the 25OHD level between M0 and M4 and between M0 and M7, but also the absolute increase of the 25OHD concentration (in ng/mL) between M0 and M4 or M7, were higher in those whose 25OHD level at M0 was < 20 ng/mL compared to those whose 25OHD at M0 was ≥ 20 ng/mL (Table III).

### Table I

Main baseline (before the first vitamin D3 dose): characteristics of the 98 subjects that were analysed. Continuous variables are expressed as mean ± SD [minimum-maximum]

<table>
<thead>
<tr>
<th>Sex</th>
<th>48 men, 50 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.0 ± 9.2 [23-66]</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2 ± 4.0 [19.3-40.7]</td>
</tr>
<tr>
<td>25OHD (ng/mL)</td>
<td>17.5 ± 9.5 [3-45.5]</td>
</tr>
<tr>
<td>Calcemia (mmol/L)</td>
<td>2.44 ± 0.08</td>
</tr>
<tr>
<td>Calciuria/creatinuria (mmol/mmol)</td>
<td>0.29 ± 0.18</td>
</tr>
<tr>
<td>Creatininemia (μmol/L)</td>
<td>79.1 ± 14.3</td>
</tr>
</tbody>
</table>

Another subject followed by the request by its GP to stop the study, a surgical intervention for breast cancer for one woman for whom the anaesthesiologist requested her to stop the study, and a professional affectation change in another area for the 7th participant. Data of the remaining 98 subjects who received the 6 vitamin D3 doses and had 3 25OHD measurements were analysed. Their main characteristics at inclusion (M0: early November 2014) before the first vitamin D3 dose are in Table I.

A high frequency of serum 25OHD values < 30 ng/mL (90.8%), < 20 ng/mL (61.2%) and < 10 ng/mL (25.5%) may be underlined.

Among the data that were collected through the questionnaire, the absence of holidays in a sunny place during Summer 2014 was associated to a lower increase in the 25OHD between M0 and M7 (P < 0.001) but not between M4 and M7, without change in calcemia, calcuria or creatininemia (Figure 1). The percentage of subjects with a 25OHD concentration < 20 ng/mL significantly decreased (P < 0.001) between M0 and M4 or M7 (Table II). At M4, only 2 participants had a 25OHD concentration slightly < 20 ng/mL (17.6 and 19.7 ng/mL), 24 had a 25OHD < 30 ng/mL, and none had a 25OHD > 60 ng/mL. At M7, all had a 25OHD > 20 ng/mL, 11 had a 25OHD < 30 ng/mL, and 2 participants had a 25OHD slightly > 60 ng/mL (62.1 and 63.2 ng/mL). The BMI was moderately but significantly and negatively correlated to the increase, expressed in ng/mL, of the 25OHD concentration between M0 and M7 (P = 0.03).

The 25OHD concentration at M0 was strongly and negatively correlated to the percent increase in 25OHD concentration at M4 (P < 0.0001), and at M7 (P < 0.0001). This relationship was not linear and presented a steeper slope for the low 25OHD at M0 (Figure 1). The percent increase of the 25OHD level between M0 and M4 and between M0 and M7, but also the absolute increase of the 25OHD concentration (in ng/mL) between M0 and M4 or M7, were higher in those whose 25OHD level at M0 was < 20 ng/mL compared to those whose 25OHD at M0 was ≥ 20 ng/mL (Table III).

### Table II

Evolution of the mean (±SD) serum 25OHD, creatinine and calcium concentration, and urine calcium/creatinine ratio during the study period. Evolution of the percentages of subjects with a 25OHD concentration below or above different thresholds

<table>
<thead>
<tr>
<th></th>
<th>M0 (before the 1st vitamin D3 dose)</th>
<th>M4 (1 month after the 3rd dose, just before the 4th dose)</th>
<th>M7 (1 month after the 6th vitamin D3 dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatininemia (μmol/L)</td>
<td>79.1 ± 14.3</td>
<td>79.2 ± 14.2</td>
<td>78.9 ± 13.9</td>
</tr>
<tr>
<td>Calcemia (mmol/L)</td>
<td>2.44 ± 0.08</td>
<td>2.44 ± 0.09</td>
<td>2.43 ± 0.08</td>
</tr>
<tr>
<td>Calciuria/creatinuria (mmol/mmol)</td>
<td>0.29 ± 0.18</td>
<td>0.28 ± 0.16</td>
<td>0.30 ± 0.19</td>
</tr>
<tr>
<td>25OHD (ng/mL)</td>
<td>17.5 ± 9.5</td>
<td>35.3 ± 8.0</td>
<td>40.1 ± 8.5</td>
</tr>
</tbody>
</table>

**Subjects with a 25OHD**

- **< 10 ng/mL:** n (%) 25 (25.5%) 0* 0*
- **< 12 ng/mL:** n (%) 34 (34.7%) 0* 0*
- **< 20 ng/mL:** n (%) 60 (61.2%) 2 (2%)* 0*
- **≤ 30 ng/mL:** n (%) 89 (90.8%) 24 (24.5%)* 11 (11.2%)*
- **> 60 ng/mL:** n (%) 0 0 2 (2%)

* P < 0.001 with respect to M0.
Discussion

We have shown that a monthly 80,000 IU vitamin D3 dose between November and April given to a group of randomly selected 98 CEA employees allowed to correct the vitamin D insufficiency (serum 25OHD < 20 ng/mL) which was initially present in more than 60% of the participants, without inducing any overdosing. Only 2% of the participants had a 25OHD slightly above 60 ng/mL after 6 months of supplementation. According to the two available epidemiologic studies in the French general population, vitamin D insufficiency (< 20 ng/mL) is found in 40–50% of the apparently healthy French subjects [3-5]. In our apparently healthy subjects who had a 25OHD measurement in November, we not only reported a higher proportion of subjects with a 25OHD < 20 ng/mL (61.2%), but also a high percentage (approximately 25%) of severe vitamin D deficiency (25OHD < 10 ng/mL). This frequency of low vitamin D status is especially high, all the more that this condition is easily modifiable thanks to a vitamin D supplementation or a modification of some nutritional and environmental habits [9]. As vitamin D testing is no longer reimbursed in France with the exception of a few clinical situations, it is now the rule to prescribe vitamin D supplementation without prior testing, at least in the general population. The challenge is thus to find the best compromise that takes into account efficacy on the one hand (prescribe vitamin D dosage that allows that most of the subjects rise their 25OHD serum level above 20 ng/mL), and cautiousness (avoiding that the 25OHD level exceeds 60–70 ng/mL, even in those with an initial 25OHD > 20 ng/mL). The vitamin D intake that allows reaching a 25OHD > 20 ng/mL in most of subjects without exceeding 60 ng/mL is debated. To identify such intake, interventional studies where various vitamin D doses are administered to several groups of volunteers are needed. It must be noted that, although such studies already exist, they have mostly tested daily dosages [10-13]. Even if daily vitamin D dosages may be considered as being more physiologic, the current practice in France is to prefer spaced-out doses in order to favour observance to this supplementation [14]. Assuming that only vitamin D3 is prescribed as it allows a much better stability of the 25OHD concentration than vitamin D2 [15,16], and that very high doses are avoided as some data suggest that they may

Table III

<table>
<thead>
<tr>
<th>Change in the 25OHD level between</th>
<th>Subjects with a baseline (M0) 25OHD &lt; 20 ng/mL</th>
<th>Subjects with a baseline (M0) 25OHD &gt; 20 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0 and M4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ng/mL</td>
<td>21.8 ± 5.4 [11.3-34.6]</td>
<td>11.7 ± 5.6 [1.4-24.1]*</td>
</tr>
<tr>
<td>In percent</td>
<td>236 ± 141% [81-827]</td>
<td>43.8 ± 24.4% [4.4-106.6]*</td>
</tr>
<tr>
<td>M0 and M7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ng/mL</td>
<td>26.8 ± 5.9 [15.0-38.6]</td>
<td>15.9 ± 7.1 [2.5-31.4]*</td>
</tr>
<tr>
<td>In percent</td>
<td>290 ± 161% [93.2-835]</td>
<td>60.7 ± 31.4% [9.3-138.9]*</td>
</tr>
<tr>
<td>M4 and M7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ng/mL</td>
<td>5.0 ± 4.2 [-6.9-14.3]</td>
<td>4.4 ± 4.6 [-12-16.8]</td>
</tr>
<tr>
<td>In percent</td>
<td>16.4 ± 13.9% [-14.2-53.4]</td>
<td>12.0 ± 13.1% [-33.1-53.7]</td>
</tr>
</tbody>
</table>

* P < 0.001 compared to those with a baseline 25OHD < 20 ng/mL.
be deleterious, especially in aged women [17], several experts claim that weekly or monthly dosages allow the same stability of the 25OHD level than daily dosages [2,18]. In a placebo-controlled trial, we have shown that a monthly dose of 50,000 IU vitamin D3 between November and April maintained the 25OHD serum concentration between 20 and 60 ng/mL in most healthy young Belgian volunteers while 84% of those who received the placebo had a 25OHD concentration < 20 ng/mL in February [19]. As 50,000 IU doses are not currently available in France, we chose to use the smallest of the large doses that are currently available in our country (80,000 IU vitamin D3) with which we obtained similar results than those obtained in our previous study with a monthly dose of 50,000 IU. Indeed, almost all participants had a 25OHD concentration between 20 and 60 ng/mL at M4 and M7. A possible explanation for these similar results while we used larger doses in the present study than in our previous study [19] may be that our subjects had a lower 25OHD level at baseline (17.5 ng/mL versus 22.0 ng/mL) with a higher percentage of subjects who presented a severe deficiency.

In the present study, we considered that, in addition of aiming to increase the 25OHD serum concentration above 20 ng/mL, the challenge was to avoid exceeding 60–70 ng/mL, even in those who were not deficient at M0 (the highest concentration at M0 was 45.5 ng/mL in one subject). Our results have shown that this was successfully achieved as only 2 subjects had a 25OHD level marginally > 60 ng/mL at M7. This may be explained by the fact that we (figure 1 and table III), and others [20] have found a negative relationship between the baseline 25OHD concentration and its increase during a supplementation with vitamin D. In other words, and for a given vitamin D dosage, the higher the baseline 25OHD, the lower its increase during supplementation. Several, possibly coexisting hypotheses exist to explain this phenomenon. First, it is possible that in case of vitamin D sufficiency, a greater proportion of the ingested vitamin D dose is sequestrated, probably in the fat tissue, and is thus not available for a liver hydroxylation [21]. Second, it has also been suggested that in case of vitamin D sufficiency, the 25-hydroxylase that is coded by the CYP2R1 gene is the only enzyme that the liver uses to produce 25OHD, and that in case of severe vitamin D deficiency, other 25-hydroxylases are able to potentialize CYP2R1 [22]. Third, it is also possible that the 24-hydroxylase that inactivates the vitamin D metabolites is less active in case of insufficient vitamin D status, inducing thus less transformation of 25OHD into 24,25 dihydroxyvitamin D (24,25OHD2) as suggested by the negative correlation between the 25OHD serum concentration and the 25OHD/24,25OHD2 ratio found in apparently healthy persons [23]. In the present study, the vitamin D supplementation was given to all participants whatever their baseline 25OHD concentration.

As several risk factors of hypovitaminosis D have been identified (i.e., ageing, having a dark skin, being overweight or obese, wearing covering clothes, avoiding outdoor activities, having a vitamin D testing during winter . . . ), many doctors may consider that it is more obvious to target a vitamin D supplementation to those who present one or more of these risk factors rather than to propose that supplementation to everybody. Because of a limited number of subjects, our study was not designed to identify such risk factors. However, we were able to identify the absence of sunny holidays during the previous summer as a significant risk of having a low 25OHD level in November.

In conclusion, we have shown in the present study that a monthly 80,000 IU vitamin D3 dose between November and April allowed correcting vitamin D insufficiency (25OHD < 20 ng/mL), without inducing overdosage in apparently healthy CEA employees. This protocol of supplementation is simple and costless and proved to be safe in our subjects. It may easily be proposed to subjects/patients who have risk factors of hypovitaminosis D.

Acknowledgments: we thank the Rottapharm Laboratory for the donation of the vitamin D3 vials.

Disclosure of interest: JCS reports lecture fees and/or travel/hotel expenses from Diasorin, Roche Diagnostics, Abbott, Amgen, Shire, MSD, Lilly, and Rottapharm; CM reports lecture fees and travel/hotel expenses from Diasorin; EC is a consultant for IDS and Diasorin and has received lecture fees from IDS, Diasorin, Roche, Abbott and Amgen; the authors SBT and PC declare that they have no competing interest.

References


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