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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Acute histopathological and biochemical changes in saphenous vein grafts during coronary artery bypass grafting: A closer look at mTOR signaling

Koroner arter baypas greftleme sırasında safen ven greftlerinde akut histopatolojik ve biyokimyasal değişiklikler: mTOR sinyalizasyonuna daha yakından bir bakış

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ABSTRACT

Background: This study aims to investigate whether acute surgical manipulation of great saphenous vein grafts during coronary artery bypass grafting alters mammalian target of rapamycin (mTOR) activation and induces early histopathological damage.

Methods: Between September 2022 and September 2023, a total of 44 elective coronary artery bypass grafting patients (38 males, 6 females; mean age: 60.8±8.3 years; range, 36 to 70 years) were included in this prospective study. Saphenous vein segments were collected pre- and post-preparation. Light microscopy and enzyme-linked immunosorbent assay were used to assess structural changes and mTOR levels.

Results: Histopathological analyses revealed endothelial disruption and subendothelial inflammatory infiltration in post-preparation samples. However, mTOR protein levels showed no significant difference between pre- and post-manipulation tissues (p=0.41).

Conclusion: Mechanical stress during great saphenous vein graft preparation causes notable endothelial injury, but does not acutely activate the mTOR pathway. These findings suggest that mTOR may not participate in early responses, but could be implicated in long-term vascular remodeling.

Keywords: Coronary artery bypass grafting, endothelial integrity, graft failure, great saphenous vein, mTOR signaling.

ÖZ

Amaç: Bu çalışmada, koroner arter baypas greftlemesi sırasında büyük safen ven greftlerinin akut cerrahi manipülasyonunun, memeli rapamisin hedefi (mTOR) aktivasyonunu değiştirip değiştirmediği ve erken histopatolojik hasara neden olup olmadığı araştırıldı.

Çalışma planı: Bu prospektif çalışmaya Eylül 2022 - Eylül 2023 tarihleri arasında, 44 elektif koroner arter baypas greftleme hastası (38 erkek, 6 kadın; ort. yaş: 60.8±8.3 yıl; dağılım, 36-70 yıl) dahil edildi. Safen ven segmentleri, hazırlanma öncesi ve sonrası olmak üzere toplandı. Yapısal değişiklikleri ve mTOR düzeylerini değerlendirmek için ışık mikroskobu ve enzim ilişkili immünosorbent test kullanıldı.

Bulgular: Histopatolojik analizlerde hazırlık sonrası örneklerde endotel bozulması ve subendotelyal enflamatuvar infiltrasyon izlendi. Ancak, mTOR protein düzeyleri hazırlık öncesi ve sonrası dokular arasında anlamlı bir fark göstermedi (p=0.41).

Sonuç: Safen ven greft hazırlığı sırasında oluşan mekanik stres, belirgin endotel hasarına yol açmakta olup, mTOR yolunun akut aktivasyonunu tetiklememektedir. Bu bulgular, mTOR'un erken dönem yanıt süreçlerine doğrudan katılmadığını, ancak uzun dönem vasküler yeniden yapılanmada rol oynayabileceğini düşündürmektedir.

Anahtar sözcükler: Koroner arter baypas greftleme, endotel bütünlüğü, greft başarısızlığı, büyük safen ven, mTOR sinyali.

Atherosclerotic coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide, with over one million deaths annually attributed to coronary events.[1] Surgical revascularization via coronary artery bypass grafting (CABG) remains a cornerstone in CAD treatment[2]

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However, the long-term success of CABG is closely tied to the patency of the grafts used. Among these, the great saphenous vein (GSV) is frequently preferred due to its availability, ease of harvesting, and suitability for sequential anastomosis.[3-6] Despite these advantages, GSV grafts are prone to progressive endothelial damage and loss of patency, with occlusion rates reaching 15% within the first year and up to 60% within a decade.[7]

Great saphenous veins are exposed to mechanical stress, ischemia, and pressurization during preparation. These factors trigger early structural and biochemical changes. Previous studies have demonstrated endothelial cell loss, subendothelial inflammation, and disruption of the vasa vasorum architecture.[8] Biochemically, decreased nitric oxide synthase (NOS) activity and increased reactive oxygen species (ROS) production have been observed, indicating the contribution of oxidative stress to early graft dysfunction.[9,10] Furthermore, intraoperative distension has been associated with increased expression of adhesion molecules and inflammatory markers.[11]

One signaling molecule thought to mediate these effects is the mammalian target of rapamycin (mTOR), which regulates vascular remodeling, cellular proliferation, and inflammatory pathways in cardiovascular tissue.[10] The mTOR is influenced by oxidative stress and, in turn, modulates endothelial function through nitric oxide (NO) production and redox balance.[11-14] While mTOR inhibition has demonstrated protective effects in experimental models, including the use of rapamycin in drug-eluting stents,[10,15] its acute biochemical activation in response to graft manipulation still remains unclear.

Understanding whether mTOR is involved in the early stages of GSV graft preparation may help clarify the molecular basis of early graft injury. In the present study, we aimed to evaluate acute changes in mTOR activation and associated histopathological alterations in GSVs before and after surgical preparation during CABG.

PATIENTS AND METHODS

This single-center, quasi-experimental, self-controlled, prospective study was conducted at Mersin University, Faculty of Medicine, Department of Cardiovascular Surgery between September 1st, 2022 and September 1st, 2023. Biochemical and histopathological changes in saphenous vein grafts before and after surgical manipulation during CABG were assessed. Patients aged between 35 and 70 years who underwent elective CABG were included in the study. During the study period, of 63 patients, 19 were excluded due to emergency status (n=6), chronic renal or hepatic dysfunction (n=8), or age outside the inclusion range (n=5). Although immunosuppressive therapy was an exclusion criterion, no patients were excluded for this reason. Finally, a total of 44 patients (38 males, 6 females; mean age: 60.8±8.3 years; range, 36 to 70 years) who met the inclusion criteria were enrolled. All procedures were performed under strict adherence to international surgical guidelines to minimize variability and ensure reproducibility. Written informed consent was obtained from each patient. The study protocol was approved by the Mersin University, Faculty of Medicine, Clinical Research Ethics Committee (Date: 31.08.2022, No: 2022/604). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Procedural details

All patients underwent median sternotomy under general anesthesia. Saphenous vein harvesting followed a standardized protocol performed by the same surgical team. During preparation, the vein was distended with saline and side branches were ligated. After completion of graft preparation, a second 2-cm segment was excised from the distal end and processed identically. Samples were, then, transferred to the relevant laboratories for analysis. Light microscopy and enzyme-linked immunosorbent assay (ELISA) were used to assess structural changes and mTOR levels.

Statistical analysis

Study power and sample size calculation were performed using the G*Power version 3.1 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). To detect a medium effect size (d=0.5) with 80% power and α=0.05 in a paired-sample design, a minimum of 34 subjects was required. Our sample of 44 patients met this requirement.

Statistical analysis was performed using IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). The normality of the data distribution was assessed using the Kolmogorov-Smirnov test to determine whether parametric statistical methods could be applied. Continuous data were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. Since the dataset followed a normal distribution, a paired t-test was used to

Table 1. Patient demographic and clinical characteristics (n=44)

Variables	n	%	Mean±SD	Min-Max
Age			60.8±8.3	36-70
Creatinine (mg/dL)			0.78±0.25	0.40-1.80
Ejection fraction			50.9±7.8	30-65
Sex				
Male	38	86.4		
Female	6	13.6		
Smoking status				
No	16	36.4		
Yes	28	63.6		
Diabetes mellitus				
No	23	52.3		
Yes	21	47.7		
Hypertension				
No	25	56.8		
Yes	19	43.2		
Hyperlipidemia				
No	16	36.4		
Yes	28	63.6		

SD: Standard deviation. Categorical variables are shown as counts and percentages. No intergroup comparisons were performed. Statistical tests included Student's t-test and Chi-square test.

compare mTOR protein levels before and after graft preparation. A p value of <0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the study population are summarized in Table 1. The mean serum creatinine level was 0.78±0.25 mg/dL, while the mean ejection fraction (EF) was recorded as 50.9±7.8%. A total of 28 (63.6%) patients had a history of smoking. Regarding comorbidities, 21 (47.7%) patients had diabetes mellitus (DM), 19 (43.2%) had hypertension (HT), and 28 (63.6%) had hyperlipidemia (HL). Age, creatinine level, and EF were all within normal physiological limits.

The comparison of mTOR protein levels between before preparation and after preparation saphenous vein samples is presented in Table 2. The mean mTOR protein level in the before preparation saphenous vein was 7.02±2.51 ng/mL/mg protein, whereas the mean value in the after preparation saphenous vein was 7.51±2.78 ng/mL/mg protein. No statistically significant difference was observed between the pre- and post-procedure mTOR protein levels (p=0.41 and p>0.05, respectively), indicating that from a biochemical perspective, no acute increase in mTOR concentration was detected following graft preparation. The variation in values between individual samples did not meet statistical significance thresholds.

Light microscopic examination of before preparation saphenous vein samples, stained with hematoxylin-eosin, revealed a well-preserved vascular architecture. The tunica intima, tunica media, and tunica adventitia exhibited a structurally

Table 2. Comparison of mTOR protein levels between unmanipulated and manipulated saphenous vein (n=44)

	Before preparation	After preparation	
Variable	Mean±SD	Mean±SD	p
mTOR (ng/mL/mg protein)	7.02±2.51	7.51±2.78	0.41

SD: Standard deviation; mTOR: Mammalian target of rapamycin. A paired t-test was used for comparison. No statistically significant difference was observed.

intact morphology, with endothelial cells maintaining their normal, cohesive structure. The integrity of the endothelial lining was distinct, reflecting an undisturbed vascular surface conducive to optimal graft function (Figure 1).

No endothelial discontinuity, cellular deformation, or inflammatory infiltration was observed in these samples. All layers of the vein wall retained their native histological organization. However, in the post-preparation group, striking alterations were observed. The tunica intima exhibited focal endothelial cell loss, highlighting regions of structural compromise. Additionally, a remarkable morphological shift in endothelial cells was noted and they appeared elongated and spindle-shaped, deviating from their normal configuration (Figure 2).

These structural changes were consistently identified across samples, and no similar features were seen in the before preparation group. Subendothelial inflammatory cell presence was noted in multiple sections, although no thrombus formation or medial dissection was present.

DISCUSSION

In the present study, we evaluated acute changes in mTOR activation and associated histopathological alterations in GSVs before and after surgical preparation during CABG. Our study results demonstrated that while significant histopathological alterations, such as endothelial disruption and subendothelial inflammatory infiltration, were observed in saphenous vein grafts following surgical preparation, no statistically significant change was detected in mTOR protein levels between pre- and post-preparation samples. These findings suggest that mTOR may not be

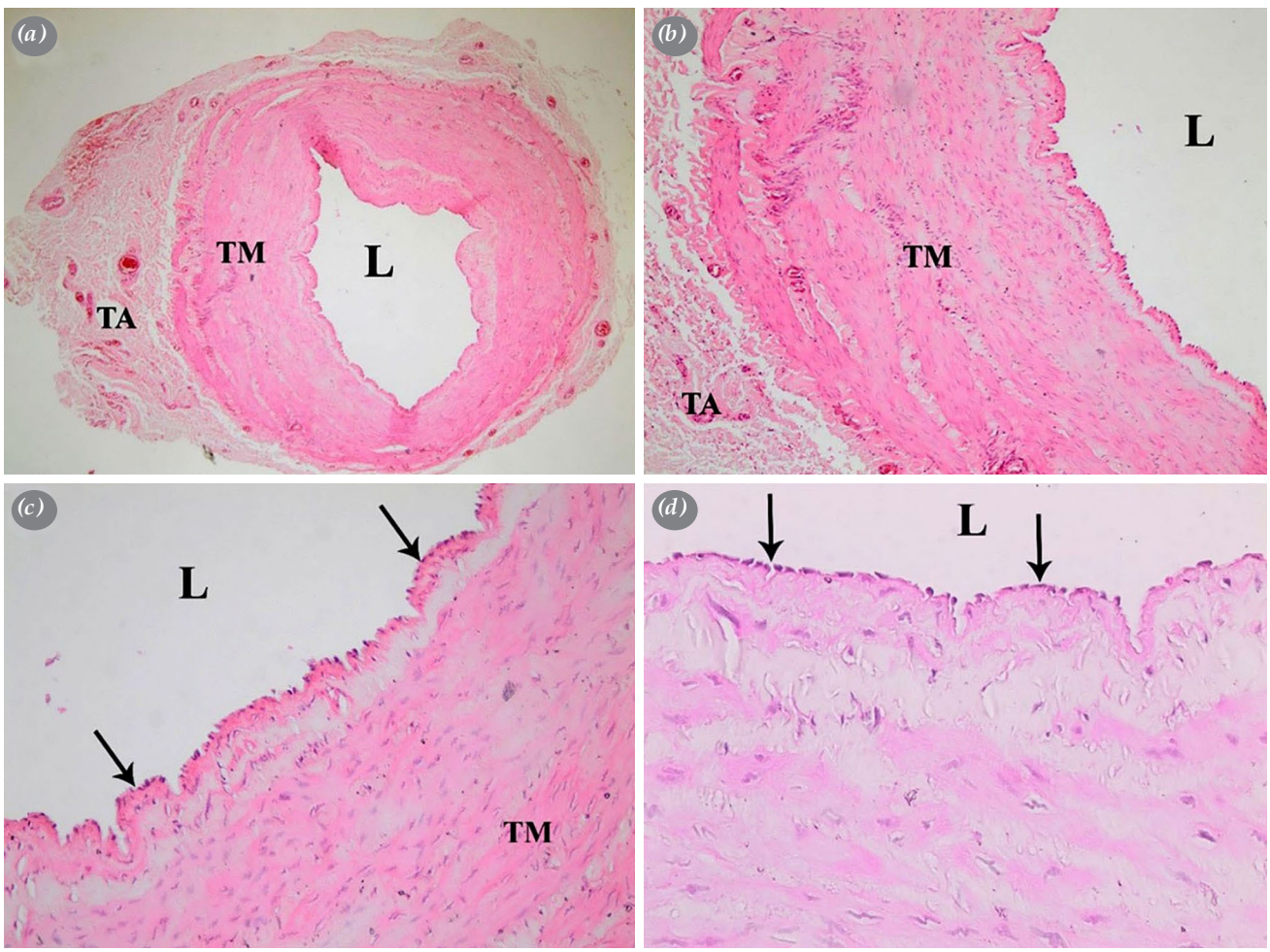

Figure 1. Before preparation (control) saphenous vein showing lumen (L), intact endothelial lining (arrow), tunica media (TM), and tunica adventitia (TA). The vascular architecture appears structurally preserved with normal endothelial morphology. **(a)** H&E, ×40, **(b)** H&E, ×100, **(c)** H&E, ×200, **(d)** H&E, ×400.

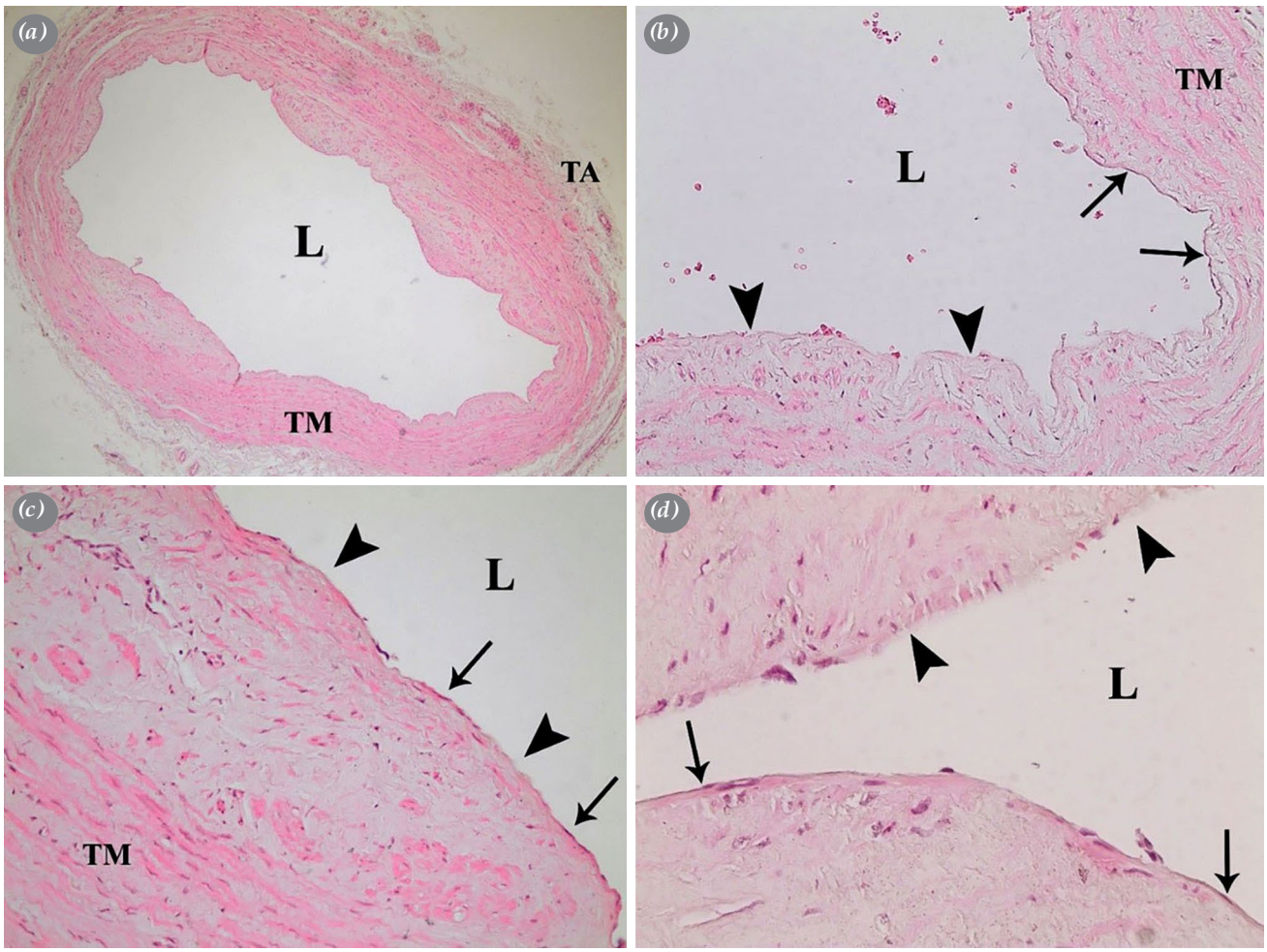

Figure 2. After preparation (study) saphenous vein showing lumen (L), elongated and spindle-shaped endothelial cells (arrow), areas of endothelial cell loss (arrowhead), tunica media (TM), and tunica adventitia (TA). Structural alterations in the endothelial layer are evident, suggesting endothelial stress and early vascular remodeling. **(a)** H&E, ×40, **(b)** H&E, ×100, **(c)** H&E, ×200, **(d)** H&E, ×400.

acutely activated during the graft manipulation phase of CABG.

Coronary artery bypass grafting remains one of the gold-standard treatment modalities for patients with advanced CAD.[16] However, the long-term patency rates of GSV grafts, which are widely used in CABG surgery, are among the most critical factors affecting surgical success.[17] Studies have demonstrated that GSV grafts are susceptible to early endothelial injury, leading to thrombosis, inflammation, and ultimately graft failure due to progressive atherosclerosis.[8] In this study, changes in mTOR activation during the surgical preparation process of GSV were biochemically assessed, and histopathological changes were analyzed.

Previous studies have shown that mechanical trauma, oxidative stress, and inflammation play critical roles in the development of GSV graft failure.[1,6-8] Our study supports this finding, as histopathological changes observed in GSV grafts during preparation indicate significant endothelial damage. Particularly, post-preparation samples revealed endothelial disruption and increased subendothelial inflammatory infiltration, suggesting that mechanical manipulation may trigger an early inflammatory response in the vein wall. This histopathological reaction is consistent with prior observations by Osgood et al.,[8] who demonstrated that mechanical distension results in endothelial dysfunction and upregulation of pro-inflammatory mediators. Similarly, Sedovy et al.[6] reported that even brief exposure to mechanical stress during GSV preparation can initiate early endothelial denudation and subendothelial edema. These findings reinforce our observation that endothelial trauma is a primary

early event during vein harvesting. Specifically, mechanical stress occurring during surgical graft preparation has been reported to reduce NO levels while increasing ROS.[10,18] Additionally, it has been demonstrated that inflammatory markers and adhesion molecules are upregulated following vein graft preparation.[11] In our study, histopathological examinations confirmed that the graft preparation process could affect endothelial integrity. However, no significant difference was observed in mTOR activation levels between before preparation and after preparation values. Although the result was not statistically significant, it offers important insight into the timing of mTOR signaling. The lack of acute activation suggests that mTOR is not a rapid responder to mechanical stress encountered during graft preparation. Instead, mTOR may require sustained stimuli or longer exposure to oxidative stress to become biochemically active. Therefore, our findings do not indicate a lack of relevance for mTOR, but rather highlight that its role may be limited or absent in the immediate perioperative phase. Recognizing this temporal limitation is essential when considering mTOR as a therapeutic target.

Although the mTOR literature is extensive, most studies focus on chronic vascular conditions or stent-based models. In contrast, our study specifically investigates acute mTOR signaling during saphenous vein graft preparation, a process that remains underexplored in the current literature. According to previous literature, mTOR functions as both a molecule exposed to oxidative stress and a regulator of oxidative stress levels.[19-22] Our study focuses on evaluating mTOR activity during the immediate intraoperative phase of saphenous vein graft preparation, a context for which there is limited direct evidence in the existing literature. By narrowing our focus to this clinical context, we aim to address a specific gap in understanding acute molecular responses during CABG. Studies have reported that mTOR inhibition enhances NO production, providing an antioxidant effect and suppressing vascular smooth muscle cell proliferation.[11-14] To illustrate, Kocak et al.[13] demonstrated that rapamycin administration increased NO levels while attenuating oxidative stress markers in a rat ischemia-reperfusion model. However, in our study, no significant changes were observed in mTOR activation levels during the acute phase of GSV graft preparation. Furthermore, mTOR plays a critical role in systemic and cardiac inflammation processes, and mTOR inhibitors such as rapamycin have been shown to counteract these effects.[10,15,23] Although mTOR activation levels did not show significant variation in our study, histopathological findings confirmed the presence of an inflammatory response following graft preparation. Although mTOR protein levels did not show a statistically significant acute change, the presence of histopathological evidence of early inflammation, without concurrent mTOR activation, raises the possibility that mTOR may not act as an immediate mediator but rather contributes to inflammation and graft remodeling over a prolonged period. This discrepancy may be due to the specific timeline of our sampling, highlighting the need for extended observational periods to fully capture dynamic molecular changes. Unlike studies reporting mTOR activation occurring in delayed or chronic phases of oxidative or inflammatory stress such as the systemic inflammatory model studied by Sahan-Firat et al.,[15] the myocardial remodeling context reviewed by Sciarretta et al.,[18] and the endothelial-specific mTOR modulation in aging vasculature described by Islam et al.[19] Our study specifically focuses on the acute perioperative phase, aiming at determining whether immediate mechanical and oxidative stress during graft preparation can activate the mTOR pathway. The absence of significant biochemical change in this timeframe suggests that mTOR is not a primary responder to acute graft manipulation.

Review of similar studies in the literature reveals that mTOR inhibitors such as rapamycin, also known as sirolimus, particularly those used in drug-eluting stents, have been shown to prevent restenosis by inhibiting vascular smooth muscle cell proliferation.[24] Sirolimus-coated stents have been reported to significantly reduce restenosis rates in coronary arteries.[24] However, saphenous vein grafts have different biomechanical properties compared to arterial structures, and studies investigating the role of mTOR in GSV grafts remain limited. Unlike arterial conduits, GSVs lack a well-developed elastic lamina and are more vulnerable to transmural pressure-induced injury. Haron et al.[25] recently emphasized that venous conduits respond differently to inflammatory stimuli, which may explain the subdued mTOR response observed in our study. This structural distinction underlines the necessity of vein-specific models in future experimental designs examining mTOR pathway activity.

Histopathological examinations revealed significant changes in endothelial integrity during the surgical preparation process of the graft.

In particular, while endothelial cells appeared intact and regularly arranged in before preparation samples, significant endothelial cell loss was detected in after preparation samples. Additionally, inflammatory cell infiltration was observed in the subendothelial area of after preparation specimens, suggesting that this may represent an inflammatory response triggered by surgical manipulation. Literature reports indicate that endothelial injury is a critical factor in vein graft failure and that oxidative stress and inflammation accelerate this process.[9-11] Although no significant changes were observed in mTOR levels in our study, previous literature suggests that mTOR may influence inflammation through indirect mechanisms, such as modulation of downstream signaling pathways such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase kinase 1 (MEK1) / extracellular signal-regulated kinases 1 and 2 (ERK1/2), and oxidative stress responses, rather than through acute changes in total protein levels.[15,18]

Compared with other studies, the histopathological findings of our study, particularly the endothelial disruption and subendothelial inflammatory infiltration observed after graft preparation, are consistent with previously reported results.[6-8,25] Previous research has shown that the vein graft preparation process promotes intimal thickening and cellular proliferation which, in turn, increases the risk of early thrombosis.[8] Consistent with these findings, our study demonstrated significant endothelial cell loss and inflammatory cell infiltration in post-preparation samples. Particularly, high-pressure vein distension has been reported to cause structural damage to endothelial cells, adversely affecting long-term graft patency.[25] Similarly, in our study, significant structural changes and endothelial cell loss were observed in the post-preparation samples.

The results of our study indicate that although mTOR does not exhibit significant acute activation, the graft preparation process may compromise endothelial integrity, potentially leading to long-term graft failure. Our findings align with previous reports suggesting that, although mTOR activation may not be immediate, it can contribute significantly to long-term vascular remodeling and inflammatory progression over time.[15,18,19] From a translational perspective, localized delivery of mTOR inhibitors, akin to drug-eluting stents, could potentially be adapted for vein grafts. However, as pointed out by Temiz-Resitoglu et al.,[24] systemic mTOR inhibition carries risks of immune suppression and impaired wound healing. Therefore, targeted delivery systems or intraoperative soaking protocols may represent promising avenues to harness mTOR modulation without systemic side effects. These findings highlight the need for further investigation into the role of mTOR in vein graft failure. Based on our clinical experience, the variability in patient response to vein grafting procedures suggests that individual mTOR pathway activity may differ depending on comorbid conditions such as diabetes or HL. Incorporating patient-specific biomarkers of oxidative stress and mTOR activation could aid in stratifying risk and personalizing intraoperative graft handling strategies. Specifically, future studies should focus on the long-term effects of mTOR on vascular remodeling and explore how oxidative stress and inflammation are modulated in vein graft failure.

Nonetheless, this study has several limitations. First, it was conducted in a single center with a limited number of patients, which restricts the generalizability of the findings. Larger, multi-center trials with longer follow-up periods are needed to validate the results. Second, the study only focused on the acute intraoperative period of saphenous vein graft preparation. Since graft failure is typically a long-term process involving chronic inflammation and remodeling, the lack of long-term biochemical and histopathological evaluations limits the study's ability to fully characterize the role of mTOR in this context. Third, we measured only total mTOR protein expression. The mTOR pathway involves complex signaling cascades, including mTORC1 and mTORC2 complexes, with distinct phosphorylation events and downstream effectors (e.g., p70S6K, 4E-BP1). Without analyzing phosphorylated forms or pathway-specific components, our ability to determine actual activation status remains limited. Fourth, although the graft preparation procedure was standardized (e.g., manual distension, branch ligation), subtle variations in surgical technique and individual patient characteristics, such as comorbidities, vein wall thickness, and vascular integrity, may have influenced the results. These factors were not quantitatively analyzed and remain potential confounding variables. Finally, the scope of our investigation was intentionally narrowed to identify whether mTOR is acutely activated during surgical handling. While this approach provides a focused biochemical snapshot, it does not allow a comprehensive understanding of mTOR's involvement across the entire graft lifespan.

Therefore, the findings should be interpreted with caution and considered hypothesis-generating rather than definitive. In this context, while the results of our study suggest no significant activation of mTOR during GSV graft preparation, further detailed investigations are required to evaluate the long-term effects of mTOR on vein graft failure.

In conclusion, our study results demonstrated that although mTOR activation was not significantly altered during the acute phase of saphenous vein graft preparation, histopathological analyses revealed endothelial damage and inflammatory infiltration. These findings indicate that mTOR may contribute indirectly to graft failure over time. Further studies are needed to explore the long-term effects of mTOR signaling and the potential benefits of targeting this pathway to improve graft outcomes.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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