ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

Collagen VI–Related Myopathies: An Educational Overview of Molecular Pathogenesis, Variability of Clinical Presentations Spectrum, Diagnostic Approaches and Management Strategies

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Publication Date: 2026/04/22

Abstract: Collagen VI–related myopathies (COL6-RM) encompass a broad clinical spectrum of inherited neuromuscular disorders ranging from severe Ullrich congenital muscular dystrophy to milder Bethlem myopathy, caused by pathogenic variants in COL6A1, COL6A2, and COL6A3. The pathogenic disruptions in collagen VI compromise extracellular matrix stability, impair autophagic flux, promote mitochondrial permeability transition, and alter fibroblast–myofiber signaling. These disorders are characterized by proximal muscle weakness, joint contractures, distal hyperlaxity, and respiratory compromise. Advances in basic science have revealed that collagen VI deficiency disrupts extracellular matrix (ECM) integrity, impairs autophagy, induces mitochondrial dysfunction, and alters the myomatrix microenvironment, collectively driving progressive muscle degeneration.

Diagnosis relies on a multimodal approach that integrates clinical assessment with muscle MRI, histopathology, and next-generation sequencing. Management remains largely supportive; however, emerging strategies, including autophagy enhancers, mitochondrial permeability transition pore (mPTP) inhibitors, extracellular matrix–targeting agents, and gene-based therapies show promise for disease modification. Advances in molecular biology have reshaped the understanding of COL6-RM and opened new avenues for targeted treatment. Robust natural history studies and biomarker development are needed to accelerate translational progress. The objective is to synthesize current evidence regarding pathogenesis, clinical presentation, diagnostic modalities, and evolving therapeutic approaches in COL6-RM.

This review integrates and synthesizes findings from molecular pathogenesis, diagnostic tools, clinical spectrum, imaging studies, and evolving management while highlighting future therapeutic directions with emphasis on recent mechanisms involving extracellular matrix dysfunction, autophagy impairment, mitochondrial dysregulation, and myomatrix remodeling.

Keywords: *Collagen VI, Myopathy, Extracellular Matrix, Autophagy, Mitochondrial Dysfunction, Ullrich Congenital Muscular Dystrophy, Bethlem Myopathy.*

How to Cite: Adedeji Okikiade; Alisha Metha; Richard Adetoye; Stephen Adetoye; A. Chidimma Diala; Tebong Aboh; Anugwa Oluchi (2026) Collagen VI–Related Myopathies: An Educational Overview of Molecular Pathogenesis, Variability of Clinical Presentations Spectrum, Diagnostic Approaches and Management Strategies. *International Journal of Innovative Science and Research Technology*, 11(4), 1508-1521. https://doi.org/10.38124/ijisrt/26apr353

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

I. INTRODUCTION

Collagen VI is a ubiquitous beaded microfilaments protein found in the stroma of the extracellular membrane and forms microfibrillar network associated with the basement membrane several tissues including the skeletal muscle, muscular fascia, myotendinous junction, tendon, adipose tissue, and skin[1][2]. This enables it to perform several functions which span from mechanical to cytoprotective roles, such as the inhibition of apoptosis and oxidative damage, the modulation of cell differentiation, autophagy and stemness and the enhancement of tumor growth and progression[2][3].

Initially, collagen VI was thought to comprise only three alpha chains (ColA1, ColA2, and ColA3). However, recent discoveries have identified three additional chains such as ColA4, ColA5, and ColA6 with each encoded by distinct genes (COL6A1-COL6A6) [1][2]. Interestingly, while the ColA4 chain is absent in humans, ColA5 and ColA6 appear to play more specialized role within ECM structures, essentially important in the pathogenesis of Collagen VI myopathies with a limited tissue distribution in human skin and muscle and may substitute for the alpha 3 chain. These findings have broadened our understanding of how collagen VI functions at the molecular level and its role in maintaining muscle integrity[2][4].

Collagen VI-related myopathies represent a spectrum of genetic disorders that primarily affect the musculoskeletal system resulting in a variable combination of muscle atrophy and weakness, joint laxity and contractures as well as respiratory compromise. These conditions arise due to mutations in genes responsible for the production of collagen VI, a key structural component of the extracellular matrix (ECM), an intricate network that provides stability, adhesion, and integrity to tissues that is essential for body support, movement, and organ protection. It is present significantly in the interstitial spaces of muscle, tendon, skin, cartilage, and the intervertebral discs[1][2][3].

Genetic mutations affecting COL6A1, COL6A2, and COL6A3, with the either the absence or malformation of the microfibril disrupt the stability and function of muscle fibers, leading to a continuum of muscle disorders with variable phenotypes: Bethlem myopathy (BM) at one end of the spectrum, with mild progressive muscle weakness as well as varying age of onset and Ullrich congenital muscular dystrophy (UCMD) being the most severe and progressive disorder, with early onset of symptoms, at the other extreme[4][5][6]. Limb-girdle muscular dystrophy and Autosomal recessive myosclerosis have been reported lately with diverse geno-phenotypic features, mainly a lesser degree of weakness and longer ambulatory period, which make it fall between both ends of the spectrum. Although these conditions differ in severity and BM generally presents with milder, progressive muscle weakness, while UCMD leads to more severe, early-onset symptoms and they all stem from defects in collagen VI synthesis and assembly. This underscores the essential role of collagen VI in muscle health, repair, and overall tissue function [1][7].

Collagen VI–related myopathies represent a continuum of neuromuscular disorders resulting from impaired structure or function of collagen VI, a microfibrillar extracellular matrix protein essential for anchoring muscle fibers to their surrounding connective tissue. The phenotypic expression of COL6-RM spans severe congenital forms to mild adult-onset presentations, with clinical variability influenced by mutation type, protein expression level, and modifier pathways.

Collagen VI plays a dual role in mechanical stability and cell signaling[5][6][7]. Its absence or dysfunction leads to ECM disorganization, defective autophagy, mitochondrial abnormalities, and increased apoptosis. These discoveries have reframed COL6-RM as disorders of both ECM architecture and cellular homeostasis, revealing new therapeutic avenues[1][4][5].

II. SPECTRUM OF COLLAGEN VI-RELATED MYOPATHIES

Collagen VI–related disorders encompass a clinical continuum ranging from severe congenital forms to milder adult-onset presentations. The major phenotypic categories include[1][7][8][9][10]:

- *Bethlem Myopathy:*

- *Typical Bethlem Myopathy:*
  Independent ambulation persists into adulthood.

- *Myosclerosis Variant:*
  Characterized by disproportionately severe contractures relative to muscle weakness, and muscles that have a firm, “woody” consistency on examination.

- *Severe Ullrich CMD (Early Severe):*
  Patients achieve sitting and occasionally knee-walking but never attain independent ambulation. Severe, early-onset contractures are typical.

- *Typical Ullrich CMD (Moderate Progressive):*
  Independent ambulation is achieved, albeit with delay, but is subsequently lost—typically between 5 and 15 years of age and almost always before age 20. Contractures are frequent and pronounced.

- *Intermediate Phenotype (Mild):*
  Patients maintain ambulation beyond age 20 into early adulthood, with contractures that are variable in severity.

- *Collagen Vi–Related Limb-Girdle Syndrome:*
  A juvenile or young adult–onset presentation marked by predominantly proximal muscle weakness with minimal or absent joint contractures.

- *Myosclerosis Myopathy*
  Represents a distinct variant characterized by early-onset, widespread, and progressive muscle and joint contractures. A defining feature is the firm, woody, and atrophic consistency of the muscles, which severely limits mobility and leads to significant functional impairment.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

➢ *Bethlem Myopathy (Bm)*

Bethlem myopathy (BM) was first recognized in 1976 by Bethlem and van Wijngaarden during their investigation of 28 individuals across three Dutch families. Their research highlighted an autosomal dominant pattern of inheritance, with patients exhibiting gradually progressive muscle weakness and the early onset of contractures[4]. These contractures were notably observed in areas such as the long finger flexors, wrists, elbows, pectoral muscles, ankles, and spine [4][11][12].BM is generally classified as a mild and slowly progressive condition. Its onset can vary significantly ,ranging from prenatal stages to adulthood that may result in a wide spectrum of clinical presentations[8].

Prenatally, there is decreased fetal movement, neonatal hypotonia, arthrogryposis, congenital hip dysplasia and torticollis are typical. Neonatal onset presents with hypotonia and delayed motor milestones, while early childhood onset shows limb-girdle weakness or joint contracture and the adult-onset patient shows variable degree of progressive muscular atrophy and weakness of proximal and extensor muscle associated with contractures of the elbow, ankle, and interphalangeal joints of the last four digits[12][13][14].

While BM shares several clinical features with other collagen VI-related myopathies, the severity of its symptoms is typically reduced[8][10][15]. The disorder predominantly affects the axial and proximal muscle groups, leading to noticeable weakness. In addition, individuals may develop varying degrees of contractures in the neck, fingers, elbows, knees, and ankles. Joint laxity, particularly in the distal limbs, and subtle skin changes are also commonly reported, such as follicular hyperkeratosis or hypertrophic scars[8][16][17].

The progression of BM is highly individual; some patients experience such mild symptoms that they maintain considerable independence, while others might eventually require assistance for outdoor mobility. However, typical Bethlem has two variants - Myosclerosis variant with prominent contractures than muscular weakness with a “woody” feel when palpated; Collagen VI-related limb-girdle syndrome on the other hand has greater degree of muscle weakness than Contracture. Importantly, despite the muscle weakness and contractures, severe respiratory complications that necessitate ventilatory support are rare[2][5][8].

➢ *Ullrich Congenital Muscular Dystrophy (Ucmd)*

In the early 1930s, Otto Ullrich identified a distinct group of pediatric patients who presented with a constellation of unusual clinical features, which he termed scleratonic muscular dystrophy (Skleratonische Muskeldystrophie). These children exhibited an atypical combination of early-onset muscle weakness and joint hyperlaxity, accompanied paradoxically by severe and progressively worsening contractures in the proximal joints[6]. Ullrich’s early characterization of this unique phenotype laid the foundation for what is now recognized as Ullrich Congenital Muscular Dystrophy (UCMD); a severe, congenital form of collagen VI-related myopathy[6][7].

UCMD typically manifests at birth, with affected individuals showing pronounced muscle weakness and significant proximal joint contractures, while the distal joints display marked hyperflexibility. Characteristic cutaneous abnormalities, including soft, velvety skin and abnormal scarring, further distinguish the clinical presentation. The functional impact of UCMD is profound: some children never achieve independent ambulation, while others who initially walk often lose the ability within a few years due to disease progression. Respiratory involvement is a hallmark feature, with most patients developing respiratory insufficiency that may require ventilatory support by the first or second decade of life. Progressive scoliosis is also common and contributes substantially to morbidity and the complexity of long-term management[2].

III. PATHOPHYSIOLOGY

Key mechanisms of Pathogenesis of Collagen VI–Related Myopathies include(**Figure 1)**:

➢ *Extracellular Matrix Disruption*

Defective collagen VI microfibrils impair linkage between basement membrane and interstitial matrix, reducing mechanical stability and susceptibility to muscle damage[5][8][9].

➢ *Autophagy Dysfunction and dysregulation*

Studies demonstrate markedly reduced autophagic flux, leading to accumulation of damaged organelles and proteins. Activation of autophagy rescues muscle degeneration in animal models[6][10][11].

➢ *Mitochondrial Dysregulation*

Failure to remove dysfunctional mitochondria increases oxidative stress and favors opening of the mPTP, a critical step in apoptosis[8][12][13].

➢ *Myomatrix Remodeling*

Altered fibroblast–myofiber interactions promote fibrosis, aberrant signaling, and impaired regeneration[8][14][15].Together, these mechanisms contribute to progressive muscle fiber degeneration and functional decline.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

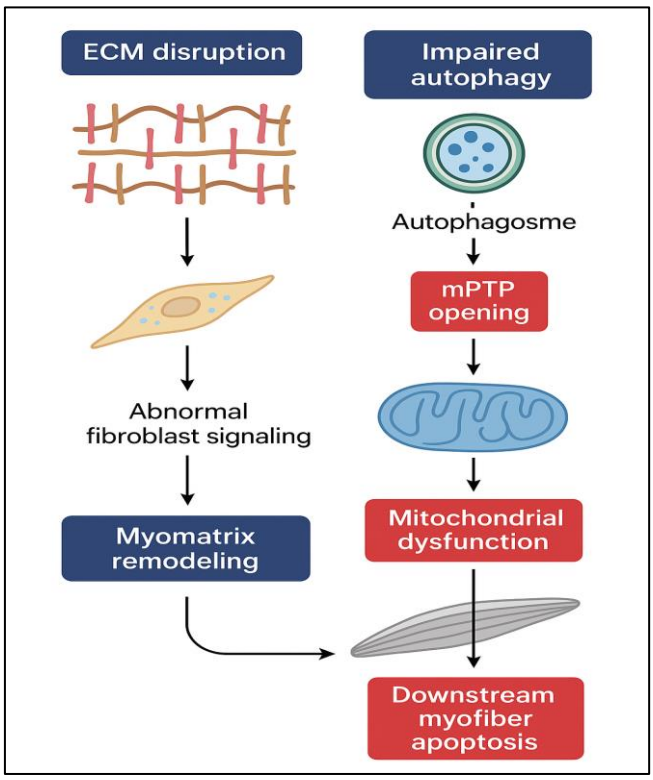

Fig 1 Schematic illustrating ECM disruption, impaired autophagy, mitochondrial dysfunction with mPTP opening, and downstream myofiber apoptosis in COL6-RM. The diagram depicts the role of abnormal fibroblast signaling and myomatrix remodeling.

In the extracellular matrix, collagen VI interacts with various matrix molecules, though the specific molecular partner that facilitates collagen VI's interaction with the muscle basement membrane remains unidentified [5][9][10]. One potential is collagen type IV, a key structural component of basement membranes[5][11][13]. Additionally, there may be indirect inferable links between Collagen VI and muscle cell surface receptors with the pathology of the disease spectrum [5][12][14][15].

Numerous studies have proposed functions of collagen VI include promoting cell adhesion, proliferation, regulation and differentiation, migration, and survival [12][13][14][15]. In a study carried out by Mereness et al., the absence of Collagen VI leads to structural changes in the lungs of mice. Decreased COL6 expression could result in developmental defects or an inability to maintain homeostasis, potentially contributing to chronic lung disease signifying the systemic functions of Collagen VI beyond musculoskeletal effects[16]. Though based on clinical observations in patients with collagen VI-related myopathies, it appears that the most critical roles of collagen VI are in muscle, tendon, and skin tissues[17][18].

Inactivation of the COL6A1 gene in mice resulted in a lack of collagen VI ,leading to muscle fiber necrosis, phagocytosis, and regeneration, with pronounced damage in the diaphragm like the muscle phenotype seen in BM [17][18]. Additionally, these collagen VI-deficient (*Col6a1*-/-) mice exhibited a loss of contractile strength and ultrastructural alterations in the sarcoplasmic reticulum and mitochondria, along with spontaneous apoptosis. A latent mitochondrial dysfunction was identified, characterized by mitochondrial depolarization and calcium deregulation upon treatment with the ATPase inhibitor oligomycin. Notably, these defects were reversible through plating myofibers on collagen VI or administering cyclosporin A, which improved muscle ultrastructure and reduced apoptosis in vivo. These findings suggest that collagen VI myopathies have mitochondrial pathogenesis that may be targeted for therapeutic intervention [15].

In the COLVI knockout muscle, an increased opening of the permeability transition pore (PTP) in the mitochondrial inner membrane was highlighted as causative for the dystrophic phenotype and became a major successfully targeted downstream defect by the therapeutical approaches assessed thus far.

IV. GENETIC BASIS

The collagen VI genes are located at distinct chromosomal sites in mammals, but their arrangement varies across species. In humans, COL6A1 and COL6A2 are found together on chromosome 21, while COL6A3 is located on chromosome 2. In mice, these genes are on chromosome 10 and chromosome 1, respectively. In most mammals, this gene organization is consistent, but in some primates, the arrangement of collagen VI genes has undergone changes[18]. In particular, the COL6A4, COL6A5, and COL6A6 genes are typically aligned in tandem and oriented in a 5′ to 3′ direction[18]. However, in humans, only the 3′ fragment of COL6A4 remains intact at the 3q24 locus. This remnant includes the exons encoding much of the triple helix and all the C-terminal region. The missing 5′ half of the gene, along with neighboring genes, has been located on the p arm of chromosome 3, oriented in the opposite direction as evidence in a pericentric inversion during human evolution[18].

A comparative analysis of other primate species reveals that many animals , such as orangutans, gibbons, and various monkey species (rhesus, baboon, squirrel monkey, marmoset), as well as prosimians like lemurs and bushbabies, have an intact COL6A4-COL6A5-COL6A6 gene cluster. However, in chimpanzees and gorillas, the COL6A4 gene locus is similarly disrupted, suggesting that the inversion occurred after orangutans branched off from the primate lineage but before the evolution of hominids, approximately 8 to 16 million years ago. This inversion split the COL6A4 gene into two segments now considered pseudogenes: COL6A4P1 at 3p and COL6A4P2 at 3q. When examining non-primate vertebrates such as marsupials, reptiles, and other placental mammals, an intact COL6A4-COL6A5-COL6A6 arrangement is found, confirming that this structure is the ancestral state for vertebrates (18).

- *Mutations and their Effects*

Mutations in the collagen VI genes (COL6A1, COL6A2, and COL6A3) play a pivotal role in the development of myopathies by disrupting the protein's

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

synthesis, assembly, and secretion, which are essential for maintaining the structural integrity of the extracellular matrix. These genetic alterations often result in misfolded proteins and impaired microfibrillar network formation, leading to decreased muscle stability and the clinical manifestations observed in conditions such as Bethlem myopathy and Ullrich congenital muscular dystrophy. While the severity of symptoms can vary, the fundamental impact on collagen VI function underscores the importance of elucidating the underlying molecular mechanisms, as this knowledge is critical for refining diagnostic criteria and guiding the development of targeted therapeutic interventions[18].

➢ *Inheritance Patterns*

Although BM had initially been identified as an autosomal dominant disorder, subsequent research has found additional autosomal recessive inheritance patterns. Foley et al. reported on two adult siblings with classic BM who inherited the condition recessively. These siblings carried compound heterozygous mutations—a single nucleotide deletion on the maternal allele and a missense mutation on the paternal allele—passed down from their parents who were unaffected carriers [19].

Similarly, UCMD was initially recognized as a recessive disorder caused by either homozygous or compound heterozygous mutations [20]. However, Pan et al. reported on a de novo heterozygous deletion of the COL6A1 resulting in a severe phenotype of classical UCMD [21].

➢ *Genetic Variations Across Regions*

Although more prevalence data is lacking, in Northern England, a study conducted by Norwood et al. identified the prevalence of both UCMD and BM as 0.13/100,000 and 0.77/100,000, respectively [22].UCMD is significantly rarer than BM despite both conditions are categorized as rare diseases.

In a Korean study involving 22 patients, the average age at symptom onset was 4.5 years, while the mean age at diagnosis was 24.9 years. The cohort included 16 patients from seven families with BM and two patients from two families with typical UCMD. Genetic analysis revealed that one UCMD patient had missense mutations in the triple-helical domain of COL6A1, while 10 BM patients had exon-14-skipping mutations. Additionally, two novel mutations were identified: c.956A>G (p.K319R) in COL6A1 and c.6221G>T (p.G2074V) in COL6A3 [23] .

A larger Japanese study of 130 families, each with 1–5 members affected by collagen VI-related dystrophy, found that 120 families carried mono-allelic variants and 10 had bi-allelic variants in COL6A1, COL6A2, or COL6A3. Among these, 60 variants were identified in COL6A1, 57 in COL6A2, and 23 in COL6A3, including 37 novel variants. Mono-allelic variants were categorized into four types: missense mutations (69, 58%), splicing mutations (40, 33%), small in-frame deletions (7, 6%), and large genomic deletions (4, 3%). Notably, 88% of the mono-allelic variants were in the triple-helical domains [24].

V. CLINICAL PRESENTATIONS

➢ *Bethlem Myopathy (BM) Symptoms and Progression*

- Mild to moderate proximal weakness
- Early-onset contractures (elbows, Achilles, long finger flexors)
- Slow progression, often ambulant into adulthood.

Despite the symptoms and progression often being associated with adulthood, BM symptoms frequently manifest in infancy. Affected infants may show signs of hypotonia, foot deformities, and torticollis, which occurs in up to 50% of cases. Typically, contractures are present at birth but resolved by age two. In early childhood, only mild muscle weaknesses may be evident, with joint hyperlaxity in distal areas instead of contractures. Some individuals may have proximal muscle weakness without significant contractures, leading to a diagnosis of limb-girdle muscular dystrophy. Conversely, others might experience primarily contractures without much muscle weakness, a condition referred to as myosclerosis, where the muscles feel stiff or "woody" [2].

Typical contractures of the Achilles tendons and elbows usually emerge during late childhood or adolescence. These contractures progressively affect the long finger flexors and shoulders, and in some cases, the spine, leading to varying degrees of spinal stiffness. A hallmark of the disease is the "Bethlem sign," where contractures of the long finger flexors prevent complete finger extension when the wrist is dorsiflexed. Even in patients with slowly advancing muscle weakness, the progression of contractures can lead to significant functional impairment. By middle age, many patients require mobility aids, with about two-thirds of individuals over 50 needing assistance such as a wheelchair or mobility scooter. While muscle strength may remain stable for several years, patients often experience a noticeable decline during their 40s and 50s. In addition to musculoskeletal issues, individuals with BM face an increased risk of restrictive lung disease, which can lead to respiratory insufficiency, especially if accompanied by obstructive sleep apnea. As a result, sleep studies are important to monitor nocturnal hypoventilation and intervene proactively if needed [5][10][12].

➢ *Ullrich Congenital Muscular Dystrophy (UCMD) Symptoms and Progression*

- Neonatal hypotonia
- Proximal weakness
- Distal hyperlaxity
- Early contractures
- Early respiratory insufficiency
- Loss of ambulation in childhood

Fetuses with UCMD may exhibit reduced prenatal movements, though the characteristic features described by Ullrich typically become apparent at birth. Newborns with this condition often present with hypotonia and muscle

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

weakness, accompanied by pronounced hyperlaxity, especially in the distal joints[5][10][12]. The hands and fingers are extremely flexible, often able to bend backward against the forearm, while the feet may be hyperextended against the shin, a finding frequently remembered by parents as one of the earliest signs. In some cases, joint contractures are also present at birth, affecting areas such as the elbows, knees, spine (resulting in kyphoscoliosis), and neck (leading to torticollis). Additionally, some infants may display clubfoot instead of the hyperflexed foot seen in others. There are some infants with UCMD who may experience transient feeding difficulties during the neonatal period, which can develop into moderate to severe dysphagia in the most severe cases. Even in the absence of noticeable dysphagia, some children may require temporary or long-term gastric feeding tube support to ensure adequate nutrition and hydration[5][10][12].

In the most severe form of UCMD, children may never achieve the ability to walk. Despite the severity, these infants can often learn to roll, crawl, and sit independently. Children with significant knee contractures preventing an upright posture may resort to walking on their knees for a period. However, most patients with classic UCMD eventually develop the ability to walk, albeit after a delay of up to two years. While these children may achieve ambulation, they often lose this ability by their early teenage years, though some may continue walking into adolescence or young adulthood[5][10][12].

Muscle weakness in UCMD is progressively disabling, worsened by the development of joint contractures in major joints, especially affecting external rotation in the shoulders, elbows, hips, knees, and ankles. While some contractures may improve in the first year, they often recur and continue to worsen over time, particularly affecting ambulation. Once patients lose the ability to walk, their muscular strength remains relatively stable, though contractures may progress, especially in the ankles, knees, hips, and elbows[5][10][12]. Scoliosis is a significant concern, often evident at the end of the first decade and sometimes requiring spinal instrumentation.Though respiratory insufficiency is rare at birth, it becomes a critical issue as the disease advances, typically manifesting after the loss of ambulation. Some patients may experience respiratory difficulties while still able to walk, with a progressive decline in forced vital capacity observed from age five to early teens[5][10][12]. Initial signs of respiratory insufficiency often appear at night, necessitating sleep studies for detection. Noninvasive bilevel positive airway pressure ventilation is usually effective for treatment, often required only during the night. However, it is crucial not to overlook respiratory support, as failure to provide adequate intervention has led to fatalities in teenagers with UCMD. Comprehensive studies are needed to better understand the long-term course of the disease under current medical standards, especially since earlier long-term outcomes were skewed by a lack of respiratory intervention, resulting in many patients succumbing to respiratory failure in their late teens. With effective respiratory support now available, other aspects of UCMD may emerge [5][10][12].

➢ *Intermediate Phenotypes*

Patients exhibit overlapping features between UCMD and BM, complicating genotype–phenotype predictions. BM and UCMD are diagnosed primarily through a combination of clinical evaluation, genetic testing, and histopathological analysis[25][26]. Clinically, the diagnosis often begins with a thorough evaluation of the patient's symptoms. Patients with BM usually present with a slow progression of muscle weakness and contractures, which can provide important clues for diagnosis, while patients with UCMD present early and more significant muscle weakness and distinctive physical features [25][26][(27].

VI. DIFFERENTIAL DIAGNOSIS OF COLLAGEN VI–RELATED DYSTROPHIES (COL6-RDS)

A number of neuromuscular and connective tissue disorders present with overlapping clinical features and may be considered in the differential diagnosis of COL6-related dystrophies. Key distinguishing features and comparative insights are summarized below:

➢ *Limb-Girdle Muscular Dystrophy (LGMD)*

LGMD encompasses a genetically heterogeneous group of muscular dystrophies characterized primarily by progressive weakness of the proximal muscles, particularly those of the shoulder and pelvic girdles. Patients typically achieve independent walking but later experience gradual loss of muscle fibers. Similar to COL6-RDs, LGMD may present with elevated creatine kinase (CK), variable age of onset, and muscle degeneration on imaging or biopsy.

- *Distinguishing Feature:*

LGMD generally lacks the early contractures, distal hypermobility, and skin abnormalities that are hallmark features of COL6-RDs *[28][29]*.

➢ *Emery–Dreifuss Muscular Dystrophy (EDMD), Contracture-Predominant Phenotype*

EDMD results from mutations in nuclear envelope proteins such as emerin, lamin A/C, or nesprins, leading to defects in nuclear architecture, mechanotransduction, and gene regulation[29]. Clinically, EDMD presents with the classic triad of:

- Early-onset contractures (often in the first decade),
- Progressive muscle weaknesses, particularly in elbows, ankles, neck, and
- Cardiac involvement, including conduction defects and cardiomyopathy.
- These early contractures may mimic Bethlem or intermediate COL6-RD phenotypes.

- *Distinguishing Feature:*

The presence of cardiac abnormalities differentiates EDMD fromCOL6-RDs*[30]*.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

➢ *Ehlers–Danlos Syndrome (EDS)*

EDS consists of a group of hereditary connective tissue disorders caused by mutations in various collagen types. Shared features with COL6-RDs include joint hypermobility and skin elasticity.

- *Distinguishing Features[31]:*

✓ Muscle weakness is typically mild or absent,
✓ Easy bruising, atrophic scarring, vascular complications, and systemic involvement are common in EDS but generally absent in COL6-RDs, and
✓ The primary collagen defects involve collagen types other than type VI. *[31]*

➢ *Congenital Muscular Dystrophy (CMD)*

CMD encompasses multiple early-onset muscular dystrophies, including merosin-deficient CMD and alpha-dystroglycanopathies[32]. Many CMD subtypes present with early hypotonia, delayed motor milestones, and elevated CK.

- *Distinguishing Feature:*

COL6-RDs display a unique pattern of proximal contractures with distal hyperlaxity, characteristic skin changes, and distinctive myomatrix disruption, which differentiate them from other CMD subtypes *[32]*.

➢ *Walker–Warburg Syndrome (WWS) / Muscle–Eye–Brain Disease (MEB)*

These severe congenital dystroglycanopathies present with generalized muscle weakness or hypotonia and elevated CK, overlapping with COL6-RDs[33].

- *Distinguishing Features:*

✓ Significant ocular malformations (e.g., retinal detachment, cataracts, microphthalmia, microcornea),
✓ Central nervous system anomalies (cobblestone lissencephaly, cerebellar hypoplasia, hydrocephalus), and
✓ The underlying hypoglycosylation of α-dystroglycan, which disrupts muscle integrity and neuronal migration, pathomechanisms absent in COL6-RDs *[33][34]*.

➢ *Autosomal Recessive Myosclerosis Myopathy*

This rare disorder presents early-onset muscle stiffness and joint contractures, similar to COL6-RDs. Distinguishing feature:

Muscle biopsy shows dense fibrous replacement, and the condition is genetically distinct from COL6-related disorders. Loss of ambulation often occurs during adolescence or adulthood *[35]*.

➢ *Diffuse Leiomyomatosis*

Primarily a smooth muscle disorder, diffuse leiomyomatosis may initially be mistaken for a skeletal myopathy due to muscle-related symptoms.

- *Distinguishing Feature:*

Although it shares some overlap with COL6A3 mutation–associated syndromes, skeletal muscle involvement is minimal, unlike in COL6-RDs *[36]*.

➢ *HANAC Syndrome (Hereditary Angiopathy with Nephropathy, Aneurysms, and Muscle Cramps)*

HANAC syndrome is caused by mutations in COL4A1. Patients may experience muscle cramps and vascular symptoms that resemble some features of COL6-RDs.

- *Distinguishing Features:*

Systemic findings such as renal involvement, small-vessel angiopathy, and arterial aneurysms are not characteristic of COL6-RDs*[37][38][39]*.

➢ *Intermediate COL6-RD (Related Dystrophies)*

This category encompasses phenotypes that exist between classic Bethlem myopathy and Ullrich CMD, demonstrating the clinical continuum of COL6-related disorders.

- *Distinguishing Features:*

These conditions share hallmark COL6-RD features which includes contractures, distal hyperlaxity, and myomatrix pathology, while differing in severity and progression *[39][40][41]*.

➢ *General Myopathies*

A wide variety of inherited and acquired myopathies can present with muscle weakness, fatigue, and elevated creatine kinase (CK). Distinguishing features of COL6-RDs:Characteristic contractures, Prominent connective tissue involvement, distal joint hypermobility, and distinctive collagen VI–related myomatrix abnormalities(36). These features help differentiate COL6-RDs from nonspecific or inflammatory myopathies *[41][42][43]*

VII. DIAGNOSIS

The diagnosis of the spectrum of myopathy could be by A. Clinical evaluation B. Genetic testing C. Muscle biopsy and immunohistochemistry/PCR: Fiber atrophy and size diversity, and aberrant Protein expression(see Table 1 and 2,Figure 2-6).

➢ *Clinical Evaluation*

Includes developmental history, contracture assessment(evaluation), gait and weakness analysis, and respiratory evaluation(Table 1 and 2).

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

Table 1 Clinical Differences Between Ullrich CMD and Bethlem Myopathy

Feature	Ullrich CMD	Bethlem Myopathy
Onset	Birth/infancy	Childhood/adulthood
Weakness	Severe, early	Mild–moderate, slow
Contractures	Early, progressive	Distal finger flexor & Achilles predominant
Joint Laxity	Distal hyperlaxity	Mild or absent
Respiratory Failure	Childhood onset	Adulthood onset or mild
Ambulation	Often lost in childhood	Preserved long-term

Table 2 Diagnostic Modalities in COL6-RM

Modality	Key Findings	Utility
Clinical exam	Proximal weakness, contractures	Initial suspicion
Muscle MRI	Central shadow, selective muscle involvement	Highly specific pattern
Biopsy	Reduced collagen VI staining	Supports diagnosis
Genetic testing	COL6A1–3 mutations	Definitive confirmation

➢ *Muscle Magnetic Resonant Imaging(MRI)*
Highly characteristic findings (see Figure 3):

- "Central shadow" in the rectus femoris
- Selective involvement of semitendinosus and gastrocnemius
- Relative sparing of sartorius and gracilis

➢ *Histopathology(see Figure 4-6)*

- Reduced or absent collagen VI immunostaining
- Mild dystrophic changes

➢ *Genetic Testing*
Next-generation sequencing(Exome/Gene panels detect) enhances detection of:

- Point mutations
- Splice variants defects
- Mosaicism
- De novo mutations
- Dominant and recessive variants.

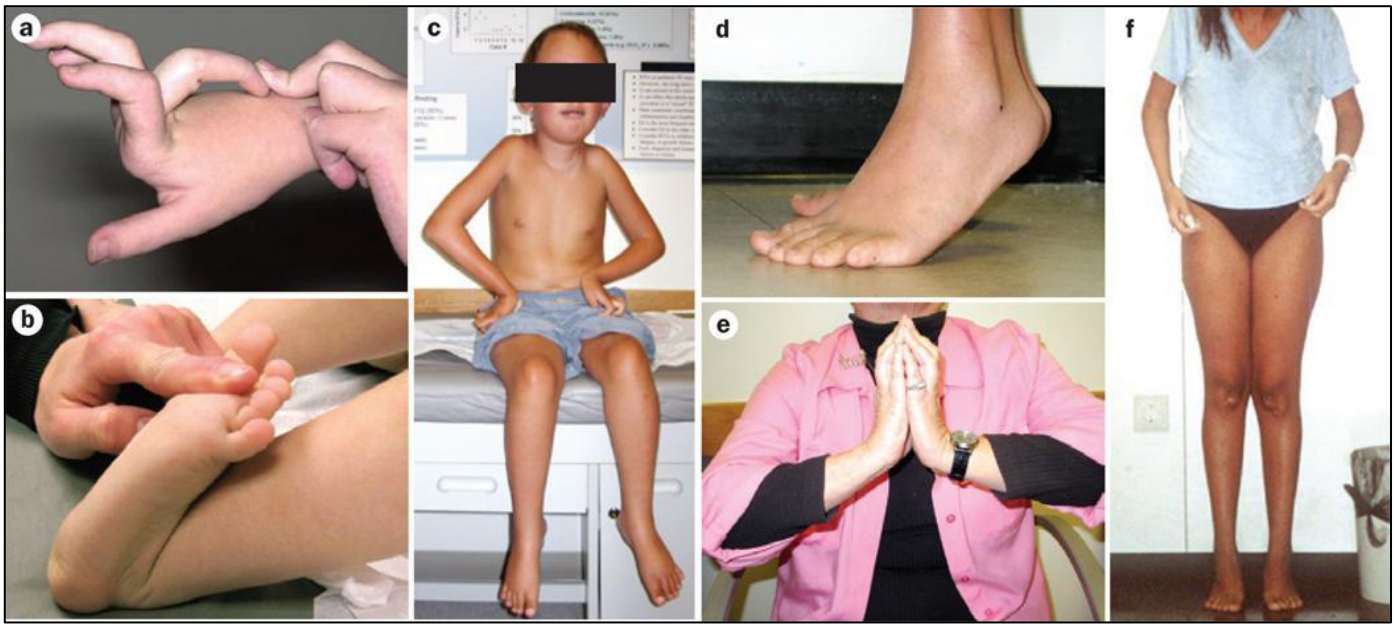

Fig 2 Patients with Ullrich congenital muscular dystrophy (CMD) and Bethlem myopathy exhibit joint hyperlaxity and progressive contractures. In Ullrich CMD, children often show significant distal joint hyperlaxity, particularly in the fingers (a, b). As the disease progresses, they may develop contractures in the shoulders, elbows, and knees (c), and may lose the ability to walk over time. Characteristic features also include a round facial appearance and mild facial erythema (c). In contrast, patients with Bethlem myopathy often present with pronounced Achilles tendon contractures (d) and typical long finger flexor contractures, preventing full extension when the palms are placed together with dorsiflexed hands and elevated elbows, known as the "Bethlem sign" (e). An adult with Bethlem may demonstrate a distinctive upper body posture resulting from elbow and shoulder contractures, as well as Achilles tendon contractures (f).

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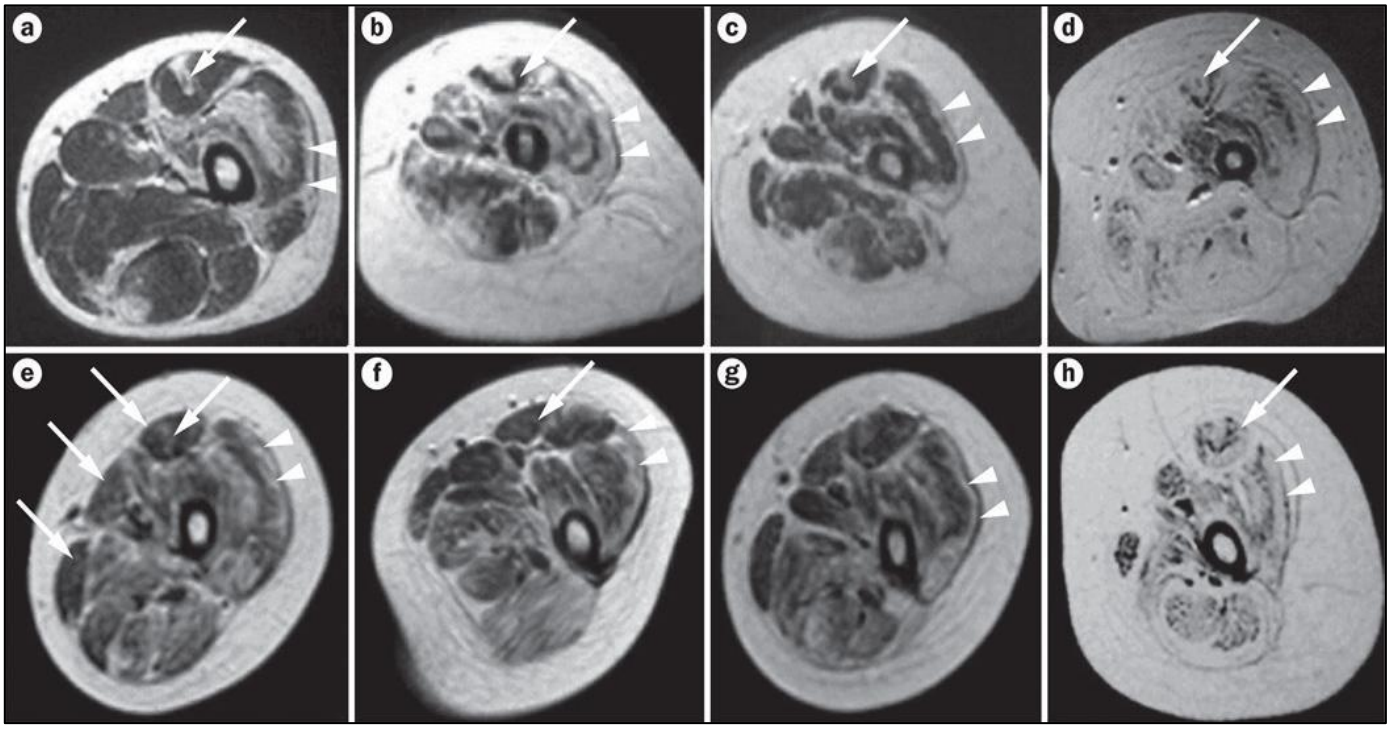

Fig 3 Muscle MRI findings in collagen VI-related myopathies reveal distinct patterns. T1-weighted MRI scans of the thigh in patients with (a–d) Bethlem myopathy and (e–h) Ullrich congenital muscular dystrophy of varying severity demonstrate characteristic fatty degeneration (highlighted as white areas). Notably, this degeneration appears along the fascia in the center of the rectus femoris (long arrows) and around the rim of the vastus lateralis (arrowheads), forming the characteristic 'outside-in' pattern. This pattern persists in patients with severe forms of the disease, as seen in parts d and h. Permission obtained from Elsevier Ltd © Mercuri, E. Neuromuscular. Disord. 15, 303–310 (2005).

NB:Representative axial MRI images demonstrating central shadowing of the rectus femoris, peripheral fatty infiltration, and selective involvement of posterior thigh muscles characteristic of collagen VI deficiency.

Molecular and genetic studies are used to confirm BM and UCMD, as they identify mutations in genes encoding collagen VI, specifically COL6A1, COL6A2, and COL6A3[44][45][46]. Park et al. utilized whole exome sequencing (WES) to diagnose a large Korean family with dominantly inherited BM caused by a mutation in the COL6A1 gene. The affected individuals exhibited slowly progressive proximal weakness and ankle contractures, initially leading to a misdiagnosis of limb-girdle muscular dystrophy (LGMD). The study emphasizes the significance of WES as a diagnostic tool, particularly in cases where traditional methods fall short due to high phenotypic variability and the potential of next-generation sequencing technologies like WES to facilitate accurate diagnosis and improve patient care [27] [44][45][46].

In addition to genetic testing, immunohistochemistry plays a crucial role; muscle and skin biopsies are analyzed for collagen VI through immunostaining, which may reveal a normal pattern despite the presence of the disease. Histopathological examination of muscle tissue from a biopsy can also provide valuable diagnostic information, revealing dystrophic changes such as muscle fiber atrophy, increased variability in fiber diameter, and myonecrosis. Furthermore, electromyography (EMG) can demonstrate myopathic features that confirm muscle dysfunction. Imaging techniques, including MRI and CT scans of the thigh muscles, may identify characteristic patterns of muscle involvement related to collagen VI-related myopathies, such as the "central shadow" sign observed in the rectus femoris. Finally, blood tests measuring muscle enzyme levels, such as creatinine kinase, may show mild elevation, indicating muscle damage [25][44][45][47].

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

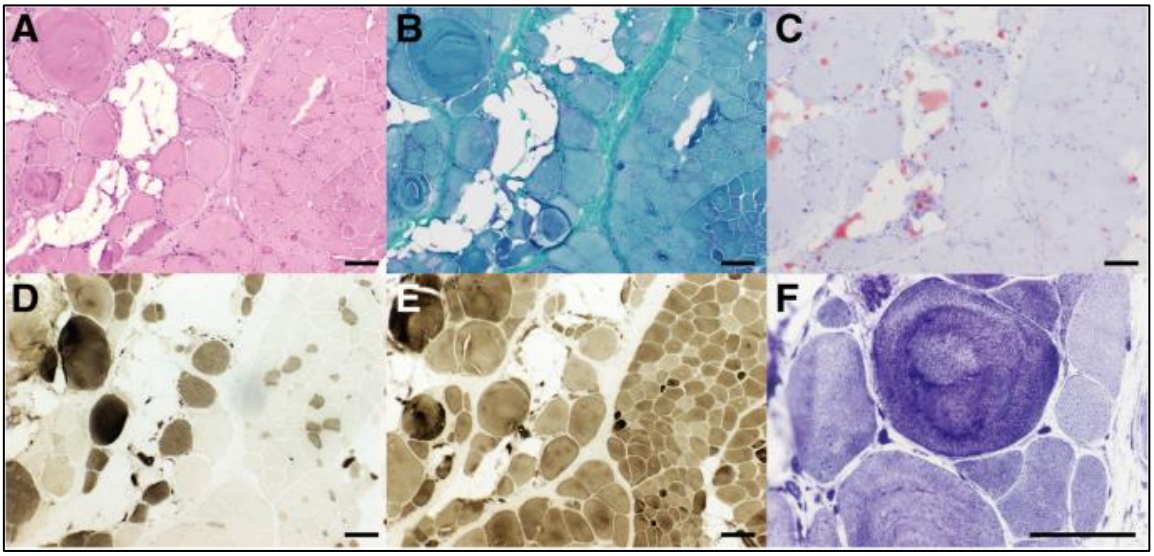

Fig 4 The muscular pathological findings (scale bar = 100 μm) include fibrosis, adipose tissue infiltration, muscle fiber rounding, increased fiber diameter variability, myonecrosis, and a few regenerating fibers observed in (a) H&E stain and (b) MGT stain. Panel (c) ORO stain highlights the predominant adipose tissue infiltration. (d) ATPase stain at pH 4.3 and (e) at pH 10.4 show equal involvement of both type-I and type-II muscle fibers with fiber type grouping. Finally, (f) NADH stain reveals disorganization of the myofibril arrangement [37].

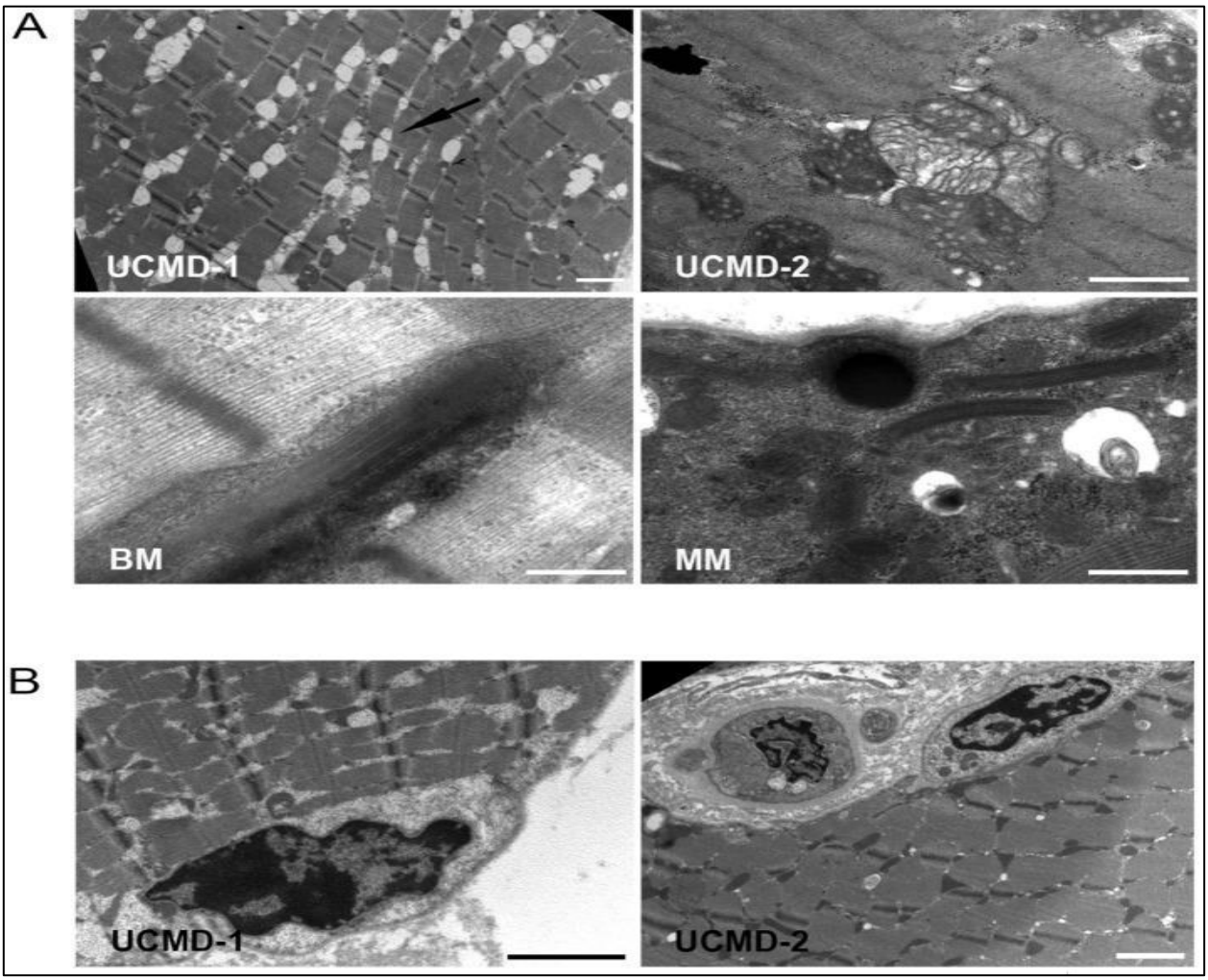

Fig 5 (A)Transmission electron microscopy of Epon-embedded muscle biopsies from UCMD, BM, and MM patients reveals consistent ultrastructural changes, including sarcoplasmic reticulum enlargement, mitochondrial abnormalities, osmiophilic bodies, and paracrystalline inclusions. (B) In UCMD patient muscle fibers, nuclear alterations indicative of apoptosis, such as irregular nuclear shape and chromatin condensation, are observed.

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

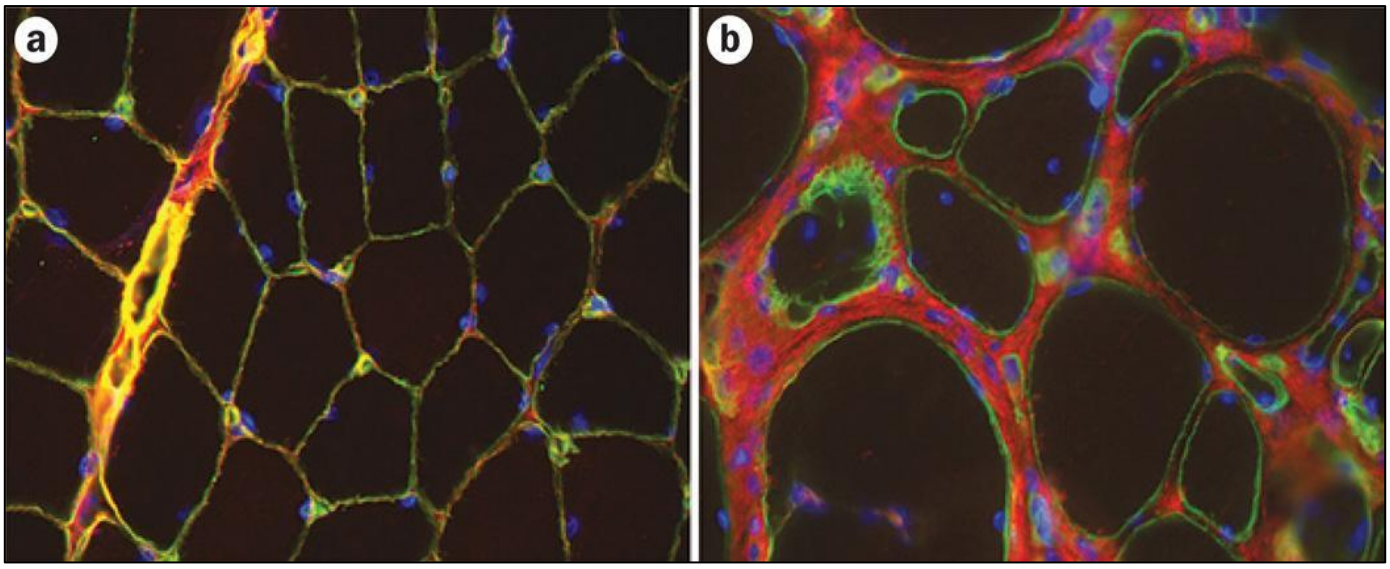

Fig 6 Immunohistochemical analysis of collagen VI in muscle tissues was performed using dual labeling for collagen VI (red) and the basement membrane marker laminin subunit γ-1 (green). (a) In a healthy individual, collagen VI and laminin γ-1 colocalize in the basement membrane, resulting in a yellow color. (b) In a patient with collagen VI-related myopathy, a gap is observed between the collagen VI and basement membrane staining. This patient has a dominant-negative mutation, causing altered collagen VI to be secreted into the matrix but failing to function or interact properly.

VIII. MANAGEMENT

➢ *Supportive Care and Counselling, Physical Therapy and Rehabilitation and Surveillance, and May Include [44][45][46][47][48]:*

- Physiotherapy and contracture management
- Orthopedic and scoliosis care
- Respiratory surveillance and noninvasive ventilation
- Occupational therapy and assistive mobility strategies
- Nutritional assessment.

Treatment strategies for both BM and UCMD center on physical therapy, orthopedic interventions, and, in some cases, pharmacologic management. Regular, tailored physical therapy remains important, emphasizing stretching to preserve joint flexibility and low-impact aerobic exercises to enhance muscle strength. Additionally, orthotic support like ankle-foot orthoses may be employed to assist with mobility and prevent further contractures. In more severe cases, surgical intervention might be necessary to correct severe contractures or scoliosis[44][45][46][47].

Mobility aids, such as wheelchairs or standing frames, become essential as muscle weakness progresses, ensuring patient safety and promoting independence. Respiratory care is crucial in UCMD, as respiratory muscle weakness can lead to restrictive lung disease. Regular monitoring of pulmonary function allows for early intervention with non-invasive ventilation, especially during sleep, and the use of cough-assist devices if needed. Pharmacologically, corticosteroids have been explored to address inflammation, although their long-term benefits and risks in BM are still under investigation [5] [44][45].

➢ *Potential therapeutic approaches:*

- Cyclosporine A and other cyclophilin D inhibitors(DEBIO-025,alisporivir)
- Low-protein diet.
- Gene therapy prospects.

Additionally, low-protein diets have emerged as a potential treatment for patients with COL6-RD by targeting cellular pathways like autophagy, which is essential for muscle health. In a pilot clinical trial, a one-year low-protein diet in patients with UCMD and BM successfully increased autophagic markers in skeletal muscle and blood leukocytes, while preserving muscle strength and function as well as showing reduced muscle cell death and improved mitochondrial function [41][48][50]. The Future directions emerging in the treatments of the disease spectrum are listed below and deserve further analysis and evaluation [4][45][48][50]:

- Pharmacologic autophagy activators
- mPTP inhibitors and mitochondrial stabilizers
- ECM-modifying biologics(ECM-targeted therapies)
- AAV-based gene delivery
- RNA repair/editing approaches
- Autophagy enhancers (e.g., cyclosporine A analogs)

- *Gene therapy Approaches (AAV, Exon Skipping, RNA Editing).*

These strategies aim to move treatment beyond symptom management toward disease modification with the ongoing research is exploring the following listed therapies [4][45][48][50]:

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr353

- ✓ Combined autophagy + mitochondrial therapies
- ✓ Biomarker-guided clinical trials
- ✓ Patient-specific stem cell models
- ✓ Longitudinal natural history registries
- ✓ Next-generation gene therapeutics tailored to collagen VI biology.

➢ *Future Directions*

Key highlighted priorities include:

- Large multicenter natural history studies
- Biomarker validation (MRI & molecular markers)
- Patient-specific induced pluripotent stem cells (iPSC) models
- Early-phase gene therapy trials
- Combination therapies targeting autophagy + mitochondrial restoration

IX. CONCLUSIONS

The spectrum of Collagen VI–related myopathies, which includes both Bethlem myopathy (BM) and Ullrich congenital muscular dystrophy (UCMD), highlight the essential role of collagen type VI in preserving skeletal muscle structure and functions. These disorders demonstrate and emphasize the complex interplay between underlying genetic mutations, extracellular matrix stability, myomatrix Remodeling ,autophagy dysfunction and dysregulation, and mitochondrial dysregulation and with highly variable clinical manifestations.

While current management remains largely supportive, advances in understanding disease mechanisms, particularly involving autophagy impairment, mitochondrial dysfunction, and myomatrix remodeling are driving the development of more precise therapeutic strategies. Emerging modalities such as autophagy-enhancing drugs, mitochondrial stabilizing therapy, ECM-modifying biologics, and gene-based interventions hold promising potential to significantly alter disease trajectories. Sustained research efforts, coupled with improved diagnostic tools and robust natural history data, are vital for translating these innovations into meaningful clinical outcomes. Ultimately, these scientific advancements offer renewed hope for more effective treatments and improved quality of life for individuals living with collagen VI–related myopathies.

➢ *Author Contributions*

AO and AM conceived the project, performed literature review, drafted the manuscript, and approved the final version. All authors contributed to the article and approved the submitted version.

➢ *Funding*

No external funding was received for this work.

➢ *Conflict of Interest Statement*

The author declares no commercial or financial relationships that could be construed as a potential conflict of interest.

➢ *Data Availability Statement*

No datasets were generated or analyzed for this review.

➢ *Ethics Statement*

This is a narrative article and neither involve human subjects nor require IRB approval.

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