Myotonic Dystrophy Type 1: A Comprehensive Literary Review

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Abstract

Myotonic Dystrophy Type 1 (DM1) is a degenerative neuromuscular disease that costs 448 million dollars in the US annually to combat. Caused by the abnormal expansion of the CTG sequence located along the Dystrophia Myotonica Protein Kinase (DMPK) gene of chromosome 19, DM1 results in several different observable effects that include, but are not limited to cataracts, facial weakness, hypersomnia, cardiomyopathy, and arrhythmias. Symptoms are attributed to the rapid degeneration of muscles that leads to weakened control over the heart, lungs, gastrointestinal systems, and face. Treatments for DM1 are limited to minimizing morbidity such as through assistive mobility devices. In pursuit of a cure, pre-clinical models have provided a foundation for deeper investigations into the pathogenesis of DM1. Ongoing studies utilize molecular genetics and pharmacology to target the underlying molecular mechanisms, fortunately, many of these studies have shown potential in pre-clinical trials. Antisense therapy targets expanded trinucleotide regions and has demonstrated recovery of cardiac muscle in mice. CRISPR/SpCas9, when injected, has shown beneficial effects in several DM1 animal models. Furthermore, given the pre-clinical success of the novel pharmacologic agent AOC 1001, clinical trials have been initiated and are ongoing. Unfortunately, due to the nuances and difficulties in treating DM1, there is currently no Food and Drug Administration-approved disease-modifying therapies, and as such DM1 represents a growing public health concern.

Keywords: Myotonic dystrophy type 1; Expanded trinucleotide repetition; Disease pathogenesis; Clinical trials, Future developments

Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disease that occurs from a gene defect in the untranslated region (UTR) of the myotonic dystrophy protein kinase gene (DMPK). DMPK is responsible for the regulation of myosins in skeletal muscle to form contractile filaments as well as the production of myotonic dystrophy protein kinases, which have a relatively unknown function. The DMPK gene is located on chromosome 19q13.3[1]. The perplexing issue is, of course, that the untranslated region where DM1 repetitions occur has no functional correlation to the production of proteins. DM1 is caused by an abnormally long repeat of CTG codons between 50-1000 repeats depending on the variant and severity, with a loose correlation to onset age based on sequence lengths. Regular repetition rates range from 5 to 34 in the average human[1]. Small expansions of 50-80 are often passed with slight genetic variations, with more instability in males[2]. Females have a much higher chance of passing large sequences of 1000 or more repeats to their offspring, which explains the main reason that rates of congenital myotonic dystrophy are nearly always maternal transmissions[2]. Repeats are

dynamic, as the length of repeats varies from different tissues and cell types. Children, in turn, may inherit longer sequences than their parents with up to 200 more repeats on average, causing genetic anticipation: a condition where symptoms have an earlier onset age each generation a disease is passed[2].

Current therapeutic investigations into DM1 aims to exploit the two underlying pathophysiologic mechanisms: RNA toxicity and RNA gain-of-function. RNA toxicity resulting from CUGBP Elav-like family (CELF) upregulation could lead to an over-expression of CUG repeats, which, in turn, exacerbates splicing defects and presents through the clinical features of DM1.[2] Abnormal expansion of CUG repeats in the DMPK gene is also thought to lead to RNA gain-of-function, achieved through sequestration of muscleblind-like proteins (MBNL). This is likely responsible for several receptor and channel defects commonly found within DM1 patients[3]. In response, several genetic treatments are being developed, including antisense-based therapies, CRISPR/Cas9 gene editing, and even clinical developments of drugs such as AOC 1001 and DYNE-101[3,4]. Although their functions vary, the general design behind each treatment is to either reduce, terminate, or prevent expression of sequence repeats in order to minimize impact in the daily life of DM1 patients[3]. Given the lack of an FDA-approved treatment for DM1, which has resulted in the current focus on improving quality of life, there is an urgent need for research to shift its efforts towards identifying a viable therapeutic option; nonetheless, the treatments explored thus far exhibit significant promise.

Background

Myotonic dystrophy (DM) occurs in 2 prevalent forms, DM1, also known as Steinert's disease, and myotonic dystrophy type 2 (DM2). A distinct separation occurs based on the location they impact. DM1, the more well-known disease, occurs on chromosome 19, while DM2 impacts chromosome 3[2]. Although similar in molecular causes (that being the unusually long repetition of a gene sequence), DM1 appears more frequently in the general populace and has a more severe morbidity and mortality[2]. This review will extensively discuss the pathophysiology of DM1 as well as current treatments and future outlooks of managing this disease.

Within DM1 there exists several further categories based on age and phenotypes of patients. These can be divided into classical, mild, childhood, and congenital myotonic dystrophy. Mild myotonic dystrophy is of least current concern and involves a CTG repetition count of between 70 to 100 repeats, resulting in mild phenotypes forming past the age of 40 on average[2]. Classical myotonic dystrophy presents itself between the early 20's to late 40's around 75% of the time[2]. In this stage, present myotonia specifically targets the forearms, jaw, hands, and leg muscles leading to muscular deterioration in the extremities[2]. Childhood myotonic dystrophy is similar in the symptoms and formations of classical DM1, but generally develops in the first decade of life[2]. Furthermore, childhood myotonic dystrophy is mainly visible through cognitive impairment in juveniles including an intelligence quotient range of 50-70 on average[2,5]. Attention deficit disorder, anxiety, and mood disorders are common[2]. Congenital myotonic dystrophy (cDM1) is present from birth and often results in repeated excess of 1000. Neonatal mortality rates are set at around 18% for infants with cDM1[2]. Until adulthood, myotonia is difficult to observe directly even with an electromyogram, yet attributes appear similar to classical myotonic dystrophy as a child ages[2,5]. Biopsies for cDM1 do not reveal signs of DM1 phenotypes in muscle weakness; instead, DNA testing is required to confirm a diagnosis[5].

Although all are different, the categories of DM1 share the common cause of expanded trinucleotide repetition, meaning that potential treatments on a molecular level can be applied relatively well regardless of the form Furthermore, this review will cover both DM1 as an entirety, along with type-specific information on molecular causes and treatments if applicable or necessary.

The exact presence of DM1 is unknown despite the necessary equipment being present to conduct a multi-national study. Similarly, the distribution of the disease is rather convoluted. Rather, North America–specifically the United States of America (US, USA) and Canada–will be in focus. DM1 is present in 13/100,000 people within the US and can vary depending on regions. Of 457 participants surveyed with DM1, 60% were women and 40% men[6]. Of the participants, the average age was 45±15 years with average age onset of 27±15 years[6]. Occupation-wise, only some 30% of individuals were found to be employed, with a majority simply unable to work–or choosing not to–due to DM debilitation[6]. Due to this fact, about 76% earn below $25,000 annually with about 17% earning more than $40,000 and a minority of 6% having an income between such a range[6]. 24% of these individuals earned no income whatsoever and were dependents[6]. Healthcare costs for DM1 are quite high. Across a 36-47 month period, DM1 costs in the US were at $16,497, more than 3.7 times higher than the national average of $5,193[7]. Nationwide tion-wide, DM (a combination of both DM1 and DM2)) currently costs about $448 million dollars[8]. Correlation has also been found between the cost of DM1 to the loss of income, as more severely impacted patients have higher debts, often paired with the glaring inability to maintain jobs[4].

Mortality of DM1 is not as severe as other muscular dystrophies, but regardless, is important to factor into the presence of the disease. Mild DM1 has an average lifespan of 60+ years, due to the limited presence of the disorder within the body[9]. Classic DM1 is more severe with lifespans of 48-55 years, while cDM1–acquired from birth–results in average lifespans of 45 years or less (non-inclusive of neonatal deaths)[9]. A majority of deaths occur from respiratory failure, cardiac arrhythmia, or neoplasms, with 50% of individuals in such cases being wheelchair-bound before death[9].

Table 1: Comparison of different DM1 phenotypes and their correlation to average onset age, clinical symptoms and repeat lengths[1,2,9]**.**

Phenotype	**Onset Age**	**Repeat Size**[a]	**Primary Clinical Signs**
cDM	Birth	>750[b]	• Infantile hypotonia • Respiratory defects • Classic symptoms in adulthood • Joint stiffness • Learning disabilities • Cardiovascular complications • GI defects
Classic	10-30 years	100-1000	• Cataracts • Myotonia

			• Weakness • Balding • Joint stiffness • Conduction defects • Cardiac arrhythmia • Respiratory failure • GI defects
Childhood Onset	1-10 years	50-1000	• Myotonia • Hypotonia • Facial weakness • Intellectual and learning disabilities • Conduction defects • Respiratory defects
Mild	20,70 years	50-150	• Cataracts • Mild myotonia • Facial weakness

a. Premutation lengths are between 34 to 49 repeats, with minor overlap to other phenotypes, while healthy individuals have ranges of 5-34 repeats on average[2,9].
b. General cDM repeats exceed 1000; however, minimum repeat lengths have been found to be as low as 730[9]

Pathophysiology

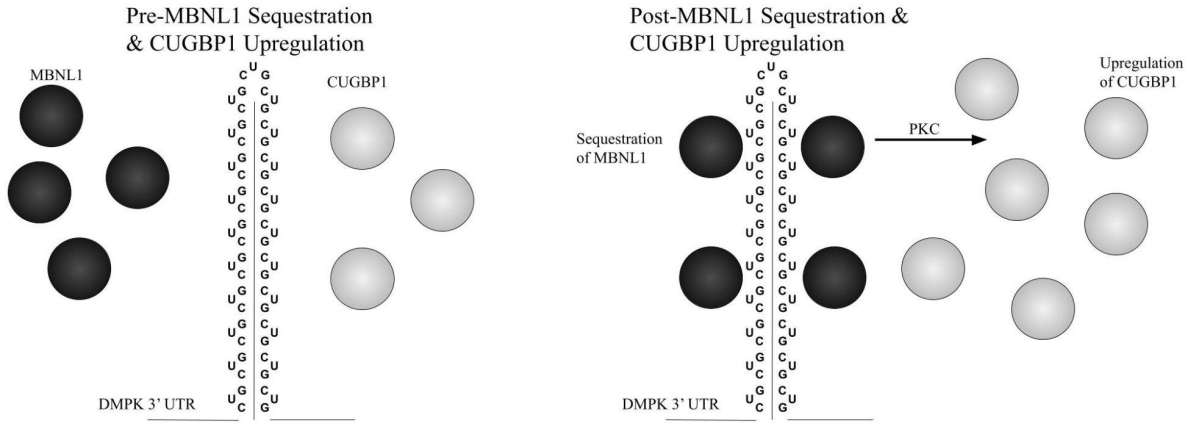
Previous mechanisms of DM1 suggested the haploinsufficiency model[10]. Haploinsufficiency is defined as partial expression of a protein due to the loss of one copy of the respective gene. It was theorized that the large repeat lengths of DM1 lead to the suppression of DMPK mRNA from producing protein. Animal models, however, highlight the insufficiency of such a theory[10]. *DMPK*-Knockout mice only displayed mild myopathy, and no myotonia, symptoms that are otherwise present in DM1[10]. While possibly a mechanism, it is incomplete and requires other support from models to produce a concrete understanding of DM1[1,10].

A likely pathogenic mechanism for DM1, supported through past evidence, is an RNA gain-of-function mechanism in which repeats in the DNA sequence are translated into abnormally long mRNA chains that do not leave the cell, instead residing in “clumps" called foci[2]. The imperfect structure leads to deregulation of muscleblind-like proteins (MBNL), which are normally responsible for the regulation of alternative splicing in skeletal and cardiac muscles[2]. In turn, they are crucial for the maintenance and development of muscles, as well as regulating RNA transport and decay. These functions are, however, inhibited when such proteins are trapped within the cellular foci of CUG repeats[2]. MBNL sequestration (specifically MBNL1, which is thought to play the most prominent role in DM1 pathogenesis) can lead to defects of several channels and receptors, including *CLC*-1 chloride channels, which leads to reduced chloride conductance in muscle fibers: a direct cause of myotonia[1,2]. Despite these facts, it is still relatively unclear whether or not MBNL deregulation is a driving factor of DM1[2].

RNA toxicity has also been suggested to play a role in activating signaling pathways that can lead to the accumulation of CUGBP1 binding proteins (part of CELF) through *in vitro* modeling[1,3]. Such models highlight the fact that CUGBP1 binds to CUG repeats in RNA sequences that, when overexpressed from PKC-mediated hyperphosphorylation and protein stabilization, could lead to the pathogenesis of DM1[1,3]. This possibility is strengthened by the abundance of CUGBP1 in the myoblasts, skeletal and heart muscle tissues[1]. The cause of such upregulation is not fully known, yet is suspected to be a response from the immune system, in which viral RNA detectors are mistakenly activated through the CUG repeats, leading to downstream phosphorylation of CUGBP1[1]. Considering the homologous nature of the two RNA binding proteins, the correlation of both MBNL and CUGBP1 is the core of current understanding of the pathogenic mechanisms of DM1.

Other pathogenic factors of DM1 involve pre-RNA processing but do not appear to be as impactful or prominent as MBNL sequestration or CUGBP1 upregulation[1]. Furthermore, given that there is no conclusive model for the pathogenic mechanism of DM1, it is crucial that future research considers an array of possible factors. Further research should focus around specific features of the disease since upcoming therapeutics show more promise in treating aspects of DM1 rather than reversing the disease's progression.

Figure 1: Representation of expanded CUG repeats in MBNL1



Adapted from "Pathogenic mechanisms of myotonic dystrophy" by Johanna E. Lee and Thomas A. Cooper, 2009.

In affected individuals, the presence of an extended CUG repeat leads to several factors within the nucleus. Firstly, the double-stranded hairpin leads to sequestration of MBNL1 proteins, which bind to the repeats with high affinity. As such, MBNL1 concentrations are far lower than normally present in unaffected individuals. The opposite remains true for CUGBP1 concentrations since extensive repeat lengths lead to activation of protein kinase C (PKC), resulting in CUGBP1 upregulation. Disrupted functions of both CUGBP1 and MBNL1 lead to the dysregulated alternative splicing events that form the typical features of DM1.

UTR=Untranslated region; PKC=Protein kinase C

Pathological Features of the Brain, Heart and Muscles

Although biopsies are not a key part of the DM1 diagnostic procedure, due to being technologically outdated by genetic testing, they still remain relatively accurate at predicting the disease[1,2]. Increased central nuclei, varied fiber diameters of 10 μm to 100 μm along with increased pyknotic clumps in the nucleus and ring fibers are common in DM1 muscle biopsies[1].

Brain matter studies reveal, in *in vivo* models, that degeneration of myelin, and axons, as well as dilation of perivascular spaces and capillary hyalinization, are common and match *in vitro* analysis[11]. White matter lesions in the anterior temporal lobe are present in DM1 and are suggested to be caused by improper interstitial fluid drainage along with the increased burden caused by microvascular changes in the brain[11]. DM1 also displays gray matter degeneration in cortical areas and thalamus[1].

The cardiac pathology of DM1 reveals ventricular myocardial fibrosis along with fatty infiltration in the conduction system to be common in the heart in autopsies of DM1 patients[12]. Cardiac arrhythmias are common causes of death in DM1 patients; however, their molecular mechanisms are unknown[1]. Analysis of ventricular myocardial samples reveals a splicing switch of SCN5A, which codes a subunit of Na^+ voltage-gated cardiac channels[1,12]. Switching adult exon 6B to fetal exon 6A resulted in slower cardiac conduction and is thought to correlate to ventricular arrhythmia[12]. At the same time, however, it is still unclear how such splicing relates to RNA toxicity, and is, therefore, speculative to the relevancy of DM1 cardiac pathology[12].

DM1 Models

Currently, DM1 is modeled in several ways, the most recent of which has been through patient-derived induced pluripotent stem cells (iPSCs) that are used to study specific tissues or cells in order to discover underlying mechanisms. iPSCs have helped capture key details of DM1, such as the discovery of disruption in Na^+ and Ca^{2+} ion channels within DM1 iPSC-derived cardiomyocytes[13]. Both channels have a direct impact on heart conduction, and disturbances assist in explaining the common symptom of cardiac arrhythmia in DM1[13]. Further iPSC testing of muscle stem cells and MyoD1 (protein) systems has allowed for the formation of complete *in vitro* skeletal models of DM1 that facilitate proper capture of MBNL1 aggregation[14]. iPSCs serve as important tools in DM1 analysis by providing a means of testing *in vivo* studies against accurate *in vitro* models that use patient-derived iPSCs for improved effective understanding.

Beyond iPSCs, DM1 is measured primarily through *Drosophila* and mice models. Several of these animal models exist, with the main *in vitro* studies being of HSA^{LR}, DM300, and $Mbnl1^{\Delta 3/\Delta 3}$ mice models[1]. Most extensively used are HSA^{LR} models, which use transgenic mice with the human skeletal actin gene that has ~250 untranslated CUG repeats to understand abnormal splicing regulators[1,15]. Their popular use is derived from the suggestion of toxic RNA gain-of-function in preclinical models, because their distinct lack of CELF1 upregulation implies that missplicing is caused by MBNL1 sequestration[15]. HSA^{LR} models also display features of myopathy despite lacking myotonia with no evident muscle wasting present[15]. DM300 models aim at studying toxic RNA gain-of-function and have 300-600 repeats that present a variety of expressions similar to DM1 including ribonuclear foci accumulating in key tissues, muscle histopathology, myotonia, progressional muscle deterioration, and glucose metabolism defects from missplicing of insulin receptor gene *ISNR*[1,15]. DM300 mice have led to DMSXL transgenic

mice models with up to 1800 repeats that are characterized by a more severe phenotype that could possibly mimic cDM1[1,15]. Both DM300 and DMSXL models recreate similar features of DM1 despite being slightly milder in comparison to other models[15]. Similar to *HSA*^{LR} models, *Mbnl1*$^{\Delta 3/\Delta 3}$ models also study abnormal splicing regulation, except through Mbnl1 knockout mice that disrupt Mbnl1 on exon 3 to mimic DM1 by eliminating CUG-binding isoforms[1,15]. These mice experience myotonia through abnormal *CLCN1* splicing but lack muscle degeneration[1,15]. These knockout lines have modeled cataracts, apathy and conduction defects along with missplicings in the heart, when losing MBNL1, and continue to suggest the RNA toxicity model of DM1[15]. Much like MBNL1, both MBNL2 and MBNL3 occur within DMPK; however, 2 separate knockout lines with contradictory results in phenotype suggest that MBNL2 and 3 may present a smaller, even non-present, role in DM1[1,15].

Clinical Conditions and Current Treatments for DM1

Cardiovascular System

As a muscular dystrophy, DM1 naturally places a heavy strain on the cardiovascular system, mainly through defects caused by conduction issues[12]. First-degree atrioventricular block is among the most common of such defects in around 25-45% of cases with clinical symptoms of slowed heart rates, palpitations, dizziness, and fatigue[12]. Others may experience no symptoms whatsoever[12]. Other arrhythmias such as atrial fibrillation and atrial fluttering are relatively common as well, ranging from a 5-30% presence in studies conducted, and are often paired with atrioventricular blockages (AV block) that can lead to asystole or bradycardia[2,12]. Along with elevated findings of ventricular tachycardia, AV block and asystoles are present in nearly 30% of all DM1-related deaths studied, making sudden onset cardiac complications the second highest cause of death for DM1[12]. For cardiac care, an electrocardiogram reading may be valuable to catch early symptoms. Readings are important to monitor as PR intervals of 240ms and QRS durations above 120 ms can increase the risk of sudden death for an individual. Medications such as beta-blockers or anti arrhythmics may be issued along with other treatments such as pacemakers; however, these are less common[9].

Muscles and Respiratory System

Muscular deterioration and myotonia are the most frequent systemic features of DM1. Myotonia in DM1 generally targets specific groups in the cranial, distal, and trunk muscles[2]. Weakness in ankle-dorsi and plantar flexors along with foot drop can lead to instability[2]. Most cases of myotonia are mild, and, therefore, do not require treatment. For more severe cases, mexiletine might be of use, as one study concluded in a randomized placebo-controlled study that up to 50% reduction of grip myotonia was reduced. 150-200 mg 3x a day could be effective for myotonia[2,9]. Muscle deterioration in very late stages is often combated with mobility assistive devices[9].

The more urgent issue of muscular deterioration is any respiratory failure that is caused as a result. Progressive weakness of the diaphragm is common as a symptom before any limb weakness[2]. Over time, damage accumulated results in aspirational difficulty that results in respiratory failure, the most common cause of death at around a 40% presence in reported

DM1-related deaths[12]. Respiratory care for DM1 is usually limited in early or mild stages of the disease. Pulmonary function tests may be conducted to evaluate function in effort to reduce the risk of primarily pneumonia[9]. Further stages of the disease may require non-invasive mechanical ventilatory support at night, especially if nocturnal hypoventilation starts occurring[9].

Gastrointestinal System

Several gastrointestinal symptoms appear in DM1 cohorts. Despite this fact, not much is understood about the pathology behind such findings. Between 48-55% of individuals experience swallowing difficulties; between 33-46% experience constipation; between 38-39% of individuals experience acid reflux, making these the most common GI-related symptoms experienced[16]. Barium swallows (where barium is tracked via x-ray after being swallowed to discover abnormalities in esophageal movements) reveal difficulty in the closing of nasal passages, along with a tendency for individuals to retain meals in the oropharyngeal recess, and upper, and lower esophagus as well[16]. In the stomach, DM1 presents a lowered rate of digestion through higher meal lag phases and slower gastric emptying[16]. Abnormal gallbladder releases were found in individuals with DM1 administered with cholecystokinin to stimulate release and rates of cholelithiasis are increased in DM1 cohorts[2,16]. In the liver, abnormal levels of alkaline phosphatase, alanine aminotransferase, gamma-glutamyltransferase, and 5' nucleotidase were present[2,16]. Although relatively nonprogressive as a condition, such enzymes can lead to cholestasis and hepatocellular damage[2,16]. Furthermore, it is unknown whether such changes are a primary effect of DM1 on the liver or secondary damage from fatty liver or biliary stasis[2]. The intestines present pseudo-obstructions commonly in DM1 patients, as symptoms such as diarrhea are often present without the indication of actual obstructions in the colon[16]. Suggestions for the cause of gastrointestinal symptoms vary but are generally between the responsibility of smooth muscle or enteric neurons in the enteric nervous system since either damage or reduced count would lead to GI disorder and possible myotonia[2]. Given that the two are tied in function, a combination of both smooth muscle and enteric neuron dysfunction might also be responsible for GI disorder; however, more research is needed in modeling each individually to determine a precise evaluation.

Generally, gastrointestinal issues do not pose much risk for DM1 patients, but treatments can be administered to specific complications such as constipation, pain, or pseudo-obstructions that will become increasingly invasive depending on severity. In some patients, gallbladder removal may be necessary if further complications arrive[16]. Medications such as gabapentin, nonsteroidal anti inflammatories, low-dose steroids, tricyclic antidepressants, and low-dose thyroid replacements may be administered for pain management[9].

Ocular Features

Ocular features such as Christmas tree cataracts are common and present in almost all cases of DM1 in the form of punctate iridescent opacities in the posterior lens capsule[17]. Other common features presented include ptosis, lower intraocular pressure (still unknown as to why it occurs), and Fuchs endothelial corneal dystrophy (theorized to be linked to DM1 through excessive RNA from mutated genes)[17]. Ophthalmologic consultations are recommended to treat ocular features case by case. In some situations, surgery, corrective lenses, or eye crutches may be recommended for excessive symptoms[9].

CNS and Neurological Health

Although varied in severity per individual, CNS changes are important features of DM1 as they are a key determinant of the quality of life. With the exception of apathy, DM1 does not present a set list of characteristics for the disease[18]. Features such as reduced IQ, memory deficiency, attention deficit, fatigue, anxiety, and depression are relatively common recurring symptoms[2,9]. Of 62 individuals tested, over 58% had at least 1 pathological personality trait[9]. Much of the symptoms associated with DM1 are a result of a weakened frontal-parietal lobe[2]. Brain MRIs highlight alterations to white matter signal intensity, something with an unknown pathogenic mechanism as of now[2]. Lower white matter fractional anisotropy was also found for DM cohorts as a key common abnormality[19]. Furthermore, mild cortical atrophy is also present with magnetic resonance spectroscopy suggesting glutamatergic neuron deterioration in the frontal cortex and white matter[9,20].

Neurological treatments for DM1 vary depending on severity. Baseline neurological evaluations are recommended along with a variety of treatments that range from medication for mood disorders to cognitive rehabilitation through psychological care[9]. Children may also receive special educational care to assist in early development[9].

Additional Features and Concluding Remarks

Several other effects of DM1 are observable in the systemic features of the disease. Insulin resistance is observed with changes in insulin signaling being reported in ~30 clinical studies over the past 60 years[21]. It is likely caused by defects in the splicing of insulin receptors, BIN1, dystrophin, and L-calcium channel transcripts[2]. Despite this, hypoglycemia rates do not appear common for DM1 patients despite such high levels of insulin[21]. Other metabolic issues such as increased cholesterol and hypertriglyceridemia are also present in DM1 cohorts[21]. Medication for such metabolic issues may be prescribed; additionally, diet changes may be implemented for patients.

The issue with current treatments for DM1 is their limited applicability. Most only correct symptoms rather than truly stop disease progression; as of now, there are no FDA approved medications for complete treatment of DM1. At minimum, a baseline consultation with the appropriate physician is required to determine an appropriate course of care for the disease. Yearly or biyearly evaluations of bodily functions are helpful to determine further treatment courses for the disease[9].

Table 2: Presence of several disorders in varying regions of DM1, along with the recommended treatments and courses of care that are currently available.

Impacted Region	Conditions	Treatments

Muscles [2,9]	Muscle weakness, myotonia	Physical therapy, mobility assistive devices, medication (e.g., mexiletine)
Heart [2,9]	Cardiac arrhythmias, cardiomyopathy	Medication (beta-blockers, anti-arrhythmics), pacemaker, ECG
Respiratory [2,9]	Sleep apnea, respiratory weakness	Continuous positive airway pressure (CPAP), ventilatory support
Gastrointestinal [9,16]	Swallowing difficulties, constipation	Dietary modifications, feeding tube if necessary, pain medication (gabapentin, nonsteroidal anti inflammatories, low-dose steroids, tricyclic antidepressants, and/or low-dose thyroid replacement) , gallbladder surgery
Eyes [9,17]	Cataracts, ptosis	Surgical removal of cataracts, ptosis crutches, corrective lenses
Central Nervous System [2,9,18]	Cognitive impairment, mood disorders	Cognitive rehabilitation, medication for mood

		stabilization, special education support for children

Lifestyle Impairment

Beyond the several burdens DM1 places on the body, it has a debilitating impact on the daily lives of individuals with the disease. Due to the progressive nature of the disease, simple tasks become increasingly difficult for the affected. Pain and general discomfort are the most prevalent burdens in the US that disrupt daily activities and about 69% of people experience such symptoms with 50% of those individuals claiming to have severe pain/discomfort[22]. This fact makes even the most basic of acts such as object handling, eating, standing, sitting, and walking are challenging for DM1 cohorts[23]. When considering the combination of such information with the challenges involved in carrying out everyday tasks, it becomes evident why even individuals with DM1 who possess a high level of functioning may struggle to maintain steady employment.

Due to the cognitive impairment involved with DM1, there is also a large social impact on individuals affected by the disease. Regular interactions as well as romantic involvement is challenging for 50% of individuals Simple planning, concentration, memory, and thought construction served difficult for over 40% of individuals tested[23]. Social interactions are also heavily impacted by DM1, as most individuals have speech impairment along with high rates of social anxiety, avoidant behavior, and apathy[23].

From such data, it is clear that DM1's presence extends beyond a simple need for scientific understanding. Due to the drastic impact it has on the basic activities of the individuals impacted, DM1 forms a low-quality-of-life environment that must be analyzed on a case-by-case basis for proper morbidity requirements that match said individual's prognosis and development of the disease.

Future Treatments

Currently, antisense oligonucleotides (ASO) appear to be the most promising of the several upcoming therapies in development. ASOs are small sequences of single-strand nucleic acid modified such that their hybridization with target RNA strands results in modulation over gene expression, normally through inhibition of RNA-binding proteins, spliceosomes, or ribosomes. ASO-based DM1 treatment generally aims at targeting CUG-expanded transcripts by either degrading the expanded RNA sequences or through steric blocking of MBNL1[24]. The former uses an RNase H pathway designed using "gapmers" that are 6-10 nucleotides followed by RNase H-competent phosphorothioate modifications that are again followed with 3-4 nucleotides at 5' 3'[24,25]. These gaps allow for RNase-mediated cleavage after binding to the correct RNA site. A steric blockade occurs with uniformly modified ASOs that prevent the

binding of RNA factors without causing degradation. In DM1, this is best used against MBNL1 sequestration. Most commonly, either phosphorothioate modifications, locked nucleic acids, or 2′-O-methoxyethyl modifications are used to stabilize such ASOs with different levels of success in *HSA*^{LR}, DM300, and a few other mice models[24,25]. The main challenges ASOs face today are their delivery since specific nucleotide sequences are required to have the greatest effect on the target tissue. Optimal delivery, therefore, becomes a must. Issues such as delivery through the nonpolar cell membrane must be resolved for ASOs to even reach their target, something that could possibly be resolved with a sort of cell-penetrating peptide chain[24]. Clinical trials by Avidity Biosciences and Dyne Therapeutics will be an important entry into understanding the current pharmacokinetics of siRNA and ASOs with specific designs toward higher uptake toward cardiac tissue and muscles[25].

The other promising line of research is into CRISPR/Cas9 mediated gene editing. Clustered regularly interspaced short palindromic repeats (CRISPR) - CRISPR associated 9 protein (CAS9) systems are breakthroughs in gene therapy for their ability to target specific genomes of eukaryotes. The primary means of delivery are viral vectors, and in DM1, a majority of trials involve modified adeno-associated virus (AAV). CRISPR/Cas9 itself utilizes small guide RNA (sgRNA) to direct Cas endonucleases to a target DNA before then binding. At this point, the Cas protein will mediate a double-strand break (DSB) in order to silence the repeats[26]. Since the first successful trial using *Streptococcus pyogenes* Cas9, there have been several other Cas proteins developed to interfere with both DNA and RNA repeats[26,27]. Furthermore, several processes exist in which CRISPR/CAS9 can be implemented to possibly treat DM1. Excising of CTG expansion sequence is the most straightforward approach in CRISPR research as a pair of sgRNA approach opposing sides of the CTG sequence and form two DSBs in an attempt to remove the incorrect sequence entirely at the DNA level[26,27]. Expanded sequences can be an obstacle for excision due to hairpins formed that interfere with sgRNA[27]. Polyadenylation signal insertion is a viable alternative approach beyond just excision. Aimed at preventing transcription of the *DMPK* CTG repeats, polyadenylation signals (PAS) are inserted upstream to terminate mRNA transcription before the arrival of RNA polymerase II[26,27]. The major obstacle of pathogenic repetitions within the gene sequence remains, however, which allows for detriments in replication to further persist[26]. A third strategy used against DM1 is gene silencing via dCas9, an enzymatically inactive protein that still remains capable of binding to DNA causing physical hybridization that prevents transcription of RNA polymerase II[26,27]. Although inherently safer (as it does not require cutting of the genome), the issue remains that dCas9 requires extended expression of the AAV genome which is difficult as AAV genomic DNA may be lost or silenced over time[26]. dCas9 proteins have also been modified toward the binding of single-strand RNA using DNA oligonucleotides in order to bind and cut RNA molecules and have shown promise in their reduction of RNA expression levels and nuclear RNA foci[26]. Despite the level of research that exists, there are still several issues regarding CRISPR/Cas9 editing that must be addressed. Pathogenic immune responses to AAV proteins may occur and, regardless of frequency, must be considered[26]. Furthermore, the separate issues of administration and unintended DSB repair also remain. Poor drug penetration makes CRISPR ineffective at tight endothelial barriers that surround blood vessels[26]. The risk of unintended DSB is low since they occur in the UTR of DMPK, but caution must still remain surrounding the administration of CRISPR/Cas9, especially in regard to genome-cutting procedures[26]. It is of high priority that germ cells are not altered in addition to somatic counterparts given that current Cas procedures are full-body treatments[27].

Several other ongoing therapies are being developed as potential treatments for DM1. Initially, the development of zinc finger nucleases and transcription-activator-like effector nucleases had been promising. These DNA-cleaving enzymes formed DSBs aimed at gene editing and were highly efficient in yeast models; however, their translation to patient-derived iPSC resulted in premature termination of transcription along with unintended off-target effects that make them suboptimal for DM1 currently[3].

Currently, the largest strides in therapy appear from the development of two N-acetyltransferase drugs, AOC 1001 (sponsored by Avidity Sciences) and DYNE-101 (sponsored by Dyne Therapeutics)[4]. The former entered Phase I/II trial (MARINA™ trial) in late 2021. The drug works via monoclonal antibodies that bind to transferrin receptor 1 conjugated with small interfering RNA to reduce levels of DMPK RNA in smooth muscle and cardiac cells[3,4]. Recently, AOC 1001 has been granted orphan designation and fast-track designation by the FDA. As of 2023 AOC 1001 has shown promise with positive topline data being announced by Avidity[4]. Dyne Therapeutics's new drug, DYNE-101 is quite similar to AOC 1001 in the binding of transferrin receptor 1[4]. The drug utilizes the conjugation of a proprietary ASO that uses RNase H-mediated cleavage to reduce located DMPK RNA, with success being demonstrated in non-human primates already[4]. These drugs theoretically have the capability to reduce myotonia and other clinical symptoms of DM1, with a possibility of becoming a relatively stable cure for DM1; however, it is still far too early to measure their success as of now, making further research critical.

Conclusion

Although DM1 may not be the most prevalent of diseases, the current limitations in therapy and the ever-emerging nature of our understanding of disease pathology makes the disease an important one to consider for future funding into breakthrough research and treatments. DM1 has a systematic prevalence in the body with abnormalities present in the heart, lungs, digestive system, liver, and face in conjunction with the phenotypically expected traits of DM1, including severe myotonia that depend on the type present[2]. The issue remains that current treatments simply target patient quality-of-life via symptomatic solutions, in part due to the lack of an FDA-approved treatment for DM1 yet available[9]. Regardless, current developments suggest promising results as the main hypotheses of RNA gain-of-function and RNA toxicity are further explored to develop new therapies. Current advancements in ASOs and CRISPR/Cas9 therapies appear to be the future of DM1 treatments, but more research is needed before these can be routinely used.

Beyond the several technical limitations of delivery in either of these approaches, the problem of patient-based care still remains. Costs for even basic rounds of ASO treatments in other diseases would be out of reach for most DM1 patients, and even with their solution, the safety risks of current treatments make them unsuitable for use due to improper delivery, immune reactions, and so forth[3,6,25]. Rather than viewing these setbacks as an insurmountable blockade, they should–instead–be viewed with the intent to overcome, given the recent progress made in DM1-based therapies since the discovery of the disease pathomechanism a few decades back. With companies like Avidity Sciences and Dyne Therapeutics pushing AOC 1001

and DYNE-101 into clinical trials, there is a very real possibility within the next few years that a proper therapy for DM1 could be fully developed[4].

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