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Mechanisms and Treatment of Femoropoplitealin-Stent Restenosis

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Abstract
The problem of stent restenosis (SRI) in the femoropopliteal artery (FP) has not yet been resolved; the predictive factors of the mechanisms and treatment in FP-ISR are unclear. The objective of this study is to investigate and give a clear explanation of the mechanisms and factors of FP-ISR that contributed to ISR, as well as a brief survey of the methods that have been used to treat FP-ISR. Methods of treatment with FP-ISR, such as medical, endovascular and bypass surgery, are used for several types of FP-ISR, the DEB device chosen as the first recommended method due to its effectiveness and ease of use.

Keywords: *Digital Natives, Digital Immigrants, Museum, TAM, Interactive Kiosk*

1. Introduction

Cardiovascular diseases increase, in recent decades, the use of small implantable medical devices called stent was also increased, which has been used to treat and control the lumen of blood vessels. Peripheral arterial disease (PAD) affects approximately 8.5 million patients in the United State and about 200,000 femoropopliteal artery (FPA) stents are used per year [1]. However, in-stent restenosis (ISR) is one of the most common risks of FPA after stent placement in arterial diseases[2][3], as well as, the risk of FP-ISR ratio is approximately between 15-40% of the placed stent [4].

There are many factors that contribute to ISR, such as those related to the patient, lesions and the design of the stent. Nevertheless, the treatment of ISR also under development for the administration of dangerous ISR, in addition, drug-coated balloons (DCBs) and drug-eluting balloons (DEBs) reduce the efficacy of FP-ISR compared to the bare-metal-stent[5], [6][7]. In addition, drug-eluting stents (DESs) and stent graft (SG) provide safety and effectiveness when treating FP-ISR in different lesions levels[8], [9][10]. The purpose of this paper is to review the mechanisms of ISR and to seek on the factors are predisposing of ISR as well as to

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demonstrate of methods are used to treat of FP-ISR up to date.

2. Mechanisms of ISR

The mechanism of ISR after the balloon-angioplasty process is a combination of some reactions such as physiological, mechanical and inflammatory obstacles; this could lead to neointimal-hyperplasia, recoil and reconstructed blood-vessel [11][12][13]. On the other hand, the use of stents within the arteries could prevent both recoil and the process of vascular reconstruction. After stent implantation, late loss of the lumen may occur because a vascular stented segment may respond as inflammatory reactions, which is a process of intimal hyperplasia [4][5]. Samples of animal data and the collection of anatomical data from some in-vivo autopsies have provided a background view of the cellular-basis of ISR. The finite element method investigated the effectiveness of thickness variation of strut stent in multi-link design model on the in-stent restenosis as well as the stent recoil and vascular injury [11]. The motivations for the ISR process are the response of the disruption in the cells of the endothelial artery layer, as well as the mechanical dilatation and the change in the layers of the middle (media) and adventitia arteries. The dark-side of the stent implantation, such as the mechanical fracture in the stent struts, leads to lesions in the blood-vessels that could proliferate smooth muscle cells (SMC), migration and inflammatory phenomena [4][6]. The change of the arterial layers can affect the circulation of the blood vessels, in addition, motivation in the intimal-hyperplasia as shown in Figure 1.

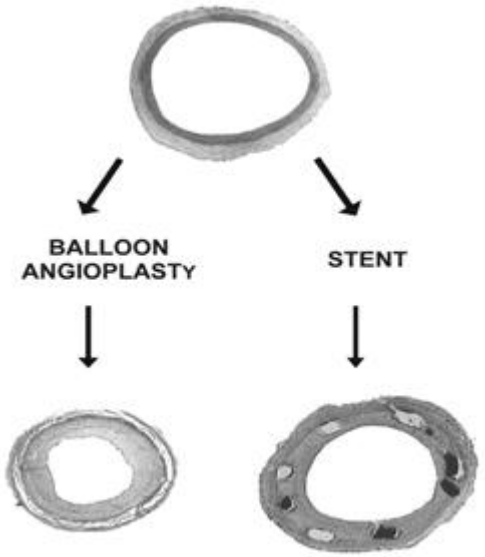

Figure 1. Mechanisms of ISR after balloon-angioplasty and stenting [17]

Metalloproteinases in the matrix of blood-vessel cells and tissue-inhibitors of metalloproteinases are very important in many pathological and physiological processes, and their expressions are regarded to classical factors of vascular risk while inflammation [18]. In contrast, the analysis of the directional atherectomy samples of early restenosis tissue in the stent showed predominantly of SMC. However, day after day as a function of time, the cellularity of the lesion decreases and the extracellular matrix becomes the component of the predominant lesion of restenosis.

In the investigation, the data suggested that neoatherosclerosis may have an important pathophysical role in the ISR process, despite the fact that SRI is mainly produced by aggressive neointimal proliferation [19]. In previous investigations of pathology of the human femoropopliteal arteries there is a greater proliferation of SMC, a more prolonged-inflammatory-reaction and more loss of lumen after stent implants compared to the balloon-angioplasty-relationship [2], [4], [20]. To explain these reactions; because the different effective forms between the stent and balloon angioplasty, such as the

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struts of the stent, react to local impact and chronic stretching in the blood vessel wall, while balloon-angioplasty can also be deep, but for it is usually used to be passing and central. The results support the concept that ISR produced from SMC hyperplasia and the proposed treatment method that was designed to prevent the reproduction of SMC that could improve the use of cardiovascular stents [15].

3. ISR predisposing-factors

After stent implantation in the FP, about 15% - 40% of the patients could experience ISR during two years of stent implantation[4], [21]–[23]. However, it is important to know the specific-factors that are related to improve the use of stent, as well as to improve stent performance and long-term stent placement, since there are some factors that could contribute to the generation of SRI, such as factors-related to patient, procedure and lesion as illustrated in Figure 2.

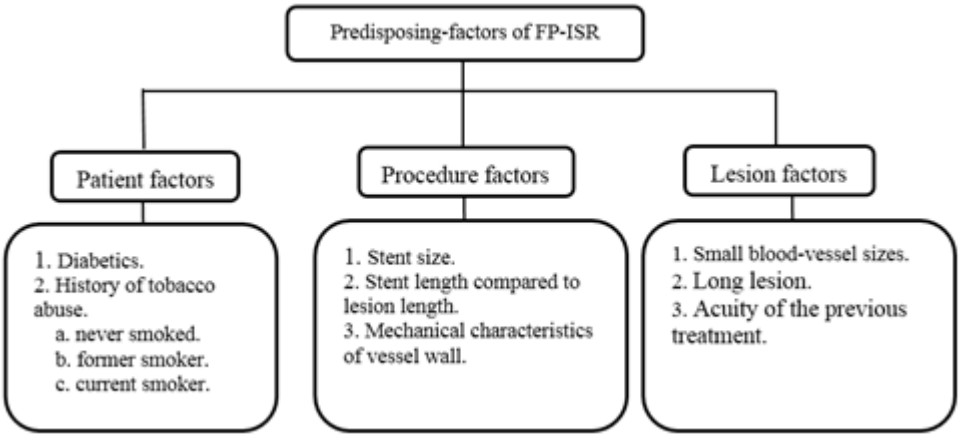

Figure 2. Predisposing-factors of FP-ISR

3.1Factors-related to patient

Factors-patient that contribute with FE-ISR are diabetics and the history of smoking[4][24][25]. The characteristics of the patient, as well as the injuries, are mutual-relations with the presence of ISR in the same patient who suffers from FE-ISR [26]. There are many important factors related to the patient, but so-far not identified, that have an impact on the probability of FE-ISR. Such as; the suggestion of a single response of possible genetic base could generate the highest of the FP-ISR classes after reiterating vascular injury [24]. However, platelets and serum would affect the chemical migration that leads to the proliferation of new cells [27], [28].

3.2 Factors-related to procedure

Factors-related to the procedure are included depending on the size of the stent such as the excessive size [29]–[31], the length of the stent segment compared to the length of the lesion [32], and the mechanical characteristics of the response of the blood-vessel wall to the implanted stent [25][26][35]. A major-predictor of posterior restenosis is the minimum diameter of the lumen posterior to the procedure and the cross-sectional area of the minimum lumen determined by intravascular-ultrasound. The study evaluated 16 of the 45 centres that chose to perform an ultrasound search, the

results showed an improvement in the stent-expansion and minimizing the revascularization contrast of the target blood-vessel with the directed angiography-alone [36]. As well as, the intravascular-ultrasound-guidance showed continuous improvement of long-term clinical-outcomes and cost-effectiveness [37]. In addition, the efficacy of choosing the appropriate stent size and oversizing of the stent correlate with the proliferation of the neointimal-vessel wall and the presence of ISR [21][23].

Stent geometry designs are playing an impact factor during stent implantation in neointimal-hyperplasia by utilizing the paradigm of numerical finite element method (FEM) the mechanical effects of five different stent geometries were compared, the results showed the printed area does not have predict-prolapse. whereas play correlated into tissue-prolapse [38].

3.3 Factors-related to lesions

The lesion-factors that influence the rate of SRI include each of the small blood-vessel sizes [23][31][40], the long lesion compared to the length of the stent [32][33],the acuity of the previous treatment and the narrowing of the lesion after treatment [26][43] and lesion-classification such; class I focal FP-ISR with length ≤ 50 mm, class II diffuse FP-ISR with length > 50 mm and class III totally-occluded FP-ISR [4]as illustrated in Figure 3.

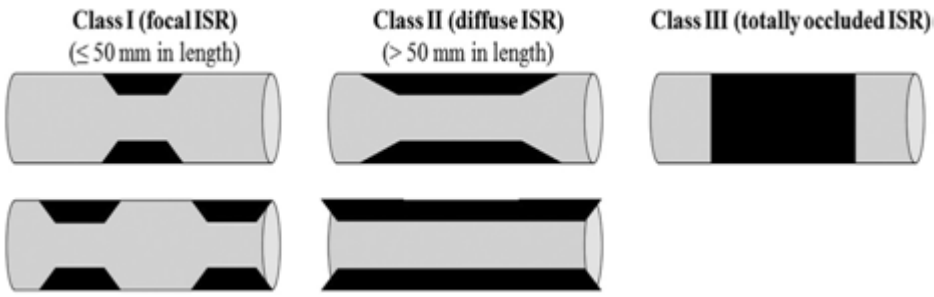

Figure 3.ISR classifications [4]

The included study of 2602 patients was divided into three groups depending on the size of the blood vessel, such as; less than 2.8 mm, from 2.8 to 3.2 mm and more than 3.2 mm; the results showed that patients with smaller vessels have a high risk of incidence of restenosis [31].

These parameters have been discussed, which may give a good indication that the factors are related to contribute to the FP-ISR that supports the stent implants, as well as to improve the durability of the stent design.

4. Treatment of FP-ISR

Still treatment of ISR is a challenge for researchers, however, many treatment methods of FP-ISR are used to manage or decrease the effectiveness of ISR. In the present study, it was discussed that the methods have been used to date to help reduce or control of ISR, such as; medical therapy, endovascular therapy and bypass surgery with its sub-branches, as shown in Figure 4. In addition, Table 1 summarizes the trials of treatment methods that were enrolled in medical centres.

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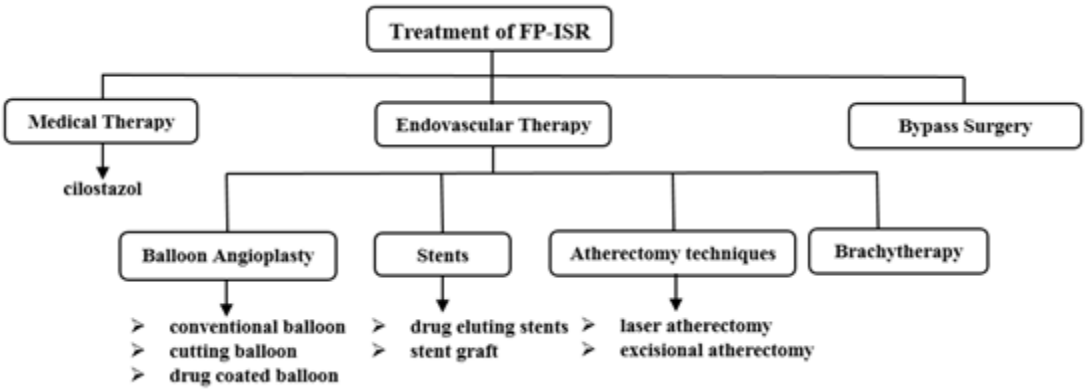

Figure 4. Treatment methods of FP-ISR

4.1 Medical-therapy

To date, the drug Cilostazol is the only medical option for treatment and to reduce the risks of FP-ISR, then, that could be supported to lead an anti-proliferative impact. the additional management of Cilostazol significantly decreases the incidence of FP-ISR after one year of drug-eluting stent [44]. In the randomized, multi-centre study, between March 2009 and March 2011, two-hundred patients with treatment of FP-lesions were evaluated using angioplasty and placement of professional stents with these self-expanding such S.M.A.R.T stents; for 12 months, the rate of restenosis was 20% for those with the Cilostazol group, compared with 49% for those who were not, suggesting that Cilostazol, the first-line of anti-plate treatment, could be used to reduce the occurrence of FP restenosis in the lesions that occur after stenting [45]. In addition, in a large-multicentre study of Japanese databases from January 2004 to December 2011 that investigated 3471 limbs of 2737 patients with FP-lesions, the primary-patency rate after endovascular treatment with Cilostazol for 12,36 and 60 months as 83%, 67% and 57% while, 73%, 56% and 47% without Cilostazol respectively; the results showed to be effective in the prevention of restenosis of FP after two years [46]. However, with the high risk of patients, treatment with Cilostazol seems to be a good result to prevent of ISR in peripheral arterial diseases (PAD) [47]. There is no minor side effect of using Cilostazol, only common side effects, such as gastrointestinal-symptoms, headache and rash.

Table 1. Summary of treatment trials

Treatment methods	Trial study name	Patients No.	Lesions No.	Lesions length mm	Primary end-point	Results	Ref.
Medical therapy (cilostazol)	STOP-IC	200	200	128±86	12 month	Angiographic-restenosis rate was 20% in cilostazol-group, whereas, 49% in non-cilostazol group.	[45]
	ZEPHYR	399	475	170±11	12 month	Restenosis-rate was 33% in cilostazol-group and 51% in non-cilostazol group.	[44]
	IN.PACT Global	131	149	170.17±100	12 month	Primary-safety was 92.7%.	[48]

DCBs	Admiral DCB	260	288	240±100	1 to 2 year	ISR treatment rate was 76.6% and 48.6% for 1 and 2 year respectively.	[49]
	SFA-Long	105	105	251±71	12 months	The primary-patency was 83.2%.	[50]
	IN.PACT Global	1406	1773	120.1	24 months	The rate of composite-safety endpoint was 81.7%.	[51]
DESs	Zilver PTX	236	236	65±40	12 months	The rate of event-free survival was 90.4% and primary-patency 83.1%	[52]
	SIROCCO	93	93	80.3	24 month	The restenosis-rate in the DESs group was 22.9% and in-stent restenosis rates were 4.7%, 9.0%, 15.6%, and 21.9%, at 6, 9, 18, and 24 months respectively.	[8]
	Zilver PTX	108	119	133±91.7	24 month	Primary-patency was 95.7%,78.8% at 6, 12 months respectively and freedom-target lesion were 96.2%, 81.0% at 6, 12 months respectively, and 60.8% at 2 years.	[9]
	Zilver PTX	236	236	140	24 month	Event-free-survival was 86.6% and primary-patency 74.8%.	[53]
Stent graft	RELINE	83	83	40 to 270	12 months	The Viabahn cohort primary-patency rates was 74.8% Vs. 28.0% of angioplasty cohort.	[10]
	SEMCBM	26	28	240.5	12 to 36 months	The primary-patency-rates of (1- and 3-year)were 85.1% and 81.4%; respectively.	[54]
Laser-atherectomy	SALVAGE	27	27	200.7±100.3	12 months	The primary-patency rate was 48%.	[55]
	PATENT	90	90	123±95.9	6 to 12 months	TLR rate were 87.8%, 64.4%,and primary-patency rate was 64.1% and 37.8% in 6-12 months, respectively.	[56]
	EXCITE ISR	250	250	19.6 ±12.0	6 months	Freedom of TLR was 73.5% and primary-efficacy endpoint rate 78.1%.	[57]
	Not-mention	24	47	60.6±40.5	6-12 months	Primary-patency was 72.6 and 58.9% in 6-12 month, and primary-assisted-patency was 93.2% and 74.6% in 6-12 months respectively.	[58]
	Randomiz	113	113	160.7	6	Patency rates was 63.6%.	[59]

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	ed				months		
EBT	Vienna-3	134	134	100.3	12 months	Patency-rates after 24 months of treating analysis was 54% and data-treated-analysis was 77%.	[60]
	Not-mention	35	42	230.5±120.3	12 to 24 months	Primary; assisted-primary, and secondary-patency were 75.2%, 89.1%, and 89.1% in 1 year and 63.7%, 80.6%, and 85.6%, in 2 years, respectively.	[61]
	VIENNA-2	113	113	>50	12 months	The patency-rate was at 6 months 45%.	[62]
Open-surgical (bypass)	BASIL	228	228	Not-mention	36 months	Balloon-angioplasty have a higher early failure-rate versus bypass surgery.	[63]

4.2 Endovascular-therapy

Many of the interested endovascular treatment methods that innovated to treat FP-ISR such as: balloon angioplasty, small mesh medical devices (stents), atherectomy techniques and Endovascular-brachytherapy (EBT).

4.2.1 Balloon-angioplasty. Firstly; conventional-balloons,(Figure 5 (a))such as the use of percutaneous-transluminal-angioplasty (PTA) in the native artery that could take advantage of the variety of atherosclerotic plaque densities in the vessel wall accompanied by a relative movement that should fracture the lesions of the plate while leading to an increase in the area of the blood-vessel section. The effects of ISR on the stent-body, which are implanted earlier through the loss of lumen cross section, therefore, the lesions would behave against the structure of the stent; however, with the difference in densities, re-expansion of the lumen of the artery through the PTA, the back-injury occurs with the same frequency frequently after the PTA of FP-ISR [4].

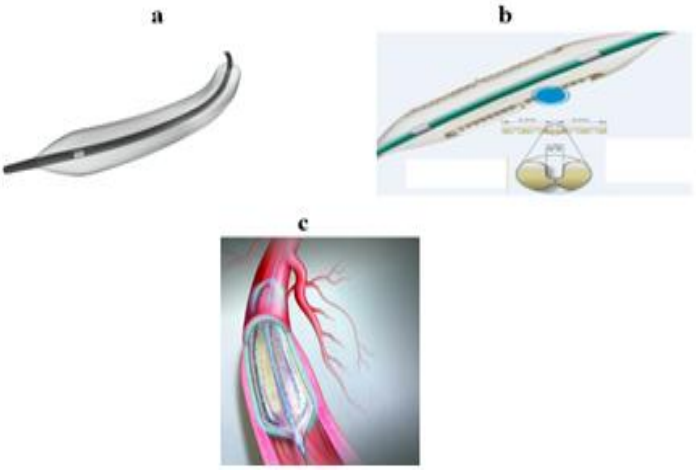

Figure 5. Types of balloon-angioplasty: a) conventional balloon, b) cutting balloon and, c) drug-coated balloon.

Secondly; cutting-balloons (CBs), (Figure 5 (b)) in the case of lesions of the de-novo artery, CB is adequate to create separate linear incisions due to the microsurgical sheets that were placed on its surface during balloon inflation, which could lead to a more controlled control during the increase of the lumen of the blood vessels with less pressure needed compared to the conventional balloon. , therefore, that leads to reduce the rate of lesions of the vessel wall, as well as ISR [64]. However, CB did not demonstrate superiority results compared to the conventional balloon for SFA-lesions of the

treatment, both methods yielded an increase of FP-ISR rate for 6 months [65], [66].

Thirdly; drug-coated-balloons (DCBs), (Figure 5 (c)) DCB is similar to the simple conventional-balloon in the procedure, but, on its surface, there is an anti-proliferation coating drug that can provide support to prevent restenosis. In addition, in the multi-centre and prospective IN.PACT Global-study, the total of 149 lesions with an average length of 17.17 ± 10.47 cm for 12-months, the images-group of ISR demonstrate a high permeability with a low rate of revascularization lesions in the target driven by the clinic when using DCB, the result confirms the effectiveness and safety of complex FP-lesions with the global study IN.PACT [48]. Moreover, the results of a multi-center include 105 patients with lesion length > 15 cm and 4-7 mm in diameter of the artery during 12 months (1-year) through the use of paclitaxel-coated balloons to treat SFA lesions; and, a good approach with IN.PACT Admiral in a long lesions of FPA [50]. Yet, another study suggests that DCBs are safe and influential during 2-years to delay and not prevent restenosis in long and complex of FPA lesions[49] ; as well as, should analyse the cost-effectiveness of routine clinical-practice in de-novo SFA lesions [67] ,and , more than five years of the follow-up period; the result to detect the effect of the drug on the local vessel found that; there are no signs of drugs in the wall of the blood vessel [68].The comparison of DCBs with drug eluting stents (DESs) for one year was performed; the results of the PF lesions of ≥10 cm in length are equally well between DCBs and DES in the treatment of PF lesions [69], and, it was suggested with a favourable tendency for the use of DES up to 36 months[70].

4.2.2 Small mesh medical devices (stents). Firstly; drug eluting stents (DESs),(Figure 6) after stent implantation, neointimal hyperplasia leads to contribute of ISR, therefore, to prevent neointimal hyperplasia; drug for the antiproliferative supply on the surface of DESs to the lesions of the plugged vessel. The sirolimus-eluting stents (SESs)and paclitaxel eluting stents (PESs)are using to treat of FP diseases.

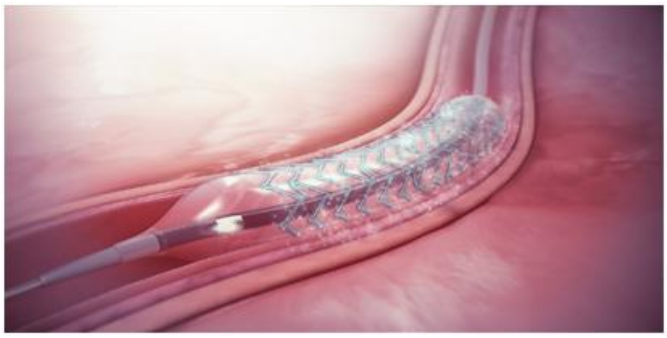

Figure 6. Shows drug -eluting stent

Randomized double-blind investigation study included 57 patients, 29 of whom were treated through SESs with an average lesion of 81.5 mm ± 41.2 during the primary endpoint of 6 months; the results showed that SES are effective, safe and able to withstand the permeability of SFA diseases [71]; and, in the SIROCCO-trial, the results show the safety, the effective and free-restenosis of the use of SESs up to 24 months for the majority of patients [8]. As well as, the multinational and random treatment of the comparative study with primary endpoint of 12 months and lesions of 65 ± 40 mm of average length was investigated by using the PESs cohort; the results showed an event-free survival of 90.4% and a primary patency of 83.1%, which led to an increased use of PESs to treat of FPA diseases [52], up to two years the maintenance of efficacy and safety for using PESs to treat of FPA diseases [53][9].

In the present year, the comparison study between DES and DCB showed the favouring of using DES rather than DCB to treat FPA diseases up to 36 months[70], yet, the nationwide analysis found that there is no

evidence of an increase in the number of deaths after using coated-drug compared with uncoated-drug stents [72].

Secondly; stent graft, such the expanded-polytetrafluoroethylene (ePTFE) covered stent, as shown in Figure 7, stent graft offered an advantage, as the neointima excluded from the wall vessel. However, the study of a single centre with 27 cases of FP-ISR in the use of ePTFE covered-stent-graft to treat an average length of lesions of 24.5 cm, the permeability rates of 1 and 3 years were 85.1 % and 81.4%, respectively, lead to a favourable use of the stent covered with ePTFE to treat FP-ISR lesions[54]. As well as, the 12-months of randomized study showed the best results to treat FP-ISR with the use of the Viabahn stent graft instead of using a standard balloon for up to one year [10].

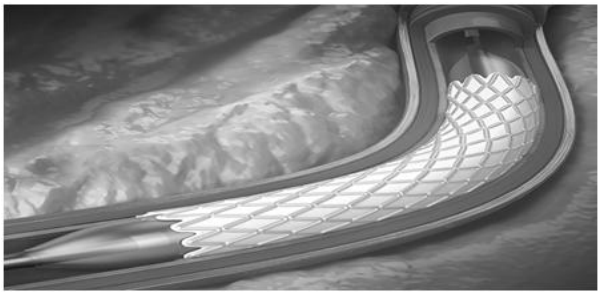

Figure 7. Expanded-polytetrafluoroethylene covered stent

4.2.3 Atherectomy techniques. Atherectomy techniques are some medical devices that are used to eliminate atherosclerosis from the wall of a blood vessel that is inside the body and this technique has been used as an alternative way to treat diseases of the FE artery [73]. We debated atherectomy techniques in two groups; as; laser-atherectomy and excision-atherectomy.

Firstly; laser-atherectomy, as shown in Figure 8 (a), the multi-centre SALVAGE study that included 27 patients from US centres, with a primary endpoint of 12 months and an average length of the lesions was 20.7 ± 10.3 cm ; to treat FP-ISR using an excimer laser followed by a self-expanding stent (Viabahn); the results of the excimer laser strategy are associated with a high level of safety and success [55]. As well as, the results of the PATENT study included 90 lesions with an average length of lesions of 123 ± 95.9 mm in five European centres with 12 months of primary endpoint established that; atherectomy with excimer laser was safe and with a high procedural success of FP-ISR treatment [56].And, the EXCITE-ISR trial study shows a higher success rate in the treatment of FP-ISR through the use of excimer-laser atherectomy followed by percutaneous-transluminal angioplasty (PTA) instead of using PTA-alone [57].

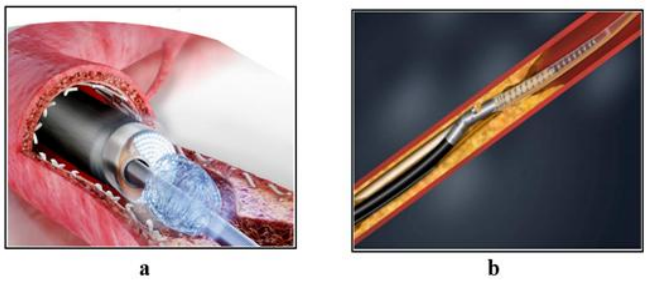

Figure 8. Atherectomy techniques: a) Laser-atherectomy and, b) Silver Hawkdevice

Secondly; excisional-atherectomy, directional atherectomy is a method used to remove plaque and re-circulate blood flow in the PAD; two devices have been used in directional atherectomy, such as Silver Hawk and Turbo Hawk, both devices have been approved by the US Food and Drug Administration, both devices are equal, but Turbo Hawk has a number of blades while Silver Hawk has a blade[74][75]as illustrated in Figure 8 (b).However, in a single retrospective clinical study with 24 patients with 47 vessels in 24 legs, the primary patency of 6 to 12 months was 72.6% and 58.9% respectively, which could conclude that performing an excision atherectomy

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provides a additional option to handle the minimum invasive treatment of the PAD [58].

4.2.4 Endovascular-brachytherapy (EBT). The beginning of the use of EBT to treat PAD (femoropopliteal region) was in 1990 through the application of a high radiation dose rate after PTA or ISR that could affect intimal-hyperplasia [76][62]. However, the results of the first randomized trial showed the effectiveness of using EBT to prevent FP-ISR, yet, the value of the study is to improve the use of EBT through the procedure of modification of the EBT and the preparation with stent implant [59]. In addition, research of the randomized study to evaluate the efficacy of Iridium-192-gamma in the treatment with EBT in a multi-centre and double-blind trial; patency rates after 24 months of treatment with FP-ISR were 54% in EBT while 27% in the placebo cohort, significantly, the results mentioned to reduce the rate of restenosis occurred with EBT gamma pathway after FP angioplasty [60]; the EBT may be favourable to treatment with FP-ISR that could lead to the possible collaboration of vascular-surgeons and radiation-oncologists [61].

4.3 Open-surgical treatment (bypass)

In general, bypass surgery (Figure 9) is a change in blood flow around the segment of the blocked artery using a segment of a graft vessel to resume normal blood flow. In addition, bypass surgery is used to treat FP-ISR problems in the upper or lower part of the knee. Furthermore, the randomized study of the BASIL study included bypass versus balloon angioplasty to analyse the treatment without amputation and general survival; the results associated a good long-term with bypass-surgery than with balloon angioplasty, however, the use of bypass after balloon angioplasty produced worse results than the use of the bypass in the first revascularization [63].

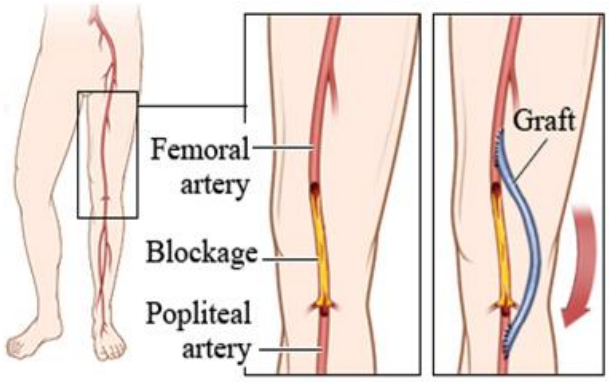

Figure 9. Bypass surgery in FP artery

5. Conclusion

In-stent restenosis (ISR) is an important drawback in the implantation of the stent; after implantation, neointimal hyperplasia leads to the reconstruction of the arterial layers, such as the proliferation of SMC and the effect of migration on the circulation of blood-vessels; angioplasty, patient genetics and stent strut design are playing a large role in the development of ISR. Many factors contributed to the ISR, such as those related to patients, procedures and lesions. Many research works are innovated to treat FP-ISR, such as medical, endovascular and bypass surgery; it is recommended that DEB devices be the first option for the treatment of FP-ISR, as it is easy to use and effective. However, DES is another option for complex lesions, such as total occlusion or with a case of ischemia of the upper extremity of diabetes, which is why, due to its permeability index to the use of directional atherectomy that leads to limit it. For the future, the improvement of DES using devices combined with rotary atherectomy requires more evaluations.

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