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Metformin treatment may be associated with decreased levels of NT-proBNP in patients with type 2 diabetes

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ABSTRACT

Purpose: Individuals with type 2 diabetes (T2DM) are at increased risk of cardiovascular disease, including heart failure (HF). In patients with T2DM elevated serum concentrations of the N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) correlate with cardiovascular morbidity and mortality. We aimed to identify predictors of increased serum NT-proBNP levels in patients with T2DM.

Methods: The study included 185 patients with T2DM treated with either oral antidiabetic agents (49.7%) or insulin (17.8%), or both (32.5%). We divided the patients into two groups: with high (>200 pg/mL) and low (≤200 pg/mL) NT-proBNP concentrations.

Results: We found differences between the patients with high and low NT-proBNP levels including age, prevalence of dyslipidemia and HF, history of previous myocardial infarction (MI), heart rate, hemoglobin level, platelet count, creatinine, urea and uric acid concentrations, use of beta-blockers, loop diuretics, metformin and insulin. In a multivariate analysis metformin was a negative predictor of increased NT-proBNP concentration. Age, history of HF and decreased estimated glomerular filtration rate (eGFR) were positive predictors. We found no correlation between NT-proBNP serum concentration and insulin treatment or history of coronary artery disease or MI.

Conclusion: Metformin correlates with lower concentrations of NT-proBNP in patients with T2DM.

Key words: Heart failure, coronary artery disease, atherosclerosis, insulin, biguanide.

INTRODUCTION

The prevalence of obesity and type 2 diabetes mellitus (T2DM) continues to grow and by 2030 is predicted to affect over 360 million individuals worldwide or 4.4% of the estimated global population [1]. Because of its impact on cardiovascular morbidity and mortality, T2DM is considered to be equivalent to cardiovascular disease [2]. Individuals with T2DM are at increased risk for coronary artery disease (CAD), myocardial infarction (MI) and, consequently, heart failure (HF) [3]. T2DM is therefore considered as stage A of chronic heart failure (CHF) in the American College of Cardiology/American Heart Association (ACC/AHA) classification [4]. Poor prognosis in patients with end-stage HF is comparable to the prognosis in patients with malignancy, and therefore early identification of patients at risk is of critical importance [5]. In patients with T2DM this could be potentially facilitated by measuring N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP), as the measurement of NT-proBNP has been useful in the prognostic evaluation of patients at an early stage (A or B) of CHF [6].

Thus, the aim of this study, was to assess serum NT-proBNP concentrations in patients with T2DM in order to identify clinical and biochemical factors associated with increased levels of this biomarker in entirely diabetic population.

MATERIALS AND METHODS

This is a preliminary, exploratory analysis of the results from the AVOCADO (Aspirin Vs/Or Clopidogrel in Aspirin-resistant Diabetics inflammation Outcomes Study), a multi-center, prospective, randomized, open-label study. The local ethics committee of the Medical University of Warsaw approved the study protocol and subjects gave written informed consent. This study was conducted in accordance with the version of the Helsinki Declaration current when the study was designed.

The study subjects were recruited consecutively from T2DM patients presenting to the outpatient clinic of the Central Teaching Hospital of the Medical University of Warsaw. Between January 2007 and October 2008, we screened 642 patients for eligibility and recruited 185 patients with T2DM who had been taking oral antidiabetic agents and/or insulin for at least 6 months. The exclusion criteria included: T2DM managed by diet control alone; age <30 or >80 years; serum creatinine concentration >2.5 mg/dl; chronic renal failure requiring dialysis; symptoms of mild/severe HF (i.e. NYHA class >2); recent history (within 12 months) of MI or unstable angina or coronary angioplasty or coronary artery bypass grafting; history of other major surgical procedures within 8 weeks; acute illness; pregnancy.

We assessed demographic information, medical history, medications, and lifestyle habits by personal interview and a review of the medical charts. All patients presented to the outpatient research unit in the morning (between 7 a.m. and 9 a.m.) after an overnight fast. Regular laboratory testing was performed using standard laboratory techniques, and included complete blood cell and platelet counts, fasting glycaemia, glycosylated hemoglobin A_{1C}, lipid profile, C-reactive protein, and serum creatinine. Blood pressure was recorded in the supine position at the time of enrollment. Hypertension was diagnosed if one of the following conditions was present: systolic blood pressure ≥130 mmHg and/or diastolic pressure ≥80 mmHg and/or use of at least one antihypertensive medication. Dyslipidemia was diagnosed if total cholesterol was ≥175 mg/dl or triglyceride ≥150 mg/dl or high-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women or if cholesterol lowering medication was used.

Measurements of NT-proBNP

Blood samples for determination of NT-proBNP were taken in the morning, after rest for at least 30 min in the supine position from the antecubital vein, collected in citrated tubes and subsequently were centrifuged and the plasma stored at −80°C until analysis. NT-proBNP was analyzed using the Roche Elecsys® 1010 bench-top analyzer for heterogeneous immunoassay (Roche Diagnostics Inc., Germany). The system involves an ElectroChemiLuminescence (ECL) machine that uses 2 polyclonal antibodies for detecting NT-proBNP. The between-run coefficient of variation for this assay platform ranges from 4.4 to 5.3% [7]. The Roche NT-proBNP assay has previously been validated for precision, specificity, stability, and utility [8]. The subjects were divided into tertiles based on plasma concentrations of NT-proBNP. Individuals in the upper tertile of NT-proBNP concentrations were classified as patients with high NT-proBNP level, and individuals in the lower and middle tertile were classified as patients with low NT-proBNP level.

Statistical analysis

Normally distributed continuous variables were presented as means ± SD, whereas variables with a highly skewed distribution were presented as medians with corresponding range. Categorical variables were presented as frequencies (percentages). Normality of distribution was assessed using histograms and quartile plots. Differences between groups with high and low NT-proBNP concentrations were analyzed using Student's *t*-test, the Mann-Whitney U-test, χ^2 test or Fisher's exact test, as appropriate. All statistical tests were performed at significance level α=0.05 (two-sided). The analysis is exploratory and therefore no formal a priori power analysis was performed.

Associations of selected variables with high NT-proBNP level were analyzed using logistic regression models. Univariate analysis was used to determine the odds ratios (OR), their 95% confidence intervals (CI) adjusted for age and gender and p-values. Multivariate analysis was performed with adjustment for age, gender, CAD status, insulin treatment and variables selected using a stepwise procedure.

RESULTS

Mean ± SD demographic data, concurrent medications and biochemical and hematological parameters for the study population are presented in *Tab. 1*, *Tab. 2* and *Tab. 3*.

The subjects were divided into tertiles based on plasma concentrations of NT-proBNP. Concentrations of NT-proBNP in patients of the lower, middle and upper tertile were <73 pg/mL, 73-200 pg/mL and >200 pg/mL, respectively. Patients of the lower and middle tertile were defined as having low concentration of NTproBNP, and patients of the higher tertile as having high concentration of NTproBNP.

Patients with high NT-proBNP concentrations were older (p<0.001) and had lower prevalence of dyslipidemia (p=0.012), higher prevalence of CAD (p<0.001), history of previous MI (p=0.006), and prevalence of CHF (p<0.001),

Table 1. **Patients characteristics grouped by NT-proBNP concentration – demographic data.**

Characteristics	NT-proBNP (0-200 pg/mL) n=122	NT-proBNP (>200 pg/mL) n=63	p
Age (years)	64.4 ± 8.2	70.2 ± 8.4	**<0.001**
Female	58 (47.5%)	27 (42.9%)	0.641
BMI (kg/m^2)	30.7 ± 5.1	30.2 ± 5.2	0.536
WHR (waist to hip ratio)	0.97 ± 0.10	0.96 ± 0.07	0.666
Waist circumference (cm)	105.1 ± 13.8	105.5 ± 12.4	0.877
Hip circumference (cm)	108.7 ± 12.4	109.6 ± 11.5	0.636
SBP (mmHg)	141.9 ± 17.7	143.9 ± 21.7	0.500
DBP (mmHg)	80.4 ± 11.4	78.6 ± 13.2	0.332
Duration of diabetes (years)	7 (4 - 15)	10 (5 - 18)	0.111
History of smoking	68 (55.7%)	39 (61.9%)	0.437
Current smoking	14 (11.6%)	5 (7.9%)	0.611
Dyslipidemia	108 (88.5%)	46 (73.0%)	**0.012**
Hypertension	109 (89.3%)	57 (90.5%)	1.000
Metabolic syndrome	104 (85.2%)	55 (87.3%)	0.825
CAD	63 (51.6%)	49 (77.8%)	**<0.001**
Prior MI	31 (25.4%)	28 (44.4%)	**0.012**
Prior stroke	7 (5.7%)	6 (9.5%)	0.371
Prior TIA	6 (4.9%)	2 (3.2%)	0.718
CHF	38 (31.1%)	39 (62.9%)	**<0.001**
Chronic renal disease (stage) **1** **2** **3** **4**	 22 (18.2%) 75 (62.0%) 23 (19.0%) 1 (0.8%)	 9 (14.5%) 22 (35.5%) 28 (45.2%) 3 (4.8%)	**0.001**

Variables are presented as means ± SD or medians (interquartile ranges) or frequencies (percentages).
BMI – body mass index; WHR – waist to hip ratio; SBP – systolic blood pressure; DBP – diastolic blood pressure; CAD – coronary artery disease; MI – myocardial infarction; TIA – transient ischemic attack; CHF – chronic heart failure; SD – standard deviation

Table 2. **Patients characteristics grouped by NT-proBNP concentration – concurrent medications.**

Characteristics	NT-proBNP (0-200 pg/mL) n=122	NT-proBNP (>200 pg/mL) n=63	p
Beta-blockers	79 (64.8%)	51 (81.0%)	**0.027**
ACE inhibitors	78 (63.9%)	40 (63.5%)	1.000
Angiotensin receptor blockers	21 (17.2%)	13 (20.6%)	0.556
Aldosterone antagonists	6 (4.9%)	7 (11.1%)	0.136
Loop diuretics	14 (11.5%)	15 (23.8%)	**0.034**
Thiazide diuretics and/or indapamide	39 (32.0%)	24 (38.1%)	0.417
Statins	85 (69.7%)	48 (76.2%)	0.392
Fibrates	17 (13.9%)	8 (12.7%)	1.000
Calcium channel blockers	47 (38.5%)	18 (28.6%)	0.197
Nitrates	6 (4.9%)	5 (7.9%)	0.514
Metformin	89 (73.0%)	29 (46.0%)	**<0.001**
Sulphonylurea derivatives	57 (46.7%)	28 (44.4%)	0.876
Alpha-glucosidase inhibitors	10 (8.2%)	2 (3.2%)	0.226
Insulin	33 (27.0%)	27 (42.9%)	**0.033**

ACE – angiotensin converting enzyme

Table 3. **Patients characteristics grouped by NT-proBNP concentration – biochemical and hematological parameters.**

Characteristics	NT-proBNP (0-200 pg/mL) n=122	NT-proBNP (>200 pg/mL) n=63	p
Hemoglobin (g/dl)	14.0 ± 1.4	13.5 ± 1.3	**0.027**
Hematocrit (%)	41.7 ± 3.7	40.4 ± 3.6	**0.019**
Leukocytes (10^3/mm^3)	7.1 ± 2.1	6.9 ± 1.8	0.621
Platelet count (10^3/mm^3)	237.0± 58.8	218.5± 59.9	**0.046**
Mean platelet volume (fl)	9.8 ± 1.1	9.7 ± 1.2	0.347
Fasting glucose (mg/dl)	126 (80; 383)	128 (85; 224)	0.858
Creatinine (mg/dl)	0.95 ± 0.24	1.14 ± 0.39	**<0.001**
eGFR (mL/min/1.73 m^2)	74.1 ± 18.8	65.1 ± 23.8	**0.011**
Total cholesterol (mg/dl)	167.0 ± 33.9	160.6 ± 38.7	0.244
Triglicerides (mg/dl)	127 (32; 488)	112 (37; 292)	0.056
HDL-cholesterol (mg/dl)	49.0 ± 14.3	48.2 ± 136	0.716
LDL-cholesterol (mg/dl)	87.6 ± 30.1	87.1 ± 32.4	0.918
HbA1c (%)	7.2 ± 1.3	6.9 ± 1.0	0.084
hsCRP (mg/L)	2.8 (0.2; 20.4)	2.6 (0.6; 70.2)	0.847
Fibrinogen (mg/dl)	439.5 ± 101.1	451.1 ± 124.3	0.496

Variables are presented as means ± SD or medians (interquartile ranges).
eGFR – estimated glomerular filtration rate; HDL – high density liprotein; LDL – low density lipoprotein; HbA1c – glycosylated hemoglobin A1c; hsCRP – high sensitive C-reactive protein; SD – standard deviation

Table 4. **Important variables impacting NT-proBNP concentration in an age and gender adjusted logistic regression model**

Variable	Odds ratio	95% CI	p
Age (for 10 years unit)	2.41	1.57-3.63	**<0.001**
BMI (for 5 kg/m^2 unit)	0.91	0.75-1.44	0.800
Male gender	1.41	0.74-2.70	0.301
Hypertension	0.91	0.31-2.73	0.873
Metabolic syndrome	1.51	0.56-4.09	0.414
CAD without previous MI	1.84	0.77-4.42	0.845
CAD post MI	2.94	1.26-6.84	**0.029**
Chronic heart failure	2.95	1.49-5.84	**0.002**
HbA1c (for 2% unit)	0.75	0.42-1.36	0.352
HGB (for 2 g/dl unit)	0.58	0.33-1.03	0.063
PLT (for 50^10^3/mm^3 unit)	0.75	0.57-0.99	0.123
Fibrinogen (for 200 mg/dl unit)	1.21	0.70-2.11	0.975
eGFR <60 mL/min/1.73m^2	3.45	1.66-7.16	**<0.001**
Metformin	0.36	0.18-0.70	**0.003**
Sulphonylurea derivatives	0.82	0.43-1.58	0.562
Insulin	2.08	1.06-4.10	**0.034**
ACE-inhibitors	1.11	0.56-2.20	0.760
Angiotensin receptor blockers	1.36	0.59-3.09	0.468
Aldosterone antagonists	1.82	0.53-6.30	0.345
Loop diuretics	2.19	0.93-5.142	0.073
Calcium channel blockers	0.61	0.30-1.22	0.162
Beta-blockers	2.18	1.01-4.70	**0.047**

BMI – body mass index; MI – myocardial infarction; CAD – coronary artery disease; HGB – hemoglobin; PLT – platelet count; eGFR – estimated glomerular filtration rate; ACE – angiotensin converting enzyme

Table 5. **Important variables impacting NT-proBNP concentration in a multiple logistic regression model.**

Variable	Odds ratio	95% CI	p
Age in years (for 10 years unit)	1.75	1.09-2.80	**0.020**
Male gender	1.99	0.92-4.32	0.082
Chronic heart failure	2.37	1.06-5.30	**0.035**
CAD without previous MI	1.44	0.54-3.80	0.679
CAD post MI	1.52	0.56-4.15	0.679
eGFR <60 mL/min/1.73m²	2.32	1.04-5.20	**0.041**
Metformin	0.45	0.21-0.95	**0.037**
Insulin	1.58	0.74-3.39	0.237

CAD – coronary artery disease; MI – myocardial infarction; eGFR – estimated glomerular filtration rate

and lower heart rate (p=0.009) than patients with low NT-proBNP concentrations (*Tab. 1*). This group of patients more often was on beta-blockers (p=0.027), more often used loop diuretics (p=0.034), less often controlled glycaemia with metformin (p<0.001) and was more often taking insulin (p=0.033) (*Tab. 2*). Among biochemical variables in high NT-proBNP group there were lower hemoglobin levels (p=0.027), and platelet count (p=0.046), higher creatinine and urea levels, lower estimated glomerular filtration rate (eGFR; p=0.011) and higher uric acid level (p=0.006) (*Tab. 3*).

Univariate and multivariate analysis of predictors for high NT-proBNP levels are shown in *Tab. 4* and *Tab. 5*. In a simple logistic regression model adjusted for age and gender, history of MI (p=0.029), CHF in NYHA class ≤2 (p=0.002), increased level of uric acid (p=0.027), insulin (p=0.034) and beta-blockers therapy (p=0.047) were directly related to higher concentrations of NT-proBNP. Only two parameters were found to be directly related to low level of NT-proBNP: metformin treatment (p=0.003) and eGFR higher than 60 mL/min/1.73m² (p=0.003) (*Tab. 4*). In a multiple logistic regression model variables significantly associated with higher levels of NT-proBNP were: CHF (OR 2.37, 95% CI 1.06 to 5.30; p=0.035), older age (for 10 years units of change OR 1.75; 95% CI 1.09 to 2.80; p=0.020), metformin therapy (OR 0.45; 95% CI 0.21 to 0.95; p=0.037) and eGFR <60 mL/min/1.73m² (OR 2.32; 95% CI 1.04 to 5.20; p=0.041) (*Tab. 5*). We have found no significant differences between males and females in NT-proBNP concentrations (OR 1.99; 95% CI 0.92-2.80; p=0.082).

DISCUSSION

In patients with T2DM, cardiovascular disease is the major cause of morbidity and mortality. Such patients develop CAD at an accelerated rate and have a higher incidence of HF, MI, and cardiac death than individuals without T2DM [9]. Managing modifiable risk factors is crucial in patients with T2DM in terms of reducing the risk of cardiovascular events [2].

In a recent cohort study NT-proBNP occurred as a strong predictor of morbidity and cardiovascular mortality in T2DM [10]. In the follow-up period of approximately 15 years, patients with increased values of NT-proBNP showed significantly higher mortality than those with lower values mainly due to cardiovascular deaths. A high level of NT-proBNP also correlates with left ventricular dysfunction [11]. Moreover, Huelsmann et al. [12] reported that low NT-proBNP level is an independent negative predictor for future cardiovascular events in patients with T2DM. In a recent study, Hamano et al. [13] reported that NT-proBNP had a high negative predictive value to exclude silent myocardial ischemia independent of other confounding risk factors.

As it was reported, NT-proBNP is an independent risk factor for mortality in patients with impaired renal function (eGFR <60 mL/min/1.73m²), and heart failure [14]. In presented study, multivariate analysis showed that patients with eGFR <60 mL/min/1.73m² were at more than 2-fold increased risk for higher NT-proBNP levels than subjects with eGFR ≥60 mL/min/1.73m².

Heart and renal failure are considered as contraindications to metformin administration due to the risk of lactic acidosis. This effect is a very rare phenomenon and the rate of lactic acidosis in patients taking metformin is similar to that in placebo controls [15]. In a recent cohort study one-year and long-term mortality among patients with T2DM and HF were lower in patients using metformin than in those taking sulphonylureas and this effect was independent of glycemic control [10]. In our study patients taking metformin had a significantly lower probability of increased NT-proBNP and observation was independent of age, gender, history of HF, CAD and MI or renal function. As metformin is contraindicated in patients with eGFR <30 mL/min/1.73m² none of the 4 patients included in our study who were in 4th stage of chronic kidney disease was taking metformin. None of the study patients was in 5th stage of chronic kidney disease.

Because NT-proBNP is an independent marker of developing HF, it is possible that metformin treatment may decrease rate of remodeling of the left ventricle and thus decrease the risk of heart failure. This hypothesis is consistent with the experimental study of Sasaki et al. [16]

who found, that metformin inhibited cardiac remodeling and prevented the progression of HF in dogs and also increased AMP-activated protein kinase (AMPK) activation and nitric oxide (NO) production. It has been shown that in rodents either AMPK activation [17-19] or NO production attenuates myocardial ischemia/reperfusion injury in the ischemic model and prevents cardiac remodeling in the pressure overload model [20, 21]. In the recent publication Yin et al. [22] demonstrated that metformin reduced infarct size by 22% in an experimental non-diabetic rat model of MI, which resulted in an improvement in left ventricular ejection fraction of 52% compared to placebo. These results may suggest, that metformin may have cardioprotective effect independent of its antihyperglycemic activity.

The main limitation of our study is that it was observational and it is impossible to account for all possible confounding influences. A prospective, randomized trial would provide definitive evidence of the benefits or otherwise of metformin in this group of patients and would help to elucidate the underlying mechanisms.

CONCLUSIONS

The results of our study showed that patients with T2DM treated with metformin had lower concentrations of NT-proBNP than those not treated with biguanid derivative. We postulate that this effect might produce additional beneficial effects on cardiovascular risk and risk of developing HF, which could be independent of antihyperglycemic mechanisms of action of metformin, but this should be confirmed in a prospective, randomized study.

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Statement of competing interests

The authors declare that they have no competing interests. The authors alone are responsible for the content and writing of this paper.

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