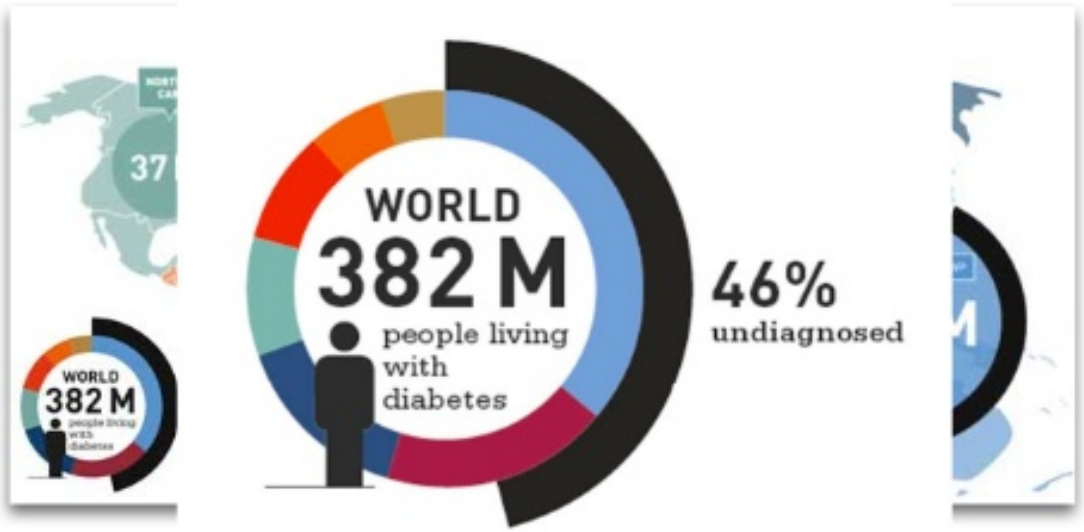
DİYABETİK AYAK GELİŞİMİNİN FİZYOPATOLOJİSİ

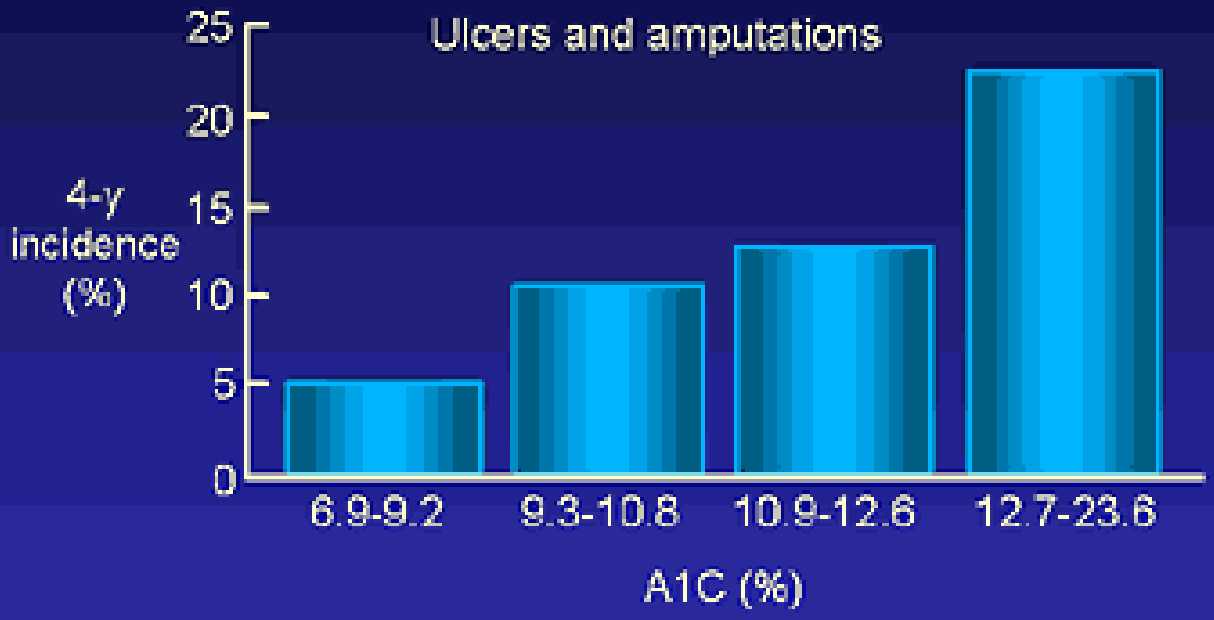
Doç.Dr.Levent KEBAPCILAR
Selçuk Üniversitesi Tıp Fakültesi

Prevalence of Diabetic Mellitus in Adults (20-75 years) 2013



Source: IDF Diabetes Atlas Sixth Edition, International Diabetes Federation 2013

Risk of Foot Complications and Glycemia in Older-Onset Diabetes Patients (WESDR)



Odds ratio 1.6 for each absolute increment in A1C of 2%

Moss SE et al. *Arch Intern Med.* 1992;152:610-616.

Diyabetik Ayak Prevelansı

- Yapılan araştırmalarda diabetik hastaların yaklaşık %15'inde yaşamlarının bir döneminde ayaklarında ülser geliştiği gösterilmiştir
- %6'sının ayak ülserleri nedeniyle hastaneye yatırıldığı tespit edilmiştir
- İlk amputasyon sonrası 5 yıl içerisinde ise %28-51'i yeni bir amputasyona gider ve bu hastaların yaklaşık %40-66'sı 5 yıl içerisinde ölürler

Slovenkai MP. Foot problems in Diabetes. Med Clin North Am 1998; 82:49-71. Calvet HM, Yoshikawa TT. Infections in diabetes. Infect Dis Clin North Am. 2001; 15:407-421.

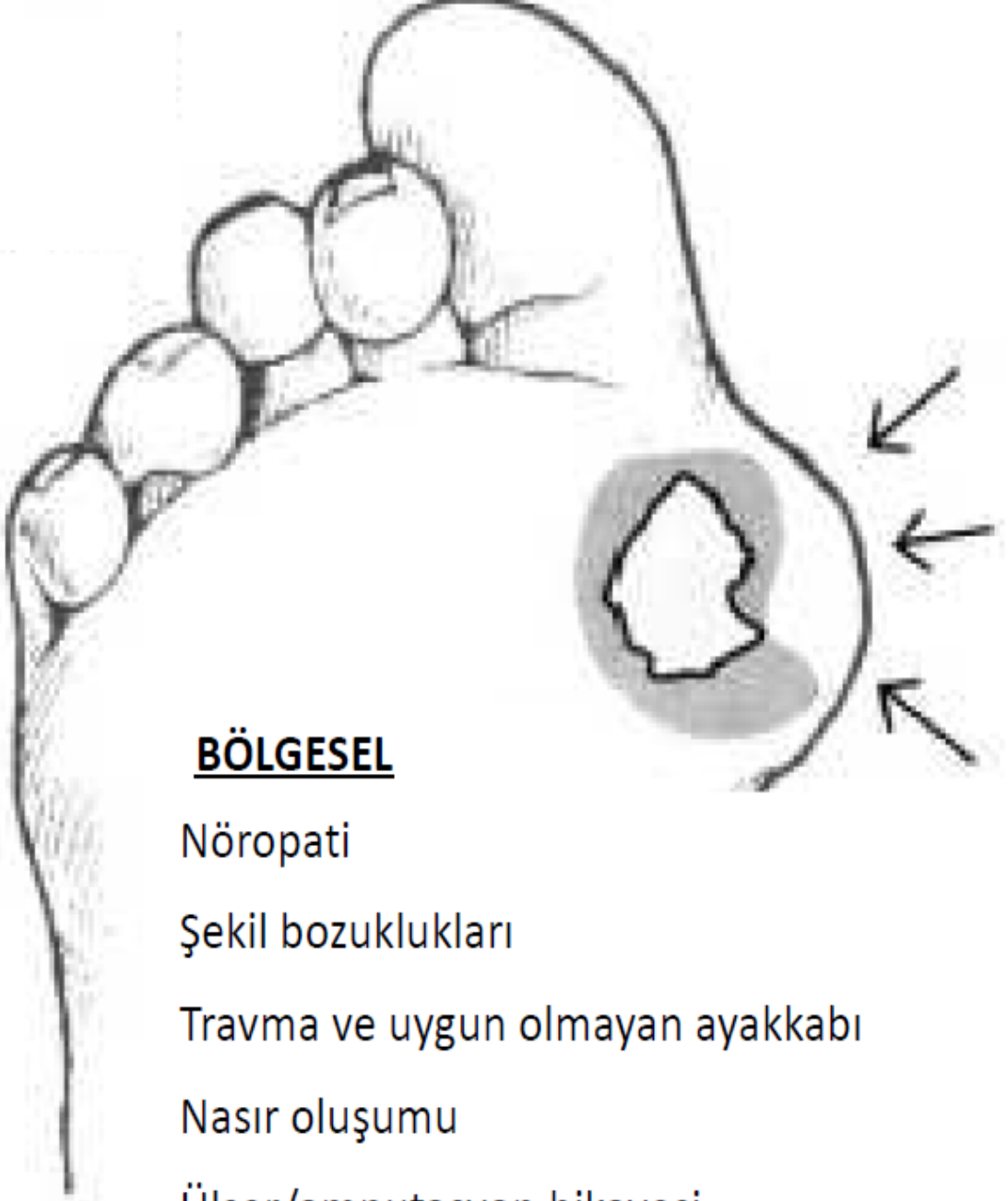
DİABETİK AYAK FİZYOPATOLOJİSİ

- Diyabetik ayak ülserleri;
- periferal nöropati,
- vasküler yetersizlik,
- enfeksiyon ve immün sistem bozukluklarının

izole veya kombine etkileri ile oluşmaktadır

Pedowitz WJ. Diagnosis and treatment of infections of the diabetic foot. Foot Ankle Clin, 1997; 2:89-98.

RİSK FAKTÖRLERİ



GENEL / SİSTEMİK

Kontrolsüz hiperglisemi

Diyabet süresi

Damarsal patoloji

Görmenin azalması

Kronik renal hastalık

İleri yaş

Erkek olmak

Sigara

BÖLGESEL

Nöropati

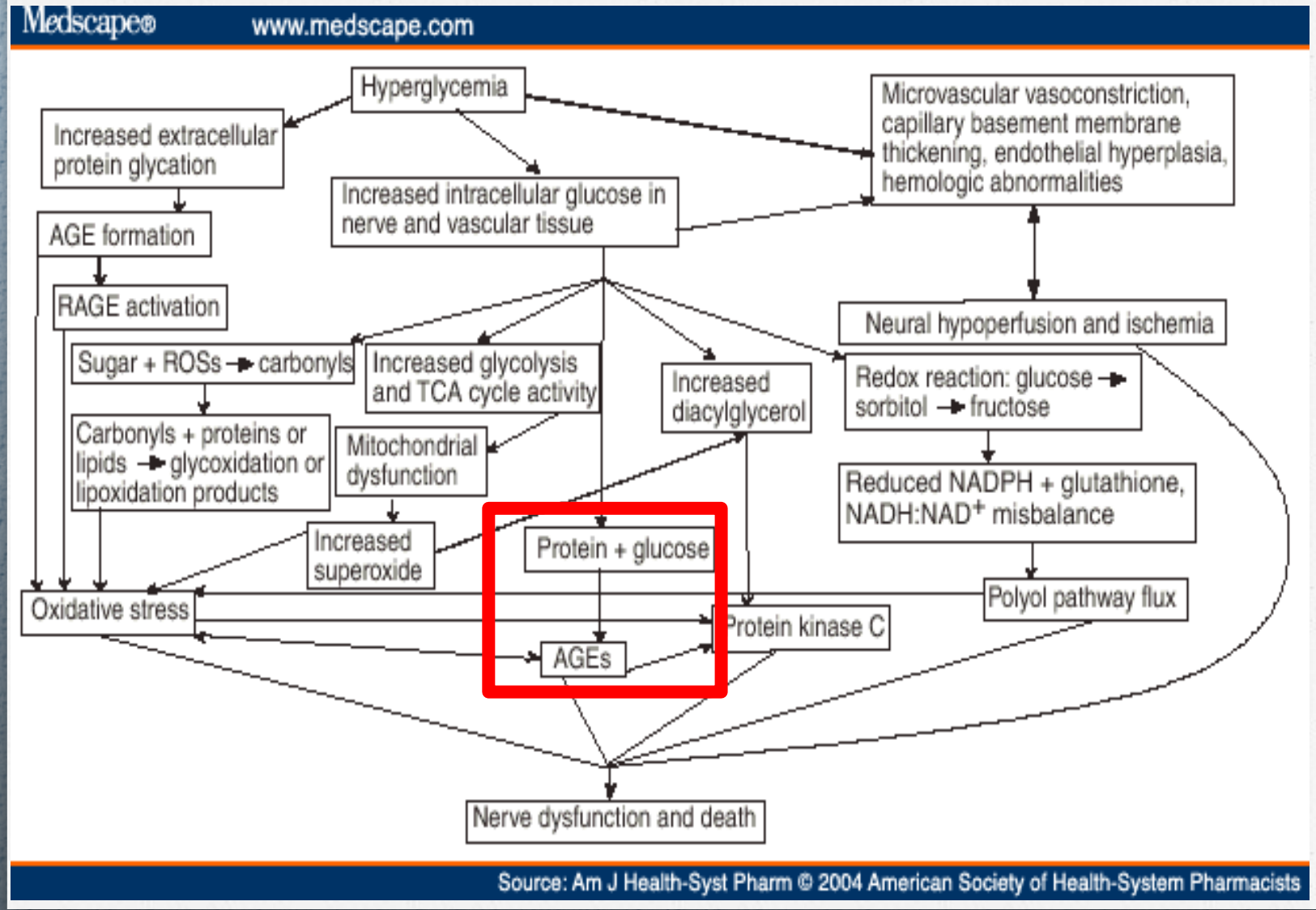
Şekil bozuklukları

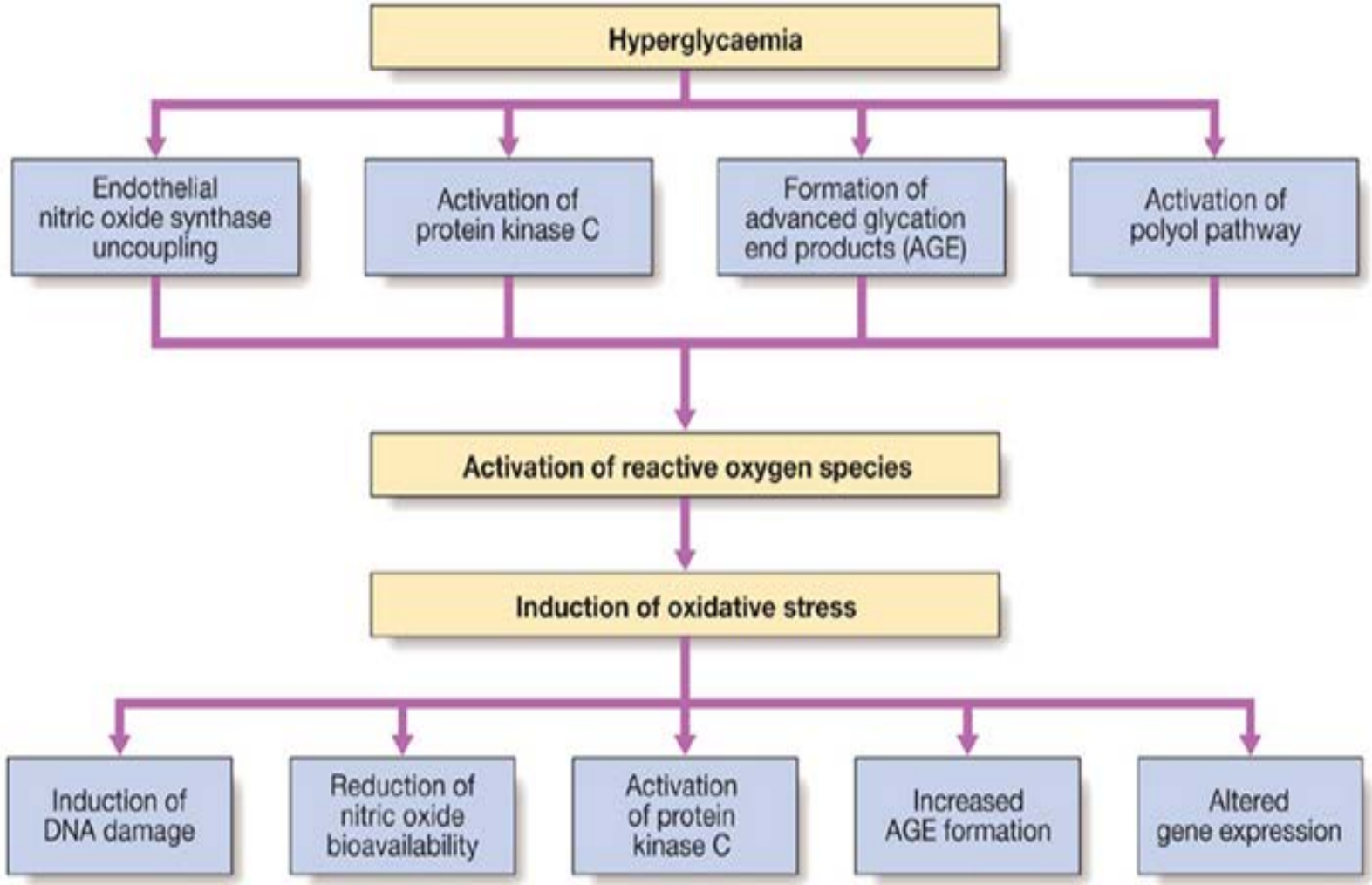
Travma ve uygun olmayan ayakkabı

Nasır oluşumu

Ülser/amputasyon hikayesi

Eklem hareketi kısıtlılığı


Medscape®
www.medscape.com
Hyperglycemia
Increased extracellular protein glycation
Microvascular vasoconstriction, capillary basement membrane thickening, endothelial hyperplasia, hemologic abnormalities
Increased intracellular glucose in nerve and vascular tissue
AGE formation
RAGE activation
Neural hypoperfusion and ischemia
Sugar + ROSs → carbonyls
Increased glycolysis and TCA cycle activity
Increased diacylglycerol
Redox reaction: glucose → sorbitol → fructose
Carbonyls + proteins or lipids → glycoxidation or lipoxidation products
Mitochondrial dysfunction
Reduced NADPH + glutathione, NADH:NAD+ misbalance
Increased superoxide
Protein + glucose
Oxidative stress
Polyol pathway flux
Protein kinase C
AGEs
Nerve dysfunction and death
Source: Am J Health-Syst Pharm © 2004 American Society of Health-System Pharmacists



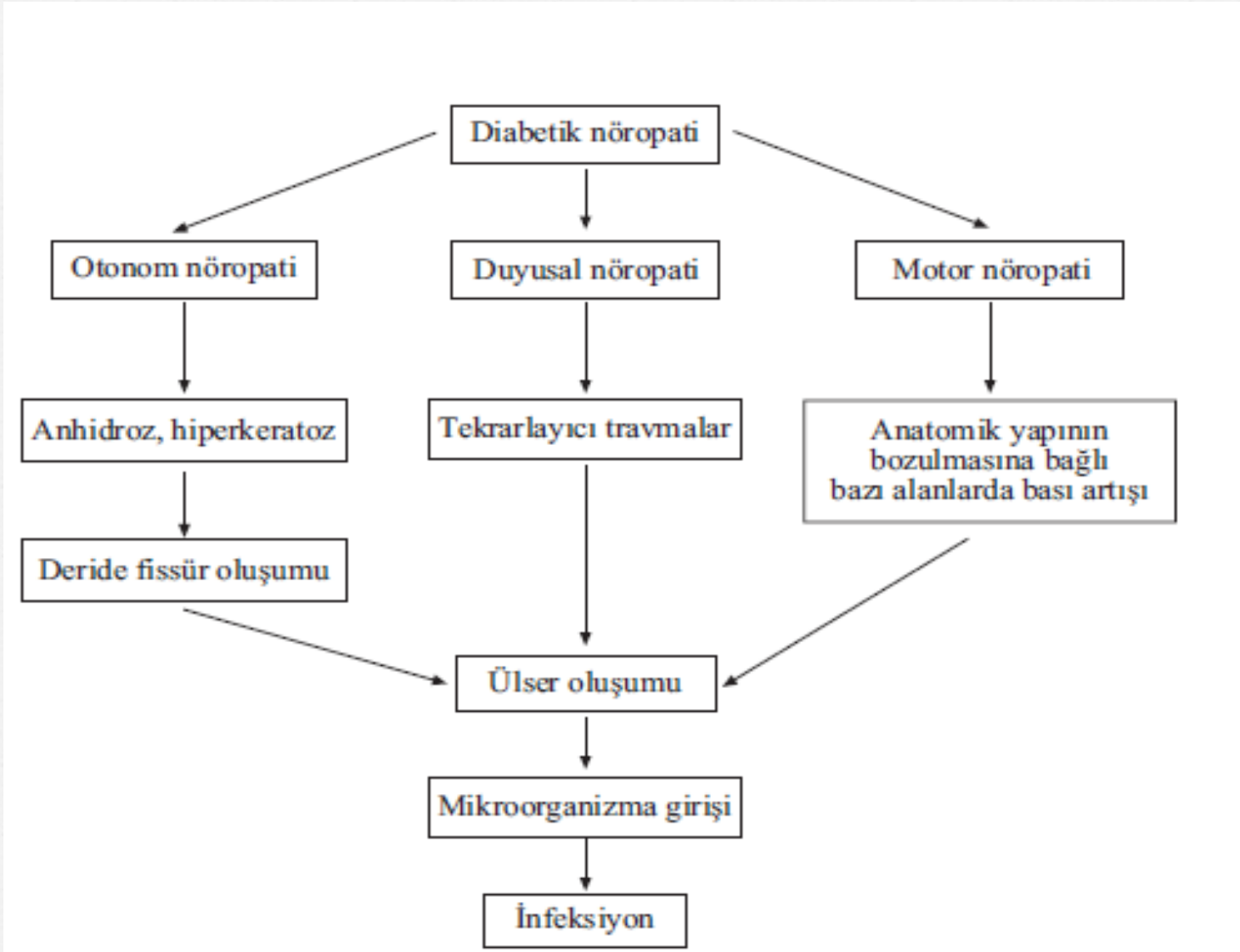
Colledge et al: Davidson's Principles and Practice of Medicine, 21st Edition

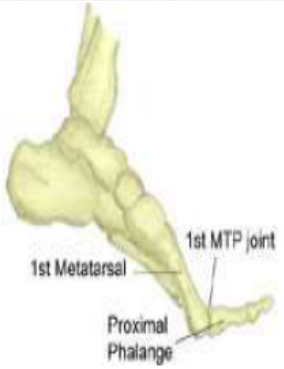
Öngörülen Patogenez:

1. Glukoz yükünün artması sonucu, özellikle sinir dokusu, retina ve böbreklerde hücre içinde sorbitol birikir, hücre içinde osmotik yük artar ve reaktif oksijen radikalleri ortaya çıkar. Sonuç: Hücre hasarı.

2. Protein kinaz C aktivasyonu, immün kompleks birikimi, endonöral ödem ve aksonal transportun bozulması gibi etmenler de nöropati gelişiminde rol oynayabilir.

JAMA. 2009 Oct 7;302(13):1451-8.


Diabetik nöropati
Otonom nöropati
Duyusal nöropati
Motor nöropati
Anhidroz, hiperkeratoz
Tekrarlayıcı travmalar
Anatomik yapının bozulmasına bağlı bazı alanlarda bası artışı
Deride fissür oluşumu
Ülser oluşumu
Mikroorganizma girişi
İnfeksiyon



Plantar fasyanın kalınlaşması →

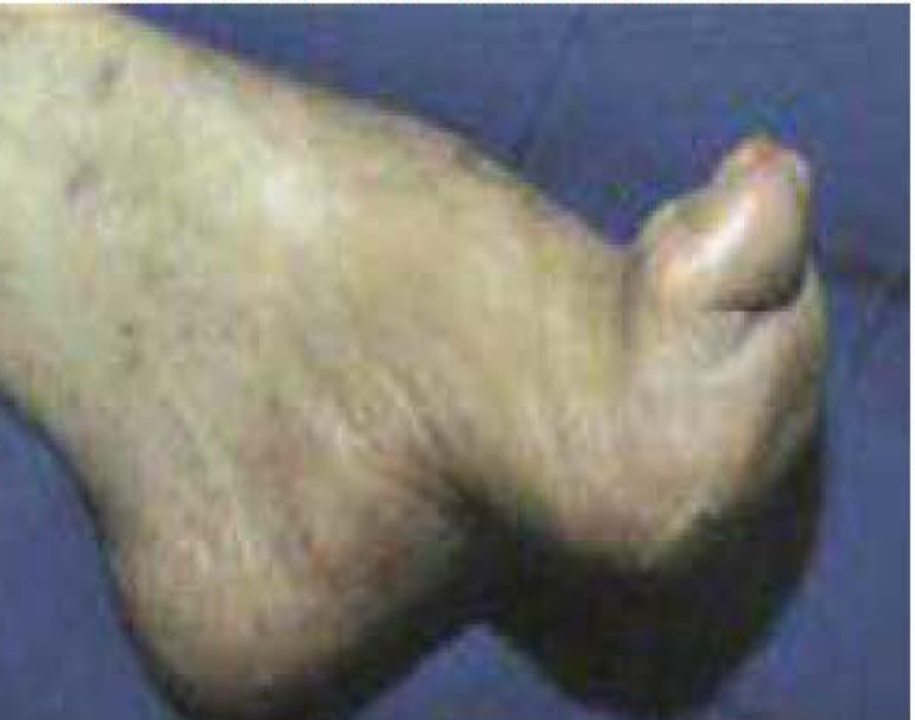
- Hallux dorsifleksiyonunda kısıtlılık,
- Plantar yumuşak dokuda incelme,
- Ciltte sertlik/gerginlik
- Nasır oluşumu

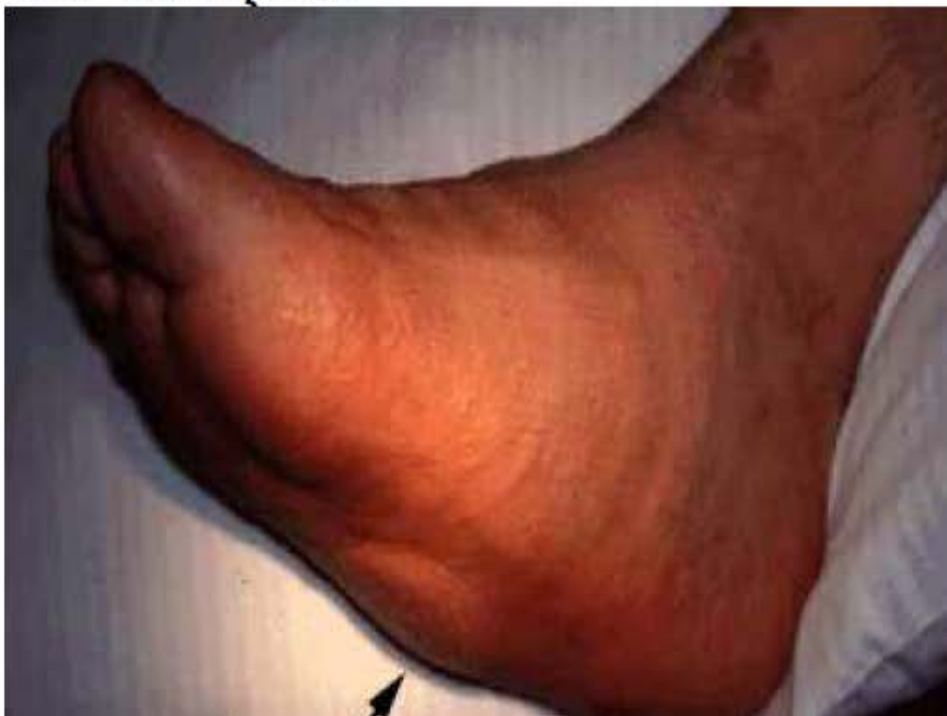
Diabetic foot dısorders: A clinical practıce guideline. THE JOURNAL OF FOOT & ANKLE SURGERY, VOLUME 45, NUMBER 5, 2006.

Kas dengesi ve yürüme bozulur.

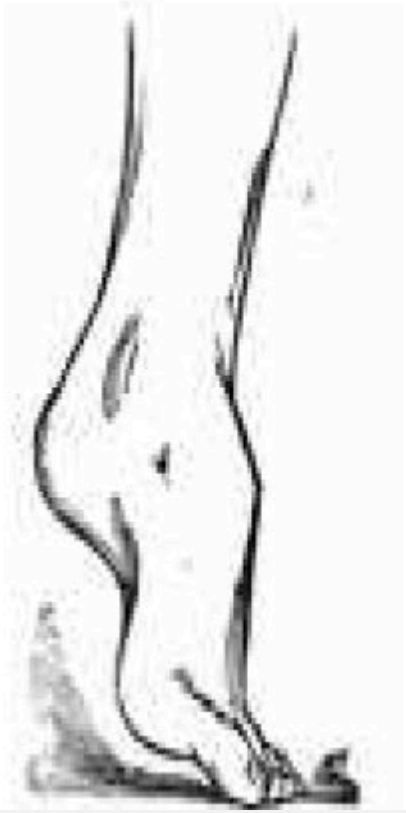
Ayakta şekil bozukluğu, iç kaslarda zayıflık ve küçük parmaklarda pençe şekli...

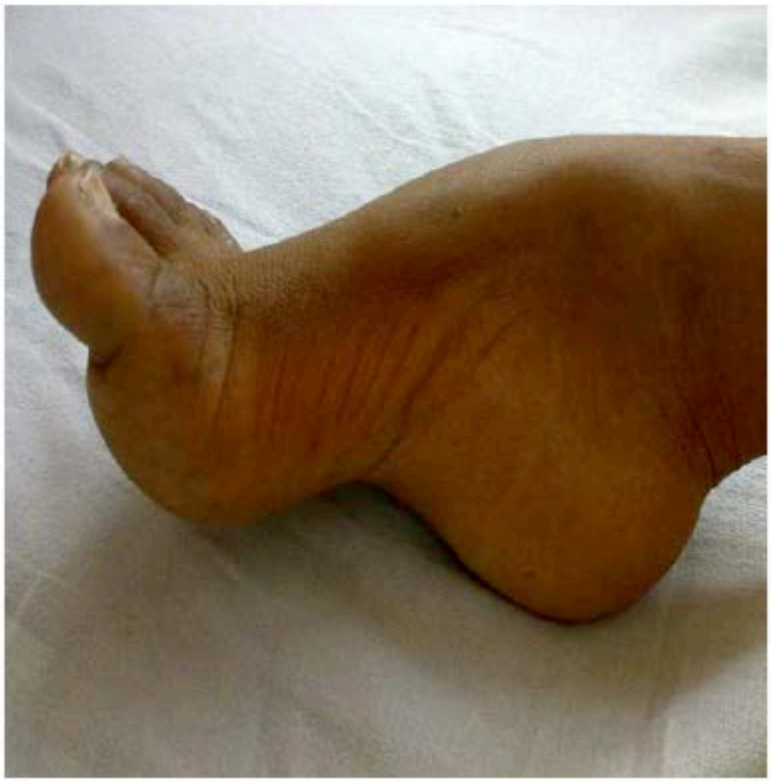
Şekil bozukluğu sonucu bası noktalarının dağılımı bozulur ve buralarda nasırlar oluşur.

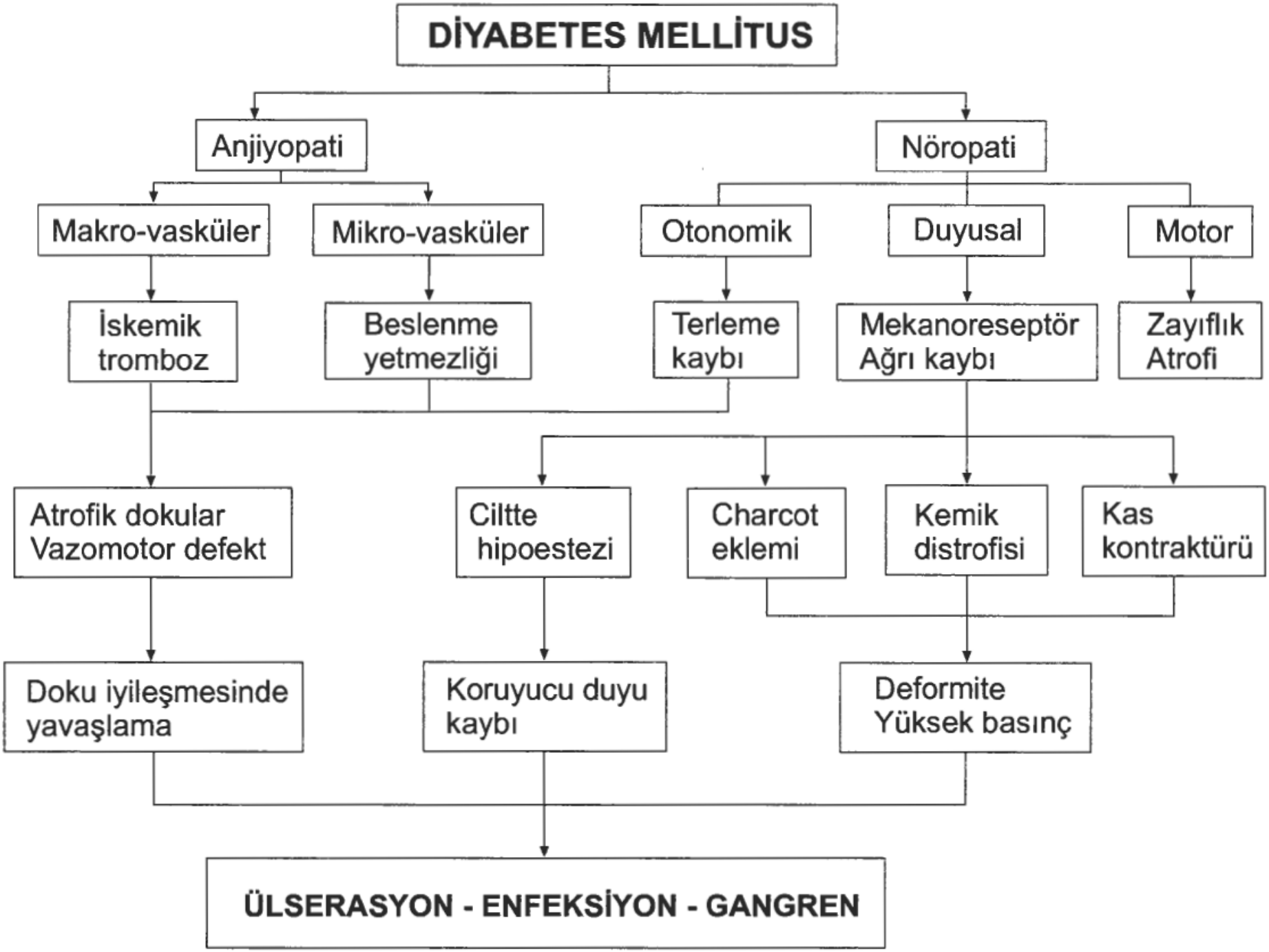




KOLLAJEN DOKUNUN GLİKOLİZASYONU






DİYABETES MELLİTUS
Anjiyopati
Nöropati
Makro-vasküler
Mikro-vasküler
Otonomik
Duyusal
Motor
İskemik tromboz
Beslenme yetmezliği
Terleme kaybı
Mekanoreseptör Ağrı kaybı
Zayıflık Atrofi
Atrofik dokular Vazomotor defekt
Ciltte hipoestezi
Charcot eklemi
Kemik distrofisi
Kas kontraktürü
Doku iyileşmesinde yavaşlama
Koruyucu duyu kaybı
Deformite Yüksek basınç
ÜLSERASYON - ENFEKSİYON - GANGREN

MİKROVASKÜLER PATOLOJİ

+

MAKROVASKÜLER PATOLOJİ

↓

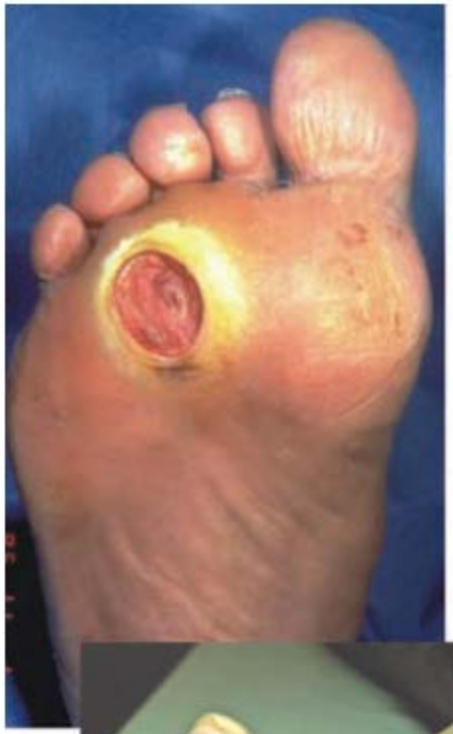
DOKULARDA İSKEMİ.

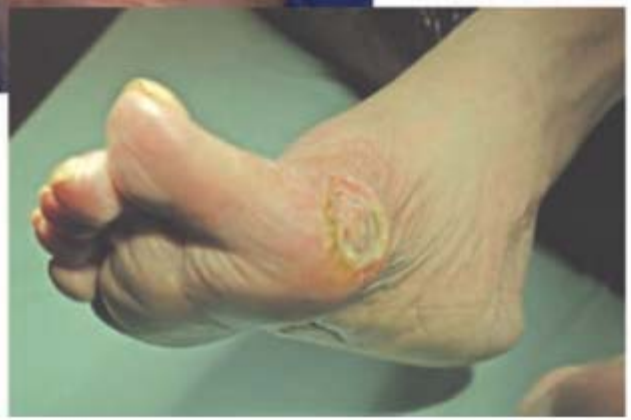
VASKÜLER YETERSİZLİK

- Diyabetiklerde büyük damarları tutan atherosklerotik tıkayıcı hastalık iskemik ülser gelişiminde esas rolü oynamaktadır

- Yapılan histolojik ve anjiografik değerlendirmeler, diabetik hastalarda tutulumun popliteal damar distalinde, tibial ve peroneal damarlarda segmental tutulum şeklinde olduğunu, fakat dorsalis pedis gibi daha distal damarlarda bu tutuluma çoğunlukla rastlanmadığını göstermektedir.

- Bu durum klinik açıdan distaldeki arterlere uygulanabilecek arteriyel rekonstrüksiyonlar (bypass operasyonları) açısından önemlidir.





Skin / Ulcer
- description, depth, location, classification

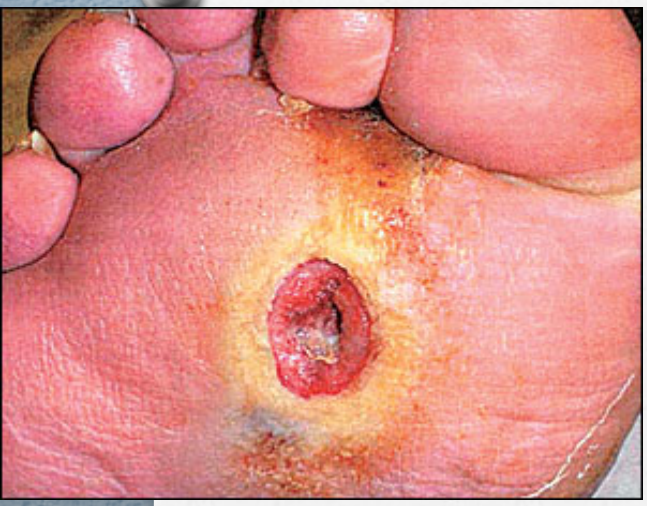
Infection
- gram stain, cultures, radiographs, scans

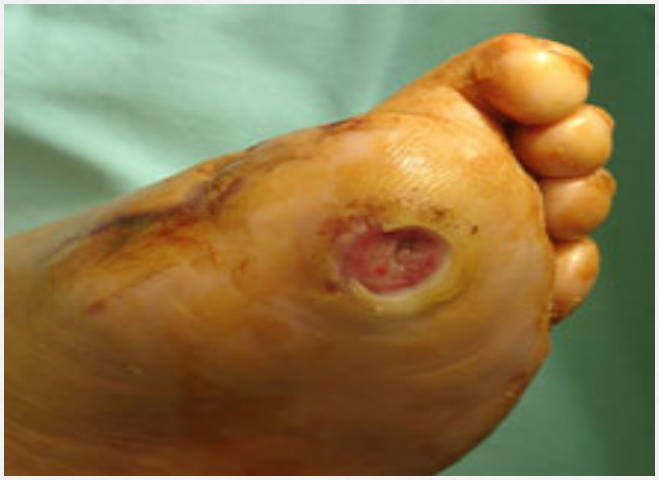
Vascular
- pulses, color, skin temperatures, Doppler, $TcPO_2$

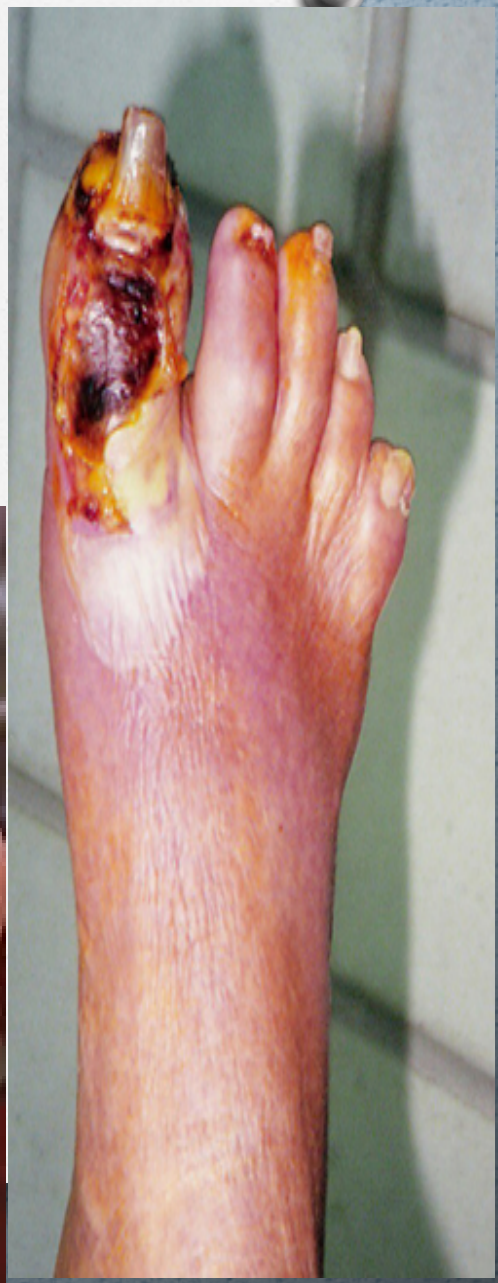
Neuropathy
- sensory disturbances, monofilament, VPT, DTRs

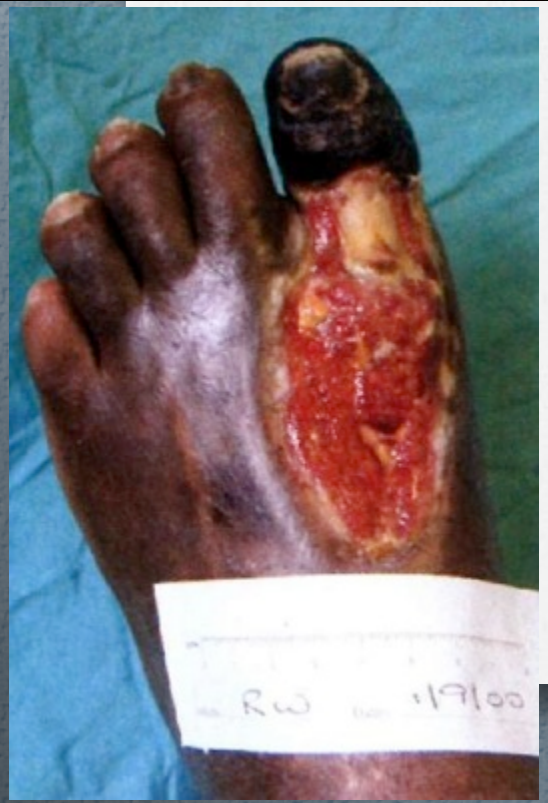
Deformity
- deformity, joint mobility, contractures

Etiology
- mechanical, thermal, chemical





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Diyabette Yara İyileşmesinde gecikme sebepleri

- Bazal mebran kalınlaşması → ülserin devam etmesine
- AGEs, TNF-α, IL-1 → kollagen sentez bozukluğu
- Yüksek glukoz → anormal proliferasyon
- Yüksek glukoz → kemotaksisin azalması, fagositoz azalması, bakteriyel öldürme yeteneğinin azalması
- Fibrinogen ve β2-macroglobulin değişiklik → iyileşme periyodunun uzamasına
- fibroblasts iyileşme peridunda defektif olması → yara yeri iyileşmesinde uzama meydana gelmesi

Citation: Diabetic Foot & Ankle 2013, **4**: 20872 - http://dx.doi.org/10.3402/dfa.v4i0.20872

HİPERGLİSEMİNİN TEDAVİSİ

- Metabolik dengenin sağlanması yara enfeksiyonunun kontrol altına alınması için şarttır.
- Kontrolsüz diyabette lökosit fonksiyonlarında bozulma olmaktadır.
- Normoglisemik durumun sağlanması veya glukoz düzeyinin en azından 200 mg/dl'nin altına düşürülmesi optimum yara iyileşmesi için bir gerekliliktir

Pomposelli JJ, Baxter JK, Babineau TJ, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. JPEN J Parenter Enteral Nutr, 1998; 22:77-81.


LOW RISK
HIGH RISK
NO RISK

RESEARCH ARTICLE

Diabetic Foot Complications and Their Risk Factors from a Large Retrospective Cohort Study

Risk factors	All diabetic foot		Foot ulcer		Gangrene		Amputation	
	Odds Ratio	[a]pvalue	Odds Ratio	[a]pvalue	Odds Ratio	[a]p-value	Odds Ratio	[a]pvalue
Charcot joint	42.53(18.16–99.62)	<0.0001	52.81(21.42–130.187)	<0.0001	-	-	30.42(8.22–112.62)	<0.0001
Peripheral vascular disease	14.47(8.99–23.31)	<0.0001	8.33(4.12–16.83)	<0.0001	62.07(24.17–159.40)	<0.0001	20.14(10.24–39.61)	<0.0001
Peripheral Neuropathy	12.06(10.54–13.80)	<0.0001	15.61(13.41–18.18)	<0.0001	6.55(3.51–12.22)	<0.0001	6.94(5.33–9.04)	<0.0001
DM Duration ≥10 yrs	7.22(6.10–8.55)	<0.0001	6.70(5.44–8.25)	<0.0001	4.00(2.23–7.18)	<0.0001	9.74(6.99–13.59)	<0.0001
Insulin use	4.69(4.28–5.14)	<0.0001	4.28(3.81–4.79)	<0.0001	4.36(3.00–6.33)	<0.0001	5.73(4.85–6.75)	<0.0001
Retinopathy	4.45(4.05–4.89)	<0.0001	3.93(3.49–4.43)	<0.0001	2.24(1.47–3.40)	<0.0001	6.24(5.31–7.32)	<0.0001
Nephropathy	4.05(3.66–4.47)	<0.0001	3.51(3.09–3.99)	<0.0001	2.59(1.67–4.03)	<0.0001	5.55(4.73–6.52)	<0.0001
Age ≥ 45 yrs	2.88(2.43–3.40)	<0.0001	2.48(2.03–3.03)	<0.0001	3.09(1.51–6.34)	<0.0001	4.03(2.86–5.66)	<0.0001
Cerebral vascular disease	2.81(2.31–3.43)	<0.0001	2.08(1.58–2.75)	<0.0001	7.62(4.34–13.36)	<0.0001	3.62(2.64–4.97)	<0.0001
Poor glycemic control	2.72(2.13–3.48)	<0.0001	3.35(2.47–4.54)	<0.0001	3.37(1.14–9.96)	0.029	1.44(0.91–2.30)	<0.0001
Coronary heart disease	2.24(1.98–2.54)	<0.0001	1.93(1.64–2.27)	<0.0001	2.83(1.72–4.67)	<0.0001	2.83(2.31–3.46)	<0.0001
Male gender	2.02(1.84–2.22)	<0.0001	1.99(1.77–2.24)	<0.0001	1.76(1.21–2.58)	0.003	2.14(1.81–2.52)	<0.0001
Smoking	1.54(1.29–1.83)	<0.0001	1.69(1.37–2.09)	<0.0001	1.98(1.02–3.85)	0.039	1.20(0.87–1.66)	0.260
Hypertension	1.51(1.38–1.65)	<0.0001	1.32(1.18–1.48)	<0.0001	2.16(1.48–3.15)	<0.0001	1.83(1.57–2.15)	<0.0001

DIABETES RESEARCH AND CLINICAL PRACTICE 114 (2016) 69–74

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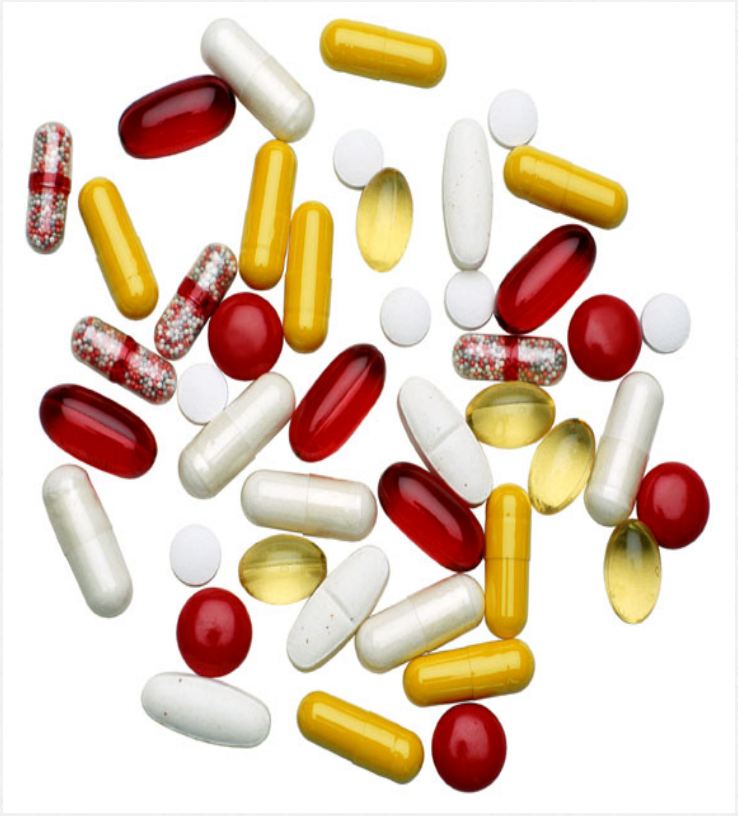
International Diabetes Federation

Factors determining the risk of diabetes foot amputations – A retrospective analysis of a tertiary diabetes foot care service

Table 2 – Factors associated with amputation in patients attending the multidisciplinary foot clinic.

	Amputations (n = 33)					Reference value	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Adjusted p value*
	No	%	Yes	%	Total				
Attendance rate									
<100%	54	72.0	21	28	75	100	2.56 (1.16–5.64)	3.84 (1.54–9.52)	0.0038
100%	79	86.8	12	13.2	91				
Charlson Index									
≤5	62	89.9	7	10.1	69	>5	0.31 (0.13–0.76)	0.32 (0.11–0.91)	0.0331
>5	71	74	25	26	96				
Hypertension									
No	33	97.1	1	2.9	34	Yes	0.09 (0.01–0.71)	0.078 (0.01–0.69)	0.0216
Yes	99	75.6	32	24.4	131				
Peripheral arterial disease									
No	98	83.8	19	16.2	117	Yes	0.47 (0.21–1.04)	0.89 (0.35–2.30)	0.811
Yes	34	70.8	14	29.2	48				
HbA1c (mmol/mol) [%]									
≤7.5	50	86.2	8	13.8	58	>58	0.52 (0.22–1.25)	2.96 (0.10–0.84)	0.0227
>7.5	82	76.6	25	23.4	107				
Previous revascularization									
No	128	82.6	27	17.4	155	Yes	0.14 (0.04–0.53)	0.08 (0.02–0.44)	0.0035
Yes	4	40	6	60	10				
Type of diabetes									
Type 1	21	15.9	10	30.3	31	Type 2	2.3 (0.96–5.52)	3.15 (1.10–9.0)	0.0321
Type 2	111	84.1	23	69.7	134				



Diabetologia (2014) 57:1703–1710
DOI 10.1007/s00125-014-3248-2

ARTICLE

Intensified insulin treatment is associated with improvement in skin microcirculation and ischaemic foot ulcer in patients with type 1 diabetes mellitus: a long-term follow-up study

Strict glycaemic control improves skin microcirculation in patients with type 2 diabetes: A report from the Diabetes mellitus And Diastolic Dysfunction (DADD) study

Diabetes & Vascular Disease Research
9(4) 287–295

DOI: 10.1177/1479164111432182
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Glucose-lowering treatment		
At randomization		
Insulin/oral (*n*)	0/10	0/10
Metformin (%)	9 (43)	7 (39)
Glimepiride/glipizide (%)	1 (5)	3 (17)
At end of study		
Insulin/oral (*n*)	21/8	0/18
Metformin *n* (%; mean dose in g/day)	8 (38; 2.0)	18 (100; 2.3)
Glimepiride/glipizide	0	0
Repaglinide *n* (%; mean dose in mg/day)	0	12 (67;2.1)
Insulin glargine (U/day; median dose and range)	30 (10–56)	–
Insulin aspart (U/day; median dose and range)	10 (0–30)	–

Strict glycaemic control improves skin microcirculation in patients with type 2 diabetes: A report from the Diabetes mellitus And Diastolic Dysfunction (DADD) study

Diabetes & Vascular Disease Research
9(4) 287–295

DOI: 10.1177/1479164111432182
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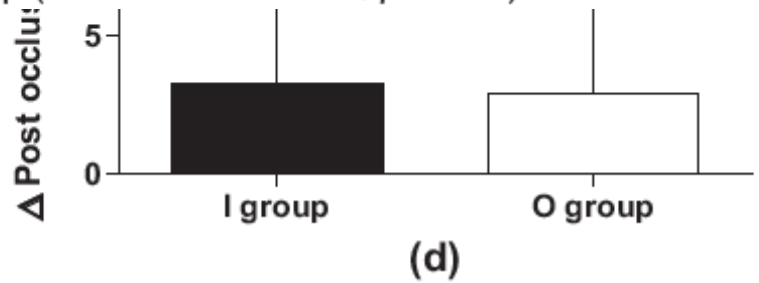
Results: Glucose control improved (reduction of HbA_{1c} I-group = -0.5%; O-group -0.7%; p=0.69). Microcirculation improved in the entire group (n=39) determined by foot Laser Doppler Fluxmetry (32.2±13.6 *vs.* 35.3±13.1 perfusion units; p<0.001) and Laser Doppler Fluxmetry following heating (68.8±34.0 *vs.* 69.3±25.1 PU; p=0.007). Improvement was more consistent with oral agents than insulin. Endothelial function expressed as flow-mediated dilatation decreased in the I-group (6.0±2.2 to 4.7±3.0%; p=0.037) but remained unchanged in the O-group (4.8±2.3 to 5.0±3.7%; n.s.).



Laser Doppler Fluxmetry following heating

Intensive versus conventional glycaemic control for treating diabetic foot ulcers (Review)

Cochrane Library

Cochrane Database of Systematic Reviews

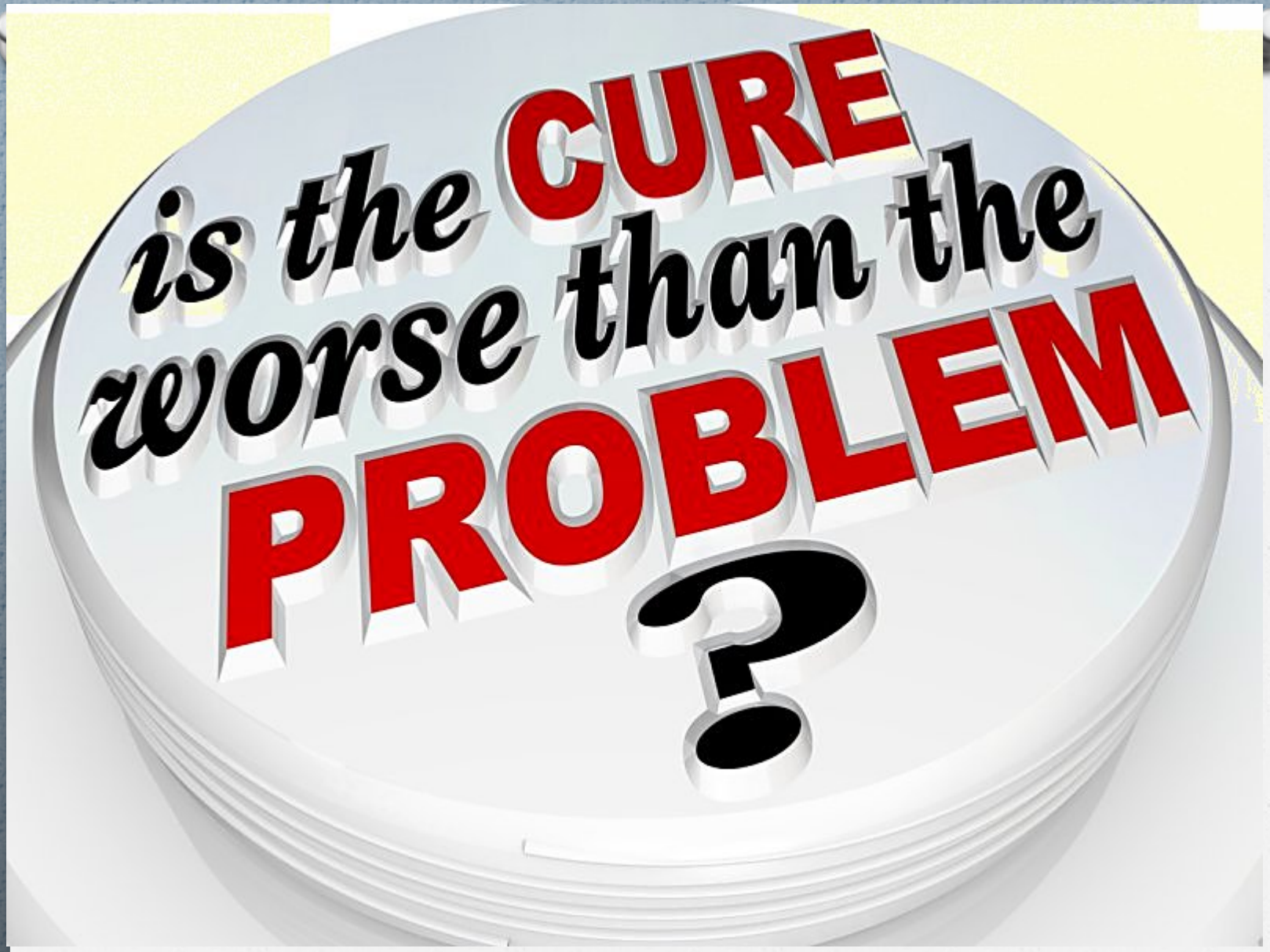
A recent observational study showed that HbA1c was an important clinical predictor of the rate of wound healing; with each 1% increase in HbA1c level associated with a decrease in the wound healing rate of 0.028 cm^2 per day (95% CI: 0.003 to 0.054)

AUTHORS' CONCLUSIONS

Implications for practice

The current review failed to find any randomised clinical trials with results. Therefore we are unable to conclude whether intensive glycaemic control when compared to conventional glycaemic control has a positive or detrimental effect on the treatment of foot ulcers. The exact role and place that intensive glycaemic control may have on treating foot ulcers remains to be resolved.

SIKI KAN ŞEKERİ KONTROLÜ


is the CURE
worse than the
PROBLEM
?

DIABETES/METABOLISM RESEARCH AND REVIEWS
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SUPPLEMENT ARTICLE

In-hospital metabolic regulation in patients with a diabetic foot ulcer: is it worthwhile?

- **American Association of Clinical Endocrinologists/American Diabetes Association and the Endocrine Society Practice Guideline**
- active foot ulceration; Both guidelines
- set pre-meal targets at <7.8 mmol/L (140 mg/dL)
- random blood glucose of <10.0 mmol/L. (180 mg/dl)

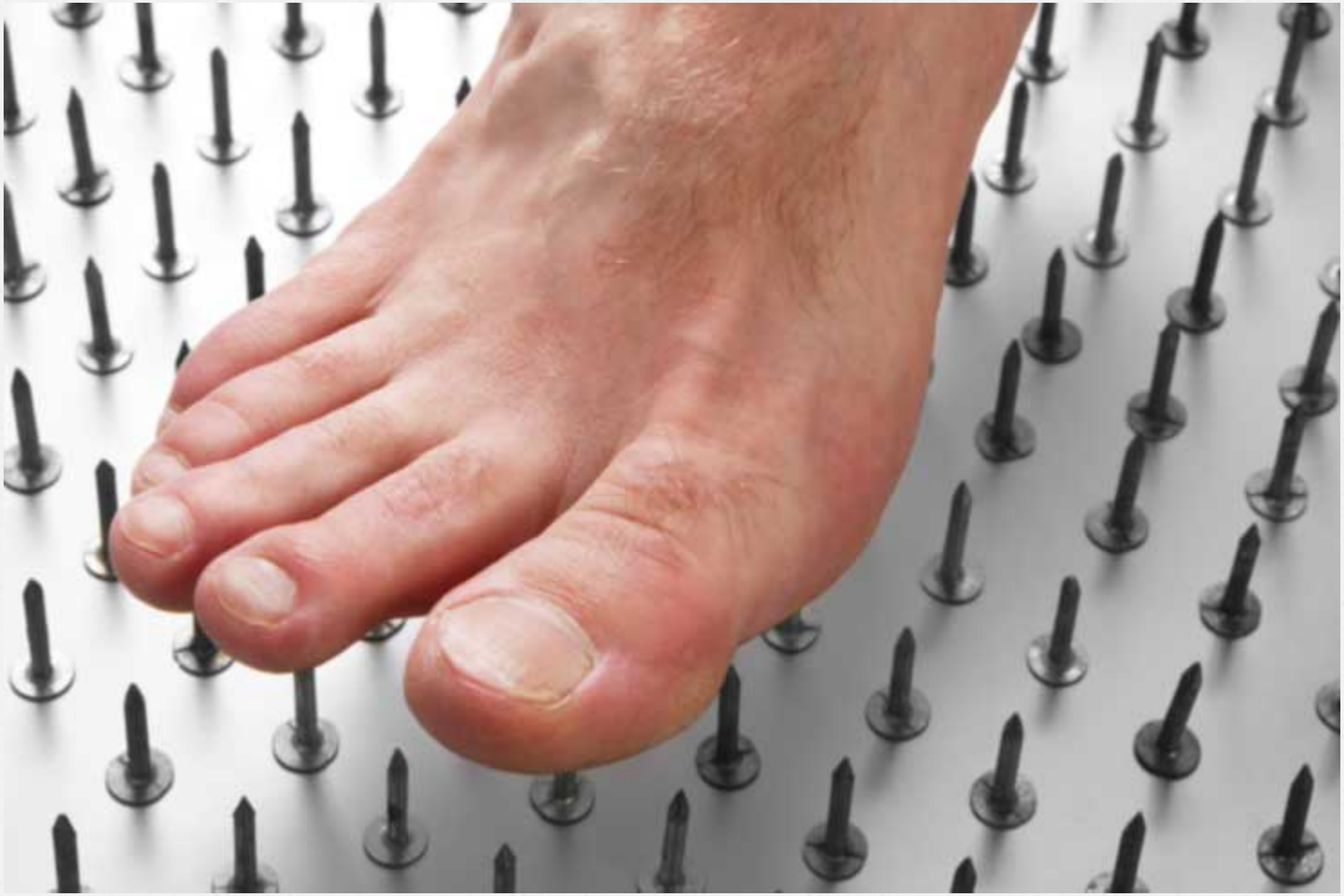
KAN ŞEKERİNİN ANİ DÜŞÜRÜLMESİ SAKINCALI MI?

Treatment induced diabetic neuropathy– a reversible painful autonomic neuropathy

Similarly, the underlying pathophysiology of this acute treatment induced neuropathy is not known. Proposed mechanisms include the development of epineurial arterio-venous shunting causing endoneurial ischemia,[2] apoptosis due to sudden glucose deprivation,[26] recurrent hypoglycemia resulting in microvascular neuronal damage,[27, 28] ectopic pain from regenerating nerve fibers,[19] ectopic firing of regenerating axon sprouts[19] (most likely due to channel or receptor upregulation) and insulin induced reduction in endoneurial oxygen tension due to opening of arteriovenous shunts.[2] Nerves of streptozotocin-induced diabetic rats appear resistant to this hypoxic effect of insulin, but with control of hyperglycemia this susceptibility re-appears.[29] A direct relationship to hypoglycemia seems unlikely; hypoglycemic neuropathy preferentially involves the motor nerves.[30] While the possibility of a nutritional deficiency has been raised when treatment induced neuropathy occurs in association with weight loss, the absence of weight loss in our subjects makes that etiology unlikely.

We and others recently have observed an increase in proinflammatory cytokines in association with experimental hypoglycemia.[31, 32] Elevated cytokine levels, including interleukin-1β, interleukin-6 and tumor necrosis factor-α have been associated with painful neuropathy.[33-35] We have also observed impaired autonomic function after experimental hypoglycemia.[36] Thus, acute treatment induced neuropathy and worsening of retinopathy after intensive glycemic control may have a common underlying pathophysiological mechanism that involves upregulation of proinflammatory cytokines. Recent data suggest

TİP 2 DİYABETTE SIKI KAN ŞEKERİ KONTROLÜ İLE PERİFERİK NÖROPATİ GEÇEBİLİR Mİ?



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ORIGINAL ARTICLE

Current glycaemic control has no impact on the advancement of diabetic neuropathy

Outcomes: Summary of ACCORD, ADVANCE and VADT

	ACCORD*	ADVANCE	VADT
A1C (%) (Intensive vs. Std)	6.4 vs.7.5 †	6.4 vs. 7.0 †	6.9 vs. 8.4 †
Nonfatal MI (%) (Intensive vs. Std)	3.6 vs 4.6% †	2.7 vs.2.8	6.3 vs. 6.1
CV Death (%) (Intensive vs. Std)	2.6 vs. 1.8 † (1.35 Hazard Ratio)	4.5 vs. 5.2	2.1 vs.1.7
Microvascular	-	nephropathy ↓ 21% retinopathy ↓ 5% NS	-
Take home	↓ risk MIs, but ↑ risk death in intensive arm	Glucose control has no impact on CV events, but ↓ Microvascular risk	Glucose control has no impact on CV events

*ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial halted intensive glucose group (2/6/08)

† significant difference between intensive and standard group

ACCORD Study Group, *NEJM* 2008, 358:2545-2559.
ADVANCE Collaborative Group, *NEJM* 2008, 358:2560-2572.
VADT Study Results ADA Scientific Session San Francisco, 2008
In Press, Diabetes Obesity and Metabolism, 2008


Prevention
is better
than cure!


TEŞEKKÜRLER