Dipeptidyl peptidase 3, a marker of the antagonist pathway of the renin–angiotensin–aldosterone system in patients with heart failure

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Aims

Recently, dipeptidyl peptidase 3 (DPP3) has been discovered as the peptidase responsible for cleavage of angiotensin (1–7) [Ang (1–7)]. Ang (1–7) is part of the angiotensin-converting enzyme–Ang (1–7)–Mas pathway which is considered to antagonize the renin–angiotensin–aldosterone system (RAAS). Since DPP3 inhibits the counteracting pathway of the RAAS, we hypothesize that DPP3 might be deleterious in the setting of heart failure. However, no data are available on DPP3 in chronic heart failure. We therefore investigated the clinical characteristics and outcome related to elevated DPP3 concentrations in patients with worsening heart failure.

Methods and results

Dipeptidyl peptidase 3 was measured in 2156 serum samples of patients with worsening heart failure using luminometric immunoassay (DPP3-LIA) by 4TEEN4 Pharmaceuticals GmbH, Hennigsdorf, Germany. Predictors of DPP3 levels were selected using multiple linear regression with stepwise backward selection. Median DPP3 concentration was 11.45 ng/mL with a range from 2.8 to 84.9 ng/mL. Patients with higher DPP3 concentrations had higher renin [78.3 (interquartile range, IQR 26.3–227.7) vs. 120.7 IU/mL (IQR 34.74–338.9), P < 0.001, for Q1–3 vs. Q4] and aldosterone [88 (IQR 44–179) vs. 116 IU/mL (IQR 46–241), P < 0.001, for Q1–3 vs. Q4] concentrations. The strongest independent predictors for higher concentration of DPP3 were log-alanine aminotransferase, log-total bilirubin, the absence of diabetes, higher osteopontin, fibroblast growth factor-23 and N-terminal pro-B-type natriuretic peptide concentrations (all P < 0.001). In univariable survival analysis, DPP3 was associated with mortality and the combined endpoint of death or heart failure hospitalization (P < 0.001 for both). After adjustment for confounders, this association was no longer significant.

Conclusions

In patients with worsening heart failure, DPP3 is a marker of more severe disease with higher RAAS activity. It may be deleterious in heart failure by counteracting the Mas receptor pathway. Prociuzumab, a specific antibody against DPP3, might be a potential future treatment option for patients with heart failure.
Background

It was recently discovered that dipeptidyl peptidase 3 (DPP3) is responsible for enzymatic cleavage of both angiotensin II (AngII) and the heptapeptide angiotensin (1–7) [Ang(1–7)] to Ang(3–7) and Ang(5–7)\(^{1,2}\) (Graphical Abstract). Ang(1–7) is part of the angiotensin-converting enzyme 2 (ACE2)–Ang(1–7)–Mas receptor (AAM) axis, which is considered the antagonistic pathway of the renin–angiotensin–aldosterone (RAAS) system.\(^3\) Activation of the AAM pathway leads to vasodilation, increased renal blood flow and increased natriuresis. The beneficial effects of angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARBs) have been partly attributed to stimulation of the Mas receptor.\(^4,5\) In contrast, breakdown of Ang(1–7) by DPP3 would inhibit the potentially beneficial effects of the AAM pathway, and might therefore have deleterious cardiovascular effects\(^4\) (Graphical Abstract). This is supported by a study showing that DPP3 infusion in healthy mice caused cardiac depression and these effects were antagonized by procizumab, a specific antibody directed against circulating DPP3.\(^6\) In patients with cardiogenic shock, higher DPP3 concentrations were associated with a higher short-term mortality and severe organ dysfunction.\(^7\)

Since activation of the RAAS plays a key role in the development and progression of heart failure (HF), the role of DPP3 might be of interest in these patients as well. However, the prevalence, predictors and clinical outcomes of elevated DPP3 concentrations in patients with HF have not yet been established. We therefore investigated the clinical characteristics and outcome related to elevated DPP3 concentrations in patients with worsening HF.

Methods

We measured DPP3 concentrations in 2314 subjects from a multinational, observational cohort of patients with chronic, worsening HF (BIOSTAT-CHF).\(^8\) DPP3 was measured in serum samples with a DPP3 luminometric immunoassay (DPP3-LIA) by 4TEEN4 Pharmaceuticals GmbH, Hennigsdorf, Germany.\(^9\) The DPP3-LIA has a measuring range between 0.06–400 ng/mL; the upper limit of normal, based on a cohort of healthy volunteers, is 40 ng/mL. We excluded 158 samples due to visible haemolysis with normal haemoglobin levels, leaving 2156 samples for the present analysis. Baseline characteristics were evaluated between the lowest three quartiles and the highest quartile of DPP3 concentrations, using a t-test or Mann–Whitney U test for parametric and non-parametric variables, respectively. A multivariable linear regression analysis was performed to identify predictors of DPP3 concentration. All variables with a \(P < 0.1\) in univariable regression were added to the multivariable regression model. Stepwise backwards selection eliminated the non-significant variables.
Results

Table 1 shows baseline characteristics comparing the highest quartile of DPP3 with the three lowest quartiles. Spearman correlations for the continuous variables showing a statistical difference in the baseline table can be found in online supplementary Table S1. Median DPP3 concentration was 11.45 ng/mL with a range from 2.8 to 84.9 ng/mL. Out of 2156 patients in whom DPP3 was measured, only 31 (1.4%) showed DPP3 levels above the median found in cardiogenic shock patients (33.4 ng/mL). Patients in the highest quartile (median DPP3: 17.95 ng/mL) vs. the other three quartiles (median DPP3 7.84, 10.13, and 12.93 ng/mL, respectively) were characterized by higher New York Heart Association class (NYHA class IV: 13.4% vs. 11.3%, P = 0.001), more frequent history of valvular surgery (12.1% vs. 6.1%, P < 0.001) as well as valvular aetiology of HF (11.0% vs. 6.9%, P = 0.003). Atrial fibrillation was more common in the highest quartile (51.6% vs. 43.3%, P = 0.001), but diabetes mellitus was less frequently present (27.5% vs. 33.0%, P = 0.020). Men had higher DPP3 concentration than women (mean 13.0 vs. 12.2 ng/mL, P = 0.010). Patients in the highest quartile showed more signs and symptoms of congestion, higher liver enzymes, lower cholesterol levels, higher renin and aldosterone, as well as higher biomarkers predictive of more severe disease compared to the lower three quartiles. Patients in the highest quartile of DPP3 were less likely to use an ACE-i/ARB at baseline. There was, however, no significant association between baseline DPP3 levels and target dose of ACE-i/ARB after 9 months of encouraged up-titration. DPP3 levels were not predictive of an inability to up-titrate ACE-i/ARB to guideline-recommended target doses.

From a multivariable linear regression analysis with stepwise backwards selection, we identified that the six strongest predictors for higher concentration of DPP3 were the absence of diabetes, higher log-alanine aminotransferase (ALT), log-total bilirubin, higher osteopontin (OPN), fibroblast growth factor-23 (FGF-23) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations (all \( P < 0.0001 \)) (Table 2). Other independent predictors of higher DPP3 concentrations were growth differentiation factor-15 (GDF-15) (beta 0.052, \( P = 0.002 \)), aldosterone concentrations (beta 0.037, \( P = 0.002 \)), female sex (beta -0.085, \( P = 0.005 \)), valvular surgery (beta 0.126, \( P = 0.009 \)), and higher alkaline phosphatase (beta 0.029, \( P = 0.025 \)). Due to missing values across several variables, the multivariable regression is based on 739 subjects.

During a median follow-up of 21 months, 561 (26%) patients died and 870 (40%) either died or had a hospital admission for HF. Mortality ranged from 20.4% in the lowest quartile to 36.0% in the highest quartile. Similarly, death or HF hospitalization occurred in 34.7% in the lowest quartile to 50.3% in the highest quartile. In a univariable survival analysis, higher DPP3 concentrations were significantly associated with an increased risk of mortality (\( P < 0.0001 \)) and with the combined endpoint of death or HF hospitalization. Although higher DPP3 concentrations were associated with worse clinical outcomes, this association was no longer significant after adjustment for potential confounders, in particular OPN and FGF-23, as well as after adjustment for the previously published BIOSTAT-CHF risk prediction model \(^{10} \) (Table 3).

Discussion

In this study, the main predictors of higher DPP3 concentrations in patients with HF were higher bilirubin, OPN and FGF-23 concentrations, while diabetes and female sex were associated with lower DPP3 concentrations. The hypothetical explanations why these variables are associated with DPP3 concentrations are depicted in the Graphical Abstract, and will be discussed below. The Graphical Abstract is meant to be hypothesis generating on the role of DPP3 in HF and should be regarded as such. As is always the case with correlations, we cannot assume causation. Moreover, we showed that patients with higher DPP3 concentration also had higher renin and aldosterone levels, higher NYHA class, more valvular disease, more signs and symptoms of congestion and higher liver enzymes. We also observed an increased risk of adverse outcome in patients with higher DPP3 levels; significance was, however, lost after adjustment for the BIOSTAT-CHF risk model.

Under normal physiological circumstances, DPP3 resides inside the cytoplasm. Our finding that bilirubin and ALT were associated with DPP3 levels as well as a history of valvular surgery, might suggest that a low degree of continuous haemolysis, possibly originating from an artificial heart valve, contributed to increased DPP3 concentrations. Alternatively these biomarkers, combined with an increase in alkaline phosphatase, could originate from liver cell decay, from right-sided congestion. Moreover, increased liver enzymes in HF, in particular total bilirubin, are independent predictors of worse outcome, thereby, along with higher NT-proBNP and GDF-15, reflecting a more diseased patient.\(^ {11} \ 12 \)

Fibroblast growth factor-factor-23 is elevated in HF and chronic kidney disease patients and correlates with disease severity. Activation of the AT\(_1\)/AT\(_2\) receptors leads to decreased expression of the Klotho receptor, the receptor for FGF-23, leading to increased concentrations of FGF-23.\(^ {13} \) AngII infusion in mice resulted in a 1.5–1.7 time increase in FGF-23 serum concentrations.\(^ {14} \) Moreover, FGF-23 attenuates the beneficial effect of ARBs on the AAM axis.\(^ {15} \)

Osteopontin is a protein associated with inflammation, angiogenesis and bone resorption, and is activated by AngII.\(^ {16} \) Several studies demonstrated that ARBs nearly normalized OPN serum concentrations and intramyocardial expression both in patients with hypertension and rats with either dilated cardiomyopathy or oxalate deposited kidney disease.\(^ {16} 17 18 \) Activation of the AAM axis is suggested to be responsible for this normalization of OPN levels.

We recently showed that men with HF have higher circulating ACE2 concentrations than women.\(^ {19} \) ACE2 is also expressed in testis tissue, potentially explaining higher serum concentrations in men.\(^ {19} \) In a healthy cohort, no sex differences regarding DPP3 could be found.\(^ {9} \) Men with HF might express higher levels of DPP3 similar to ACE2 expression. However, this sex difference theory is still debatable. In contrast, patients with diabetes mellitus exhibit lower levels of ACE2, likely due to glycosylation of the enzyme.\(^ {20} 21 \) Furthermore, in patients with diabetes mellitus, the functionality of both ACE2 and Ang (1–7) is altered.\(^ {22} \)

Recently, a monoclonal antibody specifically directed at DPP3 was designed. This antibody, procizumab, rapidly improved cardiac
Table 1 Baseline characteristics

|                                | Q1–3 combined | Q4                        | P-value (Q1–3 vs. Q4) |
|--------------------------------|---------------|---------------------------|-----------------------|
| **n**                          | 1617          | 539                       |                       |
| DPP3 (ng/mL)                   | 10.13 [8.45–12.18] | 17.95 [16.09–21.70]       |                       |
| **Demographics**               |               |                           |                       |
| Age (years)                    | 69 ± 12       | 69 ± 12                   | 0.591                 |
| Female sex                     | 447 (27.6)    | 117 (21.7)                | 0.008                 |
| Systolic blood pressure (mmHg) | 125 ± 22      | 123 ± 21                  | 0.006                 |
| Diastolic blood pressure (mmHg)| 75 ± 13       | 74 ± 12.44                | 0.011                 |
| Heart rate (bpm)               | 79 ± 20       | 80 ± 19                   | 0.485                 |
| Weight (kg)                    | 82 ± 18       | 83 ± 19                   | 0.400                 |
| NYHA class                      |               |                           | 0.001                 |
| I                              | 44 (2.8)      | 4 (0.8)                   |                       |
| II                             | 594 (37.8)    | 166 (31.7)                |                       |
| III                            | 756 (48.1)    | 284 (54.2)                |                       |
| IV                             | 178 (11.3)    | 70 (13.4)                 |                       |
| **Medication use**             |               |                           |                       |
| ACE-i/ARB                      |               |                           | 0.001                 |
| Percentage of target dose at baseline |         |                           |                       |
| 0–49%                          | 989 (61.2)    | 358 (66.4)                |                       |
| 50–99%                         | 387 (23.9)    | 135 (25.0)                |                       |
| 100%                           | 241 (14.9)    | 46 (8.5)                  |                       |
| Percentage of target dose at 9 months |         |                           | 0.068                 |
| 0–49%                          | 746 (46.1)    | 273 (50.6)                |                       |
| 50–99%                         | 496 (30.7)    | 165 (30.6)                |                       |
| 100%                           | 375 (23.2)    | 101 (18.7)                |                       |
| Beta-blockers                  | 1382 (85.5)   | 419 (77.7)                | <0.001                |
| Mineralocorticoid receptor antagonists |     |                           | 0.485                 |
| Loop diuretics                 | 1610 (99.6)   | 539 (100.0)               | 0.274                 |
| Digoxin                        | 289 (17.9)    | 116 (21.5)                | 0.070                 |
| **Medical history**            |               |                           |                       |
| Myocardial infarction          | 634 (39.2)    | 197 (36.5)                | 0.295                 |
| Coronary artery bypass graft   | 280 (17.3)    | 98 (18.2)                 | 0.695                 |
| Valvular surgery               | 99 (6.1)      | 65 (12.1)                 | <0.001                |
| PCI                            | 369 (22.8)    | 104 (19.3)                | 0.098                 |
| Atrial fibrillation            | 700 (43.3)    | 278 (51.6)                | 0.001                 |
| Stroke                         | 142 (8.0)     | 59 (10.9)                 | 0.158                 |
| Peripheral vascular disease    | 176 (10.9)    | 57 (10.6)                 | 0.904                 |
| Hypertension                   | 1030 (63.7)   | 311 (57.7)                | 0.015                 |
| Smoking                        |               |                           | 0.894                 |
| None                           | 586 (36.3)    | 201 (37.3)                |                       |
| Past                           | 807 (50.0)    | 267 (49.5)                |                       |
| Current                        | 222 (13.7)    | 71 (13.2)                 |                       |
| Diabetes mellitus              | 533 (33.0)    | 148 (27.5)                | 0.020                 |
| COPD                           | 271 (16.8)    | 103 (19.1)                | 0.237                 |
| Renal disease                  | 424 (26.2)    | 171 (31.7)                | 0.016                 |
| Treated thyroid disease        |               |                           | 0.033                 |
| No                             | 1467 (90.7)   | 474 (87.9)                |                       |
| Hypothyroidism                 | 124 (7.7)     | 47 (8.7)                  |                       |
| Hyperthyroidism                | 26 (1.6)      | 18 (3.3)                  |                       |
| Current malignancy             | 60 (3.7)      | 20 (3.7)                  | 0.999                 |
| **Heart failure aetiology**    |               |                           |                       |
| Hypertension                   | 171 (10.8)    | 48 (9.0)                  | 0.266                 |
| Cardiomyopathy                 | 401 (25.3)    | 132 (24.7)                | 0.817                 |
| Valvular disease               | 110 (6.9)     | 59 (11.0)                 | 0.003                 |
Table 1 (Continued)

|                         | Q1–3 combined | Q4 | P-value (Q1–3 vs. Q4) |
|-------------------------|---------------|----|-----------------------|
| **Clinical profile**    |               |    |                       |
| Bibasilar rales/crackles| 600 (38.2)    | 226 (43.0) | 0.058                 |
| Peripheral oedema       |               |    | <0.001                |
| Not present             | 574 (43.5)    | 153 (32.2) |                       |
| Ankle                   | 404 (30.6)    | 125 (26.3) |                       |
| Below knee              | 273 (20.7)    | 136 (28.6) |                       |
| Above knee              | 70 (5.3)      | 61 (12.8) |                       |
| Elevated JVP            | 339 (31.3)    | 129 (37.7) | 0.033                 |
| Hepatomegaly            | 202 (12.5)    | 104 (19.4) | <0.001                |
| Third heart tone        | 156 (9.7)     | 55 (10.3) | 0.754                 |
| Orthopnoea              | 532 (33.0)    | 215 (40.0) | 0.004                 |
| Dyspnoea VAS score      | 50 ± 22       | 44 ± 23 | 0.012                 |

| **Laboratory values**   |               |    |                       |
| Angiotensin-converting enzyme 259 | 5.19 (0.70) | 5.65 (0.76) | <0.001                |
| Haemoglobin (g/dL)       | 13.3 [11.9–14.5]| 13.4 [12.0–14.6]| 0.299                |
| Haematocrit (%)          | 40 [36–43]    | 41 [37–44] | 0.014                 |
| Serum creatinine (μmol/L)| 101 [83–127]  | 106 [86–141] | 0.004                |
| Urea (mmol/L)            | 11.0 [7.4–17.4]| 12.1 [8.0–19.9]| 0.006                |
| Sodium (mmol/L)          | 140 [137–142] | 139 [136–141]| <0.001                |
| Potassium (mmol/L)       | 4.2 [3.9–4.6] | 4.2 [3.9–4.6] | 0.125                |
| NT-proBNP (ng/L)         | 2469 [1098–5340]| 3333 [1520–6513]| <0.001                |
| AST (U/L)                | 24 [18–32]    | 32 [25–46] | <0.001                |
| ALT (U/L)                | 24 [16–35]    | 28 [20–47] | <0.001                |
| Alkaline phosphatase (μg/L)| 81 [63–112]  | 89 [70–128] | <0.001                |
| Gamma-GT (U/L)           | 47 [26–91]    | 81 [42–133] | <0.001                |
| Total bilirubin (μmol/L) | 13 [9–20]     | 18 [12–27] | <0.001                |
| TSH (mU/L)               | 1.85 [1.16–3.00]| 2.00 [1.32–3.20]| 0.085                |
| Glucose (mmol/L)         | 6.3 [5.4–8.0] | 6.1 [5.2–7.6] | 0.011                |
| Triglycerides (mmol/L)   | 1.2 [0.9–1.7] | 1.1 [0.9–1.5] | 0.002                |
| Total cholesterol (mmol/L)| 4.1 [3.4–5.0] | 3.9 [3.2–4.8] | <0.001                |
| HDL cholesterol (mmol/L) | 1.1 [0.9–1.3] | 1.0 [0.8–1.3] | 0.005                |
| LDL cholesterol (mmol/L) | 2.5 [1.8–3.2] | 2.4 [1.7–3.0] | 0.111                |
| bio-ADM (pg/mL)          | 33.7 [22.5–54.0]| 40.9 [26.9–74.8]| <0.001                |
| Troponin T (μg/L)        | 0.03 [0.02–0.06]| 0.03 [0.02–0.06]| 0.535                |
| Aldosterone (pg/mL)      | 88 [44–179]   | 116 [46–241] | <0.001                |
| Renin (IU/mL)            | 78.3 [26.3–227.7]| 120.7 [34.74–338.9]| <0.001                |
| FGF-23 (RU/mL)           | 192.0 [110.0–453.4]| 377.2 [155.1–1308.8]| <0.001                |
| Osteopontin (ng/mL)      | 211 [175–252] | 237 [190–285] | <0.001                |
| GDF-15 (pg/mL)           | 2535 [1616–4038]| 3647 [2041–6289]| <0.001                |
| CA-125 (U/mL)            | 36.1 [15.6–108.4]| 69.9 [21.6–201.2]| <0.001                |

Variables with a normal distribution are displayed as mean ± standard deviation; variables with a non-normal distribution as median [interquartile range]; and categorical variables as n (%).

ACE-i, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; bio-ADM, biologically active adrenomedullin; CA-125, cancer antigen-125; COPD, chronic obstructive pulmonary disease; DPP3, dipeptidyl peptidase 3; FGF-23, fibroblast growth factor-23; GDF-15, growth differentiation factor-15; GT, glutamyl transferase; HDL, high-density lipoprotein; JVP, jugular venous pressure; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TSH, thyroid stimulating hormone; VAS, visual analogue scale.

*ACE2 values are reported in relative quantification, meaning the value depicted is not an absolute concentration, but a concentration relative to the rest of the BIOSTAT-CHF index cohort.

function in an acute HF mouse model. Procizumab might therefore serve as a potential AAM activating therapy that could amplify the beneficial effects of RAAS blockers.

This study has several strengths and limitations. To our knowledge, this is the first study on DPP3 levels in HF. The large number of subjects as well as the number of biomarkers available allow for adequate positioning of DPP3 in HF. One limitation is that we could not correct for low-grade haemolysis, even though macroscopic haemolytic samples (n = 158, mean DPP3 30.6 ng/mL) were excluded. While we expect haemolysis to increase DPP3 concentrations, we could not verify this as reticulocytes, lactate dehydrogenase and haptoglobin were not available in our cohort. Another
Important limitation is the fact that concentrations of circulating DPP3 were very low in general, meaning that the hypothesized effects might be modest in patients with chronic HF. In addition, several studies have shown effects of DPP3 to be related to degradation of AngII. We cannot say with certainty whether in chronic HF DPP3 (antagonism) will affect AngII or Ang(1–7); however, given the relationship with outcome in our study, we consider an effect on the AAM axis to be more likely.

Conclusion

Dipeptidyl peptidase 3 is an enzyme that counteracts the antagonistic AAM pathway of the RAAS system. Predictors of DPP3 concentrations were related to either cell decay or to the RAAS system. Higher OPN, FGF-23 and aldosterone levels indicate more disease severity and suggest a deleterious role for DPP3 by counteracting the Mas receptor pathway. DPP3 was univariately associated with worse outcomes, but significance was lost after correction for confounders. Future research is warranted to further investigate the potential of DPP3 as an actionable biomarker in HF, alongside classic RAAS inhibitors. Prociuzimab, a specific antibody against DPP3, might be a potential future treatment option for patients with HF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

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