

THE PROGNOSTIC IMPORTANCE OF NT PROBNP IN PATIENTS WITH TYPE 2 DIABETES MELLITUS, DIABETIC CARDIOMYOPATHY AND/OR DIABETIC KIDNEY DISEASE

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Abstract

Objectives – The main objective of this study was to analyze the correlation between glycated haemoglobin (HbA1c) and N terminal pro-brain natriuretic peptide (NT proBNP), because of their direct impact on the evolution and prognostic of diabetic cardiomyopathy and/or diabetic kidney disease in patients with type 2 diabetes.

Material and methods – The present study was performed between 2010 - 2011, on a number of 255 patients with known type 2 diabetes, with and without diabetic cardiomyopathy or diabetic kidney disease. The main biological parameters determined by us were NT proBNP and HbA1c. **Results** – The lowest value of HbA1c was found in the group without cardiomyopathy and/or renal disease (8,96%). The average value of NT proBNP was significantly higher in patients with diabetic cardiomyopathy and/or diabetic kidney disease ($p < 0,01$). **Conclusions** – High values of NT proBNP were associated with high values of HbA1c, with an important statistics signification.

key words: type 2 diabetes mellitus, diabetic cardiomyopathy, diabetic kidney disease, NT proBNP, HbA1c

Background and Aims

Diabetes mellitus is a syndrome that generates more and more interesting problems from the medical point of view, due to the disease's evolution and complications' amplitude. Due to the continuous increase of diabetes incidence and prevalence, this disease is currently considered a populational disease [1].

In the same time, type 2 diabetes (T2DM) represents an important cardiovascular risk

factor, involved in the acceleration of cardiomyopathy and atherosclerosis, in fact approximate 75-80% of the diabetic patients dying of cardiovascular diseases [1].

Diabetic cardiomyopathy (DCM) represents a cardiac disease that appears in the absence of coronary artery disease or arterial hypertension. Hyperglycaemia seems to be in the centre of DCM's pathogenesis, leading to a series of maladaptive stimuli which have as a result, myocardial fibrosis and collagen

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deposition [2]. These processes are considered to be responsible for myocardial relaxation alteration, a characteristic which manifests itself through diastolic dysfunction and a subtle systolic dysfunction, echocardiographically visible. DCM's diagnosis requires confirmation elements of the disease's type and severity, as well as elements of exclusion of other aetiologies which may determine ventricular dysfunction in a diabetic patient [2-4].

The neurohormonal profile could represent a screening modality for cardiomyopathy in patients with diabetes that could be detected even from the asymptomatic period with low or moderate diastolic dysfunction. This method could even replace echocardiography, an investigation which requires trained personnel and performant equipment [5]. For that purpose, it was demonstrated that the N terminal pro-brain natriuretic peptide (NT-proBNP) represents a strong prognostic and diagnostic marker in patients suffering of diabetes and DCM, heart failure, silent cardiac ischemia and vascular complications [2, 6-9].

On the other hand, renal disease in diabetes is very frequent, being another major cause of morbidity and mortality. Diabetic kidney disease is the common term for the clinical and morpho-functional kidney manifestations associated with diabetes, and represents the main cause of end stage renal disease in countries with high economic levels. Currently, almost half of the patients from dialysis programs are diabetic patients [10].

According to NKF/KDOQI practice guide from 2007, diabetic kidney disease defines chronic kidney disease (CKD) found in a

patient suffering of diabetes, the term of "diabetic nephropathy" being reserved only for those cases which have been confirmed through renal biopsy puncture [10,11].

The urinary elimination of albumin has always represented the main criterion for the definition and diagnosis of renal disease in diabetes. Though the meaning of microalbuminuria was greatly debated, this still represents a crucial point in understanding the nature of CKD, for two reasons: the appearance of microalbuminuria marks the irreversibility of renal lesions and, on the other hand, its identification, followed by an adequate therapy, may postpone CKD's lesions progression [12].

At present, the most important medical practice guidelines recommend microalbuminuria screening in patients suffering of T2DM, even from the diagnosis, due to its importance for the evolution and prognosis of the disease [10,13,14].

Despite the existent information, concerning the diagnosis aspects raised by DCM and CKD, there are left many unknown facts left.

The aim of our study was to analyze the correlation between glycated haemoglobin (HbA1c) and NT-proBNP, because of their direct impact on the evolution and prognostic of DCM and/or CKD in patients with T2DM.

Material and Methods

The present study is an observational, cross-sectional research, performed between 2010-2011, on a number of 255 patients with known T2DM, with and without DCM or CKD, hospitalized at Clinical County Emergency Hospital Oradea.

Diagnosis of DCM was based on echocardiography and that of CKD was based on the calculation of the glomerular filtration rate (GFR).

Patients were divided into four study groups according to the presence/absence of cardiomyopathy and kidney disease:

- 78 patients: DCM– / CKD– (group 1)
 - 64 patients: DCM– / CKD+ (group 2)
 - 74 patients: DCM+ / CKD– (group 3)
 - 39 patients: DCM+ / CKD+ (group 4)
- (– = without, + = with)

Determination of glycated hemoglobin: HbA1c was measured using an immuno-turbidimetric method, from peripheral venous blood mixed with anticoagulant. The values considered normal in non diabetic subjects are between 4-6%. In diabetics' case the values between 6-7.5% show an excellent metabolic equilibrium [15].

Determination of NT proBNP: for the quantitative determination of NT-proBNP we used the immunoenzymatic dosage in chemiluminescence (CLEIA) method, with a precise release of the result in 17 minutes. The procedure (PATHPASTTMNT-proBNP) is based on the CLEIA and MAGTRATION procedure in which a marked polyclonal antibody anti pro BNP and magnetic particles, embedded in the polyclonal antibody, are mixed.

The reference values for NT-proBNP vary between laboratories. For the method used by us the limit recommended values are:

- < 125 pg / ml in patients under 75 years old
- < 450 pg / ml in patients over 75 years old

Statistical methods: Statistical analysis was done using the EpiInfo, version 6.0, software of the Center of Disease Control and Prevention - CDC (Center of Disease Control and Prevention) Atlanta, adapted to the processing of medical statistics. With Student method (t test) and χ^2 we calculated the averages of parameters, frequency ranges, standard deviations and tests of statistical significance. Averages for different parameters were considered primary data for determining the correlation coefficient (r). Bravais-Pearson correlation coefficient was used to obtain an independent indicator of the units of the two variables, which takes into account the standard deviations for the two sets of variables.

Results

No significant differences between the 4 groups according to gender, origin and age were recorded ($p > 0.05$). The mean duration of diabetes was between 10.6 and 15.1 years (Table 1).

Table 1. Study group characteristics.

	Group 1	Group 2	Group 3	Group 4
Women/Men (%)	53.8/46.2	54.7/45.3	51.4/48.6	51.3/48.7
Rural/urban (%)	46.2/53.8	46.9/53.1	44.6/55.2	43.6/56.4
Mean age (years)	63.6±7.2	66.5±8.4	65.5±6.8	68.0±8.1
Mean duration of diabetes (years)	10.6±3.3	14.8±5.1	13.9±5.8	15.1±6.4

HbA1c values for the four study groups are given in [Figure 1](#).

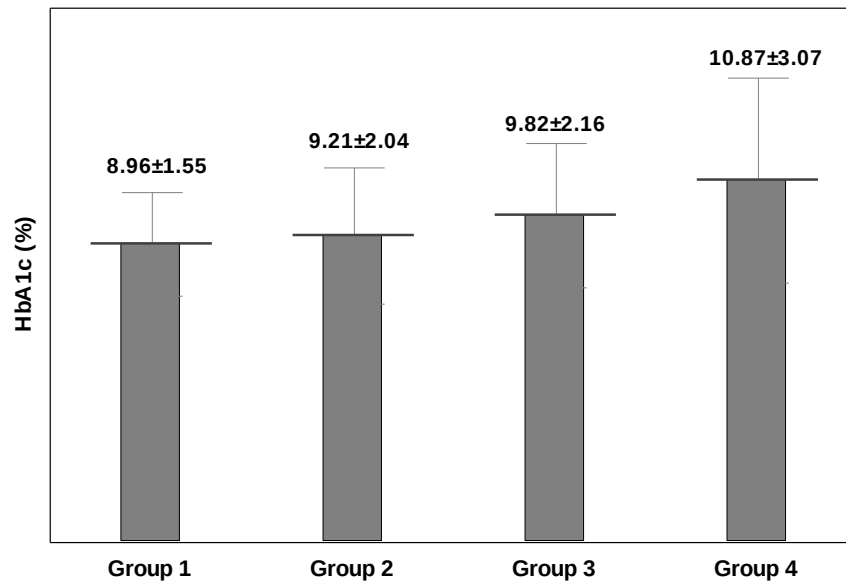


Figure 1. Average values of HbA1c.

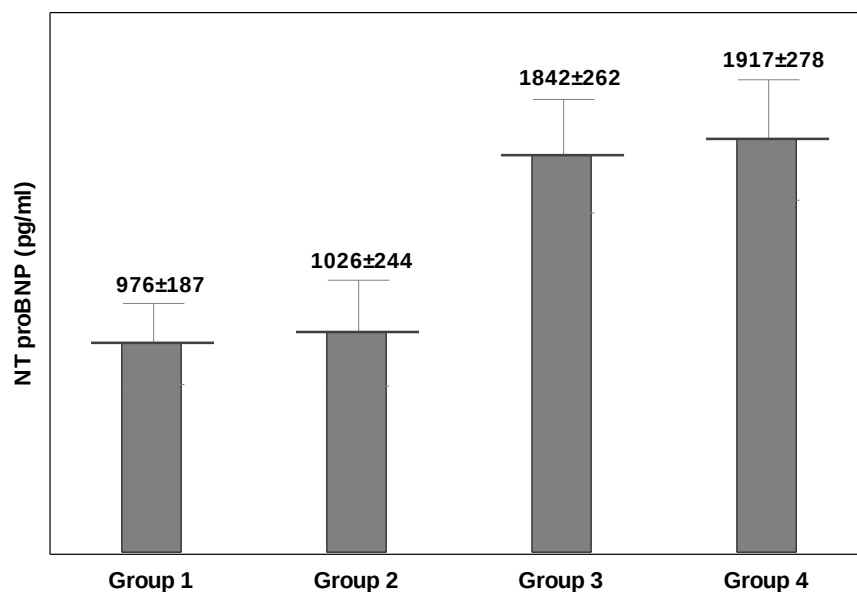


Figure 2. Average values of NT proBNP.

HbA1c varied between 6.12% and 14.53% with a mean of 9.56%, corresponding to a poor metabolic control.

The lowest value of HbA1c was found in the group without DCM and/or CKD (8.96%), significantly lower than in the group suffering

of DCM and CKD (10.87%) ($p=0.046$) ([Figure 1](#)).

NT-proBNP values for the four study groups are given in [Figure 2](#).

NT-proBNP ranged between 276 and 6120 pg/ml the average being of 1384 pg/ml.

As shown in [Figure 2](#), NT-proBNP values were significantly lower ($p<0.01$) in diabetics without DCM or CKD in comparison to those suffering of DCM without CKD (1842 pg/ml) and those with DCM and CKD (1917 pg/ml). NT proBNP values were not significantly

higher in diabetics with renal disease without cardiomyopathy (1026 pg/ml) in comparison with those without DCM and CKD ($p>0.05$).

We determined a direct strong correlation ($r=0.68$) between NT-proBNP and HbA1c, ([Figure 3](#)).

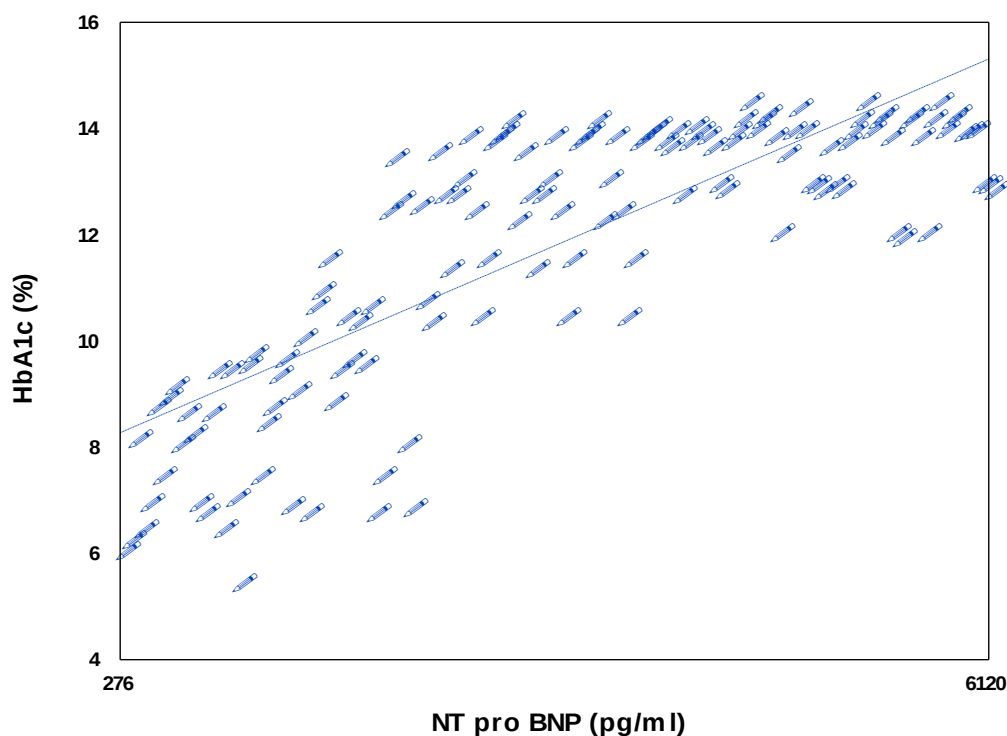


Figure 3. Correlation between NT-ProBNP and HbA1c.

Discussions and Conclusions

Our study indicated a significant correlation between plasma NT-proBNP levels and HbA1c, showing the prognostic importance of NT-proBNP in patients with T2DM, DCM and/or CKD.

The use of NT-proBNP for the assessment of cardiovascular risk is firmly established in cardiovascular guidelines [16,17]. Increased plasma levels of NT-proBNP have been demonstrated to be associated with renal impairment, cardiac arrhythmias, left ventricular dilatation, remodelling and dysfunction [16,18]. Though it is a less

accessible method due to the increased costs (however more accessible than an echocardiographic investigation), NT-proBNP determination shows a great advantage in the early identification of cardiac affection and in the institution of a precocious and efficient management of DCM.

In Tarnows et al. study in patients with T2DM, one of the many observations was that the predictive accuracy of NT-proBNP is independent of the level of albumin excretion rate [16]. The average value of NT-proBNP observed by us in these patients was high in all groups included in the study, but

significantly higher in patients with DCM and/or CKD.

In Huelsmann et al. study, an important observation was that NT-proBNP is the only variable which provides significant independent information irrespective of the chosen population, and all other variables (history of any heart disease, kidney function, LDL-cholesterol, HbA1c) strongly depend on the predefined study population [16]. In our study, the mean value of HbA1c was higher

especially in groups with DCM and/or CKD, while the average value of NT-proBNP was elevated in all 4 groups.

In conclusion, NT-proBNP is an important risk marker for cardiovascular disease, including DCM, in patients with T2DM. Although the present study was conducted over a short period of time and the number of patients was relatively small, our study suggests a direct and strong correlation ($r=0.68$) between NT-proBNP and HbA1c.

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