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High plasma chemerin is associated with renal dysfunction and predictive for cardiovascular events — Insights from phenotype and genotype characterization

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ABSTRACT

The novel adipokine chemerin, encoded by the RARRES2 gene, has been suggested to be linked to insulin resistance and to the metabolic syndrome (MetS). However, no well-defined cardiovascular profile has been reported and the association with coronary artery disease (CAD) is a matter of debate. Because there is a relation between renal dysfunction and CAD, we analyzed plasma chemerin levels and the estimated glomerular filtration rate (eGFR) in 495 patients undergoing coronary angiography for the evaluation of established or suspected stable CAD.

Chemerin levels were higher in patients with Type 2 diabetes mellitus (T2DM, n = 111) and the metabolic syndrome (MetS, n = 147) than in subjects without T2DM (191.5 ± 72.9 vs. 169.7 ± 64.7 ng/ml, p = 0.001) or the MetS (201.2 ± 71.0 vs. 163,1 ng/ml, p < 0.001), but did not differ significantly between patients with significant CAD (n = 247) and those without significant CAD (177.1 ± 67.0 vs. 171.7 ± 67.2 ng/ml, p = 0.193).

Analysis of covariance using age, sex, and BMI as covariates showed that chemerin was significantly and independently associated with eGFR (F = 49.6, p < 0.001). After an 8-year follow-up period, patients with high chemerin levels were more often affected by cardiovascular events (HR = 1.72 [95% CI 1.19–2.47], p = 0.004), even after appropriate adjustment for age, gender, BMI, as well as eGFR (adjusted HR 1.51 [95% CI 1.03–2.23], p = 0.037).

Given the cardiometabolic role of chemerin, we also applied a Cardio-Metabo Chip analysis and revealed a genome-wide significant association with SNPs (rs55709438, rs2444030, and rs3098423) located at chromosomal region 15q15–23, which were associated with metabolic traits and eGFR.

This study for the first time demonstrates that high chemerin concentrations are significantly associated with renal impairment and predictive of cardiovascular events and that 15q15–23 might have an impact on chemerin levels beyond common genetic variations in RARRES2.

1. Introduction

Chemerin is an adipokine that mediates (i) MAPK activation by G-protein coupled receptor (GPCR-signaling) [1,2], (ii) insulin resistance [3], and (iii) angiogenesis [4]. It is a protein with a large scope. It features anti-microbial [5] as well as chemotactic and inflammatory properties, plays a regulatory role for immune response [6,2,7], and has been suggested to induce contraction of the vasculature [8]. Chemerin is predominantly expressed in adipocytes [9] and important for adipocyte differentiation and metabolism [10].

Chemerin gene expression is elevated in psoriasis development [11] and further inflammatory diseases including ulcerative colitis and Crohn disease [12]. It is upregulated in Type 2 diabetes mellitus (T2DM) and obesity [1,13,14] and meta-analysis data link elevated plasma levels of chemerin to the metabolic syndrome (MetS) [15]. In addition, retinoic acid receptor responder-2 (RARRES2), encoding chemerin, is a genetic determinant of disproportionate regional body fat distribution [16].

In studies with Asian patients who underwent elective coronary angiography for suspected coronary artery disease (CAD), elevated levels

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of chemerin were shown to be significantly associated with the presence [17,18] or severity [19] of CAD. In contrast, no association between chemerin and coronary atherosclerotic plaque burden or morphology was found in a study with Caucasian patients [20]. Apart from that, chemerin, in contrast to other adipokines, has a relatively poor cardiovascular profile [21].

Of interest, it has been reported previously that kidney function is inversely related to circulating chemerin in dialysis patients [22,23] and that kidney transplantation decreased chemerin levels in patients with end stage renal disease [24]. In previous studies, we found a significant relation between renal function and coronary atherosclerosis as well as vascular events [25,26].

However, data addressing the links of chemerin with both, renal function and future cardiovascular risk in coronary patients, are still lacking.

For these reasons, we aimed at investigating the role of chemerin as a predictor for cardiovascular risk and renal malfunction in a high risk cohort of patients undergoing coronary angiography for the evaluation of suspected or established stable CAD. Furthermore, we investigated the association of cardiometabolic polymorphisms using the Cardio-Metabo Chip with circulating chemerin concentrations and aimed to replicate previously reported RARRES2 polymorphisms in that population.

2. Results

2.1. Patient characteristics

The characteristics of our patients (n = 495) were typical for patients undergoing coronary angiography for the evaluation of stable CAD, with a high prevalence of T2DM (22.5%) hypertension (77.2%) and smoking (53.5%). Plasma chemerin on average was 174.4 ± 67.1 ng/ml (mean ± SD). It was elevated in women compared with men (183.7 ± 67.3 ng/ml vs. 165.1 ± 65.7 ng/ml, $p < 0.001$) and patients with hypertension had also significantly higher circulating chemerin concentrations than those without hypertension (180.2 ± 70.9 vs. 154.8 ± 47.4 ng/ml, $p = 0.001$). With respect to T2DM and MetS, we saw a significant discrepancy between affected and unaffected subjects (191.5 ± 72.9 vs. 169.7 ± 64.7, $p = 0.001$, and 201.2 ± 71.0 vs. 163.1 ± 62.1 ng/ml $p < 0.001$ respectively). In this context, patients treated and untreated with ASA (172.0 ± 61.1 vs. 179.0 ± 77.5 ng/ml, $p = 0.710$), beta blocker (177.3 ± 68.8 vs. 171.2 ± 65.2 ng/ml, $p = 0.464$), or statins (177.2 ± 69.3 vs. 172.2 ± 65.4 ng/ml, $p = 0.786$) did not differ in terms of their chemerin concentration, whereas increased chemerin levels were observed in patients taking ACE blocker (185.2 ± 71.5 vs. 169.9 ± 64.8 ng/ml, $p = 0.005$) or AT-2 antagonists (202.0 ± 85.2 vs. 171.6 ± 64.5 ng/ml, $p = 0.034$).

We did not find a significantly raised chemerin concentration in patients with CAD compared with those without CAD (177.1 ± 67.0 vs. 171.7 ± 67.2 ng/ml, $p = 0.193$). Comparing patient characteristics with respect to tertiles of chemerin concentration (Table 1), we also revealed an association between chemerin on the one hand and metabolic as well as kidney traits on the other hand.

2.2. Association with obesity and renal function

Our study demonstrated that obese patients had significantly higher chemerin concentrations than non-obese subjects (195.6 ± 78.5 vs.

Table 1
Patient characteristics according to tertiles of plasma chemerin. Tertiles 1 through 3 of plasma chemerin range from 12 ng/ml to 145 ng/ml, from 145 ng/ml to 191 ng/ml, and from 191 ng/ml to 497 ng/ml, respectively. Data are means ± standard deviations as indicated. BMI denotes body mass index, CAD coronary artery disease, which is defined by an angiographically determined coronary artery stenosis with lumen narrowing ≥50%. T2DM denotes Type 2 diabetes mellitus, MetS the metabolic syndrome, eGFR the estimated glomerular filtration rate, CKD denotes chronic kidney disease and is defined by an eGFR smaller than 90 ml/min/1.73 m^2. CRP denotes C-reactive protein, NT-proBNP N-terminal pro brain natriuretic peptide, LDL low density lipoprotein, HDL high density lipoprotein, HbA1c hemoglobin A1c, HOMA-IR homeostasis model assessment of insulin resistance, ASA acetylsalicylic acid, ACE angiotensin converting enzyme, and AT-2 angiotensin 2. p-Values are given for trend.

	Total	1st tertile	2nd tertile	3rd tertile	p-Value
Age (years)	65 ± 11	63 ± 12	65 ± 11	68 ± 10	0.001
Male sex (%)	50.1	61.8	45.5	43.0	0.001
Waist circumference (cm)	98.5 ± 12.0	95.2 ± 11.2	99.5 ± 11.4	100.9 ± 12.8	<0.001
BMI (kg/m^2)	27.6 ± 4.6	26.5 ± 4.0	27.8 ± 4.1	28.5 ± 5.2	<0.001
Hypertension (%)	77.2	70.3	75.8	85.5	0.001
Smoking (%)	53.5	56.4	55.2	49.1	0.186
sig. CAD (%)	49.9	46.1	49.7	53.9	0.153
Extent of >50% stenoses	1.2 ± 1.6	1.0 ± 1.6	1.2 ± 1.6	1.3 ± 1.6	0.091
T2DM (%)	22.5	14.1	23.0	30.3	<0.001
MetS (%)	29.7	12.7	32.7	43.6	<0.001
eGFR (ml/min/1.73 m^2)	95.0 ± 17.6	100.9 ± 15.3	96.1 ± 15.1	87.8 ± 19.5	<0.001
ACR	68.9 ± 235.1	36.7 ± 86.7	65.9 ± 269.0	104.2 ± 289.4	0.003
CKD (%)	37.6	25.5	37.6	49.7	<0.001
CRP (mg/dl)	0.39 ± 0.61	0.25 ± 0.31	0.36 ± 0.48	0.56 ± 0.86	<0.001
Fibrinogen (mg/dl)	328 ± 72	302 ± 59	327 ± 71	355 ± 75	<0.001
NT-proBNP (pg/ml)	659 ± 1603	699 ± 1978	380 ± 871	916 ± 1693	0.382
LDL cholesterol (mg/dl)	129 ± 42	125 ± 42	135 ± 43	129 ± 40	0.446
HDL cholesterol (mg/dl)	59 ± 18	62 ± 17	59 ± 19	56 ± 18	0.001
Total cholesterol (mg/dl)	200 ± 47	195 ± 46	205 ± 47	200 ± 48	0.483
Triglycerides (mg/dl)	137 ± 90	112 ± 70	139 ± 78	160 ± 109	<0.001
Apolipoprotein A-1 (mg/dl)	158 ± 30	159 ± 29	161 ± 32	153 ± 28	0.032
Apolipoprotein B (mg/dl)	84 ± 23	78 ± 23	86 ± 23	87 ± 22	<0.001
Fasting glucose (mg/dl)	104 ± 30	99 ± 25	102 ± 27	110 ± 37	<0.001
HbA1c (%)	6.0 ± 0.9	5.8 ± 0.8	6.0 ± 0.8	6.2 ± 1.0	<0.001
HOMA-IR	4.2 ± 19.6	2.5 ± 2.9	5.9 ± 32.5	4.2 ± 7.0	<0.001
Systolic blood pressure (mm Hg)	135 ± 17	132 ± 16	135 ± 18	138 ± 18	0.002
Diastolioc blood pressure (mm Hg)	81 ± 10	80 ± 10	82 ± 10	82 ± 10	0.268
ASA treatment (%)	66.3	66.1	67.9	64.8	0.816
Beta blocker treatment (%)	51.9	53.3	47.9	54.5	0.826
ACE inhibitor treatment (%)	29.3	23.6	23.6	40.6	0.001
AT-2 antagonist treatment (%)	9.1	6.1	10.3	10.9	0.126
Statin treatment (%)	43.8	45.5	40.0	46.1	0.912
Plasma chemerin (ng/ml)	174.4 ± 67.1	112.0 ± 27.6	166.0 ± 13.4	245.2 ± 59.8	<0.001

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