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Assessment of endothelial function in relation to the presence of type 2 diabetes mellitus in patients with prior myocardial infarction: a pilot study using peripheral arterial tonometry

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ABSTRACT

Background. Endothelial dysfunction represents an early stage of atherosclerosis, while hyperglycaemia remains an important cause of endothelial dysfunction. The aim of this study was to assess endothelial function in patients with prior ST-segment elevation myocardial infarction (STEMI) in relation to the presence of type 2 diabetes mellitus (DM).

Materials and methods: Eighty three adults treated with primary percutaneous intervention for STEMI within the previous 12–18 months were enrolled in a case-control study. The control group consisted of 21 healthy volunteers. Endothelial function was assessed with peripheral arterial tonometry (PAT). The value of reactive hyperemia index (RHI) and the presence of endothelial dysfunction (defined as RHI ≤ 2.0) were respectively the primary and secondary study endpoints.

Results. RHI was significantly lower in post-STEMI subjects with concomitant type 2 DM (n = 21) than in healthy volunteers [1.70 (1.44–1.96) vs 2.15 (1.82–2.50); p = 0.006]. On the other hand, there were no significant differences in RHI between post-STEMI patients with and without type 2 DM [n = 62; RHI: 1.87 (1.59–2.39)], nor between the latter group and the control group. In terms of the secondary study endpoint, we observed a decreasing prevalence of endothelial dysfunction across the compared groups [76.2% vs 54.8% vs 38.1% for post-STEMI diabetics, post-STEMI non-diabetics and controls, respectively; p for trend = 0.013].

Conclusions. Our study indicates that endothelial function assessed with PAT is significantly worse in post-STEMI subjects with concomitant type 2 DM compared to healthy controls, but it does not seem to be substantially different in diabetic vs. non-diabetic STEMI survivors. The clinical significance of our findings warrants further investigation in adequately powered, prospective studies.

Key words: endothelial dysfunction, atherosclerosis, peripheral arterial tonometry, coronary artery disease, hyperglycemia

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Introduction

The endothelium produces substances that exert autocrine and paracrine effects and play a key role in maintaining vascular homeostasis [1–3]. Endothelial dysfunction is characterized by reduced bioavailability of vasodilatory mediators, particularly nitric oxide, and increased production of vasoconstrictive mediators, including endothelin 1. Numerous proinflammatory, proliferative and prothrombotic mechanisms are activated in dysfunctional endothelium in addition to the impairment of endothelium–dependent vasodilatation. Activated endothelium subsequently initiates adverse mechanisms underlying the development

and destabilization of atherosclerotic plaque [4, 5]. Endothelial dysfunction represents an early stage of atherosclerosis development – the main cause of coronary artery disease [5, 6], which in turn is the leading cause of morbidity and mortality in industrialized countries [7, 8].

Classic risk factors of coronary artery disease possess a limited value in predicting adverse clinical outcomes in patients after an acute coronary syndrome [9, 10]. It is estimated that in this population classic risk factors explain less than 50% of the risk of recurrent cardiovascular events [9, 10]. The consequence of these findings is that a great interest is taken in methods that could significantly improve the risk stratification in this group of patients. Great expectations in this regard lie in the assessment of endothelial function. To date, it has been clearly demonstrated that the presence of dysfunctional endothelium in coronary and peripheral arteries is an independent risk factor of future cardiovascular events [6, 8, 11–15].

Diabetes mellitus constitutes one of the main risk factors for coronary artery disease. It is estimated that it occurs in 6.4% of adults and in 20–25% of patients with a recent acute coronary syndrome [16]. The risk of death from cardiovascular causes is similar for patients with diabetes without prior myocardial infarction as it is for those with a history of myocardial infarction but without concomitant diabetes [17]. Mortality among patients with myocardial infarction and diabetes remains significantly higher compared to non-diabetics [18].

The aim of this study was to assess endothelial function using peripheral arterial tonometry (PAT) in patients with prior ST-segment elevation myocardial infarction (STEMI) in relation to the presence of type 2 diabetes mellitus.

Materials and methods

Study design and population characteristics

Eighty-three patients hospitalized between November 2005 and December 2008 for a first episode of STEMI and treated with primary percutaneous coronary intervention were enrolled in a case-control study. The cases were consecutive patients from a prospective, cohort study assessing glucose metabolism disorders and post-STEMI left ventricular systolic dysfunction. STEMI was diagnosed in accordance with international recommendations [19, 20]. The STEMI survivors were divided into two groups according to concomitant disturbances of glucose metabolism. The first group comprised patients with type 2 diabetes mellitus and the second group comprised non-diabetic individuals. Diabetes mellitus was defined as: fasting plasma glucose concentration $\geq$ 126 mg/dL (7.0 mmol/L) in at least two measurements, or plasma glucose concentration $\geq$ 200 mg/dL (11.1 mmol/L) at 120 minutes of oral glucose tolerance test (OGTT). OGTT was performed before hospital discharge (STEMI hospitalization) and three months after. Patients without diagnosed diabetes mellitus had another OGTT performed on the day of endothelial function assessment (12–18 months after STEMI). Glucose, lipid profile and HbA1c assays were performed using standard methods on the Architect ci8200 analyzer (Abbott Laboratories, Wiesbaden, Germany). We also recruited 21 healthy volunteers as a control group.

The value of reactive hyperemia index (RHI) was the primary study endpoint, while the presence of endothelial dysfunction (defined as RHI $\leq$ 2.0) constituted the secondary study endpoint.

The study protocol was approved by The Ethical Committee of Nicolaus Copernicus University (KB 74/2009).

Assessment of endothelial function

Endothelial function was assessed using PAT (the EndoPAT 2000 device, Itamar-Medical, Caesarea, Israel), which is a non-invasive, user-friendly and well-validated in terms of clinical outcomes prediction, diagnostic tool [2, 4, 8, 21–23]. The device provides reliable and reproducible results. The principle of PAT has been described in detail previously [2]. Briefly, the EndoPAT 2000 device utilizes the applanation tonometry method. A blood pressure cuff is placed on one arm, while the other arm acts as the control arm. Dedicated PAT probes are placed on one finger of each hand to assess digital volume changes accompanying pulse waves [6]. After a ten minute equilibration period, the cuff is inflated to 60 mm Hg above systolic pressure for five minutes with subsequent deflation of the cuff resulting in reactive hyperemia (RH) [21]. Computerized automatic analysis provides RH-PAT indices as a measure of reactive hyperemia. The parameter used to evaluate endothelial function is the reactive hyperemia index (RHI). According to the device's manufacturer, normal RHI values are those exceeding 2.0, while in terms of values lower or equal to 2.0, endothelial dysfunction is diagnosed [24]. The EndoPAT 2000 device is approved for use in the European Union (CE certificate) and in the United States of America (by the FDA).

All study participants fasted for 12 hours before assessments, which were carried out at 09:00 a.m. $\pm$ 1 hour, in temperatures of 22°C $\pm$ 1°C. In addition, smokers were asked to abstain from cigarettes for at least 12 hours before endothelial function assessment.

Statistical analysis

According to the Shapiro-Wilk test, the investigated continuous variables were non-normally distributed. Therefore, the results were reported as medians and interquartile ranges and non-parametric tests were applied in the statistical analysis. For comparisons among three groups, the Kruskal-Wallis (for assessment of heterogeneity), with the application of an appropriate *post hoc* test, and the Jonckheere-Terpstra (for evaluation of a trend) tests were used. Categorical variables were expressed as a number of patients presenting the given feature and a percentage of those patients in the analyzed group. Comparisons of categorical variables were performed using the χ^2 test with the Yates' correction if required. The presence or absence of trends among categorical variables was assessed with the Cochran-Armitage test. ROC (Receiver Operating Characteristic) curve analysis was used to determine the diagnostic value of RHI to identify patients after myocardial infarction with concomitant diabetes. Differences were considered significant at $p < 0.05$. The statistical analysis was carried out using the Statistica 10.0 package (StatSoft, Tulsa, OK, USA), SPSS Statistics version 19.0 (SPSS Inc., Chicago, IL, USA) and MedCalc version 12.1 (MedCalc Software, Mariakerke, Belgium).

Results

Patients

Of the 83 post-STEMI patients constituting our study group, 21 had type 2 diabetes mellitus, whereas the remaining 62 were free from this metabolic disorder. The clinical characteristics of the study participants are presented in Table 1. Post-STEMI patients with concomitant diabetes mellitus compared with non-diabetic post-STEMI patients and the control groups had a significantly higher body mass index and glycated hemoglobin concentration measured on the day of endothelium function assessment. Additionally, post-STEMI diabetic patients presented with substantially higher systolic blood pressure on the day of endothelium function assessment as compared with other groups.

Endothelial function

As shown in Figure 1, we demonstrated the presence of significant heterogeneity in RHI values among the compared groups. The use of the *post hoc* test revealed a substantially lower RHI value in post-STEMI subjects with concomitant type 2 DM than in controls [1.70 (1.44–1.96) vs 2.15 (1.82–2.50), p = 0.006]. On the other hand, there were no significant differences in

RHI between post-STEMI patients with and without type 2 DM [RHI: 1.87 (1.59–2.39)], nor between the latter group and the control group.

In terms of the secondary study endpoint, we observed a decreasing prevalence of endothelial dysfunction across the compared groups [16/21 (76.2%) vs 34/62 (54.8%) vs 8/21 (38.1%) for post-STEMI diabetics, post-STEMI non-diabetics and controls, respectively; Fig. 2]. Endothelial dysfunction was significantly more frequent among post-STEMI patients with type 2 diabetes mellitus compared with controls [odds ratio (OR) 5.20; 95% confidence interval (CI) 1.37–19.77; p = 0.016]. On the other hand, differences in the prevalence of endothelial dysfunction between post-STEMI patients without diabetes mellitus and controls (OR 1.97; 95% CI 0.72–5.43; p = 0.188) as well as between diabetic and non-diabetic STEMI survivors (OR 2.64; 95% CI 0.86–8.09; p = 0.09; Fig. 2) did not achieve statistical significance.

Additionally, we performed a ROC curve analysis among all study participants (both post-STEMI patients and healthy volunteers) in order to determine the diagnostic value of RHI in identification of diabetic patients (Fig. 3). The area under the ROC curve (AUC) achieved an acceptable value of 0.693 (95% CI 0.595–0.780; p < 0.001). The optimal cut-off value of RHI for identification of patients with type 2 diabetes mellitus was 2.02. The sensitivity, specificity, positive predictive value and negative predictive value for this cut-off point were 81.0% (95% CI 58.1–94.4%), 47.0% (95% CI 35.9–58.3%), 27.9% (95% CI 17.2–40.8%) and 90.7% (95% CI 77.8–97.3%), respectively.

Discussion

The present study demonstrates that endothelial function, assessed with PAT as a continuous variable (RHI) or evaluated in a qualitative way as the presence of endothelial dysfunction, is significantly impaired in post-STEMI patients with concomitant type 2 diabetes mellitus compared with healthy controls. Comparing the control group vs. non-diabetic post-STEMI patients vs. post-STEMI patients with concomitant type 2 diabetes mellitus, we observed a gradual deterioration of endothelial function, with an increase in total cardiovascular risk. We also found that RHI possesses a significant discriminating value in terms of identification of patients with diabetes mellitus, with particularly high sensitivity (for RHI values ≤ 2.02) and high negative predictive value (for RHI values > 2.02), but with low specificity and low negative predictive value. Nevertheless, our results indicate that endothelial function assessed with PAT does not seem to be substantially different in diabetic vs non-diabetic STEMI survivors.

Table 1. Characteristics of the study population

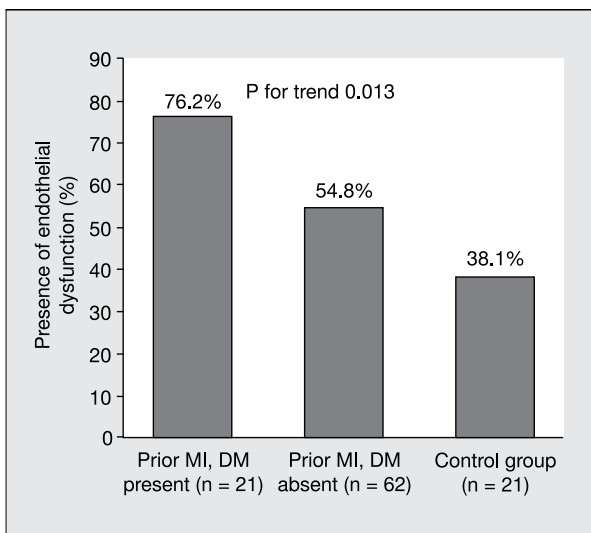| Variable	Post-STEMI patients with type 2 diabetes mellitus (n = 21)	Post-STEMI patients without type 2 diabetes mellitus (n = 62)	Control group (n = 21)	p-value for comparison between post-STEMI diabetic and non-diabetic patients	p-value for comparison among all analyzed groups
Demographic and clinical characteristics					
Male, n (%)	13 (61.9)	46 (74.2)	9 (42.9)	ns	0.031
Age (years)	64.0 (60.0–71.0)	59.5 (54.0–67.0)	58.0 (54.0–63.0)	ns	ns
Body mass index [kg/m^2]	29.9 (25.6–33.7)	27.4 (25.2–29.2)	24.2 (22.4–25.6)	0.043	0.006
History of hypertension, n (%)	14 (66.7)	31 (50.0)	0 (0)	ns	na
Current smokers, n (%)	9 (42.9)	31 (50.0)	1 (4.8)	ns	0.001
History of hypercholesterolemia, n (%)	6 (28.6)	23 (37.1)	0 (0)	ns	na
Pharmacotherapy on the day of endothelial function assessment					
Aspirin, n (%)	21 (100.0)	59 (95.2)	0 (0.0%)	ns	na
Clopidogrel, n (%)	3 (14.2)	9 (14.5)	0 (0.0%)	ns	na
Beta-blocker, n (%)	20 (95.2)	61 (98.4)	0 (0.0%)	ns	na
ACEI/ARB, n (%)	21 (100.0)	57 (91.9)	0 (0.0%)	ns	na
Statin, n (%)	20 (95.2)	56 (90.3)	0 (0.0%)	ns	na
Ca-blocker, n (%)	4 (19.1)	6 (9.7)	0 (0.0%)	ns	na
Diuretics, n (%)	9 (42.9)	9 (14.5)	0 (0.0%)	0.016	na
Insulin, n (%)	9 (42.9)	0 (0.0%)	0 (0.0%)	< 0.0001	na
Oral antidiabetic agents, n (%)	9 (42.9)	0 (0.0%)	0 (0.0%)	< 0.0001	na
Metformin, n (%)	6 (28.6)	0 (0.0%)	0 (0.0%)	< 0.0001	na
Blood pressure and laboratory parameters on the day of endothelial function assessment					
Systolic blood pressure [mm Hg]	130 (120.0–140.0)	115.0 (100.0–130.0)	120.0 (110.0–125.0)	0.044	0.047
Diastolic blood pressure [mm Hg]	80.0 (70.0–80.0)	70.0 (70.0–80.0)	70.0 (70.0–80.0)	ns	ns
Total cholesterol [mg/dL]	163.0 (152.0–184.0)	166.0 (145.0–195.0)	227.0 (206.0–250.0)	ns	< 0.0001
LDL-C [mg/dL]	91.0 (78.0–107.0)	96.0 (78.5–117.0)	152.0 (127.0–164.0)	ns	< 0.0001
HDL-C [mg/dL]	46.0 (41.0–52.0)	48.0 (40.0–53.0)	53.0 (45.0–63.0)	ns	ns
Triglycerides [mg/dL]	140.0 (88.0–194.0)	96.0 (76.0–140.0)	117.0 (85.0–159.0)	ns	ns
HbA$_{1c}$ (%)	6.5 (6.2–8.0)	5.6 (5.3–5.8)	6.0 (5.8–6.2)	< 0.0001	< 0.0001

ACE-I — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; HbA$_{1c}$ — glycated haemoglobin; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; na — not applicable due to the fact that assumptions of the χ^2 test are not fulfilled; ns — non significant

Chronic hyperglycemia plays a dominant role in the deterioration of endothelial function in patients with diabetes mellitus. It enhances oxidative stress by generating a variety of reactive oxygen species through activation of several biochemical pathways including: stimulation of the polyol pathway, increased transcription of genes for proinflammatory cytokines and plasminogen activator inhibitor-1 (PAI-1), activation of protein kinase-C, increased synthesis of advanced glycation end products (AGEs) and autooxidation of glucose with formation of ketoimines and AGEs [2, 25, 26]. Additionally, impairment of nitric oxide-dependent vasodilator effect of insulin related to insulin resistance [27] and low count of dysfunctional endothelial progenitor cells were shown in type 2 diabetes mellitus [28]. Furthermore, repeated and extensive exposure of endothelial cells to hyperglycemia accompanied by other cardiovascular risk factors impairs their vascular protective function [28, 29].
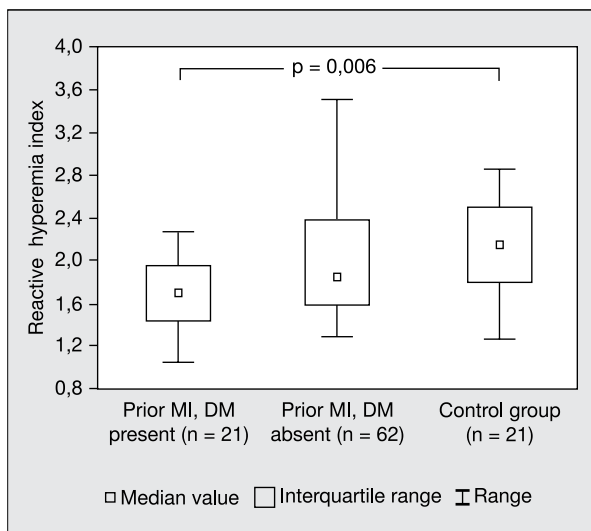
Figure 1. Comparison of reactive hyperemia indices in post--STEMI patients with concomitant type 2 diabetes mellitus (prior MI, DM present group), non-diabetic post-STEMI patients (prior MI, DM absent group) and healthy volunteers (control group). DM — diabetes mellitus; MI — myocardial infarction; STEMI — ST-segment elevation myocardial infarction. Statistical significance of p was calculated for heterogeneity among the compared groups

Figure 2. Presence of endothelial dysfunction in post--STEMI patients with concomitant type 2 diabetes mellitus (prior MI, DM present group), non-diabetic post-STEMI patients (prior MI, DM absent group) and healthy volunteers (control group). DM — diabetes mellitus; MI — myocardial infarction; STEMI — ST-segment elevation myocardial infarction
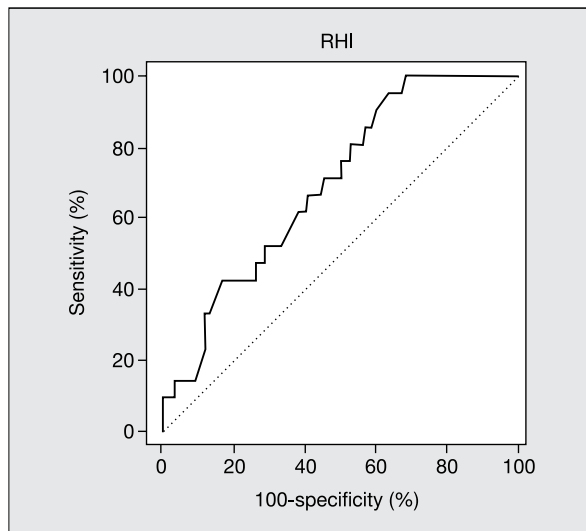
Figure 3. ROC curve assessing the diagnostic value of reactive hyperemia index to identify patients with type 2 diabetes. RHI — reactive hyperemia index

The use of applanation tonometry was prompted by the modernity of this automated data analysis, its simplicity of use, and operator independence. Importantly, the location of the plethysmograph probe on a finger prevents accumulation of distal venous blood, which may cause venous-arterial vasoconstriction. It also increases the dynamic range of changes of blood volume through arterial wall relief, prevents the backflow of venous blood that could adversely affect the measurement, as well as reduces artifacts caused by limb movements. Furthermore, simultaneous recording of blood flow on the opposite arm eliminates the influence of the autonomic nervous system on the vessels' wall tension changes [24]. The result not only shows a relationship with the occurrence of coronary artery disease risk factors [30], but also has a significant prognostic value in predicting cardiovascular events, independent of traditional risk scores [31]. Moreover, the results of endothelial function measurement using applanation tonometry correlate with endothelial dysfunction assessed with invasive [6, 8] and non-invasive methods, such as ultrasound assessment of arterial dilatation as a consequence of ischemia [8, 32, 33]. Contrary to the latter modality being to date the most widely used method acknowledged as a gold standard of non-invasive techniques of endothelial function assessment, applanation tonometry is standardized and has high repeatability of measurements [34, 35]. These properties encourage the use of applanation tonometry in clinical practice. A significant correlation has been demonstrated between the value of RHI and the pres-

ence of cardiovascular disease risk factors such as: male gender, body mass index, total cholesterol/HDL, diabetes mellitus, smoking and the treatment of lipid disorders [30, 33, 36–39].

Ruggiero et al. showed significantly impaired endothelial function, as assessed with applanation tonometry, in diabetic patients without coronary artery disease compared to healthy subjects [40]. Furthermore, Gargiulo et al. evaluated endothelial function using PAT in 183 consecutive patients undergoing elective coronary angiography in relation to the presence of concomitant type 2 diabetes mellitus. Subjects with prior myocardial infarction were excluded from the study. The authors reported that diabetic patients, regardless of the presence of coronary artery disease, demonstrated a significantly higher impairment of peripheral vascular function than non-diabetic patients without coronary artery disease [41]. Importantly, diabetic patients without coronary artery disease (n = 58) showed a similar degree of endothelial dysfunction compared with patients with established coronary artery disease without concomitant glucose metabolism disorders (n = 31). Gargiulo et al. have also demonstrated significantly worse endothelial function in patients with coronary artery disease, but without type 2 diabetes mellitus, compared with healthy subjects (n = 36). In line with our findings, the authors observed comparable RHI values in coronary artery disease patients with (n = 58) and without concomitant type 2 diabetes mellitus.

In our study, contrary to expectations, we did not find major differences in endothelial function between post-STEMI patients without diabetes mellitus compared with healthy subjects, even though the post-STEMI patients were additionally burdened with hypertension (50%) and were more likely to be smokers than controls (50.0% vs 4.8%). The only risk factor that was more pronounced in the control group was worse lipid profile values. This lack of differences could be potentially explained by the proven, beneficial effects on endothelium of drugs such as angiotensin-converting enzyme inhibitors and statins, used in the post-STEMI setting. Furthermore, we were analyzing only one index of endothelial function, while other indicators of endothelial function can possibly show differences.

Lumsden et al. evaluated endothelial function using applanation tonometry in 15 patients with type 2 diabetes mellitus suffering from recent acute coronary syndrome. They demonstrated that these patients, despite remaining on standard clinical care within six months after acute coronary syndrome, continued to show significantly worse endothelial function compared with 16 healthy subjects [42]. Similarly to their results, we found that diabetic patients on optimal medical treatment continue to show significant impairment of endothelial function after at least one year of STEMI.

Despite advances that have taken place in recent years regarding the diagnostics and treatment of patients with acute coronary syndromes and diabetes mellitus, the prognosis in this group remains worse than in patients without diabetes mellitus. Endothelial dysfunction, which plays a key role not only in the development of atherosclerosis but also in the process of restenosis, remains a diagnostic and therapeutic challenge. The complex processes underlying endothelial dysfunction in diabetic individuals require further exploration, so we can effectively fill the gaps in currently used therapies and therefore provide the best help to our patients.

Limitations of the study

Due to a limited number of patients with type 2 diabetes mellitus, the results need confirmation in a larger population. In this pilot study, we examined only endothelial vasodilator function. In the next phase, we plan to assess other indicators of endothelial function in similar groups of patients. Further studies are needed to evaluate the clinical significance of the observed relations. We cannot overlook the fact that in our study all enrolled patients after myocardial infarction received drugs with proven, beneficial effects on endothelial function.

Conclusions

Our study indicates that endothelial function assessed with PAT is significantly worse in post-STEMI subjects with concomitant type 2 diabetes mellitus compared with healthy controls. It does not seem however to be substantially different in diabetic vs. non-diabetic STEMI survivors. The clinical significance of our findings warrants further investigation in adequately powered, prospective studies.

Acknowledgements

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