EC DIABETES AND METABOLIC RESEARCH
Research Article

Evaluation of NT-PROBNP Levels in Egyptian Patients with Type 2 Diabetes

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Abstract

Background: The N-terminal pro brain natriuretic peptide (Nt-proBNP) is known to be associated with cardiac stress. This study aimed to assess Nt-proBNP levels in type 2 diabetic patients without overt cardiac complications and to evaluate it in patients with microvascular complications.

Methods: We evaluated the Nt-proBNP levels in the study population which was grouped as: group one, control healthy subjects and group 2, type two diabetic patients with and without microvascular complications.

Results: Patients with type 2 diabetes were shown to have higher Nt-proBNP levels than control subjects and patients with microvascular complications of type 2 diabetes were shown to have higher Nt-proBNP values than patients without microvascular complications.

Conclusion: Our study findings of elevated Nt-proBNP levels in type 2 diabetic patients without overt cardiac disease, suggesting that type 2 diabetes having some degree of cardiac strain, even if non clinically diagnosed and may be beneficial as screening method to guide selection of type 2 diabetic patients who need dedicated cardiac investigations.

Keywords: *Type 2 Diabetes Mellitus; N-Terminal Brain Natriuretic Peptide; Microangiopathy*

Introduction

Diabetes mellitus (DM) is a major global health concern. Recent estimates suggest that there are currently 451 million people with diabetes worldwide and this figure is projected to increase to 693 million by 2045. Importantly, estimates suggest that almost half (49.7%) of people living with diabetes remain undiagnosed [1]. The vast majority (90%) of people with diabetes have type 2 diabetes (T2D), which is linked to increased sedentary behaviour and obesity and is largely preventable. Whereas T2D was once rare in young people, increasingly we are seeing the condition diagnosed in children, adolescents and adults under the age of 30 years [2].

Diabetes is associated with a number of complications. The most devastating consequence of diabetes is its long-term vascular complications [3]. These complications are wide ranging and are due at least in part to chronic elevation of blood glucose levels, which leads to damage of blood vessels (angiopathy). In diabetes, the resulting complications are grouped under "microvascular disease" (due to damage to small blood vessels) and "macrovascular disease" (due to damage to the arteries). Microvascular complications include eye disease or "retinopathy," kidney disease termed "nephropathy" and neural damage or "neuropathy" [4].

Recently, N-terminal Brain natriuretic peptide (NT-proBNP) was reported to be associated with diabetic complications. It was proposed that NT-proBNP is a novel vascular risk factor reflecting systemic inflammation [5]. BNP is a 32-amino-acid peptide first described in porcine brain, and later found to be synthetized also by cardiac myocytes. In humans the left ventricle subjected to an increased wall tension is the main source of BNP. In the circulation, the peptide is present not only as BNP, but also as an inactive NT-proBNP resulting from the cleavage of the precursor form of BNP (proBNP) [6]. The actions of BNP include enhanced renal sodium and water excretion, vasorelaxation, and suppression of the activity of the renin-angiotensin-aldosterone system [7].

Aim of the Study

The aim of this study to detect the association of natural pro brain natriuretic peptide which is an indicator of cardiac dysfunction with type 2 diabetes mellitus even if non clinically overt.

Materials and Methods

This study is a case control study; it took place at Ismailia General Hospital. Patients attended the outpatient clinic for treatment or follow up of type 2 diabetes were eligible for the study. Cases subjected to the study were selected randomly, based on inclusion criteria, with no gender predilection. The biochemical study was done in the laboratory department. The study was approved by institutional ethical committee.

Patient selection

This study was conducted on one hundred eighty eight (188), subjects divided into two groups; group 1 (control group) composed of ninety four (94), non-diabetic healthy volunteers aged more than 50 years, 41 males and 53 females, and group 2, composed of ninety four (94), type 2 diabetic patients, aged more than 60 years both males and females with duration of diabetes over 10 years, 28 males and 66 females, patients known to have heart or renal failure were excluded from the study.

All patients and controls were subjected to clinical history taking, clinical examination: Measurement of BMI (weight in Kg/height in meter^2) [8], blood pressure measurement, fundus examination: for group 2 for detection of the presence and the severity of retinopathy.

Laboratory investigations

Urine albumin was measured by latex turbidimetry [9] method and urine creatinine was measured by Jaffe's kinetic method [10]. Albumin creatinine ratio (ACR) was calculated by dividing albumin concentration in milligrams by creatinine concentration in mmol [11].

Blood samples were collected and following tests were done: Fasting blood glucose level by colorimetric method [12], Hb A1C [13] and insulin resistance were measured using the homeostasis model assessment of insulin resistance (HOMA-IR), being calculated as fasting insulin X glucose level/22.5 [14]. Serum albumin [15] and creatinine levels [16] were also measured. Serum Human N-terminal pro-brain natriuretic peptide (NT-proBNP) analysis by ELISA Kit from the manufacturing company (Sun Red, Gentaur, Belgium).

Statistical analysis

Data was tabulated and introduced into a PC using SPSS 15.0.1. Mean, standard deviation, median, minimum and maximum values for numerical data and frequency and percentage for non-numerical data were calculated. Student t-test was used to assess the statistical significance of the difference between 2 means of 2 independent groups. Chi-square test was used for the relation between two qualitative variables.

Results

There was statistically significant difference in gender distribution and there were no significant differences in age between the two groups. There was statistically significant difference between the two studied groups in BMI, systolic and diastolic blood pressure. There was statistically highly significant difference in parameters of renal functions (creatinine, ACR and urine albumin), FBG, HbA1C. There was statistically highly significant difference between the two studied groups in Serum Human N-terminal pro-brain natriuretic peptide (NT-proBNP). On comparing both sexes, there was statistical highly significant difference of serum Human N-terminal pro-brain natriuretic peptide (NT-proBNP) in group I, and no statistical significant difference of serum Human N-terminal pro-brain natriuretic peptide (NT-proBNP) level in group II. The cut off value of the NT-proBNP levels for differentiation between the non diabetic controls and the diabetic patients was 45 pg/mL (Figure 1). Means± S.D of various parameters in the studied groups are illustrated in table 1.

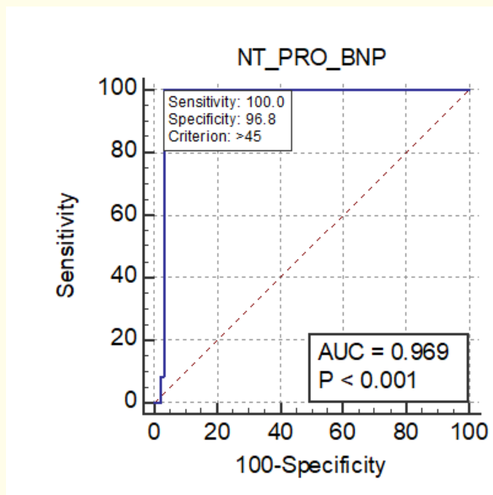

Figure 1: *ROC curves evaluation of Serum Human NT-proBNP levels in diabetic and non-diabetic patients.*

Variable (Mean ± S.D)	Group I (n = 94)	Group II (n = 94)	F	P
Age (year)	54.58 ± 3.69	58.46 ± 7.24	21.4	> 0.05
BMI: (kg/m^2)	31.29 ± 5.75	33.09 ± 6.41	4.11	< 0.05
Systolic BP (mmHg)	111.08 ± 10.5	119.05 ± 7.12	37.1	< 0.01
Diastolic BP (mmHg)	76.91 ± 5.73	83.12 ± 7.05	43.92	< 0.01
Creatinine (mg/dL)	0.94 ± 0.11	1.4 ± 0.87	27.0	< 0.01
ACR (mg/mmol)	10.38 ± 3.74	41.76 ± 17.32	294.8	< 0.01
Albumin/urine (mg/hr)	8.05 ± 3.41	20.57 ± 22.94	25.13	< 0.01
FBG (mg/dL)	88.34 ± 10.36	182.22 ± 69.43	168.12	< 0.01
Hb A1c (%)	5.46 ± 0.29	7.76 ± 1.16	347.81	< 0.01
HOMA-R	1.71 ± 0.52	5.98 ± 2.13	356.52	< 0.01
NT-PRO-BNP (pg/mL)	14.47 ± 11.5	67.56 ± 12.14	947.5	< 0.01

Table 1: *Mean ± S.D of various parameters in the two study groups.*

Discussion

Patients with type 2 diabetes represent a high risk population in terms of cardiovascular and renal complications. Such patients show a disproportionate increase in left-ventricular dysfunction and left-ventricular hypertrophy. Increased plasma BNP levels have been reported in certain patients with type 2 diabetes, in association with coronary heart disease and BNP screening has been proposed for the easy identification of subclinical diabetic cardiomyopathy [17]. Although microangiopathy represents a severe threat to the population with diabetes, macroangiopathy and subsequent cardiovascular disease are the major causes of morbidity and mortality in these patients. Screening for kidney and retinal complications is already an established part of routine diabetes care today, but there is no comparable reoccurring screening for cardiac complications of diabetes. This may simply be due to the lack of cost-effective methods.

In the present study, there was no significant differences in age distribution as cases were selected in narrow range of age (above 50 or 60 years), this was found also in previous studies [18]. There was statistically significant difference in gender distribution in the diabetic group, which was not found in the control healthy group, as the disease prevalence was significantly higher in females, this study was in concordance to many other studies, in which authors found that impaired glucose tolerance (IGT) dominates among women [19-21] and that type 2 diabetes higher among women [21,22]. On the other side, many other studies showed that the disease was more common in men [23].

In this study, body mass index (BMI) was statistically significantly higher in each of the diabetic group (group) compared to the control group. Several studies have reported a strong association between excess weight and increased risk of death, placing the overweight group at a 40% higher and the obese group at up to 300% higher risk of death than individuals whose BMI is normal (18.5 ≤ BMI < 25) [24-27]. Excess weight and physical inactivity are also associated with an increased risk of developing various diseases, particularly type 2 diabetes [28,29]. Since excess weight is an important predictor of type 2 DM, the term "diabesity" was proposed by Astrup and Finer in 2000 [30]. Specifically, In comparison to women with normal BMI, overweight, obese class I and II (30 ≤ BMI < 39.99) and class III (BMI ≥ 40) individuals face increased risks of developing type 2 DM with 7.6%, 20.1% and 38.8% greater risk respectively [31].

In this study both measures of blood pressure, systolic and diastolic were assessed in the two studied groups, there was high significant increase in both values seen in diabetic subjects in comparison with controls. The factors generally considered responsible for diabetes-related blood pressure elevation include enhanced sympathetic tone, obesity, hyperinsulinemia and structural changes in the kidney [32].

Our results was similar with results of Landsberg L, Molitch M (2004) who stated that diabetes mellitus is closely associated with prevalence of hypertension [33]. Also, other previous studies are in agreement with ours [34,35]. Diabetes and hypertension frequently occur together. There is substantial overlap between diabetes and hypertension in etiology and disease mechanisms. Obesity, inflammation, oxidative stress and insulin resistance are thought to be the common pathways. Recent advances in the understanding of these pathways have provided new insights and perspectives. Physical activity plays an important protective role in the two diseases mechanisms [36].

Some of renal function parameters were also evaluated in this study as serum urea, create nine, uric acid and albumin, urine albumin creatinine ratio (ACR) and GFR. Our results showed significant difference in these parameters in diabetic patients in comparison with the non-diabetic subjects. Amartey., *et al*. (2015) showed also increased serum urea and creatinine in diabetic subjects [37]. Diabetics are more prone to experience kidney dysfunction than non-diabetics, serum albumin and Albumin creatinine ratio (ACR) were evaluated in previous studies as Momin., *et al*. (2011) who showed increase in ACR and decrease in serum albumin in diabetics, these results were similar to ours. Although the 24-hour urine collection was previously the gold standard for the detection of microalbuminuria, it has been suggested that screening can be more simply achieved by a timed urine collection or an early morning specimen to minimize changes in urine volume that occur during the day. Use of the albumin/creatinine ratio in a timed urinary sample is now recommended as the preferred screening strategy for all diabetic patients [38].

In this study we reported significant increase of FBG, HbA1C and insulin resistance as measured by HOMA-IR in the diabetic group compared to the non-diabetic groups. This coincides with the previous studies which reported that T2DM is associated with insulin resistance and compensatory hyperinsulinemia [39,40].

Our study revealed significant increase in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in the diabetic group in comparison to non-diabetic subjects. These results are consistent with other studies [41].

Diabetes is associated with an increased risk of microvascular and macrovascular disease. B-type natriuretic peptide (BNP) and the N-terminal part of the precursor molecule proBNP (NT-proBNP), in particular, are established biomarkers of CV stress in diabetic patients [42]. Recently, data from the Framingham Heart Study identified BNP as a strong predictor of morbidity and mortality in the diabetic patients even when BNP levels were below the threshold normally used to diagnose patients with heart failure [43].

However, the true implications of NT-proBNP in clinical practice were typically influenced by confounders, such as age, sex, diabetes, and renal function. Recently, suggested that changes in liraglutide-induced lean mass and body fat were associated with increases in plasma NP levels in obese type 2 diabetic patients [44]. Finally, in this study, the usefulness of NT-proBNP levels as indicator for the occurrence of diabetes mellitus was tested using Roc curves analysis, it was found that the cut off value for differentiation between diabetic and non-diabetic subjects was 45 pg/mL, with high sensitivity and specificity. To the best of our knowledge, the present study is the first attempting to evaluate the association between NT-proBNP levels and type 2 DM in Egyptian population.

Conclusion

Our study findings of elevated Nt-proBNP levels in type 2 diabetic patients without overt cardiac disease, suggesting that type 2 diabetes having some degree of cardiac strain, even if non clinically diagnosed and may be beneficial as screening method to guide selection of type 2 diabetic patients who need dedicated cardiac investigations.

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