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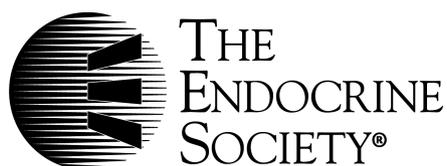
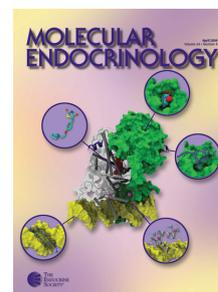
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## Plasma Procalcitonin Is Associated with Obesity, Insulin Resistance, and the Metabolic Syndrome

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**Context:** Procalcitonin, a well-known biomarker of sepsis and bacterial infections, is produced by adipose tissue and has potential as a marker for chronic low-grade inflammation.

**Objectives:** The objective of this study was to investigate whether plasma procalcitonin levels in the normal range are associated with obesity, insulin resistance, and metabolic syndrome (MS) in the general population.

**Methods:** Plasma procalcitonin (0.006–0.1 ng/ml) was measured in 3197 men and 3638 women (aged 28–75 yr) of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study using an ultra-sensitive immunoluminometric assay. MS was defined according to Adult Treatment Panel III criteria.

**Results:** Median (interquartile range) plasma procalcitonin was 0.018 (0.015–0.022) ng/ml in men and 0.014 (0.012–0.017) ng/ml in women ( $P < 0.001$ ). Plasma procalcitonin was positively associated with body mass index and waist circumference. In both sexes, cross-sectional associations of plasma procalcitonin with insulin resistance and components of the MS remained significant after adjustment for age, body mass index, waist circumference, and other covariates. The age-adjusted odds ratio (OR) for MS was 3.2 [95% confidence interval (CI) = 2.5–4.2] in men and 4.1 (95% CI = 3.0–5.5) in women, when comparing the highest with the lowest quartile of plasma procalcitonin. The multivariate-adjusted OR for MS was 1.9 (95% CI = 1.4–2.6) in men and 2.3 (95% CI = 1.6–3.3) in women. The multivariate-adjusted OR for insulin resistance was 3.3 (95% CI = 2.4–4.3) in men and 2.5 (95% CI = 1.9–3.4) in women.

**Conclusions:** Elevated plasma procalcitonin levels in the normal range are associated with measures of obesity, insulin resistance, and MS in the general population. (*J Clin Endocrinol Metab* 95:E26–E31, 2010)

There are strong links between obesity, insulin resistance, and components of the metabolic syndrome. Chronic low-grade inflammation has been implicated in the pathophysiology of these three intertwined entities (1, 2).

Procalcitonin, a 116-amino-acid polypeptide, is the precursor of calcitonin hormone produced by neuroendocrine C-cells of the thyroid and K-cells of the lung, encoded

from the calcitonin I (*CALCI*) gene on chromosome 11 (3–5). Procalcitonin is best known as a biomarker of infection and severe systemic inflammation (6, 7). Recent studies show that adipose tissue is capable of expressing and secreting procalcitonin (8–10). This makes procalcitonin a potential biomarker for obesity-related low-grade inflammation.

There are no data addressing the significance of variation in plasma procalcitonin levels in the general population. So far, procalcitonin level in the normal population has been studied only in a small sample, and only an association of procalcitonin with sex was acknowledged (11). We hypothesize that plasma procalcitonin may be associated with measures of obesity, insulin resistance, and metabolic risk factors.

## Subjects and Methods

This cross-sectional analysis was conducted on the participants from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study in the general population (age ranged from 28–75 yr) of the city of Groningen, The Netherlands. Details of the study design, recruitment, and procedures have been published elsewhere (12). Plasma procalcitonin was measured in 7690 participants from the samples of the baseline screening. At first, we excluded 25 participants with procalcitonin level higher than 0.1 ng/ml. Further exclusion was for 385 individuals who had no documented fasting blood samples or missing data for other variables, leaving 3137 men and 3638 women (total,  $n = 6835$ ) for the present analysis. The PREVEND study was approved by the local medical ethics committee, University Medical Center Groningen, and conformed to the principles outlined in the Declaration of Helsinki. All participants gave written informed consent.

Blood pressure was measured in supine position with an automatic device (Dinamap XL model 9300; Johnson-Johnson Medical, Tampa, FL). Smoking and alcohol use were based on self-reports. Metabolic syndrome was defined according to the National Cholesterol Education Program's Adult Treatment Panel III report criteria (13), as participants having at least three of the following: 1) waist circumference more than 35 in. (>88 cm) in women or more than 40 in. (>102 cm) in men, 2) blood pressure at least 130/85 mm Hg or treatment for hypertension, 3) fasting triglycerides at least 150 mg/dl ( $\geq 1.7$  mmol/liter), 4) high-density lipoprotein (HDL) cholesterol no higher than 40 mg/dl ( $\leq 1.0$  mmol/liter) in men or no higher than 50 mg/dl ( $\leq 1.3$  mmol/liter) in women, and 5) fasting blood glucose at least 110 mg/dl ( $\geq 6.1$  mmol/liter) or treatment for type 2 diabetes. Insulin resistance was assessed based on the homeostasis model assessment for insulin resistance (HOMA-IR) that is calculated using the following formula: [glucose (millimoles per liter)  $\times$  insulin (milliunits per milliliter)]/22.5 (14). We defined insulin resistance as a HOMA-IR score in upper sex-specific quartiles.

In baseline samples, serum and urinary creatinine, total cholesterol, and plasma glucose were measured by dry chemistry (Eastman Kodak, Rochester, NY). HDL cholesterol was measured with a homogeneous method (direct HDL, Aeroset System; Abbott Laboratories, Abbott Park, IL). Triglycerides were measured enzymatically. High-sensitivity C-reactive protein (hs-CRP) was determined by nephelometry (BN II; Dade Behring, Marburg, Germany). Urinary albumin excretion was measured as the mean of two 24-h urine collections by nephelometry with a threshold of 2.3 mg/liter (Dade Behring Diagnostic, Marburg, Germany). Insulin was measured with an AxSym autoanalyzer (Abbott Diagnostics, Amstelveen, The Netherlands). Procalcitonin was measured by a novel commercially available immu-

noluminometric assay (BRAHMS PCT sensitive LIA; Hennigsdorf, Germany). Assays were performed in EDTA-plasma aliquots that had been stored frozen at  $-80$  C, without previous thawing and refreezing. The intraassay CV at 0.1 ng/ml was 6%, and at 0.03 ng/ml it was 8%. The functional assay sensitivity, defined as the lowest concentration to be determined with an interassay CV of 20% was 0.007 ng/ml. The lowest detection limit was 0.006 ng/ml. The assay technique has been described previously (11). All technicians were blinded to the participants' characteristics.

Continuous variables were compared by using one-way ANOVA or a Kruskal-Wallis test, and a  $\chi^2$  test was used for the categorical variables to test for differences across quartiles of procalcitonin. We evaluated the association of log<sub>2</sub> procalcitonin level with the components (continuous) of the metabolic syndrome using univariate and multivariate-adjusted linear regression models in sex-stratified analyses. Regression coefficients with 95% confidence intervals (CI) were determined. We performed univariate and multivariate-adjusted logistic regression models to test the association between plasma procalcitonin level and presence of the metabolic syndrome and insulin resistance. The models were adjusted for age, measures of obesity, hs-CRP, tobacco smoking, alcohol use, history of cardiovascular disease, and hormone replacement therapy (for women). A  $P$  value  $\leq 0.05$  from two-sided tests was considered statistically significant. The statistical analyses were performed using SPSS version 16.0 statistical software (SPSS Inc., Chicago, IL).

## Results

Of 3197 men and 3638 women, 631 (19.7%) and 616 (16.9%) had metabolic syndrome, respectively. Median [interquartile range (IQR)] procalcitonin levels were 0.018 (0.015–0.022) ng/ml in men and 0.014 (0.012–0.017) ng/ml in women ( $P < 0.001$ ). Anthropometric and clinical characteristics of the study population are summarized in Table 1 for men and women separately. Participants with high procalcitonin levels were older, more obese, and more likely to fulfill criteria for the metabolic syndrome. They also had lower insulin sensitivity, lower creatinine clearance, higher hs-CRP, and higher urinary albumin excretion. Men with high procalcitonin were more likely to be smoker or ex-smoker, whereas women with high procalcitonin were less likely to use alcohol.

In men, across quartiles of body mass index (BMI) median (IQR) procalcitonin levels gradually increased from 0.016 (0.014–0.020) ng/ml in the first to 0.020 (0.016–0.024) ng/ml in the fourth quartile ( $P < 0.001$ ) (Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>). In women, this was from 0.013 (0.011–0.015) ng/ml in the first to 0.016 (0.014–0.019) ng/ml in the fourth quartile ( $P < 0.001$ ). In men, across quartiles of waist circumference, median (IQR) procalcitonin increased from 0.016 (0.014–0.020) ng/ml in the first to 0.019 (0.016–0.022) ng/ml in the fourth quartile ( $P < 0.001$ ). In women, this

**TABLE 1.** Anthropometric and clinical characteristics of participants according to sex-specific quartiles of plasma procalcitonin (n = 6835)

Characteristic	Procalcitonin quartiles (ng/ml)				P value
	1	2	3	4	
Male	0.008–0.015	0.016–0.018	0.019–0.022	0.023–0.098	
Female	0.006–0.012	0.013–0.014	0.015–0.017	0.018–0.098	
No. of participants					
Male	887	806	769	735	
Female	1043	906	868	821	
Age (yr)					
Male	46.0 ± 12.0	48.9 ± 12.5	51.1 ± 12.9	52.8 ± 12.9	<0.001
Female	42.5 ± 9.7	45.6 ± 10.8	49.6 ± 12.3	55.2 ± 12.3	<0.001
History of cardiovascular disease [n (%)]					
Male	60 (6.8)	58 (7.2)	75 (9.8)	81 (11.0)	0.005
Female	16 (1.5)	20 (2.2)	35 (4.0)	38 (4.6)	<0.001
BMI (kg/m <sup>2</sup> )					
Male	25.0 ± 3.3	26.0 ± 3.3	26.8 ± 3.6	27.3 ± 3.8	<0.001
Female	24.4 ± 3.8	25.2 ± 4.2	26.3 ± 4.8	27.8 ± 5.2	<0.001
Weight [n (%)]					
Male					
Normal	465 (52.4)	314 (39.0)	247 (32.1)	198 (26.9)	<0.001
Overweight	365 (41.1)	402 (49.9)	390 (50.7)	374 (50.9)	
Obese	57 (6.4)	90 (11.2)	132 (17.2)	163 (22.2)	
Female					
Normal	668 (64.0)	498 (55.0)	391 (45.0)	259 (31.5)	<0.001
Overweight	293 (28.1)	294 (32.5)	316 (36.4)	319 (38.9)	
Obese	82 (7.9)	114 (12.6)	161 (18.5)	243 (29.6)	
Waist circumference (cm)					
Male	89.6 ± 10.2	93.0 ± 10.1	95.6 ± 10.7	97.1 ± 11.5	<0.001
Female	80.0 ± 10.8	84.8 ± 11.9	90.2 ± 12.2	94.6 ± 12.3	<0.001
Systolic blood pressure (mm Hg)					
Male	124.9 ± 16.1	126.9 ± 16.6	129.9 ± 18.1	132.5 ± 18.6	<0.001
Female	113.6 ± 15.9	116.9 ± 17.8	121.0 ± 20.1	127.9 ± 21.4	<0.001
Diastolic blood pressure (mm Hg)					
Male	72.3 ± 9.1	73.5 ± 8.9	75.3 ± 9.3	76.8 ± 9.9	<0.001
Female	66.7 ± 8.4	68.1 ± 8.7	69.4 ± 9.1	71.4 ± 8.5	<0.001
Total cholesterol (mmol/liter)					
Male	5.4 ± 1.0	5.6 ± 1.1	5.8 ± 1.0	5.8 ± 1.1	<0.001
Female	5.3 ± 1.0	5.5 ± 1.1	5.7 ± 1.2	6.0 ± 1.2	<0.001
HDL cholesterol (mmol/liter)					
Male	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	<0.001
Female	1.6 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	<0.001
Triglyceride (mmol/liter)					
Male	1.3 ± 0.8	1.5 ± 0.9	1.7 ± 1.1	1.8 ± 1.5	<0.001
Female	1.0 ± 0.4	1.1 ± 0.7	1.3 ± 0.7	1.6 ± 1.0	<0.001
Glucose (mmol/liter)					
Male	4.8 ± 0.8	4.9 ± 1.0	5.0 ± 1.0	5.3 ± 1.6	<0.001
Female	4.5 ± 0.7	4.6 ± 0.7	4.7 ± 0.9	5.2 ± 1.6	<0.001
Insulin (mU/liter)					
Male	6.8 (4.9–9.7)	7.9 (5.6–11.9)	9.2 (6.2–13.2)	10.5 (6.9–15.6)	<0.001
Female	6.5 (4.8–8.7)	7.1 (5.2–10.1)	7.8 (5.5–11.2)	9.9 (6.5–15.4)	<0.001
HOMA-IR					
Male	1.4 (1.0–2.1)	1.7 (1.2–2.6)	2.0 (1.3–3.1)	2.4 (1.5–3.7)	<0.001
Female	1.3 (0.9–1.8)	1.4 (1.0–2.1)	1.6 (1.1–2.5)	2.2 (1.3–3.6)	<0.001
Tobacco smoking [n (%)]					
Male					
Never	266 (30.0)	216 (26.8)	175 (22.8)	167 (22.7)	
Quit	318 (35.9)	301 (37.3)	310 (40.3)	348 (47.3)	<0.001
Current smoker	303 (34.2)	289 (35.9)	284 (36.9)	220 (29.9)	
Female					
Never	356 (34.1)	294 (32.5)	313 (36.1)	279 (34.0)	
Quit	344 (33.0)	285 (31.5)	285 (32.8)	271 (33.0)	0.861
Current smoker	343 (32.9)	327 (36.1)	270 (31.1)	271 (33.0)	

(Continued)

TABLE 1. Continued

Characteristic	Procalcitonin quartiles (ng/ml)				P value
	1	2	3	4	
Alcohol use [n (%)]					
Male					
Never	125 (14.1)	143 (17.7)	143 (18.6)	136 (18.5)	
1–4 drinks/month	90 (10.1)	94 (11.7)	88 (11.4)	97 (13.2)	
2–7 drinks/wk	370 (41.7)	307 (38.1)	263 (34.2)	253 (34.4)	0.118
1–3 drinks/d	223 (25.1)	201 (24.9)	211 (27.4)	181 (24.6)	
≥4 drinks/d	79 (8.9)	61 (7.6)	64 (8.3)	68 (9.3)	
Female					
Never	280 (26.8)	265 (29.2)	308 (35.5)	313 (38.1)	
1–4 drinks/month	200 (19.2)	183 (20.2)	155 (17.9)	167 (20.3)	
2–7 drinks/wk	375 (36.0)	305 (33.7)	245 (28.2)	216 (26.3)	<0.001
1–3 drinks/d	173 (16.6)	130 (14.3)	147 (16.9)	105 (12.8)	
≥4 drinks/d	15 (1.4)	23 (2.5)	13 (1.5)	20 (2.4)	
Creatinine clearance (ml/min)					
Male	117.4 ± 26.5	114.3 ± 25.8	113.8 ± 28.1	111.5 ± 27.4	<0.001
Female	98.1 ± 21.4	99.1 ± 21.3	96.1 ± 25.1	91.4 ± 24.5	<0.001
Urine albumin excretion (mg/24 h)					
Male	9.1 (6.6–16.7)	9.9 (6.8–17.3)	10.7 (7.1–20.9)	13.0 (7.5–31.9)	<0.001
Female	7.8 (5.7–12.1)	8.1 (5.7–13.2)	8.5 (6.0–14.0)	10.0 (6.4–18.6)	<0.001
hs-CRP (mg/liter) (n = 6617)					
Male	0.7 (0.3–1.7)	1.0 (0.5–2.4)	1.3 (0.7–2.7)	2.0 (1.0–4.4)	<0.001
Female	0.9 (0.4–2.2)	1.1 (0.5–2.5)	1.4 (0.6–3.3)	2.3 (1.0–5.1)	<0.001

P values are based on  $\chi^2$  test for categorical data, Spearman rank correlation for ordinal data, and ANOVA or Kruskal-Wallis for continuous data, depending on the normality of the data, which are presented as mean  $\pm$  SD or median (IQR).

was from 0.013 (0.011–0.015) ng/ml in the first to 0.016 (0.014–0.020) ng/ml in the fourth quartile ( $P < 0.001$ ). Associations of components of the metabolic syndrome (waist circumference, systolic blood pressure, diastolic blood pressure, triglycerides, HDL cholesterol, glucose) and insulin resistance (fasting insulin and HOMA-IR) with procalcitonin were independent of age in linear regression analyses. Further adjustment for BMI attenuated these associations, but they remained statistically significant. Subsequent further adjustments for hs-CRP, smoking status, alcohol intake, history of cardiovascular disease, and hormone replacement therapy (for women) did not materially change these associations except for blood pressure, which lost significance in women (Supplemental Table 1).

Logistic regression analyses (Table 2) show that risk for the metabolic syndrome and insulin resistance increased across procalcitonin quartiles. In multivariate-adjusted models, the odds ratios for metabolic syndrome and insulin resistance in the highest quartile compared with the lowest were 1.9 (95% CI = 1.4–2.6) and 3.3 (95% CI = 2.4–4.3) in men and 2.3 (95% CI = 1.6–3.3) and 2.5 (95% CI = 1.9–3.4) in women, respectively.

## Discussion

To the best of our knowledge, this study explored for the first time the association of plasma procalcitonin with

measures of obesity and metabolic and cardiovascular risk factors in a large sample of the general population. An important finding is that variation in plasma procalcitonin within the normal range is associated with insulin resistance and the metabolic syndrome in apparently healthy men and women. The association of plasma procalcitonin with insulin resistance and metabolic syndrome was independent of age, measures of obesity, hs-CRP, history of cardiovascular disease, and health behaviors.

The current results are in line with experimental and observational data that suggest that plasma procalcitonin can be an inflammatory biomarker even in the absence of signs of systemic infection or sepsis (8–10, 15, 16). Human adipose tissue depots have been identified as major nonneuroendocrine calcitonin mRNA expression sites (8, 9), and *in vitro* secretion of procalcitonin by adipocytes was stimulated by activated macrophages (9). Because obesity is associated with increased macrophage infiltration into adipose tissue, a similar scenario may play a role *in vivo*. In a recent publication, an association of plasma procalcitonin with central body fat distribution was found in women with polycystic ovary syndrome (15). In line with this, we found a significant independent association of waist circumference with procalcitonin in both sexes.

The associations of plasma procalcitonin levels with insulin resistance and components of the metabolic syndrome were attenuated after adjustment for BMI and therefore partly dependent on BMI. This supports our

**TABLE 2.** Odds ratios (OR) for metabolic syndrome and insulin resistance according to sex-specific quartiles of plasma procalcitonin

	Procalcitonin quartiles (ng/ml)				P value for trend
	1	2	3	4	
<b>Men</b>					
No. of persons	887	806	769	735	
<b>Metabolic syndrome</b>					
No. of cases	94	137	169	231	
Unadjusted OR (95% CI)	1.00	1.7 (1.3–2.3)	2.4 (1.8–3.1)	3.9 (3.0–5.0)	<0.001
Age-adjusted OR (95% CI)	1.00	1.6 (1.2–2.1)	2.1 (1.6–2.7)	3.2 (2.5–4.2)	<0.001
Multivariate OR (95% CI) <sup>b</sup>	1.00	1.2 (0.9–1.7)	1.3 (0.9–1.8)	1.9 (1.4–2.6)	<0.001
<b>Insulin resistance<sup>a</sup></b>					
No. of cases	103	168	223	303	
Unadjusted OR (95% CI)	1.00	2.0 (1.5–2.6)	3.1 (2.4–4.0)	5.3 (4.1–6.9)	<0.001
Age-adjusted OR (95% CI)	1.00	1.9 (1.4–2.5)	2.8 (2.2–3.6)	4.7 (3.6–6.0)	<0.001
Multivariate OR (95% CI) <sup>b</sup>	1.00	1.6 (1.2–2.1)	2.1 (1.6–2.8)	3.3 (2.4–4.3)	<0.001
<b>Women</b>					
No. of person	1043	906	868	821	
<b>Metabolic syndrome</b>					
No. of cases	66	102	160	288	
Unadjusted OR (95% CI)	1.00	1.9 (1.4–2.6)	3.3 (2.5–4.5)	8.0 (6.0–10.7)	<0.001
Age-adjusted OR (95% CI)	1.00	1.5 (1.1–2.2)	2.2 (1.6–3.0)	4.1 (3.0–5.5)	<0.001
Multivariate OR (95% CI) <sup>b</sup>	1.00	1.3 (0.9–1.8)	1.3 (0.9–1.9)	2.3 (1.6–3.4)	<0.001
<b>Insulin resistance<sup>a</sup></b>					
No of cases	132	168	242	367	
Unadjusted OR (95% CI)	1.00	1.6 (1.2–2.0)	2.7 (2.1–3.4)	5.6 (4.4–7.0)	<0.001
Age-adjusted OR (95% CI)	1.00	1.4 (1.1–1.8)	2.1 (1.7–2.7)	3.9 (3.0–4.9)	<0.001
Multivariate OR (95% CI) <sup>b</sup>	1.00	1.2 (0.9–1.7)	1.4 (1.2–1.9)	2.5 (1.9–3.4)	<0.001

<sup>a</sup> Insulin resistance defined as cases with homeostasis model assessment score in upper quartile, namely above 2.8 and 2.3 for men and women, respectively.

<sup>b</sup> Odds ratios (OR) with corresponding 95% CI has been adjusted for age, BMI, hs-CRP, tobacco smoking, alcohol use, history of cardiovascular diseases, and hormone replacement therapy (for women) in 6617 participants with hs-CRP available.

view that circulating levels of procalcitonin are partly dependent on adipose tissue mass. However, another part of the associations was independent of BMI. Possible explanations are that circulating levels of procalcitonin are related to adipocyte function rather than mass or that other factors that link inflammation to the metabolic syndrome play a role, *e.g.* nonassessed atherosclerosis (17) or periodontitis (18).

This study extends the available information for procalcitonin to a role as a biomarker of noninfectious conditions, namely the metabolic and cardiovascular arena. Moreover, because plasma procalcitonin can now be measured within the normal range, it warrants further research into its potential to identify individuals at risk of cardiovascular and chronic metabolic disease.

There are several limitations of this study. The study is a cross-sectional investigation, and causal relationships of procalcitonin as a novel biomarker of the metabolic syndrome and insulin resistance cannot be inferred. Another limitation is the use of insulin resistance based on HOMA-IR instead of the gold standard hyperinsulinemic-euglycemic clamp technique. Although our study included apparently healthy adults, mostly recruited from Caucasians in The Netherlands, it is unclear

whether our findings would be replicable in other regions and among unhealthy individuals with cardiovascular or other comorbidities.

In conclusion, our findings based on community-based data show that higher plasma procalcitonin levels in the normal range are associated with increased measures of obesity, components of the metabolic syndrome, and greater risk of having metabolic syndrome and insulin resistance. Because associations only partly depend on BMI, plasma procalcitonin may serve as a new marker for adipocyte dysfunction, chronic low-grade inflammation, or both.

## Acknowledgments

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