RESEARCH

Serum sclerostin is negatively associated with insulin sensitivity in obese but not lean women

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Abstract

Objective: The mechanisms underlying the development of peripheral insulin resistance are complex. Several studies have linked sclerostin, an osteocyte-derived inhibitor of the Wnt/β-catenin pathway, to obesity and insulin resistance. The aim of this study was to investigate (1) whether serum sclerostin is associated with insulin sensitivity in lean and/or obese women; and (2) whether hyperinsulinaemia affects serum sclerostin concentrations.

Design: A cross-sectional study.

Methods: Insulin sensitivity was measured in lean (BMI < 25 kg/m²) and obese (BMI > 30 kg/m²) women using a hyperinsulinaemic-euglycaemic clamp. Serum sclerostin was measured at baseline and during the clamp procedure.

Results: We studied 21 lean and 22 obese women with a median age of 40 and 43 years and a median BMI of 22.4 and 33.5 kg/m², respectively. Obese women had higher serum sclerostin than lean women (122 ± 33 vs 93 ± 33 nmol/L, P < 0.01). Higher serum sclerostin was associated with lower insulin sensitivity in obese, but not in lean individuals (difference in M-value between highest and lowest quartile: −7.02 mg/kg/min, P = 0.03 and 1.59 mg/kg/min, P = 0.50, respectively). Hyperinsulinaemia did not affect serum sclerostin in lean nor obese women (P > 0.5).

Conclusion: Serum sclerostin is negatively associated with insulin sensitivity as measured with the hyperinsulinaemic-euglycaemic clamp in obese, but not lean women. This indicates a potential role of the Wnt/β-catenin pathway in regulating insulin sensitivity particularly in obese individuals. Our findings remain hypothesis-generating and should be confirmed by additional studies.

Introduction

The exact mechanisms underlying the development of peripheral insulin resistance, a hallmark of type 2 diabetes mellitus (T2DM), are complex and not yet fully understood. Many metabolic and endocrine factors are involved in the process (1, 2). In recent years, bone has increasingly emerged as an endocrine organ and several hormones derived from bone tissue influence glucose and insulin metabolism (3).

One of the mechanisms through which bone tissue may affect glucose and insulin metabolism is through secretion of sclerostin. Sclerostin is an osteocyte-derived glycoprotein which functions as an inhibitor of the Wnt/β-catenin signalling pathway (4). Without inhibitory control of this pathway, binding of Wnt proteins to their membrane-bound ligands elicit a cellular response which prevents the degradation of the intracellular protein β-catenin (5). The accumulation of β-catenin activates target genes in the cell nucleus. In bone tissue specifically, the Wnt/β-catenin pathway helps to maintain physiological bone remodelling, that is, the balance between the
resorption and formation of bone by osteoclasts and osteoblasts, respectively (6). Activation of the pathway promotes bone formation, whereas inhibition favours resorption.

An interaction between the Wnt/β-catenin signalling pathway and – more specifically – its inhibitor sclerostin and glucose and insulin metabolism is suggested in several recent studies, both in vitro and in vivo. In vitro stimulation of Wnt signalling enhances insulin sensitivity of rodent muscle cells through various mechanisms (7). In humans, correlations between serum sclerostin levels and serum parameters of insulin resistance in normal adults (8), prediabetic adults (9) and obese children and adolescents (10) have been described. These studies are, however, inconsistent in the presence and the direction of the association (11).

Adipose tissue appears to be involved in the association between Wnt signalling and insulin sensitivity. Serum sclerostin is positively correlated with fat mass (12, 13) and has been found to be higher in obese individuals in some (14), although not all (8), studies. Animal studies suggest that sclerostin is a causal factor in the development of obesity. In mice, overexpression of the Sost gene resulted in increased fat mass, whereas knockout of the Sost gene reduced adipose tissue mass and increased insulin sensitivity (15). In humans, expression of Wnt signalling genes in adipose tissue and insulin sensitivity are linked (2). We therefore hypothesised that the possible association between serum sclerostin and insulin sensitivity may be different for obese and non-obese individuals.

It may also be hypothesised that high circulating insulin concentrations affect Wnt signalling through an effect on the secretion of Wnt signalling inhibitors such as sclerostin. Hyperinsulinaemia significantly altered the expression of Wnt activators in human adipose and muscle cells (2). In humans, serum sclerostin is significantly higher in individuals with type 2 diabetes mellitus, who are also characterised by higher insulin concentrations, than in healthy individuals (16). The effect of induced acute hyperinsulinemia on the secretion of sclerostin into the circulation has, however, not been described previously.

Therefore, the aim of this study was to investigate the association between serum sclerostin and insulin sensitivity, as measured with a hyperinsulinaemic–euglycaemic clamp, in lean and obese women. The second aim is to investigate whether induced hyperinsulinaemia affects serum sclerostin levels.

### Materials and methods

#### Patients

This study was carried out as a post hoc analysis of a cross-sectional study (17). Premenopausal female participants were recruited. One reason for exclusively including women was to take into account the difference in body fat percentage and body fat distribution between men and women with similar body mass indices. Adipose tissue is proposed to play a distorting role in the association between bone and glucose metabolism. Altered Wnt signalling in specific types of adipose tissue may directly influence glucose metabolism in mice (18). Another reason is the smaller frequency in women of other factors than obesity known to be associated with impaired insulin sensitivity, such as smoking (19), hypertension and a history of cardiovascular diseases (20).

All participants were volunteers recruited through community-based strategies, that is, via flyers, posters and local newspapers. The size of the sample population was 43 individuals, with 21 lean volunteers and 22 obese volunteers. Inclusion criteria were age between 18 and 55 years old, BMI greater than 30 kg/m² and a waist circumference greater than 80 cm in the obese subgroup, BMI less than 25 kg/m² and a waist circumference less than 80 cm in the lean subgroup (17). Exclusion criteria included the presence of diabetes or impaired glucose tolerance (according to the ADA criteria (21)), medical history of hypertension or other cardiovascular disease (stroke, coronary artery disease, peripheral vascular disease, heart failure), use of medication for hypertension or diabetes, use of medication known to disturb endothelial function or glucose metabolism, family history of first-degree relative with diabetes, pregnancy and smoking. The original study protocol was approved by the medical ethics committee of the VU University Medical Center and conducted in accordance with the Declaration of Helsinki. Written consent has been obtained from each subject after full explanation of the purpose and nature of all procedures.

#### Measurements

##### Baseline measurements

During a screening visit to the clinic prior to the hyperinsulinaemic–euglycaemic clamp (HEC), anthropometric measurements and indices such as height, body weight, BMI, waist circumference and waist-to-hip ratio were obtained. Body fat percentage was measured using bioelectrical impedance analysis.
Serum sclerostin and insulin sensitivity were then included in a two-subpopulations were reported. Based on the distribution curve. The assumption of normal distribution of the outcome variable was assessed graphically by studying whether the corresponding histogram followed the normal distribution curve.

Extreme outliers were excluded, which were defined as observations that deviate below the 25th percentile or beyond the 75th percentile with a value equal to at least three times the interquartile range of the corresponding variable (23). Serum sclerostin values during hyperinsulinaemia demonstrated one extreme outlier with a value of 744 pmol/L. The presence of this extreme value could not be explained on the basis of characteristics of the specific individual. This individual was excluded from the analysis of the effect of acute hyperinsulinaemia on serum sclerostin levels.

BMI was used to stratify the study population (lean: BMI ≤ 25 and obese: BMI ≥ 30 kg/m²). Potential interaction was investigated statistically by testing interaction terms. The $P$-value of its corresponding regression coefficient was used to determine the statistical significance of the possible interaction.

Differences between lean and obese women at baseline were evaluated by performing either a student’s $t$-test or a Mann–Whitney U-test in case of normally distributed and non-normally distributed variables, respectively.

To analyse the association between serum sclerostin levels and the corrected $M$-value, linear regression analysis was performed. Linearity was investigated by categorising the serum sclerostin variable into quartiles and creating three corresponding dummy variables. Regression coefficients, corresponding $P$-values and 95% CI were reported for both the crude and adjusted models. In case of non-linearity, quartiles of the independent variable were analysed instead.

Potential confounding was investigated by performing univariate analysis. Confounding variables that caused a change of 10% or more in the regression coefficient in the relationship between serum sclerostin and the corrected $M$-value were then included in a multivariate analysis. Sclerostin appears to be associated with BMI, body fat and age (24). Since these variables are widely known to associated with insulin resistance, age and various measures of body weight and fat tissue were considered as biologically plausible confounding variables in this study.

Finally, the effect of hyperinsulinaemia on serum sclerostin was analysed using a paired student’s $t$-test. The assumption of normal distribution of the outcome variable was assessed graphically by studying whether the corresponding histogram followed the normal distribution curve.

All $P$-values smaller than 0.05 were considered statistically significant. The data were analysed using SPSS version 26.0 (SPSS, Inc.).

Statistical analysis

Demographic and clinical characteristics for the total population and separately for the lean and obese subpopulations were reported. Based on the distribution of the variables, these characteristics were described as means with S.D. or medians with interquartile ranges.

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Sclerostin

Serum sclerostin levels were measured in blood samples drawn after an overnight fast both at baseline and during hyperinsulinaemia as established during the last hour of the HEC procedure. Sclerostin was measured by the endocrine laboratory of Amsterdam UMC using an electrochemiluminescence assay (MSD 96-well MULTI-ARRAY Human Sclerostin Assay; Meso Scale Discovery), with an intra-assay CV ≤ 6.0% and an interassay CV of 11%. The lower limit of quantitation was 0.040 ng/mL.

Hyperinsulinemic-euglycemic clamp

Two peripheral venous catheters were placed in each arm (antebrachial veins) of the participants. One catheter was used to infuse insulin (Actrapid, Novo Nordisk, Bagsvaerd, Denmark) at a primed (240 mU/m²), continuous rate of 40 mU/m²/min for 2 h in order to establish hyperinsulinaemia. A 20% glucose infusion was administered at a variable rate through the same catheter to maintain euglycaemia at whole-blood glucose levels of 5 mmol/L (YSI 2300 STAT Plus Analyzer, Yellow Springs, OH, USA). Every 5 min, venous blood samples were drawn from the other catheter to ensure euglycaemia was maintained and to adjust glucose infusion accordingly.

Insulin sensitivity was expressed as the $M$-value (mg/kg lean body weight/min) and was calculated as the average rate of glucose infusion needed to maintain euglycaemia at whole-blood glucose levels of 5 mmol/L (YSI 2300 STAT Plus Analyzer, Yellow Springs, OH, USA). Every 5 min, venous blood samples were drawn from the other catheter to ensure euglycaemia was maintained and to adjust glucose infusion accordingly.

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Results

Baseline characteristics

The baseline characteristics are depicted in Table 1.

## Associations between serum sclerostin and insulin sensitivity

There was significant interaction of BMI category (lean: BMI ≤ 25 kg/m² and obese: BMI ≥ 30 kg/m²) in the association of serum sclerostin and the corrected M-value (P=0.009). We will present all the results stratified for BMI category.

In the obese but not the lean individuals, serum sclerostin fulfilled criteria for linearity. Therefore, we first performed the analyses for sclerostin quartiles in the lean group and the obese group. This demonstrated a negative association between serum sclerostin and insulin sensitivity in the obese group (P=0.026). The mean M-value of the highest quartile of serum sclerostin concentrations was 7.0 mg/kg/min lower than the M-value of the lowest quartile (Fig. 1A). There was no association in the lean group (P=0.58, Fig. 1B). In the obese group, an additional linear regression analysis with serum sclerostin on a continuous scale was performed. This revealed a significant negative linear association between serum sclerostin and insulin sensitivity in the obese individuals. For each difference of 10 pmol/L in serum sclerostin, the corrected M-value changed 0.9 mg/kg lean body weight/min (Fig. 2 and Table 2). The association weakened, yet remained statistically significant after adjustment for age, BMI, body fat percentage, fat mass, waist circumference and waist-to-hip ratio (Table 2).

## Discussion

The main finding of this study is that in obese but not lean individuals, higher serum sclerostin concentrations are associated with lower peripheral insulin sensitivity as measured with the state-of-the-art hyperinsulinaemic-euglycaemic clamp. Acute hyperinsulinaemia did not have an effect on serum sclerostin concentrations.

In our study, serum sclerostin level at baseline was significantly higher in the obese subgroup as compared to the lean subgroup. This finding is in line with most (11, 12, 13, 24), although not all (14), previous studies that investigated the relationship between serum sclerostin and obesity and body fat measures. Several hypotheses can be postulated as an explanation for this finding. Lower physical activity may offer an explanation, since an independent positive association between serum sclerostin and physical activity has been described (24). This correlation may be due to the inhibitory effect of mechanical force on sclerostin expression in bone tissue (25). A decrease in physical activity could thus cause an increase in local sclerostin production and an increase in systemic sclerostin levels. Another explanation would be that the chronic inflammation associated with obesity increases sclerostin secretion by bone tissue. Indeed, in mice,

### Table 1  Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Obese individuals</th>
<th>Lean individuals</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>43 (27-50)</td>
<td>40 (25-47)</td>
<td>0.38</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>100.9 (± 16.5)</td>
<td>65 (± 6.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>33.5 (31.9-34.5)</td>
<td>22.4 (20.2-23.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>43.8 (± 5.1)</td>
<td>25.2 (± 5.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>106.0 (100.8-115.2)</td>
<td>76.0 (72.5-84.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body fat mass (kg)</td>
<td>43.6 (35.8-51.8)</td>
<td>14.5 (12.5-21.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.89 (± 0.06)</td>
<td>0.82 (± 0.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>4.6 (± 0.8)</td>
<td>4.3 (± 0.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>66.8 (45.1-95.1)</td>
<td>29.8 (26.6-44.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Glucose concentration during the clamp (mmol/L)</td>
<td>4.9 (± 0.3)</td>
<td>5.0 (± 0.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Insulin concentration during the clamp (pmol/L)</td>
<td>647±97</td>
<td>551±103</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum sclerostin level (pmol/L)</td>
<td>122±33</td>
<td>93±33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>M-value (mg/kg/min)</td>
<td>13.2±5.1</td>
<td>16.3±4.1</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Mean values (± s.d.) or median values (interquartile range) are presented based on the distribution of the variables.
the pro-inflammatory cytokine tumour necrosis factor (TNF-α) has been shown to increase sclerostin gene expression (26, 27).

In the obese group, the negative association between serum sclerostin and insulin sensitivity was independent of age and various weight and body fat indices. The difference in this relationship between obese and lean individuals is intriguing. The presence of a negative association between serum sclerostin and peripheral insulin sensitivity in obese individuals is in accordance with the study by Daniele et al. (9). However, they did not specifically include a lean subgroup. This is of particular interest because the effect of sclerostin on Wnt signalling in adipose tissue may play an important role in the development of peripheral insulin resistance. Overexpression of sclerostin in mice has been demonstrated to not only induce lower insulin sensitivity, but also hypertrophy of adipocytes and an overall increase in body fat mass (15). In south Asian men, both increased serum sclerostin levels and decreased expression of insulin signalling genes in white adipose tissue were found (28). Also, serum sclerostin has been shown to be negatively related to estimates of insulin sensitivity of different cell types, such as muscle and liver cells, but also to insulin sensitivity of adipocytes (9). These studies show a potential interfering effect of adipose tissue on a potential effect of sclerostin on insulin sensitivity. Also, stimulation of the Wnt pathway directly influences cellular insulin signalling. In rodents, stimulation of Wnt pathway in target cells of insulin has shown to increase gene expression of multiple mediators of the insulin signalling pathway (29, 30). Accordingly, Wnt signalling stimulates glucose uptake in these cells (7).

Contrary to our findings, a recent study in children (10) showed a positive association between serum sclerostin

Figure 1
Corrected mean M-Value presented for serum sclerostin quartiles in obese (panel A) and lean women (panel B).

Figure 2
Univariate regression analysis of serum sclerostin with corrected M-value in obese women.
Table 2  Linear regression analysis of the relation between serum sclerostin and the corrected M-value in obese individuals.

<table>
<thead>
<tr>
<th></th>
<th>Regression coefficient</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td>−0.090</td>
<td>−0.15; −0.030</td>
<td>0.005</td>
</tr>
<tr>
<td>Adjusted for BMI, fat% and WC</td>
<td>−0.078</td>
<td>−0.14; −0.017</td>
<td>0.016</td>
</tr>
<tr>
<td>Adjusted for BMI</td>
<td>−0.072</td>
<td>−0.13; −0.011</td>
<td>0.024</td>
</tr>
<tr>
<td>Adjusted for fat %</td>
<td>−0.079</td>
<td>−0.13; −0.025</td>
<td>0.006</td>
</tr>
<tr>
<td>Adjusted for WC</td>
<td>−0.079</td>
<td>−0.14; −0.018</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Fat%, body fat percentage; WC, waist circumference.

and insulin sensitivity. Apart from the obvious difference in age of the study population, this contradictory finding might be related to the different measure used for insulin sensitivity, known as the homeostasis model assessment (HOMA). HOMA is mostly a measure of hepatic insulin sensitivity, whereas the hyperinsulinaemic–euglycaemic clamp primarily measures muscle insulin sensitivity. However, another recent study that used HOMA in adults did find a negative association between serum sclerostin and insulin sensitivity (8).

The effect of hyperinsulinaemia on sclerostin levels was another focus of this study, since hyperinsulinaemia has been shown to alter the expression of Wnt signalling genes in human adipose and muscle tissue (2) and activators of the Wnt pathway stimulate insulin secretion in vitro (31). We therefore hypothesised that induction of hyperinsulinaemia may have a negative feedback on Wnt signalling by promoting the expression of its inhibitors, such as sclerostin. However, serum sclerostin did not increase in the obese or lean group during the clamp. Overall, induced acute hyperinsulinaemia has no effect on serum sclerostin concentrations. Whether prolonged hyperinsulinaemia increases serum sclerostin concentrations remains to be studied.

Strengths and limitations

The main strength of this study was the use of the hyperinsulinaemic–euglycaemic clamp technique, which is considered to be the gold standard for measuring peripheral insulin sensitivity. The hyperinsulinaemia induced during the clamp procedure also enabled us to obtain serum sclerostin concentrations under hyperinsulinaemic conditions. Due to the relatively good health of the participants, the influence of disease-related confounding factors (such as side-effects of medication) on the validity of the results was negligible.

This study has several important limitations. First, only female participants were included. Findings cannot be extrapolated to men particularly because of gender specificity of body fat amount and distribution. Secondly, the obese individuals in this study had a relatively high peripheral insulin sensitivity and thus findings may not be extrapolated to other obese populations. Thirdly, the small size of the study population induces a large amount of variation due to chance and thus the risk that significant findings are missed. In our study, however, the association between serum sclerostin and peripheral insulin sensitivity in lean individuals was absent and the effect size of insulin infusion on serum sclerostin was close to zero. An increase in sample size is thus highly unlikely to have resulted in different conclusions. Another weakness of this study was its cross-sectional design. Lastly, only the role of sclerostin was studied, because we were not able to determine concentrations of other inhibitors of the Wnt/β-catenin, such as Dickkopf-1. We were also not able to measure serum markers of bone turnover, such as procollagen type I N propeptide (P1NP) or C-terminal telopeptide of type 1 collagen (CTX). Due to these limitations and the fairly strict inclusion criteria, the generalisability of these results is compromised and caution should be taken when translating the results of this study to other populations.

Future research and clinical relevance

This study should be regarded as a hypothesis-generating study, which proposes bone tissue to be associated with reduced insulin sensitivity through secretion of the bone hormone sclerostin in humans, with a possible mediating role for adipose tissue. This finding may suggest a possible new therapeutic perspective on treating insulin resistance in obese individuals, by interfering with the Wnt signalling pathway. As of recently, the use of anti-sclerostin antibodies in the treatment of osteoporosis in postmenopausal women has been officially approved by the United States FDA, and the European Medical Agency.

However, more research is needed to prove a causal relationship between higher serum sclerostin and reduced peripheral insulin sensitivity. Further research should therefore focus on exploring this relationship in larger study populations also with other measurements of Wnt signalling activity and a wide variety of body composition. Even more important are the studies after the effect of treatment with sclerostin antibodies in humans on glucose and insulin metabolism.

No in vivo evidence was found to support the other hypothesis of this study, that is, the positive feedback of...
hyperlinsulinaemia on sclerostin secretion in humans. To more fundamentally investigate this hypothesis, it would be interesting to study the effect of exposure to insulin on the expression of sclerostin genes in human osteocytes.

Conclusion

The results of this study show a negative correlation between serum sclerostin and peripheral insulin sensitivity in obese women but not in lean women and no effect of hyperinsulinaemia on serum sclerostin levels. These findings support the growing evidence of the role of bone tissue in the development of altered insulin sensitivity and the complex interaction with adipose tissue therein.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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