							events (26.7% diabetes versus 22.2% no diabetes, p=0.72).		
Leers 1998 [43]	Retrospective case series Pedal bypass grafts in ESRD	DM patients 31 (91%) 34 total age: 64 (39-85)yrs total population gender: male 59% total population	Distribution: infrapopliteal in 23 legs and infrainguinal in 13 legs of total population Severity (only in 16 patients): ABI 0.48 (0-0.95) mean, toe pressure 18 (0-78)	probably > 90% had tissue loss although this was not explicitly stated in the article Wound classification: NR Infection: NR	CAD: 28 (82%) ESRD: 100% (29 haemodialysis and 2 transplants)	Pedal venous bypass 88% total population	Average followup 13.5 (1-84) months Ulcer healing: NR Cumulative assisted primary patency at 1yr, 2ys = 62%, 62% Limb salvage: 56% at 1yr total pop and at 2yrs 50% Major amputation: 16 (39%) at 13.5months average f/u Minor amputation: 51 (26%) total population at 1yr Complications: Survival 64% at 1yr 1 periop death (2%) Mortality 36% at 1yr and 48% at 2yrs	Survival rate was 65% if had patent graft at 5 yrs versus 26% if leg off 57% of patients had one or more secondary interventions for pedal graft	
Malmstedt 2008 [44]	part of country wide observational data base (Swedvasc) Outcome after bypass surgery in diabetics	742 DM patients age: 74 (SD 9,8) gender: 42% female	Distribution: NR Severity: NR Infection: NR	82% tissue loss Ulcer classification: NR	CAD 65% CVD 19% ESRD defined as creatinine 150 umol/L 20%	261 femeralpopliteal bypasses 481 infrapopliteal bypasses	Ulcer healing: NR Limb salvage: NR Major amputation: NR Minor amputation: NR Complications: NR		Composite primary endpoint was: amputation or death With a median follow-up of 2,2 years the rate of ipsilateral amputation or death per 100 person years 30,2 (95% CI 26,6-34,2) Median time to life or limb loss was 2,3 years (CI 1,9-2,8) The use of the composite end-point renders interpretation very difficult.
Mills 1994 [45]	Retrospective case series of patients with popliteal distal vein bypass grafts	46 DM patients (total population 53) age: 62,4 (total population) gender: 37 men (total population)	Distribution: infra-popliteal Severity: NR Scoring distribution: NR	52 tissue loss Infection: NR Ulcer score: NR	ESRD 28%; CAD 57%;	Infrapoplitea lvein bypass All crural bypass	Ulcer healing: Limb salvage: 85% after 1 year (22 limbs out of 56 legs available at 1 year). Major amputation: NR Minor amputation: NR Complications: Peri-operative mortality: 2 out 53 (3,6%) Within 30 days 2 graft occlusions with subsequent 2 major amputations Mortality 1yr, 13%, 2yr		Strength: well defined cohort Weaknesses: high rate withdrawal rate, probably combination of short duration and lost-tofollow- up (not reported separately) Paper is an example of the confusion between the total population, number of diabetics, number of extremities and number of procedures.
Mohan 1996 [46]	Case series Pedal bypass graft case series	All DM patients 32 Mean age: 60 (range 42-84) yrs gender: 50% males	Distribution: popliteal artery inflow AK pop 9 BK pop 26 Severity: NR	NR 18 (51%) ulcers 15 (43%) gangrene 2 (6%) patients rest pain Ulcer score: NR Infection: NR	CAD 47% Chronic renal failure 28%	Popliteal to distal artery bypass PT 9 AT 8 DP 10 Peroneal 8 All vein grafts	Mean followup 24 (1-72) months Ulcer healing: NR 30day mortality 0% Limb salvage: 90% at 1yr, 82% at 3 years Major amputation: 5 within 20 months Minor amputation: NR Patency 1, 3yr 95%, 89% Complications: 4 failing grafts surgery revised. 3 bypass occlusions of which 2 resulted in major amputation 3 additional amp due to infection	Small study population and no information regarding drop-out rate	

							Mortality (longterm): NR		
Owen 2007 [47]	Cohort study According to 4 different levels of kidney disease	CKD 4 (eGRF 15-29): 25 DM patients out of 32 (total cohort) age: 67,5 (SD 11,5) gender: 19 males (59%) CKD 5 (eGRF < 15 and HD): 60 DM patients out of 72 (total cohort) age: 65 (SD 11) gender: 38 males (53%)	Distribution: infra-inguinal, no further data given Severity: NR	CKD 4 (eGRF 15-29): 84% foot lesions CKD 5 (eGRF < 15 and HD): 90% foot lesions Ulcer score: NR Infection: NR	CKD 4 (eGRF 15-29): CAD: 23 (71,9%) CKD 5 (eGRF < 15 and HD): CAD: 44 (61,1%)	Infra-inguinal bypass	CKD 4 (eGRF 15-29): Ulcer healing: NR Limb salvage: at 5 year 77 (Sd14) Major amputation: NR Minor amputation: NR Complications: 30 day mortality 3,1% CKD 5 (eGRF < 15 and HD): Ulcer healing: NR Limb salvage: at 5 year 50 (Sd 12) Major amputation: NR Minor amputation: NR Complications: 30 day mortality 4,2% CKD 5 mortality at 1yr 46%, 91% at 5yr SIGN 2-		A study that provides relevant data on CKD in severe forms as a prognostic factor. Infra-inguinal bypass, outflow data not provided This study was reported as a case series Probably only sufficient data on CKD 5 patients Difficult to use patency data because mortality very high
Panneton 2000 [48]	Retrospective case series Pedal bypass graft series	DM patients 157 age: 66 (30-78)yrs gender: 111 males	Distribution: NR Severity: NR Scoring system: NR	93% tissue loss 53% gangrene Wound classification: NR Infection: 27%	CAD 80 (51%), ESRD 41 (26%)	Pedal bypass graft with vein	Mean follow-up 2.7yrs Ulcer healing: NR Limb salvage: 1yr 86%, 5yr 78% Major amputation: NR Minor amputation: NR Complications: 30-day mortality 1.3%, MI 11 (7%), ARF 5 (3.2%), major amp 3 (1.8%)	A sub group of a series comparing diabetics versus no diabetics in which no differences were observed between the two groups	Comparison of diabetes and no diabetes
Pomposelli 1995 [49]	Case series Retrospective review of 367 consecutive patients undergoing 384 distal bypasses	350 DM patients, total population 367 age: 58 mean gender: 352 male; 114 female	Distribution: NR Severity: NR Scoring: NR	219 (72%) with ulcer; 47 (12%) of gangrene; 16% other indications Infection: 222 (55%) Ulcer classification: NR	Prior myocardial infarction 29%, CVD 12%, ESRD 5% (dialysis) of total population	Dorsalis pedis arterial bypass Sub group analysis of 1032 DP artery bypass All except 2 with vein	Ulcer healing: NR Limb salvage: cumulative limb salvage rate 87% at 5 years. 1yr and 2yr estimated from K-M 90% and 85% Secondary patency rates 82% at 5yrs Major amputation: 13 (3,5%) within 30 days. Total number of major amputations 30 (8,1%) within the 5 year follow up. Minor amputation: 75 (19%) Complications: 30-day mortality 1.8% myocardial infarction 5.4%. graft failures 7.5% at 30 days, Mortality 43% after 5yrs	Comorbidity subdivided in various kinds of cardiovascular disease. 43 (4.2%) failed within 30 days	Large case series, long follow up period (5 years). Outcome is rather thoroughly described. Retrospective evaluation; not based on predifend problem; there is no drop out rate reported. Outcome lim salvage wasn't defined any further. Sub-group analysis of a large 3731 bypasses to 1032 to DP arteries of which some were diabetic (865)
Pomposelli 2003 [50]	Retrospecitve case series Pedal bypass graft series	865 total population 92% diabetes age: 67 gender: 69% male	Distribution: inflow vessel 41% BK pop 29% CFA 12% AK pop 11% SFA Severity: NR No scoring	78% ulcer Infection: NR Ulcer score: NR	CAD 47% ESRD 11% Of the total population		Ulcer healing: NR Limb salvage: 78% at 5 yrs and 10yrs 58% Graft patency 85% 1yr Secondary patency at 5yrs 66% DM versus 56% no DM 51% and 76% mortality at 5 and 10yrs Major amputation: NR Minor amputation: NR Complications: 10 (1%) deaths within 30days		

							3% MI		
Pua 2008 [51]	Case series Consecutive patients receiving PTA for limb slavage	91% DM patients out of 46 total age: NR gender: NR	Distribution: NR Severity: NR No Score	37/46 patients with foot lesions Ulcer score: NR Infection: NR	33% CAD 20% CVD	Mixed 25 5 crural 16 fem-pop 3 aortoiliac	Ulcer healing: at 13months 66% patients with gangrene healed Limb salvage: 78% at 1 year. Mortality: NR Major amputation: NR Minor amputation: NR	5 technical failures	Limited information regarding patient characteristics, comorbidity and selection procedures. Foot ulcers / gangrene are not specified any further
Ramdey 2002 [52]	Prospective case series (registry) Infrainguinal revascularisation	DM patients; 92% out of a total population of 146 age: 63 (SD 13) (total population) gender:65 % (Total population)	Distribution: NR Severity: NR	Tissue loss: 91% (total population) Ulcer score: NR Infection: 48%	CAD 115 (65%) MI 64 (36%) CVD 27 (15%) ESRD: all patients	Artery Inflow Iliac or femoral 123 (70%) Suprageniculate popliteal 20 (11%) Infrageniculate popliteal 34 (19%) Outflow Iliac/femoral 1 (0.6%) Suprageniculate popliteal 17 (10%) Infrageniculate popliteal 28 (16%) Tibial 50 (28%) Dorsalis pedis 80 (45%) Tarsal 1 (0.6%)	Follow-up: no data provided Complications: 30 day morbidity 23% 30 day mortality 5% Ulcer healing: NR Patency 1,3yr: 85, 68% Limb salvage: 1 yr 80% and 3yrs 80% Major amputation: 21 Minor amputation: NR	Follow-up not specified	Follow-up not specified
Reed 2002 [53]	Retrospective case series Case series of bypass grafts originating distal to the groin	DM patients 140, total population 217, 249 procedures age: 65 (30-90) gender: 79 female	Distribution: NR Severity: NR Scoring system: NR	Necrosis 127 (80%), rest pain 27 (17%) Infection: NR Wound classification: NR	CAD 95 (60%), ESRD 53 (33%) with 35 (23%) on dialysis	Infrainguinal vein bypass graft Pedal (35%), Crural (60%) Femoropopliteal (4%),	Survival 60% 1 year, 3yrs 18% and only 5% alive at 5yrs 30 day mortality 0.6% Complications: major post-op morbidity 16 (10%) Ulcer healing: NR Limb salvage rate was 84% (SD +/-4) at 5years Major amputation: Minor amputation: 5yr patient survival was 44 (+/-5)%	Data extracted out of a cohort study comparing diabetics with non diabetics 21% secondary procedures Mean 27months f/u	
Rosenbaum 1994 [54]	Retrospective case series Case series of infrapopliteal bypass grafts	DM patients: 39 age:62.3 (45-78) gender:33 (85%) males	Distribution: NR Severity: NR Score: NR	100% tissue loss Ulcer score: Gibbons classification Infection: NR	NR	Peripheral bypass: 79% infrapopliteal Popliteal 19% Tibial/ peroneal: 48% Dorsalis pedis/plantar artery: 31% Aotobifemoral 2%	Follow-up: Mean 21,2 (2-64) months Ulcer healing: 40 limbs (of total 42 limbs) with or without foot surgery Limb salvage: Major amputation: 1 Minor amputation: NR Complications:	Data of this study may be included in other reports of this group	No life-table analysis, no information about healing time, small series; follow-up procedures unclear
Saltzberg 2003 [55]	Retrospective case series Case series of mixed bypass grafts	DM patients: 96% of total population in 51 patients all younger than 40 years age: 36 (27-40 yrs) gender:49% male All data in this table as reported on total population	Distribution: 76 bypass procedures with inflow: Common Iliac 2.6% Femoral 67% Above knee popliteal 7,9% Below knee popliteal 21.1 % Tibial artery 1.3% Severity: NR	86% tissue loss Ulcer score: NR Infection: NR	CAD 37% ESRD (creat > 2 mg/dl, dialysis or transplant) 53% (of which dialysis 29%)	Venous (95%) or prosthetic (5%) bypass with outflow: Dorsalis Pedis: 30,3% Tibial artery: 18.4% Peroneal atery 3.9% Below knee popliteal: 23,7% Above knee popliteal: 11.8% Femoral artery: 3.9% Other: 7.9%	How follow-up was performed not described; no data on follow-up reported NR Patency 1yr, 5yr 82,63% Ulcer healing: NR Limb salvage: 87% at 1 year and 77% at 5yrs Major amputation: 23.5% required amp level unspecified (12/51) Minor amputation: see above Complications: 30 days mortality rate: 0%; postoperative heart failure: 1.32%	Unspecified follow-up	

							Overall motrality 88%, 73% at 1yr, 5yrs		
Schneider 1993 [56]	Case series of pedal bypass extracted from an initial cohort study of diabetes versus non diabetes but this study compares tibial with pedal	DM patients 45 of total population n=53 age: 67 (42-78)yrs total population gender: 33males of total population	Distribution: NR Severity: ABI 0.53 total population	77% tissue loss Ulcer score: NR Infection: NR	CVD NR CAD NR ESRD NR	All pedal bypass graft with vein	Follow-up: 22.5months (SD 3.4) Ulcer healing: NR Patency 1yr,3, 5yr 70, 58, 58% Limb salvage at 1,3,5yr: 98%, 98%,95% Major amputation: NR Minor amputation: NR Complications: Peri-op 9% mortalty Mortality 27,39,50 at 1yr,3,5yr	Major amputation defined as amputation proximal to metatarsals Low numbers of patients (6) at 5yrs	
Schneider 2001 [57]	Retrospective cohort Revascularisation using either fem-distal bypass, combined SFA PTA and distal bypass grafting or short distal bypass graft	SFA PTA plus short distal bypass DM patients 12 age: 70 (13) yrs gender: 83% male Long distal bypass DM patients 46 age: 68 (11) yrs gender: 50% male Short distal bypass DM patients 52 age: 69 (11) yrs gender: 65% male	Distribution: Combined: Below knee disease plus focal SFA disease (<3cm length) Severity ABPI 0.52 (0.19) Long distal bypass: Extensive infrainguinal disease involving fempop and infrageniculate arteries Severity ABPI 0.42 (0.17) Short distal bypass: Severe infra-geniculate occlusive disease and patent fempop arteries Severity: ABPI 0.46 (SD 0.15) Scoring system: NR	All gangrene Infection: NR Wound classification: NR	Combined CAD 33%, ESRD 58% Long distal CAD 38% ESRD 74% Short distal CAD 49% ESRD 67%	Distal target vessels Combined Tibial - 25% Pedal 75% Long distal Tibial 57% Pedal 43% Short distal Tibial 35% Pedal 65%	Mean f/u 23 months Ulcer healing: NR Limb salvage at 2 years Combined 90 (9)% Long distal 78 (9)% Short distal 98 (2)% Patency all procedures 78 (+/-5)% at 2yrs, 63 (8)% 5 yrs Major amputation: NR Minor amputation: NR Complications: NR Mortality: NR No differences between groups SIGN 2-	Small sample Heterogeneous populations - different distribution of PAD Confounding by indication Drop out and loss to f/u not reported	
Sigala 2006 [58]	Case series Mixed bypass graft plus 50 PTA	All diabetics 97 with 121 procedures 66% male Mean age 68 (range 41 - 85)yrs	Distribution: Large variation Severity: NR	49 necrosis 32 gangrene, 24 ulcers, 16 rest pain, Ulcer score: NR Infection: NR	CAD 78% CVD 20% 100% ESRD	Infra-inguinal revascularisations Endovascular - 36% only 5% combination endo and open Bypass only 59% Crural artery 55% 10% crural artery only 28% femoropopliteal 18% ext iliac to femoropopliteal	Ulcer healing: NR Limb salvage: 86% at 6 mo, 75% at 12, 56% 3 yrs Major amputation: NR Minor amputation: NR Complications 12/97 patients Mortality 30day 10%, 1yr 22%, 3yr 56%	Heterogeneous population of patients with wide variation of PAD distribution and revascularisation procedures All patients had ESRD Number of infections not stated in study but outcomes reported in K-M relative to infection	Sigala 2006 PDF 845
Soderstrom 2008 [59]	Prospective case series Healing of ischaemic ulcers after infrainguinal bypass surgery	74 DM patients out of 148 total population age: NR gender: NR	Distribution: NR Severity: ABI < 0,5, systolic toe pressure < 30 mmHg. Fontaine 4 Classification: NR	Classification provided: All Fontaine IV ulcers Infection: NR	NR	Infra-inguinal bypass in all subjects, with 13 PTA inflow procedures (total population)	Ulcer healing: 63% in 12 months in the diabetic patients Limb salvage: NR Major amputation: NR Minor amputation: NR Complications: NR Mortality: NR	Median time to achieve healing 213 days Diabetes was the only risk factor which delayed tissue healing (HR 0.5 95%CI 0.3-0.8 in multivariate analysis)	Arterial run-off for patients with diabetes not specified. No specific data on diabetic patients reported other than healing
Stonebridge 1991 [60]	Case series Retrospective review of 117 diabetic patients with a popliteal artery (or below) to distal bypass	All DM patients (117) age: 64 (27-92) gender: Male:female 5:1	Distribution: tibial Severity: NR Scoring: NR	non-healing 65 (52%), gangrene 20 (16%) infection: 40 (32%) foot abscess 2 (1.6%) osteomyelitis 6 (5%) Ulcer score: NR	CAD 37/117 ESRD 17/117	pop-distal by-pass graft (129 procedures)	Ulcer healing: NR Limb salvage: NR Major amputation: 8 during mean f/u 13months: minor amputation: 34 Complications: operative mortality 0.8 %, 1yr and 3yr secondary patency rates 92% and 89%		Non data about inclusion criteria according to PAD severity.

Tannenbaum 1992 [61]	Retrospective case series Case series of pedal bypass	DM patients 53 age: NR gender: 34 male	Distribution: NR Severity: NR Score: NR	73% ulcers, Infection: 45% cellulitis, 29% osteomyelitis, 20% gangrene, 2% abscess 11 minor amps performed pre bypass	NR	DP bypass with vein	Follow-up: average 25 (SD 14) months 10 patients lost to f/u Limb salvage 1,2,3yr 98%, 98%, 95% Major amputation: NR Minor amputation: NR Patency 1,2,3yr 95%, 95%, 95% Complications: NR Mortality rate 1,2,3yr 5%,16%,16% In the patients who didnt die or major amp all ulcers healed during f/u	Study of acute sepsis in ischaemic diabetic feet Excellent limb survival and patient survival and healing No report on severity of PAD Wound infection 13%	
Taylor 1987 [62]	Retrospective case series Case series of 114 patients with infection, 43 of whom revascularised	DM patients 114 patients with a foot infection (138 limbs): 43 (48 limbs) with ischaemia and 71 without ischaemia age: NR gender: NR	Distribution: NR Severity: NR But ischemia was defined as absent pulses + ABI < 0.6 or TBI < 0,4 and abnormal wave forms Score: NR	All infected ulcers Ulcer score: NR	NR	Peripheral bypass undefined	Mean f/u 3yrs (1-11yrs) Ulcer healing: NR Limb salvage: 2yrs 87%, 4yrs 73% Major amputation: 9 (19%) at 3yr mean f/u Minor amputation: NR Complications: NR Motality rate at 1,3,5yr 19, 62, 84%	17 lost to follow-up No data on lost to follow up on revasc patients Much important data missing 4/9 amputations due to infection	
Toursarkissian 2002 [64]	Primarily a prognostic study of the use of duplex as a predictor of bypass graft failure in diabetics	DM patients 65 age: 61yrs gender: 40/64 (63%) males	Distribution: NR Severity: toe brachial index 0.2 Score: NR	61 (94%) tissue loss Infection: NR Ulcer score: NR	CAD 38%, ESRD 16%	68 limbs Femoral to distal bypass 42 BK pop distal 16 Fem pop 10 All vein bypass	Duration of f/u 12months (SD 6months) Ulcer healing: NR Limb salvage: whole group 80% at 1 yr Major amputation: 8/68 limbs at 12months (SD 6months) Minor amputation: NR Graft patency assisted primary 75% at 1 yr (estimate of K-M) Complications: nil Mortality: NR		86% Hispanic population
Uccioli 2010 [65]	Case series of pedal bypass	135 patients 144 procedures all DM patients age: 62 (SD 11)yrs gender: 78% males	Distribution: NR Severity: NR	96% tissue loss Ulcer score: NR Infection: NR	CAD 62% ESRD 20%	Dorsalis pedis bypass grafts	Median f/u 8 (1-62) months Ulcer healing: NR Limb salvage: 83% at 30 months Major amputation: 19% at total f/u (mean 8 months) Minor amputation: 36% Patency : 70% 1yr, 68% 30months Complications: 25 peri-op complications Mortality 30day 1.5% Mortality at end of study 10%	82% hispanics Study comparing outcome in various ethnic groups (hispanics versus no hispanics). Higher amp rate in hispanics	
Verhelst 1997 [66]	Retrospective case series Case study of pedal and crural bypass graft	DM patients: 33 (92% of total population n=36) age:62 (29-78)	Distribution: NR Severity: tcpO2 18 mmHg +/- 7 Score: NR	89% tissue loss Ulcer score: NR Infection: NR	CAD 44% Dialysis 4	Popliteal-to- Distal venous Bypass Grafts (n=44): Posterior tibial: 13 Anterior tibial: 10 Peroneal: 6 Dorsalis pedis/ plantar: 23	Meal follow-up 27 months (1-65) Ulcer healing: in 33/36 patients complete healing of skin lesions	Confusion between patients/ extremities. Small study. Mixture of vascular interventions. Started treating 33	

		gender: 29 males All data in this table as reported on total population					and that includes minor amputations. Limb salvage: 90, 82, 77% at 1, 3 and 5 years. Major amputation: major amputations occurred in follow up period of 27 months Minor amputation: 35 Patency 1,3yr 87%, 74% Complications: MI 1 Heart failure 1 Post-operative bypass occlusion and major amputation 3 Mortality 30days 0% Deaths: 4 during following follow-up	patients - No standard error in curve and therefore high likelihood of significantly small numbers during follow-up	
Werneck 2009 [67]	Case series Tibial PTA in patients with 'CLI' at 'high risk' restrospective case series	40 DM patients (total population 49) age:70 gender: 71% males	Distribution: All had 'severe' tibial disease, "some also had femoropopliteal PAD" Severity: NR TASC reported:	Classification: 20% Ruth 4 80% Ruth 5* Infection: NR	CAD 69% ESRD 73% of the total population	Tibial angioplasty in all and in 45% multilevel (fempop segment)	Ulcer healing: NR Limb salvage: 76% after mean f/u 8months Cumulative limb salvage rate in tibial PTA only after 1yr: approx 70% estimated from K-M Major amputation: NR Minor amputation: NR Complications: major complications occurred in 6.1% 30day mortality 2% Mortality after 1yr 10%	Angiographic success rate was 84%.	Number of pts with surgery vs. PTA not given. There are 10 amputations in diabetics. However, it is unclear how many vases were in the PTA group.
Woefle 1993 [68]	Retrospective case series Case study of mixed bypass grafts	DM patients: 72 age: 70.5 gender: NR	Distribution: Isolated Tibioperoneal Vessel Occlusive Disease Severity: NR Bypass	All with minor tissue loss Ulcer score: NR Infection: NR	CAD 41 ESRD (creat > 2 mg/dl): 18 Symptomatic carotid disease: 15	Distal Vein Graft Reconstruction: Proximal anastomosis: Below knee popliteal: 56 Anteriot tibial: 18 Distal anastomosis: ATA 10 DPA 37 PTA 13 Peroneal: 12 Plantar 3	Follow-up: no information provided how this was performed or data reported Ulcer healing: Limb salvage: at 30 days 93%, at 1 year 81%, 5yr 72% Patency: 30days 97%, 1yr 86%, 5yr 75% Major amputation: NR Minor amputation: NR Complications: mortality within 30 days 1,3% 23 patients died during follow-up (including postop mortalty)	ulcer healing not reported; total number of BK amputations not reported. No data on follow-up	
Woefle 2000 [69]	Retrospective case series of two different procedures Bypass crural versus PTA crural	Bypass DM patients 125 (130 grafts) age: 70 (50-87)yrs gender: NR Distal PTA DM patients 74 (89 limbs), 84 total age: 68 (48-89) gender: NR	Distribution: Crural Severity: NR PTA Distribution: Crural Severity: tcpO2 6.7 (0-29) Score: AHA	Bypass 127 tissue loss PTA 84 tissue loss Ulcer score: NR Infection: NR	Bypass CAD 57% CVD 18% ESRD 25% PTA CAD 48% CVD 17% ESRD 42%	Vein to DP in 63 or ant tibial artery in 20 and PT in 28 and in peroneal in 19 Angioplasty crural arteries AHA classification (1994) 1 - 8 2 - 28 3 - 26 4 - 27	Average followup probably 24months Bypass Limb salvage 80% 1yr, 73% at 3yrs and 69% at 6yrs 2.3% 30day mortality Patency 1,3,5yr = 76%, 70%, 60% 30 major amputation at 24months Minor amputations: NR	Poor information on loss to follow-up and drop out. Retrospective case series of two different procedures and not a controlled study	

							64 died during f/u PTA Limb salvage 1yr 82%, 77% at 3yrs and 77% at 5 years 30day mortality 6% 17 major amputations during 24 months Minor amputations: NR 26 deaths died during f/u Complications: Major haematoma 3 patients		
Woefle 2001 [70]	Retrospective case series Case studies infrappopliteal bypass graft	DM patients: 135 (143 procedures) age:70 (50-89) gender: NR	Distribution: extensive intra-popliteal occlusions Severity:NR	Tissue loss in 140 limbs Ulcer score: NR Infection: NR	CAD 82 (61%), ESRD 43 (16%), CVD 29 (20%),	All venous bypass with proximal anastomosis: BK popliteal 113 ATA 29 PA 1 Distal anastomosis: ATA 21 DPA 71 PTA 29 Peroneal 22 PTA of SFA prior to surgery in 37	Follow-up duration not reported Ulcer healing: NR Patency 1yr 83%, 5yr 60%, 7yr 51% Limb salvage: Limb salvage rates 30 days 94%, 1 yr 80%, 5 yrs 74%, 7 yrs 64% Major amputation: 35 during follow-up Minor amputation: NR Complications: 30 day mortality 8% Mortality 1yr 27%, 5yr 70%, 7yr 82%	No data on mean duration of followup or on severity of PAD No data on	
Zayed 2009 [71]	Retrospective series Series of combined PTA and bypass surgery	DM patients: 312 age: 188 males (40%) gender:188 males (60%)	Distribution: NR Severity: NR Classification: NR	93% tissue loss Ulcer score: NR Infection: NR	CAD 107 (34%) Dialysis: 33 (10.5%)	257 (82%) PTA, 55 (18%) surgical bypass open surgery 20 had combination of both procedures	Follow-up not defined and no data reported Ulcer healing: NR Limb salvage: NR Major amputation: 13 cases (4,1%), of these 7 had PTA, 6 had reconstructive vasc surgery Minor amputation: NR Complications: NR	follow-up PTA not specified, severity of PAD not described All amputations above or through knee	

III. Diagnosis and treatment of peripheral arterial disease in diabetic patients with a foot ulcer. A progress report.

Contents

I. Introduction

Peripheral arterial disease (PAD) causing arterial insufficiency is an important predictor of outcome of ulceration of the foot in patients with diabetes. The clinician examining a patient with diabetes and an ulcer of the foot should therefore always evaluate the vascular status of the lower extremity, specifically looking for signs of ischaemia, as up to 50% of these patients have signs of PAD[1-3]. Whenever a major amputation is under consideration, the option of revascularization should always be considered first.

In people with diabetes, atherosclerosis and medial sclerosis are the most common arterial diseases of the peripheral arteries. PAD is characterised by obstructive atherosclerotic disease reducing distal blood flow and perfusion pressure. Peripheral vascular involvement is diffuse and particularly severe in the tibial arteries, with a high prevalence of long occlusions. Moreover, collateral formation - a normal response to blockade of a large artery - is impaired in patients with diabetes rendering the tissue downstream more susceptible to severe ischaemia. Medial sclerosis (Mönckeberg sclerosis) is calcification of the tunica media producing rigid arteries - without encroachment on the arterial lumen. Thus medial sclerosis, which is frequently associated with neuropathy, does not cause ischaemia, but the rigid arterial tube may severely interfere with indirect measurement of arterial blood pressure, as discussed below[4]. In the past diabetic microangiopathy was thought to be an important cause of poor healing of a diabetic foot ulcer. However, there is currently is no evidence to support this notion and PAD is the most important cause of impaired perfusion on the foot of a diabetic patient[5].

II. Diagnosis of PAD

In all patients with a foot ulcer, evaluation should include at least a history and palpation of foot pulses. A history of intermittent claudication or ischaemic rest pain should be obtained. However, many patients with diabetes and PAD have few or atypical symptoms Severe lower extremity ischaemia and extensive tissue loss may occur without pain, frequently due to the concomitant neuropathy. In addition, the foot should be observed while elevated above the heart in a supine position and subsequently lowered in a sitting position; pallor of the foot with elevation and rubor on dependency suggest severe ischemia. The presence of a femoral bruit is also a reliable sign of PAD[6].

Palpation of pulses in the posterior tibial and dorsalis pedis arteries is mandatory. Detection of foot pulses by palpation is affected by room temperature and the skill of the examiner and pedal pulse palpation has moderate reproducibility[7]. Therefore in all patents with a foot ulcer a more objective evaluation should also be performed. This should include hand-held Doppler evaluation of the flow signals from both foot arteries (dorsalis pedis and posterior tibial). An absent or monophasic signal is an indicator of severe PAD. The ankle brachial index (ABI) should also be obtained by measuring the systolic blood pressure from both brachial arteries and from both the dorsalis pedis and posterior tibial arteries using a Doppler device and appropriately sized pneumatic cuffs. The higher ankle pressure on each side and the highest brachial pressure are used to calculate the ABI. The leg arteries in diabetic patients with a foot ulcer can be calcified, resulting in partially-compressible or non-compressible arteries and pressures are measured during limb cuff inflation that are above true systolic values. An ABI above 1.3 indicates non-compressible leg arteries, a finding in up to 1/3 of the diabetic patients with a foot ulcer[1]. While an ABI value greater than 1.3 does not provide an accurate assessment of lower extremity ischaemia, this is associated with increased cardiovascular event rates and other risk factors for PAD. Less severe calcification may result in a normal ABI (0.9-1.3) despite clinically significant PAD. An ABI < 0.9, however, is highly suggestive of PAD. Toe-pressure measurements are probably more reliable in assessing forefoot circulation in patients with diabetes, since the digital arteries are less frequently affected by calcification. A toe pressure <55 mm Hg or a toe-brachial index <0.7 strongly suggests PAD in a foot acclimatised in a warm surrounding[8].

III. Assessing severity of PAD and estimating wound healing potential

Once the diagnosis of PAD is established, attempts should be made to assess the severity of the perfusion deficit. An ABI <0.6 indicates significant ischaemia with respect to wound healing potential. As discussed above, the ABI is a gross measurement and is often unreliable in patients with ulceration of the foot and diabetes; other methods such as toe-pressures and $tcpO_2$ are often more useful. Multiple factors influence wound healing in diabetes, one of which is perfusion.

Prediction of wound healing based on perfusion testing, regardless of method, follows a sigmoidal curve. Ulceration of the foot in diabetes will generally heal if the toe pressure is >55 mmHg and the $tcpO_2$ >50. Healing is usually severely impaired when toe-pressure is <30 mmHg and $tcpO_2$ <30 mmHg. When inadequate perfusion is identified, revascularisation should always considered (see below).

In patients without clinical signs of ischaemia or with perfusion measurements suggesting only mild PAD, the effect of 6 weeks optimal wound care should be evaluated. If the wound healing response is poor, perfusion should be reassessed. Duplex ultrasound or angiography of the arteries of the lower limb should be strongly considered to assess the presence, severity, and distribution of arterial stenoses or occlusions. Detailed angiograms of belowknee and pedal arteries, especially with a dedicated assessment of the pedal circulation, are critically important in patients with diabetes.

Efforts should be made to objectively diagnose and quantify PAD in all patients with ulceration of the foot in diabetes. If PAD of sufficient severity to impair wound healing is identified, revascularisation (endovascular or bypass) should be considered in all ambulatory patients. Exceptions to this general rule may include: severely frail, elderly (or short life expectancy, <6-12 months), patients; patients with pre-existing severe functional impairment unlikely to be significantly worsened by an amputation; and patients who have such a large volume of tissue necrosis that the foot is functionally unsalvageable.

IV. Imaging modalities for PAD in diabetes

1. Colour Doppler ultrasound

Colour Doppler ultrasound (CDUS) combines real-time B-mode imaging and pulsed Doppler flow detection to provide both anatomic details and a physiologic assessment of blood flow at specific arterial sites. Most current instruments can display the Doppler flow information as either spectral waveforms or a color-flow map. By scanning sequentially from the abdominal aorta through the iliac, femoral, popliteal, and tibial arteries, the entire lower extremity arterial circulation can be directly evaluated. Classification of disease severity is based primarily on focal velocity changes derived from spectral waveforms[9]. The sensitivity of CDUS for detecting a hemodynamically significant lesion (≥50% diameter reduction) ran ges from 89% in the iliac segment to 68% at the popliteal artery. Sensitivities for predicting interruption of patency are 90% for the anterior and posterior tibial arteries and 82% for the peroneal artery[9]. The ability to evaluate the arteries below the knee is particularly important in diabetic patients. However, diffuse multisegmental involvement and calcifications may hamper the examination.

Although CDUS is noninvasive and relatively inexpensive compared to the other anatomical imaging modalities, it requires sophisticated equipment and specialized expertise and is not appropriate as a routine screening test. The best role for CDUS is as an "intermediate" diagnostic test when simple physiologic screening such as ankle-brachial indices or $TcpO_2$ indicate the presence of disease but more invasive and expensive anatomic imaging is not yet needed. In this setting, CDUS can be used to assess the location and severity of arterial lesions throughout the lower extremity and serve as the basis for initial clinical decisions, including the need for intervention and also to guide intervention when the decision to revascularise has been taken [10-12].

2. Multi-detector-row computed tomography angiography

Multi-detector-row computed tomography angiography (MD-CTA) is a low invasive imaging modality for PAD. It can be performed with any MD-CTA, however, currently 32 to 128 row scanners are used for peripheral MD-CTA and iodinated contrast media are injected intravenously. For lower extremity PAD the scan range is from the renal arteries to the foot. After data acquisition 3D reconstructions are performed. The sensitivity and specificity in comparison to the reference examination digital subtraction angiography (DSA) has been evaluated extensively. In two meta-analyses the pooled sensitivity and specificity for detecting a stenosis of at least 50% per segment were 92 -95% and 93-96%, respectively[13,14]. The advantage of MD-CTA is high image resolution for better evaluation of the small vessels in the calves. However, severe calcifications with blooming artifacts may cause difficulties to estimate the degree of stenosis in small arteries. The disadvantages of MD-CTA are the use of ionizing radiation and potentially nephrotoxic contrast agents.

3. Contrast enhanced magnetic resonance angiography

Contrast enhanced magnetic resonance angiography (CE-MRA) is also a low invasive imaging modality for PAD. Unenhanced mask images of the aortoiliac, femoropopliteal and popliteocrural area are acquired first. After injection of gadolinium as paramagnetic contrast material, contrast enhanced images are acquired. In patients with tibial artery disease hybrid CE-MRA protocols are used. The first stage is high-spatial-resolution CE-MRA of the calf and foot. The second stage (i.e., after the second injection) is aortoiliac and femoral bolus-chase CE-MRA. Hybrid techniques are more accurate for evaluating the trifurcation and foot vessels than single-injection multistation CE-MRA which may have venous contamination of the calf arteries. Alternatively, temporally resolved MRA techniques can be used[15,16]. The sensitivity and specificity of CE-MRA of peripheral arteries were both in one meta-analysis 94%[17]. However, in diabetic patients with a foot ulcer and tibial artery disease such a high accuracy can be achieved only when using hybrid techniques[18]. The advantage of CE-MRA is the use of paramagnetic contrast agents with limited nephrotoxicity and no radiation. However, disadvantages are the limited special resolution, artefacts due to flow and previous stent placement, and the limitation due implants (i.e. pacemakers) and claustrophobia.

One study reviewed and compared CE-MRA, MD-CTA and CDUS. CE-MRA had median sensitivity 94% and median specificity 99%. MD-CTA had median sensitivity 97% and median specificity 99%. CDUS had median sensitivity 90%, and median specificity 99%. The accuracy of the different techniques was similar for the detection of stenosis of 50% or more above and below the knee[19].

4. Intra-arterial digital subtraction angiography

Intra-arterial digital subtraction angiography (DSA) is still regarded as the gold standard for arterial imaging, because of its highest spatial resolution. It has the advantage of endovascular therapy during the same procedure. Disadvantage is the arterial puncture with the risk of local complications (i.e. hematoma)[20].

V. Treatment[21]

Cardiovascular morbidity and morality are markedly increased in patients with PAD, these patients have an overall mortality at 5 years of 50%[21]. In patients who had a major amputation these figures are even more dismal, with a 50% mortality at 2 years[21]. Treatment of neuro-ischaemic ulcers should therefore not be solely focused at the foot, but should also aim to reduce this poor survival. This cardiovascular risk management should include support for cessation of smoking, treatment of hypertension and prescription of a statin as well as clopidogel or low-dose aspirin.

In a patient with a foot ulcer and signs of PAD, an estimate of the probability of wound healing should be based on clinical examination and the non-invasive vascular tests described above. In addition to PAD, wound healing may be further disturbed by a complex interplay of several other factors such as poor glycaemic control, impaired collateral formation, abnormal mechanical loading of the ulcer and co-morbidities. The effect of PAD on wound healing in patients with diabetes and a foot ulcer will therefore relate in part to its severity and extent but also to these other factors. If due to the PAD the probability of healing is deemed to be too low, or if the patient has persistent ischemic rest pain, revascularization should always be considered.

Arterial revascularization can be performed through open procedures such as a bypass or more rarely via thromboendarterectomy, or in many cases an endovascular procedure - such as a balloon dilatation (percutaneous transluminal angioplasty, PTA) or an endovascular (subintimal) recanalisation. Bypass grafting using autologous vein and balloon angioplasty represent the most commonly used techniques. The aim of revascularisation is to restore direct pulsatile flow to at least one of the foot arteries, preferably the one feeding the wound or to the peroneal artery but only in case of sufficient collateral blood flow to the foot arteries, as the peroneal artery ends above the ankle. However, the common involvement of the arteries in the lower leg and the foot in combination with the impaired collateral formation render a revascularization a challenging procedure in patients with diabetes, severe PAD and ulceration of the foot[22]. Feasibility, effectiveness, repeatability, safety and costs, are the five parameters to evaluate in selecting the proper technique to be adopted.

Not all patients with diabetes, PAD and ulceration of the foot require revascularisation. Leg salvage is an indirect measure of the success of revascularisation and actually should only refer to improvement over natural limb survival. The key question is what the limb outcome would be if treated only conservatively. There are no randomized controlled clinical trials directly comparing conservative treatment with a revascularisation procedure in patients with diabetes, PAD and a foot ulcer. In patients with diabetes and critical limb ischaemia who were not revascularised, a limb salvage rate at one year of 54% was reported[21]. This rate is much lower than the limb salvage rates between 78% and 85% at one year after open and endovascular revascularisation techniques rates, as reported in the majority of the published studies[21]. Moreover, ulcer healing can be achieved in more than 60% of the patients at 12 months[21]. In contrast, minor amputation rates (and indications for minor amputation) varies considerably in the literature[21]. Peri-operative mortality rates of revascularisation procedures in patients with diabetes and an ischaemic foot ulcer is low (in most studies < 5%), but major systemic in-hospital complications were observed in about 10% of the patients in both open and endovascular series, probably reflecting the poor general health state of these patients[21]. The outcomes in diabetic patients with end stage renal disease (ESRD) is worse with a 5% peri-operative mortality and one year mortality of 40%[21]. However, even in these patients favourable results can be obtained. The majority of studies report 1-year limb salvage rates of approximately 70%[21]. In addition to ESRD, old age and preoperative functional status were strongly associated with complication rate in an extended series of infrainguinal bypass surgery in a series of diabetic and non-diabetic patients[23].

In recent decades new techniques and technologies have been introduced in treating PAD and in particular interesting results have been reported on endovascular approaches in the lower limb. The field is rapidly evolving. In general, when endovascular revascularisation and open repair or bypass of a specific lesion give equivalent short- and long-term results, endovascular techniques may probably be used first, given their lower risks and costs. There are currently no randomised controlled clinical trials comparing open with endovascular revascularisation techniques in diabetic patients with an ischemic foot ulcer. Based on the current literature, broadly speaking the major outcomes of both techniques appear similar across all studies where revascularisation of the foot was successful[21]. In the cases series where angioplasty was the preferred first-line option for revascularisation, this approach appeared feasible in most patients and favourable results were obtained; bypass surgery was only required in a minority of these patients[21]. However, the results of both open and endovascular procedures will greatly depend upon the local availability and expertise in a given center as well as the morphological distribution of PAD[23]. The local complications of PTA are understood to be scarce and minor and not to prevent bypass in the later phase, if necessary. Yet, crural interventions may have severe non-correctable outcomes[24]. Subintimal angioplasty to attempt to open up infra-popliteal occlusions is associated with technical failure rates of 20% and procedural complication rates of PTA were between 7-17% in series of patients with and without diabetes[25,26,27].

"Time is tissue" in particular in infected ischemic diabetic foot ulcers. Patients with signs of PAD and a foot infection are at particularly high risk for major limb amputation and should be treated with medical urgency, to include aggressive debridement, (intravenous) antibiotics, and rapid vascular evaluation. However, in case of severe infection in the ischemic foot, especially in patients with systemic signs of sepsis (e.g. haemodynamic instability) immediate amputation may be the only option to save life.

With the advent of less invasive endovascular revascularisation techniques, some would consider revascularisation in patients with slow to heal DFUs of <6 weeks duration who have intermediate perfusion abnormalities such as toe-pressures between 50-70 mmHg or $tcpO_2$ values between 30-50 mmHg, but this still remains controversial. In these patients the potential beneficial effects of a revascularisation should be weighed against its associated risks and costs. Clinical trials are currently lacking in this area, and the role of early revascularisation should be one of the important topics of future clinical trials.

Performing a distal revascularization procedure in patients with diabetes is frequently a challenge for the vascular specialist involved. The nature and morphology of the local pathology, usually involving the vessels below the knee (BTK), is different compared to plain atherosclerotic disease. Patients require expert assessment and BKT procedures, both open and endovascular, require specific knowledge and technical procedural skills. Moreover, a sufficient number of such procedures should be performed annually to maintain skill and emergency treatment should be possible The vascular specialists performing open and endovascular treatments should be part of a team who can deliver comprehensive multidisciplinary care to the patient with diabetes, PAD and ulceration of the foot. These procedures are no stand-alone treatment and should be part of a comprehensive care plan which should also include aggressive treatment of infection, frequent debridement, biomechanical off-loading, blood glucose control and treatment of co-morbidities.

VI. References

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