

Correlation of the myocardial performance index with plasma B-type natriuretic peptide levels in type 2 diabetes mellitus and impaired glucose tolerance

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Abstract

Background and aim: In this study, we aimed to evaluate myocardial functions in patients with diabetes mellitus (DM) and impaired glucose tolerance (IGT). We also aimed to investigate the relationship between B-type natriuretic peptide (BNP) levels and myocardial performance index (Tei index) in these patients.

Methods: A total of 38 patients with DM, 34 patients with IGT, and 40 healthy volunteers were recruited to the study. Basal clinical and laboratory findings were recorded. BNP levels of all individuals were measured. Both conventional transthoracic and tissue Doppler echocardiography were performed to all study participants.

Results: B-type natriuretic peptide levels of the diabetic group were greater than in patients with IGT and the control group. BNP levels of the IGT group were also higher than the control group. Myocardial performance index values, measured by both the conventional method and tissue Doppler echocardiography, were significantly higher in the diabetic group than in the control group. There was a significant relationship between myocardial performance index and BNP levels.

Conclusions: Myocardial functions are disturbed in patients with DM and also in patients with IGT. BNP and myocardial performance index can be used in diabetic patients and in patients with IGT to define myocardial dysfunction.

Key words: diabetes mellitus, B-type natriuretic peptide, myocardial performance index, glucose tolerance

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INTRODUCTION

Diabetes mellitus (DM) is a global health problem that affects all age groups. Preventing the complications of DM is crucial as it decreases mortality and morbidity in these patients. Cardiovascular (CV) complications are the most important cause of mortality and morbidity in diabetic patients and are responsible for nearly 75% of deaths from DM [1]. It was shown in the Framingham study that heart failure is encountered

twice as often in diabetic men, and five times more often in diabetic women, compared to non-diabetic individuals [2]. Impaired glucose tolerance (IGT) is the last stage before overt diabetes and there are many important clues showing that the development of CV complications may precede the development of overt diabetes.

B-type natriuretic peptide (BNP) level increases in the presence of both symptomatic and asymptomatic left ventri-

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cular (LV) dysfunction. It has been shown in recent studies that BNP levels are increased in patients with diabetic complications [3, 4].

Myocardial performance index (MPI) gives information about the global performance of LV by evaluating the diastolic and systolic functions of the LV. It has been shown that MPI can predict the major CV end-points [5].

Our aim in this study was to evaluate the relationship between BNP and MPI, and to test their power as a screening test for LV dysfunction in diabetic patients and patients with IGT. Beside this, we also evaluated the BNP levels and MPI of patients with IGT.

METHODS

Patient selection

Diabetic patients or patients with IGT who had been admitted to our cardiology or endocrinology outpatient clinics were included in the present study. The control group was established from healthy volunteers. Informed consent was obtained from all patients, and the study was approved by the local ethics committee.

Exclusion criteria were: heart failure, coronary artery disease, moderate or severe heart valve disease, history of cardiomyopathy, hypertension, chronic renal failure, ischaemic changes or presence of right or left bundle branch block in ECG, presence of angina pectoris, ejection fraction smaller than 55%, atrial fibrillation, usage of tiazolidinedion group oral antidiabetic drugs, and insufficient image quality.

For coronary artery disease, angina or angina equivalent complaints, ischaemic changes on ECG, positive stress test or the presence of coronary lesions including plaques in coronary angiography were accepted as diagnostic criteria.

Hypertension was defined as systolic blood pressure equal to or more than 140 mm Hg and/or diastolic blood pressure of more than 90 mm Hg measured on least two different occasions or a history of usage of antihypertensive medication.

Fasting blood glucose (FBG) levels exceeding 126 mg/dL and/or blood glucose levels higher than 200 mg/dL (obtained randomly or during the second hour of an oral glucose tolerance test [OGTT]) were used for the diagnosis of DM. Blood glucose levels between 140–199 mg/dL at the second hour of OGTT was accepted as IGT, and FBG levels between 100–125 mg/dl was accepted as impaired fasting glucose.

Laboratory investigation

Venous blood samples were obtained from all individuals for the evaluation of serum creatinine, blood urea nitrogen (BUN), haemoglobin (Hb), albumin, total cholesterol, triglyceride (TG), high density lipoprotein cholesterol, low density lipoprotein cholesterol, FBG, postprandial blood glucose (PPBG) and HbA1c levels. Blood samples were taken after at least eight hours of fasting, between 8 a.m. and 10 a.m. and collected in empty tubes and also in ethylenediamin tetraacetate (EDTA)

containing tubes. Within 20 minutes, samples were centrifuged at 3,000 rpm/min for five minutes. After the separation of serum samples, all analyses were performed. Microalbumin level at 24-hour urine sample was also measured in all patients.

To measure serum BNP levels, commercially available BNP enzyme immune assay (EIA) kits (Phoenix Europe GmbH, Karlsruhe, Germany) were used. Blood samples that had been taken in tubes with EDTA were also centrifuged at 3,000 rpm/min for five minutes and, after the separation of plasma samples, they were stored at -80°C for analysis. The BNP levels of all samples were measured by the ELISA (enzyme linked immunosorbent assay) method.

Echocardiographic examination

After detailed clinical examination, ECG of all patients were obtained in the resting supine position. Thereafter, echocardiographic images were obtained from all individuals by a Vivid 7 (General Electric Company, Indianapolis, IN, USA) echocardiography machine with a probe working at 1.5–4.5 MHz frequencies.

Standard parasternal long axis and apical four-chamber images were obtained in the left lateral decubitus position. Ejection fraction of LV was calculated according to Modified Simpson's rule. For the evaluation of mitral Doppler signals, recordings were obtained by pulsed wave Doppler sample volume below aortic valve and also at mitral valve tips, in the apical four-chamber plane. At all cardiac cycles, early diastolic filling velocity (E wave), diastasis periods, and late diastolic filling velocity (A wave) were measured, and the ratio of these periods (E/A) was calculated. E wave deceleration time (EDT) was also measured.

Isovolumic contraction time (ICT), isovolumic relaxation time (IVRT), and ejection time (ET) were measured. By dividing the sum of the isovolumic time period (ICT + IVRT) by ET, MPI was calculated.

In the apical four-chamber plane, tissue Doppler sample volume was placed to septal and lateral sides of mitral annulus and measurements were done. At the annulus level of septal and lateral walls, in order, early diastolic peak velocity (Em), late diastolic peak velocity (Am) and peak systolic flow velocity (Sm) were measured three times, and afterwards the mean value of these three measurements was calculated. (MPI measured by conventional method is here designated as MPI; MPI measured by tissue Doppler is here designated as MPI').

Statistical analysis

For analysis of results, the SPSS program (Statistical Package for the Social Sciences Program, for Windows 11.0, Chicago, IL, USA) was used. All quantitative parameters were given as mean \pm SD. Data was tested for normal distribution by Kolmogorov-Smirnov test. For comparison of quantitative values, ANOVA test was used. For testing the relationship between

en parameters in normally distributed parameters, Pearson test was used, and for parameters that were not distributed normally, Spearman's correlation test was used. To test the relationship between MPI and BNP, univariate and multivariate regression models were used. To find the optimal values for BNP and MPI to detect myocardial dysfunction, receiver operating characteristics (ROC) curve was used. Diastolic dysfunction marker was accepted as E/A < 1. Statistical significance was accepted as a p value of < 0.05.

RESULTS

Thirty eight patients with type 2 DM and 34 patients with IGT were included in the present study. The control group comprised 40 healthy volunteers. Basal characteristics of patients are summarised in Table 1. Mean diabetes duration was 9.6 years in the diabetic group. The BNP levels were lowest in the control group and highest in the DM group, and the differences between groups were statistically significant (37 ± 16 , 62 ± 19 and 76 ± 29 , $p < 0.001$).

Echocardiographic findings of patients are shown in Table 2. MPI values were highest in the DM group and lowest in the control group, and the difference was significant between all three groups ($p < 0.001$). The MPI' values were also significantly different between all three groups, which were highest in the DM group and lowest in the control group ($p < 0.001$).

In order to evaluate the relationship between BNP and mean MPI' with each other and with the other parameters, a new group made up of IGT and DM patients was formed and correlation analysis was performed (Table 3). A significant positive correlation was found between BNP levels and

mean MPI' values in this group (r value: 0.57, $p < 0.001$). It was also shown that both BNP and mean MPI' values had significant relationships with EDt, E/E' and MPI values.

In this new group, there was a relationship between age and BNP levels, but not with MPI' values. Although there was a relationship between FBG, PPBG and HbA1c with mean MPI', for BNP there was only a relationship with HbA1c. No relationship was found between LV mass index (LVMI) with BNP or with mean MPI' values.

When correlation analysis was performed, a positive correlation between BNP levels and mean MPI' values persisted in the diabetic group (r value: 0.51, $p = 0.039$). Similar results were obtained with patients belonging to the IGT group (r value: 0.56, $p = 0.02$). In univariate and multivariate regression analysis, it was shown that the relationship between MPI and BNP was independent (OR 1.557; 95% CI 1.025–2.364; $p = 0.038$).

In ROC curve analysis, the value for MPI' to detect diastolic dysfunction, with a sensitivity of 71% and specificity of 55%, was 0.54 (Fig. 1). The area under curve was 0.673. The value for BNP to detect diastolic dysfunction, with a sensitivity of 70% and specificity of 46%, was 52 pg/mL (Fig. 2). The area under curve was 0.620.

DISCUSSION

Our study showed that LV diastolic function can deteriorate before the development of overt diabetes, even in the IGT period. The significant relationship between echocardiographic parameters and BNP supports our hypothesis.

In diabetic patients, LV dysfunction can be present despite the absence of coronary artery disease or hypertension.

Table 1. Basal clinical characteristics of patients

	Control (n = 40)	IGT (n = 4)	DM (n = 38)	P
Age	53.0 ± 7.6	54.7 ± 1.6	58.3 ± 9.8	0.046*
Male	40%	38%	50%	NS
BMI [kg/m ²]	27.7 ± 5.4	29.8 ± 4.5	29.1 ± 4.8	NS
Haemoglobin [g/dL]	13.5 ± 1.3	13.6 ± 1.5	13.8 ± 1.4	NS
FBG [mg/dL]	93 ± 1	109 ± 11	147 ± 61	< 0.001#*
PPBG [mg/dL]	107 ± 21	166 ± 14	197 ± 53	< 0.001##^
HbA1c [%]	4.7 ± 0.6	5.4 ± 0.7	7.1 ± 1.1	< 0.001##^
Creatinine [mg/dL]	0.9 ± 0.2	0.8 ± 0.1	1.0 ± 0.2	NS
LDL-C [mg/dL]	114 ± 37	130 ± 32	124 ± 53	NS
HDL-C [mg/dL]	42 ± 10	43 ± 12	44 ± 11	NS
TG [mg/dL]	111 ± 66	179 ± 88	177 ± 80	0.014*^
MA [mg/day]	Was not measured	24.6 ± 17	36.4 ± 41	NS
BNP [pg/mL]	37 ± 16	62 ± 19	76 ± 20	< 0.001##^

#DM and IGT, *DM and control group, ^ IGT and control group; IGT — impaired glucose tolerance; DM — diabetes mellitus; BMI — body mass index; FBG — fasting blood glucose; PPBG — postprandial blood glucose; LDL-C — low density lipoprotein cholesterol; HDL-C — high density lipoprotein cholesterol; TG — triglyceride; MA — microalbuminuria; BNP — B-type natriuretic peptide

Table 2. Echocardiographic findings of groups

	Control (n = 40)	IGT (n = 34)	DM (n = 38)	P
EF [%]	62.8 ± 4.5	64.2 ± 4.1	64.0 ± 5.0	NS
LVEDD [cm]	4.2 ± 0.4	4.6 ± 0.2	4.5 ± 0.5	NS
LVESD [cm]	2.6 ± 0.5	2.9 ± 0.2	3.0 ± 0.3	NS
Septum [cm]	0.9 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	< 0.001* ^
PW [cm]	0.8 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	< 0.001* ^
LVMI [g/m ²]	68 ± 12	88 ± 14	84 ± 19	< 0.001* ^
Left atrium [cm]	2.9 ± 0.4	3.7 ± 0.4	3.7 ± 0.5	< 0.001* ^
EDt [msn]	179 ± 44	201 ± 47	248 ± 60	< 0.00 #* ^
ICT [msn]	50 ± 12	62 ± 17	81 ± 18	< 0.001#* ^
IVRT [msn]	76 ± 13	93 ± 25	94 ± 18	0.001* ^
ET [msn]	315 ± 47	286 ± 30	279 ± 25	0.008 ^
E/A ratio	1.3 ± 0.4	1.0 ± 0.5	0.8 ± 0.4	0.001* ^
E/E' ratio	7.0 ± 1.6	9.6 ± 4.0	10.6 ± 2.8	< 0.001* ^
MPI	0.40 ± 0.05	0.54 ± 0.18	0.61 ± 0.16	< 0.001#* ^
MPI'	0.50 ± 0.07	0.58 ± 0.12	0.64 ± 0.06	< 0.001#* ^

#DM and IGT,*DM and control group, ^ IGT and control group; IGT — impaired glucose tolerance; DM — diabetes mellitus; EF — ejection fraction; LVEDD — left ventricular end diastolic dimension; LVESD — left ventricular end systolic dimension; PW — posterior wall; LVMI — left ventricular mass index; EDt — E wave deceleration time; ICT — isovolumic contraction time; IVRT — isovolumic relaxation time; ET — ejection time; E' — mean of E' waves obtained from lateral ve septal annulus by tissue Doppler; MPI — mean of myocardial performance index values obtained from lateral ve septal annulus by conventional echocardiography; MPI' — mean of myocardial performance index values obtained from lateral ve septal annulus by tissue Doppler echocardiography

Table 3. Relationship of BNP and mean MPI' with each other and with other parameters in patients with IGT and DM

	BNP		Mean MPI'	
	CC	p	CC	p
Age	0.32	0.03	0.2	0.174
BMI	0.08	0.67	0.09	0.58
FBG	0.18	0.26	0.34	0.03
PPBG	0.27	0.06	0.38	0.02
HbA1c	0.48	0.01	0.49	0.001
EDt	0.57	0.001	0.64	< 0.001
E/A ratio	0.29	0.04	0.12	0.47
E/E' ratio	0.31	0.04	0.45	0.001
LVMI [g/m ²]	0.16	0.52	0.21	0.56
MPI	0.65	< 0.001	0.77	< 0.001
MPI'	0.57	< 0.001	—	—
BNP	—	—	0.57	< 0.001

CC — correlation coefficient; BMI — body mass index; FBG — fasting blood glucose; PPBG — postprandial blood glucose; EDt — E wave deceleration time; LVMI — left ventricular mass index; MPI — myocardial performance index measured by conventional echocardiography; MPI' — myocardial performance index measured by tissue Doppler echocardiography; BNP — B-type natriuretic peptide

Deterioration of LV function can have many causes, such as microvascular disease, myocardial fibrosis and some metabolic changes [6–12]. It has been shown in recent studies that LV diastolic functions can be disrupted before systolic functions [13–15].

In a study performed by Andersen et al. [14] on hypertensive and diabetic patients, it was shown that IVRT of diabetic patients was longer and ET was shorter compared to healthy control subjects. In our study, we found that ICT of the DM group was significantly higher than ICT of the IGT

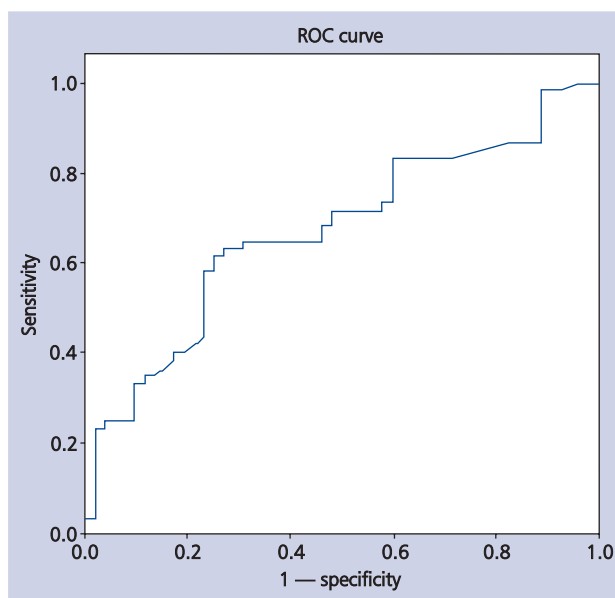


Figure 1. ROC curve analysis of myocardial performance index to detect myocardial dysfunction

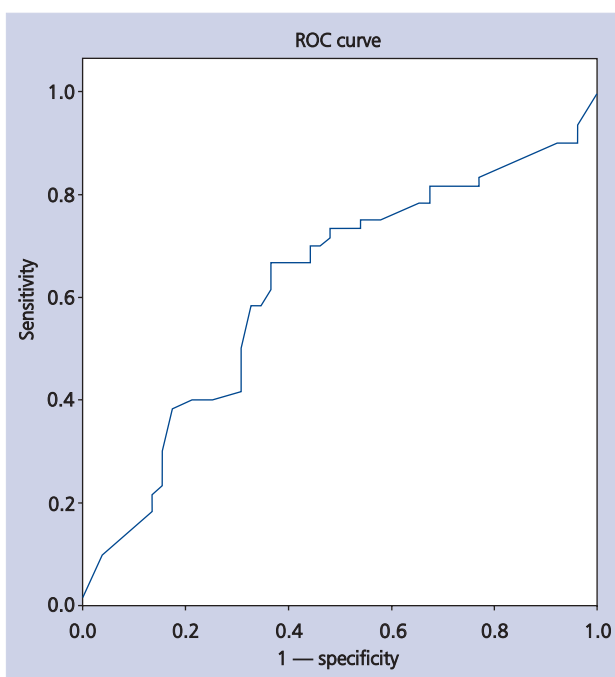


Figure 2. ROC curve analysis of B-type natriuretic peptide to detect myocardial dysfunction

group and there were significant differences in ICT, IVRT and ET values in diabetic patients compared to the control group, which showed us that there were both systolic and diastolic LV dysfunction in diabetic patients. Because the diabetic patients in our study were older and their disease duration was

longer, and because these two parameters are closely related with systolic dysfunction, it could be that the difference of ICT and ET in diabetic patients compared to the control group is caused by these two parameters.

There have been some studies conducted on patients with IGT which have focused on LV functions [16–18]. For example, in a study performed by Holzmann et al. [19], it was shown that in IGT patients the Em/Am ratio was significantly correlated with diastolic dysfunction and it was significantly related with FBG, PPBG and HbA1c. In another study by Fujita et al. [20], LVMI of IGT patients were higher than in the healthy control group and smaller than in the diabetic group, as in our study. We showed in our study that E/A and E/E' ratios and EDt, which are sensitive markers of diastolic dysfunction, were significantly different between the IGT group and the control group. But EF, ICT and ET values, which are markers of systolic functions, were not different between groups. These findings can be explained by the deterioration in diastolic functions that precede systolic dysfunction.

There is no definitive data on the exact cause of diastolic dysfunction in IGT patients. Henareh et al. [21] conducted a study on patients with impaired glucose metabolism and found a negative relationship between E'/A' and TG values. Higher TG levels in IGT patients compared to normals were significantly related with increased fat and ceramide products in the heart. Both by being harmful to the structural unity of the heart, and also by induction of apoptosis, these products can be related with diastolic dysfunction. In a similar way, glycolisation end products may accumulate in the heart and can worsen diastolic functions and increase LVMI. In our study, in line with previous studies, both TG levels and PPBG levels were significantly higher in patients with IGT compared to the control group. In addition, LVMI was higher in both the DM and the IGT group compared to the control group.

Measurement of BNP is extensively used as a marker for myocardial dysfunction. Lim et al. [22] showed that plasma BNP values were correlated with diastolic parameters and especially with E/E' ratio. Similarly, in our study we showed that there was a significant relationship between BNP and echocardiographic diastolic dysfunction parameters.

To the best of our knowledge, data about BNP levels in IGT patients is scarce. In our study, BNP levels were significantly higher in the IGT group compared to the healthy control group. This finding can be explained by the close relationship with PPBG with micro- and macrovascular organ damages [10, 23, 24]. In addition, in the literature there is no study showing the relationship between BNP and MPI in diabetic patients and in IGT patients. Our study is the first to show this relationship in both IGT and DM patients.

Diastolic dysfunction may develop in the early phase of diabetes, even in the IGT stage. As a result, in patients with

IGT and in diabetic patients, BNP and MPI can be used as a marker of myocardial dysfunction. We think that, although only BNP or only MPI is insufficient to give an idea about myocardial dysfunction, the relationship between these two parameters can be helpful in identifying the problem.

Limitations of the study

The relatively small number of patients included in the present study may be its most important limitation. The most important reason for the small number is the exclusion of hypertensive patients from our study.

CONCLUSIONS

Myocardial functions are disturbed in patients with DM and also in patients with IGT. BNP and myocardial performance index can be used in diabetic patients and in patients with IGT to define myocardial dysfunction.

Conflict of interest: none declared

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Korelacje między wskaźnikiem czynności mięśnia sercowego i osoczym stężeniem peptydu natriuretycznego typu B u chorych na cukrzycę typu 2 lub z nieprawidłową tolerancją glukozy

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Streszczenie

Wstęp i cel: Niniejsze badanie przeprowadzono w celu oceny czynności mięśnia sercowego u chorych na cukrzycę (DM) i u osób z nieprawidłową tolerancją glukozy (IGT) oraz ustalenia zależności między stężeniem peptydu natriuretycznego typu B (BNP) w osoczu i wskaźnikiem czynności mięśnia sercowego (wskaźnik Tei) u tych chorych.

Metody: Do badania włączono 38 chorych na DM, 34 osoby z IGT i 40 zdrowych ochotników. Zgromadzono dane z wyjściowego badania klinicznego i wyniki badań laboratoryjnych. U wszystkich uczestników zmierzono stężenie BNP w osoczu oraz przeprowadzono badanie echokardiograficzne, zarówno konwencjonalne przezklatkowe, jak i z zastosowaniem tkankowego doplera.

Wyniki: Stężenie BNP w osoczu było wyższe u chorych na DM niż u osób z IGT i w grupie kontrolnej. Z kolei u osób z IGT stężenie BNP było wyższe niż w grupie kontrolnej. Wartości wskaźnika Tei, oznaczonego zarówno techniką echokardiografii konwencjonalnej, jak i tkankowego doplera, były istotnie wyższe u chorych na DM niż w grupie kontrolnej. Stwierdzono istotną zależność między wskaźnikiem Tei a stężeniem BNP w osoczu.

Wnioski: U chorych na DM i u osób z IGT czynność mięśnia sercowego jest upośledzona. Stężenie BNP w osoczu i wskaźnik Tei mogą być przydatne w określeniu zaburzeń czynności miokardium u tych chorych.

Słowa kluczowe: cukrzyca, peptyd natriuretyczny typu B, wskaźnik Tei, tolerancja glukozy

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