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The Association between Serum Osmolality and Functional Myocardial Ischemia in Patients With Type-2 Diabetes Mellitus

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Abstract

Introduction: Serum osmolality(SO) is crucial to healthy vascular homeostasis, playing a vital role in tissue and organ perfusion. Although the effects of SO among diabetic patients are well known, its contribution to the development of myocardial ischemia or coronary atherosclerosis has not been well described in the literature. Our aim is to demonstrate the association between SO and coronary ischemia development.

Methods: In this study, we enrolled 205 consecutive diabetic patients who underwent coronary angiography and were diagnosed to have intermediate (50-70%) coronary lesions. Two groups were generated depending on a fractional flow reserve value ≤ 80, which is indicative of functional myocardial ischemia. Predictors of functional myocardial ischemia were also investigated.

Results: The multivariate analysis indicated that SO (p=0.043) and syntax score (p=0.013) were independently associated with functional myocardial ischemia. A SO value > 293 demonstrated a sensitivity of 82% and a specificity of 78% for the prediction of functional myocardial ischemia.

Conclusion: In this study, we demonstrated that high SO is associated with functional myocardial ischemia in diabetic patients with intermediate coronary lesions. In diabetic patients, the rheological properties of blood have been changed, which may lead to myocardial ischemia.

Keywords: Coronary artery disease, Osmolality, Functional ischemia

Introduction

Diabetes mellitus (DM) is a multi-systemic disease that emerges with glucose intolerance, insulin resistance, and courses with the involvement of various organs and tissues. DM is an important cause of mortality and morbidity, in which the leading cause of death is cardiovascular pathologies (1).

Endothelial dysfunction, increased inflammatory response, and changes in plasma lipid levels might contribute to the development of coronary artery disease in diabetic patients. It might also cause diastolic dysfunction by leading to amyloid accumulation in the myocardium. Diabetic patients with atherosclerosis have a higher risk of mortality and morbidity than non-diabetic patients. In diabetes, strict regulation of blood glucose levels decreases end organ damage, which has a positive effect on the prognosis (2, 3).

Serum osmolality (SO) is crucial for healthy vascular homeostasis, playing a critical role in tissue and organ perfusion 4. Increased glucose levels are characteristic of diabetic patients due to endothelial dysfunction and an increased inflammatory reaction, and they are associated with mortality and adverse events in many studies (5-7).

Although the effects of SO in diabetic patients are well-known, its contribution to the development of

myocardial ischemia or coronary atherosclerosis is not well described. In this study, we examined the relationship between SO and functional myocardial ischemia assessed using the fractional flow reserve (FFR) method, which is the gold standard for the diagnosis of coronary artery disease in patients with intermediate coronary lesions.

Method

Patient Characteristics

A total of 205 consecutive diabetic patients (214 lesions) who underwent coronary angiography and were diagnosed with intermediate coronary artery lesions were included in the study. All patients had strong indications for coronary angiography, such as increased levels of cardiac biomarkers, a positive treadmill test, or myocardial perfusion scintigraphy. Patients with any history of myocardial infarction (MI) in the prior week (n=6), coronary artery bypass graft (CABG) surgery, or prior percutaneous coronary intervention (PCI) (n=8) as well as patients with type-1 DM (n=5) were excluded. The local ethics committee approved this study.

Definitions

Hypertension (HT) was defined as any history of medication use or blood pressure > 140/90 mmHg obtained in two consecutive measurements. Patients whose fasting blood glucose level was > 126 mg/dL or who were on oral antibiotics/insulin medication were accepted as cases of DM. Chronic renal insufficiency was determined by a glomerular filtration rate (GFR) < 60 ml/min/1.73m2. GFR was calculated with the Cockgroft Gault formula. SO was calculated using the following Whortley formula: Osmolality=(2*Na+K) + BUN/2.6 +Glucose/18.

The hematological and biochemical analyses were performed by obtaining blood samples from all the patients following 10–12 hours of overnight fasting. The chronic medications and blood values of patients before the angiography were examined by a cardiologist. Patients who did not have any limitations were taken in for coronary angiography as scheduled.

Coronary Angiography, Syntax Score Calculation, and FFR Measurement

Using the Judkins method, coronary angiography was performed through the femoral artery for all of the patients, and the cine images were recorded at 15 fps. Next, the optimal angiographic views with minimal foreshortening were selected. Two experienced cardiologists, who were blinded to procedural data, performed all the quantitative coronary angiography (QCA) measurements using a semi-automated edge detection system (Infinix, Toshiba Medical Systems, Japan). After manually labeling the lesion start and end points, the program calculated the stenosis by automatically labeling the lesion and vessel contours. The syntax score (SS) was calculated for each patient using the SS calculator in line with the segment and localization criteria defined in the SYNTAX study. Epicardial arteries > 2 mm in segment length and with 5070%– stenosis according to QCA analysis were subjected to the FRR procedure.

Statistical Analysis

Continuous variables were expressed with mean ± standard deviation or median (interquartile range) values, whereas categorical variables were presented in percentages. Independent student t-tests and Mann–Whitney U tests were used for the comparison of continuous variables while the Chi-square test was used to compare the categorical variables. Multivariate logistic regression analysis was performed to identify the independent predictors of FFR values ≤80. The parameters used in calculating the SO (BUN, Glucose, Na, K) were excluded from the multivariate regression analysis to avoid multicollinearity. Variables that showed a significance value < 0.05 in the univariate analysis were included in the final regression model. A receiver-operating characteristic (ROC) analysis was performed to determine the optimal cutoff value of SO in the prediction of low FFR values. Data was analyzed using SPSS 22 for Mac (IBM, Armonk, NY, USA). Two-tailed p-values < 0.05 were considered to indicate statistical significance.

Results

A total of 205 diabetic patients with intermediate coronary artery lesions (a total of 214 lesions) were included in the study. The mean age of the patients involved in this study was 67, and 70% were male. The baseline hematologic and biochemical characteristics of the patients are presented in Table 1. Two groups were generated depending on FFR values: Group 1: no

ischemia (FFR > 80) and Group 2: functional ischemia (FFR ≤ 80). In the univariate analysis, statistically significant differences were observed between the groups in terms of SO (p=0.034), LDL (p=0.041), CRP (p=0.052), and SS (p=0.005). In the multivariate analysis, SS (p=0.013) and SO (p=0.043) were independently associated with functional myocardial ischemia (Table 2). SO levels according to functional myocardial ischemia status (FFR value ≤ 80) are shown in Figure 1.

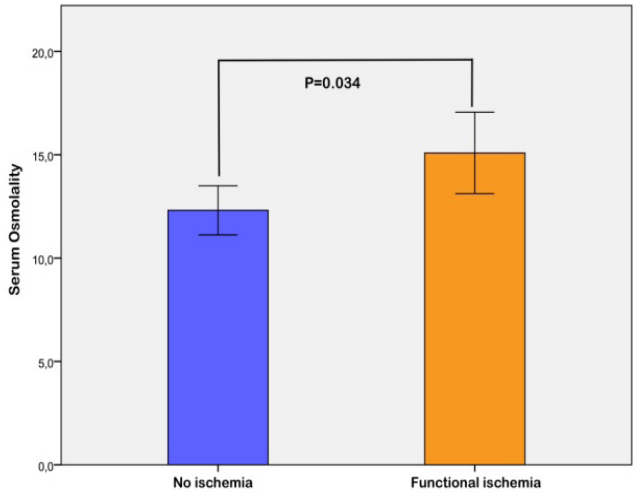

Fig1. *Serum osmolality (SO) values according to functional myocardial ischemia status*

ROC analysis was used to detect the cutoff value of SO in the prediction of functional myocardial ischemia to establish the optimal cutoff value to be used in clinical decision-making. A SO value >293 mmol/kg yielded an area under the curve (AUC) value of 0.78 (95% CI 0.72–0.86; p<0.001). Moreover, a SO value >293 mmol/kg showed a sensitivity of 82% and a specificity of 78% for the prediction of functional myocardial ischemia (Figure 2).

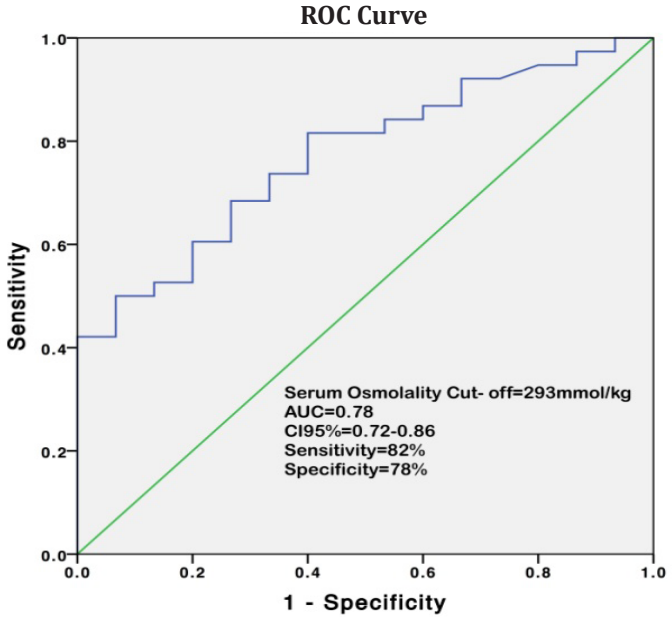

Fig2. *Receiver-operator characteristic (ROC) curve analysis for Serum Osmolality (SO) in prediction of Functional myocardial ischemia*

Table1. ***Baseline demographic, hematological and biochemical characteristics according to functional myocardial ischemia status***

Variables	Group-1 No ischemia (FFR > 80) N=82	Group-2 Functional ischemia (FFR <= 80) N=123	P value
Age (years)	63.39±9.2	62.23±7.8	0.721
Sex (Male %)	58.7	72.1	0.074
HT (%)	55.6	52.5	0.691
CRF(%)	2.4	3.1	0.722
CHD(%)	64.3	72.1	0.287
SS	12(8-16)	15(9.5-19)	**0.005**
EF(%)	53.67±6.1	53±5.8	0.422
Glucose (mg/dl)	210(119-270)	183(121-262)	0.379
Cr(mg/dl)	0.85(0.7-1.1)	0.9(0.8-1.05)	0.214
Na (mmol/l)	136±3.4	135±7.6	0.212
K (mmol/l)	4.3±0.6	4.4±0.55	0.531
Serum Osmolality (mmol/kg)	290±8.41	293±8.61	**0.034**
TG (mg/dl)	180(133-280)	199(143-236)	0.866
LDL (mg/dl)	140±26	134±30	**0.041**
HDL (mg/dl)	43±9.1	40±7.3	0.211
GGT (mg/dl)	31(20-53)	30(22-50)	0.621
AST (UI/L)	24(18-32)	23(19-35)	0.921
ALT (UI/L)	22(15-27)	23(18-32)	0.160
Albumin (mg/dl)	4±0.49	4.1±0.5	0.588
T.bilirubin (mg/dl)	0.5(0.36-0.7)	0.49(0.4-0.62)	0.782
D.bilirubin (mg/dl)	0.1(0.08-0.12)	0.1(0.09-0.12)	0.473
LDH (ng/mL)	267(221-341)	259(224-329)	0.076
CK (ng/mL)	107(69-153)	101(73-129)	0.427
CKMB (ng/mL)	23(18-35)	21(16-27)	0.172
Troponin (ng/mL)	0.02(0.01-1.15)	0.02(0.01-0.148)	0.451
CRP (mg/l)	4.1(3.2-9.8)	3.4(3.2-5.2)	**0,052**
Neutrophil (10^3 / µL)	5.4(4-6.6)	5.2(3.9-6.7)	0.462
Hemoglobin(g/dl)	14.5±1.6	14.2±1.75	0.214
HTC (%)	44. ± (6.2	43±5.2	0.132
RDW (%)	14±1.9	13.9±1.1	0.892
Platelet (10^3 /µL)	251(215-284)	238(202-263)	0.091
MPV (fl)	8.4±1.7	8.3±1.2	0.644

Abbreviations: HT, hypertension; CRF, chronic renal failure; CHD, coronary heart disease; SS, Syntax score; EF, ejection fraction; CK,creatine kinase; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C reactive protein; RDW, Red cell distribution width;

Table 2. ***Independent predictors of functional myocardial ischemia development in logistic regression analysis***

Variables	Univariate OR and 95 %CI	Univariate P value	Multivariate OR and 95 %CI	Multivariate P value
SS	1.058(1.014-1.105)	0.005	1.059(1.012-1.107)	0.013
Serum Osmolality (mmol/kg)	0.981(0.964-0.998)	0.034	0.98(0.96-0.99)	0.043
LDL(mg/dl)	0.972(0.832-1.136)	0.041	0.966(0.791-1.18)	0.737
CRP (mg/l)	1.008(0.991-1.025)	0.05	1.007(0.987-1.027)	0.495

Abbreviations:SS, Syntax score; LDL, low-density lipoprotein;CRP, C reactive protein; OR, Odds ratio; CI Confidence interval.

Discussion

In this study, we demonstrated that high SO is associated with functional myocardial ischemia in diabetic patients with intermediate coronary lesions. This is the first study in which the effects of SO on functional myocardial ischemia have been shown.

DM is one of the leading causes of coronary atherosclerosis. The deterioration in blood glucose regulation, insulin resistance, and obesity separately contribute to the development of coronary atherosclerosis (8, 9). Diabetes leads to myocardial ischemia by causing atherosclerosis in coronary arteries at the macrovascular level and by causing an increased inflammatory response, endothelial dysfunction, and vascular tonus dysfunction at the microvascular level. Thus, the prognosis of coronary atherosclerosis is worse in diabetic patients than in non-diabetic patients (2, 5).

The functional myocardial ischemia measurement is a milestone diagnostic method in the definitive diagnosis of severe coronary artery stenosis. In many recent studies, FFR has been shown to be a good diagnostic tool for estimating mortality, adverse events, response to treatment, and intervention success. In the FAME study, the percutaneous coronary intervention (PCI) method of guiding FFR was found to be cost-effective and related with better cardiovascular outcomes (10-13).

Osmolality is milliosmoles of solutes per one kilogram (or liter) of water of solution (plasma) and is calculated by osmolality divided by plasma water 14. Normal values range between 275 and 290. SO can be measured directly cryoscopically using the freezing point. It might also be indirectly measured by formularizing the solids in plasma. The simplest and most useful method recommended at this moment is the Whortley formula. Direct measurement is frequently not appropriate for point-of-care tests, whereas the indirect measurement method is more practical, and it shows a good correlation with direct measurement. Indirect measurement has also been shown to require no additional costs and to be more appropriate in clinical use (14, 15).

SO is of critical importance in tissue nutrition and homeostasis. In various studies, it has been associated with increased mortality and adverse events. In addition to coursing at higher levels in hyperglycemic situations, an increase in SO is also seen in other organ and tissue diseases (4, 7, 16-18). In kidney diseases, changes in SO have been associated with worse prognosis. For example, Kuwabara et al. determined that increased SO increased the development of end-stage kidney failure (7). Changes in blood viscosity might have various effects at the tissue and organ levels. The increased hemoglobin levels of COPD patients are related to increased levels of platelet aggregation and a tendency toward thrombosis (19), while the increased levels of plasma protein in malignity are related with hypercoagulability (20).

In the literature, there are studies examining the relationship of coronary atherosclerosis with the abovementioned situations, but there is no study that reports on the relationship between SO and functional myocardial ischemia. In our patient group, a low FFR

value was found to be related with high SO. This can be explained by the possibility of deterioration in coronary nutrition in cases of deteriorated SO in diabetic patients as well as by the possibly significant effect of SO on coronary hemodynamics at the microvascular level. Thus, the findings of the present study are important since they reveal that both the endothelium and plasma changes in diabetic patients might contribute to the development of coronary atherosclerosis and ischemia. Hence, this study might be a guide for further studies. Some advantages of the approach in this paper are that the calculation does not require any additional cost (unlike HBA1C measurement), it is easy to implement, and information is provided regarding mortality and adverse events.

Limitations

There are certain limitations to this study. One major limitation is that the measurement of direct osmolality could not be achieved. Ischemia may increase insulin resistance by causing inflammation, which may also cause an increase in serum glucose and osmolality. This may be another limitation of our study. Further studies are needed to better understand the relationship between ischemia inflammation and osmolality.

Conclusion

In diabetic patients, the rheological properties of blood have been changed, and this change may be related with functional myocardial ischemia. Acknowledging these parameters and putting them into clinical use might be useful for treatment selection and determining the timing of intervention.

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