

The relationship between glycemic control and BNP levels in diabetic patients

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Abstract

Background: *Glycemic control affects cardiovascular risk factors positively. The purpose of this study was to assess B-type natriuretic peptide (BNP) levels in patients with poorly controlled diabetes before and after glycemic regulation was achieved.*

Methods: *The study was performed in a prospective design. The study population consisted of 79 consecutive diabetic patients with poor glycemic control. All subjects underwent transthoracic echocardiography. Levels of fasting plasma glucose, glycosylated hemoglobin (HbA1c), lipid parameters, and BNP were measured before the onset of the treatment and after glycemic regulation was achieved.*

Results: *A significant decrease in BNP (95.0 [4.0–1807] ng/L vs. 52.0 [2.1–987.0] ng/L, $p < 0.001$) levels were observed, after improving glycemic control. The decrease in BNP levels was positively correlated with the decrease in HbA1c ($r = 0.345$, $p = 0.003$) and fasting plasma glucose ($r = 0.366$, $p = 0.002$). There was no correlation between the decrease in BNP levels and lipid parameters ($p = NS$).*

Conclusions: *We conclude that poor glycemic control may cause high levels of BNP which may lead to overdiagnosis of congestive heart failure. We suggest that HbA1c and fasting plasma glucose should be checked in patients with high levels of BNP. (Cardiol J 2014; 21, 3: 252–256)*

Key words: glycemic control, diabetes, BNP, echocardiography, heart failure

Introduction

Glycemic optimization is a crucial part of management in type 2 diabetes. It can be achieved by diet, weight loss, oral anti-diabetics and insulin therapy. Improving glycemic control positively affects cardiovascular risk factors such as plasma lipids, thrombotic markers, and blood pressure [1–4].

B-type natriuretic peptides (BNP) are produced in ventricular cardiomyocytes, and secreted in response to volume expansion or pressure overload. The BNP test is widely used to diagnose preclinical heart disease or to confirm the cardiac etiology in symptomatic patients. BNP can be affected by several extra-cardiac conditions such as rheumatic diseases, pulmonary diseases [5, 6].

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Although there are several studies evaluating the effect of glycemetic control on some biochemical markers such as lipids in diabetic patients, there is a limited number of controversial studies assessing the effect of the glycemetic control on the BNP levels. The aim of this study is to evaluate the relationship between the glycemetic control and the BNP levels.

Methods

The study was performed in a prospective design. The study population consisted of 79 consecutive diabetic patients with poor glycemetic control defined as glycosylated hemoglobin (HbA1c) $\geq 8.5\%$ (69 mmol/mol).

Exclusion criteria were the presence of coronary artery disease, overt heart failure (using Framingham criteria), left ventricular systolic dysfunction (ejection fraction $< 40\%$), pregnancy or lactation, hepatic or renal dysfunction, significant neurological or psychological diseases, inflammatory bowel diseases, and systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and scleroderma. Changes in antihypertensive and anti-lipidemic drugs were exclusion criteria for the study. The study protocol is in accordance with the Declaration of Helsinki. The Local Ethics Committee approved the study protocol. All patients gave their informed consents.

All subjects underwent an initial screening assessment that included a medical history and physical examination. All subjects were hospitalized for the glycemetic regulation. All subjects were administered the same type of analogue insulin treatment (Novomix[®], Novonordisk[®]) for glycemetic regulation. All subjects underwent transthoracic echocardiography before and after insulin treatment. Fasting plasma glucose, HbA1c, lipid parameters, BNP, renal and liver function tests, electrolytes, were obtained at baseline and after 2 weeks of insulin treatment.

Fasting blood samples were obtained by the venipuncture of large antecubital veins of the studied patients without stasis, after a 12-h fast. The samples were then centrifuged immediately; the plasma was separated and stored at -80°C . In order to avoid variation, all samples were studied on the same day and with the same kit. Total cholesterol (Lot No: B540, Konelab) and triglyceride (Lot No: C186, Konelab) were measured with enzymatic colorimetric tests. Low-density lipoprotein-cholesterol (LDL-C) (Lot No: C435, Konelab) and high-density lipoprotein-cholesterol (HDL-C) (Lot No: C136, Konelab) were measured with the homogeneous enzymatic colorimetric test. HbA1c

measurements were performed by ion-exchange high-performance liquid chromatography with Tosoh G7 (Tosoh, Grove City, OH).

The concentrations of BNP were determined with a 2-site sandwich chemiluminescence immunoassay (Lot No.: 22161145, reference No.: 02816634) on the ADVIA[®] Centaur[®] platform (Siemens Healthcare Diagnostic, IL, USA). The ADVIA Centaur BNP assay is a fully automated 2-site sandwich immunoassay using direct chemiluminescent technology, which applies constant amounts of 2 monoclonal antibodies. The first antibody, in the Lite reagent, is acridinium ester labeled monoclonal mouse anti-human BNP F(ab') \times fragment specific to the ring structure of BNP. The second antibody, in the solid phase, is a biotinylated monoclonal mouse anti-human antibody specific to the C-terminal portion of BNP, which is coupled to streptavidin magnetic particles. The limit of detection for this assay was 0.5 ng/L and showed that the within-run and total imprecision coefficient of variation was 3.5%. Values less than 0.5 ng/L were regarded as non-detectable.

Transthoracic echocardiography: Transthoracic echocardiography examination was performed to all subjects by using a System Three (GE Vingmed Ultrasound, Horten, Norway) cardiac ultrasound scanner and 2.5–3.5 MHz transducers.

Echocardiography of the left ventricle: The following parameters were measured from cross-sectional echocardiographic images of the left ventricle: 1) end-diastolic and end-systolic diameter [cm]; 2) fractional shortening (FS %); 3) ejection fraction (EF %).

Doppler echocardiography: Flow velocity indexes were obtained using pulsed and continuous wave Doppler from apical projections, and measurements were made utilizing the software of the ultrasound equipment. Mitral diastolic flow was obtained after the pulsed Doppler sample volume was positioned perpendicularly to the tips of the mitral valve leaflets. The Doppler cursor was then moved towards the left ventricular outflow position, and the sample volume was placed approximately 1 cm proximally to the aortic valve so that it would come in contact with the anterior mitral valve leaflet. Isovolumic relaxation time [ms] was measured as the interval between the end of the aortic click artifact and the onset of mitral inflow waveform.

The following indexes were measured from the mitral and tricuspid valve diastolic wave form: peak early (E) and atrial (A) flow velocities [m/s], E/A ratio of the left ventricular diastolic filling. Heart rate [bpm] was measured from simultaneous electrocardiogram recordings.

Pulsed Doppler tissue echocardiography:

The myocardial velocities of the left ventricle were measured sampling the mitral annulus excursion at lateral sites in the 4-chamber view. Care was taken to keep the ultrasound beam perpendicular to the plane of the annulus in order to minimize the angle between the beam and the direction of annular motion. The width of the sample volume was 3–5 mm. Measurements were focused on the systolic myocardial wave (S'), the early-diastolic (E') and end-diastolic myocardial (A') waves. Usually, several cardiac cycles were acquired and the best 2 consecutive ones were analyzed and averaged.

Statistical methods

Distribution of the continuous variables was determined by the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean ± SD, variables with skew distribution are expressed as median (minimum–maximum), and categorical variables are expressed as percentages. The paired sample t-test was used for normally distributed variables and the Wilcoxon rank-sum test for skew distributed variables. Pearson and Spearman analysis was used to identify correlations between study parameters. For all statistics, a 2-sided p value < 0.05 was considered statistically significant. All analyses were performed with SPSS 10.0 for Windows.

Results

A total of 79 diabetic patients with poor glycemic control were examined. Demographic data, clinical characteristics, and medications are shown

Table 1. Demographic characteristic and medications of subjects.

Characteristic	Patients (n = 79)
Age [years]	60.3 ± 11.3
Female/Male	53/26 (67/33%)
Hypertension	54 (68%)
Medications and treatments:	
Sulfonylurea	18 (23%)
Metformin	52 (66%)
Thiazolidinediones	21 (27%)
Dipeptidyl peptidase-4 inhibitors	20 (25%)

in Table 1. The mean age was 60.3 ± 11.3 years. The majority of patients were female (53; 67%). Mean duration of diabetes was 7.5 ± 3.5 years. Systolic blood pressure and diastolic blood pressure were significantly decreased after improving glycemic control. There was no significant change in heart rate.

All subjects had normal ejection fraction. The transthoracic echocardiographic parameters of subjects are presented in Table 2. No significant difference was found in conventional Doppler and pulsed wave tissue Doppler parameters before and after glycemic control. There was no association between the measured echocardiographic indexes and BNP levels.

Biochemical parameters before and after glycemic control are presented in Table 3. Fasting plasma glucose levels (306.3 ± 119.4 mg/dL vs. 122.5 ± 35.0 mg/dL, p < 0.001), HbA1c levels

Table 2. Conventional and tissue Doppler parameters of subjects before and after glycemic control.

	Baseline	2 weeks of glycemic control	P
Left ventricular end-diastolic diameter [cm]	4.6 ± 0.7	4.5 ± 0.6	NS
Left ventricular end-systolic diameter [cm]	3.1 ± 0.3	3.0 ± 0.2	NS
Left ventricular ejection fraction [%]	66.3 ± 4.7	64.3 ± 5.1	NS
Left ventricular septal wall thickness [cm]	1.1 ± 0.2	1.1 ± 0.2	NS
Left ventricular posterior wall thickness [cm]	1.0 ± 0.1	1.0 ± 0.1	NS
E peak [m/s]	0.72 ± 0.11	0.76 ± 0.13	NS
A peak [m/s]	0.37 ± 0.18	0.41 ± 0.23	NS
E deceleration time [ms]	209.1 ± 31.4	205.4 ± 28.1	NS
Isovolumic relaxation time [ms]	91.3 ± 12.8	89.9 ± 11.4	NS
Mitral early diastolic annular velocity of lateral wall (E') [cm/s]	12.6 ± 2.5	13.1 ± 3.2	NS
Mitral late diastolic annular velocity of lateral wall (A') [cm/s]	9.1 ± 2.1	8.4 ± 2.7	NS
Mitral peak systolic annular velocity of lateral wall (S') [cm/s]	12.5 ± 2.7	11.7 ± 2.6	NS

Table 3. Biochemical and clinical parameters before and after glycemetic control.

	Baseline	2 weeks of glycemetic control	P
Systolic blood pressure [mm Hg]	128.2 ± 9.8	122.0 ± 2.5	< 0.001
Diastolic blood pressure [mm Hg]	82.0 ± 7.8	77.0 ± 2.5	< 0.001
Heart rate [bpm]	72.6 ± 10.4	72.8 ± 11.2	NS
Fasting plasma glucose [mg/dL]	306.3 ± 119.4	122.5 ± 35.0	<0.001
Triglyceride [mg/dL]	199.5 ± 118.4	168.7 ± 92.2	< 0.001
Total cholesterol [mg/dL]	227.2 ± 47.3	207.2 ± 45.2	< 0.001
Low density lipoprotein-cholesterol [mg/dL]	151.3 ± 34.3	139.8 ± 27.8	< 0.001
High density lipoprotein-cholesterol [mg/dL]	42.7 ± 13.7	42.2 ± 14.8	NS
Gama glutamyl transferase [U/L]	32.3 ± 22.0	28.4 ± 13.0	NS
Alanine aminotranferease [U/L]	21.7 ± 8.5	22.6 ± 9.7	NS
Aspartate aminotransferase [U/L]	22.2 ± 7.6	21.6 ± 9.9	NS
Creatinine [mg/dL]	0.97 ± 0.42	0.96 ± 0.48	NS
Glycosylated hemoglobin [%]	12.1 ± 2.7 (109 ± 6)	11.0 ± 2.5 (86 ± 4)	< 0.001

(12.1 ± 2.7% [109 ± 6 mmol/mol] vs. 11.0 ± 2.5% [86 ± 4 mmol/mol], $p < 0.001$), total cholesterol (227.2 ± 47.3 mg/dL vs. 207.2 ± 45.2 mg/dL, $p < 0.001$), LDL-C (151.3 ± 34.3 mg/dL vs. 139.8 ± 27.8 mg/dL, $p < 0.001$), triglyceride (199.5 ± 118.4 mg/dL vs. 168.7 ± 92.2 mg/dL, $p < 0.001$) levels were significantly decreased, after improving glycemetic control. There was no significant change in HDL-C (42.7 ± 13.7 mg/dL vs. 42.2 ± 14.8 mg/dL, $p = \text{NS}$) levels.

A significant decrease in BNP (95.0 [4.0–1807] ng/L vs. 52.0 [2.1–987.0] ng/L, $p < 0.001$) levels was observed after improving glycemetic control. Distribution of BNP levels before and after treatment is shown in Figure 1. The decrease in BNP levels was positively correlated with the decrease in HbA1c ($r = 0.345$, $p = 0.003$) and fasting plasma glucose ($r = 0.366$, $p = 0.002$). There was no correlation between decrease in BNP levels and lipid parameters and blood pressure ($p = \text{NS}$).

Discussion

In this study, after glycemetic control was achieved, significant decrease in BNP and lipid levels was observed. To the best of our knowledge, this is the first clinical study demonstrating the effect of glycemetic control on BNP measurements.

In the previous studies, glycemetic control affects lipids positively [3, 4]. Sánchez-Quesada et al. [1] reported that optimizing glycemetic control in patients with type 2 diabetes promotes atheroprotective changes, including larger LDL size, decreased electronegative LDL, and a higher proportion of Lp-PLA2 activity in HDL. Wagner et

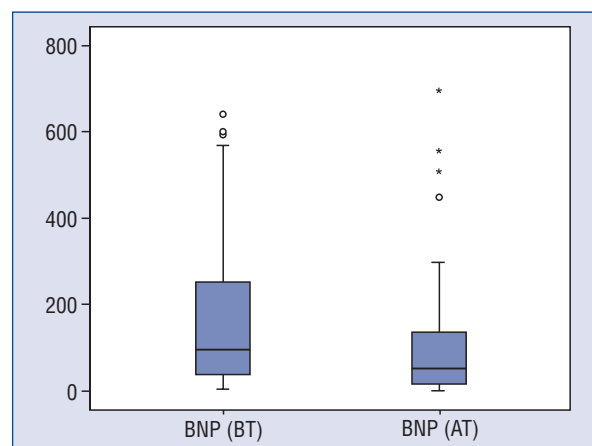


Figure 1. Distribution of B-type natriuretic peptide (BNP) levels before and after glycemetic control; BNP (BT) — BNP levels before treatment; BNP (AT) — BNP levels after treatment.

al. [2] demonstrated that improvement of glycemetic control in type 2 diabetes improves most of the components of diabetic dyslipidemia, including a shift towards larger LDL particles in subjects with phenotype B.

Chronic heart failure (CHF) has been shown to be related to diabetes mellitus (DM). Diabetics have an increased risk of developing heart failure [7], and CHF is an independent risk factor for the development of DM [8, 9]. Cardiac functions are also associated with impairment of glucose metabolism [10]. The mechanisms underlying the relation between DM and CHF have not been fully elucidated.

There are very few studies investigating the effect of hyperglycemia on BNP levels. In an experimental study, after 2 and 4 months of diabetes db/db mice developed changes indicative of cardiac failure, and their myocardium showed increased mRNA expression of atrial and BNPs [11]. Treatment with macitentan (dual endothelin receptor antagonist) prevented from such abnormalities. Ortola et al. [12] found elevated atrial natriuretic peptide (ANP) concentrations in diabetic rats and they observed reduced glomerular filtration rate after infusion of ANP in diabetic rats. They concluded that elevated endogenous ANP levels contribute to the hyperfiltration observed in early diabetes in the rats [12].

Ciftel et al. [13], investigated the NT-proBNP levels in DM and control groups. They found significantly higher NT-proBNP levels in the diabetics with left ventricular diastolic dysfunction (LVDD) than the diabetics without LVDD, and normal controls. The mean NT-proBNP levels in the diabetics without LVDD were higher (albeit not significant) than in the control group. In another study with type 1 DM, glucose infusion caused elevation of ANP, but not BNP levels. They also showed in another study that plasma concentrations of ANP and BNP were elevated in patients with type 1 DM [14, 15]. Similarly to our study, they also found that plasma BNP concentrations were related to HbA1c. The same group has also demonstrated that BNP infusion can induce microalbuminuria in type 1 DM. In another study, BNP was found to be related to HbA1c and QUICKI insulin sensitivity index in CHF patients [3].

The reason of the relation between BNP and hyperglycemia is not obvious. Hyperglycemia may be inducing dysfunction of the cardiac myocytes, and/or plasma glucose per se, may be inducing the secretion of cardiac natriuretic peptides. Endoplasmic reticulum stress associated with DM leads to cardiac myocyte apoptosis and cardiomyopathy as well [16, 17]. Endoplasmic reticulum stress may be the link between elevated BNP secretion and DM.

Conclusions

We demonstrated a significant decrease in BNP and lipid levels by achieving glycemic control. This finding emphasizes the importance of glycemic control in diabetic patients. Poor glycemic control may cause high BNP measurements which can lead to overdiagnosis of CHF. We suggest that HbA1c and fasting plasma glucose should be checked in diabetic patients with high levels of BNP.

Conflict of interest: none declared

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