



Effect of Exenatide on Aortic Stiffness and Blood Pressure Parameters

Eksenatidin Aortik Sertlik ve Kan Basıncı Parametreleri Üzerine Etkisi

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Abstract

Purpose: To evaluate the effects of exenatide and insulin glargine on systolic and diastolic blood pressure, pulse pressure, and aortic stiffness parameters.

Materials and Methods: Thirty-four patients with type 2 diabetes who were receiving metformin treatment for at least two months but naive for insulin and incretin based treatments, with body mass index (BMI) = 25-45 kg/m², were randomized into exenatide a glucagon like peptide-1 (GLP-1) analog and insulin glargine arms and were followed for 26 weeks. Aortic stiffness parameters were calculated using transthoracic echocardiography and hemodynamic data. Body weight and total body fat mass were measured by bioimpedance analysis.

Results: There was no significant change in systolic and diastolic blood pressures in both arms. When the effects on aortic stiffness parameters were evaluated there was no significant difference in the baseline and outcome values of both arms. Changes in body weight had a negative correlation with aortic stiffness β index ($r=-0.322$) and a positive correlation with aortic distensibility ($r=0.386$).

Discussion: Throughout the study period, exenatide and insulin glargine had a neutral effect on blood pressure parameters. Exenatide did not cause any change in aortic stiffness parameters. A 26-week exenatide treatment leads to loss of body weight and fat mass along with glycemic regulation. Body weight and fat mass loss have a positive impact on aortic stiffness indicators.

Keywords: Exenatide, insulin glargine, blood pressure, aortic stiffness, atherosclerosis

Özet

Amaç: Eksenatid ile insülin glarjinin sistolik ve diyastolik kan basıncı, nabız basıncı ve aortik sertlik parametreleri üzerine etkinliğini değerlendirmek.

Gereç ve Yöntemler: Başlangıçta en az 2 ay metformin tedavisi alan, insülin ve inkretin bazlı tedaviler için naif, vücut kitle indeksi (VKİ) = 25-45 kg/m² aralığında olan 34 tip 2 diyabetli hasta, glukagon like peptit-1 (GLP-1) analogu olan eksenatid ve insülin glarjin kollarına randomize edildi. 26 hafta boyunca izlendi. Aortik sertlik ölçümü transtorasik ekokardiografi ve hemodinamik veriler kullanılarak hesaplandı. Vücut ağırlığı ve total vücut yağ kütlesi biyoimpedansla ölçüldü.

Bulgular: Her iki çalışma kolunda sistolik ve diyastolik kan basıncında anlamlı değişiklik görülmedi. Aortik sertlik parametrelerine etkileri değerlendirildiğinde başlangıç ve sonuç değerlerinde anlamlı farklılık tespit edilmedi. Aortik sertlik β -indeksi ile kilo değişimi arasında negatif ($r=-0.322$) ve aortik distansibilite ile kilo değişimi arasında pozitif korelasyon tespit edildi ($r=0.386$).

Tartışma: Eksenatid ve insülin glarjin çalışma periyodu boyunca kan basıncı parametrelerine nötral etki göstermiştir. Eksenatid aortik sertlik parametrelerinde değişikliğe neden olmamıştır. 26 haftalık eksenatid tedavisi glisemik regülasyon yanında, vücut ağırlığı ve yağ kütlesi kaybına neden olmaktadır. Vücut ağırlığı ve yağ kütlesi kaybı aortik sertlik belirteçlerine olumlu etmektedir.

Anahtar kelimeler: Eksenatid, insülin glarjin, kan basıncı, aortik sertlik, ateroskleroz

Introduction

Cardiovascular diseases are the major cause of mortality and morbidity for patients with type 2 diabetes. Majority of these patients have comorbidities such as hypertension, dyslipidemia, and obe-

sity. Besides glucose control, cardiovascular protection depends on controlling comorbidities (1-3).

Arterial stiffness is a term used to describe the viscoelastic properties of the vessel wall. It is associated with aging and well-known atherosclerotic risk factors such as diabetes mellitus (DM) and hy-

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pertension (4–7). The stiffness of larger arteries may be an indicator or cause of coronary atherosclerosis. It may play a role in the development of coronary ischemia, completely independent of coronary atherosclerosis. Increased aortic stiffness is an indicator of a widespread atherosclerotic involvement of the vascular system (8–9).

Arterial stiffness and pulse pressure increase are widely used parameters in the prediction of cardiovascular disease development and mortality in the general population and among type 2 diabetic patients (10–12). The aorta is widely used to measure arterial stiffness. The most important aortic stiffness indicators are aortic distensibility and aortic stiffness index (13–15).

Many studies have revealed that aortic elasticity parameters are impaired in type 2 DM (16). Increased arterial stiffness may be one of the considerable causes in understanding the relationship between DM and increased cardiovascular risk as arterial stiffness is frequently observed in both cases (17).

As the arteries stiffen, pulse pressure depending on systolic pressure increases. Increase in systolic pressure triggers left ventricle hypertrophy, and ventricular stiffness leads to diastolic dysfunction and heart failure. A concomitant decrease in diastolic pressure reduces coronary blood flow and leads to ischemia (18–19).

The aim of this study was to compare the effects of two antidiabetics with similar glycemic effectiveness, the glucagon-like peptide-1 (GLP-1) agonist, exenatide, and insulin glargine, on blood pressure and aortic stiffness parameters.

Materials and Methods

The study was performed between June 2011 and December 2012 at one study site in Turkey. In total, 60 patients were screened, of which 34 patients were randomized using a permuted block randomization scheme.

This investigation was designed to evaluate the treatment and efficacy of a 26-week, randomized, open-label, two-arm parallel group study. The study protocol was approved by the Ethical Committee of the Kocaeli University, Turkey. The study included type 2 DM patients whose age was between 40 and 70 years, with a hemoglobin A1c (HbA1c) level of 7%–9.5% (53–80 mmol/mol), a body mass index (BMI) of 25–45 kg/m², and who have regularly used metformin 2 × 1g/day for at least two months. The patients with a history of insulin- or incretin-based treatments were excluded. The patients who had changes in the drug groups effective in the cardiovascular system and glucose control during the last three months were not included in the study. The subjects with a previous coronary angioplasty, acute coronary syndrome, and cerebrovascular event within six months; impaired hepatic and renal function; systolic blood pressure ≥180 mmHg, diastolic blood pressure ≥100 mmHg, or uncontrolled hypertension (HT); and active smokers were excluded. Twelve female and five male patients were included in the exenatide arm, and ten female and seven male patients were included in the insulin glargine arm. The study arms continued receiving metformin 2 g/day. One arm received exenatide 5 µg 2 × 1 s.c. at least 30 min before meals for four weeks. This dose was subsequently increased to 2 × 10 mcg s.c. and exenatide was continued for six months in total. The patients

in the other arm were started on insulin glargine 0.2 U/kg. Insulin injection was administered at bedtime. The dose was increased by two units in patients with a mean 3-day fasting plasma glucose (FPG) ≥100 mg/dL, which was obtained through phone visits. Dose increase was continued until FPG was between 80 and 99 mg/dL. When an FPG value of ≤60 mg/dL was achieved, the previous dose was started again and no new dose adjustments were made earlier than a week. The patients were assessed at weeks 0, 4, 12, and 26. They were evaluated at all visits through BMI measurements, blood pressure controls, routine biochemistry, and assessment of drug side effects. None of the participating patients experienced serious drug-related side effects. Two patients in the treatment arms were excluded later, one because of major depression-related treatment incompliance and another because of non-attendance to visits.

Body weight and total body fat mass assessment

The body weight and total body fat mass were measured using the bioimpedance analysis technique by using a Tanita BC-418 body composition analyser device. Waist circumference was measured at the central point of the space between the iliac crest and the lower limit of the arch. The measurements were performed in the morning on an empty stomach at screening and follow-up visits.

Blood pressure measurements

Echocardiographic measurements and blood pressure were measured by a specialized cardiologist. The cardiologist was blinded to the study groups. Simultaneous blood pressure measurement with echocardiographic examination was performed. The measurements were performed in the supine position with a sphygmomanometer. Korotkoff phase b2 and V were used to determine systolic and diastolic blood pressures. The average of three measurements was noted.

Aortic stiffness parameters assessment

Aortic stiffness β index and distensibility were assessed using a high-resolution GE Vivid 7 Dimension (GE, Davis Medical Electronics, USA) ultrasound device. The measurements were made according to the American Society of Echocardiography's proposed criteria (20). The image position was monitored with the proximal aorta right coronary and non-coronary valve cusps on the parasternal long axis were obtained clearly. Aortic sections were taken with M-mode from the line of coaptation of the aortic valve 2-cm proximal. Systolic and diastolic aortic lumen diameters were measured from the received section (Figure 1). The average of five consecutive cycles, while the data were received from the measurement, was regarded as essential. Aortic stiffness index and aortic distensibility obtained using echocardiographic and hemodynamic data were calculated.

Hemodynamic measurements

Pulse pressure (mmHg) = Systolic blood pressure – diastolic blood pressure (N; 20–40 mmHg)

Aortic stiffness β index was calculated as follows (20–21).

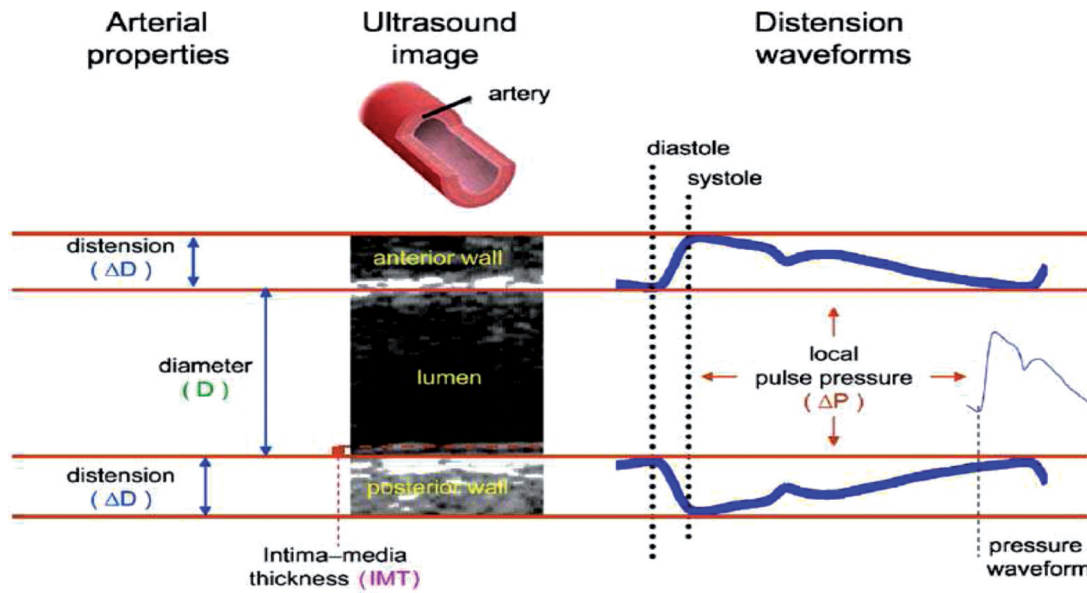


Figure 1: Ultrasound-derived arterial properties are used to determine local arterial stiffness. The two thick blue lines represent the vessel wall movement during the cardiac cycle (2).

Aortic stiffness index = $\log(SBP/DBP)/[(A_{\text{max}} - A_{\text{min}})/A_{\text{min}}]$
Ao: aorta; DBP: diastolic blood pressure; SBP: systolic blood pressure
Aortic distensibility was calculated as follows (22).
Aorta distensibility = $2 \times [(Systolic \text{ aortic diameter} - Diastolic \text{ aortic diameter}) / (Diastolic \text{ aortic diameter})] \times (\text{Aortic pulse pressure})$

Biochemical parameters

By using an Abbott Architect c16000 device, fasting plasma glucose was measured by the hexokinase method, triglyceride by the glycerol phosphate oxidase method, and total cholesterol by the enzymatic method. The calculation was done using the Friedewald formula for low density lipoprotein (LDL) cholesterol. HbA1c was measured by the high performance liquid chromatography (HPLC) technique using a Shimadzu HPLC system, Shimadzu Corporation, JAPAN.

Statistical assessment

PASW 18.0 for Windows program was used for statistical analysis. Descriptive statistics are presented as number and percentage for categorical variables, and mean, standard deviation, median, percentile 25 (Q1), and percentile 75 (Q3) are used to present numerical variables. Data assessment was conducted using the unpaired t-test for the pairwise group comparisons of the variables with a normal distribution; paired t-test for the comparisons between pretreatment and posttreatment values; the Mann-Whitney U test for the pairwise group comparisons of variables with abnormal distribution; the Wilcoxon signed rank test for pretreatment and posttreatment comparisons; a chi-square test for the comparisons of qualitative data and descriptive statistical methods (mean, standard deviation, median, and interquartile range). The results were evaluated at a significance level of $p < 0.05$ and 95%

confidence interval. The study groups were named as exenatide (group E) and insulin glargine (group I).

Results

The demographic data of Groups E and I are presented in Table 1. No difference was observed between the groups in terms of age, gender, and mean duration of diabetes.

As shown in Table 1, posttreatment body weight, mean body fat mass, and body mass index values were significantly lower in Group E, compared with their pretreatment values. In both treatment groups, waist circumferences decreased significantly.

The pre- and posttreatment percentage changes in fasting blood glucose were significantly higher in Group E than in Group I. Serum triglyceride levels decreased significantly in Group I, compared with their pre-treatment levels. The pre- and posttreatment percentage changes in triglyceride, LDL-cholesterol, and HDL-cholesterol levels in both groups were not statistically significant. HbA1c values had significantly declined with treatment in both groups, but there was no statistically significant difference between the groups (Table 1).

There was no significant difference between the effects of drugs on the cardiovascular system between both groups (Table 2).

The comorbidities of the study groups are presented in Table 3.

i. Blood pressure

There was no significant difference between pre- and posttreatment pulse pressures in Groups E and I, and pulse pressure did not change significantly with the treatment in both groups. Systolic and diastolic blood pressures did not change in both groups. No statistically significant difference was observed between the groups (Table 4).

Table 1. Demographic data and pre- and post-treatment anthropometric measurements, metabolic profiles and changes from baseline (%).

			Exenatide group	Insulin glargine group	p*
			Mean ±SD	Mean ±SD	
Age			52.18 ±7.26	53.12 ±6.99	0.703
Sex		Male	5 (29.4%)	7 (41.2%)	0.473
		Female	12 (70.6%)	10 (58.8%)	
DM age (years)			6.88 ±3.26	7.59 ±4.26	0.591
Body weight (kg)		pre-treatment	94.34 ±11.77	90.51 ±14.32	0.401
		posttreatment	88.79 ±12.94	89.66 ±14.43	0.855
		p‡	0.001	0.293	
BMI (kg/m²)		pre-treatment	35.89 ±3.7	33.21 ±4.45	0.065
		posttreatment	33.98 ±4.15	33.02 ±4.57	0.382
		p‡	0.001	0.57	
Total body fat mass (kg)		pre-treatment	36.37 ±6.91	32.46 ±7.28	0.137
		posttreatment	32.29 ±7.19	33.3 ±9.02	0.735
		p‡	0.009	0.509	
Waist circumference (cm)		pre-treatment	112.47 ±10.35	107.41 ±11.41	0.265
		posttreatment	107.79 ±8.21	106.06 ±10.87	0.603
		p‡	0.006	0.024	
HbA1c (%)		pre-treatment	7.95 ±0.81	8.11 ±0.76	0.558
		posttreatment	6.73 ±0.75	6.68 ±0.83	0.833
		p‡	0.001	0.001	
hs-CRP	pre-treatment	Median ±SD	0.87 ±0.89	0.49 ±0.42	0.221†
		Median (IQR)	0.6 (0.26–1.02)	0.33 (0.19–0.8)	
	post-treatment	Median ±SD	0.52 ±0.47	0.44 ±0.47	0.524†
		Median (IQR)	0.33 (0.16–1.02)	0.25 (0.13–0.63)	
		p	0.017	0.469	
Triglyceride		pre-treatment	173.29 ±89.38	226 ±87.32	0.092
		post-treatment	146.53 ±98.96	158.35 ±62.2	0.679
		p‡	0.217	0.001	
HDL-cholesterol		pre-treatment	44.82 ±12.06	39.29 ±8.84	0.137
		post-treatment	40.65 ±8.82	40.12 ±7.22	0.849
		p‡	0.079	0.558	
LDL-cholesterol		pre-treatment	115.82 ±25.75	110.18 ±34.96	0.595
		post-treatment	102.88 ±31.43	103.53 ±32.08	0.953
		p‡	0.150	0.367	
Endothelin-1	pre-treatment	Median ±SD	16.09 ±4.96	11.19 ±5.76	0.016†
		Median (IQR)	15.93 (11.57–19.78)	11.09 (9–14.37)	
	post-treatment	Median ±SD	12.35 ±5.65	20.06 ±9.79	0.016†
		Median (IQR)	12.07 (10.76–14.15)	17.96 (11.83–24.43)	
		p	0.026	0.008	
DM: Diabetes mellitus, BMI: Body mass index, Hb: Hemoglobin, hs-CRP:				High sensitive-CRP	
* Independent t-test, ‡ paired test, †Mann-Whitney U test, Wilcoxon Test, [•] Chi Square.					

Table 2. Distribution of the medications received by our study groups prior to the study.

Groups	β-blockers (%)	ACE/ARB (%)	Statin (%)	Fibrate (%)
Exenatide	24	88	76	12
Insulin glargine	22	88	76	6

ACE: Angiotensin-converting enzyme/ARB: Angiotensin receptor blocker.

Table 3. The co-morbidities among the study groups.

	Exenatide group	Insulin glargine group
Hypertension	17 (100%)	14 (82%)
Coronary artery disease	2 (12%)	1 (6%)
Sedentary lifestyle	1 (6%)	4 (24%)
Dyslipidemia	15 (88%)	14 (82%)
Smoking	1 (6%)	1 (6%)

Table 4. Pre- and post-treatment blood pressure and aortic stiffness parameters and change from baseline (%).

Parameters		Exenatide group Median (IQR)	Insulin glargine group Median (IQR)	p [†]
Pulse pressure	Pre-treatment	50 (40–70)	50 (40–60)	0.487
	Post-treatment	50 (50–60)	50 (45–55)	0.447
	p [‡]	0.827	1.000	
Systolic blood pressure	Pre-treatment	140 (130–150)	130 (120–150)	0.302
	Post-treatment	140 (120–150)	130 (120–140)	0.321
	p [‡]	0.747	0.811	
Diastolic blood pressure	Pre-treatment	80 (80–90)	80 (80–90)	0.406
	Post-treatment	80 (70–90)	r	0.544
	p [‡]	0.385	0.496	
Aortic stiffness β -index	Pre-treatment	2.67 (2.47–5.09)	3.73 (2.86–4.01)	0.326
	Post-treatment	2.41 (1.9–3.52)	3.29 (1.89–4.74)	0.344
	p [‡]	0.868	0.102	
Aortic distensibility	Pre-treatment	6.09 (4.94–8.03)	6.44 (4.36–7.28)	0.389
	Post-treatment	7.18 (6–10.73)	6.05 (4.28–8.81)	0.102
	p [‡]	0.653	0.227	
Change from baseline (%)				p [†]
Pulse pressure		0 (–14.29–25)	0 (–16.67–25)	0.821
Systolic blood pressure		0 (–6.67–6.67)	0 (–6.67–7.69)	0.848
Diastolic blood pressure		0 (–11.11–0)	0 (–10–0)	0.764
Aortic β -stiffness index		–20.78 (–47.27–1.49)	–10.61 (–47.62–67.71)	0.344
Aortic distensibility		21.37 (–2.88–96.9)	–0.22 (–32.91–60.55)	0.293

‡ Wilcoxon Signed Rank Test, †Mann-Whitney U Test.

Table 5. Correlation of the parameters related blood pressure and aortic stiffness parameters with certain variables.

Change from baseline (%)		BMI	Waist circumference	Fat mass (%)	Weight
Pulse pressure%	r	0.197	0.188	0.015	0.209
	p	0.264	0.288	0.938	0.235
Systolic pressure%	r	0.288	0.285	0.094	0.24
	p	0.098	0.102	0.615	0.172
Diastolic pressure%	r	0.238	0.243	0.149	0.143
	p	0.175	0.167	0.422	0.418
AO Stiffness β - index	r	–0.322	–0.29	0.051	–0.39
	p	0.063	0.096	0.784	0.023
AO Distensibility	r	0.386	0.259	0.043	0.405
	p	0.024	0.139	0.818	0.018

ii. Aortic stiffness

No statistically significant difference was observed between the mean pre- and post-treatment aortic stiffness and distensibility indices in Groups I and E. No statistically significant difference was observed between both groups (Table 4).

iii. Relationship between certain variables and blood pressure and aortic stiffness parameters

Changes in body weight had a negative correlation with aortic stiffness index and a positive correlation with aortic distensibility (Table 5).

Discussion

There are indirect methods of evaluating arterial stiffness, such as aortic stiffness index, aortic distensibility, and aortic pulse wave velocity (PWV). Faster PWV, increased index, and reduced distensibility are indicators of a stiffened aorta (10–20).

No statistically significant difference was observed between our study groups with respect to pre- to posttreatment changes in aortic stiffness parameters.

In our 26-week study, there was an average weight loss of 5.55 kg in Group E and of 0.85 kg in Group I, with a difference of ap-

proximately 4.7 kg between the groups. Weight loss improves arterial stiffness (21–23). Type 2 diabetes patients that receive weight loss treatment experience a reduction in the level of arterial stiffness besides improvements in their metabolic dysfunction (24). Indeed, there was a negative correlation between weight loss and aortic stiffness index and a positive correlation with aortic distensibility in our study (Table 5).

While there was a 4-kg reduction in body fat mass in Group E, there was a 0.8-kg increase in body fat mass Group I. There was a difference of approximately 4.8 kg (16%) in fat mass between both groups (Table 1). In a one-year study comparing insulin glargine with exenatide, a difference of 2.9 kg (13%) in the fat mass loss was observed (25). An association independent of age and systolic hypertension was observed between PWV and body weight, PWV and waist circumference, and PWV and total fat mass (particularly visceral fat mass) (20, 26–30). In a 26-week liraglutide (a GLP-1 agonist) study, reduction in fat mass actually occurred in visceral fat mass (31). In our study, a neutral change was observed in the arterial stiffness parameters in Group E. Exenatide use among obese type 2 DM patients with high cardiovascular risk has been demonstrated to improve PWV in addition to the reduction in glycemic regulation, body weight, and body fat mass (32). Although no statistically significant relationship was determined between the reduction in fat mass and aortic stiffness parameters in Group E; the results of studies conducted with similar study groups are promising (25, 32).

No statistically significant changes were observed between the pre- and posttreatment measurements of blood pressure parameters in two study groups. (Table 4). A reduction of 1–5 mmHg in systolic and diastolic blood pressures has been observed in the studies using exenatide (33, 34). This effect of exenatide was associated with renal water and sodium loss as reported in the studies with animal models and was independent of other cardiovascular risk factors (35).

The impairment of arterial elasticity is known to be the initiator of early vascular pathology, that is, atherosclerosis, among patients with diabetes (35–37). Additionally, increased aortic stiffness that resembles atherosclerosis of the aorta can be a significant indicator of peripheral vascular disease among patients with diabetes (38). Increased arterial stiffness is associated with reduced FMD (39).

Previously, we had determined that the effects of the GLP-1 agonist, exenatide, were in favor of FMD increase (40). Here, we observed that exenatide has a positive impact on weight and fat mass loss (Table 5). Weight and fat mass loss have a positive impact on aortic stiffness indicators. Hence, exenatide may positively affect aortic stiffness parameters over time.

Besides the glucose control, GLP-1 agonist treatment has positive impacts on cardiovascular comorbidities.

Our study has some advantages. During the study, the previously reported mild and medium intensity side effects in both arms were at a tolerable level. In addition, no patients had deterioration of renal function and pancreatitis attacks. The disadvantages of our study are its open-label randomization and a relatively short study period.

Author Contributions

Ethics: Yes. Patient approval: Yes. Concept: Eren Gürkan, Tayfun Şahin. Design: Eren Gürkan, Tayfun Şahin. Data Collection or Processing: Eren Gürkan, Tayfun Şahin, İlhan Tarkun. Analysis or Interpretation: Eren Gürkan, İlhan Tarkun, Tayfun Şahin. Literature Search: Eren Gürkan. Writing: Eren Gürkan. Conflict of Interest: The authors declare that they have no conflict of interest. Financial Disclosure: There is no organization that funded our research.

Statement of Human and Animal Rights: All procedure followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki declaration of 1975, as revised in 2008 (5).

Statement of Informed Consent: Informed consent was obtained from all patients for being included in the study.

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