Diabetology

Diabetes mellitus (DM)

- Chronic disease
- High morbidity, mortality, invalidity
- More than 700 000 patients in the Czech Republic
- Banting and Best – isolation of insulin (isletin) from canine pancreas

Insulin (I) and contrainsular hormones

- I – a small protein, chains A, B linked by disulphide bridges
- B (beta) cells of the islets of Langerhans
- A (alpha) cells: glucagon
- D (delta) cells: somatostatin
- PP cells: pancreatic polypeptide
- C peptide: combination of the A, B chains in proinsulin

I - secretion

- **Synthesis and secretion of I** – rise of ATP - glucose
- **Other nutrients** – ketone bodies, FA's, AA's
- **Hormonal and nervous influences**

Stimulation: growth h., glucagon, GLP-1, gastrointestinal peptide, secretin, gastrin, VIP

Inhibition: somatostatin, adrenaline, noradrenaline, prostaglandin E

Stimulation: parasympathetic system, beta-adrenerg.

I - secretion

- **Total daily production of I** – 20-40 IU

Basal: 50% (as measured by C peptide on an empty stomach), stimulated 50% (by C peptide after the meals)

- **Effect of I**

Insulin receptor

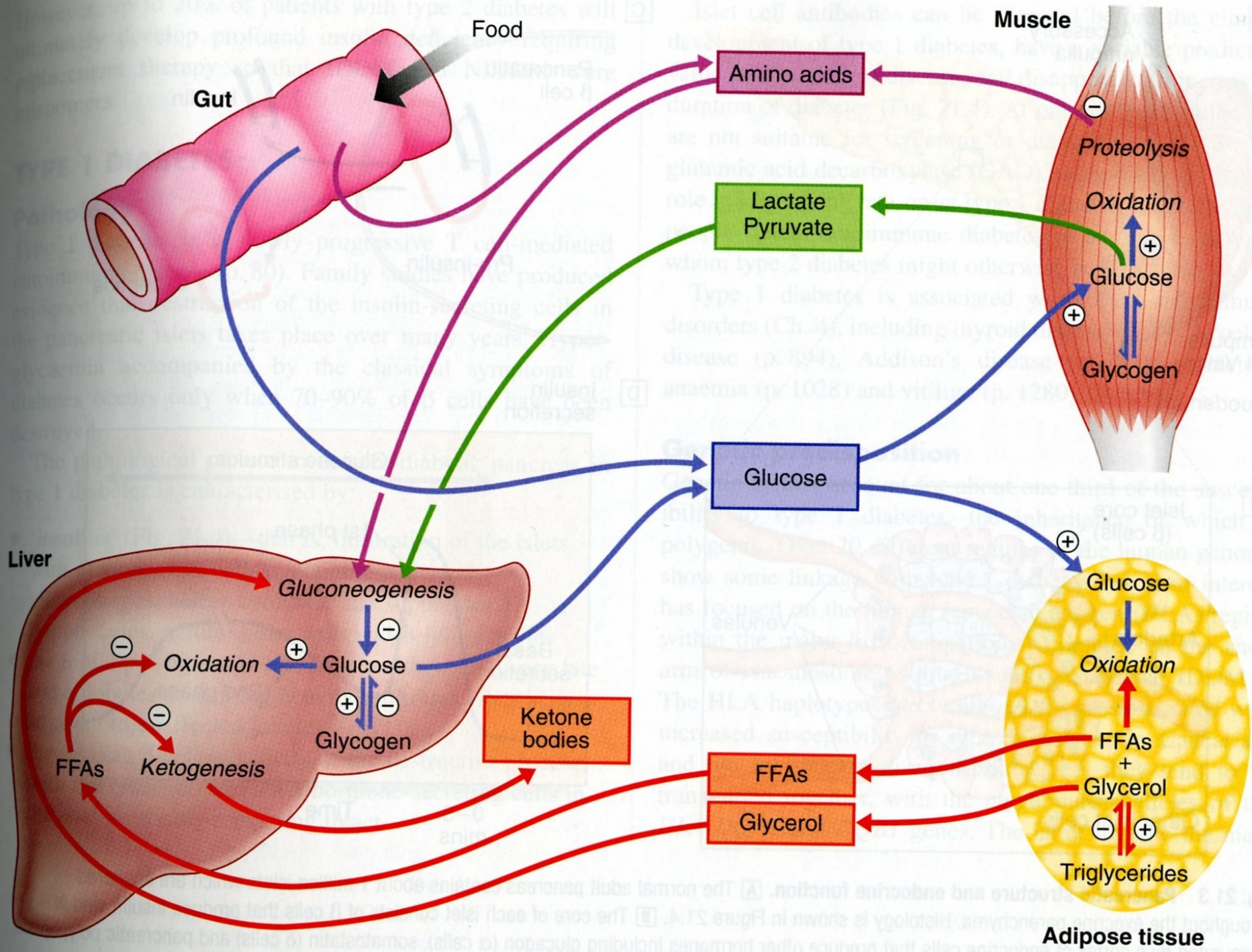
- entry of glucose (G) into the cell
- activation of intracellular enzymes

I - effect

- **Stimulation of anabolic and blockade of catabolic processes** in the metabolism of glucose, fats, and proteins
- **Target tissues**: muscles, adipose tissue, liver

I - effect

- Liver: glycogen synthesis, proteosynthesis, lipogenesis, blockade of glycogenolysis, gluconeogenesis, ketogenesis
- Muscles: GLUT-4 activation - increased uptake of glucose, glycogen synthesis, proteosynthesis
- Adipose tissue: inhibits lipolysis, increased lipogenesis


Food
Gut
Muscle
Amino acids
Proteolysis
Oxidation
Lactate
Pyruvate
Glucose
Glycogen
Glucose
Liver
Gluconeogenesis
Oxidation
Glucose
Glycogen
Ketone bodies
FFAs
Ketogenesis
FFAs
Glycerol
Glucose
Oxidation
FFAs
+
Glycerol
Triglycerides
Adipose tissue

DM classification

- **Type 1 DM**

A – autoimmunity conditional

B - idiopathic

- **Type 2 DM**

A – predominantly insulin-resistant

B – predominantly insulin-deficient

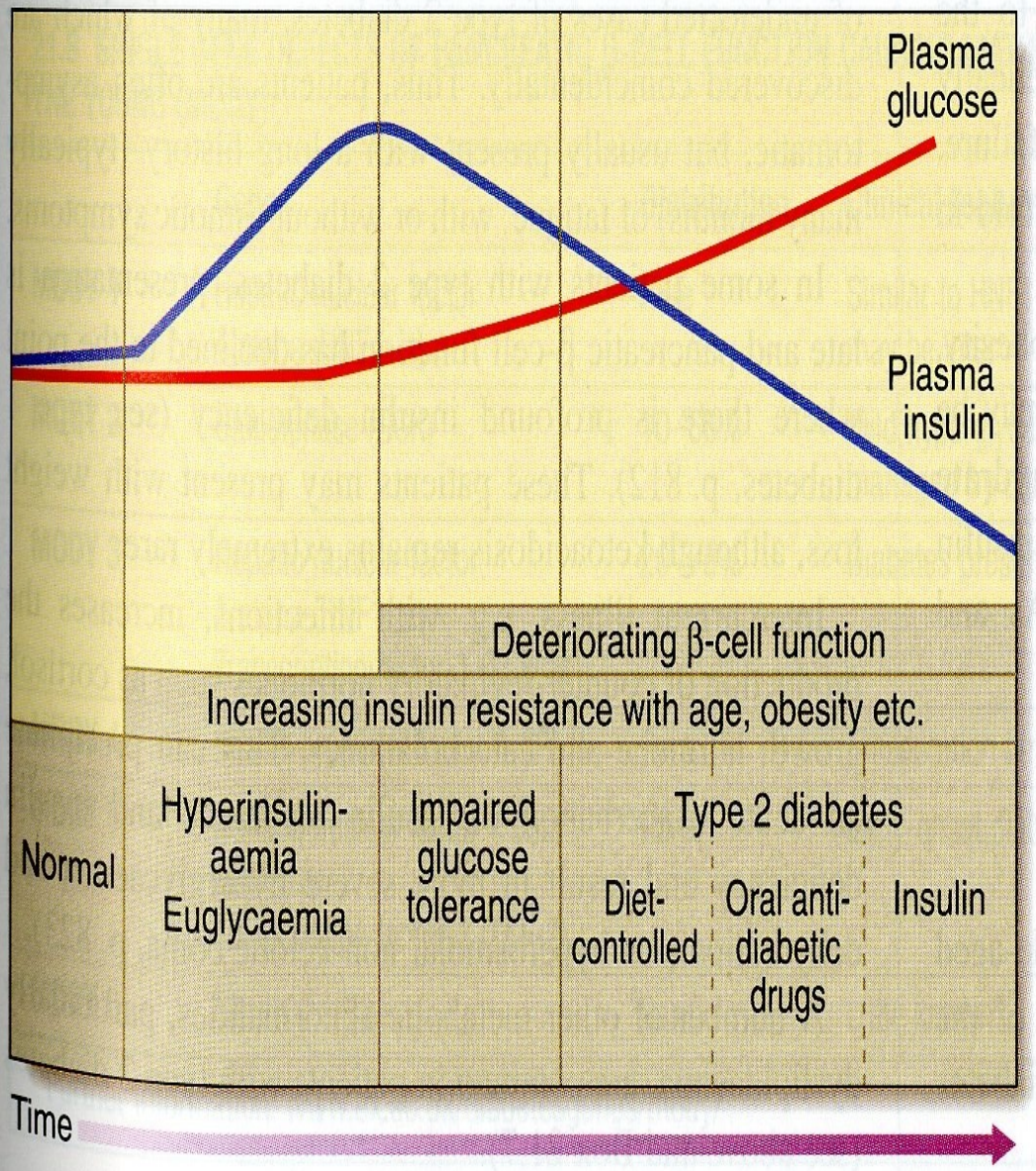


Fig. 21.6 Natural history of type 2 diabetes. In the early stage of the disorder the response to progressive insulin resistance is an increase in insulin secretion by the pancreatic cells, causing hyperinsulinaemia. Eventually the β cells are unable to compensate adequately and blood glucose rises, producing hyperglycaemia. With further β-cell failure (type 2 diabetes) glycaemic control deteriorates and treatment requirements escalate.

DM classification

- **The other specific types of DM**
- **Gestational DM (GDM)**
- **Critical disorders of glucose homoeostasis**

1. Increased glycaemia on an empty stomach
2. Impaired glucose tolerance (IGT)

Type 1 DM

- **Selective destruction of beta cells** = absolute lack of insulin = hyperglycaemia
- **A- autoimmune** – the most frequent in our country, in genetically predisposed people – HLA-DR/DQ

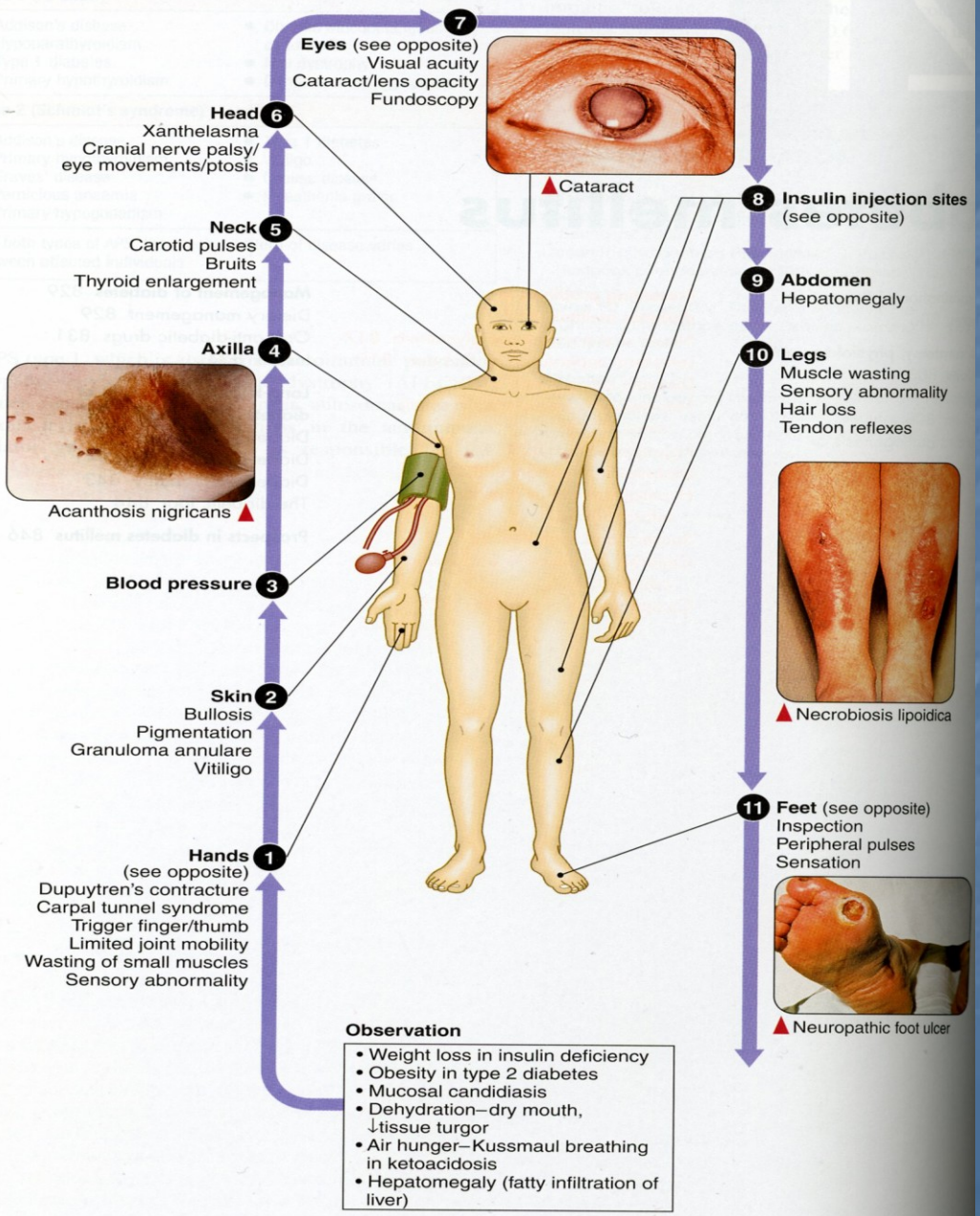
  risky DR3,DR4,DQA1,DQB1, protective DR2

  presence of circulating antibodies – 90% DM1 preclinically
- **B- idiopathic** (non-immune)

Type 1 DM

- **Triggering mechanism of autoimmune reaction** – infection, most frequently viral; toxic influences
- **Insulinitis –** clinical manifestations only after the disappearance of 40-80% of B cells depending on age
- **LADA –** in older age deceleration up to cessation of the destructive autoimmune process

CLINICAL EXAMINATION OF THE PATIENT WITH DIABETES



Type 1 DM - clinical picture

Typical symptoms

- Thirst, polydipsia
- Nycturia, polyuria
- Weight loss
- Fatigue
- Disturbance of consciousness
- Acetone odour
- Blurred vision

Other symptoms

- Recurrent infections
- Periodontitis, cariogenicity
- Symptoms of DM complications: polyneuropathic, potency disorders, affection of sight, GIT problems

Type 1 DM - clinical picture

- Hyperglycaemia, dehydration
- Metabolic acidosis, ketosis, acidotic Kussmaul respiration
- I is missing = increased unused glucosis, escalated gluconeogenesis
- Increased osmolarity = osmotic diuresis, polyuria
- Release of FA's, liver – ketogenesis from acetyl-CoA, acetoacetic acid, 3-hydroxybutyric acid
- Abdominal pain up to pseudoperitonitis diabetica

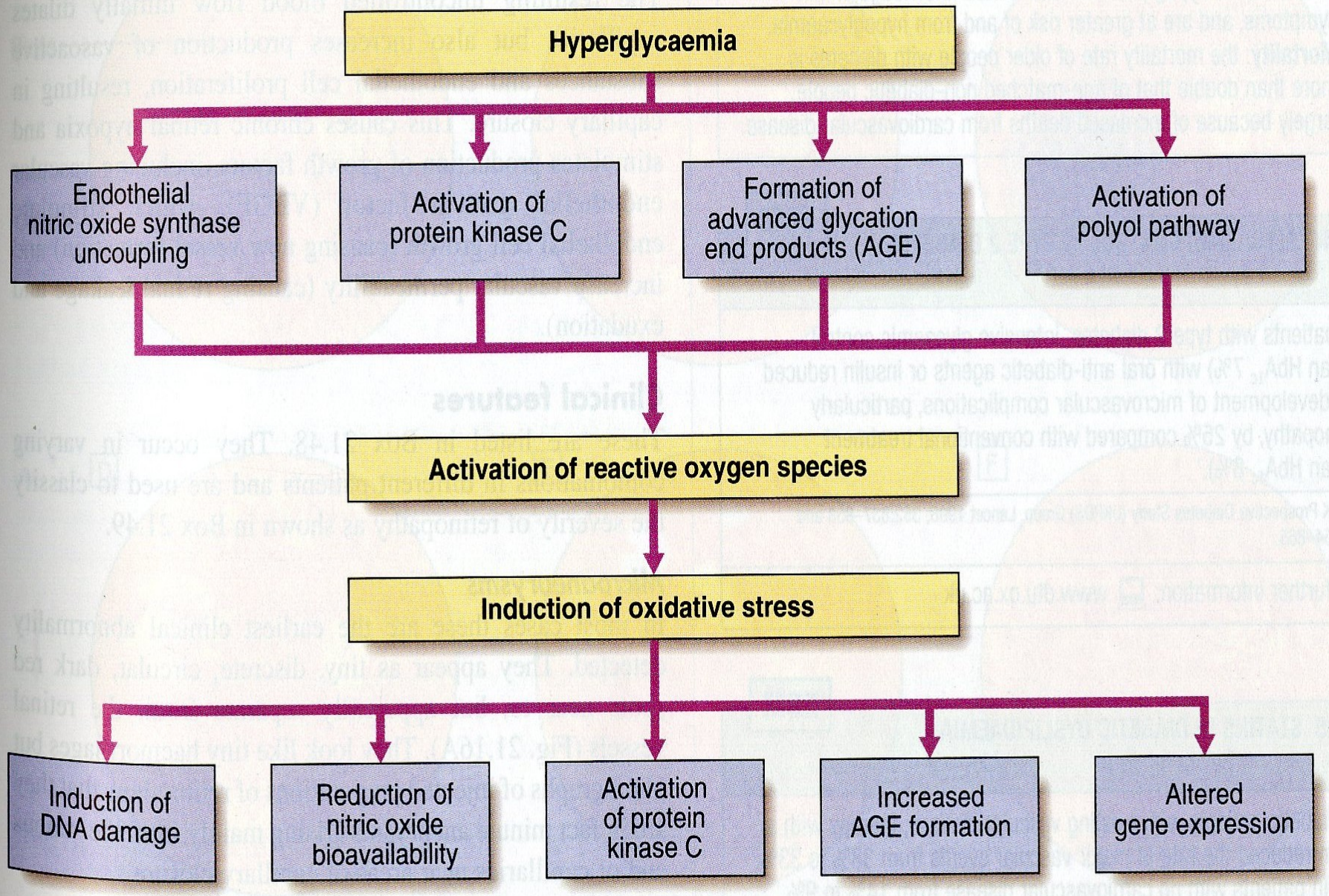


Fig. 21.15 The roles of hyperglycaemia-induced accumulation of reactive oxygen species and oxidative stress in causation of diabetic vascular complications. The induction of oxidative stress causes haemodynamic changes and endothelial and vascular dysfunction, leading to vascular damage.

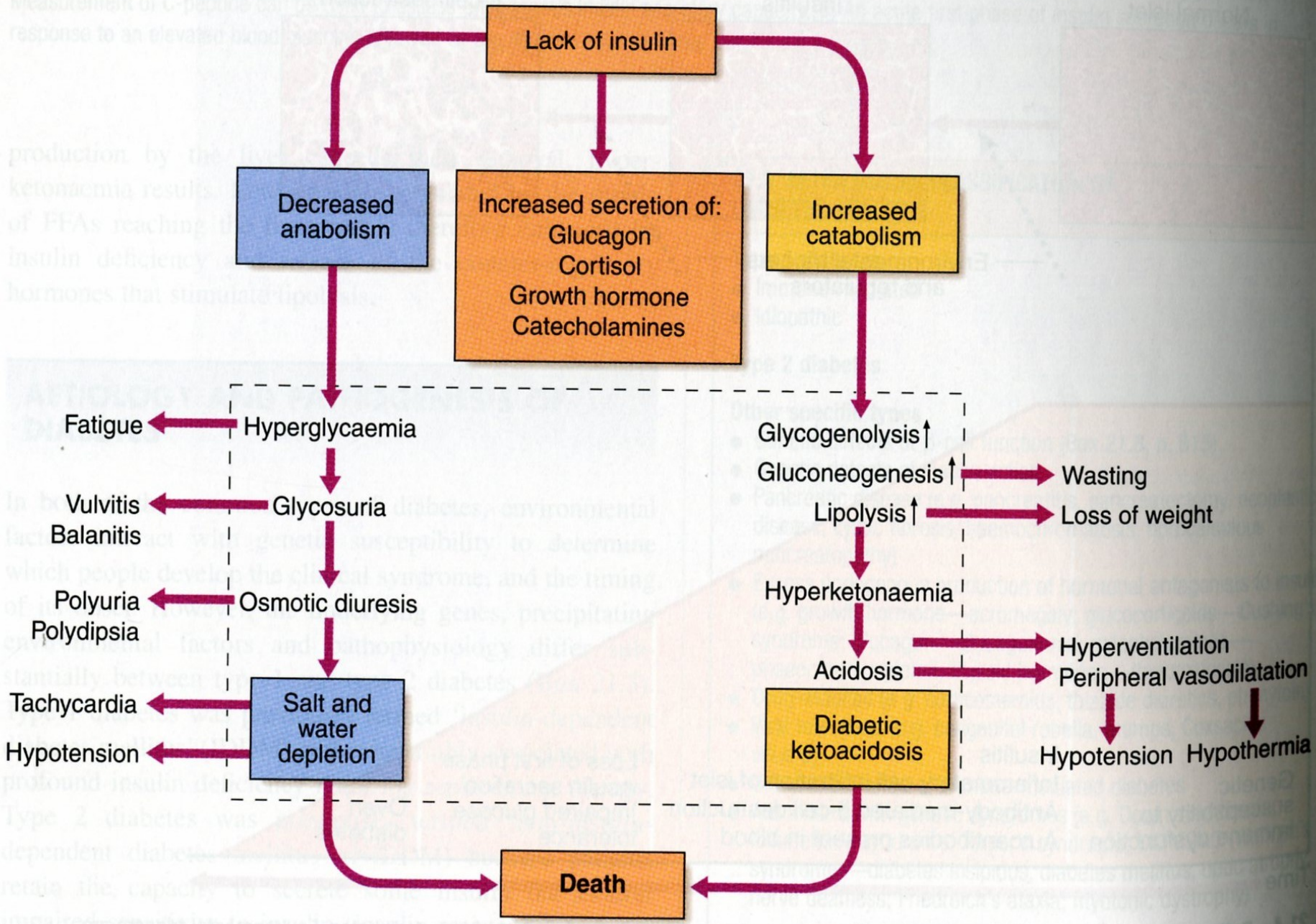


Fig. 21.5 Pathophysiological basis of the symptoms and signs of uncontrolled diabetes mellitus.

Type 1 DM - laboratorial monitoring

- Glycaemia: fasting and postprandial, HBA1c, glycosuria, ketonuria
- Astrup, Na, K, Cl, Ca, Mg, P
- Lipids, decreased activity of LPL – increased TG and VLDL
- C peptide on an empty stomach and after exertion, IRI
- Anti-GAD 65 A, ICA, IAA
- Microalbuminuria, proteinuria, creatinine clearance, examinations: neurology, ophthalmology, vascular

Type 1 DM - treatment

- **Insulin (I)** administered exogenously, simulation of physiological secretion

Prandial – preprandially with short-term I before the main meals

Basal – long-acting I, most often in the evening

Human insulins (HMR, HM NPH), insulin analogues

Type 1 DM - treatment

- **Insulin pump (CSII)** – microdoses of I in a basal and bolus programme
- **Indication:**

Unsatisfactory compensation, repeated hypoglycaemia

Progression of microvascular complications

Pregnancy planning

Transplantation of pancreas and/or beta cells

Type 1 DM - treatment

- **Diet**

Diabetic diet No. 9 – 275 or 325 g saccharides per day

8400 or 9850 kJ/d

3 main meals, snacks in the meantime. Second supper

Restriction of free saccharides, high-calorie fatty meals

Glucose meter - self-monitoring

Type 1 DM - treatment

- **Movement regimen**

Bring into harmony the movement regimen with the insulin regimen - danger of severe hypoglycaemias

Inadequate acute exhausting stress

Adequate long-time aerobic stress

Type 1 DM - compensation criteria and treatment goals

	-		-
Gl.: fasting	4.0-6.0	6.0-7.0	over 7.0
postprandial	5.0-7.5	7.5-9.0	over 9.0
HbA1c (%)	under 4.5	4.5-6.0	over 6.0
Total chol.	under 4.5	4.5-5.0	over 5.0
HDL	over 1.1	1.1-0.9	under 0.9
LDL	under 2.6	2.6-3.0	over 3.0
TG	under 1.7	1.7-2.0	over 2.0

Type 1 DM - compensation criteria and treatment goals

	+		-
BMI (kg/m2)			
Males	21-25	25-27	over 27
Females	20-24	24-26	over 26
BP	under 130/80	-	over 130/80 ?

Type 2 DM

- Overweight, obesity
- Lipid spectrum changes
- Hyperinsulinaemia, insulin resistance
- Hypertension, increased level of uric acid
- Hypercoagulation state

Metabolic sy (insulin resistance sy, Reaven syndrome)

Type 2 DM - pathogenesis

- **Insulin resistance (IR)**
- **Insulin deficiency**
- **Diminished utilization of glucose in muscles**
- **Resistance of adipose tissue to insulin**

  Increased FFA's, depositing of fat in the liver and muscles
- **Disturbance of the incretin system**
- **Disturbance of the alpha cells with hyperglucagonaemia**
- **Altered adaptive response of the kidneys to hyperglycaemia and disturbance of the renal reabsorption of glucose**
- **Manifestations of IR in the brain – appetite regulation, thermogenesis**

DM 2 type – RF S

Inconspicuous manifestation; complications in 7% on diagnosis

- Obesity
- Age over 40 years
- HT
- HLP
- Gestational DM
- Foetal macrosomia

Comparative Clin. Features of Type 1 and Type 2 DM

Type 1

- Typical age at onset

Type 2

Type 2 DM - manifestations

- **Symptoms of diabetic syndrome**
- Lower metabolic lability
- No inclination to ketoacidosis
- Acute hyperglycaemic complication – hyperglycaemic hyperosmolar coma

Type 2 DM - diagnostics

- Fasting glycaemia higher than 7.0 mmol/l
- Fasting glycaemia 5.7-7.0 mmol/l – oGTT
- oGTT (75 g glucose in aqueous solution), 2 h test higher than 11.1 mmol/l – DM
  7.9 – 11.1 = impaired glucose tolerance

Type 2 DM - therapy

- **Low-energy diet + movement**
- **Fluid intake – 2.5 l minimum**
- **Peroral antidiabetics (PAD)**
  - Affecting insulin secretion (secretagogues)
  - Affecting insulin resistance
  - Affecting absorption of saccharides from the GIT

Type 2 DM – medicaments affecting insulin (I) secretion

Sulphonylurea derivatives

- **Increase insulin secretion, 2nd-generation preparations**

Glibenclamide (Maninil), glipizide (Minidiab), gliclazide (Diaprel), gliquidone (Glurenorm), glimepiride (Amaryl)

The least possible doses 1-2x daily

Drug of choice in non-obese T2DM diabetics

Type 2 DM – medicaments affecting insulin (I) secretion

Non-sulphonylurea-type insulin secretagogues (so-called fast insulin secretagogues) (glinides)

- **They affect only stimulated (postprandial) secretion of insulin**

Repaglinide (Novonorm)

Nateglinide (Starlix)

Preprandially 3x per day in non-obese patients

Gliptins (DDP-4 inhibitors)

- Increase in the GLP-1 activity
- Stimulation of insulin secretion – via beta cells
- Suppression of glucagon secretion - alpha cells
- Influence on both fasting and postprandial glycaemia
- Combination with SU as well as MTF
- Sitagliptin (Januvia), Vildagliptin (Galvus)
- Linagliptin (Trajenta), Alogliptin (Nesina)

Type 2 DM – medicaments affecting insulin resistance(IR)

Biguanides

- Influence on liver IR, less on peripheral IR
- Metformin (Glucophage, Siofor, Metformin)
- Lactate acidosis
- CI – diseases of the liver and kidneys, states associated with a risk for tissue hypoxia = respiratory, circulatory insufficiency
- 1-2x d, 500-3000 mg/d, obese diabetics

Type 2 DM – medicaments affecting insulin resistance(IR)

Insulin sensitizers

- Influence on peripheral IR
- Thiazolidinediones – rosiglitazone (Avandia), pioglitazone (Actos) - efficient in muscular and adipose tissues
- Demanding in terms of price
- Intolerance of metformin
- Combined therapy

Type 2 DM – medicaments affecting saccharide absorption from the GIT

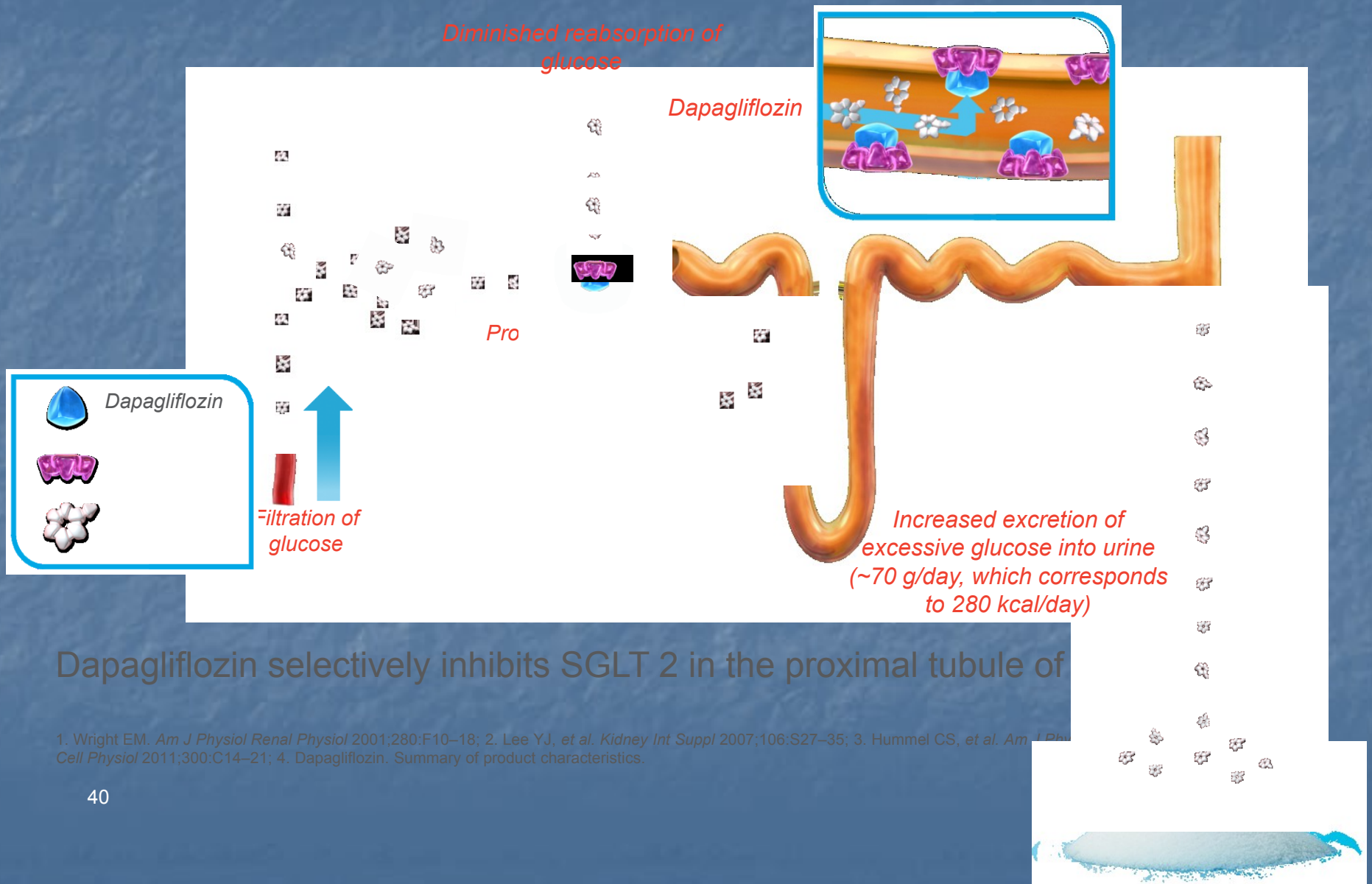
Alpha-glucosidase inhibitors

- **Deceleration of the breakdown of disaccharides =** deceleration of the postprandial increased glucose level
- **Disadvantage** – fermentative dyspepsias = flatulence, diarrhoea
- **Acarbose (Glucobay)** 3x daily

Type 2 DM – GLP-1 analogues

- Incretin antidiabetics, s.c.
- GLP-1 agonists: Exenatide (Byetta 2xd, Bydureon 1x per week)
- GLP-1 analogues: Liraglutide (Victoza 1xd)
- Low risk of hypoglycaemia: hypergl. - stimulated by beta cells, inhibited by alpha cells, normogl.- zero effect
- Weight loss – GLP-1 acts in the CNS + deceleration of stomach evacuation
- Natriuretic effect - drop of BPs
- Combination therapy with MTF, SU, TZD

Gliflozins: a novel, insulin-independent mechanism of lowering hyperglycaemia in type 2 DM[1-4]



Dapagliflozin selectively inhibits SGLT 2 in the proximal tubule of

1. Wright EM. *Am J Physiol Renal Physiol* 2001;280:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;106:S27–35; 3. Hummel CS, *et al. Am J Ph*
Cell Physiol 2011;300:C14–21; 4. Dapagliflozin. Summary of product characteristics.

Type 2 DM – combination therapy with PAD

- **Enhancement and supplementation of the effect**
- **Fixed combination**

Glibenclamid + metformin (Glibomet)

Rosiglitazone + metformin (Avandamet)

Sitagliptin + MTF (Janumet)

Vildagliptin + MTF (Eucreas)

Type 2 DM – insulin therapy

Combined therapy

- Combination of SU with a dose of intermediate-acting I for the night
- Combination of premixed I in two doses + metformin
- Preprandially 3x daily administered short-acting I + metformin

Secondary DM - the other specific types of DM

- Defect of the genetic determinant
- Impaired effect of I itself
- Disease of tissues associated with the insulinogenic tissue (pancreas)
- Chemical substances and hormones enhancing IR or blocking insulin secretion

Secondary DM - the other specific types of DM

- **Hereditary type of diabetes - MODY**

20th to 25th year of life - disturbance of insulin receptors – type A IR

- **Chronic diseases of the pancreas**

Chronic pancreatitis, ca of the pancreas, cystic fibrosis, haemochromatosis, surgery of the pancreas

Secondary DM - the other specific types of DM

- **Endocrinopathy**

Overproduction of counterregulatory hormones:

Diseases of the thyroid, pheochromocytoma, Cushing sy, acromegaly, glucagonoma

Glucocorticoids, diuretics, BB, psychotropic substances

Gestational DM

- Intolerance of G in pregnancy, especially in its second half
- Usually disappears after childbirth
- Incidence 3-4%
- IR after 20th week – high concentration of counterinsular hormones – placental lactogen, cortisol, oestrogen

Gestational DM

- Character of type 2 DM, increased postprandial glycaemia
- RF's:

  DM in family history, obesity, more than 35 years of age, glycosuria in previous pregnancy, delivery of a foetus over 4000 g
- Fasting oGTT 5.6 and higher; after 2 hrs 7.7
- Diet, insulin (fasting up to 5.3, postprand. up to 7.8)

Critical disorders of glucose homoeostasis

- Increased risk for development of all types of DM
- Association with MS, thus IR
- Increased risk of cardiovascular complications
- Fasting G 6.1 – 6.9; G in 2nd hour of oGTT 7.8 - 11.1 mmol/l
- Dispensing care, diet, weight loss

Acute complications of DM
Ketoacidotic hyperglycaemic coma

- Acute complication of type 1 DM
- Metabolic acidosis with the rise of ketone bodies, hyperglycaemia, deficit in water and ions
- Polyuria, polydipsia, dehydration, hypotension
- Ketoacidosis – nausea vomiting, acetone odour in the breath, dyspnoea

Ketoacidotic hyperglycaemic coma

- **Kussmaul respiration, signs of dehydration**
- **K depletion,** during therapeutic correction of acidosis, K is shifted intracellularly – a dramatic fall of K
- **Osmotic diuresis** – loss of Cl, Mg, Ca, phosphates

Ketoacidotic hyperglycaemic coma

- **Insulin i.v.** a bolus of 8 IU, cont. 4-8 IU/h
- **Fluids + ions**

Phys. sol. 1000 ml in 1st hour, then 500 ml for 5-8h

Glycaemia less than 15 mmol/l – 5% G

Supplementation with K: 20 mmol/h

- **Metabolic acidosis**

Correction with pH less than 7.0, $NaHCO_3$

Non-ketoacidotic hyperosmolar coma

- Complication of type 2 DM, serious prognosis
- Extreme hyperglycaemia (even more than 50 mmol/l), dehydration
- Frequent development of renal insufficiency
- Hyperosmolality (more than 340 mmol/kg)
- Fluids i.v., up to 10 l minimum, K, insulin

Lactacidotic coma

- **Metabolic acidosis – lactate accumulation**
- **Type A – presence of tissue hypoxia**

Anaemia, heart failure, shock

- **Type B without tissue hypoxia**

Diseases – DM, liver disorders

Toxic influences – alcohol, biguanides

Unsatisfactory treatment – alkalization of $NaHCO_3$, hydrogen carbonate dialysis

Hypoglycaemia and hypoglycaemic coma

- 3.3 mmol/l in the capillary plasma
- Mild – can be managed by the patient himself/herself
- Severe – help from outer environment is necessary
- Physical load, omission of a meal, increase of insulin
- Tremulousness, cold sweat, tachycardia, hunger
- Neuroglycopenic symptoms - headache, affection of fine motor activity, blurred vision
- Glucagon 1 mg i.m., 50 ml of 40% G

Chronic complications of DM

- Diabetic nephropathy
- Diabetic retinopathy
- Diabetic neuropathy
- Macrovascular complications – ischaemic heart disease, ischaemic diseases of the lower limbs, vascular diseases of the brain

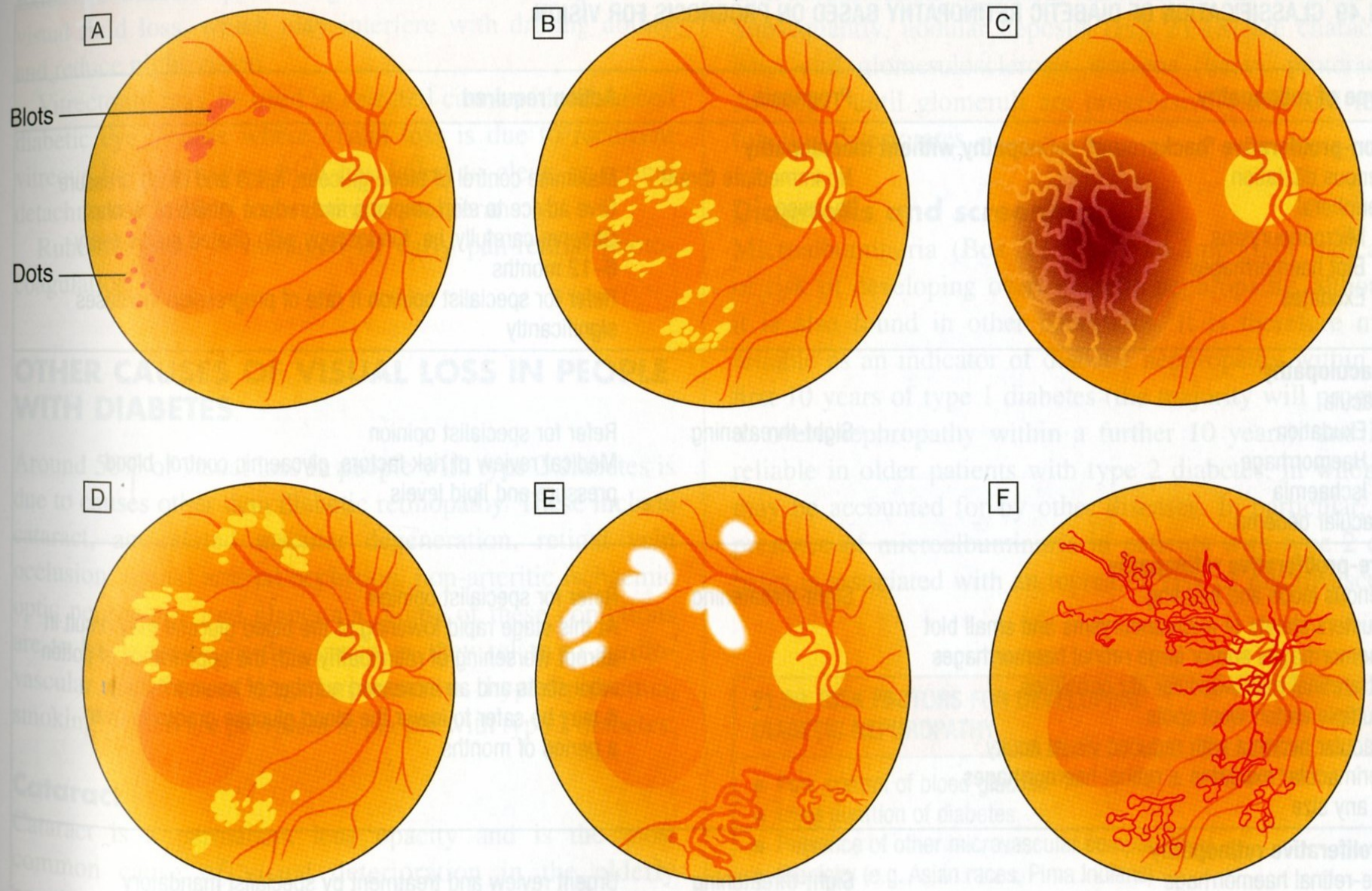


Fig. 21.16 Diagrammatic representation of diabetic eye disease. A Background diabetic retinopathy showing microaneurysms and blot haemorrhages. B Background retinopathy showing exudates. C Maculopathy showing oedema. D Maculopathy with exudates. E Pre-proliferative retinopathy showing venous changes and cotton wool spots. F Proliferative retinopathy showing neovascularisation.

Diabetic foot

- Affection of lower limbs in DM distally from the ankle
- Diabetic gangrene in 5.6%, amputation in 18.5% of diabetic foot patients
- Haemorheologic deviations + hypoxia of peripheral tissues
- Types include: neuropathic, angiopathic, mixed

Diabetic foot

- **Diabetic polyneuropathy**

The most frequent cause of ulcerations

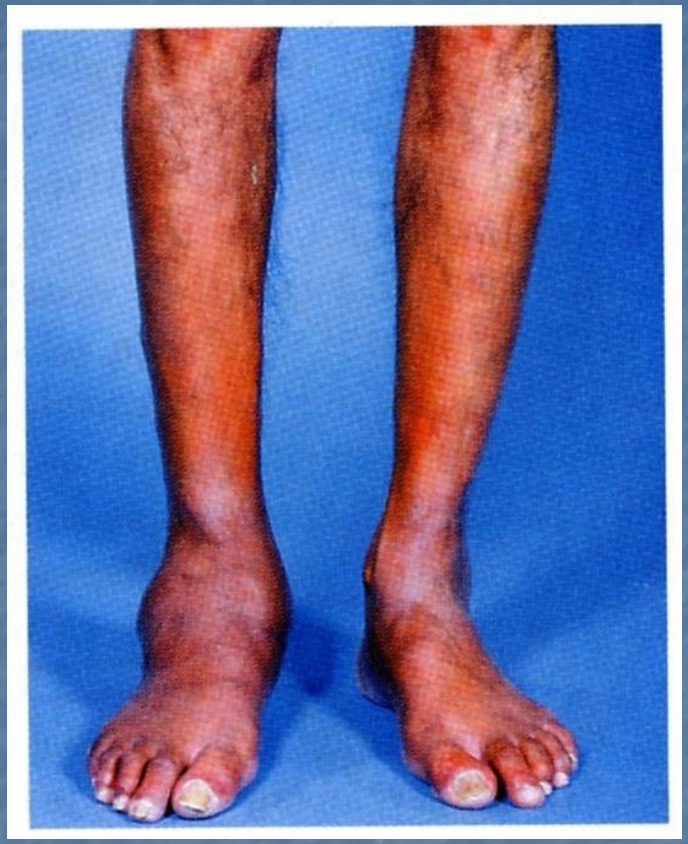
Diminished sensation of pain, temperature, pressure

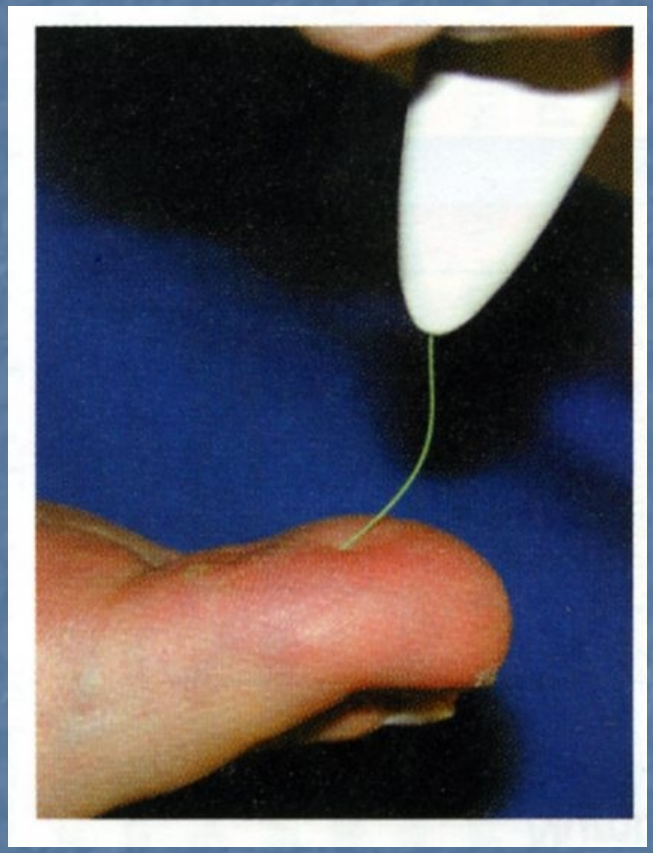
Muscular atrophy, impaired arches of the foot

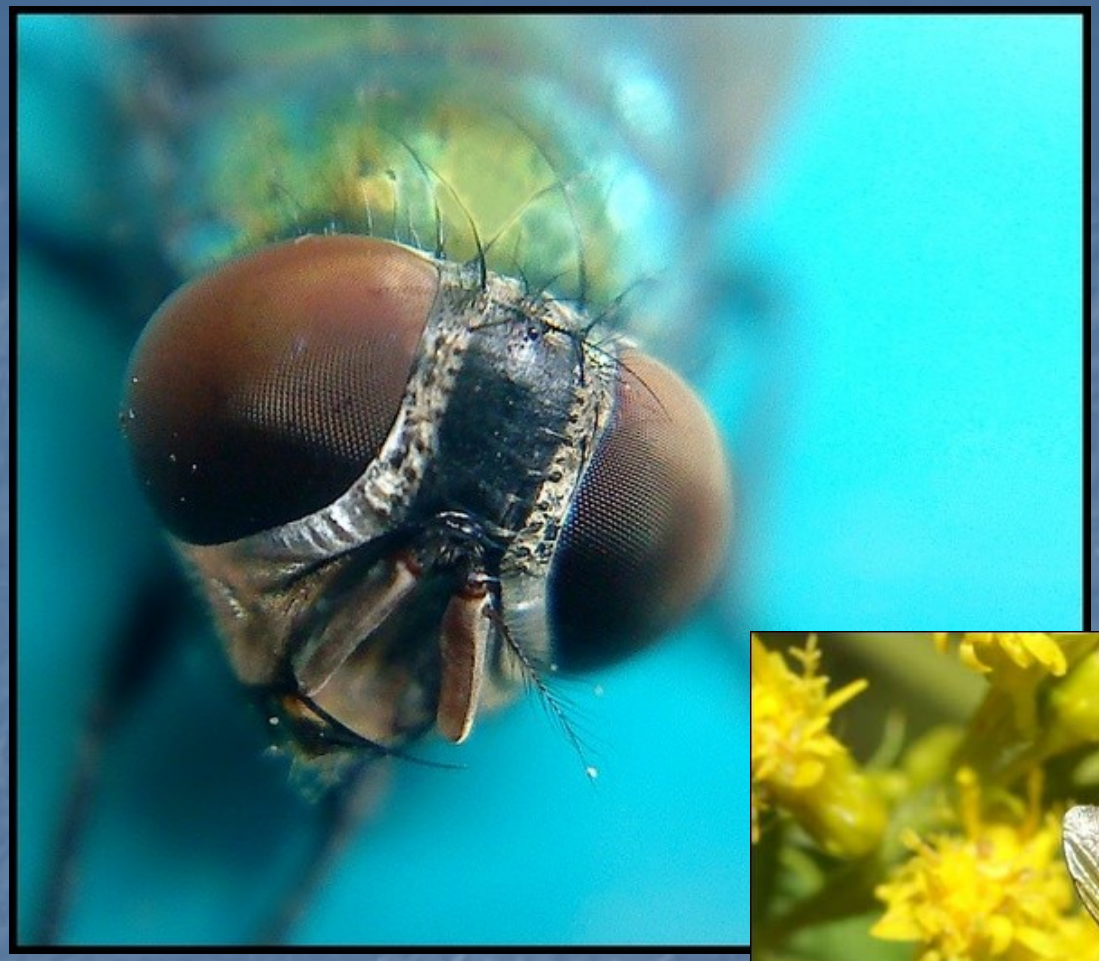
Charcot's arthropathy

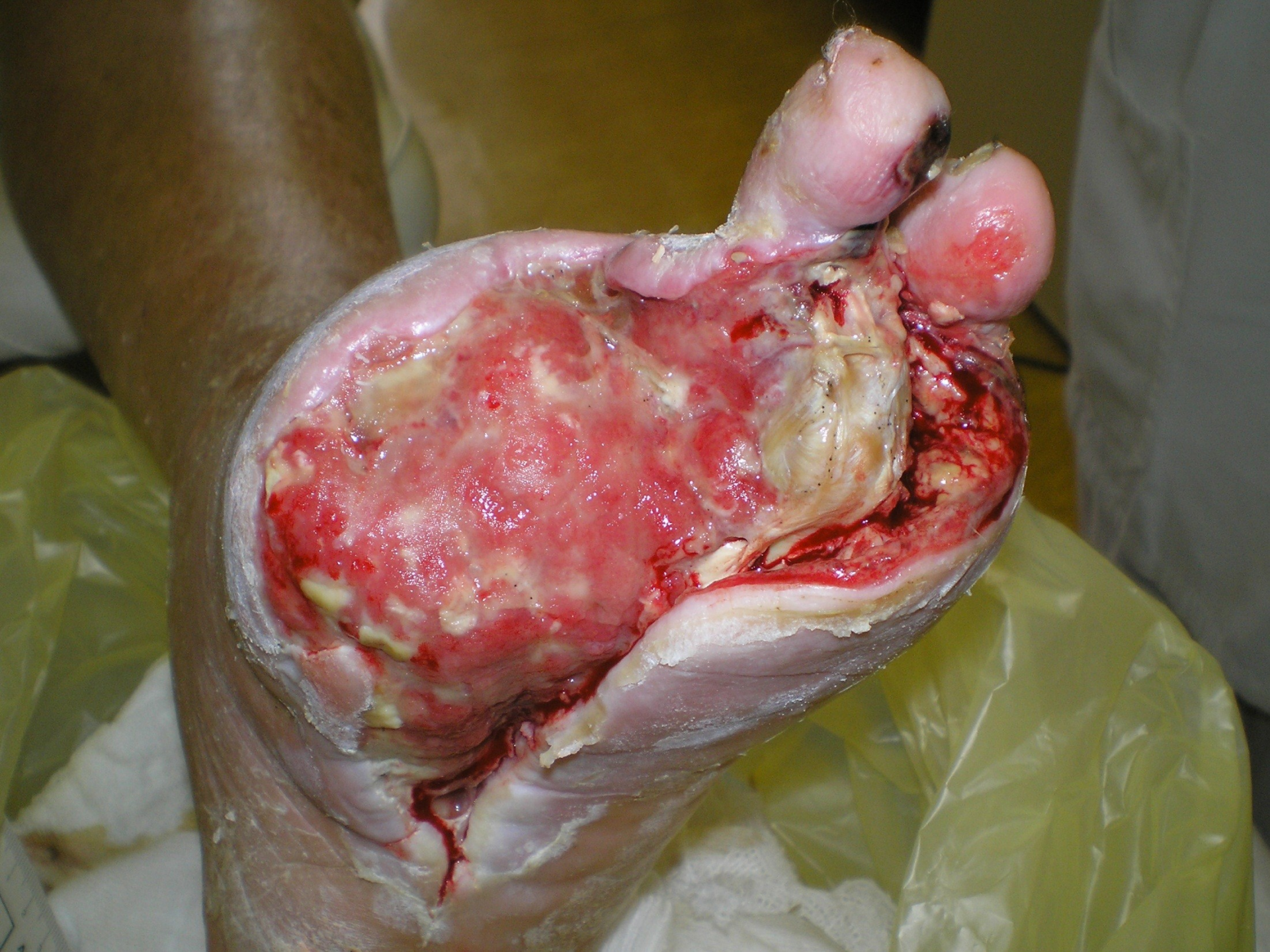
- **Diabetic angiopathy**

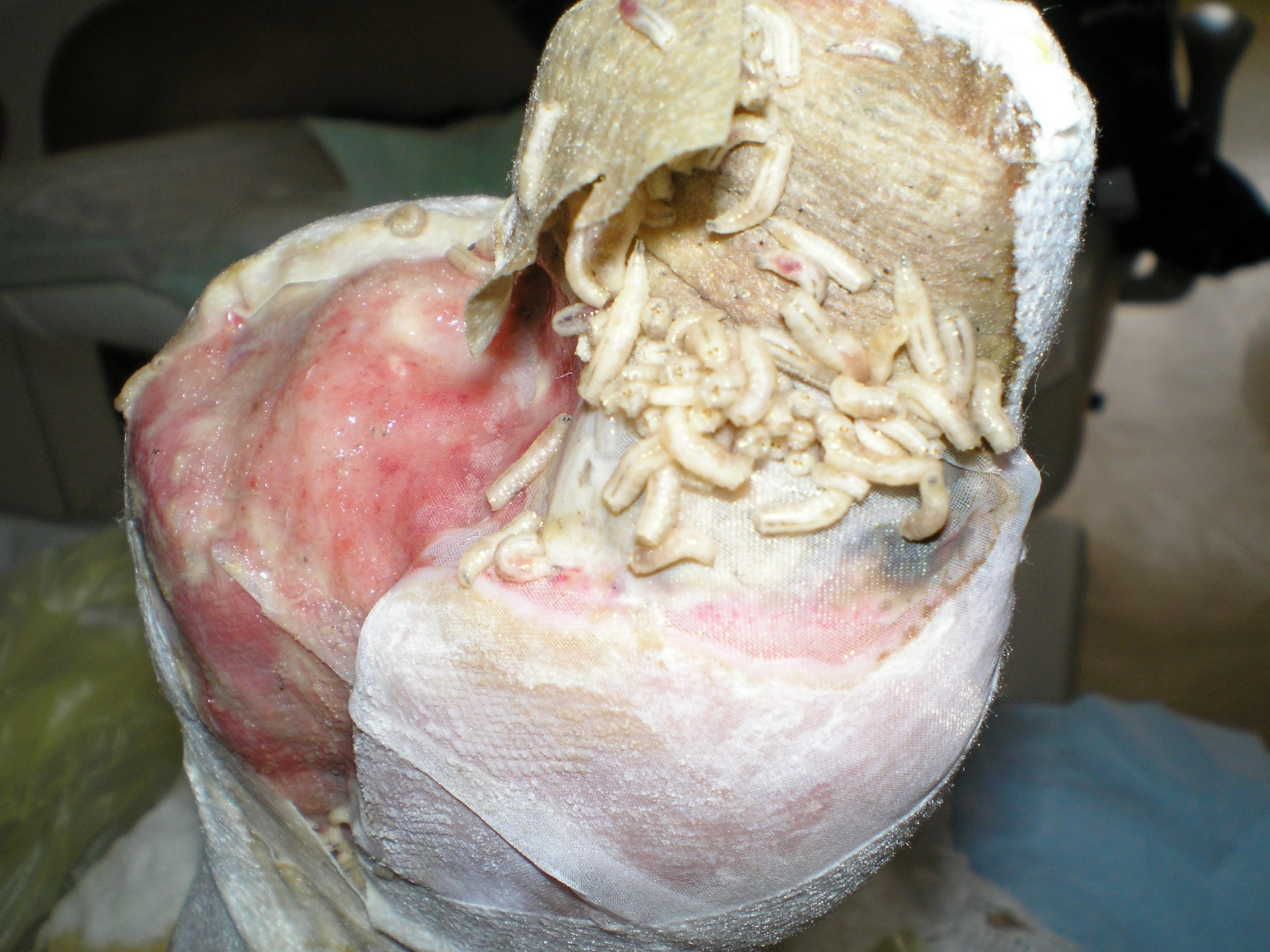
Mediocalcinosis, microangiopathy, macroangiopathy

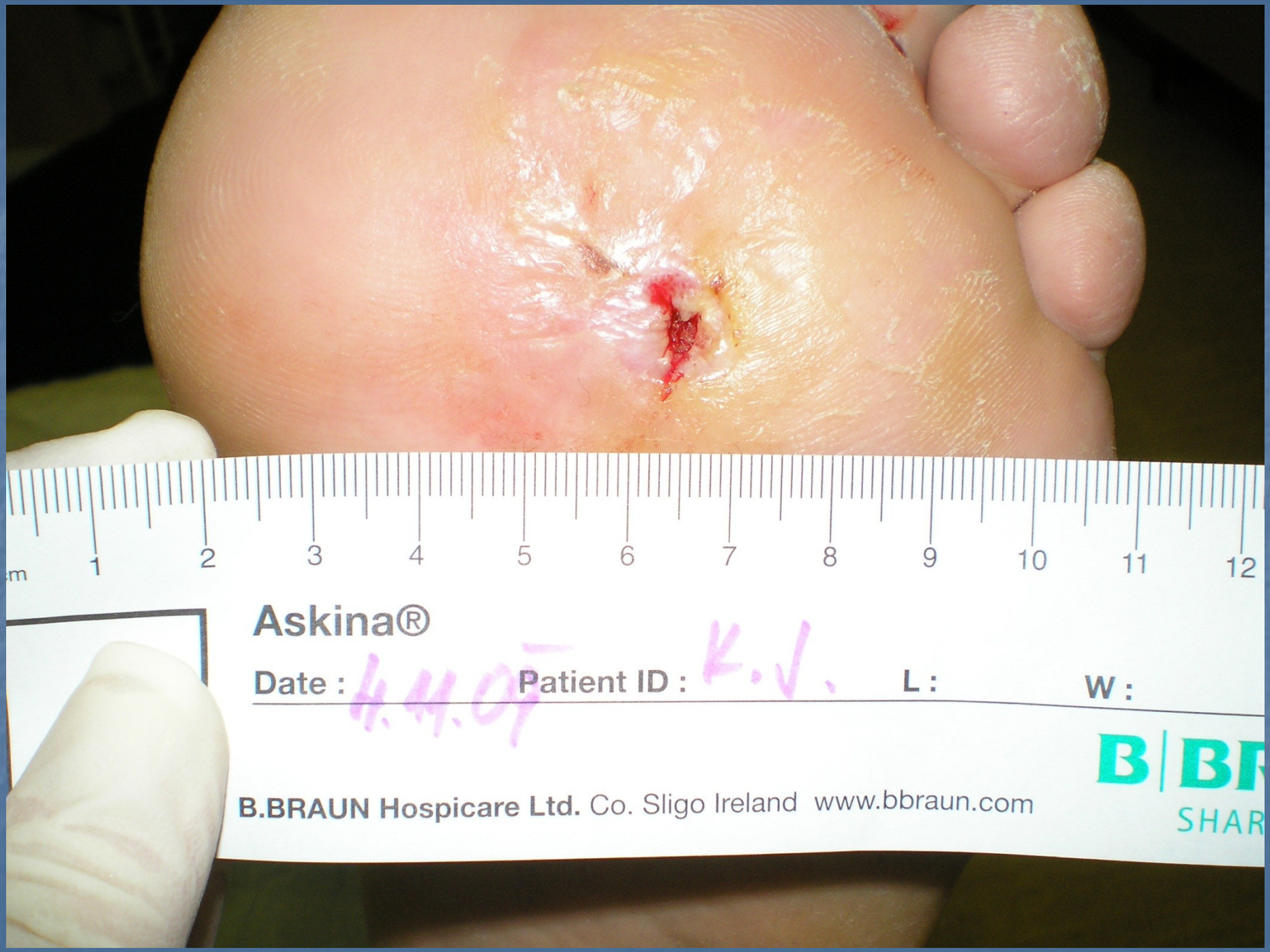








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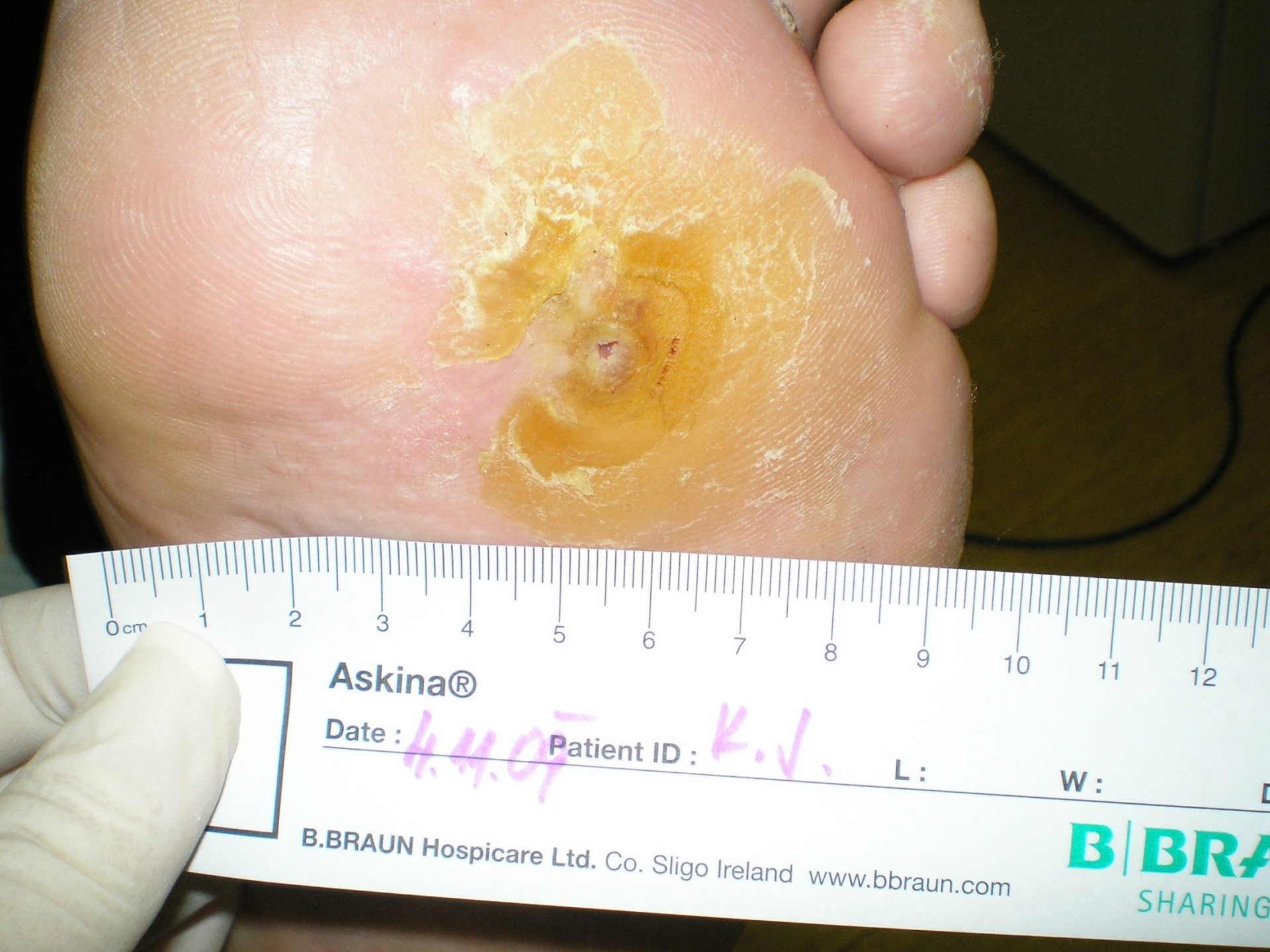
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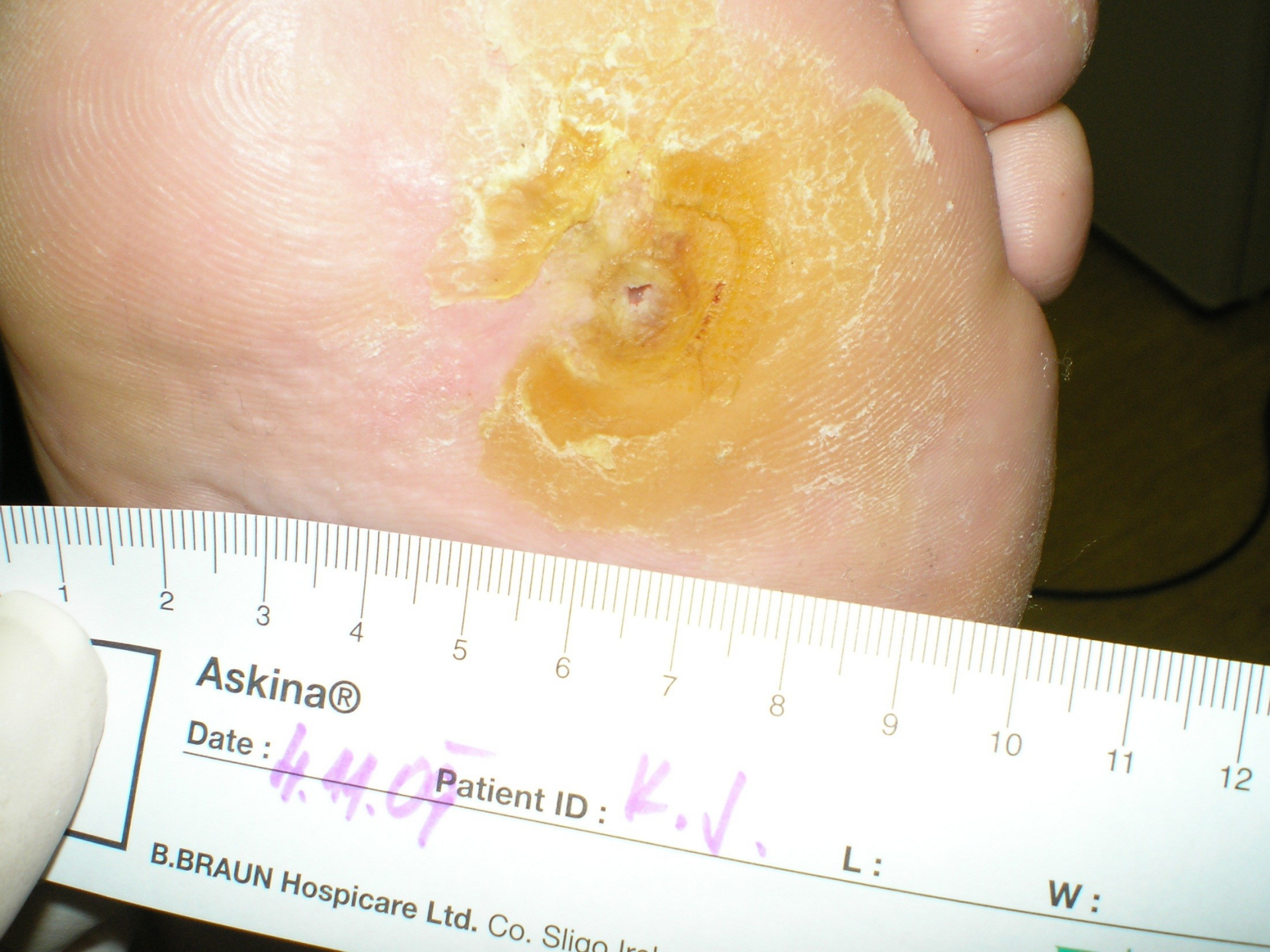
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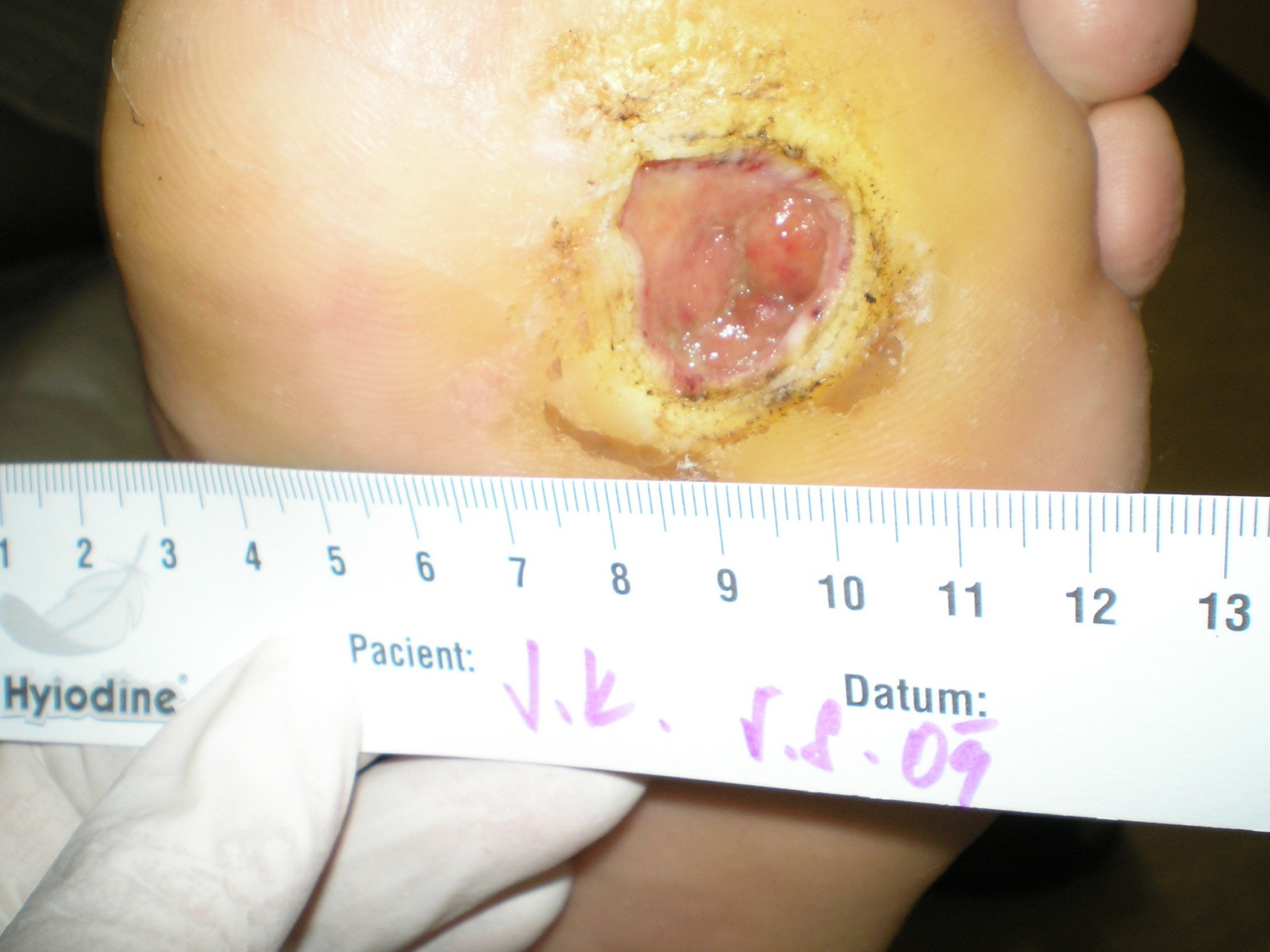
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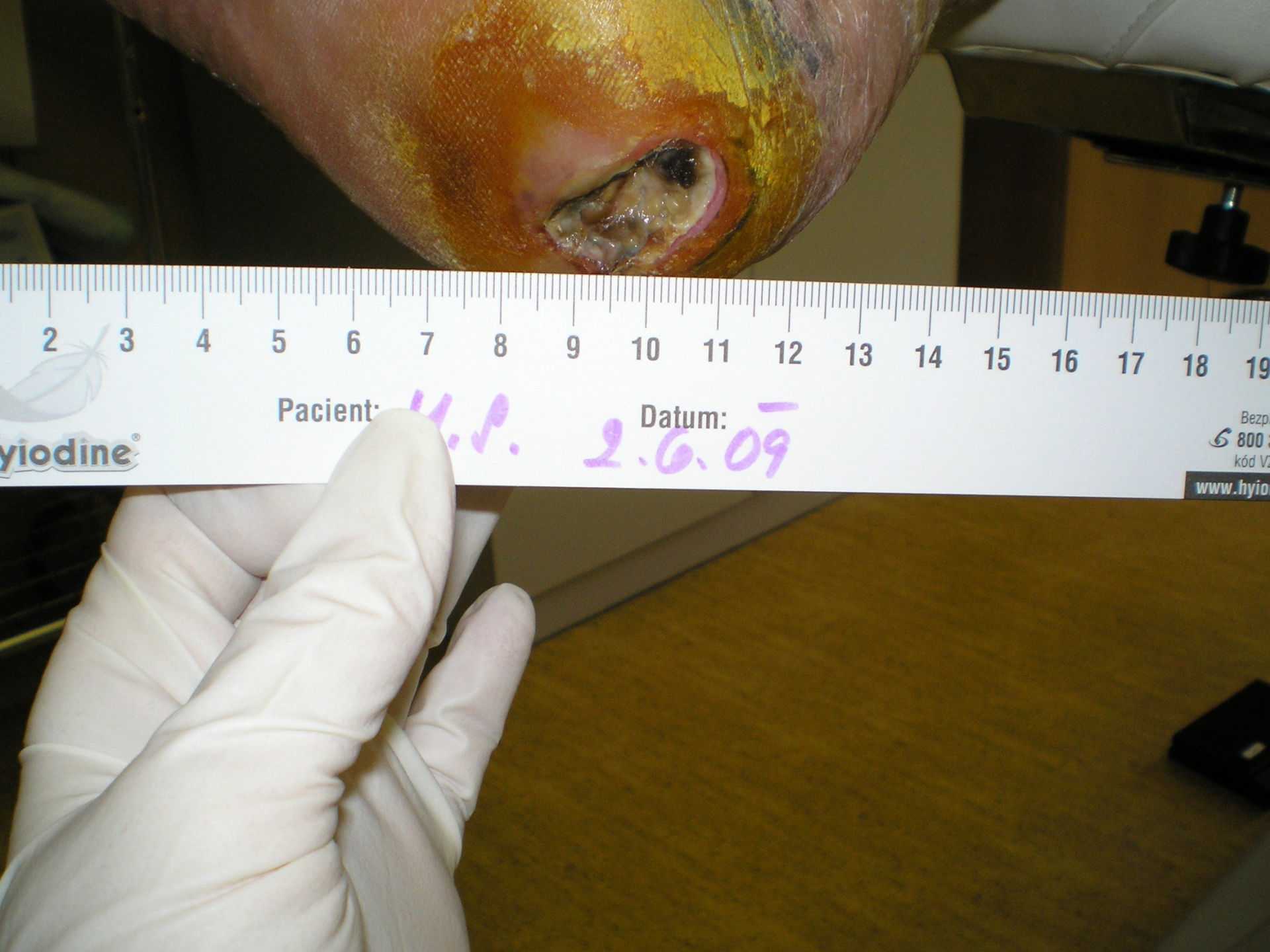
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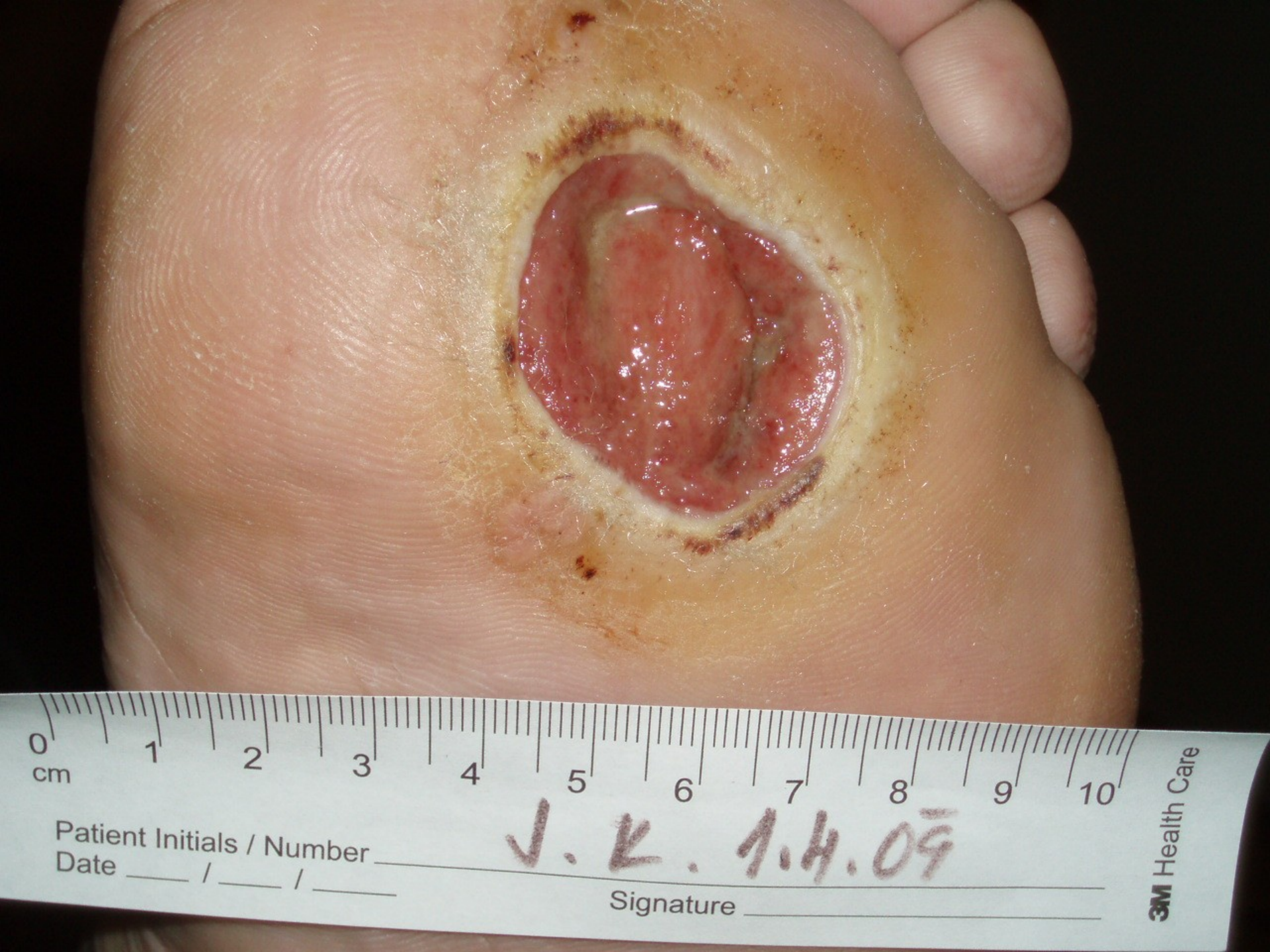
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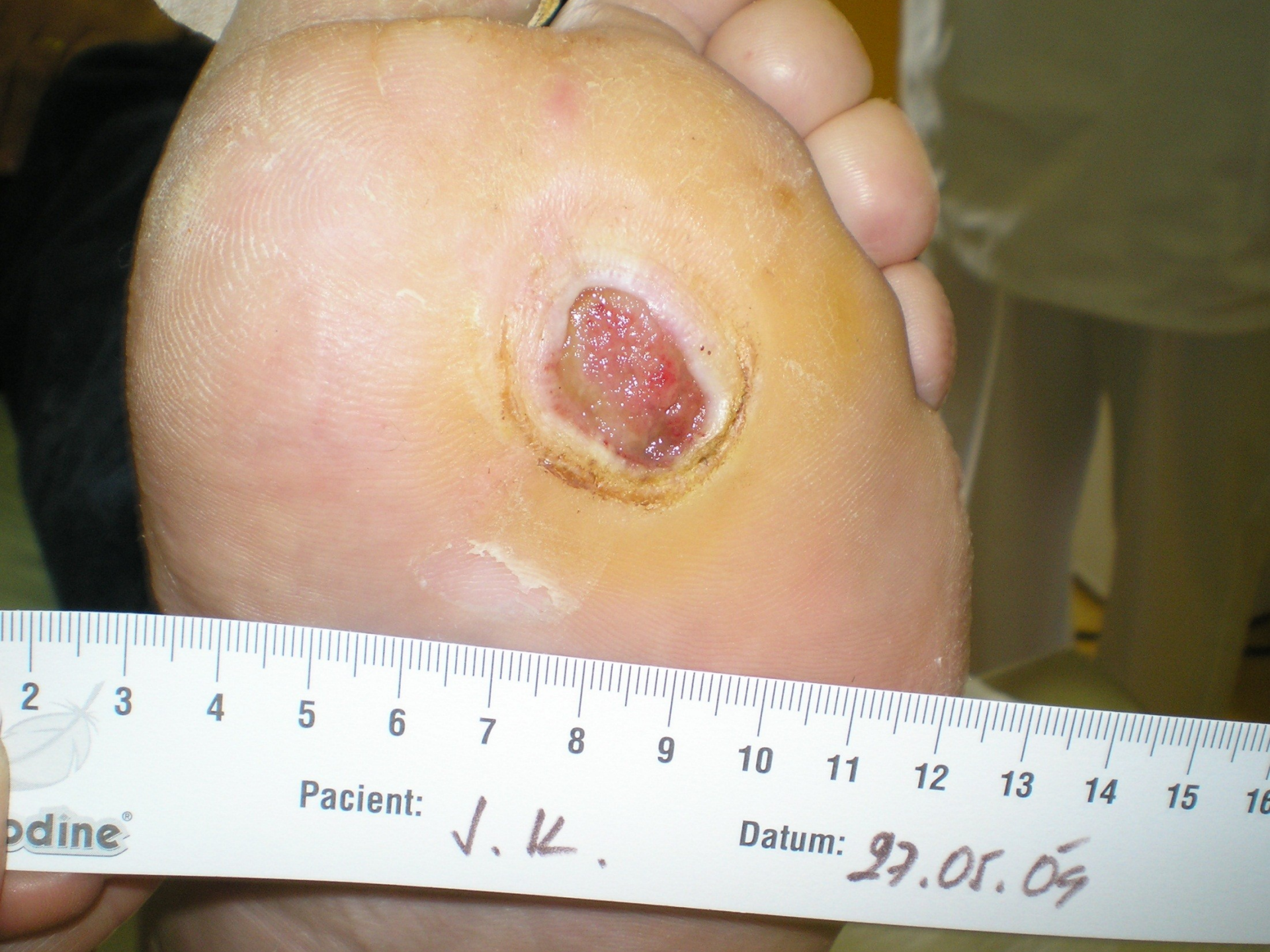
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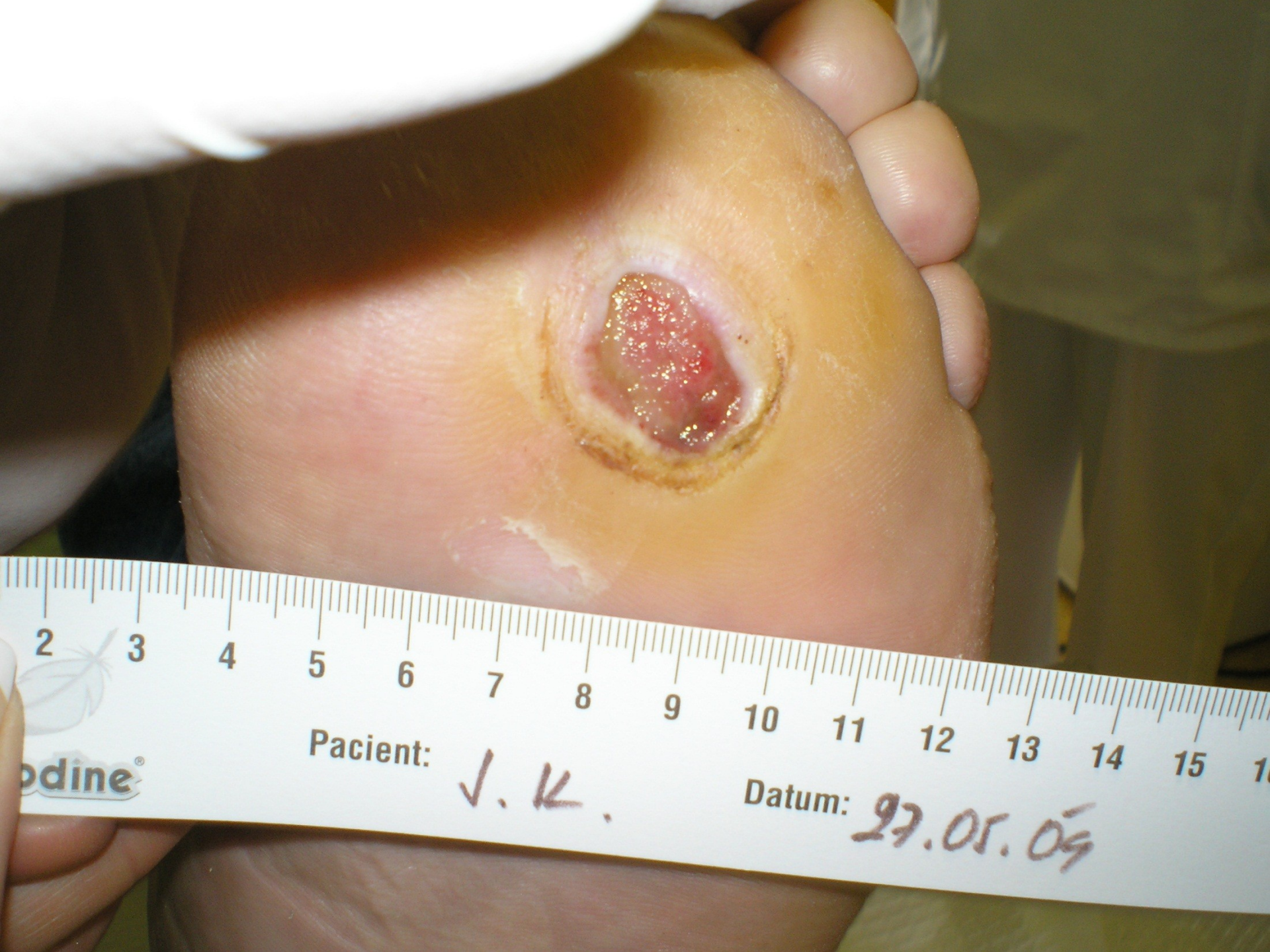
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