

Skeletal muscle atrophy

Mechanisms, fiber patterns, and clinicopathologic interpretation

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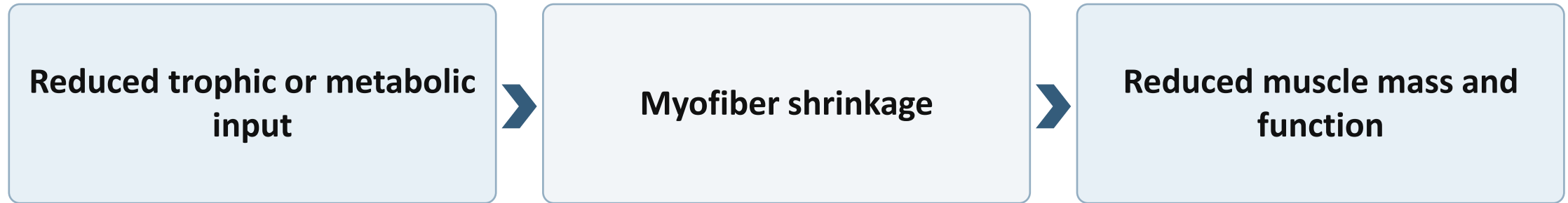
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Learning objectives

- Classify the major causes of skeletal muscle atrophy.
- Explain how denervation, disuse, and systemic catabolism reduce muscle mass.
- Recognize grouped, perifascicular, and selective type II fiber atrophy.
- Use motor-unit remodeling to interpret muscle biopsy patterns.

Atrophy is a change in size and sometimes cell number

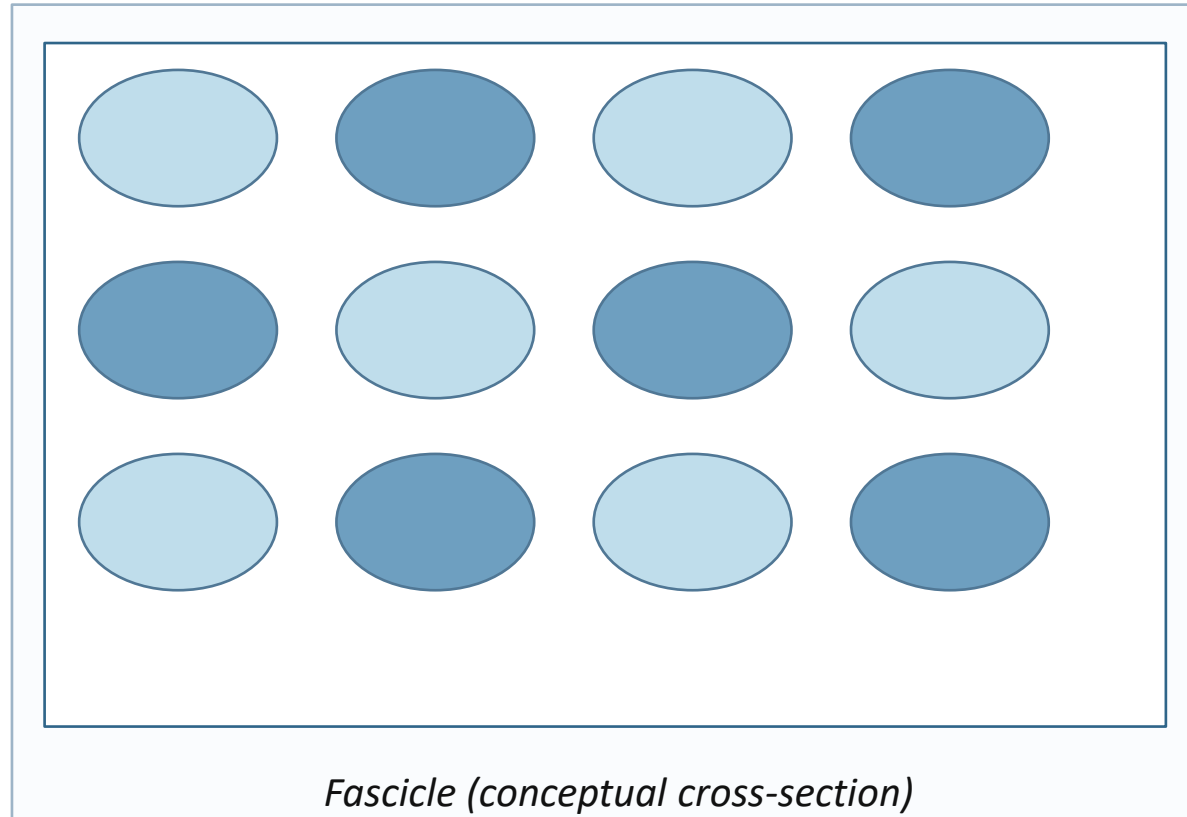


- Early loss of cell volume predominates.
- Prolonged atrophy may involve loss of myofibers.

Skeletal muscle atrophy is a shared endpoint

- Loss of innervation, disuse, cachexia, aging, and primary myopathies can all reduce muscle mass.
- Atrophy is a morphologic response—not a single etiologic diagnosis.
- The distribution of small fibers can suggest the mechanism.

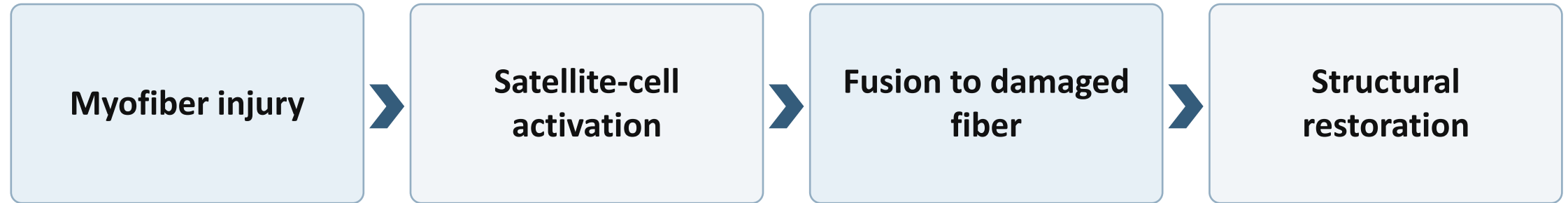
A myofiber is a large multinucleated cell



- Myoblast fusion forms myotubes that mature into myofibers.
- Multiple myofibers are organized within muscle fascicles.
- Fiber size reflects structural proteins and organelle content.

Schematic — not a histologic specimen

Satellite cells contribute to regeneration



- Regeneration is possible after transient injury.
- Chronic damage may exceed repair capacity.

Type I and type II fibers perform different tasks

Property	Type I	Type II
Dominant activity	Sustained force	Fast movement
Typical exercise	Aerobic	Anaerobic
Power	Lower	Higher
Fatigue resistance	Higher	Lower

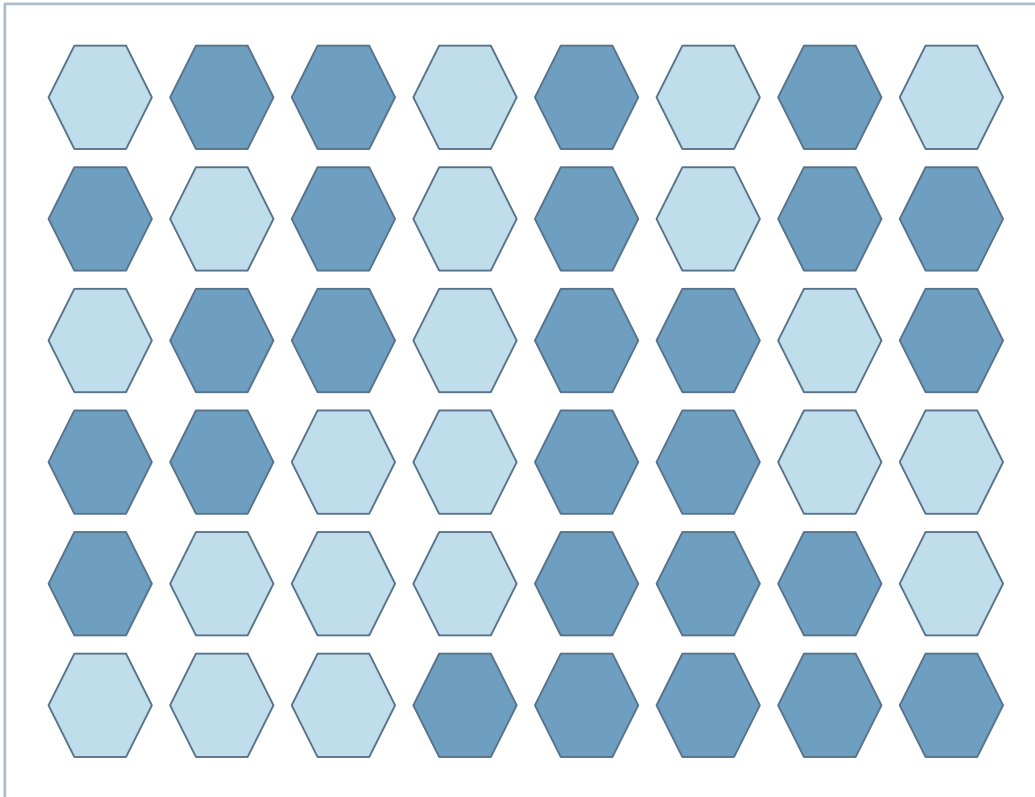
Fiber types differ in substrate and mitochondria

Property	Type I	Type II
Oxidative capacity	High	Lower
Glycolytic capacity	Lower	High
Mitochondrial density	High	Lower
Lipid content	Higher	Lower
Glycogen content	Lower	Higher

Histochemical reaction depends on fiber type

Stain / enzyme reaction	Type I	Type II
NADH-TR	Darker	Lighter
ATPase, pH 4.3	Darker	Lighter
ATPase, pH 9.4	Lighter	Darker

Normal muscle has a checkerboard admixture



 Type I  Type II

Type I and type II fibers are intermixed rather than segregated into large blocks.

- Motor units of different fiber types are intermingled.
- The checkerboard appearance is a useful baseline for recognizing remodeling.

Schematic — not a histologic image

Five major contexts lead to muscle atrophy

Denervation

Reduced use

Cachexia / malnutrition

Old age

Primary myopathy

- Each context can produce reduced muscle fiber size.
- Morphologic pattern and clinical context help separate causes.

Neuropathic and myopathic injury begin at different sites

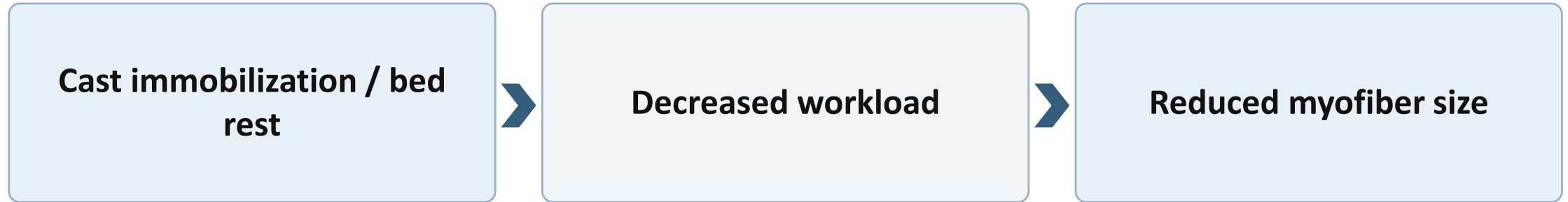
Neurogenic process

- Motor neuron or axon is injured.
- Myofibers lose innervation and trophic input.
- Grouped atrophy and fiber type grouping may emerge.

Myopathic process

- Muscle fiber is injured directly.
- Necrosis and regeneration may occur.
- Chronic injury may lead to fibrosis and fatty replacement.

Disuse produces early myofiber shrinkage



- Rapid onset after immobilization.
- Initial size reduction can be reversible.

Duration matters in disuse atrophy

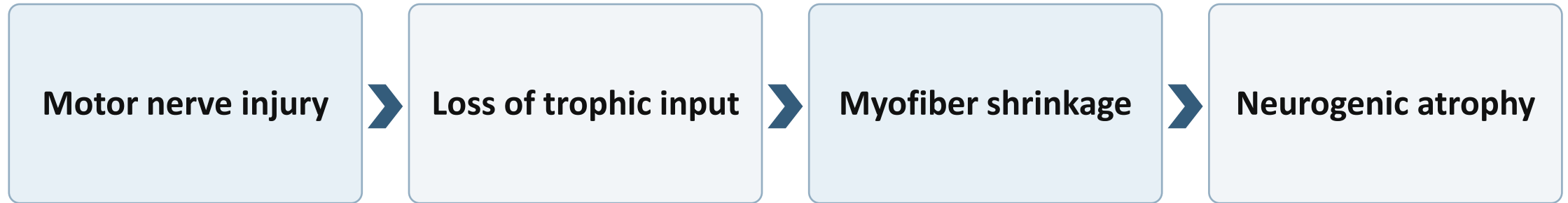
Earlier disuse

- Reduced fiber size is prominent.
- Recovery may follow return to activity.

Prolonged disuse

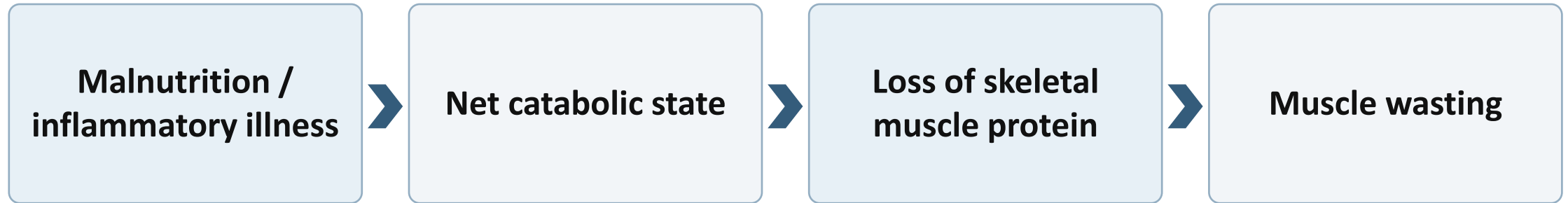
- Fiber number may also decrease.
- Apoptosis contributes to loss of fibers.
- Disuse osteoporosis can accompany muscle atrophy.

Loss of innervation interrupts muscle maintenance



- Denervated fibers may become flattened and angulated.
- A distribution of affected fibers is more informative than size alone.

Cachexia is a systemic cause of wasting



- Cancer and chronic inflammatory disease as contexts.
- The clinical syndrome must not be inferred from a biopsy pattern alone.

Old age and primary myopathies also cause atrophy

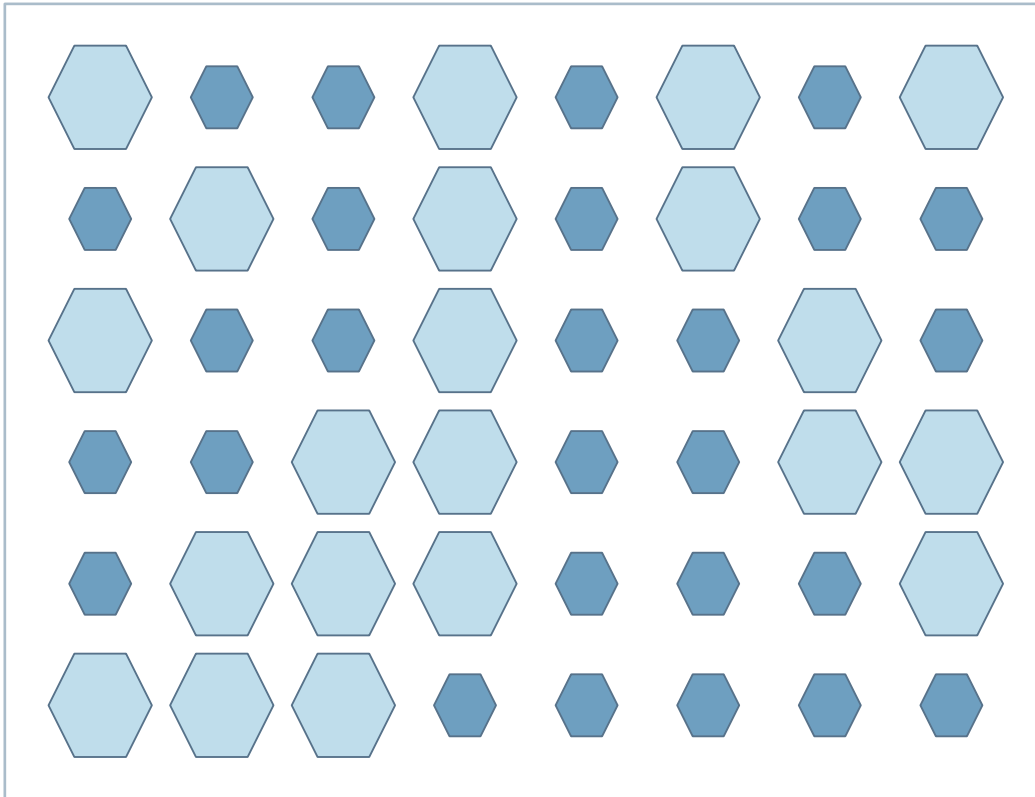
Aging-associated atrophy

- Old age is among the causes listed by Robbins.
- Age is clinical context, not a biopsy diagnosis by itself.

Primary myopathic atrophy

- Fiber loss may coexist with direct myofiber injury.
- Necrosis, regeneration, and chronic remodeling guide interpretation.

Prolonged corticosteroid exposure can selectively affect type II fibers



□ Type I □ Type II

Conceptual pattern: Type II fibers are preferentially smaller; Type I fibers are relatively spared.

- This pattern is associated with prolonged corticosteroid therapy.
- Disuse can produce a similar type II-predominant pattern.

Schematic — not a histologic image

Distribution is the first morphologic question

Observed pattern	Association
Grouped atrophic fibers	Neurogenic disease
Perifascicular atrophy	Dermatomyositis
Type II atrophy with type I sparing	Disuse or prolonged corticosteroids

Cellular atrophy reflects loss of protein balance

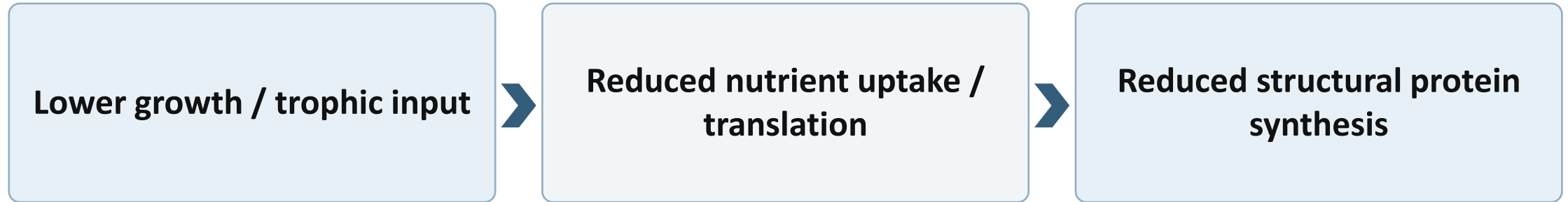
Protein synthesis decreases

- Lower trophic input reduces translation.
- Fewer structural proteins are replaced.
- Both changes contribute to cell shrinkage.

Protein degradation increases

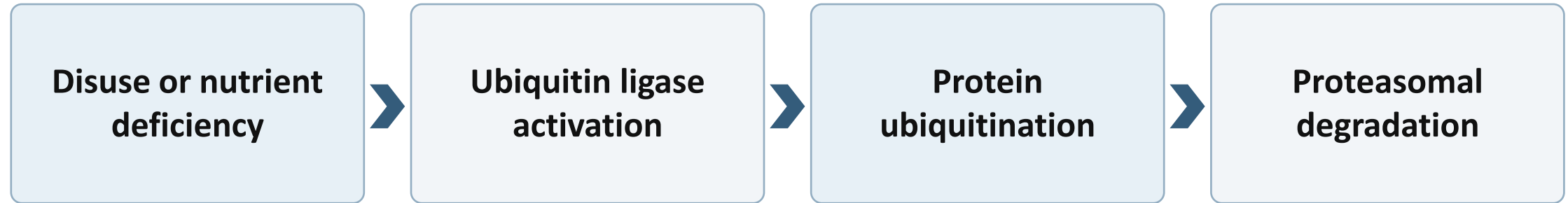
- Ubiquitin–proteasome activity rises.
- Autophagy may also increase.
- The result is net loss of cellular material.

Reduced trophic signaling lowers protein synthesis



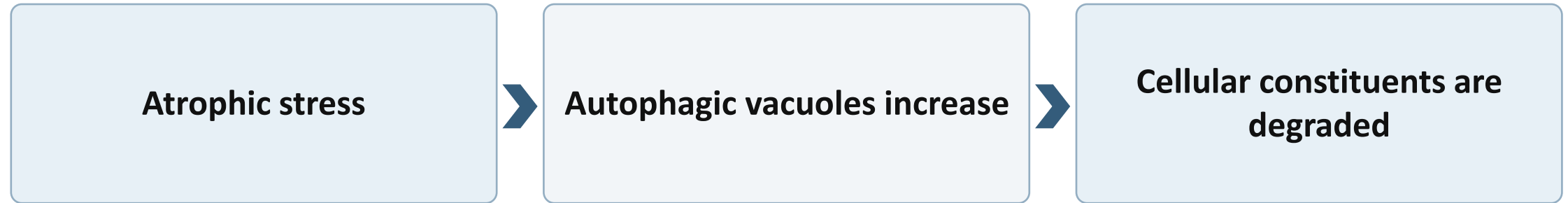
- Reduced trophic signals to diminished synthesis.
- Reduced synthesis contributes to a smaller myofiber.

Ubiquitin–proteasome signaling drives proteolysis



- The pathway is implicated in several catabolic states, including cancer cachexia.
- Diagram presents the source-level mechanism—not a disease-specific molecular assay.

Autophagy may accompany tissue atrophy



- Autophagy contributes to turnover of cellular components.
- Residual bodies can persist when material resists complete digestion.

Atrophic myofibers have fewer intracellular components

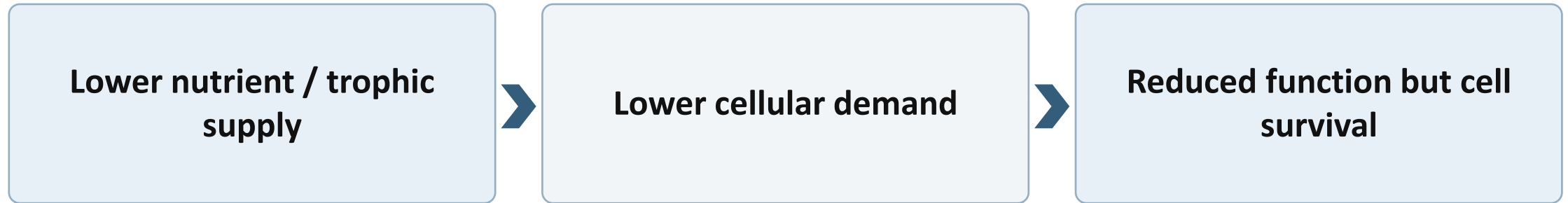
Normal myofiber

- Relatively abundant myofilaments.
- Mitochondria and rough ER support normal metabolism.

Atrophic myofiber

- Fewer myofilaments and mitochondria.
- Reduced rough ER and overall cell volume.
- Lower metabolic requirements.

Early adaptation trades capacity for survival



- Cell death is initially limited in many forms of atrophy.
- Severe or persistent adverse conditions can exceed adaptive capacity.

Reversibility depends on the context and duration

Potentially reversible

- Early disuse with myofiber shrinkage.
- Return of activity restores useful stimulation.

More persistent damage

- Long-standing disuse may reduce fiber number.
- Chronic disease can be accompanied by loss of fibers.

Atrophy should be separated from myofiber necrosis

Atrophy

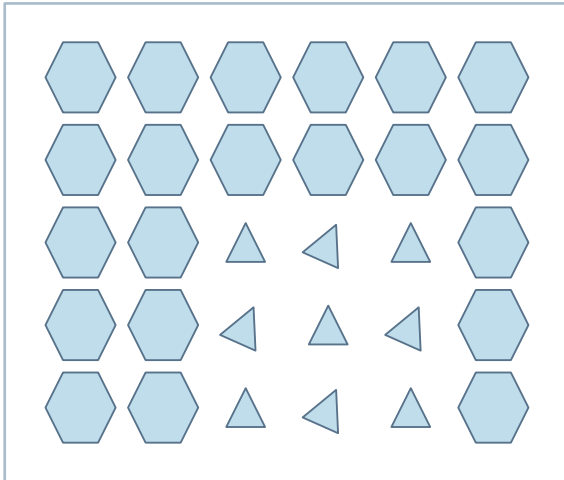
- Predominant reduction in cell size.
- Protein turnover can be altered without acute cell death.

Necrosis / regeneration

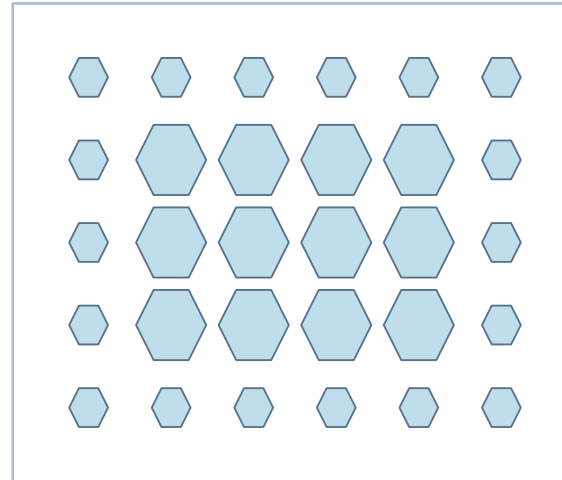
- Segmental myofiber injury and myophagocytosis.
- Satellite-cell fusion and sarcomere replacement.

Small fibers can form distinctive tissue patterns

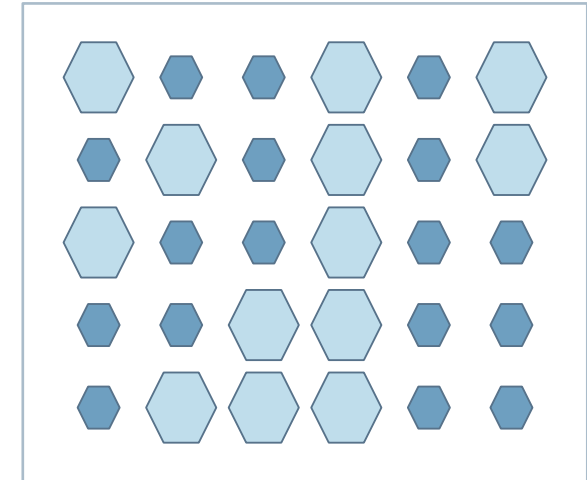
Grouped



Perifascicular



Type II-selective



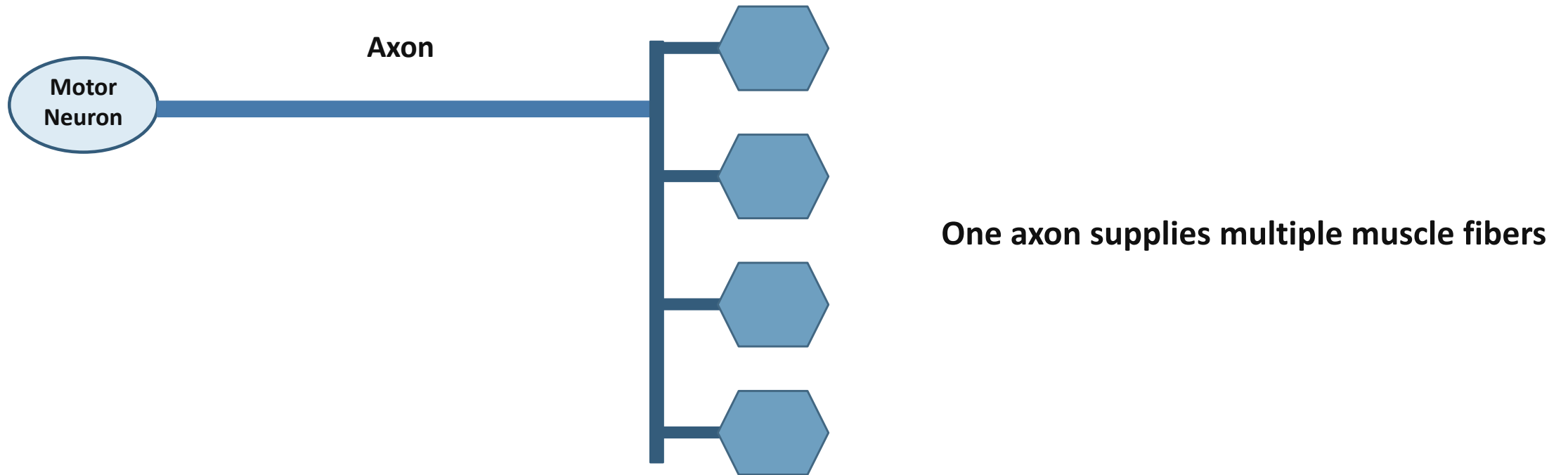
■ Type I

■ Type II

Schematic: Fiber positions and sizes are illustrative, not a histologic specimen.

Analyze position, clustering, and fiber type—not merely average fiber diameter. No single pattern should replace clinical and ancillary interpretation.

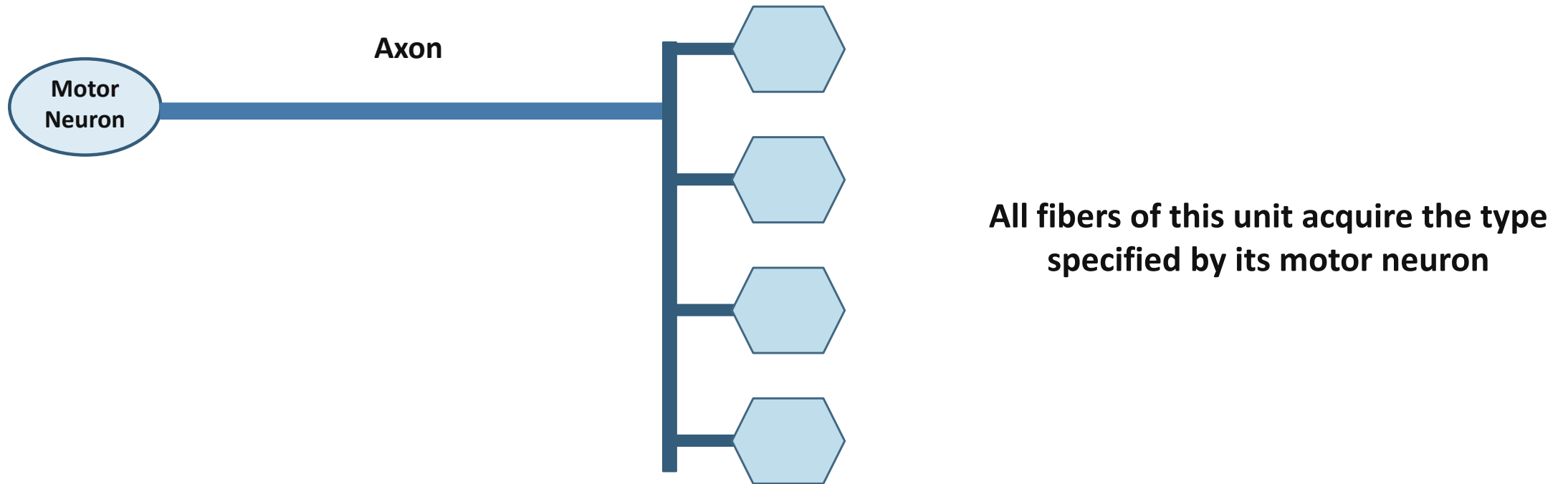
A motor unit links one motor neuron to multiple fibers



Schematic

- A motor unit consists of one motor neuron, its axon, and the myofibers it innervates.
- All fibers within a single motor unit share a functional fiber type.

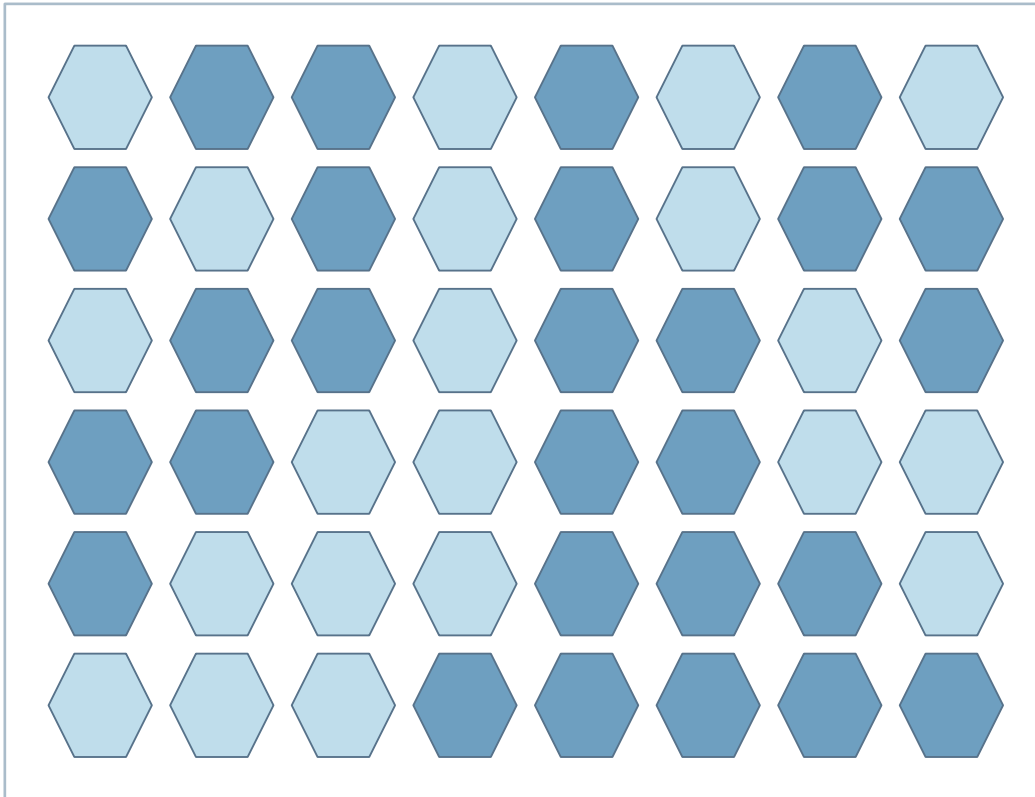
The innervating neuron determines muscle fiber type



Schematic

- Innervation influences whether an individual fiber behaves as type I or type II.
- Loss and restoration of innervation can change fiber-type identity.

Normal motor units interdigitate



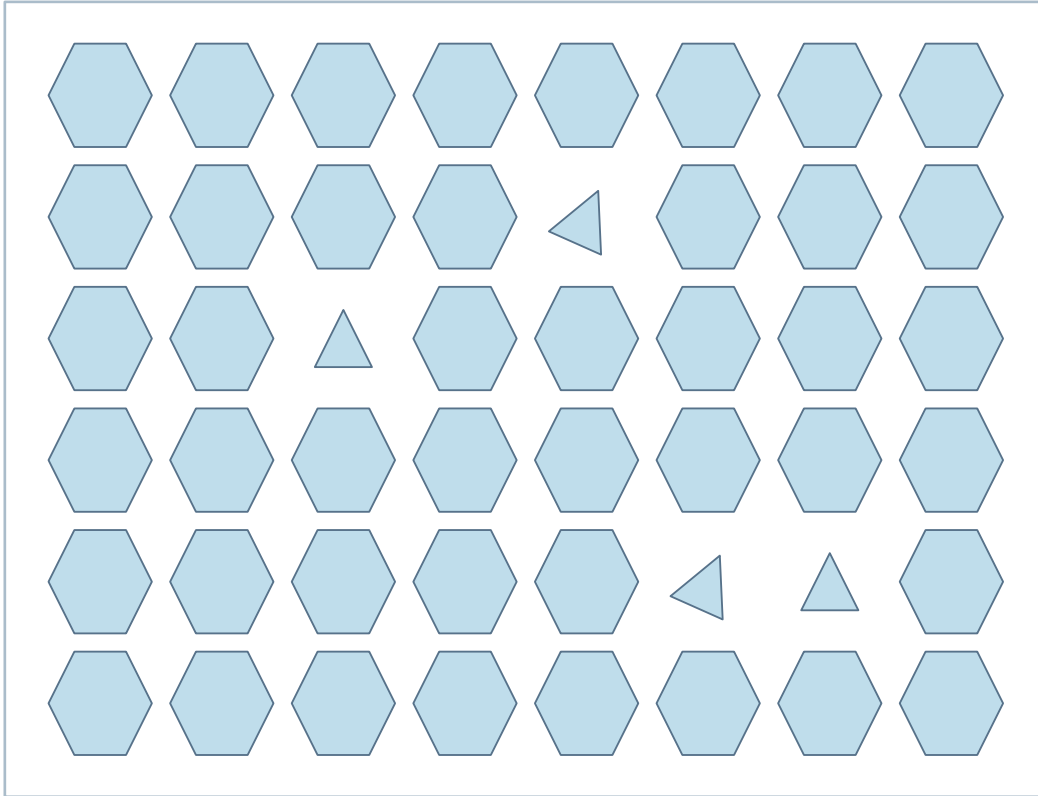
 Type I  Type II

Schematic mixed fiber types at baseline.

- Fibers belonging to different motor units are interspersed.
- Consequently, intact muscle does not show large homogeneous fiber-type territories.

Schematic — not a histologic image

Denervated fibers become small and angulated

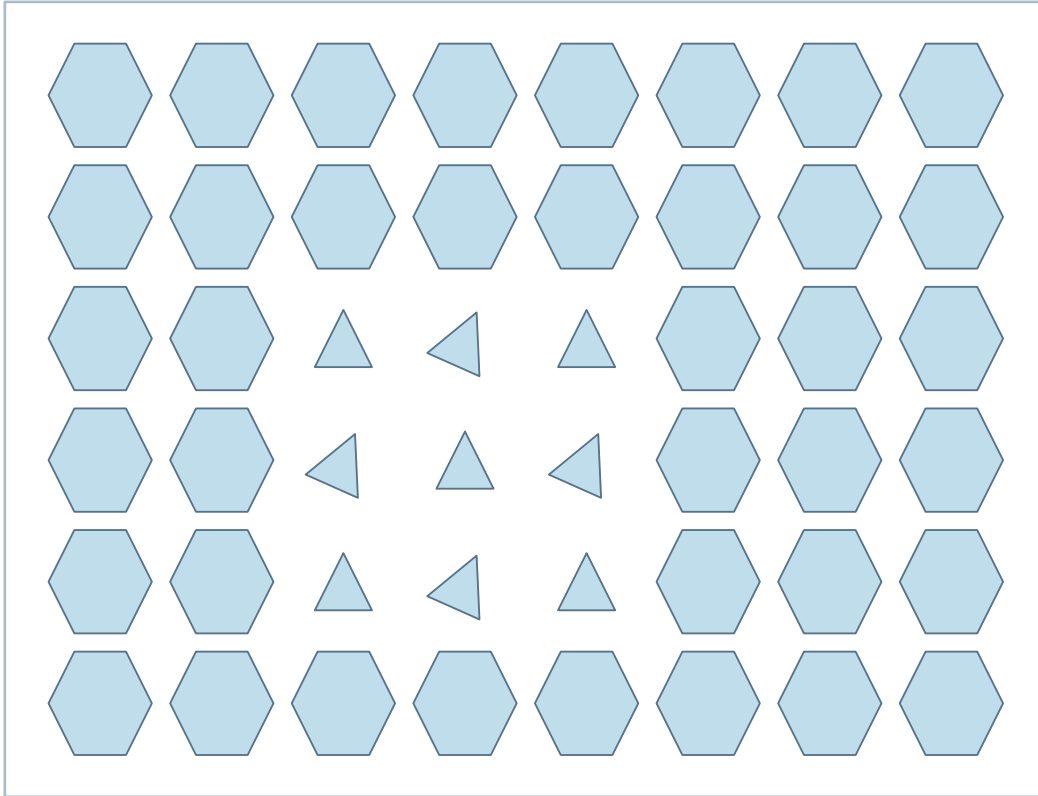


Schematic loss of size and rounded profile in a subset of fibers.

- Denervation-related atrophic fibers may be flattened and angulated.
- Shape reflects the neurogenic response.

Schematic — not a histologic image

Grouped atrophy suggests disruption of innervation

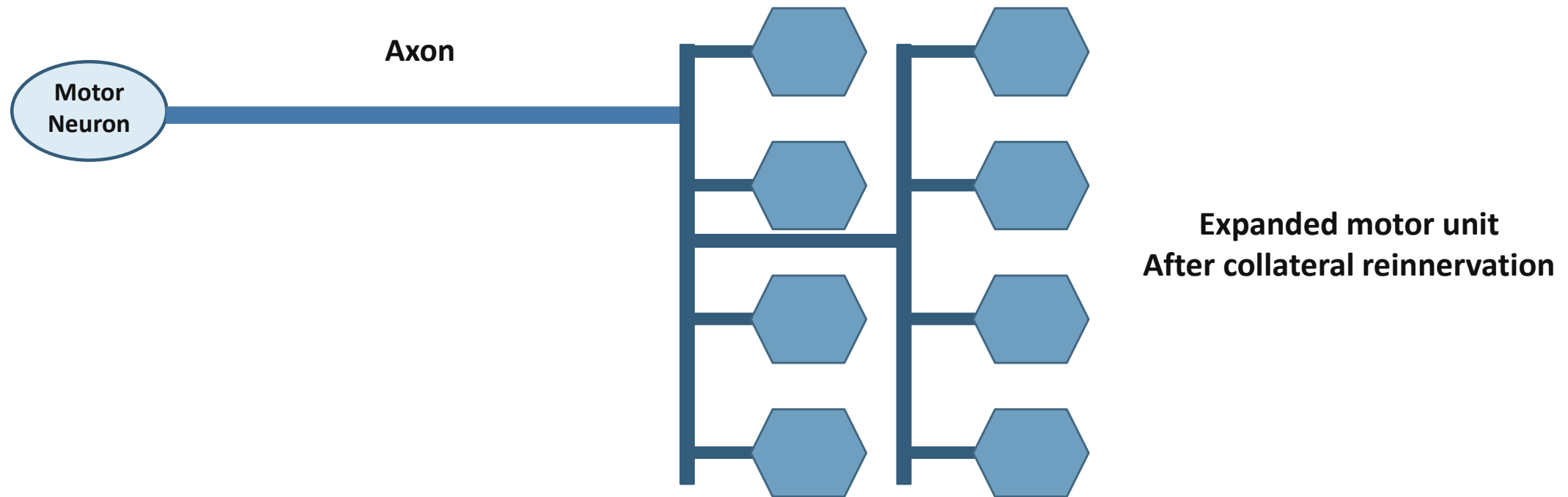


Clustered small fibers in a conceptual muscle cross-section.

- Several adjacent small fibers together form a grouped atrophy pattern.
- Robbins treats this as a characteristic neurogenic clue.

Schematic — not a histologic image

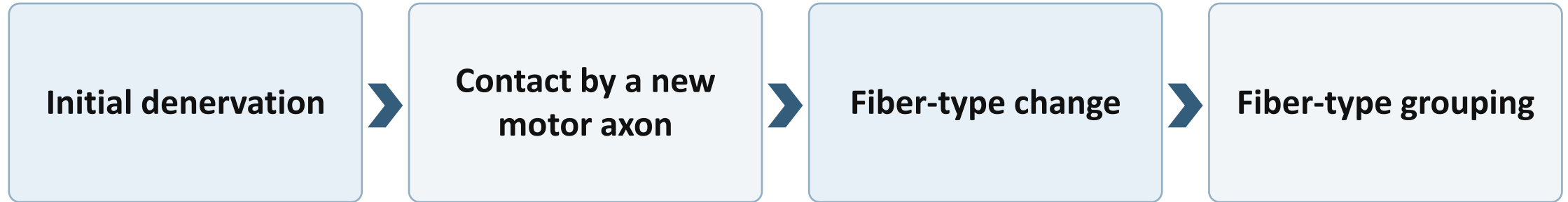
Collateral reinnervation enlarges surviving motor units



Schematic

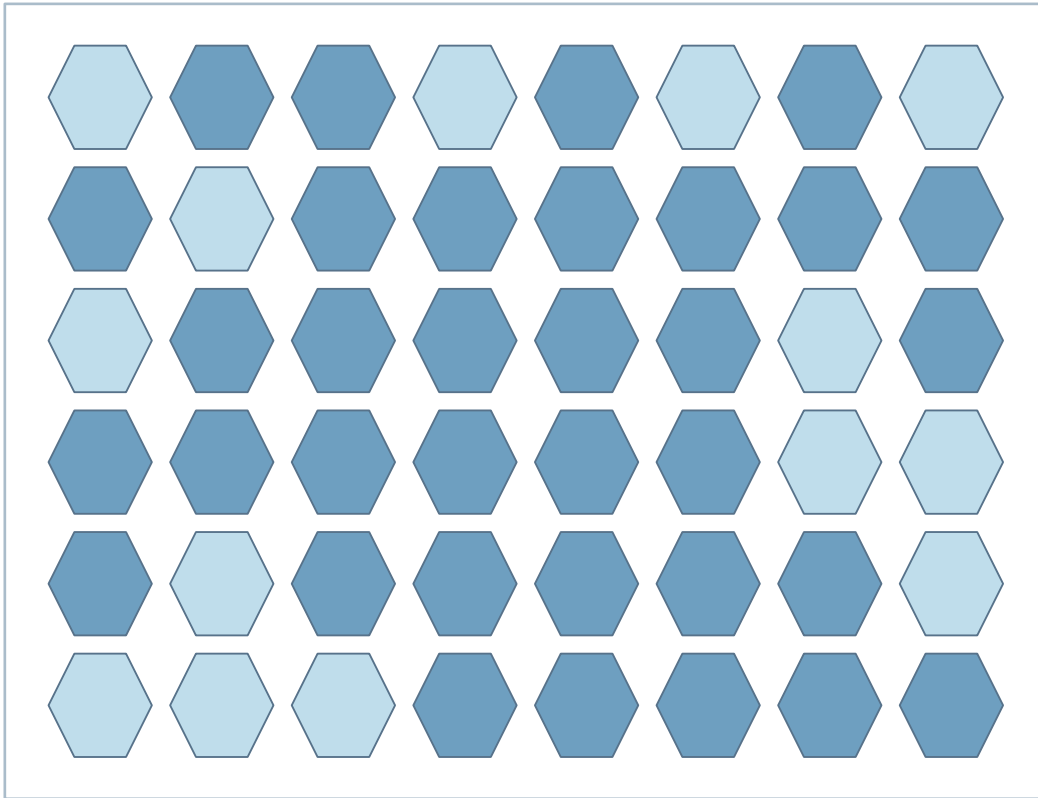
- Residual axons may reinnervate fibers abandoned by damaged axons.
- One surviving motor neuron can come to supply more myofibers.

Reinnervation may change the fiber type



- The remodeled fibers now share the type specified by their new axon.
- This explains large adjacent same-type fiber territories.

Fiber type grouping records motor-unit remodeling



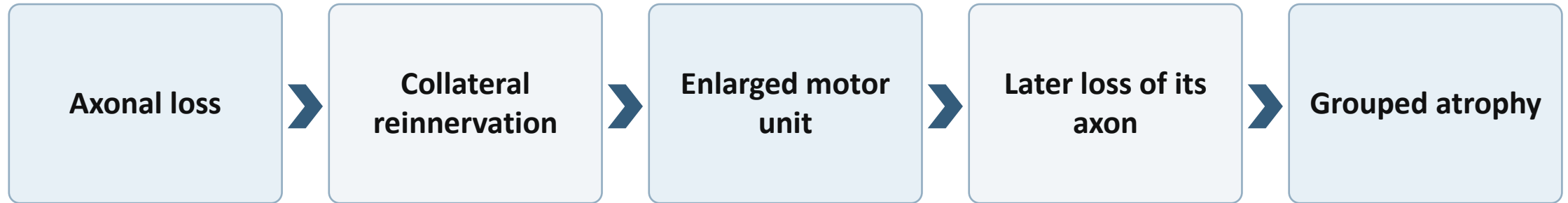
□ Type I □ Type II

Clustered same-type fibers after collateral reinnervation.

- Adjacent fibers share the same fiber type.
- This is distinct from a mere cluster of small atrophic fibers.

Schematic — not a histologic image

Grouped atrophy may recur after reinnervation

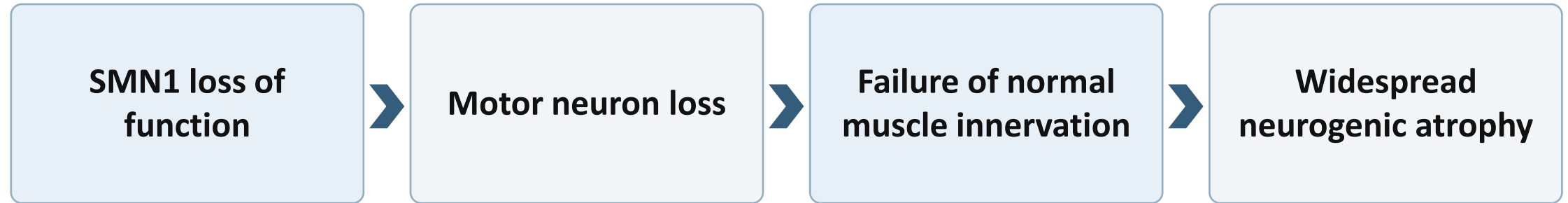


- Large remodeled motor units are vulnerable when their remaining axon degenerates.
- The sequence explains why grouping and grouped atrophy can coexist.

Neurogenic atrophy appears in several clinical settings

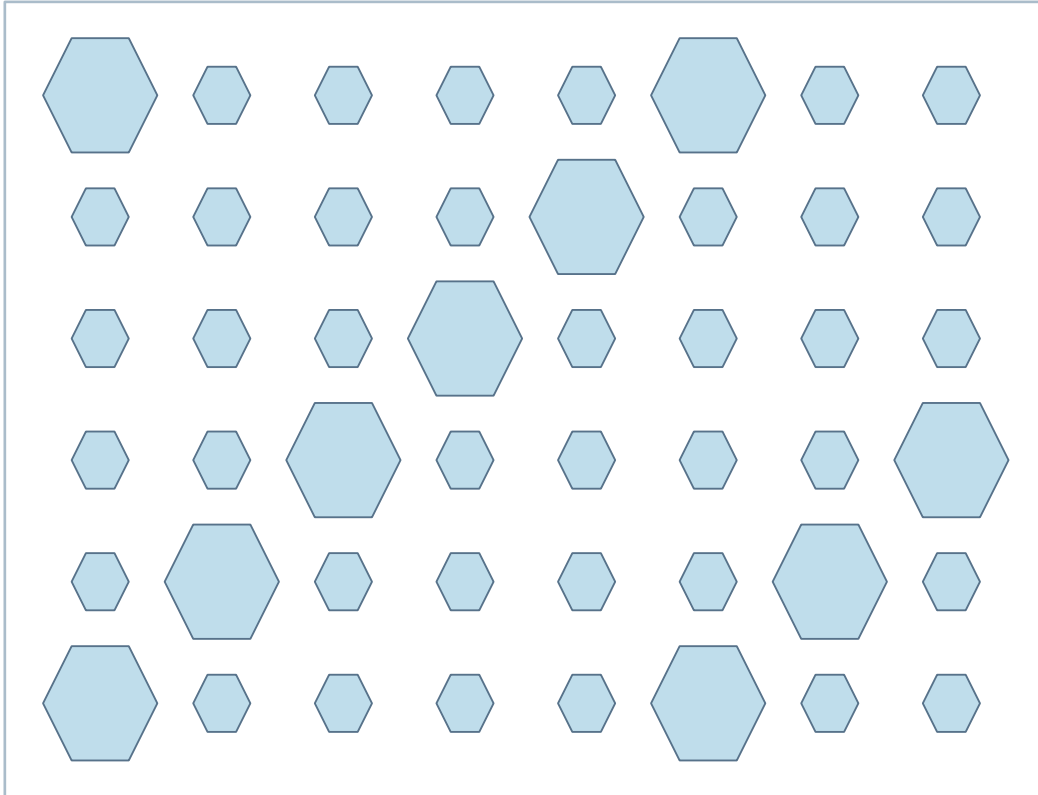
Clinical context	Level of motor-unit injury
Amyotrophic lateral sclerosis	Motor neuron degeneration
Radiculopathy	Motor root injury
Peripheral neuropathy	Peripheral nerve / axonal injury

Spinal muscular atrophy illustrates a motor-neuron cause



- Spinal muscular atrophy as autosomal recessive.
- This is an etiologic example, not a diagnosis from atrophy alone.

Severe infantile SMA shows striking fiber-size disparity

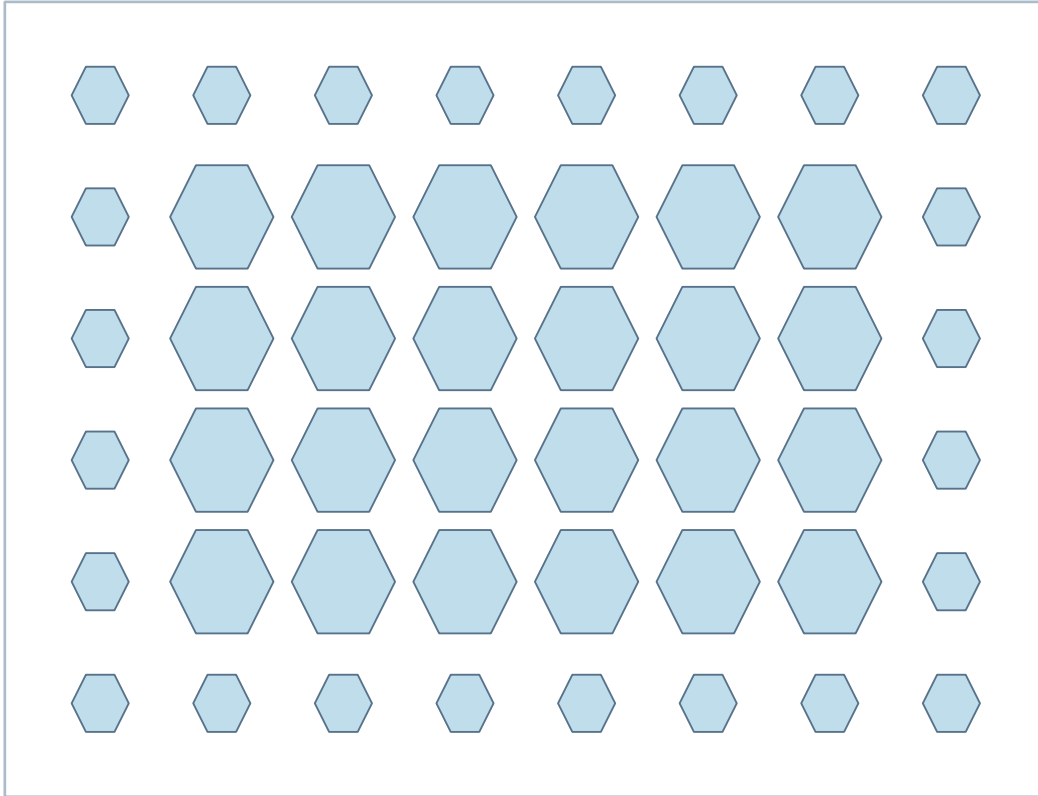


Source-described pattern: Many markedly small rounded fibers with scattered preserved or enlarged fibers.

- The larger fibers retain innervation and may hypertrophy.
- This differs in appearance from simple uniform disuse shrinkage.

Schematic — not a histologic image

Perifascicular atrophy localizes to fascicle edges



Small fibers are preferentially located along the fascicular perimeter.

- The defining feature is spatial—not simply a high proportion of small fibers.
- This as a classic dermatomyositis-associated pattern.

Schematic — not a histologic image

Dermatomyositis provides the key clinical association

- Dermatomyositis is a systemic autoimmune disease involving muscle and characteristic skin manifestations.
- The muscle weakness is typically proximal.
- Perifascicular atrophy supports the morphologic diagnosis when present.
- It is not present in every case.

Perifascicular atrophy is not universally present

Finding present

- Edge-predominant small fibers provide a useful clue.
- Interpret together with other pathologic and clinical findings.

Finding absent

- Absence does not exclude dermatomyositis.
- Avoid treating a single morphologic sign as an absolute criterion.

Grouped and perifascicular atrophy answer different questions

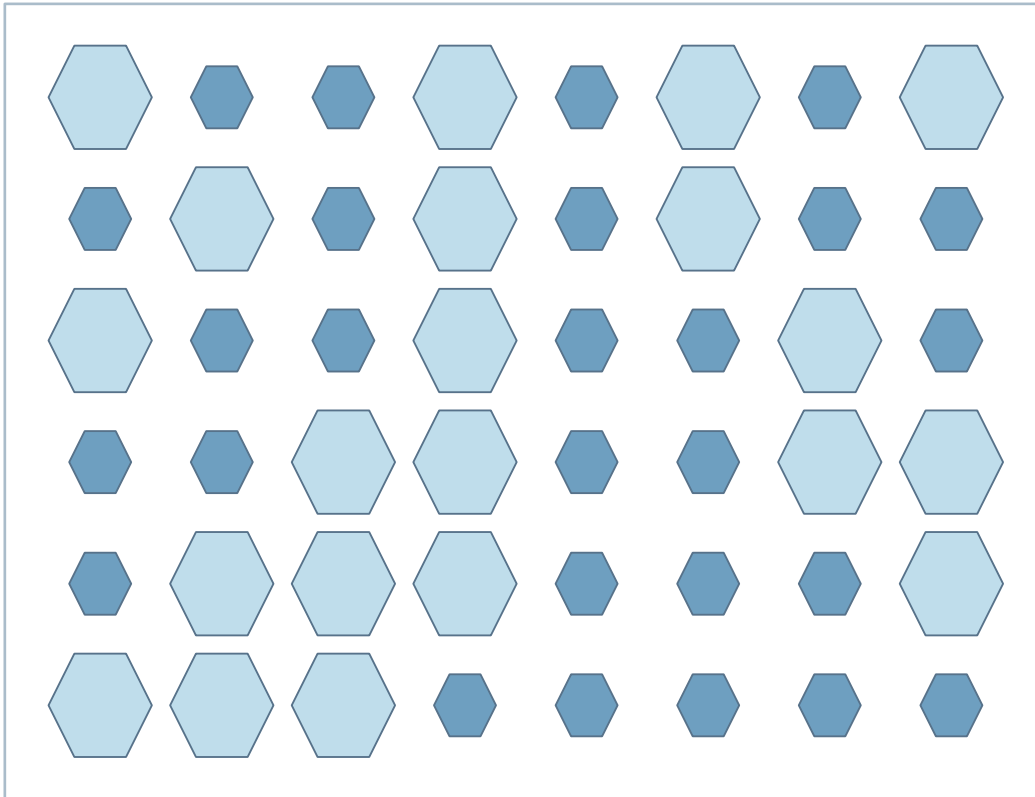
Grouped atrophy

- A cluster of neighboring small fibers.
- Supports a neurogenic mechanism.
- May follow loss of an enlarged motor unit.

Perifascicular atrophy

- Small fibers lie preferentially at fascicle margins.
- Suggests dermatomyositis.
- A spatial relation to the fascicle border.

Fiber type must be identified for selective atrophy



□ Type I □ Type II

Type II-selective shrinkage requires recognizing fiber type as well as size.

- Type II fibers may be selectively reduced with type I sparing.
- A routine size-only schematic cannot establish fiber type without appropriate typing.

Schematic — not a histologic image

Disuse and corticosteroids overlap morphologically

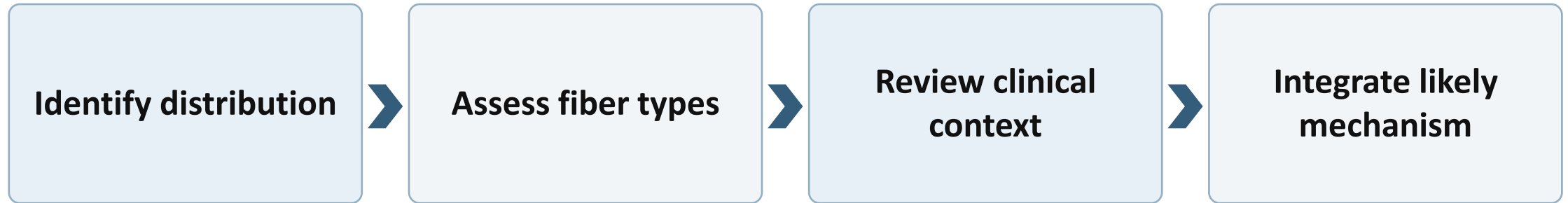
Disuse

- Reduced workload is documented.
- Type II fiber atrophy may occur.

Prolonged corticosteroid therapy

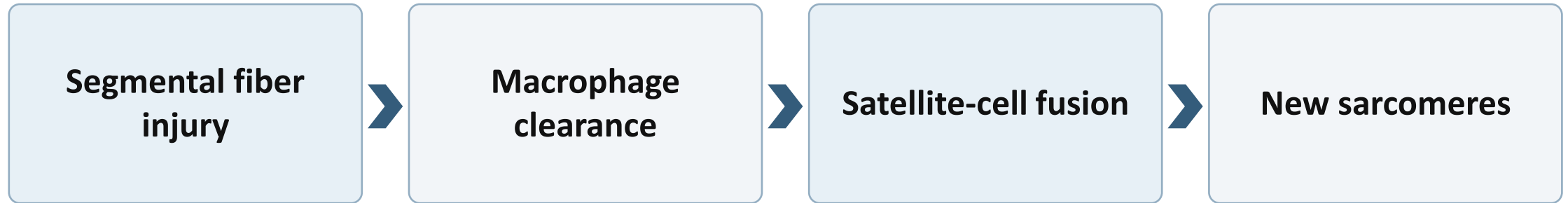
- Long-term exposure is the clinical context.
- Type II fiber atrophy may occur.

The morphology must be interpreted with history



- The same selective fiber-type pattern can have different associations.
- This is a reasoning framework, not a stand-alone diagnostic algorithm.

Myopathic injury has a different injury–repair sequence



- Direct myofiber damage can coexist with atrophic fibers.
- This pathway should not be mislabeled as simple disuse atrophy.

Creatine kinase relates to myofiber damage

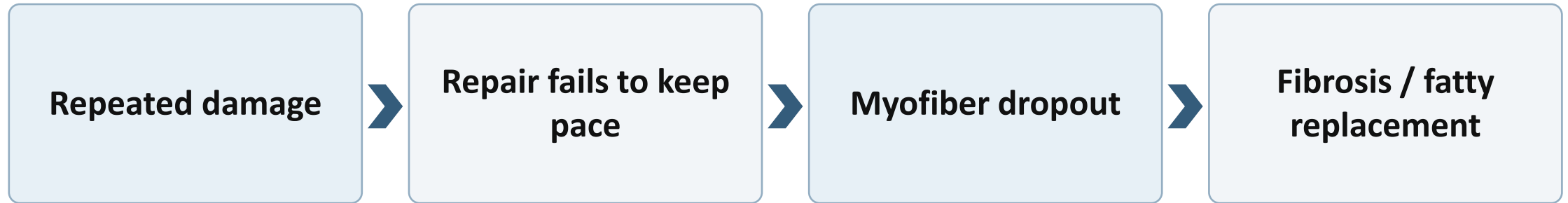
Direct injury

- Segmental degeneration releases intracellular enzymes including CK.
- CK helps document ongoing muscle damage.

Atrophy alone

- Fiber shrinkage is not identical to necrosis.
- Do not assume marked CK release from size loss alone.

Chronic myopathy can reduce muscle substance



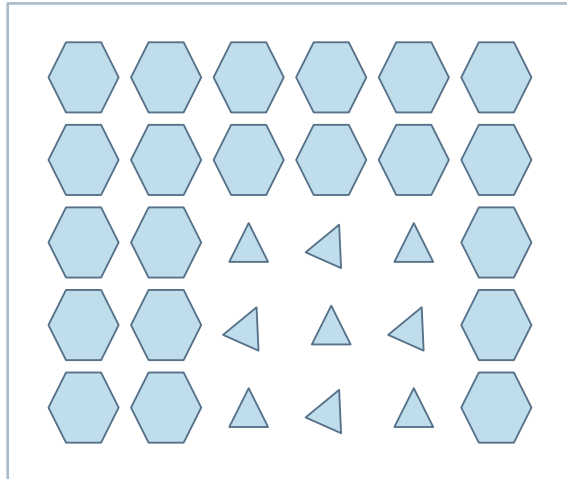
- These changes are described for chronic myopathic disease.
- They point beyond isolated atrophy toward sustained tissue injury.

Neurogenic and myopathic clues can be compared

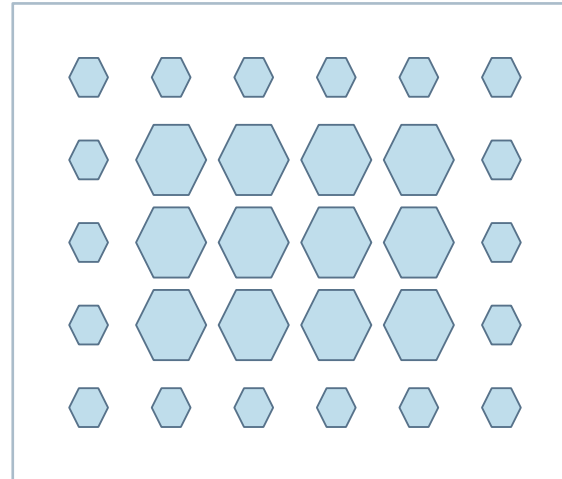
Feature	Neurogenic pattern	Myopathic pattern
Initial insult	Loss of innervation	Direct myofiber injury
Characteristic structural clue	Angulated atrophic fibers / grouping	Segmental damage / regeneration
Chronic consequences	Motor-unit remodeling	Fibrosis and fatty replacement may occur

Three diagnostic patterns: Compare distributions

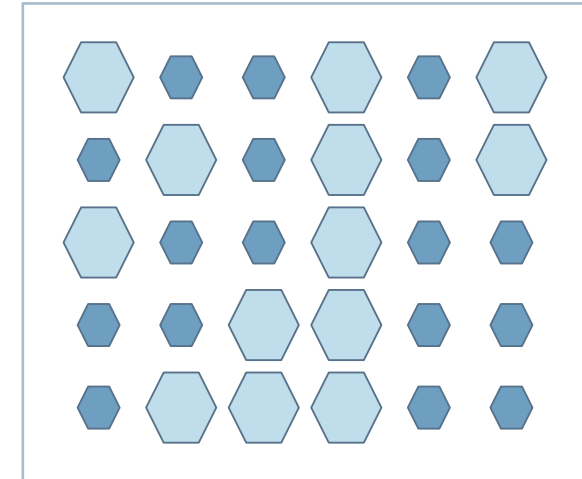
Grouped



Perifascicular



Type II-selective



 Type I  Type II

Schematic: Fiber positions and sizes are illustrative, not a histologic specimen.

Grouped = where small fibers cluster. Perifascicular = where they lie within a fascicle. Type II-selective = which fiber population is reduced.

Morphology cannot replace clinical correlation

- Pattern recognition narrows etiologic possibilities; It does not prove one cause.
- Disuse and corticosteroid exposure share type II-predominant atrophy.
- Neurogenic remodeling may show both fiber-type grouping and grouped atrophy.
- Myopathic necrosis and regeneration point to additional disease mechanisms.

Case 1 — clustered small fibers

A muscle biopsy contains small, angulated fibers in clusters. The history includes progressive weakness and peripheral nerve disease.

Which broad pathophysiologic category is favored by the biopsy pattern?

Case 1 — interpret the clustering

Neurogenic atrophy is favored.

- Grouped small/angulated fibers are a characteristic neurogenic response.
- Investigate the site and cause of motor innervation loss.
- The pattern does not identify one specific neurologic disorder.

Case 2 — fiber-type selective shrinkage

A patient has reduced muscle activity after a prolonged period of immobilization. A fiber-typed biopsy shows smaller type II fibers with relative type I sparing.

Which association is supported, and which competing history should also be checked?

Case 2 — integrate the exposure history

Disuse is supported; Prolonged corticosteroid exposure is a key alternative association.

- Both settings can yield selective type II atrophy.
- The fiber pattern cannot distinguish them without clinical data.
- Avoid diagnosing a specific myopathy from this pattern alone.

Case 3 — small fibers at fascicle margins

A patient with proximal weakness and characteristic inflammatory skin findings has a muscle biopsy with edge-predominant small myofibers.

Which distribution is present and which inflammatory myopathy does it suggest?

Case 3 — connect location to disease

Perifascicular atrophy suggests dermatomyositis.

- Preferential atrophy at fascicle borders defines the pattern.
- The association is informative, but not universally present in the disease.
- Correlate with the remaining clinical and pathologic evidence.

Synthesis: Cause, morphologic pattern, interpretation

Context	Dominant teaching clue	Caution
Denervation	Grouped atrophy; Later type grouping	Not disease-specific
Dermatomyositis	Perifascicular atrophy	May be absent
Disuse / corticosteroids	Selective type II atrophy	Two overlapping associations
Chronic myopathy	Damage, regeneration, tissue replacement	Not simply atrophy

Five principles to retain

- Atrophy is a response shared by multiple diseases.
- Distribution distinguishes grouped from perifascicular atrophy.
- Fiber typing distinguishes type II-selective shrinkage.
- Denervation and reinnervation remodel motor-unit territories.
- Biopsy findings require clinical and etiologic integration.

References and source scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 27, pp. 1116–1118.
- Chapter 27: “Diseases of Skeletal Muscle,” “Skeletal Muscle Atrophy,” and adjacent neurogenic/myopathic sections.
- Chapter 27, Table 27.2: Muscle Fiber Types; Figures 27.7–27.9 interpreted from text/captions only.
- Chapter 2, pp. 54–55: Atrophy and Mechanisms of Atrophy.