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Research Article

Association between Coronary Flow Reserve, Klotho and Fibroblast Growth Factor 23 in Patients with Acromegaly

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Abstract

Objectives: Acromegaly is a chronic endocrine disorder that is characterized by hypersecretion of growth hormone. The purpose of this study was to evaluate coronary flow reserve (CFR) in patients with acromegaly and investigate whether there is an association between fibroblast growth factor-23 (FGF-23) and Klotho levels with coronary microcirculation or not.

Methods: A total of 54 patients with acromegaly were divided into subgroups: Those with active disease and those who are in biochemical remission (serum insulin-like growth factor-1 level was within the normal range). Along with 31 healthy volunteers, the patients underwent dipyridamole-stress transthoracic Doppler echocardiography. CFR was calculated with the ratio of hyperemic to baseline diastolic peak velocities. Klotho and FGF-23 were measured using an enzyme-linked immunosorbent assay.

Results: A total of 42 (%77.8) of acromegaly patients had active disease. Acromegaly patients had lower Klotho and FGF-23 levels compared to in controls. Patients with active disease had higher FGF-23 levels and lower Klotho levels when compared to patients in remission. CFR levels of active group were lower than remission and controls (p=0.001; p=0.043, respectively). Klotho was strongly associated with CFR levels in patients with active disease (r=0.8, p=0.001).

Conclusion: Acromegaly patients have lower levels of Klotho and FGF-23 and CFR.

Keywords: Acromegaly, coronary flow reserve, Fibroblast growth factor 23, Klotho

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Acromegaly is a chronic endocrine disorder that is characterized by hypersecretion of growth hormone (GH) and, consequentially, insulin-like growth factor-1 (IGF-1). The most common cause of acromegaly is a pituitary adenoma.[1] Prolonged exposure to excess plasma levels of GH and IGF-1 causes progressive somatic disfigurement and many systemic manifestations. The estimated annual incidence is 3–4 new cases per year and prevalence is between 40 and 70 per million.[1, 2]

Cardiovascular disease is the leading cause of morbidity and mortality in acromegaly.[3] Long-term exposure to high levels of GH and IGF-1 causes the development of "acromegalic cardiomyopathy" characterized by concentric biventricular hypertrophy.[4–6] It mainly involves the left ventricle, causes diastolic dysfunction and progresses to systolic dysfunction and heart failure in case of inadequate treatment.[4] Hypertension (HT), valvular diseases, and arrhythmias are additional complications of acromegaly contributing to the worsening of cardiac functions.[7–11] Furthermore, metabolic complications such as insulin resistance, diabetes mellitus (DM), and hyperlipidemia are frequently seen in acromegaly, and these disorders contribute to increased cardiovascular

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mortality.[12, 13] Moreover, hormonal excess leads to vascular endothelial dysfunction, mainly of carotid and coronary arteries, by inducing direct vascular damage.[14]

Coronary flow reserve (CFR) is the capacity of the coronary circulation to dilate in case of increased myocardial metabolic demands, and it reflects both coronary microcirculatory function and blood flow in epicardial coronary arteries.[15] CRF can be measured non-invasively on the middle to distal portion of the left anterior descending (LAD) artery using transthoracic Doppler echocardiography (TTDE), and it shows excellent correlation with the gold standard of the CFR measurement by positron emission tomography.[16–18]

Fibroblast growth factor-23 (FGF-23) is a marker of cardiovascular disease in chronic kidney disease patients. Evidence shows that it is also associated with impaired vasoreactivity and increased arterial stiffness even in normal individuals.[19] Another marker Klotho is found to be reduced in patients with atherosclerosis,[20] however, increased in acromegaly.[21] The purpose of this study was to evaluate CFR in patients with acromegaly and investigate an association between FGF-23 and Klotho levels with coronary microcirculation.

Methods

Study Population

The study design was cross-sectional. The study protocol was approved by the Medeniyet University Goztepe Education and Research Hospital Clinical Research Ethics Committee and written informed consent was obtained from all participants.

Consecutive acromegaly patients followed in the endocrinology clinics of our hospital between March 2013 and September 2015 were invited to participate in the study. The inclusion criteria were patients having a diagnosis of acromegaly, being older than 18 years and giving consent to participate. All patients, besides the clinical features of acromegaly, had fulfilled the biochemical criteria including increased serum IGF-I levels for age and serum GH concentration >1 ng/mL during 75 g oral glucose tolerance test at the time of acromegaly diagnosis. Patients with uncontrolled DM, HT, and hyperlipidemia, decompensated heart failure, coronary artery disease, accompanying infectious or inflammatory diseases, moderate or severe valvular heart disease, and chronic renal disease stage 3 or higher were excluded. After applying exclusion criteria, 54 patients with acromegaly were divided into subgroups: Those with active disease and those who are in biochemical remission (serum IGF-1 level was within the normal range). Along with 31 healthy volunteers, the patients underwent dipyridamole-stress TTDE. For stress echo perfusion imaging, dipyridamole was injected intravenously at 0.56 mg/kg/min, during imaging.

Biochemical Assessment

Venous blood samples were obtained from all participants after overnight fasting. S-Klotho was determined using a sandwich enzyme-linked immunosorbent assay (ELISA) (Kyowa Hakko Kirin Co. Ltd, Tokyo, Japan) according to the instructions in the manufacturers product insert. Serum glucose was measured with a standard spectrophotometric method. Serum total IGF1, binding protein 3, GH, high-sensitivity CRP, thyroid stimulating hormone, free T4, and insulin were determined by solid-phase, enzyme-labeled chemiluminescent immunometric assays (Immulite 1000 immunoassay system, Siemens medical solutions Diagnostics, Los Angeles, CA, USA). Plasma lipid levels including low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TGs), and total cholesterol were measured using standardized enzymatic methods. Serum samples were analyzed for FGF-23 levels using an ELISA (Aviscera Bioscience, Santa Clara, USA). According to the manufacturer's indications, the calculated overall intraassay coefficient of variation (CV) was between 6.0% and 8.0% and the interassay CV was between 8.0% and 12.0%. The minimum detectable level of FGF-23 was typical at ~15 pg/mL.

Echocardiographic Examinations and CRF Measurement

Comprehensive transthoracic echocardiography (M-mode, two-dimensional, and Doppler) was performed with a dedicated unit (Vivid 7; GE Health-care, Port Washington, New York) by a cardiologist experienced in echocardiography. All measurements were performed in accordance with the current American Society of Echocardiography and European Association of Echocardiography guidelines. Heart rate was monitored with synchronized ECG recording. Imaging the distal portion of LAD artery was obtained in apical two-chamber view to best align with the interventricular sulcus. Following the visualization, peak diastolic coronary flow rate in the distal portion of LAD was measured by Pulsed Wave Doppler. Following the baseline measurements, 0.56 mg/kg intravenous dipyridamole infused in 4 min to achieve at least a 10% increase in heart rate. After the heart rate was increased to the desired level, peak diastolic flow measurement had repeated. An extra half dose of dipyridamole (0.28 mg/kg over a 2-min) was given if objective tachycardia could not been achieved. Average of the three highest values recorded to promote accuracy. CFR was calculated with the ratio of hyperemic to baseline diastolic peak velocities.

Statistical Analysis

Statistical analyzes were performed using SPSS statistical software package version 22 (IBM Corporation, USA). Continuous variables are expressed as mean±standard deviation and categorical variables are expressed as percentages. The Kolmogorov–Smirnov test was used to assessed whether the distribution of variables was normal. Student's t-test and Mann–Whitney U-test were used to compare normally distributed and non-normal distributed continuous variables, respectively. The relationships between CFR and other variables were assessed using Pearson's correlation coefficient and Spearman correlation test for normally and non-normally distributed data, respectively. Multivariate logistic regression analysis was used to determine the effects of gender, body mass index, HDL, and LDL cholesterol (LDL-C), TG, fasting glucose, age, and high sensitive CRP on decreased CFR value (CFR <2). For all comparisons, $P<0.05$ was accepted as significant.

Results

Study Population

A total of 54 acromegaly patients and 31 healthy volunteers were evaluated. 42 (%77.8) had active disease. The mean age of active acromegaly patients, patients in remission, and healthy controls, was 48±9, 47±7, and 45±8, respectively. 24 out of 54 acromegaly patients were men. Due to expected metabolic complications of acromegaly, the patient group had more metabolic problems. DM and HT were diagnosed in 11 (20.3%) and 13 (24.1%) patients with acromegaly, respectively. Characteristics and biochemical test results of patients with acromegaly and controls are summarized in Table 1.

Biochemical Assessment

Mean fasting blood lipid profile including LDL-C, HDL-C, TC, or TG levels was similar between groups. Mean fasting plasma glucose levels of patients in remission, with active disease, and control subjects were 100±13 mg/dl, 104±21, and 93±9 mg/dl, respectively. Klotho levels were higher in control subjects compared to patients with acromegaly and lowered in patients with active disease compared to patients in remission. FGF-23 levels were higher in control subjects than patients with acromegaly. Patients with active disease had higher FGF-23 levels than patients in remission (Table 2a).

Table 1. Characteristics of the patients

	Control (n=31)	Active (n=42)	Remission (n=12)
Age (years)	45.97±8.20	48.18±9.97	47.36±7.51
Gender			
Female	14 (45.2%)	23 (54.8%)	7 (58.3%)
Male	17 (54.8%)	19 (45.2%)	5 (41.7%)
BMI (kg/m^2)	28.00±3.93	29.28±4.19	30.96±5.38
Smoker	3 (9.7%)	11 (26.2%)	2 (16.7%)
Type 2 diabetes	1 (3.2%)	8 (19.0%)	3 (25.0%)
Hypertension	2 (6.5%)	7 (16.7%)	6 (50.0%)
Coronary heart disease	0 (0)	3 (7.1)	0 (0)
Creatinine (mg/dL)	0.79±0.15	0.85±0.31	0.82±0.15
Sodium (mg/dL)	139.30±1.74	139.55±2.31	141.00±2.65
Potassium (mg/dL)	4.35±0.39	4.44±0.32	4.40±0.41
Uric acid (mg/dL)	5.75±1.05	5.14±1.02	5.40±1.77
ALT (unit/L)	23.23±11.45	15.14±6.33	19.00±6.56
AST (unit/L)	19.09±4.69	16.62±4.22	15.20±3.70
GGT (U/L)	21.28±6.52	29.64±36.03	37.50±24.75
FBG (mg/dL)	93.42±9.19	104.88±21.13	100.67±13.26
WBC (10^3/µL)	7.11±2.30	7.11±2.12	7.50±2.26
HGB (g/dL)	14.04±2.07	12.65±1.62	12.36±2.14
Total cholesterol (mg/dL)	211.18±43.46	214.56±35.16	198.18±22.94
Triglyceride (mg/dL)	133.94±68.44	138.38±57.95	147.09±62.98
LDL (mg/dL)	135.81±37.86	13722±32.36	122.36±19.30
HDL (mg/dL)	50.19±11.20	4741±10.18	45.27±10.43

BMI: body mass index; ALT: alanine transaminase; AST: aspartate transaminase; GGT: gamma glutamyl transferase; FBG: fasting blood glucose; WBC: white blood count; HBG: hemoglobin; LDL: low density lipoprotein; HDL: high density lipoprotein.

Table 2A. Fibroblast growth factor 23, Klotho, Coronary Flow Reserve results of the groups

	Control (n=31)	Active (n=42)	Remission (n=12)	
Klotho (pg/mL)	7.19±6.65	4.53±3.83	4.66±1.43	0.560
FGF-23 (pg/mL)	474.03±391.27	373.66±371.46	300.67±116.86	0.311
Basal Diastolic peak flow rate (cm/s)	24.43±4.06	29.61±5.77	28.08±5.41	0.001**
Hyperemic diastolic peak flow rate (cm/s)	69.17±10.99	62.27±13.89	71.42±10.15	0.004**
CFR	2.91±0.71	2.20±0.45	2.59±0.48	
CFR (2.5)				
>2.5	19 (70.4)	6 (16.2)	6 (50.0)	0.001**
≤2.5	8 (29.6)	31 (83.8)	6 (50.0)	

aKruskal Wallis Test; bPearson Ki-kare Test; **p<0.01; FGF23: Fibroblast growth factor- 23; CFR: Coronary flow reserve.

Table 2B. Differences between groups

	Control vs. Active	Control vs. Remission	Active vs. Remission
CFR BASAL	0.001**	0.225	0.945
CFR PEAK	0.021*	1.000	0.021*
CFR	0.001**	0.870	0.043*

Bonferroni - Dunn Test; *p<0.05; **p<0.01; CFR: Coronary flow reserve.

Echocardiographic Examination

There was a statistically significant difference in epicardial fat, left ventricular end-diastolic diameter (LVEDd), end-diastolic interventricular septal (IVS), posterior wall (PW) thicknesses, interventricular septum systolic (IVSDs), left atrial (LA), deceleration time (DT), and isovolumetric relaxation time (IVRT). Differences between groups are showed in Table 3 . Epicardial fat thickness was higher in active, and remission groups than controls (p=0.005, p=0.007, respectively) and there was no difference between measurements of active and remission groups. Aorta diameter was higher in the active group than controls (p=0.011). LVEDd was higher in remission group than controls (p=0.022). IVSD measurements of active and remission groups were higher than controls (p=0.006; p=0.027, respectively). Furthermore, PWTd measurements were higher in active and remission groups than controls (p=0.001; p=0.027, respectively). Table 3a and 3b summarize these results.

Table 3A. Echocardiography results

	Control	Active	Remission	[a]p
Basal heart rate (beat/min)	77.96±11.56	75.59±9.59	69.30±9.74	
Peak peak heart rate (beat/min)	99.74±11.97	98.48±14.06	90.40±8.10	
Systolic blood pressure (mm/Hg)	123.35±14.03	129.91±18.03	123.50±13.34	
Diastolic blood pressure (mm/Hg)	76.17±6.73	76.61±7.66	81.00±11.01	
LVEDd (cm)	4.79±0.41	4.98±0.61	5.27±0.51	0.027*
LVEDs (cm)	2.95±0.41	3.17±0.5	3.18±0.32	0.220
IVSd (cm)	0.944±0.121	1.036±0.125	1.055±0.195	0.012*
PWTd (cm)	0.89±0.14	0.99±0.11	0.98±0.12	0.001*
Left ventricular mass index	49.08±13.04	68.6±22.07	62.02±17.32	0.001**
LA	3.07±0.32	3.63±0.63	3.86±0.36	0.001*
Aort diameter (cm)	2.91±0.37	3.18±0.44	3.03±0.2	0.014*
E.wave (cm/s)	0.79±0.18	0.76±0.19	0.77±0.17	0.900
A wave (cm/s)	0.66±0.19	0.67±0.19	0.62±0.15	0.794
E/A ratio (cm/s)	1.26±0.34	1.19±0.38	1.28±0.30	0.524
DT (ms)	178.7±44.04	226.12±68.78	200.33±34.52	0.007*
IVRT (msec)	89.81±21.28	107.95±27.09	106.09±27.06	0.018*
Lateral E (cm/s)	12.33±3.43	11.30±3.47	11.22±3.51	0.446
Lateral A (cm/s)	10.92±3.09	11.91±2.63	12.63±4.39	0.268
EE'	0.067±0.02	0.071±0.021	0.075±0.029	0.647

aKruskal Wallis Test; *p<0.05; **p<0.01; A: late diastolic peak flow velocity; A': myocardial atrial peak velocity; DT: Deceleration time; E: Early diastolic peak flow velocity; E': myocardial early peak velocity; EF: Ejection fraction; IVRT: Isovolumetric relaxation time; IVSd: Interventricular septum; LA: left atrial; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; PWTd: Posterior wall.

Table 3B. Difference between groups

	Control vs. Active	Control vs. Remission	Active vs. Remission
Aort diameter	0.011*	0.937	0.866
LVIDd	0.668	0.022*	0.168
IVSd	0.006**	0.027*	0.754
PWTd	0.001**	0.027*	1.000
LA	0.001**	0.001**	0.513
DT	0.005*	0.602	0.925
IVRT	0.017*	0.260	1.000

Bonferroni - Dunn Test; *p<0.05; **p<0.01.

LA was higher in active and remission groups than control group (p=0.001, p=0.001, respectively). DT and IVRT were higher in the active patient than controls (p=0.005, p=0.017, respectively); however, no statistically significant relation was observed between patients in remission and controls in both parameters.

CFR Measurement and its Associations with Klotho and FGF-23 levels

Mean CFR, Klotho, and FGF-23 levels are shown in Table 2a. Although control patients had higher Klotho and FGF-23 levels, there was no significant difference between groups. However, CFR levels of active group were lower than remission and controls (p=0.001; p=0.043, respectively). Due to this difference, a cutoff point for CRF was explored with Receiver Operating Characteristic curve (Fig. 1). According to groups, cutoff for CFR was found as 2.45 and below. For this CFR value, sensitivity was 83.78%, specificity 77.7%, positive predictive value 83.78, negative predictive value 77.78, and accuracy is 81.25 (Table 4). The area under the curve is 83% and standard error was calculated as 5.3%. There was a statistically significant difference between groups and CFR levels below 2.45 (p=0.001). Odds ratio was 18.083 (%95 confidence interval: 5.130–63.745).

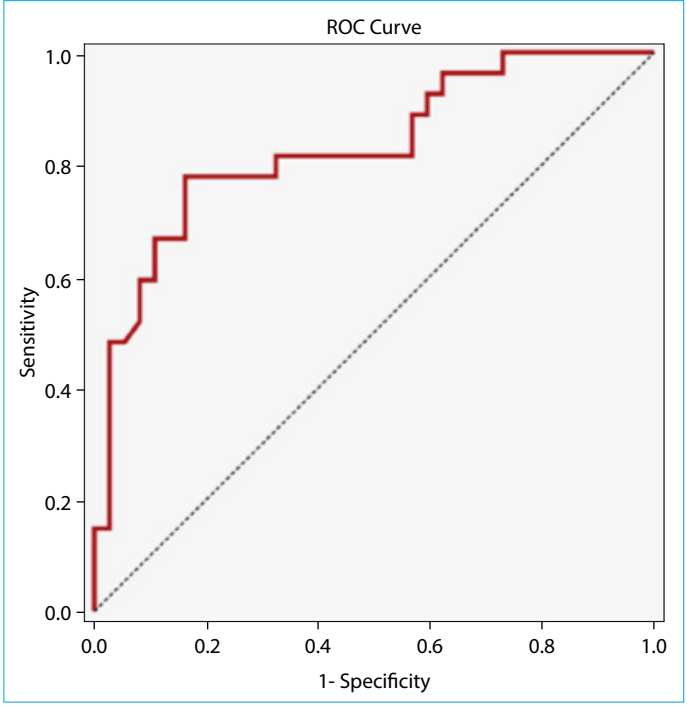

Figure 1. Receiver operating characteristic curve sensitivity.

There was no correlation between FGF-23 levels and CFR in any of the groups; however, Klotho was strongly associated with CFR levels in patients with active disease (Table 5).

Discussion

In this study, we found that CFR is reduced in acromegaly patients with active disease while CFR was similar between acromegaly patients in remission and controls.

Tellatin et al. have reported decreased CFR levels in active patients compared to patients in remission. Their report also mentioned that patients treated with somatostatin analogs had improvement in CFR measurement. These results underline the fact that earlier treatment strategies are crucial for prevention of cardiomyopathy in acromegaly patients. In addition, decreased GH levels have beneficial effects on established coronary damage in acromegaly patients with cardiomyopathy. This finding is in contrast with the studies investigating flow mediated dilatation in acromegaly. Reports of both Akgul et al. and Yaron et al. stated that foot and mouth disease was decreased in patients with acromegaly regardless of disease activity.[22, 23]

Effects of GH in cardiovascular tissue have been studied well in the past two decades. High and low GH levels have detrimental effects on the heart. The association of acromegaly with atherosclerotic risk factors (diabetes and HT) in rat models underline the fact that muscle hypertrophy is more dominant than the atherosclerotic process.[24]

Postmortem studies have shown the involvement of small vessels and the thickening of the intramural vessels in up to 22% of patients with acromegaly.[25] CFR measured with dipyridamole causes endothelium-dependent dilatation and GH influences endothelium directly through endothelial IGF-1 receptors or indirectly through effects on lipid metabolism causing abnormalities in lipid metabolism in patients with acromegaly. In addition, GH/IGF-1 are vascular growth factors and due to the stimulation of collagen deposition, they may have a role in coronary microvascular disease (CMD) in these patients.

Although the development of left ventricular hypertrophy (LVH) in patients with acromegaly is an adaptive and compensatory response, pathologic hypertrophy can lead to CMD despite the presence of normal coronary arteries in

Table 4. CFR receiver operating characteristic curve results

	Diagnostic Scan					ROC Curve		
	Cut off	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Area	95% Confidence Interval	p
CFR	≤2.45	83.78	77.78	83.78	77.78	0.830	0.726-0.934	0.001**

Table 5. Correlation analysis between CFR, Klotho, and FGF-23

	Control (n=24)	Active (n=23)	Remission (n=10)
CFR & FGF-23			
n	24	23	10
r	0.259	0.256	0.232
p	0.221	0.239	0.519
CFR & Klotho			
n	25	25	10
r	0.148	0.800	-0.098
p	0.481	0.001**	0.789
Klotho & FGF-23			
n	27	26	10
r	0.747	0.426	0.546
p	0.001**	0.030*	0.103

**p<0.01; *p<0.05; FGF23: Fibroblast growth factor- 23; CFR: Coronary flow reserve.

angiography. Pathogenetic mechanisms of CMD include structural changes (vascular rarefaction and perivascular fibrosis) and functional changes (endothelial dysfunction and dysfunction of smooth muscle).[26, 27] Functional and structural changes of the coronary microcirculation have been well documented in all models of pathologic LVH.[28] Furthermore, in patients with LVH induced by acromegaly, extravascular alterations also contribute to the impairment of microvascular function. Extravascular compression and increased left ventricular end diastolic pressure have been proposed as the main mechanisms for CMD in patients with acromegaly.[29] Our study showed a decrease in CFR in active acromegaly patients while similar CFR was observed between acromegaly patients in remission and control patients.

Acromegaly patients with active disease have higher Klotho levels that decreased after surgery.[21, 30, 31] However, we found decreased Klotho levels in acromegaly patients especially those with active disease. A possible explanation to this contrast may be that patients with acromegaly were slightly older patients than controls. Furthermore, Klotho has strong interactions with kidney disease. The fact that there were no patients with chronic kidney injury in our cohort may have influenced Klotho levels. A relatively strong correlation was observed with CFR levels in patients with active disease. Klotho has attenuating effects on mice alveolar epithelial cells.[32] The relationship between CFR and Klotho may be due to such an attenuating effect of Klotho on endothelial tissue. It may be working as a restorer of microcirculation inactive patients under the exposure of increased GH.

FGF-23 has endocrine, paracrine, and autocrine effects. It is well-documented that higher FGF-23 levels are associated with increased arterial stiffness, total body atherosclerosis, LVH and, consequently, increased cardiovascular mortality risk even in patients without kidney failure. FGF-23 requires a cofactor known as α-Klotho, protects the heart, for activation of FGF signaling.[33] Increased FGF-23 levels were observed in patients with gestational DM[34] and FGF-23 levels are associated with bone mineral density and preclinical vascular disease in patients Type 2 DM.[35] Ito et al.[36] reported that FGF-23 levels were decreased in patients with acromegaly after surgery. We hypothesized acromegaly patients may have increased levels of FGF-23; however, acromegaly patients had lower FGF-23 levels according to our study results.

There are several limitations of our study. First, the study group is comprised a relatively small number of patients enrolled from a single center. Second, we included a considerable number of acromegaly patients with diabetes, HT, and hyperlipidemia, all of which might contribute to coronary microvascular dysfunction. Furthermore, observational nature of our study is not sufficient to give a causal explanation to the results.

In conclusion, acromegaly patients have lower levels of Klotho and FGF-23 and CFR. Klotho was positively correlated with CFR levels in acromegaly patients with active disease. A study with a larger cohort can reveal more insight into preventive strategies.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Medeniyet University Goztepe Education and Research Hospital Clinical Research Ethics Committee and written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.T., F.A.; Design – M.T., F.A.; Supervision – M.T., F.A.; Materials – M.T., F.A.; Data collection &/or processing – M.T., F.A.; Analysis and/or interpretation – M.T., F.A.; Literature search – M.T., F.A.; Writing – M.T., F.A.; Critical review – M.T., F.A.

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