The Relation of QT Interval Parameters and Osteopontin in Obese Women

Obez Kadınlarda QT İnterval Parametreleri ve Osteopontin Düzeyleri Arasındaki İlişki

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ABSTRACT Objective: An elevated mortality risk has been reported in subjects with increased QT interval parameters. Higher prevalence of increased QT interval parameters has been found in patients with type 1 and type 2 diabetes, coronary heart disease and obesity. Osteopontin is a chemokine which is agreed to be an inflammatory mediator and is found to be associated with atherosclerosis, diabetes and obesity. Our aim was to investigate relationship of osteopontin and corrected QT interval and QT dispersion in obese patients. **Material and Methods:** The study included 45 obese female patients and 22 age and sex matched non obese control subjects. As well as making physical and antropometric examinations, fasting plasma glucose, post prandial plasma glucose, lipid profile, osteopontin levels were obtained in all female person. QT interval and QT dispersion were measured from electrocardiograms of all the women and corrected QT was calculated. We then compared all the parameters in two groups and seeked correlations between them. **Results:** Obese group had significantly higher plasma osteopontin levels, QTc interval and QTc dispersion than the control group. We also found positive correlations between OPN levels and QT interval parameters. **Conclusion:** In conclusion we demonstrated that obese women who had higher osteopontin levels also had longer QTc interval and QT dispersion than non obese ones. As long QT interval and dispersion are markers of increased risk of death and as osteopontin is agreed to be a marker of inflammation, and perhaps of atherosclerosis, we may speculate that high osteopontin may be used as a marker of mortality risk.

Key Words: Osteopontin; obesity; electrocardiography

ÖZET Amaç: QT interval parametrelerinde artma saptanan kişilerde artmış mortalite riski raporlanmıştır. Tip 1 ve tip 2 diyabetik hastalar, koroner kalp hastaları ve obezlerde artmış QT interval ve QT dispersiyon sıklığı saptanmıştır. İnflamatuar mediatör olarak kabul edilen bir kemokin olan osteopontin aterosklerozis, diyabet ve obezite ile ilişkili bulunmuştur. Çalışmamızda obez hastalarda osteopontin and QT interval parametreleri arasındaki ilişkiyi araştırıldı. **Gereç ve Yöntemler:** Çalışmaya 45 obez, 22 nonobez kontrol kadınları dahil edildi. Bütün kadınlarda antropometrik değerlendirmelere ek olarak açlık kan şekeri, tokluk kan şekeri, lipid profili ve osteopontin tetkikleri yapıldı. Vakaların elektrogramlarından QT intervali ve QT dispersiyonu, düzeltilmiş QT hesaplandı. Sonra iki grup içindeki tüm parametreler kıyaslandı ve aralarında korelasyon araştırıldı. **Bulgular:** Obez grubun kontrol gruptan daha yüksek osteopontin değerlerine ve uzamış QTc interval ve QT dispersiyonuna sahip oldukları saptandı. Ayrıca osteopontin ile uzamış QTc intervali ve QT dispersiyonu arasında pozitif korelasyon bulundu. **Sonuç:** Sonuç olarak yüksek osteopontin seviyelerine sahip obez kadınların nonobez olanlara oranla uzamış QTc interval ve QT dispersiyonuna sahip olduklarını saptadık. Uzamış QT parametreleri artmış mortalite riskine sahip olduğundan ve osteopontinin inflamasyon ve belki ateroskleroz belirteci olduğu kabul edildiğinden yüksek osteopontin değerlerinin mortalite riski belirleyicisi olarak kullanılabileceği spekülasyonunu yapabilir miyiz, diye düşünmekteyiz.

Anahtar Kelimeler: Osteopontin; obezite; elektrokardiyografi

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The QT interval reflects the total duration of ventricular myocardial depolarization and repolarization; its prolongation is associated with sudden death and poor survival.[1] An excess mortality risk has been reported in normal subjects with QT interval prolongation.[2] Higher prevalence of corrected QT interval (QTc) and QT interval dispersion(QTd) prolongation has been found in patients with Type 1 diabetes,[3-6] Type 2 diabetes,[7-9] coronary heart disease,[10] and end stage renal disease.[11]

Osteopontin (OPN) is an extracellular matrix associated protein involved in monocyte motility, inflammatory immune response, mineralization in bone and kidney, cell survival, inflammation, and tumour biology[12-18] and is expressed in activated macrophages, T cells, osteclasts, hepatocytes, smooth muscle, endothelial and epithelial cells.[12-16] OPN plasma levels are found elevated in various diaeases including atherosclerosis, inflammatory bowel disease, granulomatous inflammatory disease, rhematoid arthritis, multiple sclerosis, several types of cancer, obesity, and cardiac fibrosis.[16,17,19]

As the atherosclerotic lesion is proved to be highly inflammatory,[15] inflammatory cytokines are accepted to predict cardiovascular events such as coronary heart disease, stroke and congestive heart failure.[13,14,17] OPN is also agreed to be an inflammatory mediator[17] and as OPN levels were found to be associated with the presence and extent of coronary artery disease, it may be speculated that increased expression of OPN may promote the development of atherosclerosis.[14,20]

The chronic inflammation associated with obesity; an important risk factor for atherosclerosis; is determined by increased systemic concentrations of inflammatory markers and cytokines in patients and animal models of obesity.[16] The main origin of this systemic inflammatory response is shown to be located in adipose tissue.[21] Adipose tissue produces a number of inflammatory cytokines which may be found elevated in the serum of obese patients like OPN.[22] It was also confirmed that QTc and QTd have been prolonged in obesity[23-26] and weight loss has been accompanied by shortening of QTc and QTd.[27,28]

Keeping in mind the complex relations among atherosclerosis, obesity, and OPN we investigated the relationship of OPN and QT interval parameters in obese women.

MATERIAL AND METHODS

This study was carried out between September 2008 to December 2008 in the Outpatient Clinic Ankara Education and Research Hospital. The study included 45 morbidly obese female patients and 22 age and sex matched nonobese control subjects. All the women were normotensive.

Patients with male gender, diabetes mellitus, glucose intolerance, conditions which may effect metabolic parameters (such as tiroid dysfunctions in history or nowadays), pregnancy, chronic diseases such as hypertension, infection, coronary artery disease and who were taking medicine were excluded. As females and males have different amount of fat tissue, in order to obtain a homogenous group we included only females in our study. The local ethics commitee approved this study and all the subjects gave written informed consent. The study was performed according to the Helsinki Declaration 2008.

After detailed physical examination, body weight, height, waist and hip circumference, waist-hip ratio (WHR) and body fat were measured. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Women were classified according to BMI such as obese ≥ 30 kg/m^2. Waist and hip circumferences were measured when fasting by a non elastic measurement, as upright position.

Blood pressure was determined at least three times at the right upper arm, and the mean was used in the analysis. The patients who were taking antihypertensive drugs or patients whose determined mean blood pressure levels ≥140/90 mmHg were accepted as hypertensive and excluded.

Blood was withdrawn after 12h of overnight fasting, at 08.30 a.m. for fasting plasma glucose (FPG), serum total and HDL cholesterol, triglyceride, and osteopontin levels. Another blood sample was taken for postprandial plasma glucose (PPPG) 2 hours after breakfast.

Electrocardiograms (ECG) were obtained for QT interval analysis. Subjects were excluded from the present study if they were not in sinus rhythm, had bundle branch block, or had other interventricular conduction delay. These exclusions were imposed as interpretation of such ECGs is difficult and the resultant prolonged QT intervals may be misleading. It was written that the cause of cardiac death might be wrongly construed as a function of the duration of intraventricular conduction delays.[29] RR and QT intervals were manually measured in five consecutive cycles on lead V5 by two experts on a 12 lead resting ECG printed at a paper speed of 25 mm/s. The QT interval was taken from the beginning of the QRS complex to the end of the downslope of the T wave. The QT interval corrected for the previous cardiac cycle length (QTc) was calculated according to the Bazzet's Formula ($QTc= QT/ RR^{½}$).[30] The QTc for each subject was taken as a mean value of the five calculated intervals. The QT dispersion was defined as the difference between the longest and the shortest QT interval in any lead and at least 10 leads had to be assessable for an ECG to be included in the analyses.

Plasma glucose, total cholesterol, triglyceride (TG) and high density lipoprotein (HDL) cholesterol concentrations were determined by enzimochalorimetric spectrophotometric methods in a Roche/Hitachi molecular PP autoanalyser. Low density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol were calculated by the Friedewald Formula (VLDL= TG/5; LDL= Total cholesterol-HDL-TG/5).

An indirect measure of insulin resistance was calculated from the fasting plasma insulin (μ unite/mL) x fasting plasma glucose (mmol/L)/22. 5 formula as homeostasis model assessment (HOMA-IR).

For the measurements of OPN, 5 mL blood samples were collected in EDTA containing tubes. These blood samples were santrifuged 4000 cycle/ min in 30 minutes. Plasma was then stored at -80°C. Plasma OPN levels were measured by an enzyme-linked immunosorbent assay (ELISA) using a commertaily available kit (Human OPN assay kit, Biotec USA).

After calculating the statistical analysis of the obese and nonobese control groups, we made the correlation analysis of the obese group.

By using SPSS version 11,5 (Customer ID 30000105 930) we performed the calculations. We presented our data as mean ± SD. Student t-test was used to compare the groups in a parametric way. One way variation analysis (ANNOVA) was used to compare study groups with each other. We used Tukey's multiple comparison test for post hoc analysis. A p value of < 0.05 was considered as statistically significant. Pearson correlation coefficient was used for the correlation analysis.

RESULTS

We performed the study with 45 obese patients and 22 nonobese control subjects. All the demographic and laboratory findings of obese patients and control groups were compared and demonstrated in Table 1.

TABLE 1: Characteristics of patient and control groups.

	Patients (n= 45)	Control (n= 22)	p
Age (yr)	43.65 ± 9.08	40.60 ± 7.96	NS
BMI (kg/m^2)	34.78 ± 5.15	22.28 ± 2.62	< 0.001
Waist circumference (cm)	97.60 ± 11.35	72.86 ± 6.32	< 0.001
Hip circumference (cm)	115.22 ± 10.36	97.68 ± 5.52	< 0.001
WHR	0.85 ± 0.18	0.74 ± 0.04	= 0.008
Body fat (%)	33.81 ± 8.54	13.87 ± 5.31	< 0.001
FBG (mg/dL)	98.00 ± 11.63	88.27 ± 10.08	< 0.001
PPBG (mg/dL)	117.60 ± 23.40	97.31 ± 17.58	< 0.001
Cholesterol(mg/dL)	207.60 ± 41.22	174.59 ± 27.03	< 0.001
TG (mg/dL)	150.13 ± 66.75	103.86 ± 62.06	= 0.008
LDL (mg/dL)	124.95 ± 37.65	98.77 ± 21.32	= 0.004
VLDL (mg/dL)	30.02 ± 13.35	20.77 ± 12.41	= 0.008
HDL (mg/dL)	52.50 ± 12.08	55.18 ± 12.33	NS
HOMA-IR	2.95 ± 1.43	1.79 ± 0.97	< 0.001
QTc (ms)	540.10 ± 40.10	400.00 ± 10.00	< 0.001
QTd (ms)	61.00 ± 12.10	42.00 ± 0.90	< 0.001
OPN (ng/mL)	289.99 ± 82.03	245.87 ± 55.24	= 0.026

BMI: Body mass index, WHR: Waist hip ratio, FBG: Fasting blood glucose, PPBG: Post prandial blood glucose, TG: Triglyceride, LDL: Low density lipoprotein cholesterol, VLDL: Very low density lipoprotein cholesterol, HDL: High density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment, QTc: Corrected QT, QTd: QT dispersion, OPN: Osteopontin. Data are presented as mean ± SD. NS: Nonsignificant.

TABLE 2: Summary of correlation analysis of obese patients.

n= 45	OPN	BMI	QTc	QTd	HOMA-IR
OPN	1	p< 0.05 r= 0.302	p< 0.05 r= 0.316	p< 0.05 r= 0.399	
BMI	p< 0.05 r= 0.302	1			p< 0.05 r= 0.355

BMI: Body mass index, HOMA-IR: Homeostasis model assessment, QTc: Corrected QT, QTd: QT dispersion, OPN: Osteopontin.

In Table 1 obese and control groups were compared. As expected BMI, waist and hip circumference, WHR, body fat measurements were found to be significantly higher in obese group than control group (respectively p< 0.001, p< 0.001, p< 0.001, p= 0.008, p< 0.001) (Table 1).

Significantly higher FBG, PPBG, total and LDL, VLDL cholesterol, TG, HOMA-IR, QTc, QTd and OPN levels were observed in obese patients than nonobese subjects (respectively p< 0.001, p< 0.001, p= 0.001, p= 0.004, p= 0.008, p= 0.008, p< 0.001, p< 0.001, p< 0.001, p= 0.026) (Table 2). However no differences were observed in obese patients and control women as age, HDL cholesterol levels.

We then made the correlation analysis in obese group and found statistically significant positive correlation between OPN and QTc, QTd, BMI, between BMI and HOMA-IR (Table 2).

DISCUSSION

Our data showed that OPN levels of obese patients were significantly higher than those levels of nonobese controls, also QTc and QTd of the obese patients were increased. In obese group OPN levels were found to be positively correlated with QTc and QTd.

The QT interval corresponds to the time necessary for the complete ventricular electrical excitation and recovery and is therefore the measurement of the duration of the electrical systole, which includes ventricular depolarization and repolarization that is the total duration of the ventricular electrical activity.[31] The QT interval varies inversely with heart rate so that the higher the heart rate the shorter QT and vice versa. Accordingly it should be corrected for heart rate, thus generating the QTc. QT dispersion results from inhomogenity of repolarization times, and is a marker of arrhythmogenesis. QTc and QTd are increasingly being recognized as prognostic factors for sudden death in patients with coronary heart disease[10,32], chronic heart failure,[33] peripheral vascular disease,[34] chronic renal disease[11] and essential hypertension.[35] Prolonged QT interval parameters were also determined in Type 1[3-6] and Type 2 diabetes mellitus[7-9] and obesity.[23-28]

OPN is an inflammatory marker mainly derived from adipose tissue and also induces the expression of other inflammatory cytokines and chemokines in peripheral blood mononuclear cells.[36] It was observed that plasma OPN levels were increased in overweight and obese patients, and further elevated in obesity associated diabetes.[16,37-39] Weight loss was shown to reduce OPN plasma levels in obese.[37,39] Kepping in mind the relation of atherosclerosis with inflamation, OPN was also investigated in studies about atherosclerosis and it was reported that OPN was a novel component of human atherosclerotic plaques.[40] It was also shown that OPN expression on atherosclerotic plaques was closely related with the severity of atherosclerosis and calcification.[41] In our obese patients, OPN levels were found to be higher as intervals of QTc and QTd . Positive correlation between QT interval parameters and plasma OPN levels comfirmed the relation between them. As in our study we demonstrated that OPN correlated with QT intervals, it will be an interesting question if we can use OPN as a risk marker of arrhythmias or sudden death at least in follow-up of the patients. One may put forward the opposition of the higher price of measuring OPN levels, compared to recording QT intervals; we are only making a speculation and posing the question as; who can predict what scientific developments may exhibit in the future.

The pathologies of QTc prolongation remains poorly understood, although cross-sectional studies suggest a role for several risk factors including

female sex, ischemic heart disease, high glycemic levels, gene mutations, blood pressure.[42] A higher prevalence of QTc prolongation in women than in men has been reported by other investigators[43]. Sex based or sex hormone associated differences in myocardial cell function have also been documented[44]. As the identification of risk factors for prolonged QTc is of clinical relevance and it would enable the targeting of people at high risk of cardiovascular events and enable the application of risk lowering strategies we intended to tightly follow up our female obese patients.

Gunti et al. found an independent association between incidence of QTc prolongation and BMI in their Type 1 diabetic patients, but only in women. Their finding suggested that being extremely thin or overweight is not beneficial for women with diabetes.[42] In our study our obese subjects who had high BMI, waist and hip circumference, WHR, body fat ratio had prolonged QTc and QTd as well as high OPN levels, but we could not be able to show any correlation, positive or negative between QT interval parameters and those obesity parameters. We think that in order to enlighten the discrepancy between our and their study, further examinations are needed.

A close relation between increased QTc and higher plasma glucose concentrations has been reported in nondiabetic subjects.[45] A link between hyperglycemia and prolonged QTc was also suggested in diabetics.[42] Acute hyperglycemia might have prolonged QTc probably by increasing the cytosolic calcium content, including oxidative stress and enchancing sympathetic activity.[42] In the present study, in spite of the higher plasma glucose levels either fasting or post prandial (higher but all in normal limits) in obese patients, no correlation was found between QT intervals and glucose levels. In numerous studies in diabetic and obese patients OPN levels were found to be high, if there is a relation between OPN levels and QT interval prolongation, a possible influence of blood glucose on QT intervals can not be excluded, and is worthy of further investigation.

In healthy young subjects QT interval was not found to be related to lipid parameters.[46] Total, LDL and VLDL cholesterol levels were higher in our obese patients, as well as QTc and QTd intervals but no correlation was found between these parameters. In a study of Korean healthy subjects, in normoglycemic female subjects, insulin resistance was found to be an independent determinant of the prolongation of QTc.[47] In our study HOMA-IR of obese group was statistically high, likewise we did not find a correlation between QT intervals and HOMA-IR. We hope that more satisfying results will be obtained, if we continue our studies with larger patient groups.

QTc is increasingly being recognized as prognostic factors for coronary heart disease and sudden death.[1,2,48] To reverse the high cardiac death rate, there is a need for a simple screening test, enabling early detection at a time when overt cardiac disease is absent. Identifying such high risk patients should enable us to target interventions earlier in order to reduce cardiac mortality and morbidity. The critical QTc value that confers particular vulnerability to ventricular arrhythmias probably varies individually[3], but Rana et al. recommends a cut of value of 510 ms to examine the patients with echocardiography, exercise testing or electrophysiological testing to detect reversible cardiac abnormalities, such as left ventricular dysfunction, reversible coronary ischemia and malignant arrhythmias.[29] We wonder if our obese patients with prolonged QT interval are also in danger of arrhytmias. It was advised to treat these patients with ultra aggresive statin, or ultra tight blood pressure control or early revascularisation or implantable cardiac defibrilators. We think whether this strategy will be cost effective or not, but it seems to worth investigating further.

In conclusion, data obtained in our study showed that in obesity which is a risk factor of atherosclerosis, plasma OPN level is high and QTc and QTd intervals are prolonged. Our study, besides reminding us about the dangers of QT interval parameters in obesity, makes us think about using OPN as a marker of atherosclerosis as well as a risk factor of arrhythmogenesis and using OPN plasma levels in evaluating the results of preventative measures of arrhythmias and sudden death.

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