

Bone in Health and Disease

Learning Outcomes

- Describe the anatomical and molecular structure and function of bone
- Explain the process of bone remodelling and how it contributes to bone homeostasis
- Describe osteoclasts and how they resorb bone
- Describe osteoblasts and how they form bone
- Describe osteocytes and their role in the skeleton
- Explain the RANKL / OPG system in osteoclast differentiation and how it's regulated in RA.
- Define focal vs systemic bone loss in RA and explain how osteoclasts contribute.
- Describe how the inflamed synovium, via TNF, IL-1 and IL-6, causes bone destruction in RA.
- Describe how antiresorptive therapies protect bone in RA.

Types of Bone Loss in RA

Rheumatoid arthritis (RA) leads to three distinct types of bone loss:

- **Peri-articular Osteopenia:** This refers to bone loss occurring near the joints, specifically in the trabecular bone, which is the internal structure of the bone.
- **Focal Bone Erosion:** This is a severe condition where significant portions of the cortical bone at the joint are eroded, resembling a "munch" taken out of the bone. Fortunately, most patients receive treatment before reaching this stage.
- **Systemic Osteoporosis:** This type of bone loss occurs throughout the skeleton and develops after the onset of RA. It results in thinning of both trabecular and cortical bone, increasing the risk of fractures.

Bone Structure and Function

The skeleton consists of both cortical and trabecular components, serving structural and metabolic functions.



Importance of the Skeleton

The skeleton serves several critical functions:

- **Mechanical Function:** It supports muscles for movement, including those necessary for breathing.
- **Protective Role:** The skeleton protects vital organs, such as the brain (skull) and heart/lungs (rib cage), and a protected environment for hematopoiesis
- **Metabolic Role:** The skeleton stores minerals, particularly calcium, which is essential for maintaining blood calcium levels and supporting various bodily functions.
- Source of **hormones and cytokines** that influence other organs (e.g. FGF23, osteocalcin)

Extracellular Composition of Bone

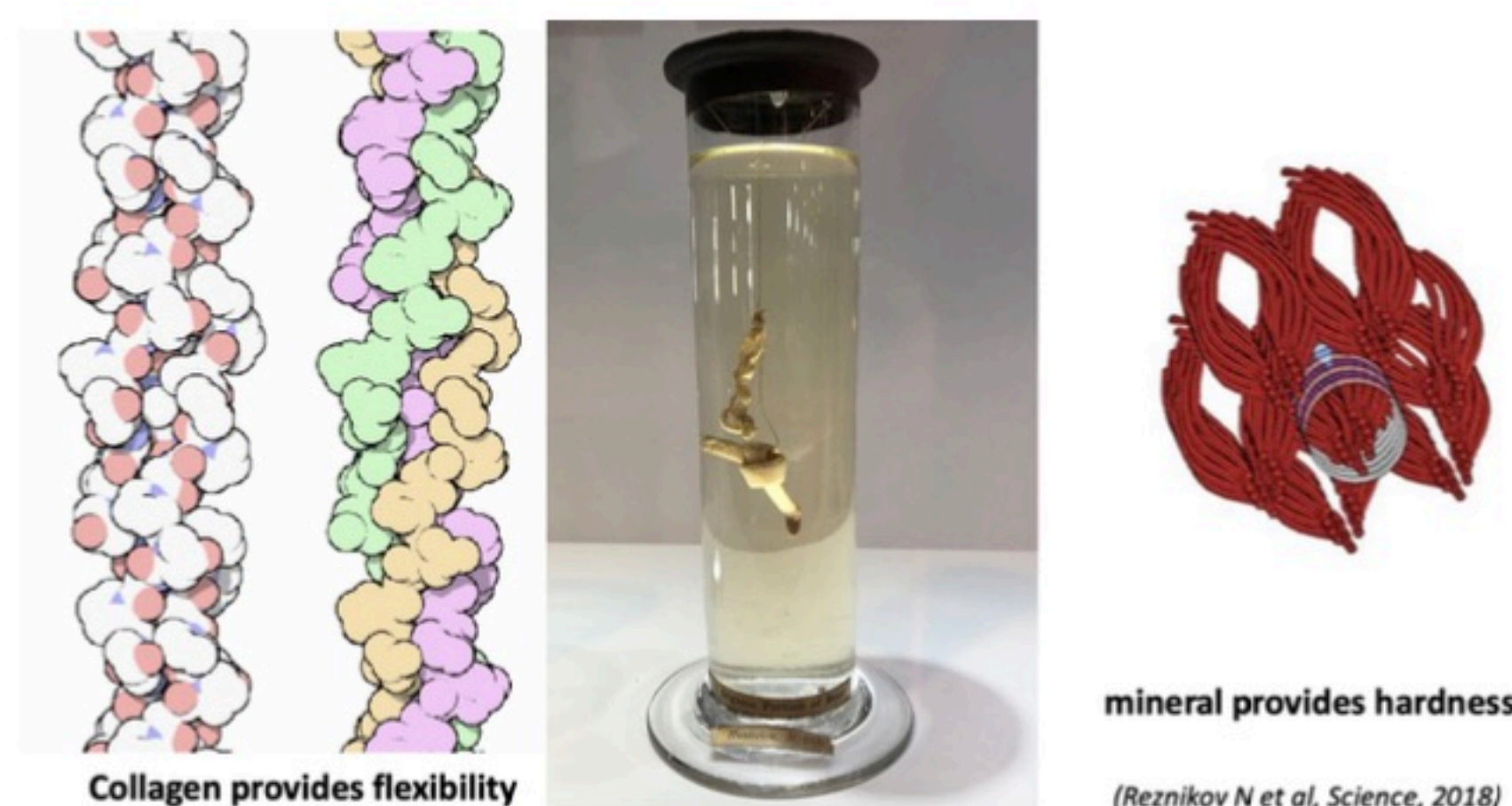
Bone consists of two main components:

- **Organic Matrix (30%):** Composed mainly of type I collagen, this matrix provides flexibility, structure, and elasticity and is referred to as osteoid before mineralization.
 - Produced by osteoblasts
 - Collagen binds and orients other proteins
 - Collagen also promotes accumulation of mineral
- **Mineral Crystals:** Approximately 65% of the bone matrix is made up of calcium phosphate crystals (hydroxyapatite), which contribute to the hardness of the bone (compressive strength)

The balance between these components is crucial; an imbalance can lead to bones that are either too soft or too hard, increasing the risk of injury.

Collagen and Mineral Crystals

Collagen has a triple helix structure that provides flexibility. Recent studies show that mineral crystals wrap around collagen fibers, enhancing the bone's strength. Historical experiments, such as those by John Hunter in the 1870s, demonstrated that removing calcium from bones left only collagen, which became soft enough to tie into knots, highlighting collagen's flexibility.



Non-Collagenous Proteins

In addition to collagen, bones contain non-collagenous proteins that play various roles:

- They assist in the mineralization process and stabilize mineral crystals.
- They attract and mediate attachment of bone cells (osteoblasts/osteoclasts) to the surface, facilitating bone remodeling, and release growth factors to stimulate them
- Some non-collagenous proteins, like osteocalcin, are released into circulation to regulate calcium metabolism in other body parts.

These proteins are essential for maintaining bone health and function, as they help coordinate the activities of bone-forming cells (osteoblasts) and bone-resorbing cells (osteoclasts).

Osteoclasts

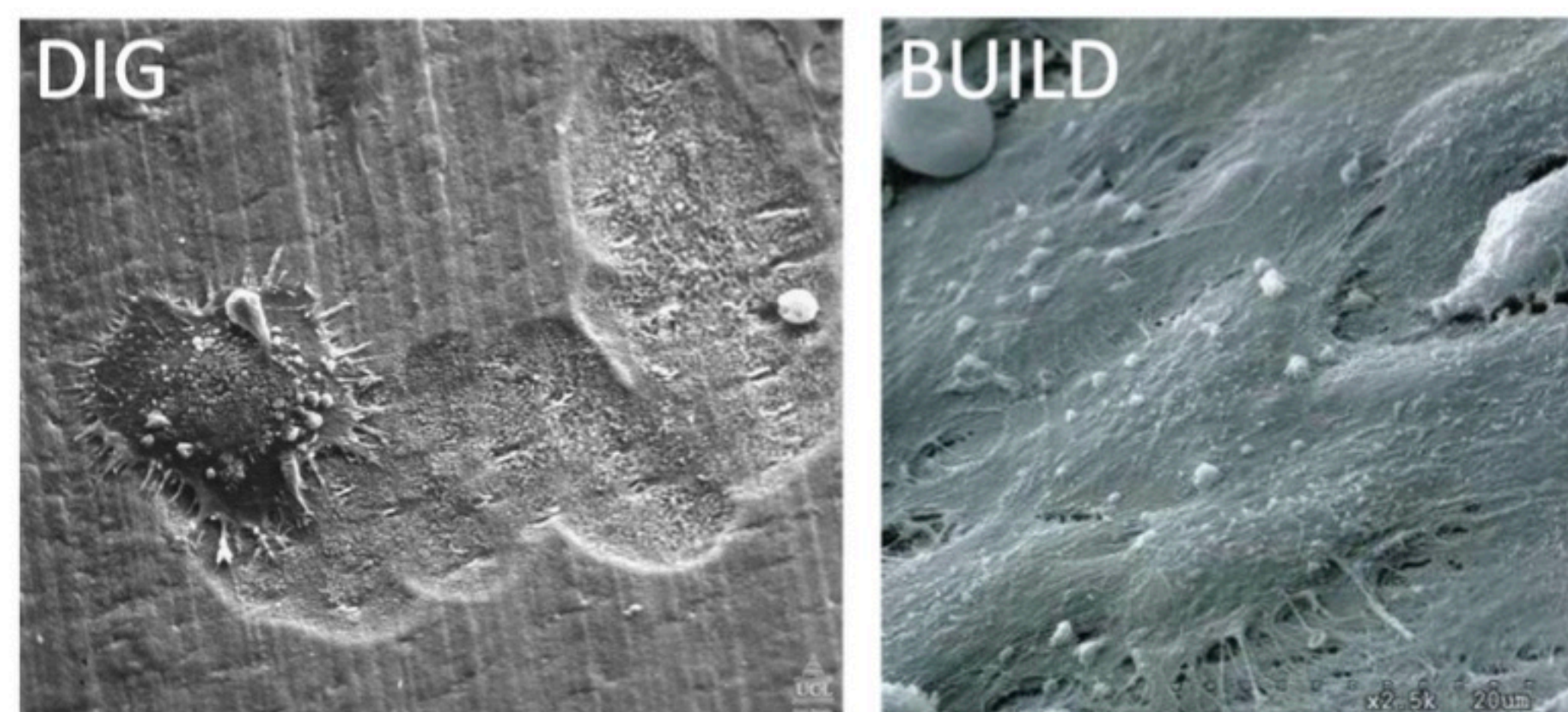
Osteoclasts are specialized cells that resorb bone tissue, effectively removing it from the skeletal structure. They play a significant role in conditions such as rheumatoid arthritis, where they contribute to bone destruction. An electron microscope image shows osteoclasts actively digging into the bone surface.

- Function: Bone resorption
- Role in diseases: Contributes to bone destruction in rheumatoid arthritis
- Mechanism: Remove both collagenous matrix and mineral components of bone

Osteoblasts

Osteoblasts are less visible due to their close association with one another, forming tight junctions. They work in teams to build bone, akin to a brick-laying crew. Their primary function is to create new bone tissue, replacing what osteoclasts have resorbed.

- Function: Bone formation
- Teamwork: Work closely together to build bone
- Analogy: Similar to a construction team laying bricks



Osteoclasts

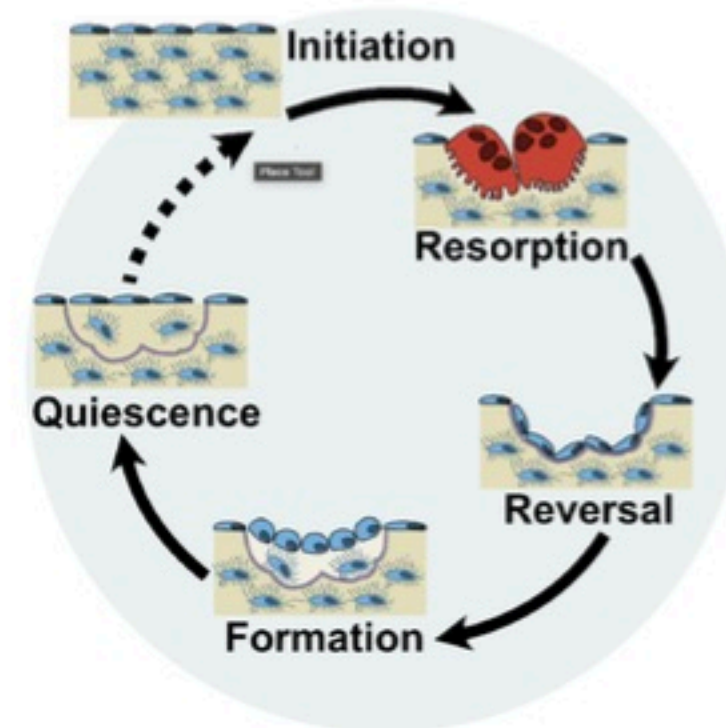
Balance is important!

Osteoblasts

Bone Remodeling Cycle

The balance between osteoclasts and osteoblasts is crucial for maintaining bone health. Throughout life, the skeleton undergoes a continuous remodeling process, with the entire skeleton being replaced approximately every 10 years.

- Remodeling Cycle:
 - **Resorption:** Osteoclasts resorb small pockets of bone.
 - **Reversal:** occurs where the surface is prepared for new cells.
 - **Formation:** Osteoblasts form new bone, which eventually mineralizes.
 - **Quiescence:** The site enters a quiescent phase until the next cycle.
- Importance of Remodeling:
 - Repairs micro-damage from normal physical activity.
 - Regulates calcium availability in the bloodstream.
 - Adapts to increased mechanical load from activities.

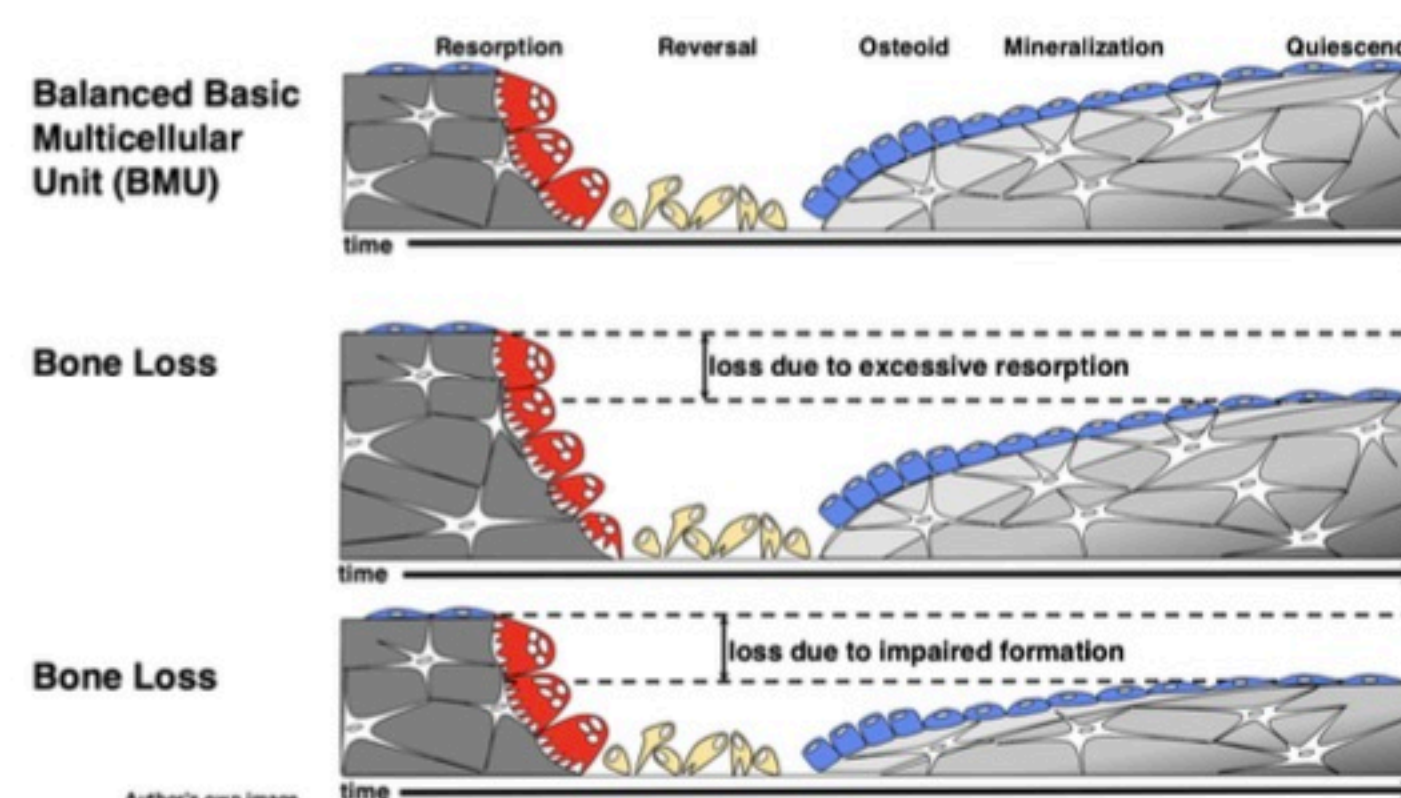


Initiated asynchronously throughout the skeleton, at sites that are geographically and chronologically separated.

Basic Multicellular Unit (BMU)

The remodeling process occurs in what is known as a Basic Multicellular Unit (BMU), which consists of multiple cells working together. An imbalance between osteoclast and osteoblast activity can lead to bone loss, particularly in conditions like osteoporosis.

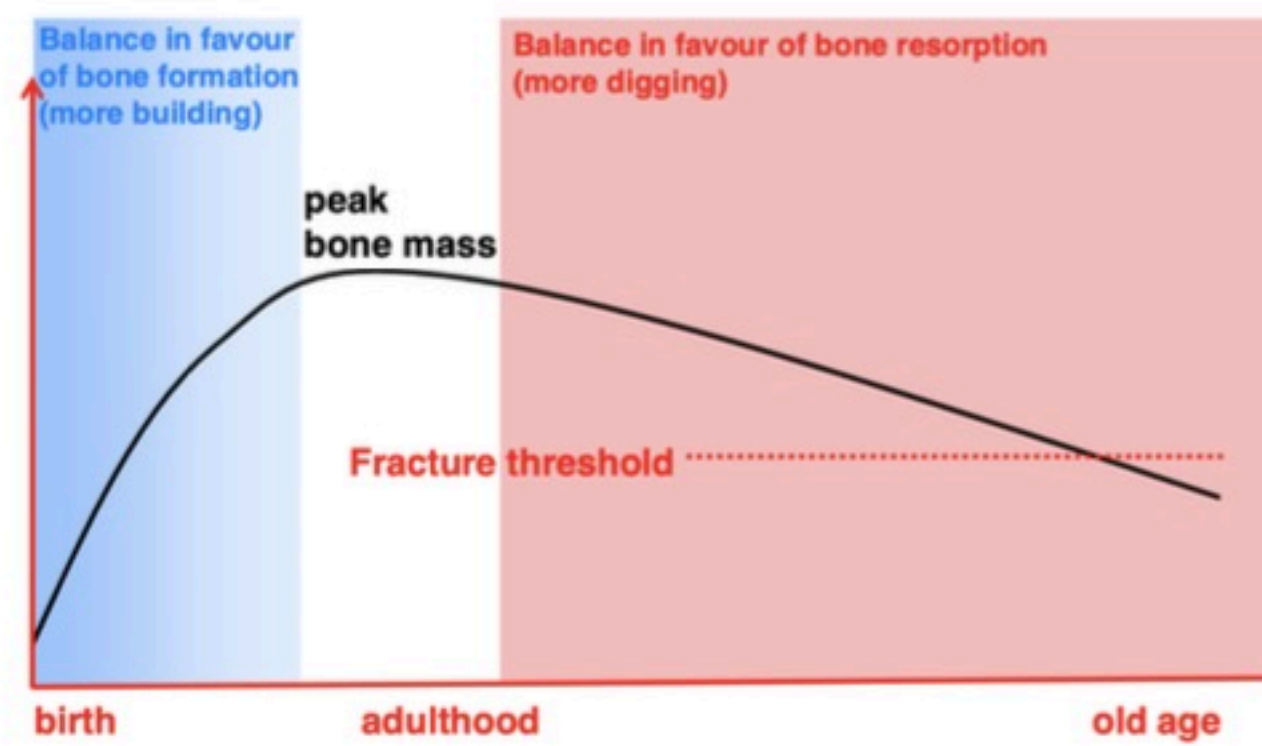
- Imbalance Consequences:
 - Excessive resorption leads to bone loss.
 - Insufficient formation fails to keep up with normal resorption.



Bone Mass Changes Over Time

Bone mass is not constant throughout life. It increases from birth to adulthood and gradually declines with age. This decline can lead to conditions such as osteoporosis, where the risk of fractures increases due to decreased bone density.

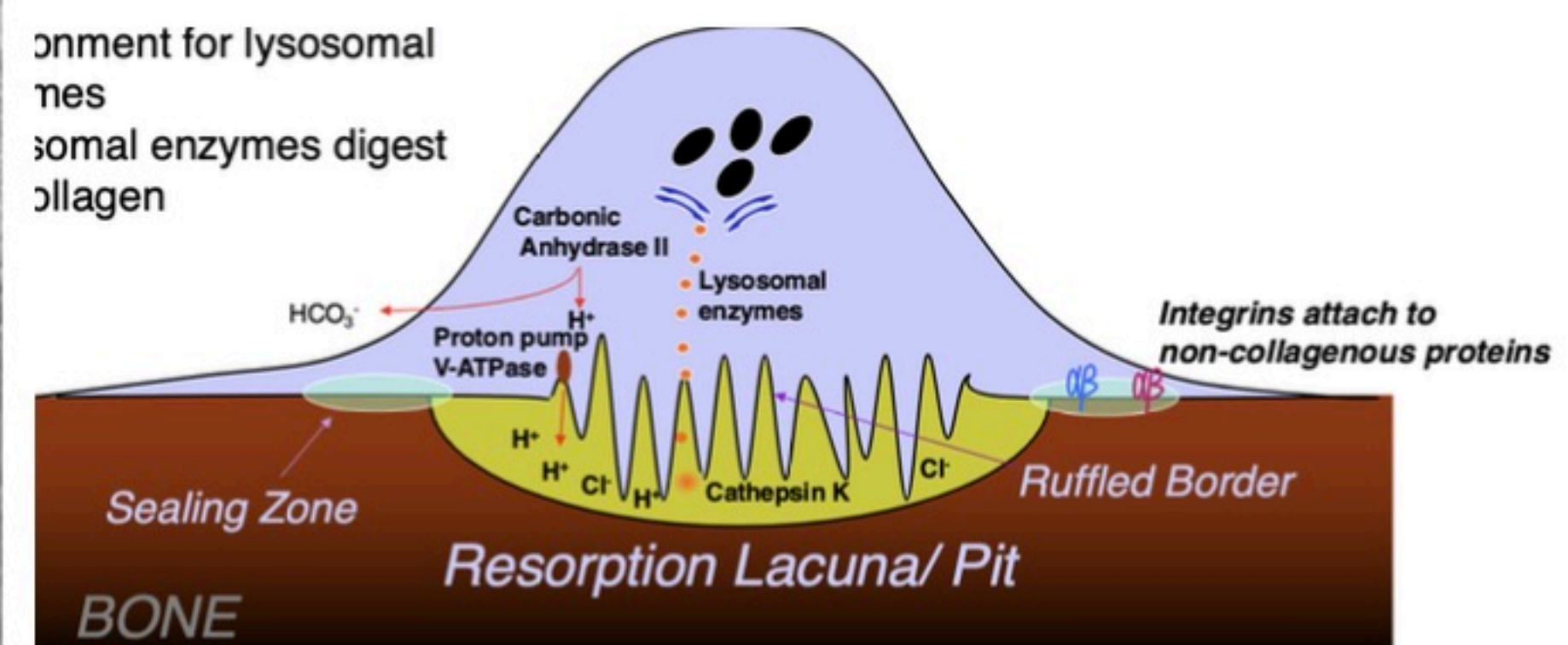
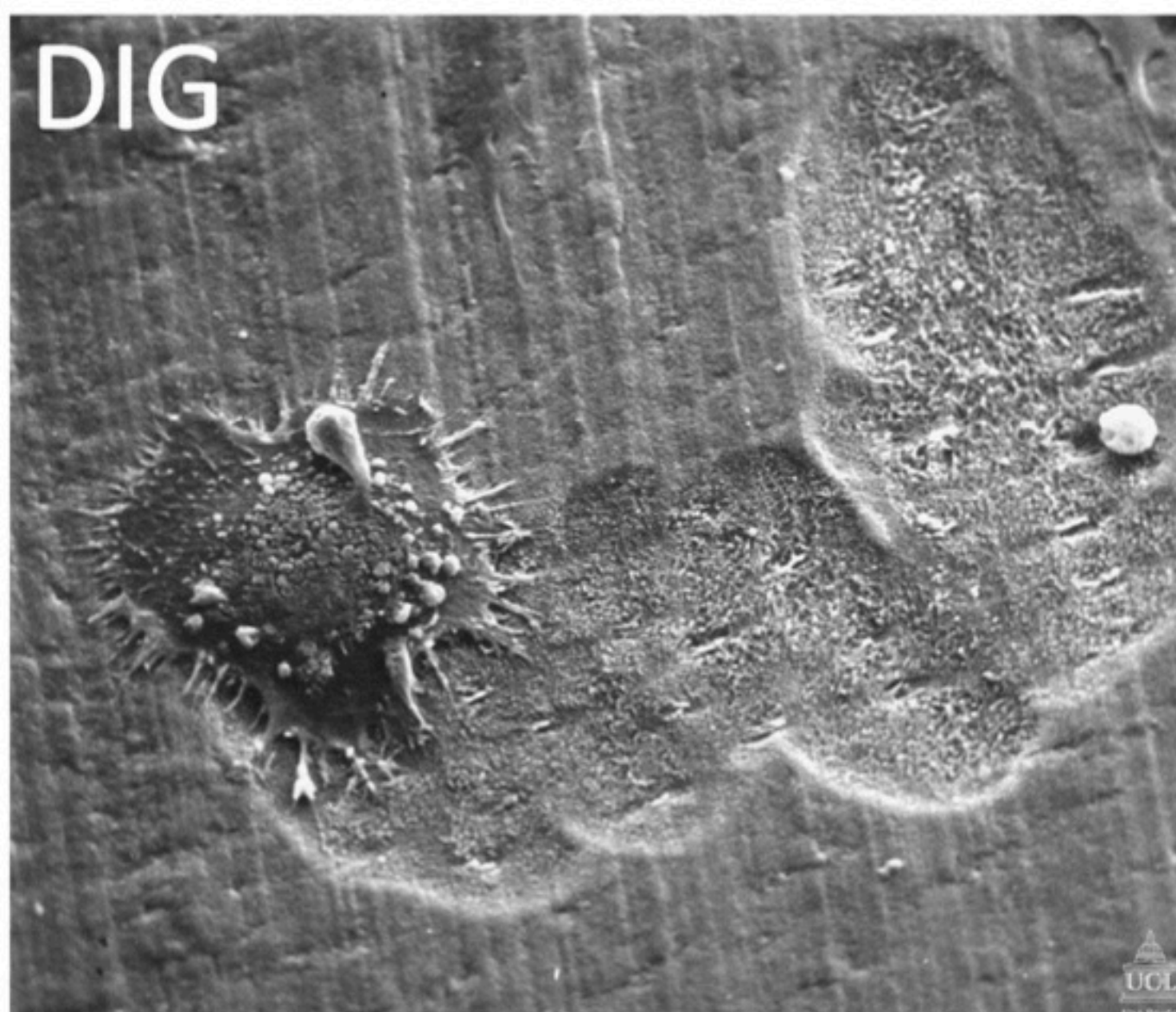
- Growth Phase: Bone formation exceeds resorption, leading to increased bone mass.
- Aging Phase: Resorption outpaces formation, resulting in gradual bone loss.



Mechanism of Osteoclast Function

Osteoclasts are derived from hematopoietic cells in the bone marrow and form through the fusion of precursors into multinucleated cells. They are highly motile and attach to the bone surface, creating a ruffled border that increases their surface area for resorption.

- Ruffled Border:
 - Increases surface area for ion exchange.
 - Creates an acidic microenvironment for mineral removal.
- Resorption Process:
 - Resorbs bone mineral and collagenous matrix
 - Cells move across the bone surface, leaving a trail of resorbed bone
 - Acidic environment dissolves mineral components (e.g. calcium).
 - Lysosomal enzymes like cathepsin K under low pH digest collagen.



Diagnosis and Treatment

Learning Outcomes

- Describe the different disease stages of type 1 diabetes leading to clinical diagnosis
- Know the basic risk factors and biomarkers used for predicting risk and disease progression
- Explain basic principles for treatment and management of type 1 diabetes

Type 1 Diabetes

Type 1 diabetes results from the immune system destroying beta cells, leading to an absolute deficiency of insulin. This destruction causes dysregulated blood glucose levels, requiring insulin injections from the onset of the disease. The immune-mediated destruction is irreversible, and no lifestyle changes can prevent this process. Despite the need for insulin therapy, maintaining a healthy diet and exercise regimen remains important for managing overall health and blood glucose control.

Type 2 Diabetes

Type 2 diabetes primarily involves insulin resistance, where the body's tissues do not respond properly to insulin, despite its normal or increased production. Over time, the beta cells attempt to compensate by producing more insulin, leading to hyperinsulinemia. Eventually, these cells become exhausted and fail to produce sufficient insulin, resulting in dysregulated blood glucose levels similar to type 1 diabetes. Unlike type 1, type 2 is often preventable through lifestyle modifications such as diet and exercise, although it is not curable.

Differences in Treatment Approaches

In type 1 diabetes, insulin injections are necessary immediately because of the absence of beta cells. In contrast, type 2 diabetes may initially be managed with oral medications and lifestyle changes, with insulin therapy introduced later if needed. The goal of these drugs is to improve insulin sensitivity and control blood glucose levels. Specific mechanisms of action of these drugs are outside the scope of this module, but they generally aim to enhance the body's response to insulin or reduce glucose production.

Prevention and Management

Type 2 diabetes can often be prevented through healthy lifestyle choices, including balanced diet and regular exercise. Conversely, type 1 diabetes cannot be prevented because it stems from autoimmune destruction of beta cells. Nonetheless, individuals with type 1 diabetes require ongoing insulin management and a healthy diet to maintain blood glucose control and prevent complications.

Stages of Type 1 Diabetes Development

Stage 1: Risk Factors and Autoimmunity Initiation

Genetic and environmental factors increase the risk of developing type 1 diabetes. The initial event, likely an autoimmune response, triggers the destruction of beta cells. Detection at this stage involves identifying autoantibodies against beta cell antigens in the blood, with individuals still maintaining normal blood glucose levels due to sufficient functional beta cells.

Stage 2: Early Autoimmune Activity and Blood Glucose Changes

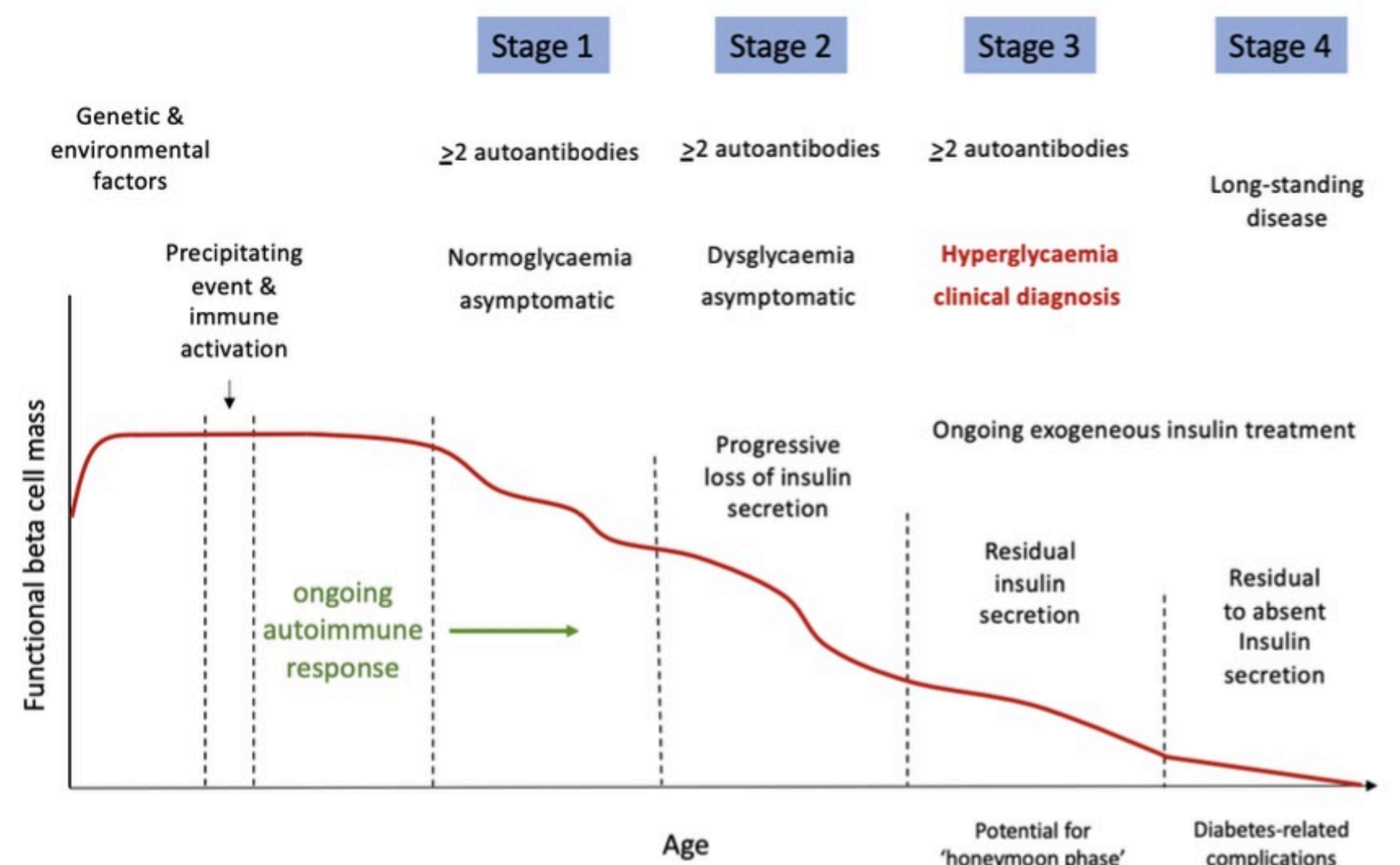
At this stage, individuals have more than two autoantibodies, and blood tests reveal abnormal or elevated blood glucose levels, especially after carbohydrate intake. There is also a decline in insulin production and beta cell mass, although symptoms are not yet apparent. Special tests, such as glucose tolerance tests, can detect these early changes.

Stage 3: Onset of Clinical Diabetes

Individuals continue to have multiple autoantibodies, but now exhibit hyperglycemia and clinical symptoms of diabetes. Insulin production is insufficient, necessitating treatment with exogenous insulin. This stage marks the transition from preclinical to clinical diabetes, with the disease becoming more apparent and requiring medical intervention.

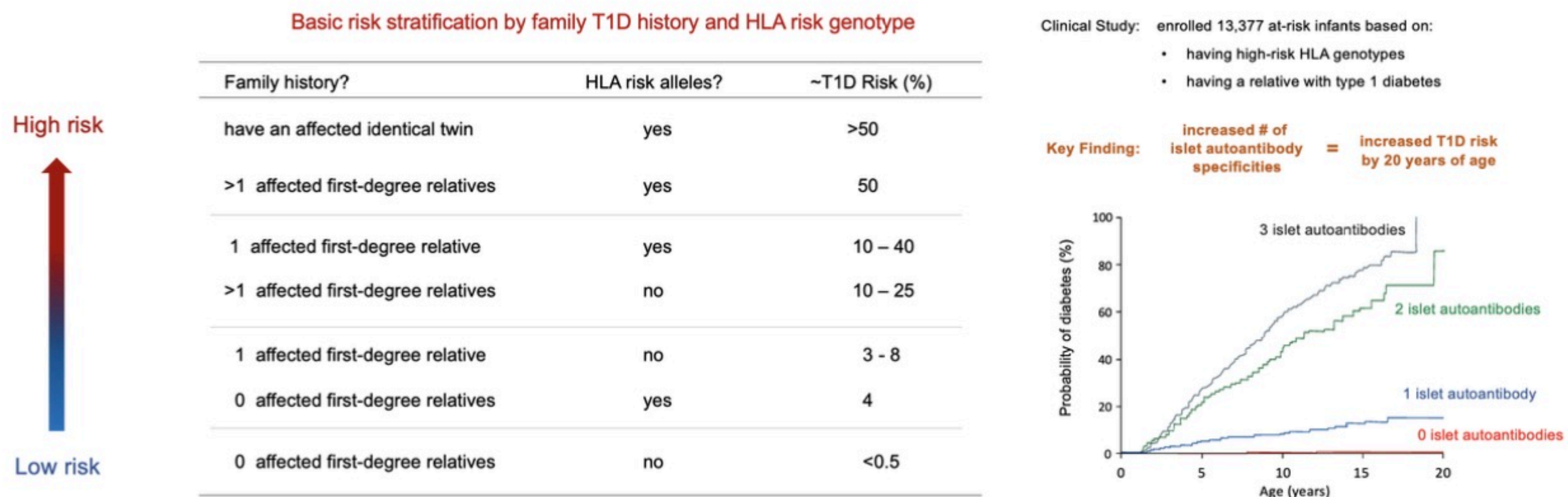
Stage 4: Long-term Complications

This stage involves the development of long-term diabetes complications, especially if blood glucose levels have been poorly managed. These complications include neuropathy, retinopathy, nephropathy, and cardiovascular issues. The progression from stage 1 to stage 3 varies among individuals, influenced by genetic predisposition and environmental exposures.



Predicting and Diagnosing Type 1 Diabetes: Genetic and Immunological Markers

Family history and specific HLA alleles are key genetic risk factors. The presence of certain HLA risk alleles, especially in individuals with a family history, significantly increases the likelihood of developing type 1 diabetes. Risk assessment involves analyzing these genetic markers and autoantibodies in the blood.



Autoantibodies as Predictive Biomarkers

Autoantibodies targeting beta cell antigens serve as important biomarkers. The number and specificity of these autoantibodies correlate with the risk of developing diabetes. For example, having three or more autoantibodies against different islet cell antigens strongly predicts the development of type 1 diabetes by age 20. The presence of fewer autoantibodies indicates a lower risk.

Risk Stratification and Disease Progression

Combining family history, HLA genotypes, and autoantibody profiles allows clinicians to stratify risk levels. Individuals with multiple autoantibodies are almost certain to develop diabetes, with the timing varying based on individual factors. However, predicting the exact age of onset remains challenging due to variability in disease progression.

Assessing Beta Cell Function and Disease Monitoring: Indirect Measurement of Beta Cell Mass

Direct measurement of pancreatic beta cell mass in living individuals is currently not feasible. Instead, indirect methods are used to assess beta cell function, such as measuring insulin or C-peptide levels in the blood. These indicators reflect the ability of remaining beta cells to produce insulin in response to glucose.