Effect of Telemedicine Dietary Intervention on Endothelial Function in Patients with Type 2 Diabetes Mellitus on Mediterranean Diet

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ABSTRACT **Background:** Patients with type 2 diabetes mellitus (T2DM) have a high rate of cardiovascular disease (CVD). The Mediterranean diet is preferred for CVD prevention. Endothelial dysfunction is demonstrated early in T2DM.

Objectives: To study the effects of dietary intervention of T2DM patients without known CVD on endothelial function and vascular inflammation.

Methods: A prospective study enrolled 22 patients with T2DM. Patients were divided randomly into two groups: an intervention group with 12 patients (55 ± 7 years old, 6 women) and a control group with 10 patients (59 ± 10 years old, 5 women). Clinical evaluation included body mass index (BMI) and endothelial function measured by the flow mediated percent change (FMD%). Fasting blood was drawn on entry to the study and 3 months later, measuring C-reactive protein (CRP), intercellular adhesion molecule-1 (ICAM-1), total cholesterol, triglycerides, and glycosylated hemoglobin (HbA1C%). The intervention was based on weekly telephone calls by a clinical dietitian for 3 months.

Results: In the intervention group CRP and ICAM-1 were reduced (from 4.2 ± 3.3 mg/dl to 0.4 ± 0.5 mg/dl, $P = 0.01$ and from 258.6 ± 98.3 ng/ml to 171.6 ± 47.7 ng/ml, $P = 0.004$). Endothelial function (FMD%) was improved (from 0.5 ± 8.0% to 9.5 ± 11.5%, $P = 0.014$). No change was observed in BMI, HbA1C%, total cholesterol, and triglycerides levels in either group.

Conclusions: Patients with T2DM on the Mediterranean diet who received a weekly telephone call for 3 months improved their endothelial function with reduction of markers of inflammation.

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KEY WORDS: diabetes mellitus, endothelial function, Inflammation, Mediterranean diet, telemedicine

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Type 2 diabetes mellitus (T2DM) is characterized by a two-fold to fourfold increased risk of cardiovascular disease (CVD). This change is generally attributed to the adverse effects of hyperglycemia and oxidative stress on vascular biology. It has also been shown that patients with pre-diabetic conditions, such as impaired fasting glucose and impaired glucose tolerance, are at increased risk of cardiovascular disease as well [1]. The term *endothelial dysfunction* refers to a condition in which the endothelium loses its physiological properties: the tendency to promote vasodilation, fibrinolysis, and anti-aggregation. Endothelial cells secrete several mediators that can alternatively mediate either vasoconstriction such as endothelin-1 and thromboxane A2, or vasodilation such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor. Nitric oxide is the major contributor to endothelium-dependent relaxation in conduit arteries, whereas the contribution of endothelium-derived hyperpolarizing factor predominates in smaller resistance vessels. In patients with T2DM, endothelial dysfunction appears to be an early phenomenon thought to be caused by a lack of nitric oxide production and activity. Endothelial repair is accomplished through endothelial progenitor cells (EPCs). Patients with T2DM lack EPCs and display an impaired ability to regenerate damaged endothelium and blood vessels [2].

According to the American Diabetes Association recommendations, several eating patterns are recommended for patients with T2DM and pre-diabetes like the Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH), and plant-based diets [3]. The Mediterranean diet reduces the number of lipoproteins particles and it could be part of the mechanism responsible for the lower cardiovascular (CVD) risk observed in Mediterranean countries [4]. A long-term intervention with the Mediterranean diet rich in olive oil improved the postprandial lipemia and remnant cholesterol plasma concentrations. Both are considered independent predictors of CVD [5]. Mediterranean diet improves control of T2DM through improved insulin sensitivity, glucose homeostasis, insulin secretion, and endothe-

lial function, with a reduction in markers of inflammation and inhibition of adhesion molecules [6].

Anti-inflammatory and anti-oxidative pathways are considered the main mechanistic pathways by which the Mediterranean diet produces its cardiometabolic beneficial effects in T2DM: increased consumption of high-quality foods inhibits the activation of the innate immune system, reduces pro-inflammatory cytokines, and enhances anti-inflammatory cytokines. This result may favor the generation of an anti-inflammatory milieu, with improved insulin sensitivity and endothelial function at the vascular level, and may prevent metabolic syndrome, T2DM, and atherosclerosis [7].

Our T2DM patients live in the northern part of Israel and have eaten a Mediterranean diet since the day they were born. They were hospitalized with uncontrolled hyperglycemia (without ketoacidosis).

We aimed to study the effects of personal dietary intervention with a weekly telephone call to provide guidance on their vascular reactivity and systemic inflammation, the main mechanisms leading to CVD.

PATIENTS AND METHODS

TRIAL DESIGN

This pilot prospective study was conducted to evaluate the role of individual dietary interventions in patients with T2DM on vascular reactivity in patients with inadequately controlled T2DM over 12 weeks. Eligible patients were asked to join the study and to sign a consent form. The study was approved by the internal review board of the Padeh Medical Center. The patients were randomized to join the intervention group or the control group. All patients received personal dietary instructions from a clinical dietitian before they were discharged. They underwent clinical and laboratory examinations. They all were scheduled to return to the clinic to undergo the same series of examinations 3 months after discharge.

DIETARY INTERVENTION

Basic diabetes self-management education (DSME) before discharge from the hospital was conducted for every patient in the clinical trial (both groups). The intervention was based on a weekly telephone call conversation with each of the participants in the intervention group for 3 months. The dietician stressed the importance of eating a Mediterranean diet, eating the right amounts of food as was determined, and encouraging patients to be active daily. Patients in the control group were not followed weekly, and were only asked to come for a second visit in 3 months.

Clinical evaluation included the clinical data (age, weight and height, and measurement of the endothelial function using the brachial artery method).

The laboratory evaluation included a level of glycosylated hemoglobin (HbA1C%), total cholesterol, triglyceride level, C-reactive protein (CRP), intercellular adhesion molecule 1 (ICAM-1).The clinical and the laboratory examinations were done twice, on entry to the study and 3 months afterwards.

ENDOTHELIAL FUNCTION

Endothelial function was performed early in the morning, patients were fasting, did not take their medications in the morning of the examination, and did not drink coffee or tea 24 hours before the vascular evaluation. Endothelial function was evaluated by the brachial artery method, measuring flow mediated diameter percent change (FMD%). Patients were lying comfortably in a quiet room for 10 minutes before the blood pressure cuff was placed above the antecubital fossa. A baseline rest image was acquired. Thereafter, arterial occlusion was created by cuff inflation to approximately 50 mmHg above median blood pressure for 5 minutes. Cuff deflation induced a high-flow state through the brachial artery and the longitudinal image of the artery was recorded continuously 30 seconds before to 2 minutes after cuff deflation. Post-deflation brachial artery diameters at 50, 60, and 70 seconds were measured and the difference between the average of these measurements and the baseline brachial artery diameter was calculated, divided by the baseline diameter, multiplied by 100, to get the FMD% [8].

INCLUSION CRITERIA

All diabetic patients who were older than 18 years of age could enter the study, both men and women.

EXCLUSION CRITERIA

Patients with known CVD (old myocardial infarction, cerebrovascular event, heart failure); renal failure (even mild); dementia; cancer (active or within the last 5 years); recent surgery (within the last 6 months); chronic infection (within the last 6 months); or any chronic autoimmune, inflammatory, or infectious disorder (e.g., systemic lupus erythematosus, human immunodeficiency viruses) were excluded. Patients who were not able to sign a consent form and those who were not willing to come for a follow-up visit 3 months after discharge were not included.

STATISTICAL ANALYSIS

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to examine the normality of the data. The non-parametric Mann–Whitney U test was used to compare between the two groups, and the non-parametric Wilcoxon signed-rank test was used to find the change over time within the same group. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

RESULTS

PATIENT POPULATION

The study comprised 22 patients with type 2 diabetes mellitus (T2DM), 12 in the intervention arm (aged 55 ± 7 years old, BMI 29.9 ± 1.3, 6 women) and 10 in the control arm (aged 59 ± 10 years old, BMI 32.0 ± 1.5, 5 women). The participants had completed the clinical and laboratory examinations at both time points.

No significant difference was observed between the two groups of patients in age, BMI, HbA1C%, cholesterol, triglycerides, CRP, ICAM-1 levels, and FMD% (endothelial function). In the control group BMI did not change, neither was HbA1C%. Cholesterol levels were increased (162 ± 30 mg% to 172 ± 45 mg%, $P = 0.04$). Triglyceride levels were not changed, and CRP decreased but without statistical significance (from 5.6 ± 9.2 mg/dl to 2.0 ± 3.4 mg/dl, $P = 0.07$) [Table 1] [Figure 1A]. No change was observed in ICAM-1 levels and no significant change was observed in endothelial function (FMD%) [Figure 1B, Figure 1C].

In the intervention group BMI was not changed, and even though HbA1C% was decreased it did not reach a statistical difference (from 8.1 ± 1.9 to 7.5 ± 1.6, $P = 0.08$). Cholesterol and triglyceride levels were not changed, but CRP levels were reduced from 4.2 ± 3.3 mg/dl to 0.4 ± 0.5 mg/dl, $P = 0.01$ [Table 1, Figure 1A]. ICAM-1levels were also reduced from 258.6 ± 98.3 ng/ml to 171.6 ± 47.7 ng/ml, $P = 0.004$ [Figure 1C]. A significant improvement was observed in endothelial function from 0.5 ± 0.8% to 9.5 ± 11.5%, $P = 0.014$ [Figure 1B].

Analyzing the dietary intake of the T2DM patients in both groups shows that patients in the control group did not change the energy, total fat, saturated fat, trans fat, carbohydrates, and sugar intake within the 3 months of follow up, while patients in the intervention arm lowered significantly the intake of the energy consumption, as well as fats, carbohydrates and sugars [Table 2].

Table 1. Clinical, biochemical characteristics of T2DM patients

	Baseline	After 3 months	*P* value
Intervention group* (Age 55 ± 7 years)			
Body mass index, kg/m2	29.9 ± 1.3	29.2 ± 1.1	NS
HbA1C%	8.1 ± 1.9	7.5 ± 1.6	0.08
Cholesterol (mg%)	177 ± 8.5	166 ± 10.5	0.216
Triglycerides (mg%)	147 ± 9.5	150 ± 19.5	0.378
Control group (Age 59 ± 10 years)**			
Body mass index, kg/m2	32.0 ± 1.5	32.5 ± 1.5	NS
HbA1C%	7.8 ± 0.6	7.0 ± 0.5	0.437
Cholesterol (mg%)	162 ± 30	172 ± 45	0.04
Triglycerides (mg%)	163 ± 19	200 ± 49	0.407

*Intervention group included 12 patients
**Control group included 10 patents

DISCUSSION

We found that diabetic patients who received personal dietary guidance and follow-up (a weekly phone call conversation) managed to improve significantly their endothelial function and to reduce systemic inflammation without any change in their weight, glycosylated hemoglobin level, or lipid profile. Endothelial function and systemic inflammation play a pivotal role in atherosclerosis and CVD.

Figure 1 The difference between CRP, endothelial function, and ICAM-1 levels before and after 3 months of telemedicine intervention
CRP = C-reactive protein, ICAM-1 = intercellular adhesion molecule-1
[A] CRP in the intervention arm was $P = 0.01$
[B] Endothelial function in the intervention arm was $P = 0.01$
[C] ICAM-1 in the intervention arm was $P = 0.004$

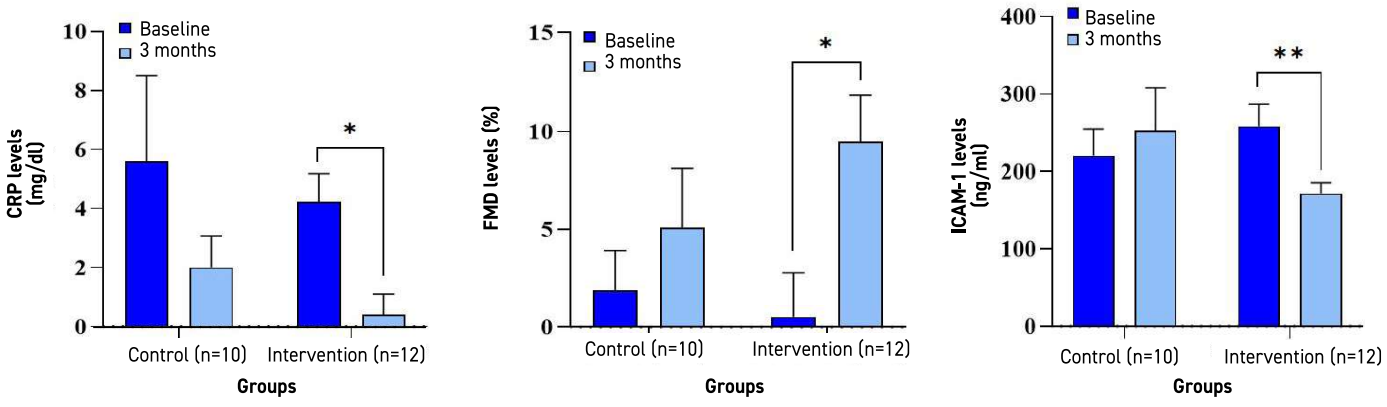

Table 2. Dietary parameters in both groups

	Baseline	After 3 months	*P* value
Intervention group* (Age 55 ± 7 years)			
Energy, Kcal	2982 ± 246	2366 ± 126	**< 0.05**
Total fat, grams	110 ± 9	95 ± 5.5	**< 0.05**
Saturated fat, grams	32 ± 2.5	28 ± 2	**< 0.05**
Trans fat, grams	2.1 ± 0.3	1.6 ± 0.15	**< 0.05**
Carbohydrates, grams	370 ± 33.5	260 ± 13.5	**< 0.05**
Sugar, grams	104 ± 8.5	83 ± 7	**< 0.05**
Control group (Age 59 ± 10 years)**			
Energy, Kcal	2861 ± 188	2821 ± 239	0.875
Total fat, grams	115 ± 9	119 ± 11	0.814
Saturated fat, grams	35 ± 4	37 ± 4.5	0.505
Trans fat, grams	2.1 ± 0.15	2.1 ± 0.19	0.721
Carbohydrates, grams	329 ± 21	288 ± 36	0.347
Sugar, grams	107 ± 7	111 ± 11	0.724

*Intervention group included 12 patients
**Control group included 10 patents
Bold indicates significance

Several dietary foods have been shown to affect the endothelium. Brown rice improved the endothelial function of diabetic patients, compared with white rice, which did not have the same effect [9]. There was no difference in the lipid profile change in both diet groups, but CRP was inhibited in the brown rice group compared with the white rice diet group. A study that followed diabetic patients found that eating 60 grams daily of soy nuts for 8 weeks significantly increased the antioxidant capacity and the brachial artery flow, with a significant decrease in total and LDL-cholesterol, and in E-selectin level [10]. After 4 weeks of a diet enriched with apple polyphenols the glycemic control was much better, and after 4 more weeks of treatment, free plasma glucose and the serum uric acid levels were significantly decreased compared to the baseline measurements and the placebo group. The endothelial function was improved in this group as well [11]. Other diet modalities include a hypocaloric low-fat diet and hypocaloric very low carbohydrate diet. When these two diets were compared, the low-fat diet experienced a significantly greater enhancement of endothelial function [12].

The Mediterranean diet is based on the traditional foods of countries surrounding the Mediterranean Sea. It is considered one of the healthiest dietary patterns to prevent chronic diseases. A meta-analysis that summarized 13 meta-analyses with a total of 12,625,301 patients demonstrated that greater adherence to the Mediterranean diet leads to reduced overall mortality, CVD, coronary artery disease, myocardial infarction, overall cancer incidence, neurodegenerative diseases and T2DM [12]. It is believed that the beneficial effects of the Mediterranean diet are attributed to its influence on traditional CVD risk factors [13-15]. This diet is effective in reducing weight, BMI, waist circumference, and total cholesterol, and increasing HDL-cholesterol. The Mediterranean diet was associated with reduced risk of T2DM, with a better glycemic control and reduced insulin resistance [15]. Several studies suggested anti-inflammatory effects that influence the vascular wall, which could explain the link between Mediterranean diet and reduced risk of CVD [16]. The studies that evaluated inflammatory parameters found an inverse relationship between Mediterranean diet, CRP and interleukin 6 [16,17]. To understand the mechanism of the beneficial effects of the Mediterranean diet, a clinical study was conducted to investigate the effects of Mediterranean diet (108 patients with T2DM) or a low fat diet (107 patients with T2DM) on endothelial stem cells and the carotid intima-media thickness (CIMT). At the end of the study both CD34+KDR+ and CD34+KDR+CD133+ stem cells were increased in patients who got the Mediterranean diet compared with patients who got the low-fat diet ($P < 0.05$ for both). The rate of regression of the CIMT in patients with the Mediterranean diet was higher and the rate of progression was lower. The changes in the CIMT were inversely correlated with the changes in EPC levels [18,19]. Another mechanism that could explain the beneficial effects of the Mediterranean diet was demonstrated in a study that showed that this diet increased plasma antioxidant capacity and improved endothelial function with inhibition of interleukin 6 and ICAM-1 levels [20].

LIMITATIONS

The small sample size is a major limitation. We considered this study to be a pilot study, and based on our findings we are planning to perform a bigger study with variable populations and in different ages.

CONCLUSIONS

Personal care on a weekly basis can affect endothelial function and lower CVD risk.

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References

1. Kirpichnikov D, Sowers JR. Diabetes mellitus and diabetes-associated vascular disease. *Trends Endocrinol Metab* 2001; 12: 225-30.
2. Fadini GP, Sartore S, Agostini C, Avogaro A. Significance of endothelial progenitor cells in subjects with diabetes. *Diabetes Care* 2007; 30: 1305-13.
3. American Diabetes Association. Standars of Medical Care in Diabetes–2017 abridged for primary care providers. *Clin Diabetes* 2017; 35 (1): 5-26.
4. Perez-Martinez P, Ordovas JM, garcia-Rios A, et al. Consumption of diets with different type of fat influences triacylglycerols-rich lipoproteins particle number and size during the postprandial state. *Nutr Metab Cardiovasc Dis* 2011; 21 (1): 39-45.

5. Pirillo A, Norata GD, Catapano AL. Postprandial lipemia as a cardiometabolic risk factor. *Curr Med Res Opin* 2014; 30 (8): 1489-503.
6. Esposito K, Maiorino MI, Bellastella G, et al. Mediterranean diet for type 2 diabetes: cardiometabolic benefits. *Endocrine* 2017; 56: 27-32.
7. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002; 39 (2): 257-65.
8. Kondo K, Morino K, Nishio Y, et al. Fiber rich diet with brown rice improves endothelial function in type 2 diabetes mellitus: a randomized controlled trial. *PLOS ONE* 2017; 12 (6): e0179869
9. Sedaghat A, Shahbaziam H, Rezazadeh A, et al. The effect of soy nut on serum total antioxidant, endothelial function and cardiovascular risk factors in patients with type 2 diabetes. *Diabetes Metab Syndr* 2019; 13: 1387-91.
10. Cicero AFG, Caliceti C, Fogacci F, et al. Effect of apple polyphenols on vascular oxidative stress and endothelium function: a translational study. *Mol Nutr Food Res* 2017; 61 (11).
11. Barbosa-Tanez RL, Dambeck U, Li L, et al. Acute endothelial benefits of fat restriction over cardohydrate restriction in type 2 diabetes mellitus: beyond carbs and fats. *Nutrients* 2018; 10: 1859.
12. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomized trials. *Eur J Clin Nutr* 2018; 72 (1): 30-43.
13. Gajendragadkar PR, Hubsch A, Maki-Petaja KM, et al. Effects of oral lycopene supplement on vascular function in patients with cardiovascular disease and healthy volunteers: a randomized controlled trial. *PLOS ONE* 2014; 9: e99070.
14. Casas R, Sacanella E, Urpi-Sarda M, et al. The effects of the mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. *PLOS ONE* 2014; 9: e100084.
15. Storniolo CE, Rosello-Catafau J, Pinto X, et al. Polyphenol fraction of extra virgin olive oil protects against endothelial dysfunction induced by high glucose and free fatty acids through modulation of nitric oxide and endothelin-1. *Redox Biol* 2014; 2: 971-7.
16. Estruch R. Anti-inflammatory effects of the Mediterranean diet: the experience of the PREDIMED study. *Proc Nutr Soc* 2010; 69: 333-40.
17. Nordmann AJ, Suter-Zimmermann K, Bucher HC, et al. Meta-analysis comparing Mediterranean to low fat diets for modification of cardiovascular risk factors. *Am J Med* 2011; 124: 841-51.
18. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systemic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc Dis* 2014; 24: 929-39.
19. Maiorino MI, Bellastella G, Petrizzo M, et al. Effect of a Mediterranean diet on endothelial progenitor cells and carotid intima-media thickness in type 2 diabetes: follow-up of a randomized trial. Eur J Prev Cardiol 2017; 24 (4): 399-408.
20. Ceriello A, Esposito K, Sala LL, et al. The protective effect of the Mediterranean diet on endothelial resistance to GLP-1 in type 2 diabetes: a preliminary report. Cardiovasc Diabetol 2014; 13: 140-9.

Capsule

A metabolic shift into kidney cancer

Deficiency in the metabolic enzyme fumarate hydratase distinguishes a particularly aggressive and lethal form of kidney cancer. **Crooks** and co-authors investigated the molecular basis for why this subset of kidney tumors rapidly grow and metastasize. Deficiency in fumarate hydratase led to the accumulation of the metabolite fumarate, resulting in the modification and inactivation of factors involved in mitochondrial DNA replication and proofreading. Subsequently, mitochondrial DNA mutations increased, leading to loss of mitochondria and a metabolic shift to aerobic glycolysis.

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Capsule

A population-based study of genes previously implicated in breast cancer

Population-based estimates of the risk of breast cancer associated with germline pathogenic variants in cancer-predisposition genes are critically needed for risk assessment and management in women with inherited pathogenic variants. In a population-based case–control study, **Hu** et al. performed sequencing using a custom multigene amplicon-based panel to identify germline pathogenic variants in 28 cancer-predisposition genes among 32,247 women with breast cancer (case patients) and 32,544 unaffected women (controls) from population-based studies in the Cancer Risk Estimates Related to Susceptibility (CARRIERS) consortium. Pathogenic variants in 12 established breast cancer-predisposition genes were detected in 5.03% of case patients and in 1.63% of controls. Pathogenic variants in *BRCA1* and *BRCA2* were associated with a high risk of breast cancer, with odds ratios of 7.62 (95% confidence interval [95%CI] 5.33–11.27) and 5.23 (95%CI 4.09–6.77), respectively. Pathogenic variants in *PALB2* were associated with a moderate risk (odds ratio, 3.83; 95%CI 2.68–5.63). Pathogenic variants in *BARD1*, *RAD51C*, and *RAD51D* were associated with increased risks of estrogen receptor–negative breast cancer and triple-negative breast cancer, whereas pathogenic variants in *ATM*, *CDH1*, and *CHEK2* were associated with an increased risk of estrogen receptor–positive breast cancer. Pathogenic variants in 16 candidate breast cancer–predisposition genes, including the c.657_661del5 founder pathogenic variant in *NBN*, were not associated with an increased risk of breast cancer.

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