The Pathophysiology of Diabetes Mellitus

PHRM 142: Physiology and Pathophys III

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Overview

- Diabetes Mellitus & its Major Types
- Pathogenesis of Type I Diabetes
- Pathophysiologic Basis for Hyperglycemia and Ketoacidosis
- Type II Diabetes & Insulin resistance
- Acute and Chronic Complications of Diabetes

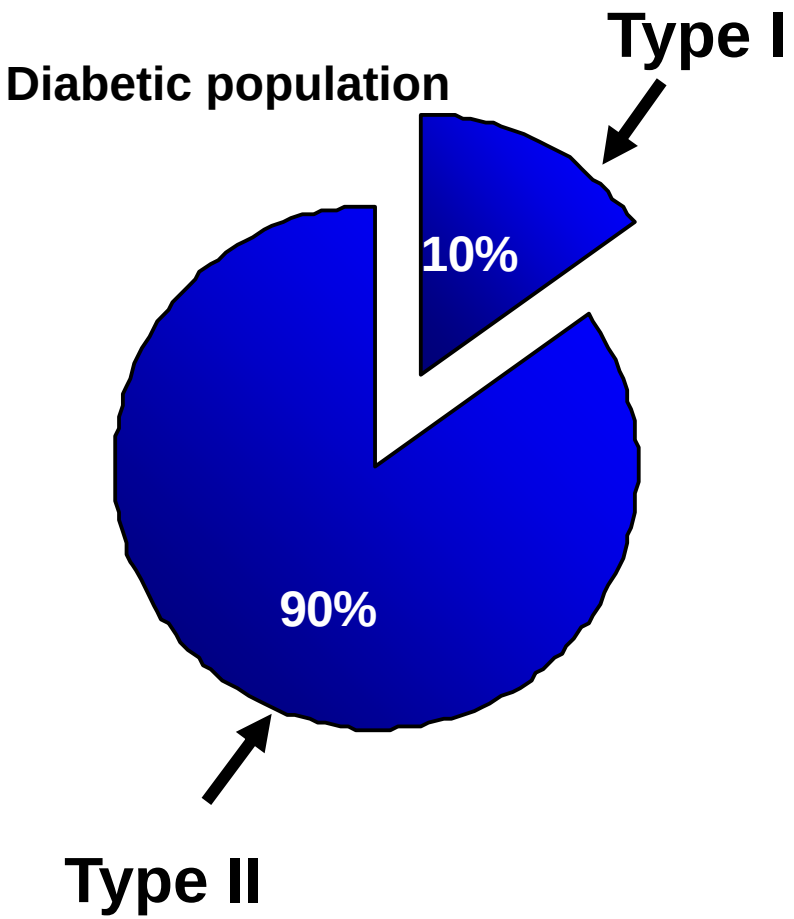
Diabetes Mellitus, Facts

- 6th leading cause of death in the US.
- Associated with coronary artery disease, blindness, kidney failure, nerve damage, extremity amputations & other chronic conditions.
- About 26 million in the US (8.3% of the population)
  - 19 million have been diagnosed.
  - 7 million are unaware!!!
- Pre-diabetes (79 million American)
- Direct & indirect cost attributable to diabetes in 2012 was more than $245 billion, up from $174 billion in 2007 ($176+$69) [ADA, American Diabetes Association].

Different Forms of Diabetes Mellitus

- **Type I diabetes mellitus** (insulin-dependent diabetes mellitus, **IDDM)**
  - Autoimmune type 1 diabetes mellitus (type 1A)
  - Non-autoimmune or idiopathic type 1 diabetes mellitus (type 1B)

- **Type II diabetes mellitus** (non-insulin-dependent diabetes mellitus, NIDDM)



Other Specific types

- Diabetes associated with genetic defects of B cell function
  - "**maturity-onset diabetes of the young" (MODY):**
    - MODY 1 hepatic nuclear factor 4a (*HNF4A*) gene mutations
    - **MODY 2** glucokinase (*GCK*) gene mutations
    - MODY 3 hepatic nuclear factor 1a (*TCF1*) gene mutations
    - MODY 4 insulin promoter factor 1 (*IPF1*) gene mutations
    - MODY 5 hepatic nuclear factor 1b (*HNF1* b) gene mutations
    - MODY 6 neurogenic differentiation 1 (*NEUROD1*) gene mutation
    - MODY X unidentified gene mutation(s)
- Diabetes associated with insulin gene mutation
- Diabetes associated with genetic defects in insulin action *(insulin receptor gene mutations)*

"Other specific types"

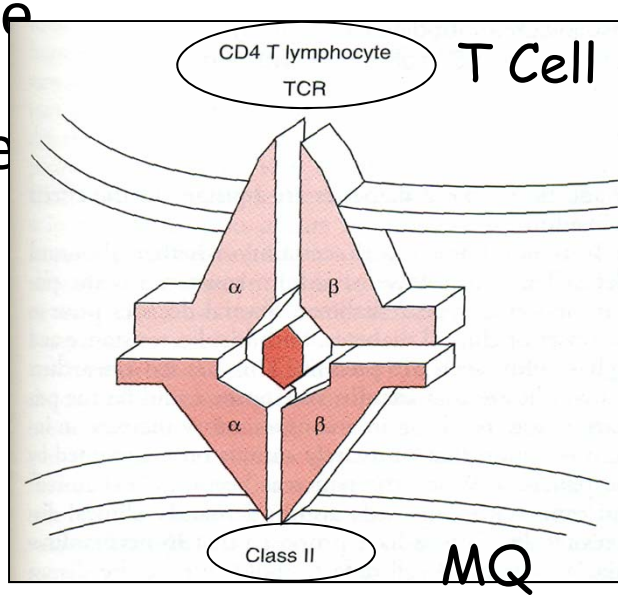
- Diabetes secondary to disease of the exocrine pancreas
  - Pancreatitis
  - Trauma, Pancreatectomy
  - Neoplasia
  - Cystic fibrosis
- Diabetes secondary to endocrionpathies
  - Acromegaly
  - Cushing's syndrome
  - Pheochromocytoma
  - Hyperthyroidism & Aldosteronoma

"Other specific types"

- Diabetes associated with drug therapy (or chemical induced)
  - Epinephrine, Glucocorticoids, Thyroid hormones
  - Diazoxide and Thiazides
  - β_2-Adrenergic agonists
  - α-Interferon
- Diabetes secondary to infections (eg.,Congenital rubella)
- Other genetic syndromes associated with diabetes (eg., Down's syndrome)
- Gestational Diabetes Mellitus (GDM)

Pathogenesis of Type I Diabetes

- Mostly results from ***T cells-mediated autoimmune destruction of β cells***; a process with linkage to certain HLAs (human leukocyte antigens); Class II-HLA are strongly associated with Type I diabetes.
- ~95% of patients with type I have either HLA- DR3 or DR4
- ***Auto-antibodies*** serve as markers of disease
- Most patients with Type I, at diagnosis have circulating antibodies to islets:
  - islet cell antibodies (ICA), insulin autoantibody (IAA), glutamic acid decarboxylase (GAD), tyrosine phosphatase



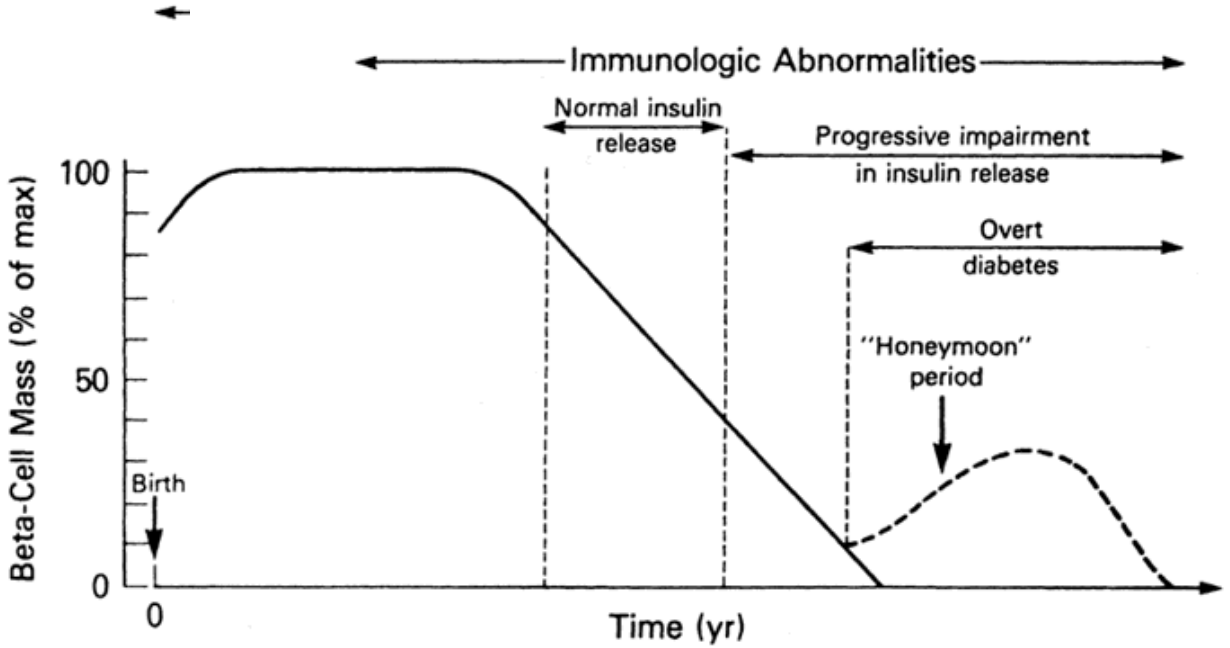
Type I Diabetes; Absolute deficiency of insulin

1) A long preclinical period marked by the presence of immune markers when β cells destruction occurs.

2) Hyperglycemia occurs when 80%-90% of β cells are destroyed.

3) Transient remission (the so-called, “honeymoon” phase).

4) Established disease with associated risk for vascular complications & death.



Laboratory Findings in DM

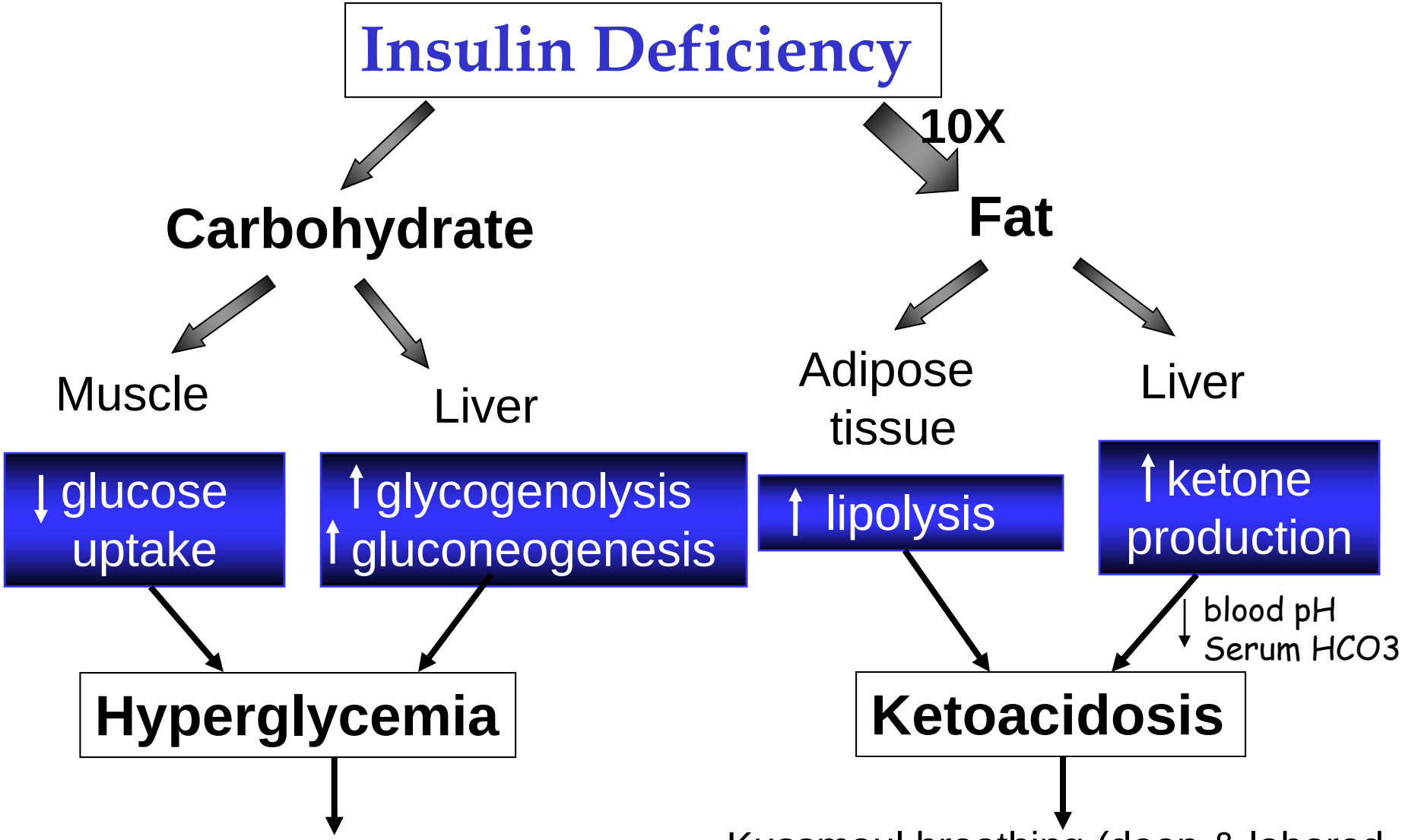
- Blood glucose testing (OGTT)
  - Fasting plasma glucose >=126mg/dl
  - 2-h after glucose load >=200mg/dl

- Urinalysis
  - Glycosuria; using urine glucose as an index of blood glucose.
  - Renal threshold for G ~180 mg/dl of blood; G doesn't appear in urine until blood G rises above this level.

- Glycated hemoglobin assay (HbA1c) ← AGEs
  - Normal range: <5.7%
  - Prediabetes: 5.7-6.4%
  - Diabetes >6.6%

Advanced glycation end products
Glycation of myelin may contribute to the impairment of nerve conduction!

- Serum Ketone body determinations
  - β-hydroxybutyrate, acetoacetate & acetone

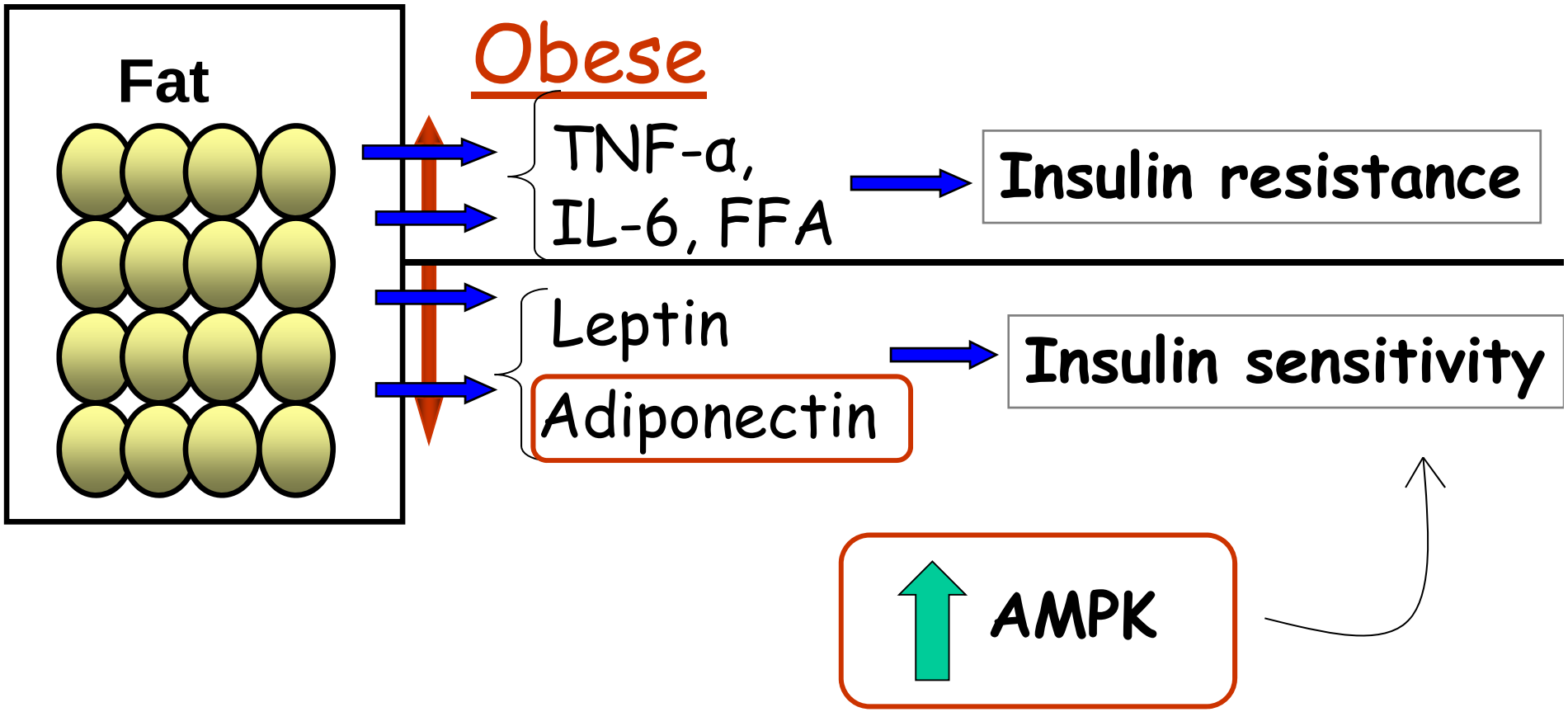


Pathophysiologic Basis Underlying Hyperglycemia & Ketoacidosis

Diabetes Mellitus

	TYPE I	TYPE II
Etiology	Autoimmune destruction of pancreatic β cells	Insulin resistance, with inadequate β cell function to compensate
Insulin levels	Zero	Typically higher than normal
Insulin action	Zero	Decreased
Insulin resistance	Not part of syndrome, but may be present (e.g., in obese patients)	Yes
Age of onset	Typically <30 years	Typically >40 years
Acute complications	Ketoacidosis	Hyperglycemia (can lead to hyperosmotic seizures and coma)

Type II Diabetes and Obesity



AMPK: Adenosine 5'-monophosphate-activated protein kinase

Diabetes Mellitus

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Age of onset	Typically <30 years	Typically >40 years
Acute complications	Ketoacidosis (β-hydroxybutyrate, acetoacetate, acetone)	Hyperglycemia (can lead to hyperosmotic seizures and coma)
Chronic complications	Neuropathy Retinopathy Nephropathy Peripheral vascular disease Coronary artery disease	Same as Type I

Effects of Hyperglycemia

- Hyperosmolality of blood
- Dehydration of cells, lethargy, fatigue and weakness
- Visual disturbance caused by diffusion of glucose into the lens & subsequent swelling.
- Recurrent infections & prolonged wound healing
- Coma, if untreated

Ketoacidosis

- Results from increased peripheral lipolysis and hepatic ketogenesis due to insulin deficiency (primarily Type 1).
- Associated with hyperglycemia (>250 mg/dL)
- Acidosis - pH < 7.3
- Serum bicarbonate depletion - < 15 mmol/L
- $H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$
- Serum positive for ketones (β-hydroxybutyrate, acetoacetate, and acetone)
- Extreme acidosis leads to cardiac & neurological complications:
  - cardiac symptoms: hypotension & tachycardia
  - neurological symptoms: lethargy, coma, seizures.

Chronic Complications of Diabetes

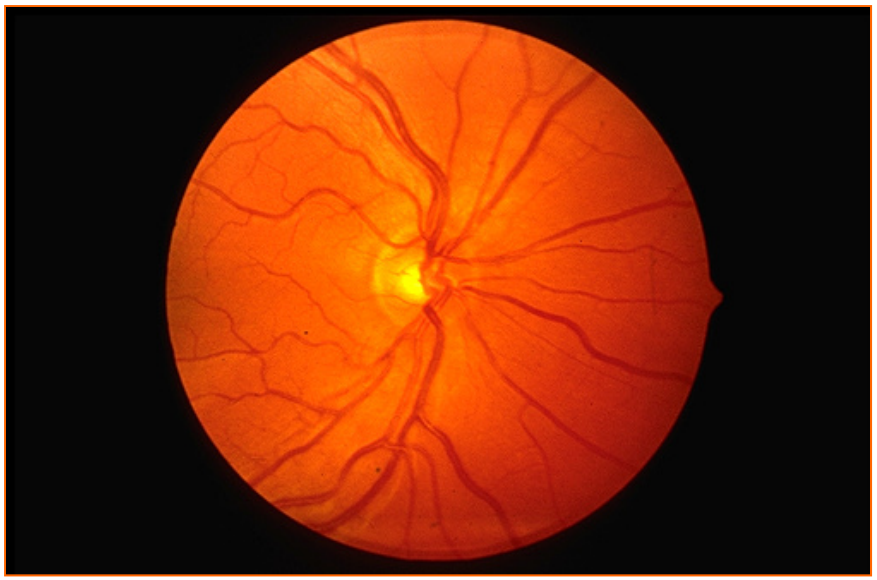
- **Microvascular complications** involves capillary abnormalities affects eyes, kidneys & ANS leading to diabetic *retinopathy*, *nephropathy* & *neuropathy*

1. Glomerular hyperfiltration
2. Microalbuminuria (urine albumin excretion of 300> >30 mg/ day).
3. Macroalbuminuria (>300 mg/day and hypertension)
4. Increase in serum creatinine and reduction in GFR
5. End-stage renal disease (ESRD), GFR < 10 ml/min
   - DM is the leading cause of ESRD in the US; a major cause of death in type 1 and 2.

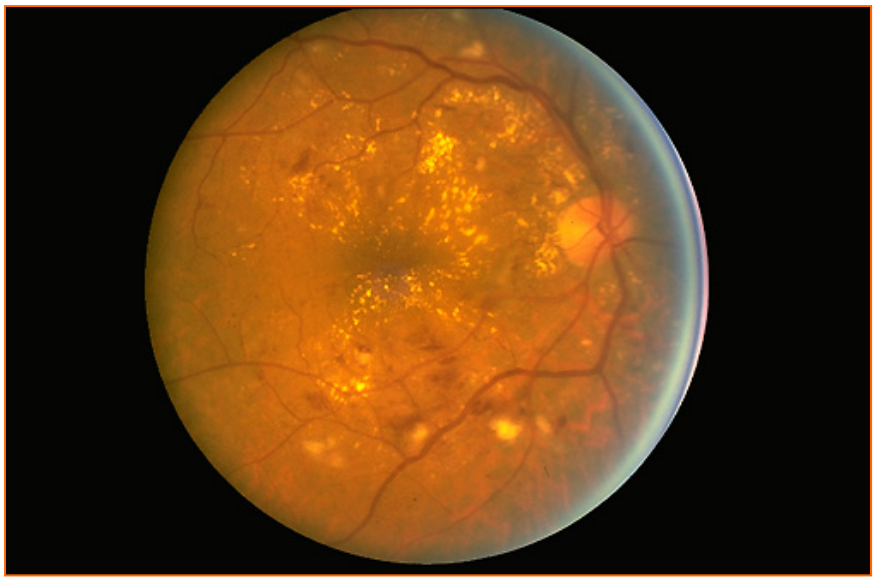
Chronic Complications of Diabetes

- **Macrovascular complications** such as coronary artery disease due to atherosclerosis and peripheral vascular disease.
- Both micro- and macrovascular disease contribute to high morbidity and mortality rates associated with diabetes.

Long Term Complications



Normal appearance of the retina



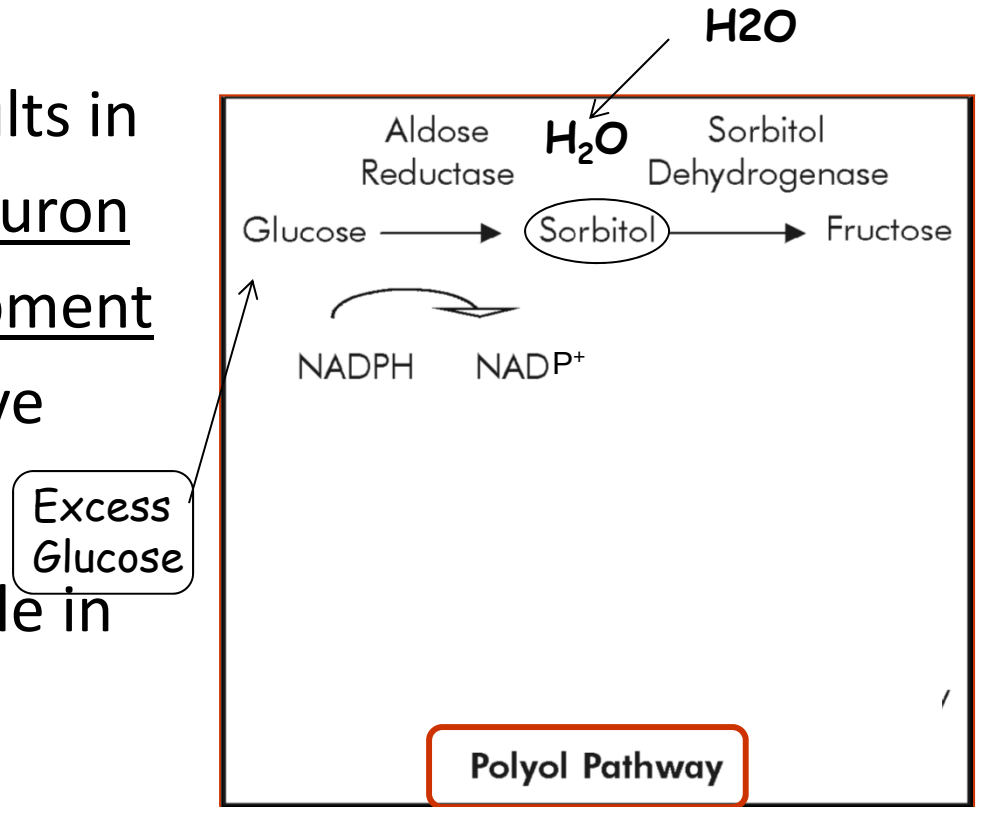
Diabetic retinopathy

Diabetic Cataracts

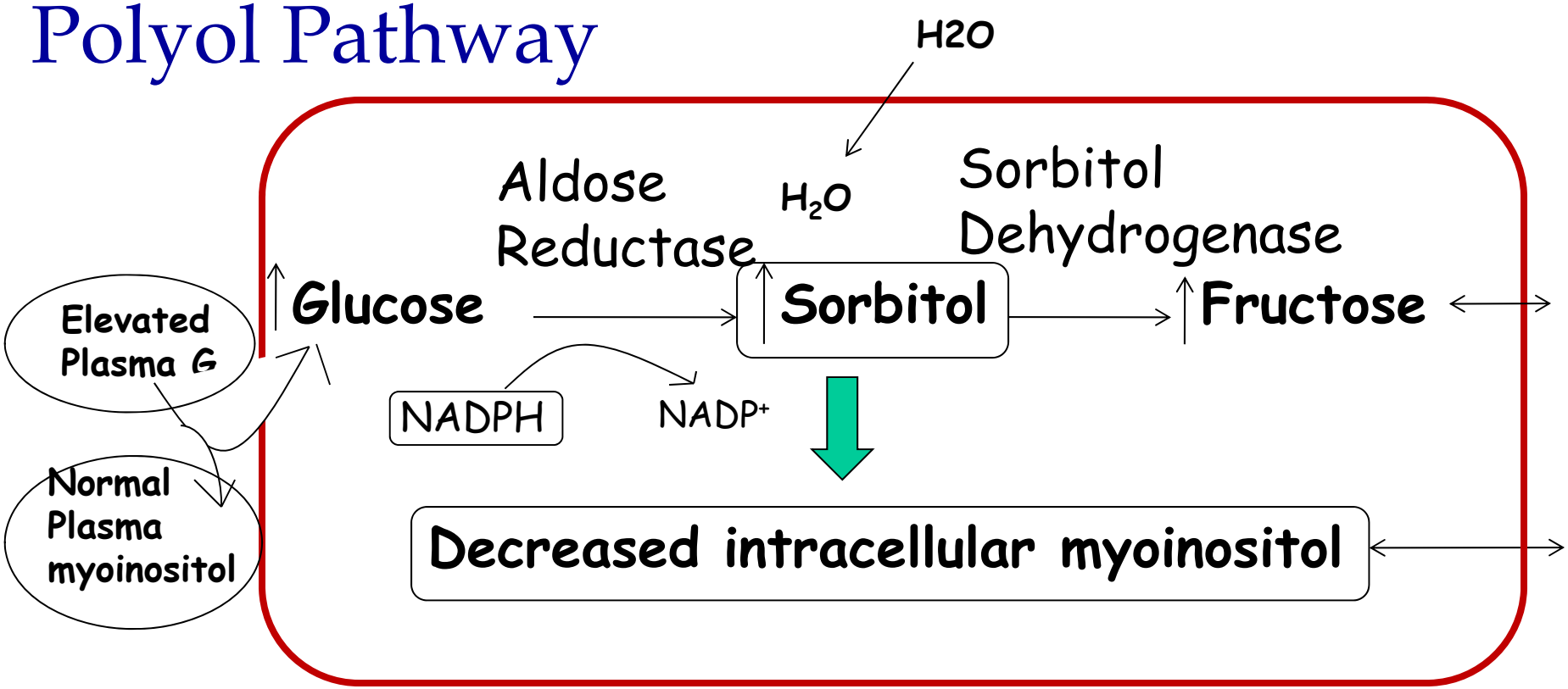
- A clouding of the lens with impairment of vision.
- Linked closely with uncontrolled hyperglycemia and activation of *polyol pathway**
- Requires surgical intervention

Hyperglycemia & Polyol Pathway

- G uptake into peripheral nerve is insulin independent, it is proportional to blood G conc.
- Excess G is shunted into the polyol pathway & converted to *sorbitol* & *fructose*. This occurs in tissues such as the lens, retina, arterial wall, and cells of peripheral nerves.
- Accumulation of sorbitol results in osmotic stress that causes neuron damage and cataract development (by osmotic swelling of the eye lens).
- Polyol pathway plays a key role in cataractogenesis of diabetes.



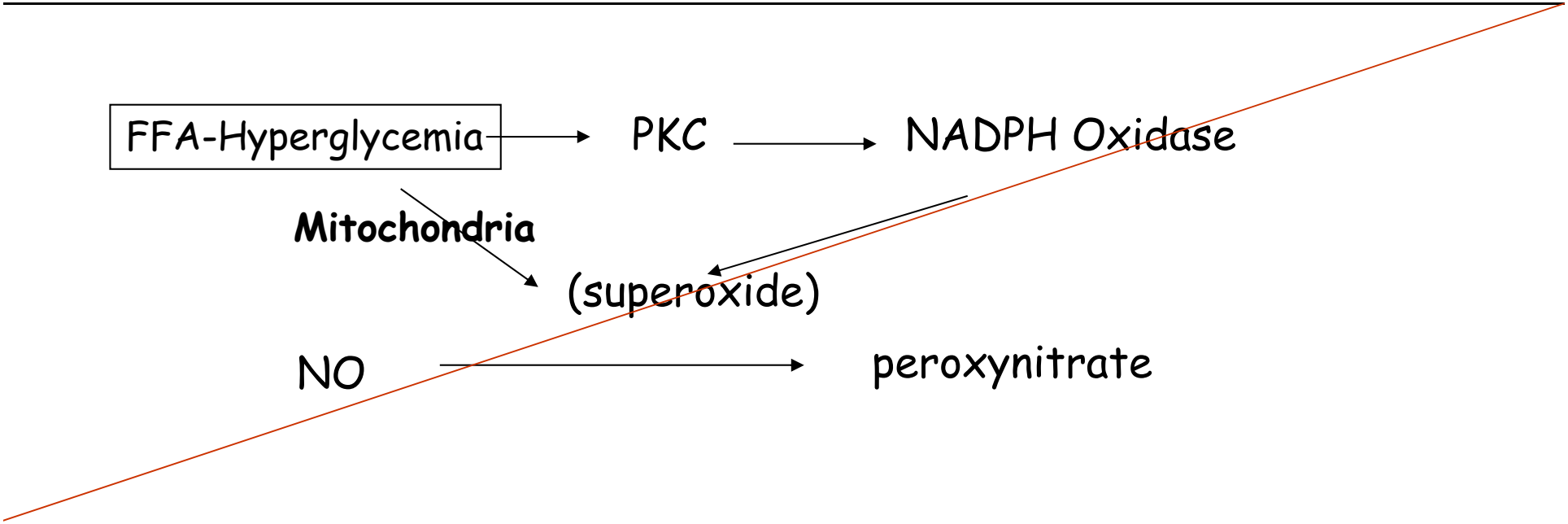
Polyol Pathway



- Hyperglycemia increases intracellular sorbitol, which in turn is associated with depletion of intracellular myoinositol levels.
- Reduction of myoinositol may contribute to altered nerve function and neuropathy.
- Hyperglycemia may also decrease myoinositol directly by inhibiting its uptake.
- Loss of NADPH leads to vascular dysfunction & impairs blood supply to nerve.

Free radical and Oxidative stress

- In diabetes, free radical generation (eg., superoxide) is enhanced.
- Free radicals could damage nerve by direct toxic effects or perhaps by reducing NO in the vascular endothelium, thereby reducing nerve blood flow.



Aortic atherosclerosis from minimal at the bottom to severe at the top.

Diabetics tend to have more advanced, extensive atherosclerosis.

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Cardiovascular Research

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Gender difference in rat aorta vasodilation after acute exposure to high glucose: Involvement of protein kinase C β and superoxide but not of Rho Kinase

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Abstract

Objectives: Several reports suggest that acute hyperglycemia affects male and female vascular beds differently. However, little is known about the interactions between hyperglycemia and gender in the vasculature. The objectives of our study were to investigate if there is a gender-based difference in the relaxation response of rat aorta after acute exposure to high glucose concentration, and the potential role of protein kinase C-beta (PKCβ), superoxide, and Rho kinase in the gender-specific effect of acute high glucose on the relaxation response.

Methods: Endothelium-dependent dilator responses to acetylcholine (ACh, 10^{-8} to 10^{-5} M) were obtained before and after 3 h treatment with Krebs' solution containing high glucose (46 mM) in aortic rings pre-contracted with phenylephrine (2 μM) taken from female and male Sprague–Dawley rats. Similar experiments were generated in the presence of 1 μM LY379196, a selective PKCβ inhibitor, 25 μM MnTMPyP, a superoxide dismutase mimetic, or 1 μM Fasudil, a Rho kinase inhibitor. Furthermore, protein expression of PKCβ isoforms was measured by Western blotting.

Results: We demonstrated that a 3 h incubation with elevated level of glucose impairs ACh responses only in the female rat aortic rings. Inhibition of PKCβ or superoxide production but not Rho kinase prevents the high glucose-induced impairment of endothelium-dependent relaxation of female rat aorta. In addition, PKCβ2 expression is significantly higher in the female rat aorta than that in male rat aorta.

Conclusion: These results suggest that the gender difference in the impairment of endothelium-dependent vasodilation after acute exposure to high glucose in rat aorta is possibly due to differences in PKCβ2 expression.

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Keywords: Endothelial function; Diabetes; Gender; Nitric oxide; Protein kinase C

Am J Physiol Heart Circ Physiol 294: H2411–H2420, 2008.
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Sexual dimorphism in rabbit aortic endothelial function under acute hyperglycemic conditions and gender-specific responses to acute 17β-estradiol

Aditya Goel,[1] Der Thor,[1] Leigh Anderson,[2] and Roshanak Rahimian[1]

[1]*Department of Physiology and Pharmacology, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton; and* [2]*Department of Anatomical Sciences, Arthur A. Dugoni School of Dentistry, University of the Pacific, San Francisco, California*

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Goel A, Thor D, Anderson L, Rahimian R. Sexual dimorphism in rabbit aortic endothelial function under acute hyperglycemic conditions and gender-specific responses to acute 17β-estradiol. *Am J Physiol Heart Circ Physiol* 294: H2411–H2420, 2008. First published March 7, 2008; doi:10.1152/ajpheart.01217.2007.—Epidemiological data suggest that hyperglycemia abrogates the gender-based cardiovascular protection possibly associated with estrogens. This study was designed to investigate *1*) whether rabbit aortic rings show gender differences in the development of abnormal endothelium-dependent vasodilation (EDV) under acute hyperglycemic conditions, *2*) the potential role of PKC isoforms and superoxide (O_2^-) in acute hyperglycemia-induced vascular dysfunction, and *3*) the effect of acute estrogen administration on hyperglycemia-induced endothelial dysfunction in male and female rabbits. EDV to ACh was determined before and after 3 h of treatment with high glucose (HG) in phenylephrine-precontracted aortic rings from male and female New Zealand White rabbits. Similar experiments were conducted in the presence of inhibitors of PKC-α, PKC-β, and PKC-δ or an O_2^- scavenger. The effect of acute estrogen administration was evaluated

35). Despite the epidemiological data, the mechanisms underlying the loss of premenopausal female-specific cardiovascular protection in hyperglycemia/diabetes are not clear.

Hyperglycemia brings about several changes in the vascular homeostasis. One of the hallmarks of hyperglycemia-induced vascular disease is endothelial cell dysfunction, characterized by impaired nitric oxide (NO)-dependent vasodilation. Endothelium-dependent vasodilation (EDV) is generally used as a reproducible parameter to probe endothelial function under different pathological conditions. Impaired EDV has been described in diabetes, and the degree of impairment of relaxation was shown to be correlated with glycemic control (48). We recently showed that acute exposure to high glucose (HG) reveals a gender difference in the development of impaired EDV in rat aorta (15), but because different species may react differently to a comparable stimulus (30), it remains to be established whether the above-mentioned sexual dimorphism is

Am J Physiol Heart Circ Physiol 303: H1183–H1198, 2012.
First published September 14, 2012; doi:10.1152/ajpheart.00327.2012.

Sex differences in mesenteric endothelial function of streptozotocin-induced diabetic rats: a shift in the relative importance of EDRFs

Rui Zhang,[1] Der Thor,[1] Xiaoyuan Han,[1] Leigh Anderson,[2] and Roshanak Rahimian[1]

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Submitted 19 April 2012; accepted in final form 5 September 2012

Zhang R, Thor D, Han X, Anderson L, Rahimian R. Sex differences in mesenteric endothelial function of streptozotocin-induced diabetic rats: a shift in the relative importance of EDRFs. *Am J Physiol Heart Circ Physiol* 303: H1183–H1198, 2012. First published September 14, 2012; doi:10.1152/ajpheart.00327.2012.—Several studies suggest that diabetes affects male and female vascular beds differently. However, the mechanisms underlying the interaction of sex and diabetes remain to be investigated. This study investigates whether there are *1*) sex differences in the development of abnormal vascular responses and *2*) changes in the relative contributions of endothelium-derived relaxing factors in modulating vascular reactivity

is insufficient evidence to establish the mechanism(s) underlying the loss of this female-specific cardiovascular protection in premenopausal patients with diabetes.

Endothelial dysfunction is an early sign of diabetic vascular diseases. Endothelial dysfunction can be defined as a reduced endothelium-dependent vasorelaxation (EDV) to vasodilators, such as acetylcholine (ACh) and bradykinin, or flow-mediated vasodilation. Thus EDV is generally used as a reproducible parameter to investigate endothelial function under various pathological conditions. Impaired EDV has been observed in

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Cardiovascular pharmacology

Sexual dimorphism in rat aortic endothelial function of streptozotocin-induced diabetes: Possible involvement of superoxide and nitric oxide production

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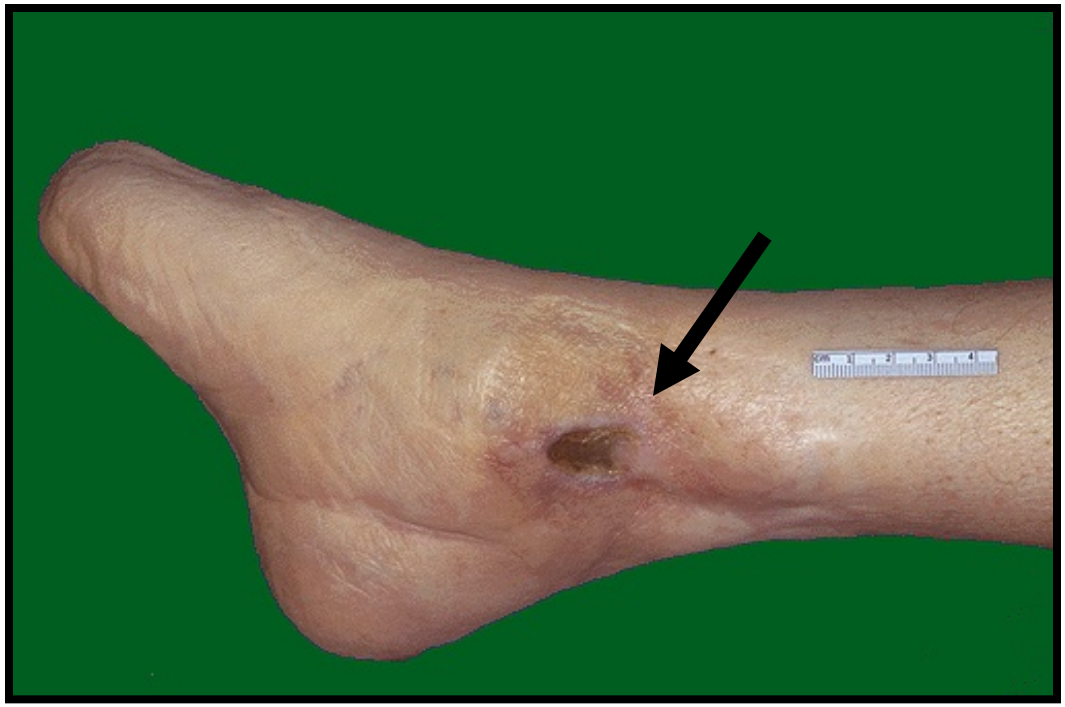
A diabetic foot ulcer with a previous healed amputation!



- **Etiology includes <u>peripheral neuropathy*</u> and <u>peripheral vascular disease</u>.**
  - *Impaired sensory perception (eg., pain, temperature) increases chances of unnoticed trauma & eventually leads the loss of sensation.

Treatment of Diabetes

There is no cure for diabetes!