Association between the Circulating Total Osteocalcin Level and the Development of Cardiovascular Disease in Middle-aged Men: A Mean 8.7-year Longitudinal Follow-up Study

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Aim: Recent studies have suggested that the serum osteocalcin level is associated with various cardiovascular risk factors. The aim of this study was to determine whether the serum total osteocalcin level is associated with the development of cardiovascular disease (CVD).

Methods: A total of 1,290 men 40-78 years of age were enrolled. The subjects were followed regularly at the Health Promotion Center on an outpatient basis and during hospitalization for a mean of 8.7 years, and the incidence of CVD (coronary heart disease [CHD] and stroke) was determined.

Results: At baseline, the body mass index, body fat percentage, fasting glucose, homeostasis model assessment-insulin resistance, triglyceride and non-high density lipoprotein (HDL) cholesterol levels were inversely and the HDL cholesterol levels were positively associated with the serum osteocalcin levels. In addition, the prevalence of diabetes or metabolic syndrome decreased as the osteocalcin tertile increased. However, no differences were observed in the prevalence of hypertension across the osteocalcin tertiles. Incident CVD occurred in 74 (5.7%) of the study subjects (29 patients with CHD and 47 patients with stroke). According to the Cox proportional hazards models, however, there were no statistical differences in the development of stroke, CHD or CVD across the osteocalcin tertiles after adjusting for other risk factors for CVD, including age, body mass index, current smoking, low-density lipoprotein cholesterol, diabetes, hypertension and the serum creatinine level.

Conclusion: In conclusion, the serum total osteocalcin level was not associated with the development of CVD after adjusting for other risk factors for CVD in this cohort.


Key words: Osteocalcin, Cardiovascular disease, Coronary heart disease, Stroke

Introduction

Mounting evidence supports the existence of a close relationship between CVD and bone metabolism. In women, the loss of hip bone mineral density (BMD) has been shown to be associated with an increase in total mortality, particularly that due to coronary heart disease (CHD), after adjusting for other confounders during an average follow-up of 3.2 years1). In addition, an increase in the total hip BMD has been demonstrated to be independently associated with a decreased age-adjusted relative risk for all-cause and CVD mortality in older men2). In agreement with these findings, recent studies have reported an inverse
association between calcification in the abdominal aorta and the bone mass at the lumbar and femoral levels. Furthermore, a significant negative correlation has been reported between the pulse wave velocity (PWV), a surrogate marker of CVD, and the hip BMD, which persists after adjusting for age, mean arterial pressure and serum lipids, in post-menopausal women.

As a plausible explanation of the relationship between CVD and bone metabolism, these two conditions share common risk factors, including age, estrogen depletion, a sedentary lifestyle, smoking, alcohol consumption and dietary factors, such as the level of calcium intake and deficiencies in vitamins C and K. However, it is difficult to explain all aspects of the relationship based only on these common risk factors, and there may be a missing link between CVD and bone metabolism.

Recently, the osteoblast-specific protein, osteocalcin, was suggested to be a central factor involved in the cross-talk between bone and energy metabolism, and accumulating human evidence has demonstrated that the serum osteocalcin level is inversely associated with impaired glucose tolerance. In addition, the serum osteocalcin level has been shown to be inversely correlated with the body mass index (BMI), homeostatic model assessment-insulin resistance (HOMA-IR), triglycerides, leptin and number of metabolic syndrome traits, positively correlated with adiponectin and significantly and negatively correlated with the brachial artery PWV and intima-media thickness in men following additional adjustments for other cardiovascular risk factors. Moreover, the serum total osteocalcin level was found to predict all-cause and CVD-related mortality in a prospective cohort study of community-dwelling older men 70-89 years of age.

However, little is still known about whether the aforementioned findings are merely correlations or if osteocalcin directly affects the development of CVD. Therefore, we performed this study in order to determine whether the serum osteocalcin level is independently associated with the development of CVD (CHD and stroke) over an 8.7-year mean follow-up period.

Methods

Study Population

A detailed description of the study design and methods has been published previously. Briefly, the study subjects were recruited from among patients who visited the Health Promotion Center of the Samsung Medical Center between January 1997 and December 1997. A total of 2,435 subjects (1,761 men and 674 women) 20-78 years of age were enrolled and followed up regularly at the Health Promotion Center on an outpatient basis and during hospitalization for a mean of 8.7 years. Of the 2,435 subjects, we limited the study participants to 1,290 men, 40-78 years of age, for whom the serum total osteocalcin levels had been determined. These subjects were subsequently followed up for a mean of 8.7 years. This study was approved by the Institutional Review Board and Ethics Committee of Samsung Medical Center and complied with the Declaration of Helsinki.

Definition of CVD and Other Measurements

In this study, CVD was defined as the occurrence of CHD and/or stroke. CHD included angina pectoris, myocardial infarction and congestive heart failure, as determined by the presence of typical symptoms, elevation of cardiac enzymes and the findings of electrocardiograms, echocardiography, stress tests and/or coronary angiography. Stroke included cerebral infarction, hemorrhagic stroke, transient ischemic attack, vertebrobasilar insufficiency and complete occlusion of the internal carotid arteries, as determined on carotid vascular Doppler, computed tomography or magnetic resonance imaging and/or the presence of accompanying neurologic signs or symptoms. Patients with incidental lacunar infarction on brain imaging were not considered to have incident stroke. Metabolic syndrome was defined using the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria. Diabetes was defined according to the presence of one of the following items: a fasting glucose level of ≥ 126 mg/dL (≥ 7.0 mmol/L); the use of diabetes medication; a self-reported physician diagnosis; and a glycated hemoglobin (HbA1c) level of ≥ 6.5%. Hypertension was defined as a systolic or diastolic blood pressure of ≥ 140/90 mmHg or the previous self-reported use of anti-hypertensive medications, and alcohol intake was defined as the consumption of more than three drinks per day (> 30 g ethanol/day). The percentage of body fat was measured using a bioelectrical impedance analysis (InBody 3.0; Biospace, Seoul, Korea).

At baseline, the subjects were assessed for CHD, stroke, hypertension and diabetes, as determined according to a standardized questionnaire and their medical records and followed regularly for the new onset of CHD or stroke. In order to ascertain the incidence of CVD, all data were collected from the Health Promotion Center on an outpatient basis and during hospitalization.
The serum total osteocalcin level was measured at the time of sampling in 1997 and analyzed according to the Metra TM Osteocalcin system (Quidel Corp., Santa Clara, USA) using a Dade Behring ELISA-Processor III (Behring Diagnostics, Inc., Somerville, USA) with intra- and inter-assay CVs of 4.8-10.0% and 4.8-9.8%, respectively.

### Statistical Analysis

All data are presented as the mean ± SD or proportion, except for skewed variables, which are presented as the median (interquartile range, 25%-75%). Because the distributions of the serum levels of triglycerides, gamma-glutamyl transpeptidase (γGT), lipoprotein (a), plasminogen activator inhibitor (PAI)-1 and HOMA were skewed, natural logarithmic transformation was applied in the statistical analyses. In the interest of simplicity, non-transformed median values are presented in the tables and text. A one-way ANOVA was used to compare the means between the tertiles of the osteocalcin level. The linear-by-linear association χ²-test was used to conduct a trend analysis between the tertiles. Pearson correlation coefficients were calculated to evaluate the associations between the osteocalcin levels and the clinical and laboratory measurements. A Kaplan-Meier survival curve was used to compare the development of CVD according to the osteocalcin tertile. A Cox proportional hazards regression with backward selection model was used to calculate the adjusted hazard ratio (HR) for incident cases of cardiovascular disease among the subjects based on the osteocalcin tertile. The lowest osteocalcin tertile was used as a reference, and the results for the analyses are presented as the HR with the 95% confi-

### Table 1. Baseline characteristics according to the serum total osteocalcin tertile

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 1290)</th>
<th>Low tertile (n = 433)</th>
<th>Middle tertile (n = 439)</th>
<th>Upper tertile (n = 418)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteocalcin (nmol/L, range)</td>
<td>1.30 ± 0.47</td>
<td>0.81 ± 0.21</td>
<td>1.28 ± 0.11</td>
<td>1.83 ± 0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(0.27-3.69)</td>
<td>(0.27-1.08)</td>
<td>(1.09-1.45)</td>
<td>(1.47-3.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.6 ± 6.2</td>
<td>49.7 ± 6.2</td>
<td>49.8 ± 6.4</td>
<td>49.2 ± 5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.9 ± 2.3</td>
<td>24.2 ± 2.1</td>
<td>23.8 ± 2.2</td>
<td>23.6 ± 2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>22.4 ± 4.5</td>
<td>22.9 ± 4.1</td>
<td>22.1 ± 4.5</td>
<td>22.1 ± 4.7</td>
<td>0.011</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121.6 ± 14.3</td>
<td>122.0 ± 13.9</td>
<td>121.3 ± 14.4</td>
<td>121.5 ± 14.6</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83.5 ± 10.2</td>
<td>83.9 ± 10.0</td>
<td>83.1 ± 10.1</td>
<td>83.5 ± 10.5</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.79 ± 1.17</td>
<td>5.95 ± 1.57</td>
<td>5.82 ± 1.02</td>
<td>5.58 ± 0.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>5.4 ± 0.7</td>
<td>5.5 ± 0.9</td>
<td>5.4 ± 0.6</td>
<td>5.3 ± 0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Glycated hemoglobin (mmol/mol)</td>
<td>36 ± 7</td>
<td>37 ± 9</td>
<td>36 ± 7</td>
<td>35 ± 5</td>
<td>0.001</td>
</tr>
<tr>
<td>Log HOMA-IR</td>
<td>1.75 (1.25-2.40)</td>
<td>1.88 (1.34-2.59)</td>
<td>1.80 (1.23-2.45)</td>
<td>1.63 (1.20-2.23)</td>
<td>0.001</td>
</tr>
<tr>
<td>Log HOMA-B%</td>
<td>66.0 (46.8-90.5)</td>
<td>68.0 (47.0-93.2)</td>
<td>65.8 (45.0-87.7)</td>
<td>65.2 (49.5-92.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.17 ± 0.82</td>
<td>5.24 ± 0.82</td>
<td>5.14 ± 0.81</td>
<td>5.13 ± 0.82</td>
<td>0.089</td>
</tr>
<tr>
<td>Log triglycerides (mmol/L)</td>
<td>1.49 (1.07-2.06)</td>
<td>1.59 (1.14-2.22)</td>
<td>1.42 (1.07-2.01)</td>
<td>1.44 (1.02-1.95)</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.27 ± 0.30</td>
<td>1.24 ± 0.29</td>
<td>1.27 ± 0.29</td>
<td>1.30 ± 0.31</td>
<td>0.032</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.13 ± 0.74</td>
<td>3.17 ± 0.76</td>
<td>3.11 ± 0.73</td>
<td>3.10 ± 0.74</td>
<td>NS</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mmol/L)</td>
<td>3.90 ± 0.83</td>
<td>4.00 ± 0.82</td>
<td>3.87 ± 0.83</td>
<td>3.83 ± 0.83</td>
<td>0.008</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>100.4 ± 10.1</td>
<td>100.3 ± 10.1</td>
<td>99.9 ± 10.4</td>
<td>100.9 ± 9.9</td>
<td>NS</td>
</tr>
<tr>
<td>Log γGT (U/L)</td>
<td>30.0 (22.0-45.0)</td>
<td>34.0 (24.0-52.0)</td>
<td>29.0 (22.0-47.0)</td>
<td>27.5 (21.0-39.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uric acid (μmol/L)</td>
<td>344.2 ± 64.4</td>
<td>345.4 ± 64.6</td>
<td>347.3 ± 64.9</td>
<td>339.8 ± 63.6</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen (μmol/L)</td>
<td>9.16 ± 1.75</td>
<td>9.28 ± 1.78</td>
<td>9.05 ± 1.69</td>
<td>9.15 ± 1.77</td>
<td>NS</td>
</tr>
<tr>
<td>Log lipoprotein (a) (μmol/L)</td>
<td>0.46 (0.25-0.89)</td>
<td>0.41 (0.22-0.81)</td>
<td>0.46 (0.26-0.90)</td>
<td>0.49 (0.28-0.93)</td>
<td>0.055</td>
</tr>
<tr>
<td>Log plasminogen activator inhibitor-1 (μg/L)</td>
<td>26.0 (16.0-39.0)</td>
<td>29.0 (18.0-43.5)</td>
<td>26.0 (17.0-38.0)</td>
<td>23.0 (15.0-37.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Alcohol intake (%)</td>
<td>399 (30.9)</td>
<td>146 (33.7)</td>
<td>141 (32.1)</td>
<td>112 (26.8)</td>
<td>0.029</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>583 (45.2)</td>
<td>191 (44.1)</td>
<td>199 (45.3)</td>
<td>193 (46.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>373 (28.9)</td>
<td>131 (30.3)</td>
<td>116 (26.4)</td>
<td>126 (30.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>118 (9.1)</td>
<td>57 (13.2)</td>
<td>41 (9.3)</td>
<td>20 (4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>427 (33.1)</td>
<td>171 (39.5)</td>
<td>153 (34.9)</td>
<td>103 (24.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The data are expressed as the mean ± SD, median (interquartile range) or frequency. NS, not significant.
Incident CVD occurred in 74 (5.7%) of the study subjects (29 cases of CHD and 47 cases of stroke) during the mean 8.7-year follow-up period. Compared with the lowest osteocalcin tertile (reference group), no differences were observed in the middle or upper osteocalcin tertiles for the development of CVD according to the Kaplan-Meier survival curve (Fig. 1). Separately, the development of CHD and stroke was not associated with the baseline serum total osteocalcin level (both \( p > 0.05 \)). In addition, the serum total osteocalcin level was not associated with the development of CHD, stroke or CVD in women only or both men and women (data not shown).

The results of the Cox proportional hazard model analysis are shown in Table 2. The independent variables included in the models comprised age, BMI, current smoking, low-density lipoprotein (LDL) cholesterol, diabetes, hypertension, the serum creatinine and serum osteocalcin levels according to the tertile. Consequently, age (HR, 1.05; 95% CI, 1.02-1.09), current smoking (HR, 2.18; 95% CI, 1.36-
The serum total osteocalcin level was not associated with incident CVD across the tertiles. The results for stroke and CHD were similar to those for CVD.

**Discussion**

Accumulating evidence has indicated an association between the serum osteocalcin level and favorable metabolic phenotypes and atherosclerosis parameters\(^{12-16}\). First, it has been reported that an elevated osteocalcin level is associated with better glycemic control, improved insulin sensitivity and/or insulin secretory capacity\(^{12-14}\). In addition, some small longitudinal studies have shown the serum total osteocalcin concentration to be associated with changes in the fasting plasma glucose level and risk of incident diabetes\(^{21}\). Second, the osteocalcin level has been reported to be associated with a decreased fat mass and low prevalence of metabolic syndrome and its traits\(^{7, 15}\). The serum osteocalcin level is also reported inversely associated with waist circumference, fasting glucose, triglycerides, insulin resistance defined according to the HOMA-IR and leptin and positively associated with adiponectin\(^{15}\). In addition, in the same study, the subjects in the highest osteocalcin quartile exhibited a lower risk of metabolic syndrome after adjusting for age, gender, smoking, serum creatinine and statin and estrogen use\(^{15}\). Third, an inverse relationship was recently reported between the serum osteocalcin level and parameters of atherosclerosis, including the brachial artery PWV and intima-media thickness, in 179 men following adjustment for age, duration of diabetes, BMI and serum creatinine\(^{15}\). More directly, the serum osteocalcin levels were significantly lower in the angiographically-proven CHD group than in the non-CHD group and decreased in association with the number of diseased vessels involved. Furthermore, the odds ratios for CHD have been reported to decrease as the serum osteocalcin quartile increases after adjusting for other conventional risk factors for CHD in Chinese adults\(^{22}\). Another cell-based study demonstrated that treatment with uncarboxylated osteocalcin prevents free fatty acid-induced apoptosis in insulin-stimulated endothelial cells in a phosphatidylinositol 3-kinase/Akt-dependent manner\(^{23}\).

Despite the association between an increased serum osteocalcin level and a decreased cardiometabolic risk, to date only a few longitudinal follow-up studies have investigated the effects of osteocalcin on the development of CVD. In a longitudinal observational cohort study conducted among 126 hemodialysis patients, a lower median level of serum osteocalcin was significantly associated with the development of CVD after adjusting for age, sex, time of hemodialysis, previous history of CVD, presence of diabetes and the serum calcium X phosphate product and parathyroid hormone levels over a period of five years (HR, 2.925; 95% CI, 1.048-9.066; \(p=0.04\))\(^{24}\). However, another longitudinal study reported somewhat contrary results; all-cause and cardiovascular mortality was highest in the subjects in the highest total osteocalcin quintile among elderly men during a median 5.2-year follow-up\(^{17}\). However, the relationship was U-shaped, with both the lowest and highest osteocalcin quintiles associated with an increased risk following adjustment for age and the waist/hip ratio and further adjustment for other risk factors for CVD and medical comorbidities. Therefore, the authors argued that there may exist an optimal range of serum total osteocalcin that identifies better health outcomes. In addition, they speculated that the increased mortality observed among patients with lower osteocalcin levels may be related to insulin resistance, although other mechanisms, such as increased bone turnover, play a role in men with higher osteocalcin levels\(^{17}\).

In the present study, the subjects were followed for at least six years and, of the 1,290 subjects, 578

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**Table 2. Serum total osteocalcin and the development of cardiovascular disease**

<table>
<thead>
<tr>
<th>Osteocalcin lower tertile (reference)</th>
<th>Stroke</th>
<th>CHD</th>
<th>CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>middle tertile</td>
<td>0.71 (0.36-1.41)</td>
<td>0.79 (0.32-1.96)</td>
<td>0.78 (0.44-1.35)</td>
</tr>
<tr>
<td>upper tertile</td>
<td>0.69 (0.34-1.39)</td>
<td>1.05 (0.44-2.50)</td>
<td>0.83 (0.48-1.44)</td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (1.01-1.10)</td>
<td>NS</td>
<td>1.05 (1.02-1.09)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.99 (1.11-3.58)</td>
<td>NS</td>
<td>2.18 (1.36-3.50)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.33 (1.29-4.24)</td>
<td>2.54 (1.20-5.38)</td>
<td>2.60 (1.62-4.17)</td>
</tr>
</tbody>
</table>

NS, not significant; CHD, coronary heart disease; CVD, cardiovascular disease

The data are adjusted for age, BMI, current smoking, LDL-cholesterol, diabetes, hypertension and serum creatinine.
observed in control patients). Furthermore, another artery with endothelial dysfunction compared to that artery disease as well as those with normal coronary increased in patients with severe multi-vessel coronary osteocalcin has been reported to be significantly 

KDR according to the explanations. First, the effects of osteocalcin on the is unclear. However, there are several possible between our results and the findings of previous stud-

ies is evident (data not shown).

The reason for the conflicting data observed between our results and the findings of previous stud-

ies is unclear. However, there are several possible explanations. First, the effects of osteocalcin on the development of cardiovascular disease may vary according to the γ-carboxylation status; however, we only measured the total form of osteocalcin. Second, elevated serum osteocalcin is a marker of bone turnover and the serum undercarboxylated osteocalcin levels in particular are elevated in elderly women in association with a reduced bone mineral density and elevated hip fracture risk. In addition, osteoporosis and CVD share common risk factors, including aging, smoking, physical inactivity, diabetes, hypertension and inflammation, and patients with osteoporosis have an increased incidence of CVD. Therefore, it is possible that an elevated serum osteocalcin level is a predictor of the development of CVD. As a plausible mechanism, it has been suggested that the actions of osteocalcin are closely linked to atherosclerosis. The percentage of CD34+/KDR+ and CD34+/CD133+/KDR+ endothelial progenitor cells costaining for osteocalcin has been reported to be significantly increased in patients with severe multi-vessel coronary artery disease as well as those with normal coronary arteries with endothelial dysfunction compared to that observed in control patients. Furthermore, another study reported that the undercarboxylated osteocalcin levels were higher in the common carotid artery calcification group than in non-calcification group among 92 patients with essential hypertension. Collectively, there may be a link between osteocalcin and atherosclerosis and/or vascular calcification.

There are several limitations associated with this study, and interpretations should be made with caution. For example, this study was primarily conducted based on data obtained from the medical records of a retrospective cohort, which may have resulted in bias, especially in the assessment of cardiovascular events. However, we made every effort to ascertain the true incidence of cardiovascular events; the rate of CVD events was determined using a standardized questionnaire distributed by trained nurses at the Health Promotion Center and we determined the frequency of CVD on an outpatient basis and during hospitalization based on the detection of signs or symptoms and the findings of biochemical tests and imaging workups. In addition, because our institute is one of the largest tertiary centers in Korea, cases lost to follow-up were relatively few in number. Second, according to the initial observations of Lee et al. only the under-
carboxylated form of osteocalcin has biologic effects. However, we did not differentiate serum osteocalcin with respect to the gamma-carboxylation status; that is, carboxylated and undercarboxylated osteocalcin. Third, we did not fully consider the effects of altered bone turnover, osteoporosis or medications on the serum osteocalcin levels. However, we limited the study subjects to 1,290 men, 40-78 years of age, who are less likely to have osteoporosis or receive calcium, vitamin D or osteoporosis medications compared with women. In agreement with our expectations, the serum total osteocalcin levels were not correlated with aging in our study population (data not shown) and thus the effects of altered bone turnover on the serum osteocalcin level may have been minimal.

Despite these limitations, this study differed from previous studies in that it investigated the causal relationship between the serum osteocalcin level and the development of CVD with regard to the following issues. First, this study was conducted using a relatively large number of study subjects with a long-term follow-up period. Second, we determined the incidence of CVD based on signs or symptoms in addition to validated methods, including biochemical tests and imaging, whereas other studies identified cardiovascular events using only self-reported questionnaire data and medical diagnosis codes. Third, we divided CVD into the categories of stroke and coronary heart disease and determined the association between the serum total osteocalcin level and the occurrence of stroke and coronary heart disease separately.

Conclusion

In the present study, the serum total osteocalcin level was not associated with the development of stroke, CHD or CVD in a relatively large sample size
with a long-term follow-up period. Recently, we reported that the circulating osteocalcin level was not associated with incident type 2 diabetes in the same cohort. Therefore, contrary to the results of animal studies, it appears that the serum total osteocalcin level has minimal cardiovascular and glycemic effects and its clinical relevance may be limited in humans.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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