Journal of Experimental and Clinical Medicine
Deneysel ve Klinik Tıp Dergisi

Clinical Research **doi:** 10.5835/jecm.omu.29.03.004

N-terminal pro-B-type natriuretic peptide and insulin resistance in overweight and obese subjects

Obez ve fazla kilolu kişilerde N-terminal pro-B-tip natriüretik peptid ve insülin direnci

Aytekin Alcelik*[a], Eyup Aytekin[a], Mehmet Tosun[b], Gülali Aktaş[a], Selim Ayhan[c], Serkan Ozturk[c], Mehmet Fatih Ozlu[c], Haluk Savli[a], Mehmet Yazici[c]

[a]*Department of Internal Medicine, İzzet Baysal Medical Faculty, Abant İzzet Baysal University, Bolu, Turkey*
[b]*Department of Biochemistry, İzzet Baysal Medical Faculty, Abant İzzet Baysal University, Bolu, Turkey*
[c]*Department of Cardiology, İzzet Baysal Medical Faculty, Abant İzzet Baysal University, Bolu, Turkey*

ARTICLE INFO

Article History
Received 18 / 07 / 2012
Accepted 20 / 07 / 2012

*** Correspondence to:**
Aytekin Alcelik
Abant İzzet Baysal University,
Medical Faculty
Department of Internal Medicine,
Bolu, Turkey
e-mail: aytekinalcelik@yahoo.com

Keywords:
NT-proBNP
Obesity
Insulin resistance
Body mass index
Overweight
Waist circumference

Anahtar Kelimeler:
NT-proBNP
Obezite
İnsülin direnci
Vücut kitle indeksi
Fazla kilolu
Bel çevresi

ABSTRACT

Several studies have been conducted to investigate B-type natriuretic peptide (BNP) levels in different obese populations. However, in these studies BNP levels were lower in obese population with an unclear mechanism which has not been explained yet. We sought to investigate the relationship among plasma NT-proBNP levels, obesity and insulin resistance in subjects with no known heart disease. The study population consists of two groups. Subjects with a body mass indexs (BMI) of ≤25 kg/m^2 were classified as lean group (LG, n=30), BMI of >25 kg/m^2 were classified as overweight and obese group (OG, n=78). Severe hypertension, heart failure, ischemic heart disease, renal or hepatic insufficiency, age >65, pregnancy and malignancy were excluded. There was a negative correlation between NT-proBNP and weight (r=-0.379, p=0.004) and BMI (r=-0.286, p=0.030) in LG, but there was no such reverse correlation between NT-proBNP and BMI (r=-0.057, p=0.463) in OG. We performed multivariable logistic regression analyses to examine predictors of obesity levels. There were not any significant relation between these predictors and obesity. Insulin levels had a strong association with obesity level however this association was still insignificant (p=0.054). In LG group, there was a negative correlation between NT-proBNP and BMI. There was no correlation between NT-proBNP and homeostatic model assessment (HOMA) and insulin levels (r=-0.035, p=0.789) in LG group, but there was a statistically significant negative correlation between BNP and HOMA (r=-0.219, p=0.009) and insulin levels (r=-0.252, p=0.002) in OG group. Race and ethnicity may contribute this association.
J. Exp. Clin. Med., 2012; 29:179-182

ÖZET

Farklı obez popülasyonlarda B-tip natriüretik peptid (BNP) seviyelerini araştıran bazı çalışmalar yapılmıştır. Henüz tam açıklanamayan bir mekanizma ile obezlerde BNP düzeyleri sıklıkla düşük olarak saptanmaktadır. Bilinen kalp hastalığı olmayan bireylerde plazma NT-proBNP seviyeleri, obezite ve insülin direnci arasındaki ilişkiyi araştırmayı amaçladık. Çalışma popülasyonumuz iki gruptan oluşmaktaydı. Vücut kitle indeksi (VKİ) ≤25 kg/m^2 olanlar zayıf grubuna (LG, n=30), >25 kg/m^2 olanlar ise fazla kilolu ve obez grubuna (OG, n=78) alındı. Ciddi hipertansiyonu, kalp yetmezliği, iskemik kalp hastalığı, böbrek veya karaciğer yetmezliği, malignitesi olan hastalar, gebeler ve 65 yaş üstü hastalar çalışmaya alınmadı. Zayıf hastaların grubunda NT-proBNP ile kilo (r=-0,379, p=0,004) ve VKİ (r=-0,286, p=0,030) arasında negatif bir ilişki varken, obez grupta NT-proBNP ve VKİ arasında böyle bir ters korelasyon saptanmadı. Obezite seviyelerinin belirteçlerini saptamak için çok değişkenli lojistik regresyon analizleri yaptık. Bu belirteçler ile obezite arasında anlamlı ilişki saptanmadı. İnsülin seviyelerinin obezite ile güçlü bir ilişkisi vardı ancak yine de bu ilişki istatistiksel anlamlılık düzeylerine ulaşamıyordu (p=0,054). Zayıf hasta grubunda NT-proBNP ve VKİ arasında ters korelasyon vardı. Aynı grupta NT-proBNP ve homeastatik modelde değerlendirme (HOMA) ve insülin seviyeleri (r=-0,035, p=0,789) arasında korelasyon yoktu, ancak obez grupta BNP ve HOMA (r=-0,219, p=0,009) ve insulin seviyeleri (r=-0,252, p=0,002) arasında istatistiksel olarak anlamlı ters ilişki vardı. Irk ve etnik köken bu farklılığa katkıda bulunuyor olabilir.
J. Exp. Clin. Med., 2012; 29:179-182

Journal of Experimental and Clinical Medicine 29 (2012) 179-182

1. Introduction

B-type natriuretic peptide (BNP) has a key role in circulation and salt-water (Levin et al., 1998; Kalra et al., 2001). The Framingham Heart Study demonstrated that plasma BNP levels predicted the risk of death and cardiovascular events in without heart failure individuals (Wang et al., 2004). A lot of data have shown that the plasma BNP level was affected by age and obesity in the general population (Redfield et al., 2002; Wang et al., 2004). Based on this association between obesity and BNP, several studies have been conducted to investigate BNP levels in different obese populations. However, in these studies BNP levels were lower in obese population with an unclear mechanism which has not been explained yet. This condition is named as "The paradox of low BNP levels in obesity" currently (Clerico et al., 1999; Taylor et al., 2006; Tosa et al., 2009; Clerico et al., 2012).

The effect of obesity on the development of cardiovascular disease has been well known (Hubert et al., 1983). Overweight and obese individuals have an increased cardiovascular mortality risk than lean subjects (Wang et al., 2007). Plasma BNP/NT-proBNP values are inversely related to body mass index (BMI) in both healthy subjects and patients with heart failure (Hubert et al., 1983; Clerico et al., 1999; Wang et al., 2004; Taylor et al., 2006; Tosa et al., 2009; Clerico et al., 2012). Several studies have reported various association of natriuretic peptides levels with insulin resistance (Olsen et al., 2005; Alcelik et al., 2007; Wang et al., 2007; Tassone et al., 2009). Recently, Khan et al. (2011) reported that natriuretic peptide levels are lower both in non-obese and obese patients with insulin resistance. Peripheral clearance and degradation of natriuretic peptides, sex steroid hormones, adipokines, pathophysiological conditions and pharmacological treatment have been focused as the cause of low BNP levels in obese, but the potential effects of insulin resistance have not been studied enough yet.

We sought to investigate the relationship among plasma NT-proBNP levels, obesity and insulin resistance in subjects with no known heart disease.

2. Materials and methods

Subjects

The study population consists of two groups. Subjects with a BMI of ≤25 kg/m^2 were classified as lean group (LG, n=30), BMI of >25 kg/m^2 were classified as overweight and obese group (OG, n=78). Anthropometric measurements obtained in this study included height, weight, BMI, and waist circumference. We measured abdominal circumference at the umbilical level. Blood pressure was measured with a sphygmomanometer in the sitting position on the right arm. Fasting blood samples (10 ml) were drawn into tubes containing EDTA. Severe hypertension, heart failure, ischemic heart disease, renal or hepatic insufficiency, age >65, pregnancy and malignancy were excluded. Informed consent was obtained from each individual, and the study protocol was approved by the ethics committee of our institution.

Definitions

Height and weight were measured for the calculation of the BMI (BMI=weight (kg)/height^2 (m^2)). Overweight was defined as BMI values ≥25 kg/m^2 and obesity as BMI values ≥30 kg/m^2. Homeostatic model assessment (HOMA) was calculated with the formula (Matthews et al., 1985): Insulin (mIU/l) x glucose (in mmol/l)/22.5.

NT-proBNP measurement

Venous blood samples were centrifuged within 15 minutes of collection, at 3000 rpm for 10 minutes, and the supernatant plasma was then transferred into polypropylene tubes at -80°C until the assays were determined. Plasma concentrations of NT-proBNP were measured by immunoassay "immunolite 2000 analyzer" (Siemens Healthcare Diagnostics, Deerfield, IL, USA), and the reference range was 0 to 125 pg/mL.

Statistical analysis

Continuous variables were described by the mean ± standard deviation (SD) while interrelationships were examined using Pearson's correlation and t test. Data for non-normally distributed variables were expressed as medians and interquartile ranges and interrelationships examined using Spearman's correlation, Mann-Whitney U test, and Wilcoxon signed ranks test as appropriate. Stepwise linear multiple regression analysis was performed. We used SPSS software package 17.0 (SPSS, Chicago, IL) for statistical analysis. Student's two-tailed t-test was applied to compare continuous variables, and the chi-square test was used for categorical data. P-value less than 0.05 were considered statistically significant.

3. Results

Seventy-eight patients with overweight-obesity (OG) and thirty lean subjects (LG) were recruited into the study. Table 1 indicates the clinical characteristics of the study subjects. Body weight (85.5±15.5 kg vs. 65.9±8.9kg, p<0.001), BMI (31.8±5.8 kg/m^2 vs. 23.3±1.1 kg/m^2, p<0.001), insulin (8.92±8.8 µIU/mL vs. 5.6±5.3 µIU/mL, p=0.020) and HOMA (2.3±2.6 mmHg vs. 1.3±1.3 mmHg, p=0.012) were higher in

Table 1. Clinical characteristics of the subjects studied

	Overweight and obese (n=78)	Nonobese (n=30)	P
Age (yr)	43.1±11.4	39.9±8.7	0.120
Gender (M/F)	27/51	12/18	0.603
Smoking (n)	11	8	0.126
Systolic blood pressure (mmHg)	121.5±16.2	115.3±15.0	0.073
Diastolic blood pressure (mmHg)	74.9±9.9	76.3±7.6	0.506
Waist circumference (cm)	108.6±13.1	94.4±2.9	<0.001
Height (cm)	163.8±9.2	167.4±9.1	0.068
Weight (kg)	85.5±15.5	65.9±8.9	<0.001
BMI (kg/m^2)	31.8±5.8	23.3±1.1	<0.001
Creatinine (mg/dl)	0.72±0.11	0.73±0.13	0.772
Fasting glucose (mg/dl)	102.9±23.5	97.1±18.1	0.220
Insulin (µIU/mL)	8.92±8.8	5.6±5.3	0.020
HOMA	2.3±2.6	1.3±1.3	0.012
LDL (mg/dl)	119.7±30.4	111.0±41.3	0.296
HDL (mg/dl)	42.2±8.2	42.5±12.7	0.907
NT-proBNP (pg/mL)	60.1±38.4	60.1±34.2	0.997

the OG.

There was a reverse correlation between NT-proBNP and weight (r=-0.379, p=0.004) and BMI (r=-0.286, p=0.030) in LG group, but there was no such reverse correlation between NT-proBNP and BMI (r=-0.057, p=0.463) in OG group. Reverse correlation between NT-proBNP and weight in OG group continues with a reduced statistical significance (r=-0.178, p=0.024). Similarly, there was no correlation between NT-proBNP and HOMA and insulin levels (r=-0.035, p=0.789) in LG group, but there was a statistically significant reverse correlation between NT-proBNP and HOMA (r=-0.219, p=0.009) and insulin levels (r=-0.252, p=0.002) in OG group. Independent t test revealed that Insulin (p=0.02) and HOMA (p=0.012) values were significantly different between groups while other values were not different (p>0.05).

Table 2. Multivariable logistic regression analyses to examine predictors of obesity levels

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-.292	1.178		-.248	.805
	Gender	.002	.166	.002	.012	.990
	Age	-.006	.005	-.133	-1.084	.281
	Diabetes	.146	.161	.110	.909	.366
	Hypertension	.090	.125	.083	.721	.473
	Hyperlipidemia	-.173	.138	-.125	-1.251	.214
	Waist circumference	-.003	.006	-.098	-.587	.559
	Body mass index	.058	.016	.819	3.616	.001
	Weight	-.001	.007	-.054	-.223	.824
	Hemoglobin	-.025	.143	-.085	-.171	.865
	Platelet	.000	.001	-.106	-1.030	.306
	MPV	.018	.048	.038	.369	.713
	Fasting Glucose	.004	.004	.207	1.039	.302
	Creatinine	.236	.573	.063	.412	.682
	LDL	.000	.001	.034	.365	.716
	HDL	-.004	.005	-.095	-.891	.376
	Triglyceride	.000	.000	-.160	-1.485	.141
	Insulin	.045	.023	.812	1.957	.054
	HOMA	-.137	.085	-.727	-1.611	.111
	NT-proBNP	.001	.001	.078	.814	.418

a. Dependent Variable: Obezite

We subgrouped the remaining 94 patients after excluding subjects with diabetes into LG2 and OG2. Waist circumference, weight and BMI (p<0.001) were different between groups while other basal values were not different. HOMA was significantly different between groups (LG2: 1.25±1.22, OG2: 2.07±2.30, p=0.028). NT-proBNP values were lower in OG2 than LG2 group but this difference was not significant (LG2: 60.87±34.67, OG2: 57.28±35.79, p=0.481). NT-proBNP levels and BMI (r=-0.293, p=0.03) were reversely correlated in LG2 group, but this association was not significant in OG2 group (r=-0.118, p=0.167).

There was a significant reverse correlation between NT-proBNP and insulin (r=-0.288, p=0.001) and HOMA (r=-0.267, p=0.002) in OG2 group, but there was no such association between NT-proBNP and insulin (r=0.210, p=0.273) and HOMA (p=0.002) in LG2 group.

We performed multivariable logistic regression analyses to examine predictors of obesity levels (Table 2).

There were not any significant relation between these predictors and obesity. Insulin levels had a strong association with obesity level however this association was still insignificant (p=0.054).

4. Discussion

Most of the studies that observed obesity revealed a negative correlation between BMI and BNP (Clerico et al., 1999; Wang et al., 2004; Taylor et al., 2006; Tosa et al., 2009; Khan et al., 2011; Koizumi et al., 2011; Clerico et al., 2012). This correlation is referred to "natriuretic handicap phenomenon". Numerous opinions have been put forward to explain the pathopyhsiological mechanisms of this phenomenon. Dessi et al. (1997) explained this phenomenon by the strong relation with obesity and hypertension in their study (Dessi-Fulgheri et al., 1997). It has been suggested the mechanism of this relation that renal sodium and water retention which may contribute by increased activation of the sympathetic and renin-angiotensin systems. The natriuretic peptide system plays a key role in the regulation of this system. It has been speculated that obese individuals have an impaired natriuretic peptide response, and the phrase natriuretic handicap has been used to describe this phenomenon. Also, Khan et al. (2011) reported that natriuretic peptide levels are lowers both in nonobese and obese patients with insulin resistance. They claimed as a result of their study; the natriuretic handicap observed in obese individuals could be attributable in part to insulin resistance. They declared the race of the patients (which was predominantly European white) was an important limitation in their study. In our study we found a reverse correlation between NT-proBNP and insulin resistance in obese (with or without diabetes) patients. We found no such correlation in nonobese subjects. We think similarly to Khan et al, that in the guide of this correlation, the key factor of this association is the insulin resistance which is the most important component of obesity.

In nonobese group in our study, there was a reverse correlation between NT-proBNP and BMI which was similar to the literature. This correlation weakens in the obese group and becomes statistically insignificant. When we interpreted our results with data in the literature, we may claim that NT-proBNP is associated with insulin resistance in obese and BMI in nonobese populations. Race and ethnicity may contribute this association. Different results between obese and nonobese populations in our study may be due to the location of Turkey between Europe and Asia.

Our study has some limitations. The single-center nature of this investigation may limit its applicability to the general population. Subjects have not undergone echocardiographic examinations. Because of relatively limited size of sample, the interpretation of results should be cautious.

REFERENCES

Alçelik, A., Cinemre, H., Alçelik, A.G, Özhan, H., Dindar, G. (2007). Brain natriuretic peptides levels in type2 diabetes treated with rosiglitazone. MN Kardiyoloji. 14, 321-327.

Clerico, A., Giannoni, A., Vittorini, S., Emdin, M., 2012. The paradox of low BNP levels in obesity. Heart Fail. Rev. 17, 81-96.

Clerico, A., Iervasi, G., Mariani, G., 1999. Pathophysiologic relevance of measuring the plasma levels of cardiac natriuretic peptide hormones in humans. Horm. Metab. Res. 31, 487-498.

Dessi-Fulgheri, P., Sarzani, R., Tamburrini, P., Moraca, A., Espinosa, E., Cola, G., Giantomassi, L., Rappelli, A., 1997. Plasma atrial natriuretic peptide and natriuretic peptide receptor gene expression in adipose tissue of normotensive and hypertensive obese patients. J. Hyperten. 15, 1695-1699.

Hubert, H.B., Feinleib, M., Mcnamara, P.M., Castelli, W.P., 1983. Obesity as an independent risk factor for cardiovascular-disease - a 26-year follow-up of participants in the framingham heart-study. Circulation. 67, 968-977.

Kalra, P.R., Anker, S.D., Coats, A.J.S., 2001. Water and sodium regulation in chronic heart failure: The role of natriuretic peptides and vasopressin. Cardiovasc. Res. 51, 495-509.

Khan, A.M., Cheng, S., Magnusson, M., Larson, M.G., Newton-Cheh, C., McCabe, E.L., Coviello, A.D., Florez, J.C., Fox, C.S., Levy, D., Robins, S.J., Arora, P., Bhasin, S., Lam, C.S., Vasan, R.S., Melander, O., Wang, T.J., 2011. Cardiac natriuretic peptides, obesity, and insulin resistance: Evidence from two community-based studies. J. Clin. Endocr. Metab. 96, 3242-3249.

Koizumi, M., Watanabe, H., Kaneko, Y., Iino, K., Ishida, M., Kosaka, T., Motohashi, Y., Ito, H., 2011. Impact of obesity on plasma B-type natriuretic peptide levels in Japanese community-based subjects. Heart Vessels. 27, 287-294.

Levin, E.R., Gardner, D.G., Samson, W.K., 1998. Mechanisms of disease - Natriuretic peptides. New Engl. J. Med. 339, 321-328.

Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C., 1985. Homeostasis model assessment - insulin resistance and beta-cell function from fasting plasma-glucose and insulin concentrations in man. Diabetologia, 28, 412-419.

Olsen, M.H., Hansen, T.W., Christensen, M.K., Gustafsson, F., Rasmussen, S., Wachtell, K., Borch-Johnsen, K., Ibsen, H., Jørgensen, T., Hildebrandt, P., 2005. N-terminal pro brain natriuretic peptide is inversely related to metabolic cardiovascular risk factors and the metabolic syndrome. Hypertension, 46, 660-666.

Redfield, M.M., Rodeheffer, R.J., Jacobsen, S.J., Mahoney, D.W., Bailey, K.R., Burnett, J.C., 2002. Plasma brain natriuretic peptide concentration: Impact of age and gender. J. Am. Coll. Cardiol. 40, 976-982.

Tassone, F., Gianotti, L., Rolfo, F., Visconti, G., Borretta, G., Feola, M., 2009. B-type natriuretic peptide levels and insulin resistance in patients with severe ischemic myocardial dysfunction. J. Endocrinol. Invest. 32, 805-809.

Taylor, J.A., Christenson, R.H., Rao, K., Jorge, M., Gottlieb, S.S., 2006. B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide are depressed in obesity despite higher left ventricular end diastolic pressures. Am. Heart J. 152, 1071-1076.

Tosa, S., Watanabe, H., Iino, K., Terui, G., Kosaka, T., Hasegawa, H., Ito, H., 2009. Usefulness of plasma BNP levels as a marker of left ventricular wall stress in obese individuals. Int. Heart J. 50, 173-182.

Wang, T.J., Larson, M.G., Keyes, M.J., Levy, D., Benjamin, E.J., Vasan, R.S., 2007. Association of plasma natriuretic peptide levels with metabolic risk factors in ambulatory individuals. Circulation. 115, 1345-1353.

Wang, T.J., Larson, M.G., Levy, D., Benjamin, E.J., Leip, E.P., Omland, T., Wolf, P.A., Vasan, R.S., 2004. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. New Engl. J. Med. 350, 655-663.

Wang, T.J., Larson, M.G., Levy, D., Benjamin, E.J., Leip, E.P., Wilson, P.W.F., Vasan, R.S., 2004. Impact of obesity on plasma natriuretic peptide levels. Circulation. 109, 594-600.