Original Article

The Relationship Between Epicardial Adipose Tissue and Insulin Resistance in Obese Children

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Abstract

Background: **Insulin resistance (IR) is an important disorder in obese children because it is closely related to cardiovascular diseases. Epicardial adipose tissue (EAT) plays a role in the development of IR due to secreted bioactive molecules, and the inflammatory process of these molecules may cause atrial electromechanical delay (EMD).**

Objective: **The objective of our study was to determine the relationship between EAT and EMD with IR in obese children.**

Methods: **Ninety-four obese patients were included in the study. IR was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and defined as HOMA-IR greater than the 90th percentile in an age- and sex-specific percentile curve. Patients were divided into two groups according to their IR. All patients underwent echocardiographic examinations. Statistical significance was set to a two-sided p-value < 0.05.**

Results: **EAT was significantly higher in the IR group ($p < 0.001$). The optimal cut-off value for EAT to predict IR was found to be > 3.85 mm, with 92.5% specificity and 68.5% sensitivity ($p = 0.002$). In the multivariate logistic regression model, EAT (OR = 1.256, 95% CI: 1.016–1.53, $p = 0.035$) was also associated with IR after adjustment for variables found to be statistically significant in univariate analysis. Inter- and intra-atrial EMD was significantly prolonged in the IR group compared to the group without IR ($p < 0.010$; $p = 0.032$ respectively).**

Conclusion: **In our study, we revealed that EAT was positively correlated with IR and was an independent predictor of IR. (Arq Bras Cardiol. 2020; [online].ahead print, PP.0-0)**

Keywords: **Pericardium; Adipose Tissue; Obesity; Child; Insulin Resistance; Echocardiography/methods.**

Introduction

Obesity is a major health problem worldwide due to its growing prevalence and early development in life.[1-3] The number of overweight people tends to progressively increase in both developed and developing countries, and the proportion of obese people is around one third of the normal adolescents population.[4-6] As a result, complications of obesity, such as metabolic syndrome, type 2 diabetes mellitus (DM), cardiovascular disorders, respiratory disorders, and psychosocial problems tend to increase.[7,8]

Obesity is typically associated with insulin resistance (IR) and glucose metabolism disorders. Adipose tissue stored in subcutaneous and visceral tissues plays an important role in the development of IR via the active proteins it secretes.[9] The distribution of this adipose tissue is equally important, with intra-abdominal fat accumulation being closely linked to IR.[10] Additionally, it is already known that subcutaneous fat tissue is correlated to IR whether or not DM is present.[11,12] Recent studies have demonstrated that extra-abdominal visceral fat deposits like mediastinal and epicardial adipose tissue (EAT) are also related to IR.[9,13,14] The association between obesity-dependent insulin resistance and EAT has not been fully explained.

Childhood obesity is an important risk factor for atrial fibrillation whereas structural remodeling is very important.[15] In many studies, this close relationship was investigated with electromechanical delay (EMD), which is one of these echocardiographic markers defined as the temporal delay between the detected onset of electrical activity and the realization of force in the myocardium. EMD is an indicator of atrial conduction heterogeneity and can also be obtained easily by tissue Doppler imaging (TDI).[16] In addition, it has been demonstrated that EMD is prolonged in diseases associated with insulin resistance.[17,18] However, the relationship between electromechanical delay and insulin resistance in obese patients has not been studied.

The aim of our study was to determine the relationship between EAT and insulin resistance. In addition, the relationship between insulin resistance and electromechanical delay was investigated.

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Methods

Study Population

For this prospective and cross-sectional study, 94 obese patients aged 8–18 years admitted to the Kahramanmaraş Sütçüimam University Pediatric Endocrinology outpatient clinic between August 2018 and February 2019 were included. An outpatient clinic nurse performed all anthropometric measurements, including weight and height with the patients wearing underwear only. Body mass index (BMI) was calculated by dividing body weight into kilograms by the square of height in meter. Obesity was defined as BMI greater than the 95th percentile in an age- and sex-specific percentile curve. A value above the 99th percentile was defined as morbid obesity.[19]

All patients' insulin resistance was calculated, and they were categorized on the basis of insulin resistance. Insulin resistance was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (fasting plasma glucose (mmol/L) × fasting plasma insulin (mU/L)/22.5) and defined as HOMA-IR greater than the 90th percentile in an age- and sex-specific percentile curve.[20]

Patients with DM, Cushing Syndrome, known insulin resistance; those using drugs for insulin resistance; those having hypoglycemia; those with known metabolic cardiovascular and hepatic disorders; and those with poor acoustic windows for echocardiography were excluded. Demographic and laboratory data of the patients were recorded. All patients underwent standard transthoracic echocardiography including tissue Doppler examination and echocardiographic examinations were performed by an expert cardiologist. The same cardiologist evaluated pre-discharge TTE results of 20 randomly selected patients to assess the reproducibility of EAT thickness and tissue Doppler parameters for atrial electromechanical delay. Using the Bland-Altman method, the mean difference in terms of intra-observation was 3.8% (0.23 ± 0.54%), indicating good reproducibility.

Echocardiography

Transthoracic echocardiographic examinations were performed by expert echocardiographers who were blind to the patients' clinical information with the Vivid 7® cardiac ultrasonography system (GE VingMed Ultrasound AS; Horten, Norway) using 2.5- to 5-MHz probes. The echocardiographic images were taken in left lateral and supine positions and 2D, M-mode, pulsed, and color flow Doppler echocardiography examinations were performed in every patient. Parasternal long and short axes, apical and subcostal windows were used to obtain Doppler tracings and two-dimensional images. Left and right atrial diameters left ventricular end-systolic and end-diastolic diameters, as well as the posterior and septal wall thicknesses of the left ventricle at diastole, were quantified. Left atrial volumes were quantified with the disc method LV ejection fraction (EF) with the Simpson's rule. LV diastolic function was quantified using mitral inflow velocities, i.e. peak E (early diastolic), peak A (late diastolic), E/A ratio as well as E-wave (DT) deceleration time and isovolumic relaxation time (IVRT).

Echocardiographic assessment and quantification of epicardial fat were done by identifying the echo-free space between the outer lining of the myocardium and the visceral layer of pericardium. Its measurement was made perpendicular to the free wall of the right ventricle in the parasternal long-axis window. The measurement level was at the mid ventricle and the timing was set to end-diastole, with an average of 3 cardiac cycles being taken. To align the ultrasound beam perpendicular to the right ventricular free wall, aortic annulus was accepted as the anatomic landmark.[21]

Tissue Doppler Echocardiography (TDE)

The pulsed Doppler sample volume was placed at the level of LV lateral mitral annulus, septal mitral annulus, and RV tricuspid annulus from an apical four-chamber view. The time interval from the onset of the P-wave on surface ECG to the beginning of the late diastolic wave (Am), which is called PA, was taken from the lateral mitral annulus (lateral PA), septal mitral annulus (septal PA), and RV tricuspid annulus (tricuspid PA). The difference between septal PA and tricuspid PA (septal PA − tricuspid PA) was identified as an intra-atrial electromechanical delay while the difference between lateral PA and tricuspid PA (lateral PA − tricuspid PA) was identified as inter-atrial electromechanical delay.[16]

Statistical Analysis

All statistical analyses were performed using the SPSS version 14 (SPSS Inc., Chicago, IL, USA) software package. Statistical significance was set to a two-sided p-value < 0.05. Categorical variables were expressed as number and percentage while continuous variables as mean±standard deviation (SD) or median and interquartile ranges (IQR), depending on their normality of distribution. The normality assumption of the data was determined using the Kolmogorov Smirnov test. The independent sample t-test and Mann–Whitney U test were used to compare the groups' means. The Chi-square test was used to compare categorical data. Correlation analyses were performed using the Pearson correlation test for normally distributed variables and Spearman correlation test for non-normally distributed variables. An optimal cut-off point was determined for EAT to predict IR using the receiver operator characteristic (ROC) curve analysis MedCalc (v12.7.8). This was accomplished by determining the area under the curve (AUC) with 95% confidence interval. The best cutoff value for EAT was determined by calculating the highest sum of sensitivity and specificity-1. The IR and available variables were analyzed for correlation using the univariate analysis. Variables with significant correlation in the univariate analysis were entered in the multivariate logistic regression model using the backward stepwise method along with other potential confounders to determine independent predictors of IR.

Results

Enrolled patients were divided into two groups based on the presence of insulin resistance. Forty patients had insulin resistance and 54 patients did not. Both groups had similar age and gender distribution. ($p = 0.102$, $p = 0.069$, respectively). Among the anthropometric measurements, weight, height, and

BMI were significantly greater in patients with insulin resistance. Additionally, diastolic and systolic blood pressure measurements were significantly greater in the IR group. A comparison of laboratory parameters revealed that the IR group had significantly higher serum insulin and glucose levels ($p < 0.001$, $p = 0.002$, respectively). The other laboratory parameters were similar between the groups (Table 1). Among standard echocardiographic measurements, EAT thickness was significantly increased in the group with IR ($p = 0.004$). Other standard echocardiographic and laboratory parameters were similar between the two groups. Atrial electromechanical delays recorded from different annular segments are given in Table 2. Lateral and septal PA was significantly higher in the IR group (62.2 ± 8.3 vs. 56.6 ± 8.4, $p = 0.002$; 46.1 ± 6.1 vs. 42.7 ± 5.9, $p = 0.019$ respectively). Tricuspid PA was similar between the groups. Inter- and intra-atrial EMD was significantly prolonged in the IR group compared to the group without insulin resistance (23 (18–30) vs. 19.5 (15–23.5), $p < 0.010$; 9.5 (6.2–10.0) vs. 6 (4–9.2), $p = 0.032$, respectively)

The echocardiographic parameters that showed correlations with HOMA-IR are summarized in Table 3. EAT thickness, inter- and intra-atrial EMD, lateral and septal PA were positively correlated to HOMA-IR.

The best cut-off value for EAT for the prediction of insulin resistance was >3.85 mm, with 92.5% specificity and 68.5% sensitivity (AUC = 0.672; 95% CI, 0.563–0.781; $p = 0.002$ (Figure 1).

In the multivariate logistic regression model using the backward stepwise method, EAT thickness (OR = 1.256, 95% CI: 1.016–1.53, p=0.035) and SBP (OR = 1.039, 95% CI: 1.007–1.072, $p = 0.015$) still remained significant predictors of IR after adjusting for the confounding variables, which were both found to be statistically significant in the univariate analysis (Table 4).

Discussion

This study investigated the relationship between epicardial adipose tissue and insulin resistance among obese children. It has been shown that epicardial adipose tissue is positively correlated to IR and an independent predictor of IR.

IR denotes a condition of relative insensitivity of peripheral tissues (e.g. muscle, liver, and adipose tissue) to the effects of the hormone. IR plays a pivotal role in the development and progression of cardio-metabolic risk factors that, in association with obesity, due to lipolytic effects of adipocytes, leading to large amounts of free fatty acids and impaired secretion of adipokines, both involved in the modulation of insulin sensitivity.[20-22] Although the prevalence of IR is variable among obese patients, Gabato et al. reported it to be 29.1% in their study.[23] In many other studies, this rate has been shown to be over 50%.[24-27] In our study, the rate of IR was found to be 43%. The reason for this difference can be explained by the use of constant HOMA-IR value in other studies, but, in our study, we used HOMA-IR percentile values according to age and gender.

The HOMA-IR is a proxy estimate of IR based upon the relationship between fasting glucose and insulin levels, with higher values of HOMA-IR representing more severe IR.[10] Increased IR and HOMA-IR values increase cardio-metabolic risk. There is no evidence of an association between IR measures and incident AF.[28] Many studies have shown that IR is closely related to atrial functions.[29,30] In our study, it was observed that HOMA-IR values were positively correlated with atrial tissue Doppler parameters which are indicative of atrial function in obese children and tissue atrial conduction was increased in the IR group.

Obesity causes prolongation of electromechanical conduction time by many mechanisms such as fat inflammation on the atrial wall, increase in sympathetic nervous system activity, increased inflammatory process, adipokinin dysregulation and activation of pro-fibrotic signaling pathways. Electromechanical conduction prolongation has been shown to be prone to atrial fibrillation.[31] IR, which is frequently associated with obesity, has an effect on atrial functions due to existing subclinical inflammation. In our study, both intra- and inter-atrial conduction time was found to be higher in obese children with insulin resistance, according to the literature, compared to the non-IR group. This may be explained by the inflammatory process associated with insulin resistance and by the delayed transmission of this inflammatory process on the atrial tissue. In the light of this information, it can be said that obese children who have insulin resistance may be more prone to atrial fibrillation.

Epicardial fat is a visceral fat accumulation that has most of the pathophysiological properties of other visceral adipose tissues, like lipid deposition and release of hormones, cytokines, and chemokines; and it also causes local inflammation.[32-35] It has been shown that body fat distribution, particularly abdominal fat distribution, is correlated with epicardial adipose tissue.[33] Hence, the relationship between epicardial adipose tissue thickness obtained from echocardiography and a number of pathological conditions such as metabolic syndrome, coronary artery disease, hyperlipidemia, blood pressure elevation, and IR has been studied in obese adult and pediatric patients. Epicardial adipose tissue causes the development and/or worsening of IR by increasing free fatty acids, TNF, IL1, IL6, and resistin release and decreasing adiponectin levels.[36] Several studies that examined the relationship between epicardial adipose tissue and IR demonstrated a correlation between epicardial adipose tissue and BMI in obese adults.[37-39] Abacı et al. showed a significant correlation with epicardial fatty tissue among obese children.[40] In line with the literature available, our study demonstrated a correlation between BMI and epicardial fatty tissue. Ishorbagy et al. reported that epicardial fatty tissue was larger in amount in obese patients than in healthy controls, although it did not predict metabolic syndrome.[41] Similarly, Abacı et al. suggested that epicardial fatty tissue failed to predict IR among obese children.[40] On the other hand, we found that epicardial fatty tissue was an independent predictor of IR. The cause of this discrepancy is that our study was a nested case-control study that only included patients instead of healthy controls. Another important reason was that in our study, IR was taken using determined percentiles according to age and gender.

The relationship between arterial blood pressure and IR has been shown in many studies [42,43] In our study, we found that systolic blood pressure is an independent predictor of IR. This may be due to increased fat tissue in the body that plays an important role in IR and subclinical inflammation caused

Table 1 – Baseline characteristics of study patients

	Obese patients with insulin resistance (n = 40)	Obese patients without insulin resistance (n = 54)	p
Age, median (IQR), years	13 (11–16)	12 (9–15)	0.102
Height, median (IQR), m	1.65 (1.55–1.70)	1.60 (1.43–1.65)	0.009
Weight, mean ± SD, kg	83.47 ± 21.22	64.13 ± 18.24	< 0.001
BMI, median (IQR)	31.8 (28.1–36.9)	29.7 (25–32.3)	0.019
Female/male (n)	20/20	37/17	0.069
SBP, median (IQR), mmHg	110 (100–130)	100 (80–130)	0.003
DBP, median (IQR), mmHg	80 (70–90)	70 (60–80)	0.016
Heart rate, mean ± SD, beats/min	72 ± 6	72 7	0.945
Laboratory findings			
Blood glucose, mean ± SD, mg/dL	92 ± 8	87 ± 6	0.002
Insulin, median (IQR), µIU/L	32.5 (24.6–42.7)	13.6 (10.4–16.8)	< 0.001
HbA1C, median (IQR), %	5.5 (5.2–5.6)	5.4 (5.1–5.6)	0.590
Urea, mean ± SD, mg/dL	9.9 ± 3.2	9.5 ± 1.9	0.606
ALT median (IQR), U/L	25 (16–34)	22 (17–28)	0.167
AST mean ± SD, U/L	24.9 ± 8.7	25.3 ± 7.5	0.807
Total Protein, median (IQR), g/dL	7.6 (7.3–7.9)	7.6 (7.2–8.0)	0.672
Albumin, mean ± SD,	4.7 ± 0.2	4.8 ± 0.4	0.577
Triglycerides, median (IQR), mg/dL	131 (112–155)	118 (90–154)	0.289
Total cholesterol, mean ± SD, mg/dL	171.2 ± 32.3	160.6 ± 21.5	0.079
HDL cholesterol, mean ± SD, mg/dL	41.8 ± 9.0	41.0 ± 8.7	0.686
LDL cholesterol, median (IQR), mg/ dL	89.5 (73.2–113.7)	86.5 (73–104.5)	0.491
TSH, median (IQR), mIU/L	2.55 (1.15–3.16)	2.79 (2.06–3.87)	0.061
T4, median (IQR), ng/dL	1.21 (1.13–1.33)	1.17 (1.06–1.30)	0.172
Cortisol, mean ± SD, µg/Dl	10.4 ± 6.4	10.0 ± 4.8	0.760
WBC, median (IQR), $x10^3/mm^3$	8330 (7232–10150)	8385 (7365–9900)	0.921
Hemoglobin, mean ± SD, g/dL	13.8 ± 0.9	13.5 ± 1.0	0.171
Platelet count, mean ± SD, $10^3/mm^3$,	333 ± 77	340 ± 72	0.595
RDW, median (IQR), %	13.6 (13.1–14.2)	13.4 (12.8–14.0)	0.147
Echocardiographic parameters			
EF, median (IQR), %	70 (70–72)	72 (70–72)	0.667
LVDD, mean ± SD, mm	4.3 ± 0.5	4.1 ± 0.4	0.059
LVSD, mean ± SD, mm	3.3 ± 0.6	3.2 ± 0.5	0.329
LA diameter, median (IQR), cm	3.0 (3.0–3.4)	3.1 (3.0–3.3)	0.792
RA diameter, mean ± SD, mm	3.3 ± 0.5	3.2 ± 0.5	0.165
RV thickness, median (IQR), cm	0.50 (0.42–0.60)	0.50 (0.40–0.55)	0.121
RV diameter, median (IQR), mm	2.7 (2.4–3.0)	2.5 (2.2–2.8)	0.176
Posterior wall thickness, median (IQR), mm	0.80 (0.70–0.90)	0.70 (0.70–0.80)	0.111
Septal thickness, median (IQR), mm	0.80 (0.70–0.90)	0.70 (0.70–0.90)	0.664
Epicardial adipose tissue, median (IQR), mm	7.15 (5.5–8.8)	5.5 (3.3–7.7)	0.004

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TSH: thyroid stimulating hormone; RDW: red cell distribution width; EF: ejection fraction; LVDD: left ventricle end diastolic dimension; LVSD: left ventricle end systolic dimension; LA: LEFT atrium; RA: right atrium; RV: right ventricle; WBC: white blood cell. Data are presented as mean±standard deviation (SD), number and percentage, or median and interquartile ranges (IQR). p < 0.05 was considered statistically significant.

Table 2 – Comparison of atrial electromechanical delay parameters measured by tissue Doppler imaging

	Obese patients with insulin resistance (n = 40)	Obese patients without insulin resistance (n = 54)	p
Lateral PA, mean±SD, ms	62.2 ± 8.3	56.6 ± 8.4	0.002
Septal PA, mean ± SD, ms	46.1 ± 6.1	42.7 ± 5.9	0.019
Tricuspid PA, mean ± SD, ms	38.0± 5.8	36.1 ± 4.7	0.088
Inter-atrial EMD, median (IQR), ms	23 (18–30)	19.5 (15–23.5)	0.010
Intra-atrial EMD, median (IQR), ms	9.5 (6.2–10.0)	6 (4–9.2)	0.032

PA: Time interval from the onset of P-wave on surface ECG to the beginning of Am wave interval with tissue Doppler echocardiography; EMD: Electromechanical delay, IQR: Interquartile ranges.

Table 3 – Echocardiographic parameters that correlate with HOMA-IR

Variables Correlating with HOMA-IR		
	R	P
Epicardial adipose tissue	0.422	< 0.001
Inter-atrial EMD	0.360	< 0.001
Intra-atrial EMD	0.345	0.001
Lateral PA	0.451	< 0.001
Septal PA	0.305	0.001

HOMA-IR: homeostatic model assessment for insulin resistance; PA: time interval from the onset of P-wave on surface ECG to the beginning of Am wave interval with tissue Doppler echocardiography; EMD: electromechanical delay.

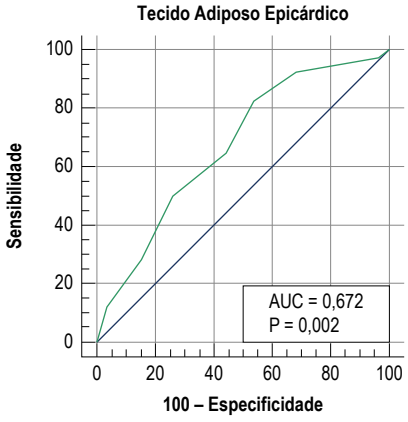

Figure 1 – *Receiver operator characteristic (ROC) curve of EAT to predict insulin resistance.*

by inflammatory cytokines, such as IL-6, IL-1 and TFN-alpha secreted from this adipose tissue. Subclinical inflammation can both impair endothelial function and increase blood pressure by decreasing NO release. Another possible mechanism is: there may be sympathetic activation of both the obesity and the obesity-related inflammatory process.[36,44-47]

Our study had some limitations: its main limitation was the relatively small sample size. Echocardiographic EAT is a linear measurement. Thus, it may not assess the total epicardial fat volume that varies at several myocardial locations. As a result of EAT, metabolically active tissue, inflammatory cytokines and inflammatory markers could be investigated in future studies. The absence of waist circumference measurement was another limitation, precluding the determination of a relationship between waist circumference and epicardial fat.

Conclusion

In conclusion, epicardial adipose tissue is a cheap, easily accessible parameter that can be easily measured with echocardiography and used to identify insulin resistance among children. Since atrial electromechanical delay increased in obese children with insulin resistance, it should be followed closely for atrial fibrillation.

Table 4 – Univariate and multivariate analysis for predicting insulin resistance

	Univariate Analysis						Multivariate Analysis					
	B	S.E.	Wald	P	OR	%95 CI	B	S.E.	Wald	P	OR	%95 CI
Epicardial adipose tissue	0,275	0,098	7,886	0,005	1,317	1,087–1,596	0,228	0,108	4,423	0,035	1,256	1,016–1.553
Systolic blood pressure	0,044	0,015	8,384	0,004	1,045	1,014–1,077	0,038	0,016	5,896	0,015	1,039	1,007–1.072
Diastolic blood pressure	0,049	0,019	6,959	0,008	1,050	1,013–1,089						
PA Lateral	0,078	0,027	8,661	0,003	1,081	1,026–1,139						
PA Septum	0,095	0,038	6,386	0,012	1,100	1,022–1,184						
Inter-atrial EMD	0,066	0,029	5,123	0,024	1,068	1,009–1,130						
Intra-atrial EMD	0,149	0,065	5,352	0,021	1,161	1,023–1,318						
Height	3,845	1,671	5,292	0,021	46,737	1,767–1236,369						
Weight	0,032	0,011	8,804	0,003	1,033	1,011–1,055						

All the variables from Table 1 and Table 2 were examined and only those significant at p < 0.05 level are shown in univariate analysis. Multivariate logistic regression analyses including all the variables in univariate analysis with the enter method. p < 0.05 was considered statistically significant. Non-significant variables in the multivariate logistic regression analysis were not included in table. B: Beta coefficients; CI: Confidence interval; EMD: Electromechanical delay. OR: odds ratio; PA: time interval from the onset of P-wave on surface ECG to the beginning of Am wave interval with tissue Doppler echocardiography; S.E.: standard error; Wald: Wald test.

Author contributions

Conception and design of the research: Güneş H; Acquisition of data and Statistical analysis: Güneş, H, Temiz F; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Güneş H, Güneş, H, Temiz F.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Kahramanmaraş Sütçü İmam University under the protocol number 349/2019. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all patients participants included in the study.

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