Original Paper

nephron Clinical Practice

Nephron Clin Pract
DOI: 10.1159/000366449

Received: March 20, 2014
Accepted: August 4, 2014
Published online: November 4, 2014

Clinical and Biological Determinants of Sclerostin Plasma Concentration in Hemodialysis Patients

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Key Words
Sclerostin · Bone turnover · Vascular calcification

Abstract
Background: Sclerostin is a potent inhibitor of bone formation, but the meaning of its serum levels remains undetermined. We evaluated the association between sclerostin levels and clinical or biological data in hemodialyzed patients (HD), notably parathormone (PTH), biomarkers of bone turnover, vascular calcifications and mortality after 2 years. ***Methods:*** 164 HD patients were included in this observational study. The calcification score was assessed with the Kauppila method. Patients were followed for 2 years. ***Results:*** Median sclerostin levels were significantly ($p < 0.0001$) higher in HD versus healthy subjects ($n = 94$) (1,375 vs. 565 pg/ml, respectively). In univariate analysis a significant association ($p < 0.05$) was found between sclerostin and age, height, dialysis vintage, albumin, troponin, homocysteine, PTH, C-terminal telopeptide of collagen type I, bone-specific alkaline phosphatase and osteoprotegerin, but not with the calcification score. In a multivariate model, the association remained with age, height, dialysis vintage, troponin, homocysteine, phosphate, PTH, but also with vascular calcifications. Association was positive for all variables, except PTH and vascular calcifications. The baseline sclerostin concentration was not different in survivors and non-survivors. ***Conclusions:*** We confirm a higher concentration of sclerostin in HD patients, a positive association with age and a negative association with PTH. A positive association with phosphate, homocysteine and troponin calls for additional research. The clinical interest of sclerostin to assess vascular calcifications in HD is limited and no association was found between sclerostin and mortality.

This work was presented in part as a poster at the 2013 ASN Congress in Atlanta, Ga., USA.

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Introduction

Sclerostin, produced by the SOST gene, is an osteocyte-specific glycoprotein and is presented as a potent inhibitor of bone formation [1, 2]. In humans, mutation of the SOST gene will lead to sclerosteosis and Van Buchem disease, autosomal recessive skeletal dysplasia characterized by generalized bone overgrowth [1, 3]. Sclerostin inhibits, via high-affinity binding, the low-density lipoprotein receptor-related protein 5 and 6 (Lrp-5/6) [4]. Lrp-5/6 are co-receptors for activation of β-catenin-dependent signaling downstream of Wnt [5]. This so-called canonical pathway is a key in the mechanical stimulation of the osteoblast-mediated bone formation [6]. It is actually well known that bone surface that experiences high mechanical strains is stimulated and that mechanical loading so improves bone mass and strength [7]. Osteocyte is now considered as the mechanoreceptor in bone [8]. Animal models of mechanical loading have shown that sclerostin was the protein of choice involved in the phenomena of bone mechanosensibilization. A greater strain on the bone induces a downregulation of the SOST gene and a decreasing secretion of sclerostin by the osteocytes. Because sclerostin decreases osteoblast activity, its inhibition will lead to an increase in bone formation [9]. If the role of sclerotin in bones is more and more well known, the meaning of sclerostin concentrations in the plasma remains to be precised [10, 11]. Nevertheless, discovery of this new pathway in bone formation has opened new perspectives in the field of osteoporosis therapy. First clinical trials with anti-sclerostin antibodies in postmenopausal women have shown an impressive gain in term of bone mineral density (BMD) [12, 13].

Dialysis patients are prone to bone abnormalities [14]. In this context, the measurement of sclerostin could be of interest and first studies have demonstrated a potential role of sclerostin both in the diagnostic of bone turnover and the prediction of bone loss [15, 16].

In hemodialysis (HD) patients, vascular calcifications are precocious, frequent and excessive [17, 18]. The Wnt signaling pathway could be implicated in the development of these vascular calcifications [19, 20]. Moreover, some authors have described, in HD patients, a strong expression of sclerostin in the region of vascular calcifications either in calcified valves or in the skin of patients with calciphylaxis [21, 22]. It seems thus logical to study the potential association between sclerostin levels and the intensity of vascular calcifications [11, 15, 21]. Moreover, the association between the level of vascular calcifications and mortality has been described in HD patients [23]. In this context, limited data have suggested that sclerostin could be predictive of mortality in HD patients [24].

In this work, we studied the potential association between clinical and biological data in HD patients. We verified if we found the usual negative relationship between sclerostin levels and PTH. Moreover, we analyzed the potential association between sclerostin and several biomarkers of bone turnover, either formation or resorption bone biomarkers. We also studied the potential association between sclerostin and vascular calcifications or mortality.

Methods

Prevalent HD patients from three independent centers in Liège and surrounding areas, Belgium, were included in this study (Centre Hospitalier Universitaire du Sart Tilman, Centre Hospitalier Régional de 'La Citadelle', Centre Hospitalier 'Bois de l'Abbaye' de Seraing).

Vascular calcifications were assessed by lateral X-ray radiography (the Kauppila method) and the score (between 0 and 24) was established by the same experienced investigator (L.M.) [25]. The following clinical data were considered: age, gender, weight, height, body mass index, dialysis vintage, previous cardiovascular disease, hypertension, diabetes and smoking habit. Hypertension was defined as blood pressure >140/90 mm Hg and/or treatment for hypertension. Diabetes status was extracted from electronic medical files and/or defined according to the treatment of diabetes. Previous cardiovascular disease was defined as the history of myocardial infarction, percutaneous coronary artery intervention, cardiac surgery, peripheral artery disease or cerebrovascular disease. Data were extracted from electronic medical files and completed by interviews. Smoking habit was defined as current smokers. The following laboratory data were studied: calcium, phosphorus, albumin, magnesium, C-reactive protein (CRP) (measured on the Modular; Roche, Mannheim, Germany), intact parathormone (PTH) (measured on Elecsys; Roche), troponin T (high-sensitive assay, measured on the Modular), 25-OH vitamin D, bone-specific alkaline phosphatase (b-ALP) (measured on Liaison; Diasorin, Stillwater, Minn., USA), C-terminal fibroblast growth factor (FGF-23), fetuin A, osteoprotegerin (OPG) (ELISA; Biovendor, Czech Republic), homocysteine (measured by high plasma liquid chromatography), C-terminal telopeptide of collagen type I (CTX), intact amino-terminal propeptide of type I procollagen (PINP) (measured on ISYS; IDS, Boldon, UK) and tartrate-resistant acid phosphatase 5b (TRAP-5b) (ELISA; IDS). The patients were followed after sclerostin measurement and data about global mortality are available for 2 years. Sclerostin was measured with the TECO ELISA (TECO Medical, Sissach, Switzerland). Intra- and interassay CV for sclerostin was <10%. Normal data were obtained from 94 consecutive young healthy patients undergoing routine chemical analyses (median age 31 years, 50 women). These subjects had glomerular filtration rate (GFR) >60 ml/min/1.73 m^2 and we checked for the absence of inflammation and normal concentration of albumin, calcium and phosphorus. One healthy subject was however excluded from the

Table 1. Main clinical characteristics and biological data of the global population

Age, years	74.0 (62.8; 80.5)
Male gender, %	44
Weight, kg	67.5 (59.0; 79.0)
Height, cm	162±9
Body mass index, kg/m^2	25 (23; 30)
Dialysis vintage, months	22.5 (11; 44)
Previous CVD, %	65
Hypertension, %	87
Diabetes, %	44
Smoking habit, %	21
Calcium, mmol/l	2.15±0.16
Phosphate, mmol/l	1.48 (1.3; 1.9)
Magnesium, mmol/l	0.88±0.15
Albumin, g/l	38 (36; 40)
CRP, mg/l	5.0 (2.5; 12.9)
Intact PTH, pg/ml	257 (125; 430)
25-OH vitamin D, ng/ml	22 (12; 32)
b-ALP, µg/l	16 (11; 23)
CTX, pg/ml	1,595 (1,013; 2,381)
PINP, ng/ml	218 (112; 383)
TRAP-5b, U/l	5.25 (3.95; 7.05)
OPG, pmol/l	9 (12; 16)
Homocysteine, µmol/l	25 (19; 33)
Troponin T, µg/l	0.04 (0.02; 0.07)
FGF-23, RU/ml	2,902 (1,007; 7,130)
Fetuin A, µg/ml	225 (190; 281)
Calcification score (maximum score is 24)	15 (5; 15)
Sclerostin, pg/ml	1,375 (963; 1,830)

CVD = Cardiovascular disease; CRP = C-reactive protein; PTH = parathormone; b-ALP = bone-specific alkaline phosphatase; CTX = C-terminal telopeptide of collagen type I; PINP = intact amino-terminal propeptide of type I procollagen; TRAP-5b = tartrate-resistant acid phosphatase 5b; OPG = osteoprotegerin; FGF-23 = fibroblast growth factor 23.

analysis for clinical reasons (history of malleolus osteonecrosis) and another one for both analytical and statistical reasons (outlier, according to Tukey's method). Human subjects' procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975. Our study has been approved by the ethic committee of our university hospital.

Statistical Analysis

Data are expressed as mean ± SD when distribution was normal and as median and interquartile range if not. Normality was assessed by the Anderson-Darling test. Normal reference values were calculated according to the robust method, a non-parametric percentile method (2.5th and 97.5th percentiles). Regression analysis was used to study the potential linear relationship between sclerostin and clinical or biological data. Multivariate analysis was performed using stepwise forward selection in 'Proc GLMSelect' (SAS 9.3) in an attempt to model sclerostin, using all available information. We also defined subgroups according to sclerostin tertiles. We studied whether there were variables which were different according to these tertiles using ANOVA followed by Tukey's post hoc test for multiple pairwise comparisons. We performed a Kaplan-Meier univariate survival analysis. All statistical analyses were conducted using MedCalc (Mariakerke, Belgium) and SAS 9.3 (SAS Institute, Inc., Cary, N.C., USA).

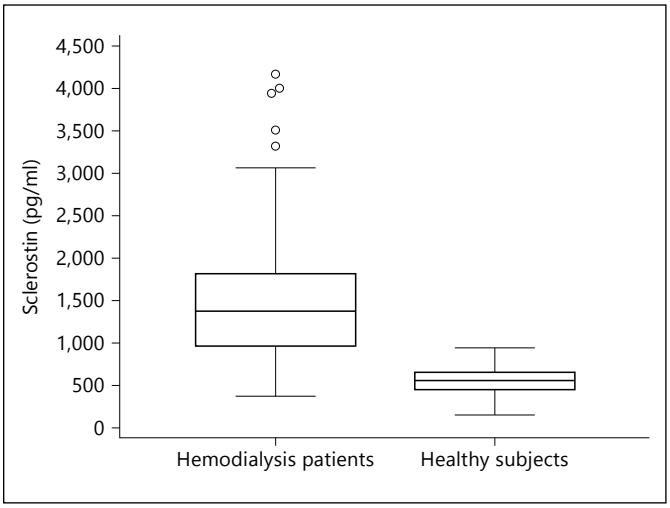

Fig. 1. Median concentrations of sclerostin in hemodialyzed (n = 164) and healthy population (n = 94): 1,375 (963; 1,830) vs. 565 (443; 660) pg/ml; p < 0.0001.

Results

Clinical and biological variables of the global population (n = 164) are summarized in table 1. In our HD patients, the concentration of sclerostin was 1,375 (963; 1,830) pg/ml, with no difference between men and women. These concentrations are higher than the median concentration observed in our healthy population 565 (443; 660) pg/ml (p < 0.0001) (fig. 1). The 'normal' lower and higher limit for sclerostin was 231 and 880 pg/ml, respectively. Normal concentrations of sclerostin were significantly higher in men [615 (550; 720) pg/ml, n = 42] than in women [485 (418; 590) pg/ml, n = 50] (p = 0.0004). The normal higher limit in men and women were 990 and 776 pg/ml, respectively. According to these two results, 80% of HD patients have sclerostin concentrations higher than the upper normal reference value.

We found a significant linear association in univariate analysis (p < 0.05) between sclerostin and age, height, dialysis vintage, albumin, magnesium, troponin T, homocysteine, PTH, CTX, b-ALP and OPG (table 2). No such

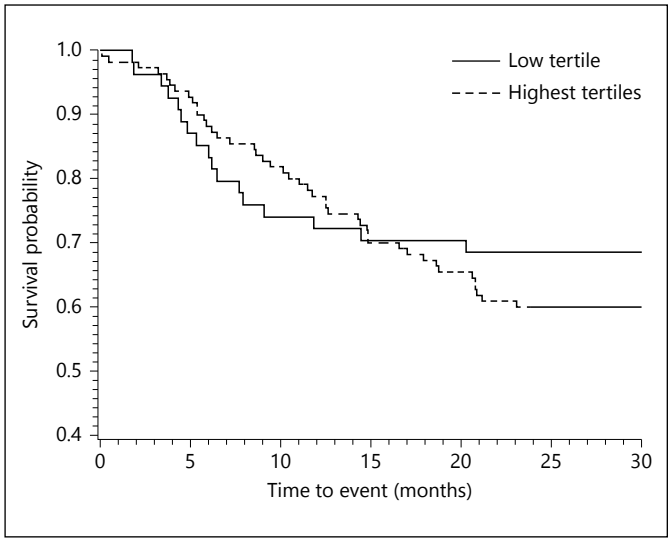

Fig. 2. Kaplan-Meier curves showing survival probability after 2 years between patients in the lowest tertiles versus the two high tertiles of sclerostin. The difference is not significant.

Table 2. Pearson correlation coefficients for sclerostin and other variables

Variable	Pearson correlation coefficient	p value
Age	0.258	0.0008
Height	0.187	0.0169
Dialysis vintage	0.156	0.046
Mg	0.197	0.0002
Troponin T	0.290	0.0002
Albumin	0.166	0.034
Homocysteine	0.206	0.0083
PTH	–0.295	0.0001
CTX	–0.188	0.0159
BALP	–0.199	0.0107
OPG	0.320	<0.0001

correlation was found between sclerostin levels and the calcification score. In the multivariate model, a significant association ($p < 0.05$) was still found between sclerostin and age, height, albumin, troponin T, homocysteine, dialysis vintage, phosphate, PTH and vascular calcifications. Sclerostin was positively correlated with age, height, albumin, phosphate, troponin T, homocysteine, and dialysis vintage. Correlations were negative with PTH and vascular calcifications. This multivariate model explains 42% of the sclerostin variability.

We compared by ANOVA the variables in the subgroups defined by tertiles of sclerostin (table 3). Compared to patients in the lowest tertile of sclerostin (<1,130 pg/ml), we found that patients in the highest tertiles (>1,660 pg/ml) have significantly higher troponin T, albumin, OPG and homocysteine concentrations and lower PTH, CTX and b-ALP concentrations. Troponin T was also significantly higher in the highest tertile compared to the intermediate tertile. Calcification scores were not different between tertiles.

After 2 years, we observed a mortality rate of 37.2%, i.e. 61 patients. Survivors were significantly younger [71 (57; 79) vs. 78 (71; 85) years, $p < 0.0001$] and had the following baseline characteristics: higher albumin levels [39 (37; 41) vs. 37 (35; 40) g/l, $p = 0.0069$], higher CTX levels [1,875 (1,103; 2,634) vs. 1,249 (947; 1,913) pg/ml, $p = 0.0022$], lower CRP levels [4.4 (1.8; 10.5) vs. 8.3 (4.3; 18.5) mg/l, $p = 0.0092$], lower troponin T levels [0.03 (0.02; 0.05) vs. 0.05 (0.03; 0.08) µg/l, $p < 0.0001$]. Other variables of table 1 were not different between survivors or non-survivors. Baseline sclerostin concentration was not different in survivors and non-survivors after 2 years of follow-up. Also, patients with baseline values higher than the median value, i.e. 1,375 pg/ml, have the same mortality at 2 years than patients with low concentrations. Considering tertiles of sclerostin, we did not observe any difference of mortality between the tertiles (fig. 2).

Discussion

In this study, we confirmed that sclerostin concentrations are significantly higher in HD patients than in a healthy young population [15, 21, 26]. The higher concentration of sclerostin observed in HD is still not fully understood. It could be due to a decreased renal excretion of sclerostin in chronic kidney disease (CKD), which could be expected regarding the molecular weight (22.5 kDa) of the protein. An important study from Pelletier et al. [27] showed a negative correlation between sclerostin and *measured* GFR in 90 subjects at different stages of CKD. An increased production of sclerostin due to other mechanisms cannot be excluded. For example, as HD patients (especially among the oldest ones) are limited in physical activity [28], the higher sclerostin levels could also be due to a lower load in mechanical stress, as it has been demonstrated in diverse ill populations [26, 29, 30]. Another hypothesis could be a sort of 'sclerostin resistance' in CKD, as it is observed with PTH [31]. Clearly, additional studies are required

Table 3. Variables with significantly different concentrations (mean ± SE) in the subgroups defined by tertiles of sclerostin (ANOVA analysis, $p < 0.05$)

Variable	Group 1 (n = 54) <Pct33	Group 2 (n = 55) [Pct33–Pct66]	Group 3 (n = 55) >Pct66	1 vs. 2	1 vs. 3	2 vs. 3
Troponin T, μg/l	0.046±0.007	0.043±0.006	0.086±0.012	NS	<0.05	<0.05
Albumin, g/l	36.70±0.71	38.78±0.44	38.82±0.50	<0.05	<0.05	NS
Homocysteine, μmol/l	25.31±1.48	27.41±2.00	36.60±4.66	NS	<0.05	NS
Intact PTH, pg/ml	426.4±48.4	339.5±35.9	231.6±21.5	NS	<0.05	NS
CTX, pg/ml	2,248±215	1,889±163	1,555±132	NS	<0.05	NS
b-ALP, μg/l	31.5±6.7	19.5±1.7	16.2±1.5	NS	<0.05	NS
OPG, pmol/l	11.0±0.6	13.6±0.7	15.2±1.0	NS	<0.05	NS

both in CKD and HD patients and the debate is not closed.

The concentrations we observed in our cohort of 164 HD patients (1,505 ± 715 pg/ml) are different compared to those published in other HD cohorts [26]. Differences could be explained, at least in part, by the different clinical characteristics of the cohorts, notably the age. Indeed, we confirmed that one main positive determinant of sclerostin concentration is age [15, 21, 24, 27, 32]. Aging is associated with sarcopenia, decreased physical activity and decreased mechanical loading on bones, leading to sclerostin activation [26, 29]. Thus, sclerostin could also act as a mediator in the well-known decreased bone quality associated with aging. Differences in the assays used to measure sclerostin may actually greatly impact the results and explain differences in sclerostin levels between studies [33, 34]. Indeed, Durosier et al. [34], measuring sclerostin in 187 healthy subjects aged 65 years with three different ELISA assays, found as high as 20- and 30-fold difference between the assays. These analytical differences could be still more relevant in the context of end-stage renal disease where inactive fragments could accumulate [21]. There is thus an urgent need of standardization between the assays.

The association we observed between sclerostin levels and height in the multivariable model is discrepant compared to the results observed in the literature [27, 34–37]. The association with height, and thus to bone length, could be however logical from a physiological point of view as the protein is principally secreted by osteocytes.

Both in physiological and clinical studies, PTH impacts sclerostin levels and PTH actually downregulates sclerostin activation. A negative correlation is thus observed between PTH and sclerostin levels [34, 38–40]. The interaction between PTH and sclerostin is however not fully understood as both intermittent and continuous PTH infusion decreased sclerostin expression [41] whereas only intermittent PTH injection has an anabolic effect on bone [10]. In a HD population, like other authors, we found a negative correlation between PTH and sclerostin concentrations [15, 24, 26]. Interestingly, we also found a negative correlation between sclerostin and b-ALP, the recommended biomarker to evaluate bone turnover in HD patients, and between sclerostin and CTX, one of the main biomarkers of bone resorption [14]. In univariate analysis, we also found a trend to a negative association with other bone turnover biomarkers (Trap-5B and PINP) (data not shown). In HD patients, Evenepoel and colleagues [24, 32] also found a negative correlation between b-ALP and sclerostin levels both in 100 HD and 154 CKD patients. In 117 CKD patients (non-HD), other authors found a negative correlation between sclerostin and CTX but no correlation with PINP or alkaline phosphatase [31]. An important study in 60 HD patients with bone biopsies demonstrated that sclerostin was negatively correlated with histomorphometric parameters of turnover and with osteoblast numbers. Sclerostin was considered as useful and superior to PTH for the positive, but not the negative, prediction of high bone turnover [15]. Unfortunately, b-ALP was not measured in this last study. Moreover, correlation is not causation as underlined by the authors of the editorial [10]. Our results also suggest that sclerostin levels are negatively influenced by high bone turnover in HD patients. However, we must keep in mind that all associations between sclerostin and bone biomarkers were lost in the multivariate analysis and only PTH remains significantly associated. Moreover, PTH seems to directly act and inhibit sclerostin production [38–41]. Therefore, another hypothesis could that the primary determinant of sclerostin concentration in dialysis patients is actually PTH, which itself act on bone, leading to high or low

bone turn over and eventually influencing bone biomarkers.

In univariate analysis, the higher association with sclerostin is obtained with troponin T levels ($r = 0.29023$, $p = 0.0002$) and this parameter was also relevant in the multivariate model. Troponin T concentrations are higher in HD patients [42]. Interestingly, troponin T concentration has been shown to be predictive of mortality in HD patients [42, 43]. The role of troponin T as a predictor of global mortality is also found in our cohort of 164 patients. Whatever the mechanisms involved to explain the link between sclerostin and mortality, the significant correlation between sclerostin and troponin T concentrations opens a new area of research in HD patients.

The association we found with homocysteine is not unique. Indeed, Urano et al. [37] in their cohort of postmenopausal women and Morales-Santana et al. [44] in their cohort of type 2 diabetic patients also found such a positive association. The relevance of this result is still unclear and deserves further studies.

In our population, we found a significant positive association between phosphate and sclerostin concentrations in the multivariable model. This association was independent of PTH and FGF-23 levels. Such an association was also found in two other CKD (but non-HD) cohorts [27, 31]. Phosphate has a central role both in the pathogenesis of renal osteodystrophy and in the development of vascular calcifications. Of interest, in an animal CKD model of adynamic bone disease, high dietary phosphate intake was associated with a high expression of sclerostin coding gene [45]. Our results must however be carefully considered as therapies interfering with phosphate levels were not taken into account in the analysis.

In our study, we found no association between sclerostin and the calcification score in the univariate analysis, but the association became significant and negative in the multivariate model. However, this association remained relatively poor. The interest of sclerostin to detect or estimate vascular calcification at the individual level in clinical practice is thus probably low. In the CKD population, Claes et al. [32] found, in 154 CKD patients, that the absence of calcifications was identified as an independent predictor of higher level of sclerostin. In this study, the univariate analysis showed a positive correlation between calcification score but, surprisingly, this correlation became negative (low sclerostin associated with high calcification score) in the multivariate analysis [32]. At the inverse, in 67 HD patients, other authors found a lower sclerostin concentration in patients without aortic valve calcifications compared to patients with aortic valve calcification [21].

In a post hoc analysis of 100 HD patients, Viaene et al. [24] described a better survival in patients with higher sclerostin levels. Patients with higher values had a better survival when adjusted for age and gender. However, in this study, the association between sclerostin and mortality was lost in the full adjusted model. In our study, and contrary to Viaene et al. [24], sclerostin was not predictive of global mortality. This absence of association with mortality persisted when troponin T was excluded from the statistical model (data not shown).

There are limitations in our study. Our population was a prevalent HD population and studies in incident subjects would be of interest. Because physical activity influences sclerostin levels [26, 29, 30], such data in our elderly HD patients could be of interest. Another limitation of our study is the absence of BMD measurement. In CKD patients, two studies found a positive association between sclerostin and BMD results [26, 46]. Another limitation is that our data about mortality are limited to the global mortality and data about cardiovascular mortality are not available. Lastly, we used the Kauppila method to detect calcifications, which is not the most sensitive method. Once again, the levels of sclerostin concentrations must be interpreted with caution because the lack of standardization between the assays.

In conclusion, we confirmed a higher concentration of sclerostin in prevalent HD patients. We also confirmed that sclerostin is positively associated with age and negatively with PTH. We also showed an inverse association between sclerostin and biomarkers of bone turnover in HD patients. The positive association with phosphate, homocysteine and especially with troponin T is original, promising and calls for additional research. Moreover, the clinical interest of sclerostin to assess vascular calcifications in HD is probably limited. Finally, in our population, we did not find any role for sclerostin to predict mortality.

Acknowledgements

We thank Pierre Lukas, Agnès Carlisi, Romy Gadisseur, Michelle Focan and Arnaud Borsu for their help with the samples (collect and measurements) and Rosalie Bonmariage and Isabelle Mourad for editorial assistance.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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