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Orgınal Article

The Mediterranean Diet Effects on in-Stent Restenosis

Akdeniz Diyetinin Stent Restenozu Üzerine Etkileri

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Highlights

- It has recently become the focus of clinical studies that feeding a Mediterranean diet may help prevent cardiovascular events and atherosclerosis.
- Restenosis rates are lower in stented patients who score high on the Mediterranean diet.

Abstract

Background: There is evidence that Mediterranean diet nutrition can help prevent cardiovascular events and atherosclerosis, but researchs are limited. Despite advances in interventional techniques, medical treatments, and lower cardiovascular disease (CVD) mortality, increasing percutaneous coronary interventions have made in-stent restenosis (ISR) an important problem in interventional cardiology. This study aims to assess the relationship between in-stent restenosis and the Mediterranean diet score.

Material and Method: The diet quality of 100 patients with ISR and 100 patients without ISR was determined and compared using a scoring method (5, 6, 9, and 10 points) using the 'Mediterranean Diet Compliance Scale'.

Results : Patients with ISR had lower Mediterranean diet scores (odds ratio [OR]: 0.572, 95% confidence interval [CI]: (0.480-0.681), p<0.001). The ISR and Mediterranean diet score had a significant negative correlation (p<0.001, r = -0.679).

Conclusion: In our study, we found that patients who scored high on the Mediterranean diet had a lower risk of ISR, and there was also a negative correlation between the Mediterranean diet and ISR. It is the first study to look at the effects of the Mediterranean diet on patients with a previous percutaneous coronary intervention. This study, examining the relationship between the Mediterranean diet and ISR, may aid in understanding the pathophysiology of ISR.

Keywords: In-stent restenosis; Mediterranean diet score; Coronary artery disease

ÖZ

Amaç: Akdeniz diyeti ile beslenmesinin kardiyovasküler olayları ve aterosklerozu önlemeye yardımcı olabileceğine dair kanıtlar vardır, ancak araştırmalar sınırlıdır. Girişimsel tekniklerdeki ilerlemelere, tıbbi tedavilere ve düşük kardiyovasküler hastalık (KVH) mortalitesine rağmen, artan perkütan koroner girişimler stent içi restenozu (SİR) girişimsel kardiyolojide önemli bir sorun haline getirmiştir. Bu çalışma, stent içi restenoz ile Akdeniz diyeti skoru arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Materiyal ve Metod:SİR'u olan 100 hastanın ve SİR'u olmayan 100 hastanın diyet kalitesi belirlendi ve 'Akdeniz Diyet Uyum Ölçeği' kullanılarak bir skorlama yöntemi (5, 6, 9 ve 10 puan) ile karşılaştırıldı.

Bulgular:SİR'u olan hastalarda Akdeniz diyeti puanları daha düşüktü (olasılık oranı [OR]: 0,572, %95 güven aralığı [CI]: (0,480-0,681), p<0,001). SİR ve Akdeniz diyeti puanı arasında anlamlı bir negatif korelasyon vardı (p<0.001, r = -0.679).

Sonuç:Çalışmamızda, Akdeniz diyetinden yüksek puan alan hastaların SİR riskinin daha düşük olduğunu ve ayrıca Akdeniz diyeti ile SİR arasında negatif bir korelasyon olduğunu bulduk. Daha önce perkütan koroner girişim geçirmiş hastalarda Akdeniz diyetinin etkilerini inceleyen ilk çalışmadır. Akdeniz diyeti ile SİR'u arasındaki ilişkiyi inceleyen bu çalışma, SİR'nin patofizyolojisinin anlaşılmasına yardımcı olabilir.

Anahtar Kelimeler: Stent içi restenoz; Akdeniz diyeti puanı; Koroner arter hastalığı

Introduction

Cardiovascular disease (CVD) continues to be the leading cause of morbidity and mortality in developed countries, imposing a significant economic burden on the healthcare system and society(1-3). Cardiovascular risk has been shown to be influenced by lifestyle and dietary habits(4-6). Evidence supports that certain individual nutrients and foods provide cardiovascular benefits(7, 8). Examining general dietary patterns, on the other hand, may provide a more powerful tool for assessing dietary habits by assessing the synergistic and cumulative effects of specific nutrients on cardiovascular health(7).

The Mediterranean diet is a dietary pattern that is becoming increasingly popular owing to its health benefits, such as CVD prevention(9). Typical Mediterranean dietary habits and styles include a high consumption of fruits, vegetables, monounsaturated fats, fish, whole wheat, legumes, and nuts, as well as a low consumption of red meat(10). In primary prevention, the Mediterranean diet has been shown to be effective in lowering the cardiovascular risk (11). In this context, the PREDIMED study found that the Mediterranean diet had a higher long-term benefit for CVD than a low-fat diet(11). Another study that compared the Mediterranean diet to another low-fat diet found that it reduced plaque load in the carotid arteries and was more effective in secondary prevention(7). A Mediterranean-style diet has the potential to be anti-inflammatory, antioxidant, and cytoprotective(8, 12, 13).

Despite advances in interventional techniques and medical treatments, as well as lower CVD mortality, increasing percutaneous coronary interventions have made in-stent restenosis (ISR) an important problem in interventional cardiology(14, 15). Although ISR is linked to a variety of inflammatory markers(14, 16), no studies have investigated a possible association between the Mediterranean diet and ISR.

This study aims to assess the relationship between ISR and the Mediterranean diet score.

Materials and Methods

Study design

200 patients with stable or unstable angina pectoris underwent coronary drug-eluting stent implantation and were divided into the restenosis group and non-restenosis group.

Patient population

The clinical protocol was approved by the institutional Medical Ethics Committee no:364, and the study was conducted according to the ethical guidelines outlined in the Declaration of Helsinki. All patients were informed about the study, and their written consent forms were obtained.

A total of 200 patients with the chronic coronary syndrome who underwent coronary stent implantation after coronary angiography at Süleyman Demirel University of Research and Application Hospital were included in this study. The patients were divided into 2 groups according to the results of coronary angiography: the restenosis group (>50% diameter stenosis, n=100) and the non-restenosis group (<50% diameter stenosis, n=100). Patients were excluded from analysis if they had clinical evidence of cancer, chronic inflammatory disease, or any active infectious disease and those who did not want to do the diet questionnaire.All laboratory data were obtained from venous blood samples up to 6 hours before stent implantation. Total WBC, neutrophil, lymphocyte, and monocyte counts were calculated using an automated blood cell counter (ADVIA 2120i Hematology System, Siemens Healthcare Diagnostics, Deerfield, Illinois). NLR was calculated as the preprocedural ratio of neutrophils to lymphocytes, which were obtained from the same blood samples. CRP levels were measured by an immunonephelometric method (Roche Diagnostics GmbH, Marburg, Germany). Coronary interventions were performed according to current practice guidelines and recorded in digital storage for quantitative analysis. The degree of coronary stenosis was visually estimated by experienced interventional cardiologists. A luminal narrowing >50% in a major subepicardial vessel (left anterior descending, left circumflex, or right coronary artery) was defined as significant stenosis. Each patient received aspirin plus clopidogrel (loading dose 300 or 600 mg) before or during coronary intervention. Unfractionated heparin 100 U/kg was administered at the beginning of the procedure to keep the activated clotting time >200 seconds. The access site for percutaneous coronary intervention (PCI) was at the physician's preference (femoral or radial).Usage of glycoprotein IIb/IIIa inhibitors and predilatation or post-dilatation after stent implantation of the lesion was at the operator's discretion. Successful PCI was defined as a <20% decrease in diameter stenosis and residual stenosis <50% in diameter with final Thrombolysis In Myocardial Infarction grade 3 flow without any major complication. After stent placement, clopidogrel was used for one year, and aspirin was used indefinitely. During routine clinical follow-up, coronary angiography was performed secondarily in patients with stable or unstable angina pectoris. Control coronary angiograms were recorded with the Judkins technique and interpreted by two independent cardiologists who were blinded to patients' data. Stent

restenosis was accepted as narrowing >50% in an otherwise normal diameter, including 5 mm proximal and distal to the stent edge, according to results of control coronary angiographies. Intra- and interobserver variabilities of stent restenosis analysis were minimal in a representative subset of 50 patients. Interpretations of the two investigators on the presence or absence of ISR were agreed in 98% (49 of 50) and 98% (49 of 50), respectively. One investigator assessed intraobserver variability. The two readings were concordant for the presence or absence of ISR in 90% (45 of 50) and 96% (48 of 50), respectively. Patients with chronic total occlusions, bifurcation lesion stenting, and stenting longer than 60 mm were excluded from the study. Patients diagnosed with diabetes mellitus at the time of admission were excluded from the study.

The use of oral antidiabetic drugs or the use of insulin was accepted as diabetes criteria. Glucose levels at the time of admission were recorded.

Questionnaire of Mediterranean diet adherence

Questionnaire on Mediterranean diet adherence" is a questionnaire validated in Turkish (17). In the questionnaire of Mediterranean diet adherence, 14 questions were asked by the researcher (Table 1) (18). Colored visual images belonging to foods were used to assess the portion sizes consumed by individuals (19). We assessed the individual consumption of vegetables, fruits, legumes, nuts, whole grains, fermented dairy products, fish and monounsaturated fats, average alcohol, and red meat according to the scoring method of (≤5, 6-9 or ≥10 points) (18). Individuals with higher points were considered to be fed more consistently with the Mediterranean diet(20).

Table 1. Validated 14-item Questionnaire of Mediterranean diet adherence.

Questions	Criteria for 1 point
1. Do you use olive oil as main culinary fat?	Yes
2. How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals, etc.)?	≥4 tbsp
3. How many vegetable servings do you consume per day? (1 serving : 200 g [consider side dishes as half a serving])	≥2 (≥1 portion raw or as a salad)
4. How many fruit units (including natural fruit juices) do you consume per day?	≥3
5. How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving: 100–150 g)	<1
6. How many servings of butter, margarine, or cream do you consume per day? (1 serving: 12 g)	<1
7. How many sweet or carbonated beverages do you drink per day?	<1
8. How much wine do you drink per week?	≥7 glasses
9. How many servings of legumes do you consume per week? (1 serving : 150 g)	≥3
10. How many servings of fish or shellfish do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish)	≥3
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, orcustard?	<3
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving 30 g)	≥3
13. Do you preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage?	Yes
14. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomatoand onion, leek, or garlic and simmered with olive oil)?	≥2

Statistics analysis

All statistical analyses were performed using SPSS for Windows version 19.0 (SPSS, Chicago, IL). The number of each group was adjusted to 100 patients. We calculated the minimum number of individuals that should be sampled with 90% power and 0.05 Type-I error as at least 44 (R 3.0.1. open source program). The primary effect variable was calculated as ± 0.18. For the descriptive statistics of the data, mean, standard deviation, rate, and frequency values were used. The Kolmogorov–Smirnov test was used to evaluate whether the distribution of continuous variables was normal. For the analysis of parametric data, Student's t-test was used. For the analysis of nonparametric data, the Mann–Whitney U test was used. The Pearson's $\chi 2$ test was used to compare the categorical variables between groups. Pearson correlation analysis was used to assess the correlation between the number of ISR and the Mediterranean diet score. Statistical significance was defined as $p<0.05$.

Results

The basic parameters of both groups are shown in Table 2. Diabetes, smoking, Hs CRP, stent length, and Mediterranean diet score were observed to be statistically different between the two groups. Parameters that were considered to be risk factors for ISR were evaluated with logistic regression analysis. We included Diabetes Mellitus, Smoking, Hs-CRP, and Mediterranean diet score in these risk factors. Each risk factor was evaluated by univariate analysis to investigate its interaction with ISR. We evaluated all the parameters in which we observed interaction with multivariate analysis. Multivariate logistic regression analysis showed that patients with ISR had lower Mediterranean diet scores (odds ratio [OR]: 0.572, 95% confidence interval [CI]: (0.480-0.681), $p<0.001$) (Table 3). The significant negative correlation between the ISR and the Mediterranean diet score is shown in Figure 1 ($p<0.001$, r= -679).

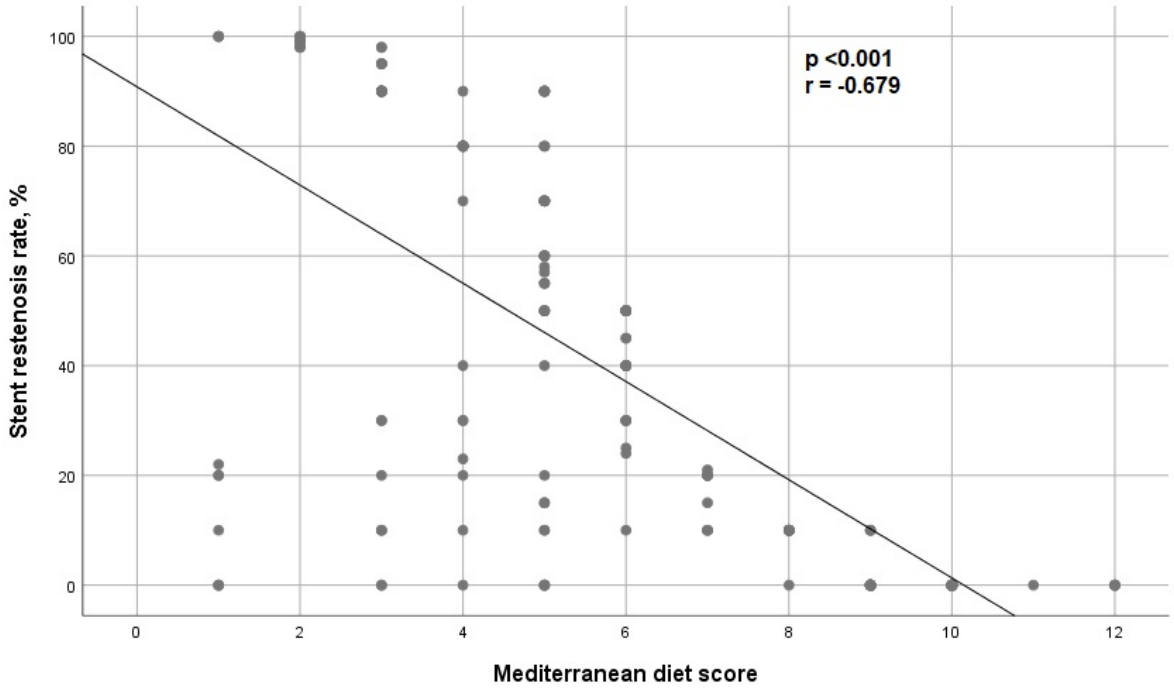

Figure 1: Correlation between Mediterranean diet score and stent restenosis

Table 2. Baseline characteristics, laboratory findings, procedural characteristics and Mediterranean diet score of the study groups (n=100).

Parameters	Patients without stent restenosis	Patients with stent restenosis	P value
Age, years	64.5 ± 12.2	67.1 ± 10.1	0.097
BMI, kg/m2	28.1 ± 5.8	28.2 ± 4.9	0.915
Female, n (%)	38 (38.0)	32 (32.0)	0.374
Diabetes Mellitus, n (%)	30 (30.0)	46 (46.0)	**0.020**
Hypertension, n (%)	46 (46.0)	55 (55.0)	0.203
Dyslipidemia, n (%)	27 (27.0)	32 (32.0)	0.438
Family history, n (%)	23 (23.0)	26 (26.0)	0.622
Smoking, n (%)	38 (38.0)	55 (55.0)	**0.016**
Glucose, mg/dl	119.4 ± 50.7	128.2 ± 57.6	0.257
Creatinine, mg/dl	1.04 ± 0.45	1.05 ± 0.37	0.913
Uric Acid, mg/dl	6.1 ± 2.9	6.4 ± 3.5	0.770
WBC, $10^3/mm^3$	8.1 ± 4.3	8.4 ± 3.5	0.975
Hemoglobin, g/dL	13.9 ± 1.9	13.8 ± 2.2	0.752
Platelete, $10^3/mm^3$	235 ± 62	247 ± 71	0.212
Total cholesterol, mg/dL	193.5 ± 49.3	188.9 ± 54.9	0.524
Triglyceride, mg/dL	118.6 ± 81.8	130.7 ± 129.6	0.447
LDL-cholesterol, mg/dL	126.3 ± 40.9	120.2 ± 45.9	0.337
HDL-cholesterol, mg/dL	45.0 ± 11.2	45.1 ± 11.0	0.945
Hs-CRP, mg/L	5.79 ± 3.1	10.6 ± 8.1	**< 0.001**
LVEF, %	49.2 ± 9.7	50.1 ± 9.1	0.526
Time between 2 procedures, month	18 ± 5.7	19 ± 7.3	0.421
Stent length, mm	31.75 ± 11.1	37.4 ± 16.7	**0.006**
Stent diameter, mm	2.74 ±0.41	2.68 ± 0.35	0.213
Mediterranean diet score	7.43 ± 2.87	4.32 ± 1.38	**< 0.001**

Abbreviations: Data are given as mean ± SD, number (n). BMI, Body mass index; HDL, high density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricle ejection fraction; WBC, white blood cells.

Table 3. Multivariate logistic regression analysis to predictig the ISR.

	Univariable OR (95% Cl)	P value	Multivariable OR (95% Cl)	P value
Diabetes Mellitus	1.988 (1.112-3.554)	**0.020**	1.036 (0.267-4.015)	0.541
Smoking	1.194 (1.134-3.506)	**0.016**	2.687 (0.704-10.257)	0.148
Hs-CRP	1.108 (1.052-1.068)	**< 0.001**	1.076 (1.019-1.136)	**0.007**
Stent length	1.033 (1.009-1.052)	**0.007**	1.033 (1.002-1.064)	**0.035**
Mediterranean diet score	0.562 (0.477-0.663)	**< 0.001**	0.572 (0.480-0.681)	**< 0.001**

Abbreviations: CI, confidence interval; Hs-CRP, high-sensitivity C-reactive protein; OR, Odds ratio.

Discussion

In our study, we found that patients who scored high on the Mediterranean diet had a lower risk of ISR, and there was also a negative correlation between the Mediterranean diet and ISR. It is the first study to look at the effects of the Mediterranean diet on patients with a previous percutaneous coronary intervention.

Numerous studies in recent years have revealed a link between nutrition and cardiovascular disease(10, 21, 22). The Mediterranean diet is widely regarded as one of the healthiest to prevent cardiovascular disease and metabolic syndrome (23). People in the Mediterranean region consume moderate amounts of ethanol, low meat and meat products, and eat a substantial amount of vegetables, fruits, fish, nuts, whole wheat, and legumes(24, 25). The Mediterranean diet's primary source of fat is olive oil, and major constituents of the Mediterranean diet have been shown to have potential cardiovascular protective such as antioxidant and anti-inflammatory effects(26). Several clinical trials have been conducted to determine the effect of the Mediterranean diet on markers of atherosclerosis progression, mainly in primary prevention. In a randomized controlled trial involving over a thousand patients, Torres et al. demonstrated that the Mediterranean diet reduced plaque load in the carotid arteries and improved secondary prevention(7). Similar findings were also found in the PREDIMED study(27). The Mediterranean diet significantly reduced the incidence of the composite endpoints of cardiovascular death, stroke, and myocardial infarction, according to the same study(28). The biological mechanisms by which the Mediterranean diet protects against CVD remain unknown. The Mediterranean diet's high concentration of bioactive phytochemicals with antioxidant and anti-inflammatory properties explains why its consumption lowers circulating inflammatory biomarkers associated with atherogenesis(29).

The invention of the coronary stent in 1987 transformed the field of interventional cardiology by lowering the incidence of restenosis following balloon angioplasty(30). Compared to percutaneous transluminal coronary angioplasty alone, coronary stents significantly reduced the angiographic and clinical restenosis rate. This notable advancement resulted in a significant reduction in the frequency of major adverse cardiac events following percutaneous coronary interventions, owing primarily to a decrease in target vessel revascularization(31)**.** Furthermore, intracoronary stents improve procedure success rates while also increasing procedure safety by reducing the need for emergency coronary artery bypass graft surgery. Consequently, stents are widely used in the "real world" of clinical coronary interventional practice(32).

However, coronary stent implantation is indeed associated with the complication of in-stent restenosis (ISR)(33, 34). ISR remains common and a challenge for interventional cardiologists. Whatever percutaneous approach is used to treat the in-stent restenotic lesion, including balloon angioplasty, stenting, rotational atherectomy, or laser angioplasty, 30-80% of patients will develop restenosis within the stent, stent margins, or both. Therefore, knowledge about the evolution of ISR is critical for effective prevention and safe intervention strategies. Among the factors that may cause ISR are vessel diameter, lesion length, bare metal stent use, and patient-related factors such as diabetes (especially insulin requirement)(32). However, the underlying causal mechanisms remain unclear. Nonetheless, the common intersection of many possible reasons points to inflammation as the most significant risk factor for restenosis(26, 35, 36).

Our findings show that the Mediterranean diet can reduce the risk of ISR through unknown mechanisms, including increased insulin sensitivity and other effects such as anti-inflammatory and antioxidant content.

Study limitations

Some limitations of our study include a cross-sectional design, a small sample size, and no MACE follow-up data. In addition, the diabetic status of the patients could not be evaluated clearly. This is one of the limitations of our study. In addition, we could not analyze ISR subgroups such as acute, subacute, and chronic due to missing data. To validate our findings, multicenter prospective longitudinal studies with larger sample sizes should be used.

Conclusion

This study may help us understand the relationship between the Mediterranean diet and ISR and may lead to new research. The Mediterranean diet, in addition to current medical treatments, is likely to play a protective role in the treatment of coronary artery disease. Our country is primarily agricultural, with the Mediterranean climate dominating roughly one-fifth of the land area. Furthermore, while the Mediterranean diet is "sustainable," it is a fundamental nutrition model for current and future generations thanks to this feature. The spread of the Mediterranean diet as a health policy may benefit the country's economy and public health. A multidisciplinary approach with a specialized team, rather than medical treatment options alone, may be more effective in preventing and treating the disease. In light of these data, it is clear that maintaining a Mediterranean diet throughout life can reduce the risk of coronary artery disease.

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