TYPE 2 DIABETES MELLITUS (T2DM) IS A HETEROGENEOUS CONDITION THAT IS RELATED TO BOTH DEFECTIVE INSULIN SECRETION AND PERIPHERAL INSULIN RESISTANCE.

- . Insulin resistance is a major cause of T2DM leads to elevated free fatty acid (FFA) levels which increases beta-cell mass and insulin secretion to compensate for insulin insensitivity. Chronic increase of plasma FFA levels results in disturbances in lipid metabolism, which contributes to decreased beta-cell function and lipotoxicity thus promoting T2DM.

Pathogenesis of Diabetes Mellitus (DM), Type II

Unhealthy Lifestyle: i.e. over-eating, obesity, inactivity

Intraperitoneal cavity accumulates "visceral fat" (aka. "abdominal fat"), which is an endocrine organ that secretes:

- Inflammatory mediators
- Adipokines
- Free fatty acids (FFAs)

Note: "adipokines" are inflammatory mediators released from adipose tissue (e.g. TNFalpha). The more adipose tissue a patient has, the more adipokines are released.

Genetic Susceptibility: Polygenetic or monogenetic factors (i.e. maturity-onset diabetes of the young (MODY)) can predispose insulin resistance

Aging: Beta-cell mass declines with aging, so those predisposed to insulin resistance may develop Type II DM as they age.

Medications: i.e. corticosteroids, anti-psychotics, highly-active anti-retrovirals, progestin-only oral contraceptives

Complex, unclear actions on body tissue

Insulin resistance
(liver, muscle, adipose tissue become less responsive to insulin, and thus less able to use glucose as a fuel source)

Lipotoxicity: FFAs inhibit function of GLUT2 on Beta-cells, ↓ glucose import

Beta-cells do not recognize high blood glucose → ↓ insulin secretion

Initially, beta-cells of the pancreas work overtime to ↑ Insulin secretion

Blood [glucose] is kept normal

Over many years, as insulin resistance worsens, Beta-cells "tire out", ↓ insulin secretion **(relative insulin deficiency)**

Glucotoxicity: hyperglycemia is directly toxic to Beta-cells

Hyperglycemia

Since cells can't use glucose, body perceives a state of "starvation", thus mobilizing triglycerides into FFAs, to be used as fuel by cells.

Over many more years: Beta-cells deteriorate until they finally stop producing insulin, **(absolute insulin deficit)**

Type II Diabetes Mellitus

Note: There is a HUGE genetic basis for Type II DM: high concordance rate between family members (90% for monozygotic twins), and if a first-degree relative is affected, the risk for other family members is 5-10x above baseline.

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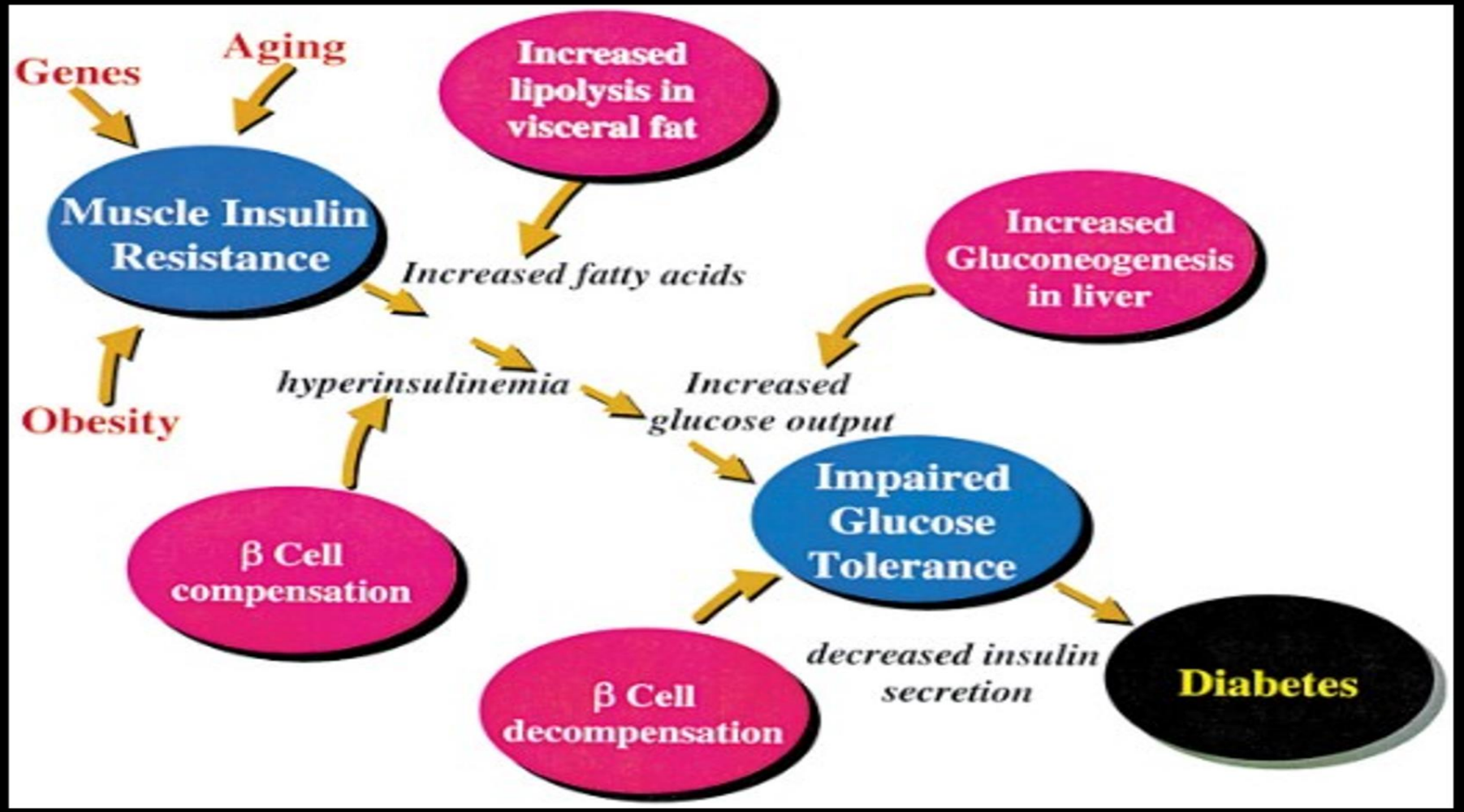
Published **July 11, 2013** on www.thecalgaryguide.com

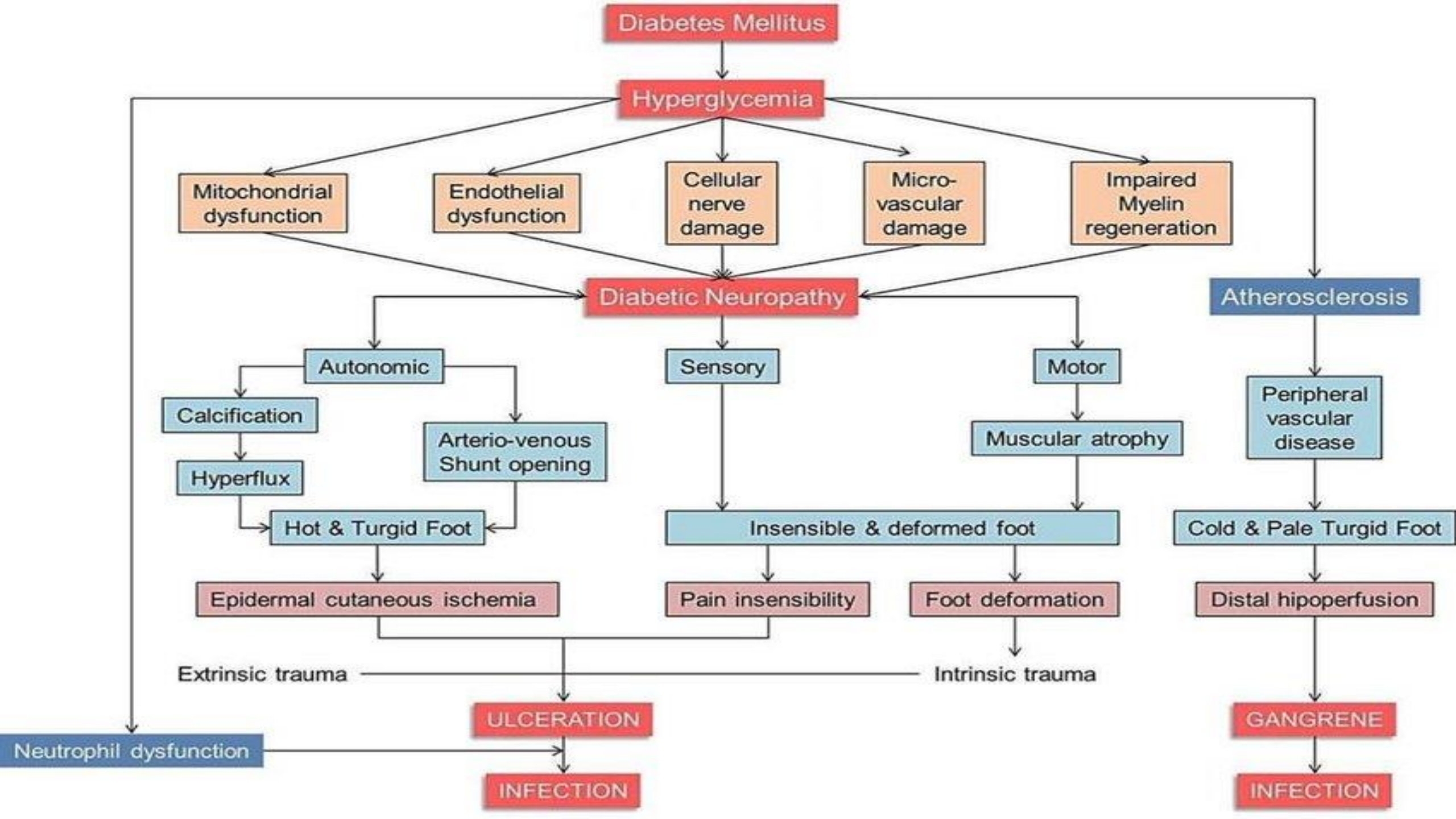
Figure 1



Cell 2001 104517 -529DOI: (10.1016/S0092-8674(01)00239-2)

- Early recognition of the etiology of foot lesions and prompt management of foot ulcers are essential for successful outcome
- . Diabetes mellitus is a state of chronic hyperglycemia, consisting of changes in carbohydrate, protein and fat metabolism. As a consequence of the long duration of diabetes mellitus, late complications can develop. Foot is in its structure very complex, combined with many large and small bones connected with ligaments, directed by many small and large muscles, interconnected with many small and large blood vessels and nerves.

- . Every of these structures can be changed by nutritional, defensive and reparatory mechanisms Primary prevention of DF includes all measures involved in appropriate maintenance of nutrition, defense and reparatory mechanisms
- .First, it is necessary to identify the high-risk population for DF, in particular for macrovascular, microvascular and neural complications.
- The high-risk population of PwDM should be identified during regular examination and appropriate education should be performed. In this group, it is necessary to include more frequent and intensified empowerment for lifestyle changes, appropriate diet


Diabetes Mellitus
Hyperglycemia
Mitochondrial dysfunction
Endothelial dysfunction
Cellular nerve damage
Micro-vascular damage
Impaired Myelin regeneration
Diabetic Neuropathy
Atherosclerosis
Autonomic
Sensory
Motor
Calcification
Hyperflux
Arterio-venous Shunt opening
Muscular atrophy
Peripheral vascular disease
Hot & Turgid Foot
Insensible & deformed foot
Cold & Pale Turgid Foot
Epidermal cutaneous ischemia
Pain insensibility
Foot deformation
Distal hipoperfusion
Extrinsic trauma
Intrinsic trauma
ULCERATION
GANGRENE
Neutrophil dysfunction
INFECTION
INFECTION

- pathophysiology of the diabetic foot ulcer and soft-tissue infection

  - neuropathy,
  - trauma
  - peripheral artery occlusive disease

- More than 60% of diabetic foot ulcers are the result of neuropathy
- Generalized symmetric distal polyneuropathy is the most common
- Neuropathy in diabetic patients is manifested in the motor, autonomic, and sensory components of the nervous system.
    - _ Damage to the innervations of the intrinsic foot muscles leads to an imbalance between flexion and extension of the affected foot. This produces anatomic foot deformities that create abnormal bony prominences and pressure points, which gradually cause skin breakdown and ulceration

Autonomic neuropathy: leads to a diminution in sweat and oil gland functionality. As a result, the foot loses its natural ability to moisturize the overlying skin and becomes dry and increasingly susceptible to tears and the subsequent development of infection

The loss of sensation as a part of peripheral neuropathy exacerbates the development of ulcerations. As trauma occurs at the affected site, patients are often unable to detect the insult to their lower extremities. As a result, many wounds go unnoticed and progressively worsen as the affected area is continuously subjected to repetitive pressure and shear forces from ambulation and weight bearing.

Ischemia

- Atherosclerosis of the lower limb is 2 to 3 times more common in diabetic patients, compared to the normal population.
- Investigators reported that atherosclerosis in diabetic patients is more prominent in tibial and fibular arteries of the calf, and arteries of the foot are relatively spared.

- Micro and macrovascular complications are one of the leading causes of diabetic complications. Microvascular complications cause skin damage, infection, and impaired wound healing.[11]
- The vascular changes which are responsible for foot problems include stiff arteries due to calcification of the smooth muscle cells in the arterial wall (mediasclerosis). Consequently, the stiff arteries are unable to expand in response to systolic pressure, which can lead to the movement of plaques in calf arteries.[12]

- ABI is the ratio of the blood pressure in the lower limb to the blood pressure of the arms. It is calculated by dividing the systolic blood pressure of the ankle by the systolic blood pressure of the arm.

It is a non-invasive method to assess the lower extremty arterial system and to detect the presence of arterial occlusion disease.

- Even in the presence of neuropathic foot ulcers, the reason of non healing wounds could be due to impaired blood supply to the tissue,

Trauma

Trauma to the foot is frequently the trigger of diabetic foot ulcer development, and repetitive trauma and pressure to the area prevent healing