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N- Terminal Pro Brain Natriuretic Peptide among Patients with Metabolic Syndrome in Duhok City

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Abstract

Background and objectives: Previous studies have demonstrated that serum NT-proBNP was lower in the general population with MetS. NPs are a set of peptide-hormones that are well known for their role in cardiovascular homeostasis. The present study aims at determining the NT-proBNP serum levels in patients who have MetS in comparison to subjects apparently healthy and inhabiting Duhok city/ Kurdistan Region/Iraq.

Methods: A cross sectional research was conducted between 1st of June 2019 and 29th of May 2020 at Duhok Diabetic Clinic. NT-pro BNP level was determine in 80 subjects with MetS (20 Males and 60 Females; 20-70 years) and 20 apparently healthy subjects. The data were analyzed by using the SPSS software version 23.T-test was used to compare between proportions.

Results: The mean ± SD of all demographic parameters (WC, SBP, and DBP) were significantly higher in subjects with MetS in comparison to apparently healthy subjects except age which was none significant.The parameters of biochemistry(triglyceride, TC,FBS, and insulin) in subjects with MetS also were substantially higher compared to apparently healthy subjects with the exception of HDL-C and NT-proBNP, which in apparently healthy subjects were higher compared to the MetS. The current data indicate that the NT-proBNP differentiates significantly between ages, BMI, DBP, FBS, and TG, with TC ($p<0.05$).

Conclusions: Metabolic components are correlated with a lower serum concentration NT-proBNP. These figure out increase the probability that decreased serum levels of NT-proBNP are an indicator of MetS, which could have important pathophysiological and clinical consequences.

Key words: Metabolic syndrome, Natriuretic peptide,Dyslipidemia, blood pressure.

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Introduction

Metabolic syndrome is composed of a set of abnormal physical and laboratory findings that take place as a result of the integration of physiological, clinical, biochemical, and metabolic factors. As a result, atherosclerosis, CVD, and overall mortality noticeably increase [1].

The principle physiological and clinical indications of metabolic syndrome are represented by reduced high density lipoprotein-cholesterol, elevated TGs, high BP as well as increased FBS which are in direct relation to the increase of adipogenesis and weight gain at large; and to intra-abdominal and increased waist circumferences [2]. MetS is mainly caused by elevated calorie food intake, i.e. lack of exercise and over nutrition side by side with some other factors, namely epigenetic, genetic, as well as environmental [3], [4], [5].

NT-proBNP, i.e. the circulating hormones caused by secretion from ventricular myocytes, underlines araised ventricular mechanical load and stress and stands for an inactive fragment of prohormone proBNP [6],[7]. NT-proBNP represents cardiac biomarkers confirmed for the purpose of assessing the left ventricular dysfunction and CHF [3]. Individuals with high left ventricular end-diastolic pressure have lower levels of NT-proBNP in obese [8]. There is activation of the reninangiotensin-aldosterone system in obese patients [9]. There is binding of the common receptor, guanylyl cyclase-A by the brain natriuretic peptide. This results in biologic actions via a cGMP-dependent pathway which practices a restraining impact on the RAAS axis [10]. Accordingly, the RAAS may be activated by low levels of natriuretic peptide. This may add to metabolic syndrome development in obese people in particular [11].

Two studies byLi *et al*. (2011) and Sezen *et al.* (2009) indicated a level of NT-proBNP in metabolic syndrome similar to that in normal subjects. This is on one hand[12], [13]. On the other hand, Olsen *et al.* (2005) found out a decreased level of NT-proBNP level in MetS side by side with a blunted NT-proBNP pulse pressure relationship in these patients[14].

In the current study, the role of NT-proBNP has been studied from different perspectives so as to shed light on the pathophysiological impact of hypertension as a component of MetS in the subject; which has a great function in the development of CVD. Since this study endeavors to predict the role of a significant potential risk factor, especially in subjects with metabolic syndrome, it may be the seminal work carried out in the Region as it focuses on subjects with metabolic syndrome and others who are apparently healthy in Duhok /Kurdistan Region/Iraq.

Patients and method

Biochemical analysis

Estimation of serum NT-pro BNP

Detection of serum NT-pro BNP, TC, HDL-C, triglyceride, insulin and blood glucose using specific kit (Roche) according to company protocol instructions using cobas 6000 autoanalyzer machine[15].

Statistical analysis

Through the SPSS software version 23 the data were analyzed and indicated as the normal and mean division. In comparison with proportions, T-test was used. In

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addition, one-way variance analysis (ANOVA) was used to compare different groups. Pearson correlation was used for the estimation of the relationship between variables. A p-value of < 0.05 has been statistically important in all experiments.

Results

The current study comprises 100 subjects, 80 with metabolic syndrome and 20 apparently healthy subjects. Table 1 demonstrates the laboratory and demographic properties of the study subjects. The mean ± SD of all demographic parameters (BMI, SBP and DBP) in patients with metabolic syndrome were substantially higher relative to relatively healthy people, with the exception of age, which did not matter. Same while biochemical parameters (triglyceride, TC,FBS, insulin, and HOMA-IR) were significantly higher in subjects with MetS in comparison to apparently healthy subject except HDL-C and NT-proBNP which were higher in apparently healthy subject in comparison to metabolic syndrome.

Table 1 general characteristic features of study population.

Study Variables		Mean ± SD		*P*- Value
		Metabolic syndrome (n=80)	Apparently healthy subject (n=20)	
Sex (No. and %)	Male	20 (25%)	10 (50%)	
	Female	60 (75%)	10 (50%)	
Age (years)		50.61 ± 10.90	51.20 ±11.53	NS
BMI (kg/m^2)		34.83 ± 5.89	23.15 ± 1.12	< 0.001
Waist circumference (cm)		114.53 ± 10.62	90.95 ± 6.63	< 0.001
SBP (mmHg)		139.81 ± 17.61	118.00 ± 5.71	< 0.001
DBP (mmHg)		87.62 ± 8.03	77.25 ± 3.79	< 0.001
Cholesterol (mg/dl)		182.33 ± 42.09	150.65 ± 31.21	< 0.01
Triglyceride (mg/dl)		226.23 ± 132.91	105.30 ± 29.63	< 0.001
HDL- Cholesterol (mg/dl)		37.88 ± 8.07	45.30 ± 8.50	<0.01
FBS (mg/dl)		195.53 ± 67.62	90.60 ± 7.45	< 0.001
Insulin (µU/mL)		36.31 ± 24.28	6.65 ± 1.87	< 0.001
HOMA-IR		17.23 ± 12.43	1.40 ± 0.40	< 0.001
NT-proBNP (pg/ml)		36.31 ± 13.68	53.05 ± 11.62	< 0.001

Serum NT-proBNP and waist circumference (WC)

Table 3.5 illustrates the mean±SD of serum NT-proBNP levels ranked on the base of by waist circumference. Patients and apparently healthy subjects with central obesity had lower levels of serum NT-proBNP in comparison to those with normal group (p< 0.001).

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Table 2 Serum NT-proBNP levels ranked on the base of waist circumference

Variable	mean±SD		*p*- value
	(WC) <102 cm in male, <88 cm in female (N=20)	(WC) ≥102 cm in male, ≥88 cm in female (N=80)	
NT-proBNP (Pg/ml)	53.05±11.68	36.31±13.68	<0.001

Serum NT-proBNP and systolic blood pressure (SBP)

Regarding systolic blood pressure, Table 3 demonstrates that there was no statistically significant distinction in NT-proBNP between high systolic blood pressure subjects in comparison with normal subjects (P>0.05).

Table 3 serum NT-proBNP levels stratified by systolic blood pressure.

Variable	mean±SD		*p*-value
	SBP <130 mmHg (N=43)	SBP ≥130 mmHg (N=57)	
NT-proBNP (Pg/ml)	38.60±18.88	40.45±11.01	NS

Serum NT-proBNP and diastolic blood pressure (DBP)

Regarding DBP, Table 4 demonstrates thatpatients with normal DBP and apparently healthy subjects got a mean of the serum NT-proBNP level (p< 0.001) that was significantly higher in comparison to the subjects with high DBP.

Table 4 serum NT-proBNP levels stratified by diastolic blood pressure.

Variable	mean±SD		*p*- value
	DBP <85 mmHg (N=40)	DBP ≥85 mmHg (N=60)	
NT-proBNP (Pg/ml)	49.22±15.14	33.28±10.74	<0.001

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Serum NT-proBNP and fasting blood sugar (FBS)

The mean±SD of the levels of serum NT-proBNP ranked on the basis of fasting blood sugar is presented in Table 5. Patients and apparently healthy subjects with high blood sugar had lower levels of serum NT-proBNP in comparison to those with normal group ($p< 0.001$).

Table 5 serum NT-proBNP levels stratified by fasting blood sugar.

Variable	mean±SD		*p*- value
	Serum FBS level <100 mg/dl (N=20)	Serum FBS level ≥100 mg/dl (N=80)	
NT-proBNP (Pg/ml)	53.05±11.66	36.31±13.68	<0.001

Insulin and serum NT-proBNP

The mean±SD of the levels of serum NT-proBNP ranked according to insulin is shown in Table 6. Patients and apparently healthy subjects with normal insulin had higher levels of serum NT-proBNP in comparison to those with high insulin group ($p< 0.05$).

Table 6 Levels of Serum NT-proBNP ranked according to insulin

Variable	mean±SD		*p*- value
	Level of Serum insulin <24.9 µU/mL (N=46)	Level of Serum insulin ≥24.9 µU/mL (N=54)	
NT-proBNP (Pg/ml)	43.80±15.65	36.12±13.29	<0.05

Serum NT-proBNP and HDL-cholesterol

Table 8 illustrates the mean±SD of the levels of serum NT-proBNP ranked according to the HDL-cholesterol. There was no significant relation in NT-proBNP between subjects with low HDL-C and normal group ($P> 0.05$).

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Table 8 serum NT-proBNP levels stratified by HDL-cholesterol.

Variable	mean±SD		*p*- value
	Level of Serum HDL-C<40 (mg/dl) in male, <50 (mg/dl) in female(N=72)	Level of Serum HDL-C ≥40 (mg/dl) in male, ≥50 (mg/dl) in female (N=28)	
NT-proBNP (Pg/ml)	38.84±14.91	41.75±14.78	NS

Serum NT-proBNP and triglyceride (TG)

Regarding triglyceride, Table 7 demonstrates that there was a highly significant relation in serum NT-proBNP levels ($p< 0.01$).

Table 7 levels of Serum NT-proBNP Ranked according to triglyceride.

Variable	mean±SD		*p*- value
	Level of Serum TG<150 mg/dl (N=45)	Level of Serum TG≥150 mg/dl (N=55)	
NT-proBNP (Pg/ml)	44.06±14.63	36.05±14.16	<0.01

Correlation analysis

According to Pearson correlation coefficient (r), there were significant negative correlation of NT-proBNP with BMI, DBP, TC, triglyceride, fasting blood sugar, insulin and HOMA-IR. Furthermore, NT-proBNP was significantly positive correlations in age. On the other hand, NT-proBNP shows non-significant correlation with systolic blood pressure and HDL-C (Table 9).

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Table 9 correlation between NT-proBNP (pg/ml) and Study Population Parameters.

Parameters	(r)	*p*- value
Age (years)	0.442	<0.001
BMI (kg/m^2)	-0.350	<0.001
Waist circumference (cm)	-0.401	<0.001
SBP(mmHg)	0.103	NS
DBP(mmHg)	-0.390	<0.001
Total cholesterol (mg/dl)	-0.324	<0.01
Triglyceride (mg/dl)	-0.307	<0.01
HDL-C (mg/dl)	0.144	NS
FBS (mg/dl)	-0.225	<0.05
Insulin (µU/mL)	-0.311	<0.01
HOMA-IR	-0.280	<0.01

Discussion

Overview

The current study is the principal cross sectional study that estimates the serum NTproBNP level among patients with metabolic syndrome in Duhok city. It has put forward clear evidence that subjects with Mets had lower levels of NTproBNP in comparison to apparently healthy subjects. The results also confirm a negative association between serum NTproBNP levels and the whole metabolic syndrome components save elevated blood pressure and HDL-cholesterol.

Wang et al. (2007) analysed the association between serum levels of BNP and the metabolic risk factors in 3333 Framingham study participants who had no heart failure. It was found out that BNP had positive association with SBP and HDL-C, yet its association with BMI, DBP, total cholesterol, fasting glucose and insulin resistance was negative[16]. Olsen *et al*. reported similar findings in a large-scale Danish investigation [14] and arrived at results that were compatible with the results of the current research. However, to the present researcher's best knowledge, this study is

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viewed as the pioneering one in terms of examining the individual and collective effects of serum NT-proBNP levels among subjects with metabolic syndrome in Duhok, Kurdistan Region (Iraq).

Serum NT-proBNP and obesity

In the whole population of the current study,levels of serum NT-proBNP were significantly higher in normal weight in comparison to overweight and obese ($p< 0.001$) (Table 3.4). In spite of that, again in the whole study population, there had been lower levels of serum NT-proBNP in persons having central obesity compared to the normal group ($p< 0.001$) (Table 3.5). There was also a significant negative correlation between BMI and waist circumference ($r= -0.350$, $p<0.001$; $r= -0.401$, $p<0.001$) in both (MetS subjects and apparently healthy subjects) respectively (table 3.15).

As already highlighted, there is a close link between the NP system and adiposity [17], [18]. The abundant availability of NP clearance receptors in adipose tissue [19]suggests adipocytes participation in removing NPs from the circulation. On this basis, there is an increase of the clearance of natriuretic peptide concomitant with the possible occurrence of a condition of decreased NP concentration in obese patients. Added to that, there are potential ipolytic impacts of NPs in the isolated human fat cells and in adipocytes in vivo through cyclic guanosine monophosphate (cGMP)-medicated phosphorylation [20]. Hence, there could be an increase inskeletal muscle and lipid accumulation in adipose tissue [21], and the perpetuation of the obese state by a reduced NP signalling.

In the cohorts of the Framingham Heart Study, people who are obese had lower serum BNP levels compared to those with normal weight [17].Also recently, there has been a negative association between serum BNP and BMI[17], [22].

Blood pressure andserum NT-proBNP

It has been illustrated that in the whole population of the current study the serum NT-proBNP levels were significantly higher in normal diastolic blood pressure in comparison to the abnormal group ($p< 0.001$) (Table 3.7). This is on one hand. On the other hand, concerning NT-proBNP levels, there was no significant relation in NT-proBNP between subjects with high SBP and those in the normal group ($p> 0.05$) (Table 3.7).

There was a negative correlation betweenlevels of serumNP and all the components of MetS except elevated blood pressure and HDL-C. Just opposite to other metabolic factors, in Li's study, there was an association between elevated SBP and higher BNP levels [13].In line with such data, the current study has come out with the finding that there was an association between the low serum NT-proBNP levels and almost all the components of the Mets save the elevatedSBP as there was an association with higher serum NT-proBNP levels. This indicates that there is a haemodynamicimpact of blood pressure on the NP synthesis. The oversight that there are more different relations between serum NT-proBNP levels and SBP than to other metabolic components proposes the separate segregation of blood pressure from other MetS components [23]. In their Insulin Resistance Atherosclerosis Study, Hanley *et al.* [23] a head factor analysis was used for the identification of 2 "factors", namely a

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metabolic factor that consisted ofglycaemic measures, BMI, triglycerides, and HDL-C, and a blood pressure factor which comprised DBP and SBP . There was also a correlation between fasting insulin and the metabolic factor, but not with that of the blood pressure.

Blood glucose, insulin and serum NT-proBNP

The current study indicates that in normal heart peoples, a negative association existed between fasting blood sugar and insulin on one hand and with serum Nt-proBNP levels in contrast. Added to that, the level of serum NT-proBNP levels were significantly lower in patients of MetS subgroups ranked according toFBS and insulin than the apparently healthy subjects. In the whole study population, lower mean values of serum NTproBNP levels were found in the patients and apparently healthy subjects with high blood sugar and high insulin levels in comparison to those in the normal group, at the time when the differences were statistically significant ($p < 0.001$) ($p < 0.05$) (Table 3.8, 3.9).

According to Bao*et al.* (2011) there was an inconsistent relationship between fasting glucose and BNP[24]. They found out a negative association between fasting glucose and NT-proBNP. However, inOlsen *et al.'s* study *(*2005).There was a consistent inverse relationship between insulin level and NTproBNP level. It has been suggested by some experimental perceptions that low NP levels could predispose to insulin resistance (IR)[14]. Johnston *et al. (*1989) stated that a greater activation of the renin-angiotensin system could be resulted from a reduced natriuretic peptide activity[25]. Also, the improvement of insulin resistance via various mechanisms is promoted by the activation of the renin-angiotensin system [26]; hence subsuming the inhibition of intracellular insulin signalling, enhancement ofinflammation, oxidative stress, reduce of adipocyte differentiation, and a diminishedperfusion to the pancreas and skeletal muscle.

Serum NT-proBNP and lipid profile

In this study, lipid profile was investigated in subjects with Mets and apparently healthy subject. The comparison between groups illustrated that serum total cholesterol levels varied significantly among groups (metabolic syndrome: 182.33 ± 42.09 mg/dl, apparently healthy subject: 150.65 ± 31.21mg/dl, $P< 0.01$). The same result was obtained for triglyceride (metabolic syndrome: 226.23 ± 132.91 mg/dl, apparently healthy subject: 105.30 ± 29.63 mg/dl, $p < 0.001$). in contrast, the variation in serum HDL (metabolic syndrome: 37.88 ± 8.07 mg/dl, apparently healthy subject: 45.30 ± 8.50 mg/dl, $p < 0.01$ (Table 3.1). as we illustrated in (table 3.11, 3.12) patients and apparently healthy subjects with high cholesterol and high triglyceride had lower levels of serum NT-proBNP in comparison to those with normal weight ($p < 0.05$). in contrast, no statistically significant distinction in Nt-proBNP was found between subjects with low HDL-C and normal group ($p > 0.05$) (Table 3.13).

In the previous large-scale investigations, a negative correlation was found between serum NT-proBNP as well as serum total cholesterol and triglyceride, yet the association was positive with HDL-C [16].The causal relationship between natriuretic peptide and cholesterol or triglyceride is unclear and might not be direct. There could

be promotion of lipid accumulation inskeletal muscleand adipose tissue by reduced natriuretic peptide signalling could promote [21] whichresults in the advancement of visceral adiposity that are associated with dyslipidemia.

Conclusions

On the basis of the results arrived at by the present study, it is concluded that:

- The majority of the study participants were female, obese and overweight, abnormalwaistcircumference and hyperglycemia.
- Metabolic components are correlated with a lower serum concentration NT-proBNP. These figure out increase the probability that decreased serum levels of NT-proBNP are an indicator of MetS, which could have important pathophysiological and clinical consequences.
- HighBMI, waistcircumferences, DBP, FBS, insulin, cholesterol and triglyceride levels showed low levels of NT-proBNP levels.
- There were significant association betweengender, age, components of metabolic syndrome and serum NT-proBNP.
- Serum NT-proBNP is negatively correlated withBMI, TC, Triglyceride, blood glucose, insulin, DBP and HOMA-IR.
- NT-proBNP had a significant positive correlation with age.

Conflict of Interests.

There are non-conflicts of interest .

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الخلاصة

الخلفية والأهداف: أظهرت الدراسات السابقة أن مصل ن–تيرمينال برو برين ناتريورتيك ببيتايد كان أقل في عموم السكان الذين لديهم متلازمة الايض مقارنة بالأشخاص الأصحاء ظاهريا. ناتريورتيك ببيتايد هي عبارة عن مجموعة من هرمونات الببتايد المعروفة جيدا بدورها في توازن القلب والأوعية الدموية. تهدف الدراسة الحالية إلى تحديد مستويات مصل ن–تيرمينال برو برين ناتريورتيك ببيتايد في المرضى الذين لديهم متلازمة الايض مقارنة بالأشخاص الأصحاء ظاهريا المقيمين في مدينة دهوك / إقليم كردستان / العراق.

طريقة العمل: تم إجراء بحث مقطعي في الفترة ما بين 2019/6/1 و 2020/5/29 في مركزامراض السكر بمدينة دهوك. تم تحديد مستوى مصل ن–تيرمينال برو برين ناتريورتيك ببيتايد في 80 شخصا لديهم متلازمة الايض (20 ذكر و60 أنثى، 20–70 عاما) و 20 شخصا يبدو أنهم يتمتعون بصحة جيدة. تم تحليل البيانات باستخدام الإصدار 23 من برنامج (اس بي اس اس). تم استخدام (تي–تيست) للمقارنة بين النسب.

النتائج: اظهرت النتايج ان معدل عامل التلف لجميع القيم الديموغرافية (محيط الخصر وضغط الدم الانقباضي وضغط الدم الانبساطي) أعلى بشكل ملحوظ في الأشخاص الذين لديهم متلازمة الايض مقارنة بالأشخاص الأصحاء ظاهريا باستثناء العمر، والذي لم يكن ذات علاقة. كانت قيم الكيمياء الحيوية (الدهون الثلاثية، الكوليسترول الكلي، نسبة السكر في الدم، و نسبة الأنسولين) في الأشخاص الذين يعانون من متلازمة الايض أعلى أيضا مقارنة بالأشخاص الأصحاء ضاهريا باستثناء (كوليسترول البروتين الدهني عالي الكثافة و ن–تيرمينال برو برين ناتريورتيك ببيتايد)، والتي كانت أعلى في الأشخاص الأصحاء ظاهريا مقارنة مع اشخاص الذين لديهم متلازمة الايض. تشير البيانات الحالية إلى أن ن–تيرمينال برو برين ناتريورتيك ببيتايد يفرق بشكل كبير بين الأعمار، مؤشر كتلة الجسم، ضغط الدم الانبساطي، نسبة السكر في الدم، والدهون الثلاثية, والكوليسترول الكلي (P اقل من 0.05)

الاستنتاجات: المكونات الايضية تكون مرتبطة مع سيرم منخفضة التركيز ل ن–تيرمينال برو برين ناتريورتيك ببيتايد. وهذا يظهر زيادة الاحتمالية بأن مستويات مصل ن–تيرمينال برو برين ناتريورتيك ببيتايد المنخفضة هي مؤشر على متلازمة الايضية، والتي يمكن أن يكون لها عواقبسريرية ومرضية فسيولوجية.