Association of Cardiac Pro-B-Type Natriuretic Peptide Levels with Metabolic Risk Factors in Young Obese Egyptian Patients: A Focus on Normotensive vs. Hypertensive Patients

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ABSTRACT

Introduction: In practice, there is increasing recognition of the importance of BNP in the pathophysiology, diagnosis and prognosis of certain cardiac disorders, as ischemic cardiac dysfunction and heart failure. The association of BNP to obesity and characteristics of the metabolic syndrome in adults and aged patients is well established, but that in pediatrics needs thorough elucidation.

Methods: The aim of this study was to assess the association of plasma β-type natriuretic peptide (BNP) levels and metabolic risk factors in 40 young (average age was 13–17 years) obese normo- and hypertensive pediatric patients. This is achieved by assessment of serum levels of glucose, insulin, lipid profile as well as the proinflammatory cytokines, TNF- α, interleukin (IL)-6 and IL-23. The assessed metabolic indicators were compared with that of healthy control young subjects with normal BP (120/80 mmHg).

Results: Contrasting the reported studies in adult populations, the result of the present study showed that β-type natriuretic peptide (BNP) levels are positively associated with characteristics of the metabolic syndrome; Blood pressure, BMI, HOMA index and the lipid profile in both obese groups. The hypertensive obese group evidenced an increased proinflammatory state, leading to the increased levels of serum levels of TNF-α, IL-6 and IL-23, compared to the obese normotensive group.

Conclusion: Early detection of pro-BNP levels in pre-HTN stage is an effective method of prevention of cardiovascular disease. Moreover, proinflammatory mediators, TNF-α, IL-6 should be included in primary screening tests for evaluation of hypertensive patients. However, the prognostic relevance of increased pro-BNP for risk of developing cardiac insufficiency in severely obese patients needs to be further evaluated.

Keywords - Obese normotensive, hypertensive, Pro-BNP, ICAM, interleukins and lipid profile.

Abbreviations: Pro-BNP, pro-B type of natriuretic peptide; TG, triglycerides; TC, total cholesterol; LDL-c, low density lipoprotein-cholesterol; HDL-c, High density lipoprotein-cholesterol; TNF- α, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-23, interleukin-23.

1. INTRODUCTION

The metabolic syndrome (MetS) is a worldwide problem, which refers to a constellation of coronary heart disease (CHD) risk factors including obesity and abdominal fat distribution, glucose intolerance, hyperlipidemia, hypertension, reflecting the underlying insulin resistance (1). The burden of MetS is likely to continue to rise, largely due to decreased physical activity and increased obesity in our society, not only among adults and aged population, but has spread to the young population as well. Although the clinical utility of this designation is controversial (2), there is widespread consensus that it describes a subgroup of individuals with a high risk of cardiovascular disease (3). Previous studies reported the association of obesity with levels of natriuretic peptides, which are cardiac hormones that play critical roles in ventricular remodeling, salt and water homeostasis, and the regulation of vascular tone (4,5).

Brain natriuretic peptide (BNP) is synthesized in myocardial cells as a response to increased wall stress in relation to heart failure or acute myocardial ischemia as a prohormone that is cleaved into BNP and N-terminal proBNP (Nt-proBNP). High BNP as well as high Nt-proBNP are new promising cardiovascular (CV) risk

markers and have been associated with high blood pressure (BP), left ventricular (LV) hypertrophy, and albuminuria.(6)

It has been hypothesized that a reduced natriuretic peptide response, called a natriuretic handicap, contributes to the increased susceptibility of obese individuals to fluid retention, hypertension, and heart failure (4). Despite the well-documented associations between natriuretic peptide levels and obesity (7), data on relations with other metabolic risk factors are controversial. Olsen and colleagues (6) reported an inverse association between N-terminal pro-B-type natriuretic peptide levels and plasma lipids, glucose, and insulin, although the prevalence of metabolic risk factors in that sample was relatively low. Other studies have not found an association between plasma natriuretic peptide levels and hyperlipidemia (8) or hyperglycemia (9). Low natriuretic peptide levels were associated with each component of the metabolic syndrome except hypertension. Elevated systolic blood pressure was associated with higher natriuretic peptide levels, which likely reflects the hemodynamic influence of blood pressure on natriuretic peptide synthesis (10, 11).

Though the childhood obesity turned to an epidemic state, few studies focused on its impact on the level of BNP. As obesity and the metabolic syndrome are known to be related to a state of chronic low grade inflammatory stress state, we sought to elucidate the association of plasma natriuretic peptide levels with metabolic risk factors as well as the proinflammatory cytokines, TNF-α, IL-6 and Il-23, in obese pediatric cohorts in Egypt.

2. MATERIALS AND METHODS

2.1 Subjects

In this prospective non-randomized study, we enrolled 20 obese normotensive and 20 hypertensive young Egyptian patients from the Pediatric Outpatient Clinic at the Endemic Disease Hospital at Cairo University, Egypt. The average age was 13–17 years, including both genders (27 males and 28 females). Informed consent was obtained from all patients and controls. Fifteen volunteers (age and sex matched; 6 females, 9 males) with normal BP (120/80 mmHg) and healthy hemodynamic and biochemical parameters were recruited in our study as a healthy control group. Group I was composed of 20 young obese normotensive patients (11 females and 9 males, age range 13-17 years (10.7±2.78 years). Group II included 20 young obese hypertensive patients (11 females and 9 males, age range 13-17 years. On the other hand, the study protocol was approved by the local ethics committee, and informed written consent was obtained from the parents of the patients and volunteers before entering the study.

Inclusion criteria for both groups were pediatric age (≤ 18 years) when diagnosed with obesity (BMI >20-25); added to normotension according to JNC-7 classification for group I, while hypertension for group II.

Exclusion criteria included presence of autoimmune disease, acute kidney injury or with unsatisfactory vascular access or any other known condition that would alter cytokine levels. Moreover, none of our patients had received antibiotics, anti-inflammatory or corticosteroid medications during the study period.

Clinical assessments included complete history taking, past medical and disease history for confirming the appropriateness of the patients to the inclusion criteria. BP and MBI monitoring were according to the international guidelines.

2.2 Blood sampling and Biochemical analyses

Venous blood samples were obtained (after overnight fasting) from all patients/controls and were divided into two aliquots: one part was anticoagulated and plasma separated for NT-pro-BNP assessment. The remainder of the samples were allowed to clot and sera were then separated by centrifugation (3500 rpm, 20 min, 25°C) was stored at -20°C for later biochemical determinations. Serum levels of fasting glucose, Insulin and the lipid profile (T-Chol, HDL-C and TG) were analyzed using Synchron CX5 autoanalyzer (Beckman, USA) and LDL-cholesterol levels were calculated by using the Friedewald formula. Also, pro-inflammatory markers such as tumor necrosis factor (TNF)-α, interleukin (IL)-6 and interleukin IL-23 using commercially available enzyme-linked immunosorbent assay kits (R&D Systems Inc., Minneapolis, MN, USA). Plasma level of NT-pro BNP was quantitatively assessed via ELISA according to Maisel et al (11).

2.3 Statistical analysis

All data were expressed as mean ± SD. All analyses utilized SPSS 15.0 statistical package for Windows (SPSS Inc., Chicago, IL). A one-way analysis of variance (ANOVA) was employed for comparisons of means of the different groups. A p-value < 0.05 was accepted as statistically significant with LSD test as the post –hoc test. Correlation analyses were done using Pearson's correlation.

3. RESULTS

Characteristics of the study participants are listed in Table 1; their mean age was 13–17(10.7±2.78) years. Overall, 20 young obese normotensive young patients (11 females and 9 males), as well as 20 young obese hypertensive patients (11 females and 9 males) were enrolled in the study. According to the JNC-7 classification the obese hypertensive patients in group 2 were classified as stage 1 hypertension. Table 2 shows the progressive elevation of N-BNP levels from obese normotensive to hypertensive individuals. The N-BNP levels in normotensive obese group increased significantly approximately 6-fold ($P< 0.01$), compared to control group. Moreover, the latter value doubled in the hypertensive obese group (from 420.2 pg/ml ± 95.6 to 848.25pg/ml ± 139.3). Similar pattern of progressive elevation of glycolytic markers was evident in the levels of glucose, insulin, hence insulin resistance (HOMA IR-index). The lipid profile; TG, TC, LDL-C, HDL-C; showed a 3-fold significant increase in the

normotensive obese group, however were not altered in the hypertensive obese group.

The levels of the assessed proinflammatory cytokine markers; TNF-α, IL-6 and IL-23 are presented in table 3. It shows significantly increased levels of TNF-α, IL-6 and IL-23 by 217.39%, 356.66% and 528.75%, respectively (P< 0.01), in obese normotensive patients when compared with control healthy individuals group. While the pattern in the obese hypertensive patients shows higher levels;1173.91%, 1350.0% and 153.12%, respectively (P< 0.01), compared to their normotensive counterparts.

3.1 Correlations between BNP and the metabolic risk factors

Results of multiple linear regression models relating Log pro-BNP with metabolic risk factors are shown in Table 4. In obese normotensive and hypertensive patients, positive associations were observed between plasma pro-BNP levels and fasting blood glucose (r = 0.35), insulin (r = 0.31; 0.34), HOMAIR-index (r = 0.3;0.33), TG (r = 0.31;0.34), TC (r = 0.21;0.27), LDL-C (r = 0.28;0.33), HDL-C (r = 0.24;0.26), TNF-α (r = 0.31;0.38), IL-6 (r = 0.17,0.22) and IL-23 (r = 0.29;0.33), all at P= 0.05.

Table 1 Participant Characteristics

	Control-patients (N=15)	Obese –normotensive patients (N=20)	Obese hypertensive patients (N=20)
Age(years)	14.5 ± 1.45	14.6 ± 1.3	14.8 ± 1.4
Diastolic BP(mmHg)	80	81.25 ± 2.75	86 ± 3.2 *b
Systolic BP(mmHg)	120	120.75 ± 5	143.3 ± 8.7 # a
BMI	21.2 ± 1.2	32.5 ± 0.7 # a	33.3 ± 0.74 # a

Values are means ± SDM for control healthy, obese normotensive and hypertensive patients groups (I and II). Values are statistically significant at [a] P<0.01, Values are statistically significant at [b]P<0.05. Values (*) is significantly different from control group; (#) significantly different from normotensive obese patients using one way ANOVA (SPSS program).

Table 2 Plasma Pro- BNP and metabolic parameters in control, obese normotensive and hypertensive patients

	Control-patients (N=15)	Obese –normotensive patients (N=20)	Obese hypertensive patients (N=20)
Pro- BNP(pg/ml)	73.06 ± 11	420.2 ± 95.6 *[a]	848.25 ± 139.3 *# [a]
Glucose (mg/dl)	78.2 ± 4.7	108. 4 ± 4.5 * [a]	122.9 ± 6.7 *# [a]
Insulin(µIU/ml)	5.5 ±0.66	8.8 ± 0.63 * [a]	13.2 ±0.8 *# [a]
HOMA IR-index	1.06 ± 0.06	2.34 ± 0.1* [a]	4.00 ± 0.21 *# [a]
TG(mg/dl)	75.8 ± 10.36	208.45 ± 21.8 * [a]	206.9 ± 27.5* [a]
TC(mg/dl)	132.06 ± 7.2	301.4 ± 22.7 * [a]	301 ± 27.6 * [a]
LDL-C(mg/dl)	77.2 ± 4.7	208.95 ± 18.6* [a]	210.45 ± 19.5 * [a]
HDL-C(mg/dl)	39.73 ± 3.5	50.7 ±3.57* [a]	49.2 ± 4.1* [a]

Values are means ± SDM for control healthy, obese normotensive and hypertensive patients groups (I and II). Values are statistically significant at [a]P<0.01. Values (*) is significantly different from control group; (#) significantly different from normotensive obese patients using one way ANOVA (SPSS program).

Table 3 Serum endothelial and inflammatory markers in control, obese normotensive and hypertensive patients

	Control-patients (N=15)	Obese –normotensive patients (N=20)	Obese hypertensive patients (N=20)
Cytokine markers TNF-α (ng/ml)	2.3 ± 4.7	7.3 ± 1.9 *[a]	29.3 ± 7.6 *#a
IL-6(ng/ml)	1.2 ± 0.2	5.48 ± 1 *[a]	17.4 ± 3 *#a
IL-23(ng/ml)	16 ± 3.1	100.6 ± 14.9*[a]	40.5 ± 10.5 *#a

Values are means ± SDM for control healthy, obese normotensive and hypertensive patients groups (I and II). Values are statistically significant at [a]P<0.01. Values (*) is significantly different from control group; (#) significantly different from normotensive obese patients using one way ANOVA (SPSS program).

Table 4 Correlations between BNP and the metabolic risk factors in the studied groups

	Control-patients (N=15)	Obese –normotensive patients (N=20)	Obese hypertensive patients (N=20)
Glucose (mg/dl)	r= 0.33 P< 0.05	r= 0.35 P< 0.05	r= 0.35 P< 0.05
Insulin(µIU/ml)	r= 0.32 P< 0.05	r= 0.31 P< 0.05	r= 0. 34 P< 0.05
HOMA IR-index	r= 0.29 P< 0.05	r=0.30 P< 0.05	r=0.33 P< 0.05
TG(mg/dl)	r=0.26 P< 0.05	r= 0.31 P< 0.05	r= 0.34 P< 0.05
TC(mg/dl)	r= 0.15 P< 0.05	r=0.21 P< 0.05	r= 0.27 P< 0.05
LDL-C(mg/dl)	r=0.22 P< 0.05	r=0.28 P< 0.05	r=0.33 P< 0.05
HDL-C (mg/dl)	r=0.24 P< 0.05	r=0.24 P< 0.05	r= 0.26 P< 0.05
TNF-α (ng/ml)	r=0.29 P< 0.05	r=0.31 P< 0.05	r=0.38 P< 0.05
IL-6(ng/ml)	r=0.15 P< 0.05	r=0.17 P< 0.05	r= 0.22 P< 0.05
IL-23(ng/ml)	r=0.30 P< 0.05	r= 0.29 P< 0.05	r= 0.33 P< 0.05

HOMA IR-index, Homeostasis Model of Assessment - Insulin Resistance; TG, triglycerides; TC, total cholesterol; LDL-c, low density lipoprotein-cholesterol; HDL-c, High density lipoprotein-cholesterol; TNF- α, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-23, interleukin-23.

4. DISCUSSION

B-type natriuretic peptide (BNP), a neurohormone synthesized in the cardiac ventricles, is released as preproBNP and then enzymatically cleaved to the N-terminal-proBNP(NT-proBNP) and BNP upon ventricular myocyte stretch. In practice, there is increasing recognition of the importance of BNP in the pathophysiology, diagnosis, prognosis and treatment of certain cardiac disorders, as left ventricular dysfunction in selected patient groups (12-14), and other studies have shown an association of proBNP with subclinical cardiovascular diseases (15, 16).

To the best of the authors' knowledge, the current study is the first approach to evaluate plasma pro-B-type natriuretic peptide levels in young population and assess its association with metabolic risk factors in obese normotensive vs hypertensive patients. The results of the present study revealed a significant increase in pro-B-type natriuretic peptide levels in both obese young groups, compared to their control counterparts. Furthermore, the hypertensive obese patients showed higher levels, compared to other normotensive obese group. The positive association of pro-B-type natriuretic peptide with obesity and factors of metabolic syndrome in young patients, in the current study, contradicts the reported studies on adult and aged obese patients with or without metabolic syndrome (7-9).

The relationship between obesity and hypertension is well established in adults and children (17, 18). The combination of obesity, hypertension and other cardiovascular risk factors significantly increases the probability of adverse cardiovascular outcomes, and raises considerations for aggressive treatment strategies (17). In our study, obese subjects displayed higher BP levels with higher BMI than non-obese individuals even in the normotensive range which may contribute to their susceptibility to hypertension and related disorders (19,20). Though Mehra et al. (21) reported decreased BNP levels in obese individuals with CHF, we could not confirm these results in our survey. Conversely, we found higher pro-BNP concentrations in our obese patients. Our findings align with the results from a different study in which equivalent concentrations of increased A-type natriuretic peptide and BNP were found in obese normo- and hypertensive individuals (22).

Natriuretic peptides are shown to correlate with measures of cardiac dysfunction. Pro- BNP also has been shown to be independent risk markers for cardiovascular disease in patients with diabetes (23-25). Our data also suggest that the elevation in pro- BNP in obese normotensive and hypertensive individuals could be largely mediated by insulin resistance, because the obesity relationship was attenuated with adjustment for HOMA-IR in two different epidemiological cohorts. These findings highlight the influence of metabolic factors, particularly insulin resistance, on the Pro- BNP and suggest a potential mechanism for susceptibility to hypertension-related disorders in individuals with insulin resistance (26, 27). The present study revealed that NP levels decrease during

acute hyperinsulinemia in patients in normotensive and hypertensive groups. The current results are in alignment with that of Halbirk et al. (28), however have not been replicated by other investigators (29-32). Obesity still remains the leading cause of coronary heart disease (CHD) in developed countries and control of the cardiovascular disease (CVD) epidemic requires a multifaceted strategy targeting modifiable risk factors for CHD. Although the link between low LDL-cholesterol and the prevention of CVD is well established, many patients remain at risk of CVD despite having LDL-cholesterol levels below recommended targets. Thus, increasing attention is being focused on other lipoprotein fractions, such as HDL and triglycerides, as potential targets of therapy. Elevated triglyceride levels combined with reduced HDL-cholesterol, referred to as atherogenic dyslipidaemia, are common lipoprotein abnormalities that affect up to 60% of high-risk patients and there is emerging evidence that combined abnormalities of the triglyceride-HDL axis are especially associated with adverse cardiovascular outcomes (33). The current study revealed significant associations between elevation of plasma Pro- BNP and TG, TC and LDL- and HDL-C in obese normotensive and hypertensive patients. The current results suggested that a Pro-BNP level was associated with secondary cardiovascular risk in patients with incident CHD and, therefore, will likely emerge as promising targets for CVD diagnosis. Also, plasma triglyceride, LDL-, and HDL-cholesterol levels were significantly related to secondary CHD risk independent of a broad range of covariates and traditional risk factors.

Plasma pro-BNP level is currently related to cytokine markers levels (table4). Previous studies have investigated a limited numbers of inflammatory markers which have been demonstrated to be related to mainly concentric LVH in hypertensive patients (34-36). In the present study, several markers of inflammation were studied and higher levels of TNF-α, IL-6 and IL-23 associated with pro-BNP were observed in obese normotensive and hypertensive patients.

The finding of elevation of pro-BNP and endothelial markers were confirming the active participation of mast cells in the progression of myocardial fibrosis in rats with postmyocarditis- dilated cardiomyopathy (37). Furthermore, the role of TNF-α, IL-6 and IL-23 in progressive LV dysfunction and remodeling in rats has been previously investigated (38). It was concluded that sustained, pathophysiologically relevant circulating concentrations of TNF-α, IL-6 and IL-23 were sufficient to provoke deleterious changes in LV structure and function. The major finding with respect to myocardial function was that a continuous infusion of TNF-α led to a time-dependent depression in LV function that was evident at the level of the intact ventricle as well as in the isolated cardiac myocyte itself (37).

In conclusion, early detection of pro-BNP levels in pre-HTN stage is an effective method of prevention of cardiovascular disease. Moreover, proinflammaory mediators, TNF-α, IL-6 should be integrated to pro-BNP as primary screening tests for and used for the risk stratification and evaluation of hypertensive patients. However, the prognostic relevance of increased pro-BNP for risk of developing cardiac insufficiency in severely obese patients needs to be further evaluated.

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