

Toxic Myopathies and Myopathy With Metabolic Changes

Pathologic mechanisms · Morphology · Clinicopathologic interpretation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

Different mechanisms can yield the same clinical presentation.

- Classify drug- and hormone-associated muscle injury by its primary cellular target.
- Explain muscle necrosis, vacuolation, selective atrophy, and thick-filament loss.
- Distinguish direct drug toxicity from immune-mediated necrotizing myopathy.
- Apply exposure history and morphology to focused diagnostic reasoning.

Scope: Acquired muscle disease

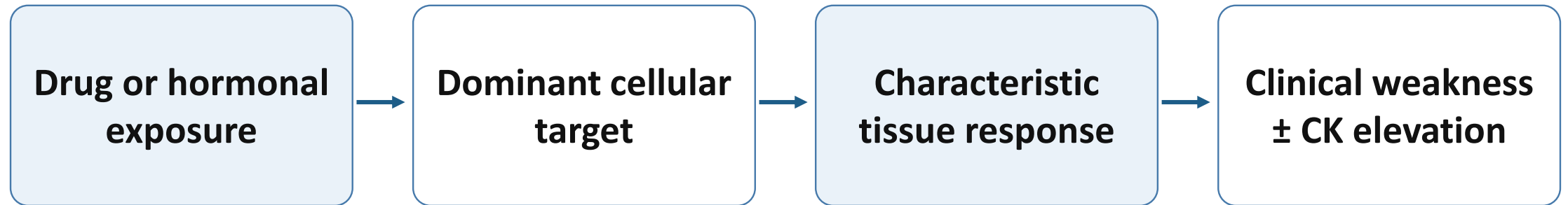
Medications, non-medicinal substances, and hormonal states may produce weakness and muscle injury.

- The effects are not restricted to one pathologic mechanism.
- Some exposures cause myofiber necrosis; Others preferentially injure organelles.
- Still others produce fiber-type-selective atrophy or sarcomeric protein loss.
- Creatine kinase (CK) may rise with muscle damage, but phenotypes differ.

Six mechanisms at a glance

Mechanism	Representative exposure	Pathologic emphasis
Direct myonecrosis	Statins · fibrates · high-dose alcohol	Myofiber necrosis
Immune mediated	Statins · checkpoint inhibitors	Necrosis with limited inflammation in IMNM
Mitochondrial	Zidovudine	Organelle injury
Lysosomal	Hydroxychloroquine · chloroquine	Vacuolar change
Protein catabolism	Corticosteroids · critical illness	Type II atrophy or myosin depletion
Hormonal	Thyroid excess or deficiency	Functional and structural changes

The exposure-to-phenotype framework



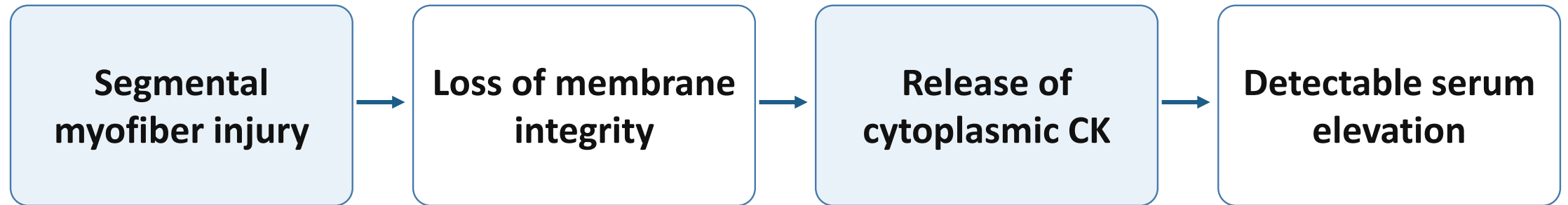
Mechanistic relationship—not a diagnostic algorithm

A common symptom need not imply a common mechanism.

Weakness and CK are not the mechanism

Observation	What it establishes	What it does not establish
Proximal weakness	A clinically important functional deficit	Whether the cause is necrotic, atrophic, or organellar
Elevated serum CK	Leakage of muscle cytoplasmic enzyme	A unique etiology or immune pathogenesis
Drug exposure	A plausible cause to investigate	Proof of direct toxicity without further correlation

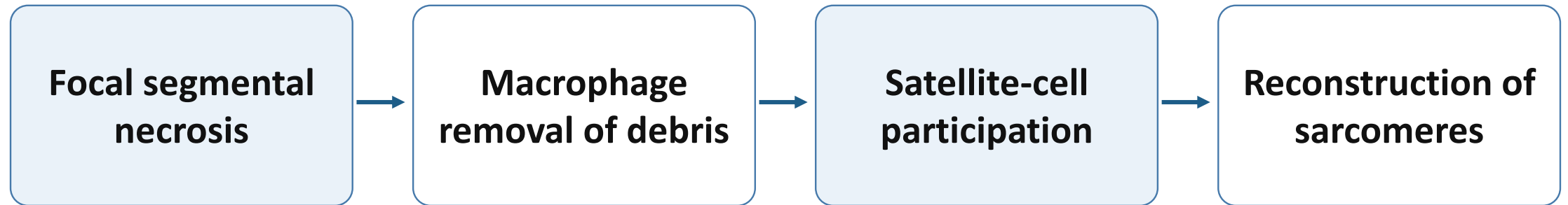
Why damaged myofibers release CK



Mechanistic relationship—not a diagnostic algorithm

CK is a marker of damaged muscle, not a mechanism-specific biomarker.

Necrosis, myophagocytosis, regeneration



Mechanistic relationship—not a diagnostic algorithm

Regeneration follows clearance of necrotic myofiber material.

Interpret CK within the muscle phenotype

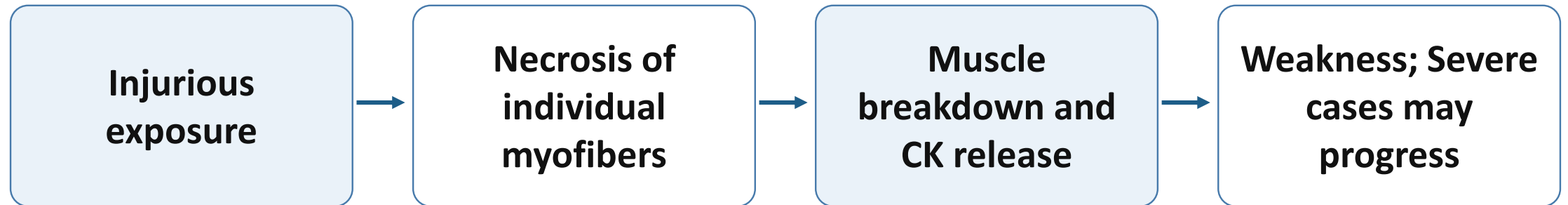
CK elevation is clinically useful, but its interpretation depends on the associated pattern.

- Direct myofiber necrosis can release abundant cytoplasmic enzymes.
- Morphologic fiber atrophy is mechanistically different from fiber necrosis.
- A toxic exposure and an immune-mediated process may initially resemble one another.
- Integrate exposure, weakness, muscle morphology, and the clinical course.

Acute myonecrotic agents

Agent / class	Source-supported association	Clinical implication
Statins	Acute necrosis of individual fibers	Rhabdomyolysis possible when severe
Fibrates	Acute myofiber injury and necrosis	Consider in drug exposure history
High-dose alcohol	Acute myofiber injury and necrosis	Non-medicinal exposure may be relevant

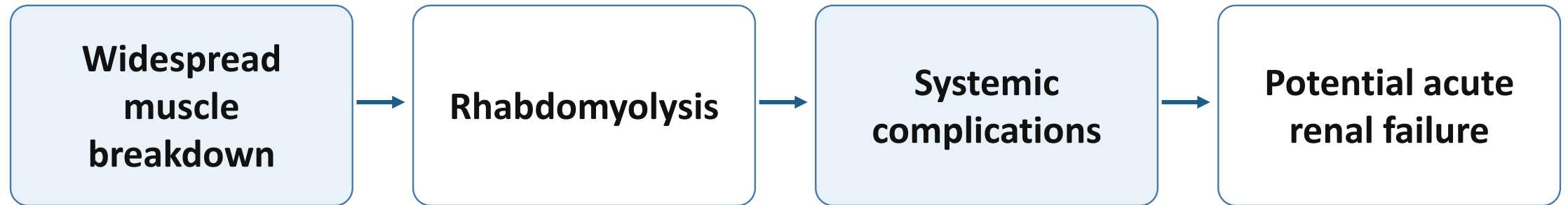
Direct toxicity: Segmental injury



Mechanistic relationship—not a diagnostic algorithm

“Direct” refers to toxic myofiber injury, not to a biopsy pattern uniquely diagnostic of a drug.

Severe myonecrosis may become rhabdomyolysis



Mechanistic relationship—not a diagnostic algorithm

The renal complication is explicitly emphasized; No incidence or threshold is specified.

Renal risk is a major consequence

The severity of myofiber necrosis determines whether the problem remains localized or becomes systemic.

- Rhabdomyolysis is a severe form of muscle breakdown.
- Acute renal failure is a recognized complication.
- Clinical assessment must therefore extend beyond limb weakness.
- The source does not specify CK cutoffs or a treatment algorithm.

Direct statin toxicity: Predisposing factors

**Increased risk of direct
statin toxicity**

Higher statin dose

Age >65 years

Renal failure

Hepatic failure

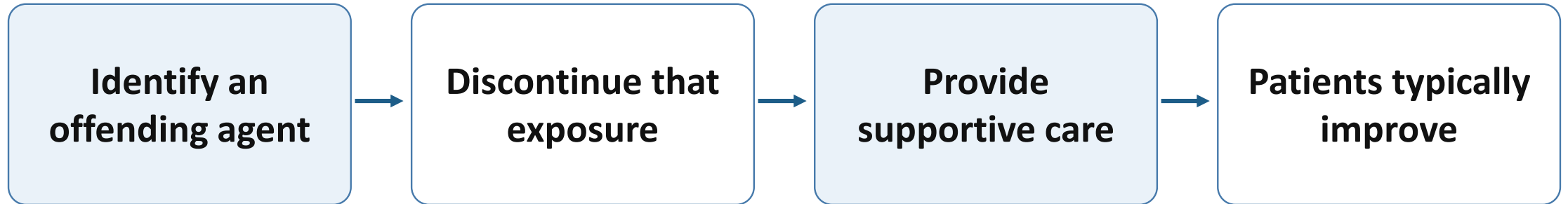
Hypothyroidism

Statin exposure is not one phenotype

The same drug class can be associated with different causal pathways.

- Direct statin myotoxicity is dose- and host-factor-associated.
- Statin exposure may also be associated with immune-mediated necrotizing myopathy.
- The initial presentation may not distinguish these mechanisms reliably.
- Risk factors for direct toxicity should not be equated with diagnostic criteria for IMNM.

Expected course of direct toxicity



Mechanistic relationship—not a diagnostic algorithm

A typical improvement after withdrawal; It does not guarantee full or immediate recovery.

Case 1 · suspected direct myonecrosis

HYPOTHETICAL PRESENTATION

An older adult taking a statin develops new muscle weakness with elevated CK. Renal impairment and hypothyroidism are also present.

Which source-supported factors strengthen the possibility of direct statin toxicity?

REASONING PROMPTS

- Drug dose matters.
- Age over 65, renal failure, and hypothyroidism are recognized risk factors.

Case 1 · reasoning

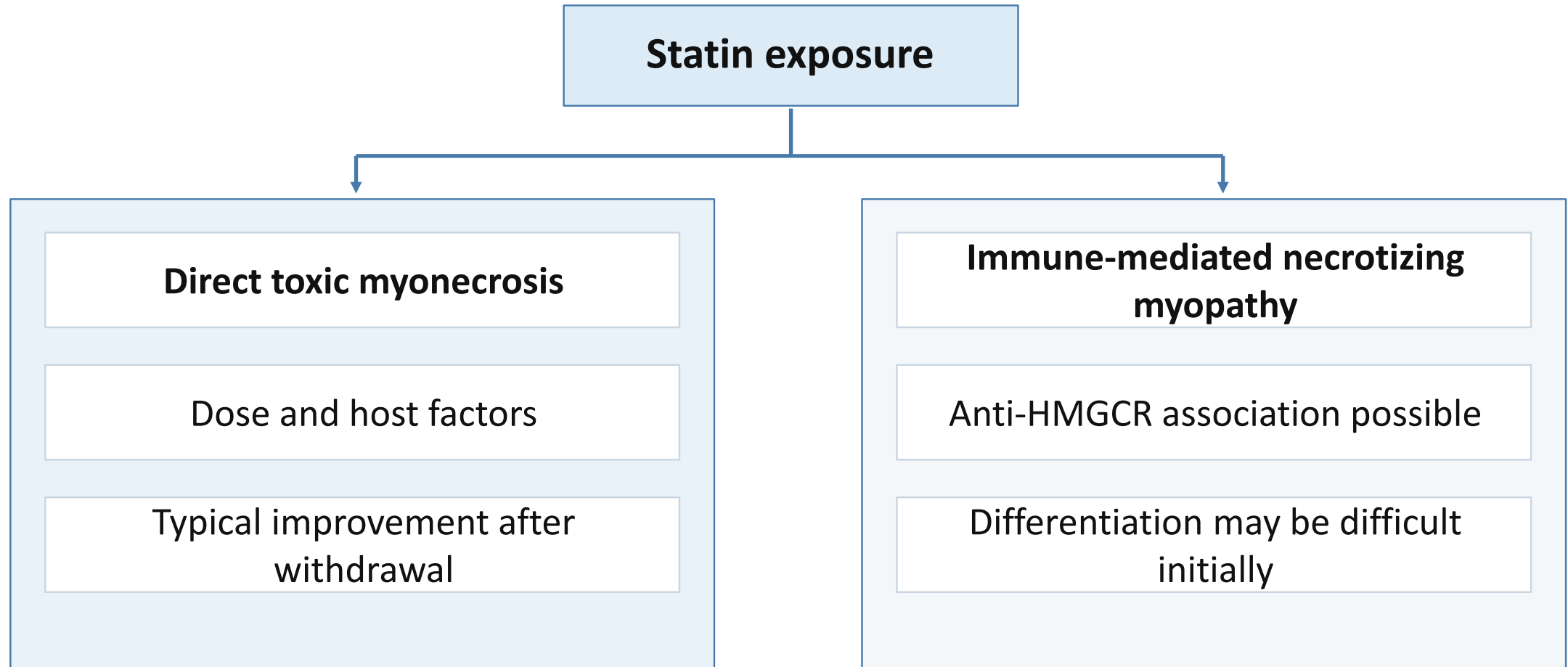
The exposure and host factors support a direct toxic pathway, but they do not prove it.

- Higher statin dose is associated with greater direct toxicity risk.
- Renal failure and hypothyroidism are additional risk factors.
- Severe necrotic injury warrants attention to rhabdomyolysis and renal effects.
- A distinct immune-mediated pathway remains part of the differential.

Immune-mediated drug-associated myopathy

Exposure	Robbins association	Interpretive issue
Statins	May trigger immune-mediated myopathy	Direct toxicity versus IMNM
Immune checkpoint inhibitors	May trigger immune-mediated myopathy	Exposure alone does not define subtype
No preceding statin exposure	Anti-HMGCR IMNM can still occur	Statin history is not obligatory

Two routes from statin exposure



IMNM: Tissue injury out of proportion to inflammation

Immune-mediated necrotizing myopathy (IMNM) is defined by prominent myofiber necrosis.

- Typically high CK and rapidly progressive weakness.
- Necrotic and regenerating fibers are randomly intermixed.
- Associated inflammatory infiltrates may be sparse.
- Minimal inflammation therefore does not by itself exclude an immune process.

Anti-HMGCR myopathy and statin history

Antibodies to HMG-CoA reductase occur in a subset of IMNM.

- HMG-CoA reductase is involved in cholesterol synthesis.
- Antibodies are described in patients previously exposed to statins.
- They are also described in statin-naïve patients.
- Never use statin exposure alone as a requirement for this antibody-associated phenotype.

Anti-SRP: A separate IMNM association

Antibodies to the signal recognition particle (SRP) identify another associated IMNM group.

- Anti-SRP IMNM may be especially severe.
- Dysphagia occurs more often in this subset.
- Cardiac involvement may develop.
- These features provide context, but the lecture remains focused on toxic and metabolic myopathies.

Checkpoint inhibitors and immune injury

Immune checkpoint inhibitors are another medication class implicated in immune-mediated myopathy.

- The defining issue is immune-associated muscle damage, not direct organelle toxicity.
- The exact pathology and severity must be established in the affected patient.
- Robbins gives the association without drug-specific diagnostic cutoffs.
- Avoid assuming that every affected patient has anti-HMGCR or anti-SRP antibodies.

Direct statin toxicity versus IMNM

Feature	Direct toxic pathway	Immune-mediated necrotizing pathway
Pathogenesis	Myofiber-toxic injury	Immune-mediated muscle injury
Clinical pattern	Weakness and CK elevation	Often severe weakness and high CK
Biopsy concept	Necrosis may occur	Prominent necrosis / regeneration; sparse inflammation
Drug withdrawal	Typical improvement with withdrawal	Cannot be assumed sufficient from exposure alone

Case 2 · severe weakness after statin exposure

HYPOTHETICAL PRESENTATION

A person receiving a statin develops rapidly progressive weakness and a striking CK elevation. Biopsy shows scattered necrotic and regenerating myofibers with little inflammation.

Which competing pathway deserves attention?

REASONING PROMPTS

- Necrotizing morphology with sparse inflammation can occur in IMNM.
- Statin exposure also permits direct toxicity.

Case 2 · pathologic interpretation

Do not infer direct drug toxicity merely because a statin preceded the myopathy.

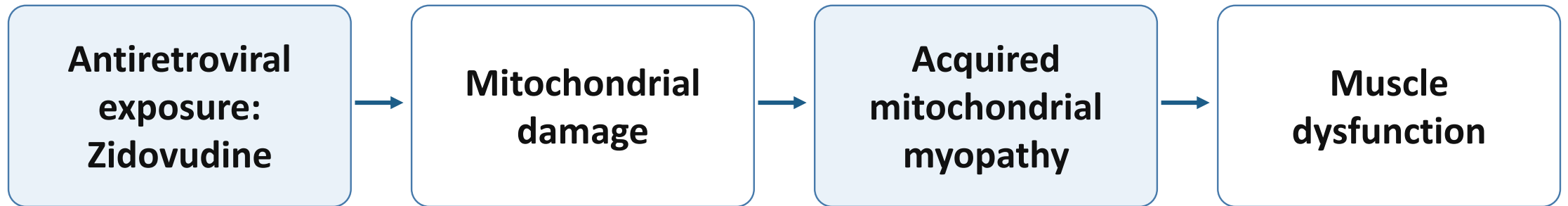
- The biopsy pattern is compatible with IMNM in the appropriate setting.
- Sparse inflammatory cells do not disprove an immune-mediated necrotizing process.
- Anti-HMGCR and anti-SRP are relevant antibody associations in the adjacent Robbins section.
- Clinical evaluation must distinguish the processes rather than collapse them.

Mitochondria are another drug target

A toxic myopathy can result from injury to an intracellular energy-producing organelle.

- Zidovudine as an acquired mitochondrial myopathy exposure.
- This mechanism differs from sarcolemmal injury with acute necrosis.
- Inherited mitochondrial disorders also exist, but are a separate etiologic category.
- The central diagnostic task is to match the exposure to the mechanism.

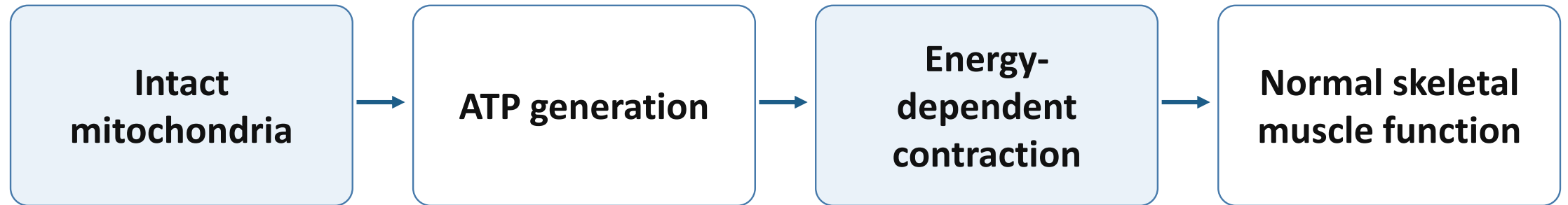
Zidovudine and acquired mitochondrial injury



Mechanistic relationship—not a diagnostic algorithm

The source identifies this association; No frequency or exposure threshold is given.

Energy generation and muscle function



Mechanistic relationship—not a diagnostic algorithm

Mitochondrial disease can compromise ATP production. This is a general concept from the adjacent Robbins mitochondrial section.

Acquired versus inherited mitochondrial myopathy

Dimension	Acquired drug-associated	Inherited mitochondrial disease
Initiating cause	Exogenous mitochondrial toxicant	Pathogenic genetic alteration
Example or context	Zidovudine exposure	Nuclear or mitochondrial genes
Teaching boundary	A toxic myopathy subtype	Separate inherited disease topic

Case 3 · a mitochondrial exposure clue

HYPOTHETICAL PRESENTATION

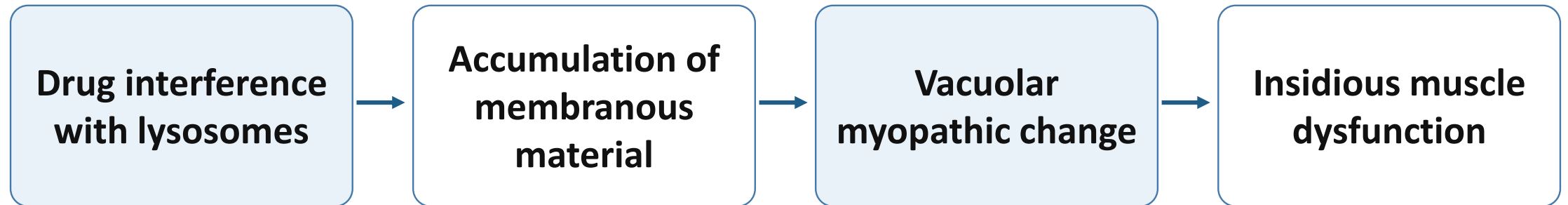
A patient using zidovudine develops muscle weakness. The team considers a medication-associated acquired mitochondrial myopathy.

Which cellular target is explicitly associated with this medication?

REASONING PROMPTS

- Mitochondria are the implicated target.
- Do not infer a particular genetic defect from the drug history.

Lysosomal dysfunction: A different route



Mechanistic relationship—not a diagnostic algorithm

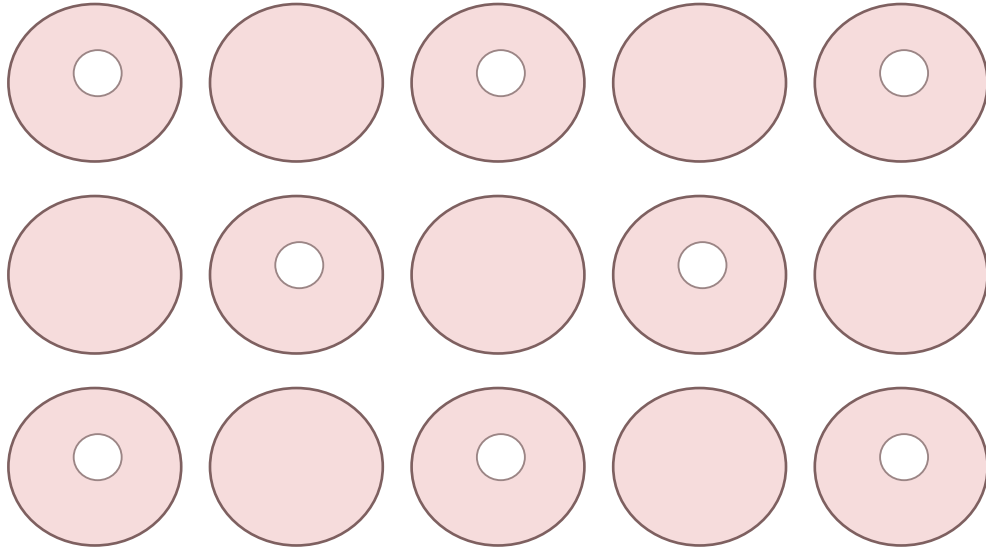
The source describes lysosomal-storage-disease-like changes, not inherited storage disease.

Chloroquine and hydroxychloroquine

These agents may cause insidious toxic myopathy through interference with lysosomal function.

- The clinical time course may be gradual rather than acutely necrotizing.
- Muscle pathology can resemble a lysosomal storage disorder.
- Vacuoles are a major tissue clue.
- Cardiac muscle may show a similar drug-related process.

Vacuoles as the light-microscopic clue

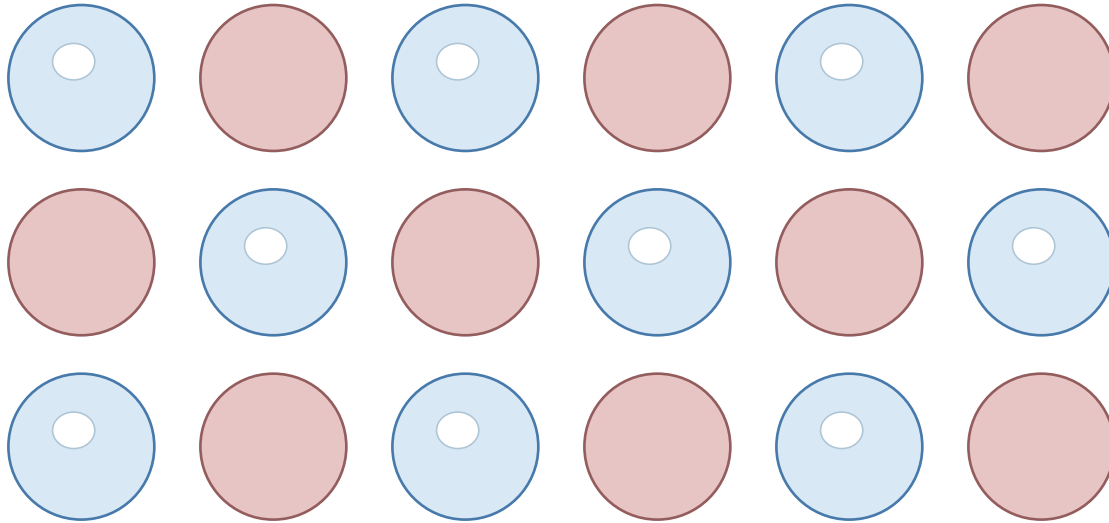


READING THE SCHEMATIC

1. Myofiber cross-section
2. Intracytoplasmic vacuoles
3. Interpret with medication history

Conceptual schematic: Intrafiber vacuolation; Not a real histologic specimen.

Type I fibers are preferentially involved

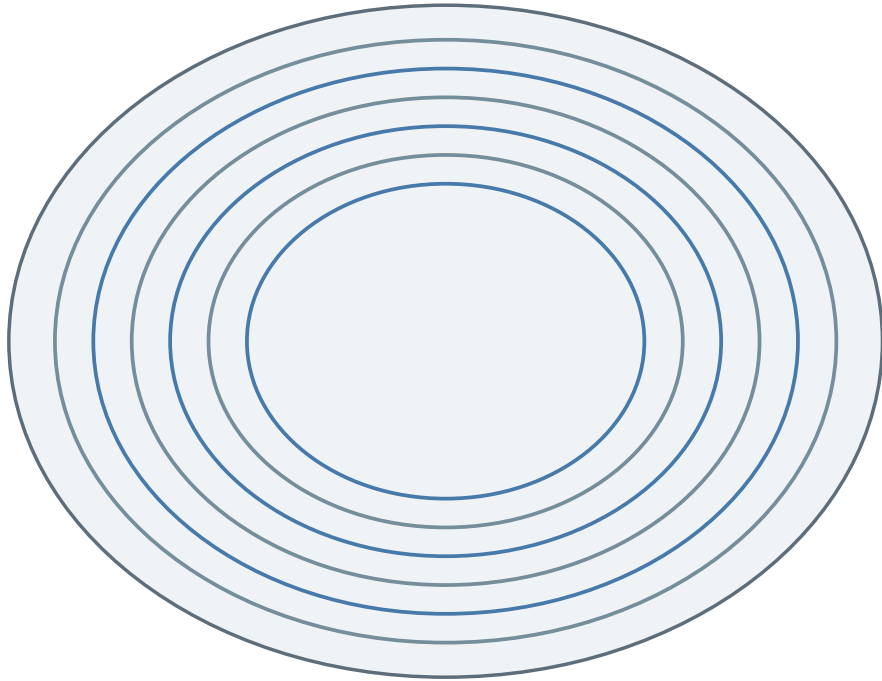


READING THE SCHEMATIC

1. Type I fibers: Preferential vacuolation
2. Type II fibers: Less prominently affected
3. Fiber typing provides mechanistic context

Conceptual fiber-type map; Not an ATPase-stained biopsy.

Lamellar inclusions on electron microscopy



READING THE SCHEMATIC

1. Whorled lamellar membranous aggregates
2. Ultrastructural correlate of organelle injury
3. Do not equate with every rimmed vacuole

Native vector schematic of membrane whorls; Not an electron micrograph.

Why the heart also matters

The pathologic effect of lysosomal-toxic medication exposure is not necessarily confined to skeletal muscle.

- Cardiac involvement with chloroquine or hydroxychloroquine.
- Cardiac muscle may exhibit similar pathologic changes.
- A skeletal-muscle-focused history can miss this extra-skeletal dimension.
- The source gives no specific cardiac prevalence or screening protocol.

Acquired vacuolar change versus storage disease

Feature	Drug-related lysosomal dysfunction	Inherited lysosomal storage condition
Proposed etiology	Drug interference with lysosomes	An inherited metabolic mechanism
Biopsy overlap	Vacuolation / membranous aggregates	May resemble vacuolar myopathy
Key discriminant	Drug history and disease context	Independent evaluation of inherited disease

Case 4 · vacuoles on muscle biopsy

HYPOTHETICAL PRESENTATION

A patient on prolonged hydroxychloroquine therapy develops slowly progressive weakness. Muscle biopsy shows vacuolation; Whorled lamellar membrane structures are seen on electron microscopy.

What is the most coherent mechanism?

REASONING PROMPTS

- The drug can interfere with lysosomal function.
- The acquired condition may mimic a lysosomal storage disease.

Case 4 · interpreting the biopsy

The combination of exposure, course, and morphology favors a drug-associated lysosomal lesion.

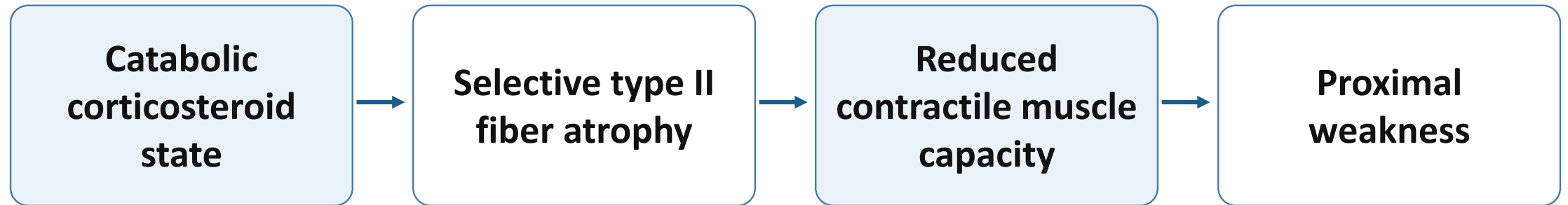
- Insidious onset fits chloroquine/hydroxychloroquine-associated myopathy.
- Vacuoles preferentially involve type I fibers in the Robbins description.
- Lamellar membranous material is the ultrastructural clue.
- The pathologist should avoid diagnosing inherited storage disease solely from a vacuolated fiber.

Corticosteroids: A catabolic muscle phenotype

Endogenous and exogenous catabolic corticosteroid exposure can lead to muscle weakness.

- The hallmark change is selective type II myofiber atrophy.
- Proximal weakness is the common functional correlate.
- This is a predominantly atrophic pattern rather than a primary vacuolar one.
- The morphologic target helps separate it from acute myonecrosis.

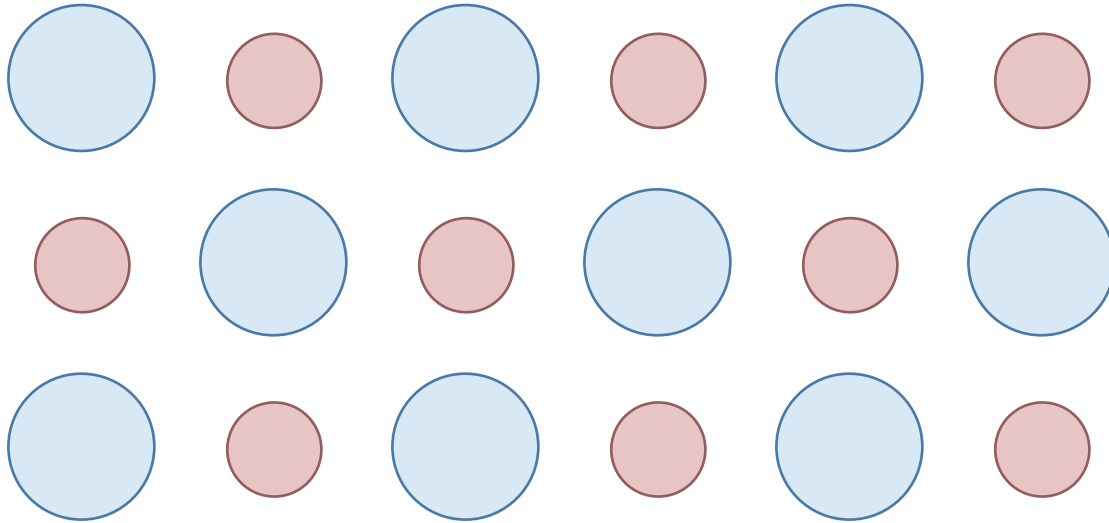
Steroid effect: Protein balance to atrophy



Mechanistic relationship—not a diagnostic algorithm

Schematic causal organization of the source-described association.

Type II fiber atrophy: Selective pattern



READING THE SCHEMATIC

1. Type II fibers reduced in diameter
2. Type I fibers relatively preserved
3. Compare with drug-related vacuolation of type I fibers

Conceptual type I/type II fiber map; Not clinical histology.

Proximal weakness has multiple causes

Proximal weakness alone is insufficient to assign a drug mechanism.

- Corticosteroid states: Selective type II atrophy.
- Thyrotoxicosis: Proximal weakness may be acute or chronic.
- Toxic necrosis: Individual myofiber damage and CK leakage.
- Immune-mediated necrotizing myopathy: Severe weakness with prominent necrosis.

Critical illness myopathy: Clinical setting

A distinct acquired neuromuscular disorder may arise in critically ill patients in the intensive care unit.

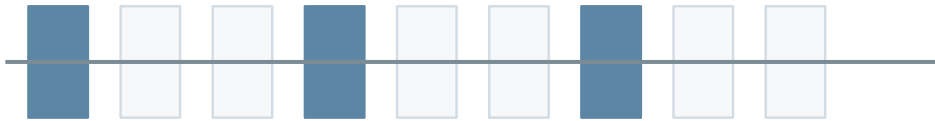
- Robbins also calls it myosin-deficient myopathy.
- A described context includes corticosteroids and depolarizing neuromuscular blocking agents.
- Mechanical ventilation is part of the clinical setting.
- Profound weakness can become an obstacle to recovery.

Critical illness: Myosin thick-filament loss

Intact sarcomere: Thick-filament zone



Myosin-deficient state: Fewer thick filaments

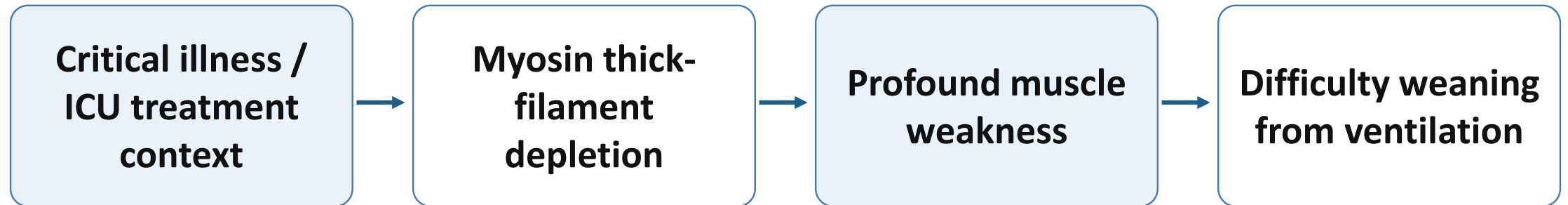


READING THE SCHEMATIC

1. Relatively selective myosin thick-filament degradation
2. Loss of contractile protein content
3. Severe functional muscle weakness

Simplified sarcomere illustration; Spacing is schematic, not ultrastructural evidence.

Why ventilator weaning becomes difficult



Mechanistic relationship—not a diagnostic algorithm

This is a clinically important consequence explicitly cited.

Steroid myopathy versus critical illness myopathy

Feature	Catabolic steroid myopathy	Critical illness myopathy
Setting	Endogenous or exogenous steroid excess	Severe ICU illness and treatment context
Dominant morphologic change	Selective type II atrophy	Relatively selective thick-filament myosin loss
Clinical consequence	Proximal weakness	Profound weakness, difficult ventilator liberation

Case 5 · ICU weakness

HYPOTHETICAL PRESENTATION

A ventilated ICU patient receiving corticosteroids and depolarizing neuromuscular blockers has profound weakness that impedes ventilator weaning.

Which named pathologic phenotype is emphasized?

REASONING PROMPTS

- Critical illness / myosin-deficient myopathy.
- Relatively selective loss of sarcomeric myosin thick filaments.

Thyroid disease belongs in this differential

Thyroid dysfunction causes acquired myopathic changes without requiring an exogenous medication.

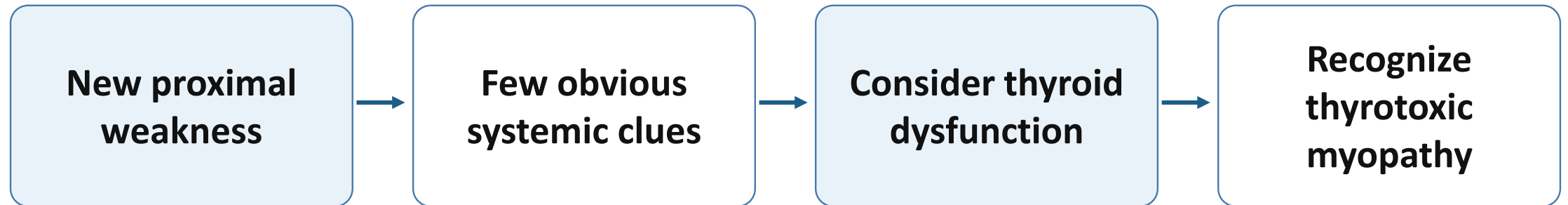
- Both excess and deficiency of thyroid hormone are associated with muscle symptoms.
- The weakness pattern and associated systemic findings differ.
- Hypothyroidism also has specific tissue changes described in the source.
- Do not assume all endocrine myopathy produces the same biopsy signature.

Thyrotoxic myopathy

Thyroid-hormone excess commonly produces acute or chronic proximal weakness.

- Weakness may arise before other obvious signs of hyperthyroidism.
- Both acute and chronic presentations are recognized.
- A proximal pattern can resemble medication-associated weakness.
- The temporal order of symptoms is therefore diagnostically relevant.

The diagnostic trap in thyrotoxicosis



Mechanistic relationship—not a diagnostic algorithm

The source emphasizes that weakness can precede typical hyperthyroid manifestations.

Exophthalmic ophthalmoplegia: Described findings

A characteristic ocular syndrome that can accompany thyrotoxic myopathy.

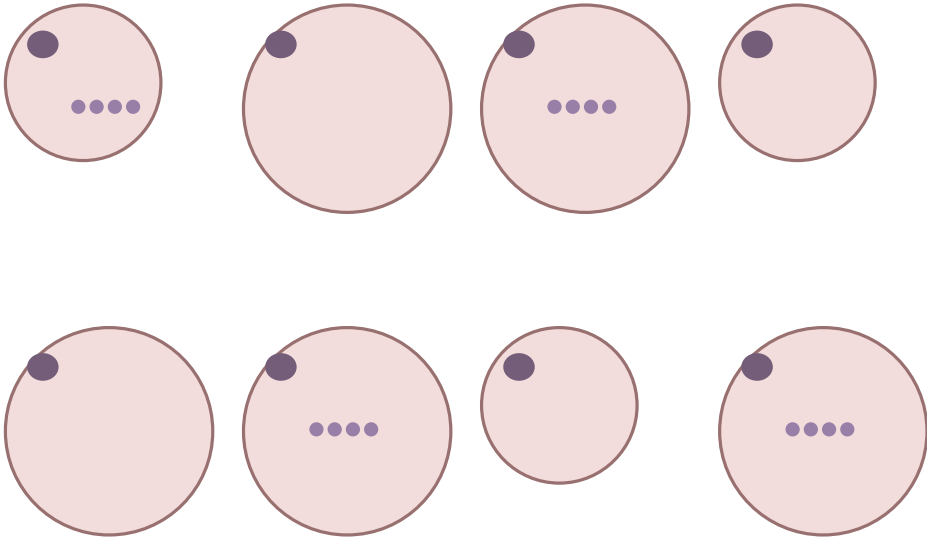
- Swelling of the eyelids.
- Edema of the conjunctiva.
- Diplopia.
- These features are clinical clues to the associated thyroid disorder.

Hypothyroid muscle symptoms

Thyroid-hormone deficiency can produce an aching, slow-moving muscular phenotype.

- Muscular cramping and aching may be prominent.
- Movement can become slow.
- Reflex responses may be slowed.
- Symptoms should be correlated with thyroid dysfunction before attributing them to a primary myopathy.

Hypothyroid myopathy: Structural changes



READING THE SCHEMATIC

1. Myofiber atrophy and abnormally located nuclei
2. Glycogen aggregates
3. Occasional connective-tissue mucopolysaccharides

Native illustration of reported findings; Not a tissue photomicrograph.

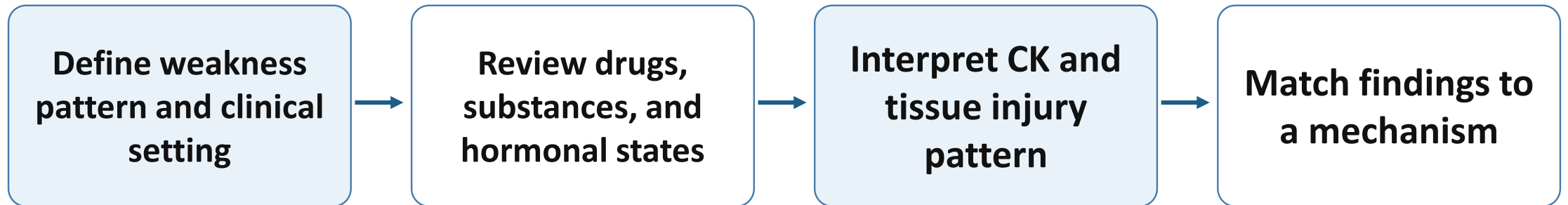
Thyrotoxic versus hypothyroid myopathy

Feature	Thyroid excess	Thyroid deficiency
Common muscle presentation	Acute or chronic proximal weakness	Aching, cramping, slowing of movement
Associated clue	May precede other hyperthyroid signs; ocular findings	Slowed reflexes
Tissue changes highlighted	Not specified in this source section	Atrophy, internal nuclei, glycogen, occasional mucopolysaccharide

Morphology-to-exposure crosswalk

Morphologic feature	Most relevant category	Important caution
Myofiber necrosis	Acute toxic injury or IMNM	Necrosis does not identify mechanism alone
Type I vacuolation	Chloroquine / hydroxychloroquine	Can mimic a storage disorder
Type II atrophy	Corticosteroid state	Different from thick-filament depletion
Myosin thick-filament loss	Critical illness myopathy	Interpret in ICU context
Glycogen aggregates + atypical nuclei	Hypothyroid myopathy	Integrate clinical endocrine findings

A mechanism-first diagnostic approach



Mechanistic relationship—not a diagnostic algorithm

An educational reasoning scheme derived from the source; Not a formal diagnostic guideline.

Common interpretive pitfalls

Avoid confusing a reproducible histologic finding with a unique diagnosis.

- High CK plus statin exposure does not prove a direct toxic pathway.
- Little inflammation does not rule out IMNM.
- Vacuoles do not, on their own, diagnose an inherited lysosomal disease.
- Proximal weakness occurs in steroid, thyroid, and necrotizing processes.
- ICU weakness must be considered in the critical-illness context.

Rapid recognition: Six clinical clues

Clue	Mechanism to consider	Characteristic associated finding
Higher-dose statin + risk factors	Direct necrotic toxicity	CK elevation $\pm$ rhabdomyolysis
Statin + rapidly progressive weakness	Immune-mediated myopathy	Necrotizing biopsy pattern possible
Zidovudine exposure	Mitochondrial damage	Acquired mitochondrial myopathy
Hydroxychloroquine + vacuoles	Lysosomal dysfunction	Lamellar ultrastructure
Prolonged catabolic corticosteroid state	Selective type II atrophy	Proximal weakness
ICU + difficult weaning	Myosin-deficient myopathy	Thick-filament depletion

Integrative problem · the vacuolar trap

HYPOTHETICAL PRESENTATION

Biopsy of a weak patient shows vacuoles. A preliminary report suggests “storage disease.” Medication review reveals hydroxychloroquine therapy.

Which one additional observation would reinforce an acquired toxic pathway?

REASONING PROMPTS

- Whorled lamellar membranous structures on ultrastructure.
- A type I–predominant vacuolar pattern.

Interpretation · vacuolar differential

Drug-mediated lysosomal impairment is an important acquired mimic of metabolic storage disease.

- Hydroxychloroquine/chloroquine history has high etiologic relevance.
- Type I–predominant vacuolation matches the cited Robbins morphology.
- Lamellar membrane whorls reinforce lysosomal dysfunction.
- The clinical–pathologic synthesis must precede labeling an inherited condition.

Integrative problem · proximal weakness

HYPOTHETICAL PRESENTATION

Two adults present with proximal weakness. One receives long-term corticosteroids; The other has hyperthyroidism with few obvious systemic signs.

Why does the shared clinical pattern not establish a shared pathologic process?

REASONING PROMPTS

- Corticosteroid exposure favors selective type II fiber atrophy.
- Thyrotoxic myopathy can precede obvious hyperthyroid signs.

Interpretation · phenotype versus etiology

Proximal weakness is a localization pattern, not a causal classification.

- A steroid-associated atrophic mechanism is one explanation.
- A thyroid-related functional myopathy is another.
- Necrotic and immune-mediated muscle diseases can also weaken proximal muscles.
- Exposure, clinical context, and pathology must be read together.

Summary: Injury target determines the clue

Cellular target	Exposure class	Teaching clue
Myofiber	Statin / fibrate / high-dose alcohol	Necrosis and CK release
Immune-associated injury	Statin / checkpoint inhibitor	Consider necrotizing immune myopathy
Mitochondrion	Zidovudine	Acquired organelle damage
Lysosome	Chloroquine / hydroxychloroquine	Vacuoles and lamellar aggregates
Fiber protein / sarcomere	Steroid state / critical illness	Type II atrophy or myosin loss
Endocrine-regulated muscle	Thyroid dysfunction	Different excess-versus-deficiency phenotypes

Primary reading and source boundaries

CORE TEXTBOOK

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026). Peripheral Nerves and Skeletal Muscles.

Main section: “Toxic Myopathies and Myopathy With Metabolic Changes.”

Related source context: “Myopathic Changes,” “Immune-Mediated Necrotizing Myopathy,” and “Mitochondrial Myopathies.”

Illustrations in this presentation are original native PowerPoint schematics; no synthetic diagnostic specimens are shown.