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Endothelial dysfunction in psoriatic arthritis patients: correlations between insulin resistance and disease activity

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Abstract. – OBJECTIVE: Cardiovascular atherosclerotic comorbidities represent an important cause of morbidity and mortality in patients diagnosed with psoriatic arthritis. In both atherosclerosis and Psoriatic arthritis, inflammation plays a pivotal role. Psoriatic arthritis is considered as an independent risk factor for the development of atherosclerosis with accelerated evolution. Development of atherosclerosis is initiated by the endothelial cell dysfunction along with inflammation and insulin resistance. The main aim of the study was to evaluate the endothelial function in Psoriatic arthritis patients, and to identify if it is related to the insulin resistance and Psoriatic arthritis disease activity.

PATIENTS AND METHODS: In this case-control study, a group of 32 age and gender matched healthy controls was formed and compared to the group of 32 Psoriatic arthritis patients. We assessed the following parameters: Disease Activity in Psoriatic Arthritis Score, Homeostatic Model Assessment for Insulin Resistance, serum levels of the tumor necrosis factor alpha (TNFα), and the endothelial dysfunction by means of the flow-mediated dilation at brachial artery. The Student's *t*-test, the Pearson correlation and the ANOVA test were used to perform the statistical analysis of the data obtained; *p*-value <0.05 was considered as statistically significant.

RESULTS: Compared to the patients in the control group, TNFα and Homeostatic Model Assessment for Insulin Resistance were increased (*p*-value <0.001), and flow-mediated dilation at brachial artery was decreased (*p*-value <0.001) in the disease group. In Psoriatic arthritis patients, significant correlations were found between Disease Activity in Psoriatic Arthritis Score and Homeostatic Model Assessment for Insulin Resistance (r=0.8143, *p*-value <0.001), and between Disease Activity in Psoriatic Arthritis Score and flow-mediated dilation at brachial artery % (r= -0.8376, *p*-value <0.001). Psoriatic arthritis patients treated with Methotrexate exhibited reduced values of Disease Activity in Psoriatic Arthritis Score and Homeostatic Model Assessment for Insulin Resistance and increased values of flow-mediated dilation at brachial artery, when compared with the untreated patients.

CONCLUSIONS: Endothelial dysfunction is present in Psoriatic arthritis patients and has a significant correlation with both, the course of the disease and the insulin resistance.

Key Words:
Endothelial dysfunction, Insulin resistance, Psoriatic arthritis.

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Introduction

Psoriatic arthritis, a type of chronic inflammatory arthritis associated with psoriasis, affecting both males and females in equal proportions, estimated to have incidence rate of approximately 83 cases per 100,000 healthy subjects and a prevalence of approximately 133 cases per 100,000 healthy subjects[1]. Due to chronic inflammation the vessel walls are extensively affected, resulting in atherosclerosis[2]. The overall morbidity and mortality rates are significantly high in Psoriatic arthritis patients with cardiovascular atherosclerotic changes[3]. Many studies[3-6] have documented the similarities in inflammatory mechanisms seen in Psoriatic arthritis and atherosclerosis, demonstrating that Psoriatic arthritis can be perceived as an independent risk factor with a potential to augment the atherosclerotic process.

Atherosclerosis is a progressive process that requires a very long duration of time to develop (many years), commencing with the initial step of endothelial dysfunction. Various immune-mediated inflammatory mechanisms associated with Psoriatic arthritis are considered to be involved in the development of insulin resistance, endothelial dysfunction, followed by atherosclerosis, and finally resulting in cardiovascular comorbidities, further deteriorating the quality of life[3,7-10].

Some studies have demonstrated that the Psoriatic arthritis is associated with increased risk of insulin resistance; the more active/aggressive/acute the Psoriatic arthritis is, the higher is the insulin resistance found in the patient[11]. Inflammatory cytokines (TNFα, IL1, IL17, and IL23) contribute to insulin resistance and endothelial dysfunction in active/acute phase of Psoriatic arthritis patients[12-14]. The treatment of Psoriatic arthritis patients consists of Conventional Disease Modifying Anti-Rheumatic Drugs: Methotrexate, Leflunomide and Sulfasalazine.

The main objective of this study was to evaluate the endothelial function in Psoriatic arthritis patients, and to identify the correlation between endothelial dysfunction, insulin resistance and Psoriatic arthritis activity.

Patients and Methods

This case-control study was performed in Department of Internal Medicine, Rheumatology unit between July 2016 and February 2019. A total of 32 Psoriatic arthritis patients according to the Psoriatic Arthritis Criteria Classification were included and comprised the disease/experimental group[15]. In addition to this, we formed a control group of age and gender matched 32 healthy individuals. Before the commencement of the study, written informed consents were obtained from the individuals in both the groups. Ethical approval was obtained in concordance to the Helsinki declaration, from the Ethics Committee of the University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania.

Individuals under the age of 18 years, pregnant or breastfeeding females, having diabetes mellitus or impaired glucose tolerance, atherogenic dyslipidemia, arterial hypertension, documented cardiovascular or cerebrovascular diseases, chronic kidney disease, thyroid dysfunction, smokers (both, present and past), on medications (corticosteroids, anti-tumor necrosis factor) were excluded from the study. Oral glucose tolerance test was performed in both the groups.

On enrolment, the Psoriatic arthritis activity was assessed using the Disease Activity in Psoriatic Arthritis Score (Disease Activity in Psoriatic Arthritis) and insulin resistance was assessed by Homeostatic Model Assessment of Insulin Resistance index, using fasting insulin and glucose values, in both the study groups[16].

Biochemical Markers

For analyzing the biochemical markers, the blood samples were collected from patients in specific vacutainers, without anticoagulants, which were then left to coagulate. The vacutainers were centrifuged at 2000-2500 rpm, for 10 minutes, and the decanted serum samples were fractionated using the Eppendorf (EP) tubes and frozen for 5 days at -20°C and biochemical markers were detected.

Quantitative determination of the glucose in patients' serum was done by enzymatic method with hexokinase using the Roche/Hitachi Cobas c501 automatic analyzer. The Analytical Measurement Range with this technology was 2-750 mg/dl and the normal range of fasting serum sample was considered between 70-90 mg/dl. The serum insulin levels were determined using the electrochemiluminescence immunoassay (ECLIA) method with Cobas e602 analyzers. This technique has the repeatability of the sample with CV: 3.2-3.7% and the intermediate precision with CV: 4.2-4.6%. For quantitative determina-

tion of CRP in patients' serum, the immunoturbidimetric assay was used, with Roche/Hitachi Cobas c501 automatic analyzer. The Analytical Measurement Range with this technology being between the range of 0.03-35.0 mg/dl. The Chemiluminescent Immunoassay was used for the determination of the serum levels of Tumor necrosis factor alpha (TNFα), pro-inflammatory cytokine. With this technique (QuantiGlo ELISA Kit, R&D Systems Inc. Minneapolis, MN, USA) intra-assay precision had a CV of 3.5-8.5%, inter-assay precision had a CV of 6.3-8.3% and assay range of 2.2-7.000 pg/ml.

Measurement of Endothelial Dysfunction

The B-mode ultrasound with the Siemens Acuson X300 Ultrasound System with 10 MHz linear transducer was used to measure the flow-mediated dilation of the brachial artery for assessment of the endothelial dysfunction. In order to perform this investigation, certain conditions were mandatory: the room temperature between 20-25°C, avoidance of caffeine, vitamin C, and high-fat food. The initial diameter of brachial artery (Di), coincident with the R wave of the electrocardiograph trace was noted. Then, brachial ischemia was induced, using pneumatic cuff inflated to a pressure of 50 mmHg above the systolic arterial blood pressure. After an ischemic period of 5 minutes, the pneumatic cuff was deflated, and the diameter of the brachial artery 60 seconds post-deflation (Df) was measured. Using the formula flow-mediated dilation at brachial artery =[(Df–Di)/Di] ×100, flow mediated dilation was calculated. Endothelial dysfunction was defined at a flow-mediated dilation at brachial artery less than 11.1%[17].

Statistical Analysis

The Microsoft Excel was used to perform the statistical analysis: the Student's *t*-test, the Pearson correlation (r positive and/or negative correlations) and the ANOVA test. All data are presented as mean ± standard deviation. The value of *p*-value <0.05 implies statistical significance.

Results

Baseline demographics of patients with Psoriatic arthritis experimental group and control group are presented in Table I.

TNFα and insulin resistance (expressed by means of Homeostatic Model Assessment for Insulin Resistance) were significantly higher in Psoriatic arthritis patients *vs.* healthy controls. Psoriatic arthritis patients exhibited endothelial dysfunction (expressed as reduced flow-mediated dilation at brachial artery), compared to the healthy controls (Table II).

Based on Disease Activity in Psoriatic Arthritis Score values, Psoriatic arthritis patients were classified as: remission (3 patients), low disease activity (7 patients), moderate disease activity (11 patients), and high disease activity (11 patients). The treatment of Psoriatic arthritis patients consisted of Conventional Disease Modifying Anti-Rheumatic Drugs: Methotrexate, Leflunomide and Sulfasalazine (Table III).

TNFα and insulin resistance increased, while endothelial dysfunction worsened with the increase of Psoriatic arthritis activity (Table IV).

Methotrexate administration was associated with low values of TNFα (*p*-value <0.0001), Disease Activity in Psoriatic Arthritis Score (*p*-value <0.0001), HOMA-IR (*p*-value <0.001) and elevat-

Table I. Characteristics of the study subjects.

Parameter	Value (mean ± standard deviation)	
	Psoriatic arthritis patients	Healthy controls
Sex [n (%)]	32	32
Males	13 (40.62%)	13 (40.62%)
Females	19 (59.37%)	19 (59.37%)
Mean age (years)	44.28 ± 8.23*	44.03 ± 6.90
Mean length of Psoriatic arthritis evolution (months)	26.34 ± 9.67	-
The drugs used by Psoriatic arthritis patients at the initial evaluation	Methotrexate (13 patients) Leflunomide (11 patients) Sulfasalazine (8 patients) Biologics (none)	-

Baseline demographics of the studied population: *$p > 0.05$-not significantly different from control group; n = number of patients and controls, Psoriatic arthritis = psoriatic arthritis.

Table II. Monitored parameters values in Psoriatic arthritis patients and controls.

Parameter	Psoriatic arthritis patients	Healthy controls	*p*-value
DAPSA	20.06 ± 10.96	-	
HOMA-IR	4.49 ± 1.54	1.26 ± 0.18	< 0.001
FMD (%)	9.52 ± 2.14	13.59 ± 1.35	< 0.001
TNFα (pg/ml)	31.23 ± 15.75	3.89 ± 1.66	< 0.001

p-value < 0.05-significantly different from control group; DAPSA = Disease Activity in Psoriatic Arthritis Score, HOMA-IR=Homeostatic Model Assessment for Insulin Resistance, FMD = Flow mediated dilation, TNFα = tumor necrosis factor alpha.

Table III. Therapeutic scheme in Psoriatic arthritis patients.

Drug	Number of psoriatic arthritis patients				
	Remission	Low disease activity	Moderate disease activity	High disease activity	Total
Methotrexate	n = 3	n = 7	n = 2	n = 1	n =13
Leflunomide	-	-	n = 4	n = 7	n = 11
Sulfasalazine	-	-	n = 5	n = 3	n = 8

Psoriatic arthritis = psoriatic arthritis, n = number of patients.

ed values of flow-mediated dilation at brachial artery (*p*-value <0.0001) compared to the therapy instituted with other DMARDs (Leflunomide, Sulfasalazine) (Table V).

In Psoriatic arthritis patients, significant correlations have been identified between disease activity (expressed as Disease Activity in Psoriatic Arthritis Score) and insulin resistance (expressed as Homeostatic Model Assessment for Insulin Resistance) (r=0.8143, *p*-value <0.001), respectively FMD (r= -0.8376, *p*-value <0.001). On the other hand, Homeostatic Model Assessment for Insulin Resistance was correlated with TNFα (r=0.6548, *p*-value <0.001), and with flow-mediated dilation at brachial artery (r= -0.8020, *p*-value <0.001) (Figure 1).

Discussion

According to the European League Against Rheumatism (EULAR) recommendations for the management of Psoriatic arthritis, the fifth overarching principle mentions the importance of cardiovascular diseases screening and treatment in these patients[18]. This study highlighted that the Psoriatic arthritis patients exhibit high insulin resistance, correlated with the activity of this rheumatic disease (r=0.8143, *p*-value <0.001). The flow-mediated dilation assessment in the brachial artery demonstrated the presence of endothelial dysfunction. The results obtained indicated the presence of endothelial dysfunction in patients

Table IV. Monitored parameters according to the Psoriatic arthritis activity.

Parameters	Status of disease activity				
	Remission	Low disease activity	Moderate disease activity	High disease activity	*p*-value
DAPSA	2.47 ± 0.21	8.06 ± 2.93	21 ± 4.38	31.55 ± 2.88	< 0.0001
TNFα (pg/ml)	6.89 ± 1.7	18.14 ± 7.11	32.17 ± 8.39	45.27 ± 12.36	< 0.0001
HOMA-IR	1.89 ± 0.49	3.32 ± 1.02	4.74 ± 0.93	5.68 ± 1.08	< 0.0001
FMD (%)	13.65 ± 0.38	10.38 ± 1.69	8.71 ± 0.97	7.51 ± 0.89	< 0.05

p-value < 0.05-significantly different according to the disease activity; DAPSA = Disease Activity in Psoriatic Arthritis Score, TNFα = tumor necrosis factor alpha, HOMA-IR = Homeostatic Model Assessment for Insulin Resistance, FMD = Flow mediated dilation.

Table V. Monitored parameters according to the psoriatic arthritis therapeutic regimen.

Parameter	Therapeutic regimen		*p*-value
	Methotrexate	Other DMARDs (Leflunomide, Sulfasalazine)	
DAPSA	9.44 ± 7.33	27.32 ± 5.83	< 0.0001
TNFα (pg/ml)	19.05 ± 10.88	39.57 ± 12.96	< 0.0001
HOMA-IR	3.40 ± 1.48	5.23 ± 1.08	< 0.001
FMD (%)	11.41 ± 2.02	8.23 ± 0.92	< 0.0001

Baseline demographics of the studied population: *p > 0.05-not significantly different from control group; n = number of patients and controls, Psoriatic arthritis = psoriatic arthritis.

with Psoriatic arthritis, without the presence of the cardiovascular risk factors or manifestation of CVD, correlated with disease activity (r=-0.8376, p-value <0.001) and insulin resistance (r= -0.802, p-value <0.001). As the Psoriatic arthritis activity (expressed as Disease Activity in Psoriatic Arthritis Score) increased, the endothelial dysfunction (expressed as flow-mediated dilation at brachial artery) worsened (p-value <0.05). Hence, new drugs targeting IL 17 and 23 have been proposed in the management of psoriasis and psoriatic arthritis with very promising results[19,20].

Recent studies[21-25] have highlighted that the risk of CVD is indeed higher in Psoriatic arthritis patients: ischemic heart disease, cerebrovascular diseases, and peripheral vascular diseases. Immune-mediated inflammatory mechanisms associated with active Psoriatic arthritis are involved in development of insulin resistance, endothelial dysfunction, followed by atherosclerosis, and cardiovascular comorbidities. Consequently, severe endothelial dysfunction accelerates the process of atherosclerosis[3,8]. Psoriatic arthritis is associated with high levels of proinflammatory cyto-

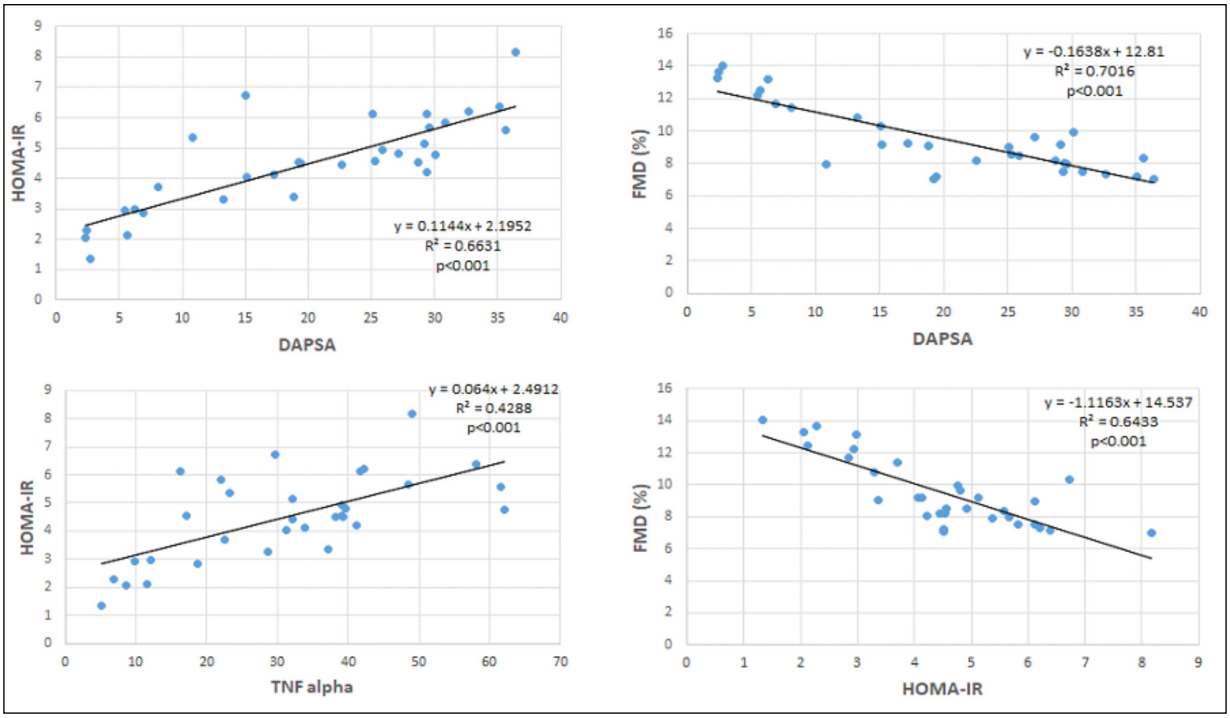

Figure 1. Pearson correlation in Psoriatic arthritis patients. p-value < 0.05-significantly different according to the therapeutic regimen; r-the Pearson's positive or negative correlation; DAPSA = Disease Activity in Psoriatic Arthritis Score, TNFα = tumor necrosis factor alpha, Homeostatic Model Assessment for Insulin Resistance = Homeostatic Model Assessment for Insulin Resistance, FMD = Flow mediated dilation.

kines, such as TNFα, IL1, IL17, and IL23. These proinflammatory cytokines promote insulin resistance in liver and fat tissues and contribute to impairment of insulin action on human skeletal muscles[11,13,14,26]. Dessein et al[27] identified that the insulin resistance was highly prevalent in patients with inflammatory arthritis, a possible response explaining the insulin resistance. Research results of a study conducted by Boehncke et al[28] supported the concept of the role of insulin resistance in the development of the "psoriatic march". Cytokine storm witnessed in COVID-19 patients can cause further aggravation of symptoms in persons suffering from chronic inflammatory disease, but the studies[29-31] are yet to be conducted for further evaluation. In the study conducted by Qureshi et al[32] on 1813 female patients with psoriasis, the relative risk of diabetes mellitus in psoriatic women compared with women without psoriasis was 1,63 times higher.

Insulin resistance and diabetes mellitus risk in Psoriatic arthritis patients were identified by Shapiro et al[33] and Solomon et al[34] in their studies. Studying 50 patients with Psoriatic arthritis and 25 controls, Abogamal et al[11] identified insulin resistance among the Psoriatic arthritis patients (p-value <0.05). Moreover, the authors demonstrated a significant positive correlation between insulin resistance (expressed as Homeostatic Model Assessment for Insulin Resistance) and Psoriatic arthritis activity (highlighted by Disease Activity in Psoriatic Arthritis Score) (p-value <0.05)[11]. Endothelial dysfunction represents the first step in atherosclerosis development. Inflammation, which is a characteristic feature of active Psoriatic arthritis represents the link between Psoriatic arthritis and atherosclerosis. Psoriatic arthritis patients display high serum levels of proinflammatory cytokines (TNFα, IL1, IL17, and IL23) that may promote endothelial dysfunction leading to atherosclerotic plaque formation[2,35,36]. Intense disease activity is associated with more severe signs of atherosclerosis[30]. Gonzalez-Juanatey et al[37] identified that the endothelial dysfunction was present in patients with Psoriatic arthritis compared with healthy controls (p-value=0.008), revealing a possible correlation with C-reactive protein (p-value <0.04)[37].

Yilmazer et al[38] showed that flow-mediated dilation at brachial artery % was significantly decreased among the patients with Psoriatic arthritis than the control group (p-value=0.01). Studying 40 Psoriatic arthritis patients and 40 controls, Shrama et al[39] demonstrated a significant reduction of flow-mediated dilation at brachial artery in patients with Psoriatic arthritis than in controls (8.3% *vs.* 10.8%, p-value=0.007). Another study[39] concluded an inverse correlation between flow-mediated dilation at brachial artery and PASI (Psoriasis Area and Severity Index) score, as a composite index of Psoriatic arthritis activity.

In our study, treatment with Methotrexate has been associated with low values of TNFα (p-value <0.0001), Disease Activity in Psoriatic Arthritis Score (p-value <0.0001), Homeostatic Model Assessment for Insulin Resistance (p-value <0.001) and elevated values of flow-mediated dilation at brachial artery (p-value <0.0001) as compared to the other DMARDs (Leflunonide, Sulfasalazine). Chin et al[40] assessed the Methotrexate effect on the risk of developing cardiovascular events in Psoriatic arthritis patients and revealed its protective effect (RR 0.48; 95% CI 0.29-0.81). Eder and Gladman[2] highlighted that the risk of developing endothelial dysfunction and atherosclerosis was increased in patients with Psoriatic arthritis without treatment with DMARDs (RR 1.33; 95% CI 1.13-1.58). Deyab et al[41] showed in their study that the use of Methotrexate in Psoriatic arthritis patients improved the disturbed parameter of endothelial dysfunction. A systematic review published by Brezinski et al[42] demonstrated that in patients with the endothelial dependent vasodilation in psoriatic arthritis is impaired, and it is ameliorated by the treatment with TNFα inhibitors.

However, the small number of Psoriatic arthritis patients included in our study, serves as one of the major limitations, as the results obtained cannot be generalized. Similarly, confounders were not factored-in and the study control size was small, which further adds to the study limitations. However, our results contribute to the increasing body of evidence and could therefore encourage other research entities to conduct large scale trials, which unfortunately, at our study center was not possible due to the overall small number of psoriatic arthritis cases enrolled.

Conclusions

Psoriatic arthritis patients present endothelial dysfunction, first step in atherosclerosis development. Endothelial dysfunction is significantly correlated with Psoriatic arthritis activity, assessed by Disease Activity in Psoriatic Arthri-

tis Score, and with insulin resistance. Active Psoriatic arthritis represents an important risk factor for atherosclerosis development. Hence, the measurement of endothelial dysfunction as a prognostic marker should be considered to monitor the evolution of the disease and to ensure better management of the patients. The patients in our study sample who were treated with methotrexate benefitted more when compared with the other patients who were on sulfasalazine or leflunomide. Larger studies are required to generalize the study results.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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These authors contributed equally as Co-first authors: Flavia-Corina Alexandru Babalic, Claudia Borza and Ciprian Ilie Rosca.

Authors' Contribution
F.C.A.B.: study design, data curation, analysis, C.B: study evaluation, drafting the article, consent formalities, C.I.R.: study concept, drafting the article, validation of results, C.V.G.: data collection and evaluation, C.D. B.: data collection and evaluation, O.AM.: protocol establishment, M.D.P.; statistical analysis, P.M.: assessment and data collection, S.C.C.: drawing conclusions, A.S.*: reviewed the manuscript, quality check, supervision, N.R.K.*: study design, writing and editing, drawing conclusion, A.EC.: supervision, study design.

Consent for Publication
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Ethics Approval
Ethical approval was obtained in concordance to the Helsinki declaration, from the Ethics Committee of the University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania, for conducting this study.

Informed Consent
Before the commencement of the study, written informed consents were obtained from the individuals in both the groups.

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