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The novel adipokine CTRP1 is significantly associated with the incidence of major adverse cardiovascular events

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HIGHLIGHTS

- CTRP1 is associated with obesity-linked disorders.
- CTRP1 is associated with future major adverse cardiovascular events.
- CTRP1 is associated with cardiovascular risk beyond its association with obesity-linked disorders.

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ABSTRACT

Background and aims: The recently identified adiponectin paralogue C1q and tumor necrosis factor-related protein 1 (CTRP1) has been associated with obesity-linked disorders and coronary atherosclerosis. So far, the impact of circulating CTRP1 on the incidence of future cardiovascular events is unclear. Therefore, we aimed at investigating the association between CTRP1 and future cardiovascular risk.
Methods: We measured CTRP1 serum levels in 539 patients undergoing coronary angiography for the evaluation of established or suspected stable coronary artery disease (CAD). Prospectively, we recorded major adverse cardiovascular events (MACE), defined as the incidence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke over a follow-up period of 8 years.
Results: At baseline, obesity, the metabolic syndrome, type 2 diabetes, and non-alcoholic fatty liver disease were significantly associated with increased CTRP1 (all p-values ≤ 0.001). Prospectively, MACE rates were lowest in the first quartile (15.3%) and increased over the second (23.7%) to the third and fourth quartile (each 29.0%; $p_{trend} = 0.008$). Moreover, after multivariable adjustment, CTRP1 was significantly associated with future MACE, with adjusted HRs of 1.83 [1.04–3.23]; $p = 0.037$, 2.16 [1.25–3.75]; $p = 0.006$, and 1.80 [1.03–3.15]; $p = 0.038$, for CTRP1 quartiles two, three and four, respectively, when compared to quartile one.
Conclusions: We conclude that high serum levels of CTRP1 are significantly associated with future MACE.

1. Introduction

Far from being metabolically inert, adipose tissue acts as a highly active endocrine organ by releasing into the circulation numerous polypeptide hormones and cytokines, collectively termed adipokines [1,2]. One of the most intensely studied adipokines is the hormone adiponectin, which exhibits well documented anti-diabetic, anti-atherogenic, and anti-inflammatory properties and is down-regulated in obesity and diabetes [3].

In 2004, Wong et al. characterized a novel, highly conserved family of adiponectin paralogues, referred to as complement C1q tumor necrosis factor-related proteins (CTRP1-15) [4,5]. Members of the CTRP family share the same modular organization with adiponectin containing a globular C1q domain, which has a three-dimensional structure

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Table 1
Baseline patient characteristics of the total patient cohort and with respect to CTRP1 quartiles.

	CTRP1 quartiles				p_{trend}
	Quartile 1 n = 134 (≤350.5 ng/ml)	Quartile 2 n = 135 (351.0–425.9 ng/ml)	Quartile 3 n = 135 (427.0–523.5 ng/ml)	Quartile 4 n = 135 (≥524.0 ng/ml)	
Age (years)	70 [60–76]	69 [58–73]	69 [61–74]	69 [63–74]	0.752
Male gender % (n)	75.4 (101)	74.8 (101)	66.7 (90)	57.8 (78)	0.001
BMI (kg/m^2)	26.3 [25.0–28.7]	27.0 [24.7–29.6]	27.4 [25.3–30.3]	28.8 [25.8–31.8]	< 0.001
Obesity % (n)	17.2 (23)	22.2 (30)	27.4 (37)	40.0 (54)	< 0.001
Hypertension % (n)	76.1 (102)	78.5 (106)	77.8 (105)	87.4 (118)	0.032
Systolic blood pressure (mmHg)	135 [125–145]	135 [120–150]	140 [125.5–150]	140 [130–150]	0.045
Diastolic blood pressure (mmHg)	80 [77–85]	80 [80–90]	80 [80–90]	80 [80–90]	0.028
Metabolic syndrome % (n)	29.9 (40)	36.3 (49)	41.5 (56)	54.8 (74)	< 0.001
Fasting glucose (mg/dl)	97 [90–105]	98 [90–111]	102 [93–115]	108 [95–138]	< 0.001
T2DM % (n)	23.1 (31)	23.0 (31)	25.9 (35)	44.4 (60)	< 0.001
Significant CAD % (n)	73.1 (98)	62.2 (84)	60.0 (81)	57.8 (78)	0.010
Extent of CAD	1 [0–3]	1 [0–3]	1 [0–2]	1 [0–3]	0.241
LVEF (%)	65.0 [50.3–75.8]	63.0 [59.0–72.0]	65.0 [55.0–74.0]	63.0 [50.8–75.0	0.921
Smoking % (n)	15.7 (21)	14.1 (19)	14.1 (19)	16.3 (22)	0.891
C-reactive protein (mg/dl)	0.21 [0.09–0.37]	0.21 [0.11–0.44]	0.24 [0.13–0.49]	0.27 [0.16–0.59]	0.003
Fibrinogen (mg/dl)	317 [284–362]	317 [281–367]	327 [290–368]	343 [290–403]	0.006
BNP (pg/dl)	11.8 [9.0–37.5]	9.5 [9.0–38.3]	18.4 [9.0–64.2]	17.3 [9.0–62.0]	0.070
Cholesterol (mg/dl)	197 [173–225]	195 [164–225]	184 [156–226]	188 [166–224]	0.254
LDL cholesterol (mg/dl)	129 [102–155]	125 [98–148]	121 [93–158]	123 [99–154]	0.490
HDL cholesterol (mg/dl)	55 [47.5–67]	56 [46–67]	55 [46–65]	55 [43–66]	0.227
Triglycerides (mg/dl)	105 [81–146]	110 [82–165]	117 [81–162]	115 [82–166]	0.232
Statin therapy % (n)	54.5 (73)	52.6 (71)	54.1 (73)	47.4 (64)	0.306
Aspirin, % (n)	64.4 (85)	59.0 (79)	72.9 (97)	71.6 (96)	0.050
ACE inhibitors, n (%)	27.6 (37)	31.9 (43)	39.3 (53)	31.1 (42)	0.323
AT-II receptor blockers, n (%)	10.4 (14)	13.3 (18)	14.1 (19)	12.6 (17)	0.577
Beta blocker agents, % (n)	59.0 (79)	51.9 (70)	62.2 (84)	61.5 (83)	0.343
Anti-diabetic therapy[a] % (n)	41.9 (13)	45.2 (14)	57.1 (20)	56.7 (34)	0.127
eGFR (ml/min/1.73 m^2)	97.7 [87.4–107.0]	100.0 [85.3–111.2]	92.6 [83.8–108.4]	90.2 [85.3–106.5]	0.024
NAFLD % (n)	36.0 (45)	42.9 (54)	52.0 (64)	58.7 (74)	< 0.001

BMI, body mass index; T2DM, type 2 diabetes mellitus; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; NAFLD, non-alcoholic fatty liver disease.

[a] Only subjects with T2DM: among patients with anti-diabetic medication 39.5%, 64.2%, and 38.3% were receiving – alone or in combination – sulfonylurea, biguanides, and insulin, respectively. Continuous variables are given as median [interquartile range, defined as the range from the 25th to the 75th percentile]. Coronary artery stenoses with stenotic narrowing ≥50% were defined as significant CAD. The extent of CAD was defined as the number of ≥50% lesions.

similar to tumor necrosis factor alpha [6]. One of these CTRPs, CTRP1, has been recognized to play a major role in glucose and energy homeostasis [4,7,8].

Increased serum CTRP1 levels have been reported to be associated with the presence of coronary artery disease (CAD) [9–12], low coronary collateralization [13], and congestive heart failure [14] in humans and to promote atherogenesis in mice [11]. However, the association between circulating CTRP1 and the risk of future cardiovascular events is unclear. Therefore, we prospectively analyzed the association of serum CTRP1 with the 8-year incidence of major adverse cardiovascular events (MACE) in a well characterized cohort of angiographied coronary patients.

2. Materials and methods

2.1. Study subjects

The present study included 539 consecutive Caucasian patients, who were referred to elective coronary angiography for the evaluation of established or suspected stable CAD at the academic teaching hospital Feldkirch, Austria. Detailed information on the recruitment protocol and the determination of baseline characteristics is given in the Supplementary Data. During a mean follow-up period of 5.9 ± 2.2 years (with a total of 8 years) cardiovascular events were recorded. MACE was defined as a three-point composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Time and causes of death were regularly obtained from a national survey (Statistik Austria, Vienna, Austria) or from hospital records. The present study has been approved by the Ethics Committee of the University of Innsbruck, Austria, and written informed consent was given by all participants.

2.2. Serum CTRP1 levels

Serum CTRP1 levels were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Biovendor, Brno, Czech Republic; article number: RD191153100R).

According to the manufacturer's information the assay has a calibration range of 3.13–100 ng/ml, with a detection limit of 0.016 ng/ml, an intra-assay coefficient of variation (CV) of 2.7%, and an inter-assay CV of 8.5%. Based on our own measurements, an intra-assay CV of 5.4% was measured by calculating the average value from the individual CVs for all of the duplicates of the calibrators and internal controls used in each plate. An inter-assay CV of 10.9% was measured by testing CTRP1 control samples (high and low concentrations) on each plate.

2.3. Statistics

Normal distribution was checked using the Kolmogorov-Smirnov test and the Shapiro-Wilk-Test, respectively. CTRP1 values were approximately not normally distributed and, therefore, were divided into quarters or log-transformed for further statistical analyses. Differences in baseline characteristics according to CTRP1 quartiles were tested for statistical significance with the Chi-squared tests for trend for categorical and Jonckheere-Terpstra tests for continuous variables, respectively. Results are given as median [interquartile range, defined as the range from the 25th percentile to the 75th percentile]. Survival curves

were generated using the Kaplan-Meier method and compared using the Log-Rank-Mantel-Cox-tests. Hazard ratios (HRs) and 95% confidence intervals of the HRs were derived from univariable and multivariable Cox proportional hazards models; log-transformed continuous variables were z-transformed for these analyses. p-values < 0.05 were considered significant. Statistical analyses were performed with SPSS 25.0 for Windows (IBM, Armonk, New York, USA).

3. Results

3.1. Baseline data

Clinical and biochemical baseline patient characteristics stratified by quartiles of CTRP1 are given in Table 1. High body mass index (BMI), systolic blood pressure, diastolic blood pressure, fasting glucose, C-reactive protein (CRP), and fibrinogen, low estimated glomerular filtration rate (eGFR), as well as female gender, obesity, hypertension, the metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver disease (NAFLD) were significantly associated with increased CTRP1 at a nominal p-value < 0.05.

3.2. Prospective study

Out of the 539 patients initially included in the present study, 15 were lost to follow-up. In 127 out of the remaining 524 subjects (24.2%) MACE (52 cardiovascular deaths, 47 nonfatal myocardial infarctions, and 28 nonfatal strokes) occurred during the follow-up period. Univariate Cox regression analysis revealed that in our cohort baseline T2DM, LDL cholesterol, HDL cholesterol, angiographically significant CAD, the extent of CAD, left ventricular ejection fraction (LVEF), eGFR, CRP, fibrinogen as well as brain natriuretic peptide were significantly associated with MACE, as shown in Table 1 in the associated data article [15].

Fig. 1 shows Kaplan-Meier curves for the cumulative MACE rate according to quartiles of CTRP1. MACE rates were lowest in the first quartile (15.3%) and increased over the second (23.7%) to the third and fourth quartile (each 29.0%, log-rank p-value = 0.008). Hazard ratios together with respective 95% confidence intervals for CTRP1 quartiles two, three and four compared to quartile one are given in Table 2. CTRP1 was significantly associated with the incidence of future MACE after adjustment for age, sex, BMI, T2DM, significant CAD at angiography, hypertension, smoking, LDL cholesterol, HDL cholesterol, and eGFR (adjustment models 1 and 2 in Table 2). When entered as a continuous variable, CTRP1 was significantly associated with the risk of MACE univariately (HR 1.21 [1.02–1.45]; $p = 0.032$) as well as in the full adjusted model (HR 1.22 [1.01–1.47]; $p = 0.042$). Also, after adjustment for age, sex, BMI, T2DM, significant CAD at angiography, hypertension, smoking, LDL cholesterol, HDL cholesterol, eGFR, and, additionally, for the extent of CAD and LVEF the association between CTRP1 and MACE remained significant (see Table 2 in the associated data article [15]).

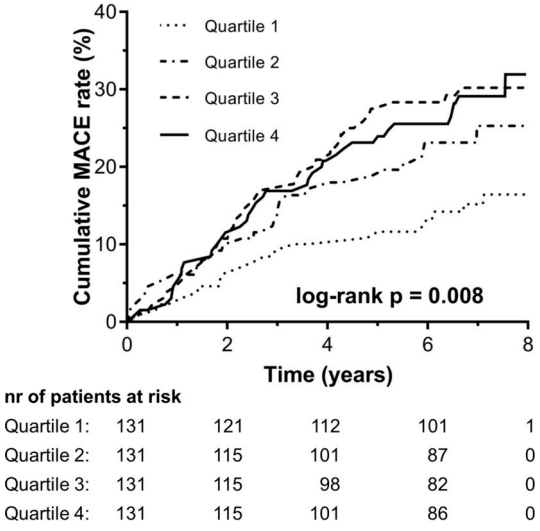

Fig. 1. Kaplan-Meier curves of MACE according to CTRP1 quartiles. MACE, major adverse cardiovascular events.

As stated above, fibrinogen and CRP levels were significantly associated with CTRP1 quartiles (Table 1) and controlling for the effects of these two variables may lead to overadjustment. However, in an exploratory analysis, even with further adjustments for fibrinogen and CRP in addition to age, sex, BMI, T2DM, significant CAD at angiography, hypertension, smoking, LDL cholesterol, HDL cholesterol, and eGFR the association between CTRP1 and MACE remained significant (see Table 2 in the associated data article [15]).

To further investigate the influence of cardiovascular risk factors on the association between CTRP1 and MACE, subgroup analyses were performed (Fig. 2). Subgroup analyses stratified by gender, T2DM, and significant CAD at angiography showed that CTRP1 levels were significantly associated with MACE particularly in men, in patients with T2DM, and in subjects with angiographically significant CAD. No significant interaction between CTRP1 and cardiovascular risk factors on the incidence of MACE could be observed (all $p_{interaction}$ values ≥ 0.05).

4. Discussion

Increased CTRP1 has been cross-sectionally associated with cardiovascular disease [9–12]. In the present prospective study, we demonstrate, for the first time, that high serum CTRP1 levels are significantly linked with an increased risk of future MACE.

CTRP1 is primarily secreted by stromal cells of adipose tissue [4], but is also expressed in the heart, kidney, liver, in skeletal muscles and sexual glands [5,16]. In rodents, CTRP1 lowers blood glucose levels [4] and increases energy expenditure by activating the AMPK signaling cascade to increase fatty acid oxidation in the skeletal muscles [7,8]. However, the picture is more complex, as CTRP1 expression is induced by inflammatory cytokines indicating that CTRP1 expression may be associated with a low-grade chronic inflammation status in adipose tissues [17]. Moreover, despite the beneficial metabolic actions of CTRP1 in whole body energy homeostasis, several clinical studies demonstrated that CTRP1 levels are increased in patients with obesity-linked disorders, including the MetS [18], T2DM [19–21], hypertension [22], or NAFLD [23], which could be also confirmed by our study.

These close associations between CTRP1 and obesity-related traits may have contributed to the significant linkage between CTRP1 and future cardiovascular risk. Moreover, these traits may be part of the causal pathway or represent potential mediating factors in the association between CTRP1 and MACE. However, multivariable Cox regression analyses revealed that the association between CTRP1 and MACE remained robust when metabolic parameters and inflammatory markers were included in the model. Therefore, CTRP1 predicts the incidence of MACE beyond its association with an unfavorable metabolic profile.

MACE constitutes the last step of the development of atherothrombotic disease and eventually are precipitated by thrombogenic factors, which could be linked with CTRP1 levels. In fact, in our study CTRP1 was positively associated with fibrinogen, which aside from being an acute phase reactant of inflammation has crucial mechanistic roles in platelet crosslinking, platelet aggregation, and thrombus formation [24] and is a risk factor for adverse cardiovascular events [25,26]. However, after inclusion of fibrinogen into our multivariable Cox regression analysis, association between CTRP1 and MACE still

Table 2
Association between CTRP1 quartiles and the incidence of MACE. Results from Cox regression analyses.

	CTRP1 quartiles				p_{trend}-value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Unadjusted hazard ratio (95% CI)	1[reference]	1.67 [0.95–2.92]; $p = 0.075$	2.10 [1.22–3.61]; $p = 0.007$	2.04 [1.18–3.50]; $p = 0.010$	0.007
Adjusted[a] hazard ratio (95% CI) + age, sex, and BMI	1[reference]	1.76 [1.00–3.10]; $p = 0.049$	2.27 [1.31–3.90]; $p = 0.004$	2.26 [1.26–3.83]; $p = 0.006$	0.004
Adjusted[b] hazard ratio (95% CI) + age, sex, and BMI, T2DM, CAD, smoking, hypertension, LDL-C, HDL-C, and eGFR	1[reference]	1.96 [1.11–3.45]; $p = 0.020$	2.32 [1.34–4.01]; $p = 0.003$	2.02 [1.16–3.53]; $p = 0.013$	0.012

Adjustment model [a] adjusts for age, sex, and body mass index (BMI); model [b] adjusts for age, sex, and BMI, type 2 diabetes mellitus (T2DM), angiographically significant coronary artery disease (CAD), hypertension, smoking, LDL cholesterol, HDL cholesterol, and estimated glomerular filtration rate (eGFR). Age, BMI, LDL cholesterol, HDL cholesterol, and eGFR were log-transformed before included in multivariable Cox regression analyses.

remained significant.

On a molecular level it has been shown that CTRP1 activates the p38 MAPK/NF-kB pathway increasing the expression of adhesion molecules and synthesis of inflammatory cytokines and chemokines [11,27]. Furthermore, CTRP1 expression itself is induced by inflammatory cytokines [11,17]. As previously reported [11] and also observed in our study, CTRP1 levels are linked to increased levels of the pro-inflammatory marker CRP, which also represents a well-established blood-based cardiovascular risk factor [28,29]. Controlling for CRP in multivariable Cox regression analysis may, therefore, lead to over-adjustment potentially masking the effect of CTRP1 on MACE. Notably, in an explanatory analysis, after additional adjustment for CRP in multivariable Cox regression analysis, the strength of the association between CTRP1 levels and MACE was attenuated, but remained significant. However, it cannot be excluded that the linkage between CTRP1 and other markers of inflammation may have contributed to an increased cardiovascular risk. In this connection CTRP1 has been shown to stimulate expression of interleukin-6 [30,31], an inhibition of which has recently been proven to decrease cardiovascular event rate [32,33].

Our study has strengths and limitations. By design, our study population was composed of angiographied coronary patients of European ancestry; our results therefore are not necessarily applicable to other ethnicities or the general population. However, the high-risk patient population we chose to investigate is of particular clinical interest. Also, studies on the association between CTRP1 and cardiovascular disease in humans are scarce, mostly of small sample sizes, and limited to a cross-sectional study design. Our prospective study represents the first observation linking CTRP1 to future cardiovascular event risk in angiographied patients confirming its previously assumed role as a predictor of incident cardiovascular disease. However, the observational design of our study precludes conclusions with regard to causal relationships and the biological mechanism, which lead to the increased risk for MACE by CTRP1, remain unclear. We cannot rule out that our results may have been influenced by confounders that were not collected in our study. In this regard, any relationships of CTRP1 with other circulating cardiovascular adipokines, such as adiponectin [34] or CTRP12 [35], which have been correlated with serum CTRP1 [19,20] but were not measured in our study, could not be investigated in our study.

In conclusion, our study shows a significant association of serum CTRP1 with future cardiovascular events in coronary angiographied patients. Further studies appear necessary to clarify the causal role of CTRP1 in these findings.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

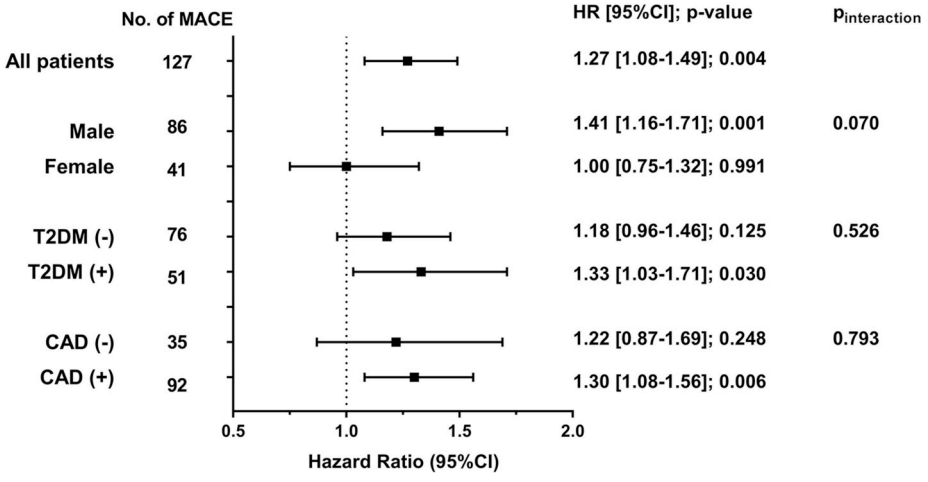

Fig. 2. Association between CTRP1 and MACE in subgroup analyses. CTRP1 quartiles were used. Hazard ratios and 95% confidence intervals were obtained from multivariable Cox regression analysis adjusted for age and body mass index (BMI) in case of subgroup analysis stratified by gender and for age, BMI, and sex in case of remaining subgroup analyses. T2DM, type 2 diabetes mellitus; CAD, angiographically significant coronary artery disease.

Author contributions

H.D. and A.M. designed the study, interpreted the data, and wrote the manuscript. A.M. performed statistical analyses. A.L. and CH.S. contributed to design and discussion. J.E. and K.G. performed molecular analyses. CH.S. and A.V. were responsible for patient recruitment and provided clinical characteristics. A.L., EM.B., CH.S., and P.F. reviewed/edited the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.04.222.

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