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Magnetic Resonance Imaging as a Biomarker for Duchenne Muscular Dystrophy

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Abstract

Muscular dystrophy is a hereditary musculoskeletal disorder caused by a mutation in the dystrophin gene. Duchenne muscular dystrophy (DMD) is one of the most common, and progresses relatively faster than other muscular dystrophies. It is characterized by progressive myofiber degeneration, muscle weakness and ultimately ambulatory loss. Since it is an X-linked recessive inheritance, DMD is mostly expressed in males and rarely expressed or less severe in females. The most effective measurement tool for DMD is magnetic resonance imaging (MRI), which allows non-invasive examination of longitudinal measurement. It can detect progressive decline of skeletal muscle size by measuring a maximal cross-sectional area of skeletal muscle. Additionally, other techniques in MRI, like T_2-weighted imaging, assess muscle damage, including inflammation, by detecting changes in T_2 relaxation time. Current MRI techniques even allow quantification of metabolic differences between affected and non-affected muscles in DMD. There is no current cure, but physical therapist can improve their quality of life by maintaining muscle strength and function, especially if treatment (and other forms of medical intervention) begins in the early stages of the disease.

Key Words: Duchenne muscular dystrophy; Eccentric exercise; Fatty infiltration; Inflammation; Magnetic resonance imaging; Muscle damage; Muscular dystrophy.

Introduction

Muscular dystrophies are genetic disorders caused by abnormalities in various genes (Aartsma-Rus et al, 2006; Dalkilic and Kunkel, 2003; Emery, 2002a; Fokkema et al, 2005). Among them, a mutation of dystrophin gene coding for the protein dystrophin causes Duchenne muscular dystrophy (DMD), which affects 1 in 3,300~6,000 boys (Emery, 1991; Emery, 2002b; Mendell et al, 2012). The dystrophin protein is an intricate part of the dystrophin-associated protein complex and links subsarcolemmal cytoskeleton and extracellular matrix (Ibraghimov-Beskrovnaya et al, 1992; Ozawa et al, 2001; Rybakova et al, 1996; Sutherland-Smith et al, 2003). It is also an essential structural component of the muscle membrane, and provides mechanical stability in skeletal muscle (Mizuno et al, 1994; Moens et al, 1993; Ohlendieck et al, 1993; Petrof et al, 1993). That is, a mutation in the dystrophin gene breaks the dystrophin-associated protein complex supporting integrity of the skeletal muscle membrane and transmitting force. Additionally, the fragility caused by the absence of the dystrophin protein is aggravated by repeated intensive contraction because the muscle fibers are unable to endure eccentric contraction without structural integrity (Allen and Whitehead, 2011; Brussee et al, 1997; Deconinck and Dan, 2007; Petrof et al, 1993). An increase in skeletal muscle fatty tissue and severe muscle atrophy is observed as the child ages and then ambulatory loss is seen at around 8~12 years (Beltran et al, 2015; Brooke et al, 1989; Bushby et al, 2010; Desguerre et al, 2009; Moxley et al, 2010;

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Pardo et al, 2011). Ultimately, premature death occurs in the early twenties due to cardiac and respiratory muscle failure (Fraser et al, 2012; Lovering et al, 2005). It is very important to detect pathological changes in skeletal muscle before functional declines so that intervention can begin as early as possible.

Invasive Measurement

Muscle biopsy today is a widely accepted assessment tool to diagnose and measure the disease progression in DMD (Maunder-Sewry et al, 1980). However, this invasive tool is limited to only a small amount of tissue at a time and narrow limits. Additionally, it has been demonstrated that a DMD-affected muscle has different characteristics and progression varying by muscle region in a single muscle. The bigger issue is that the muscle biopsy may not be effective to evaluate the cardiopulmonary system, where monitoring is especially important in the late stages of the disease. Therefore, various non-invasive techniques involving X-rays, computed tomography (CT), and magnetic resonance imaging (MRI) are currently promoted as alternatives to the invasive method. These alternatives can be used without temporal and spatial limitations as they allow longitudinal measurements covering the entire body.

Non-Invasive Measurements

Plain X-ray

X-ray equipment is among the most frequently used, inexpensive, convenient, and old-fashioned tool in many clinical setting. The X-rays can penetrate objects, but the amount of X-rays reaching the detector varies according to the object being filmed (McKinnis, 2013) (Figure 1). For example, bones containing higher calcium absorb more X-rays than muscles and appear white on X-ray film while muscles show up in shades of gray. X-ray film provides enough resolution in shades of white and black to interpret pathological changes and abnormalities in bones and joints, but it is limited to an anatomic view of body structure. The limitations of X-rays in the diagnosis of disease led to the advent of CT, which provides a clear, well-contrasting cross-sectional image even between skeletal muscles in the body.

Computed tomography

CT, also known as X-ray CT, CT scanning, or computerized axial tomography scanning, provides a higher quality of tomographic images using many X-ray images (Heckmatt and Dubowitz, 1983). Unlike simple X-rays, CT shows cross-sectional images of a target object without overlapping various objects on a single image. Additionally, pathological changes in muscle can be cleary and easily verified on

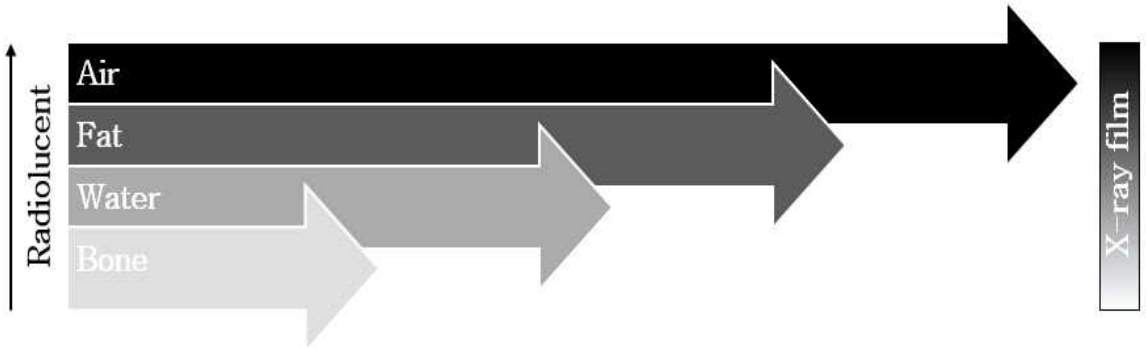

Figure 1. Anatomy in four primary shades of grey.

high-resolution and high-contrast images. Recent advances in technology allow 3-dimensional images of tumors, hemorrhaging, and even coronary arteries (Goodpaster et al, 2000; Jones et al, 1983; Liu et al, 1993; Termote et al, 1980). Due to the quality of the images, it has been used for much clinical research in preventive medicine as well. However, imaging tools based on X-ray penetration use ionizing radiation, which comes with the risk of undesirable side effects.

Magnetic resonance imaging

Unlike X-ray imaging tools, MRI does not expose the target to radiation. The magnetic resonance (MR) image was first introduced as a one-dimensional image in 1952 by Herman Carr, whereas current MRI provides the opportunity to quantify fatty infiltration, inflammation and edema in muscle using T_1- and T_2-weighted MR techniques (Carr and Purcell, 1954; Garrood et al, 2009; Goodpaster et al, 2004; Lamminen, 1990; Matsumura et al, 1988).

T_1-weighted imaging has proven to be extensively in agreement with measurement of morphologic changes in muscle (Akima et al, 2012; Mathur et al, 2010). Generally, the size of skeletal muscle is strongly related with muscle function. Thus, T_1-weighted imaging provides cross-sectional area (CSA) imaging of muscle and has been invaluable in medical diagnosis. However, muscle size does not directly correlate to the muscle function in DMD. Wokke and colleagues have shown that in boys aged 8~15 with DMD, the maximal CSA (CSAmax) of the triceps surae muscle (medial gastrocnemius, lateral gastrocnemius, and soleus) was 52% larger, yet the boys had less functional ability and muscle strength than the age-matched controls (Wokke et al, 2014). This paradoxical finding is due to pseudohypertrophy resulting from fatty infiltration and replacement of fibrotic tissue in muscle (Grindrod et al, 1983). When it comes to DMD, the T_1-weighted technique is appropriate to measure the proportion of contractile tissue in muscle rather than quantitative measurements of muscle size (Akima et al, 2012).

MRI is also useful to quantitatively measure muscle quality including biophysical and pathophysiological properties using the T_2-weighted MR techni-

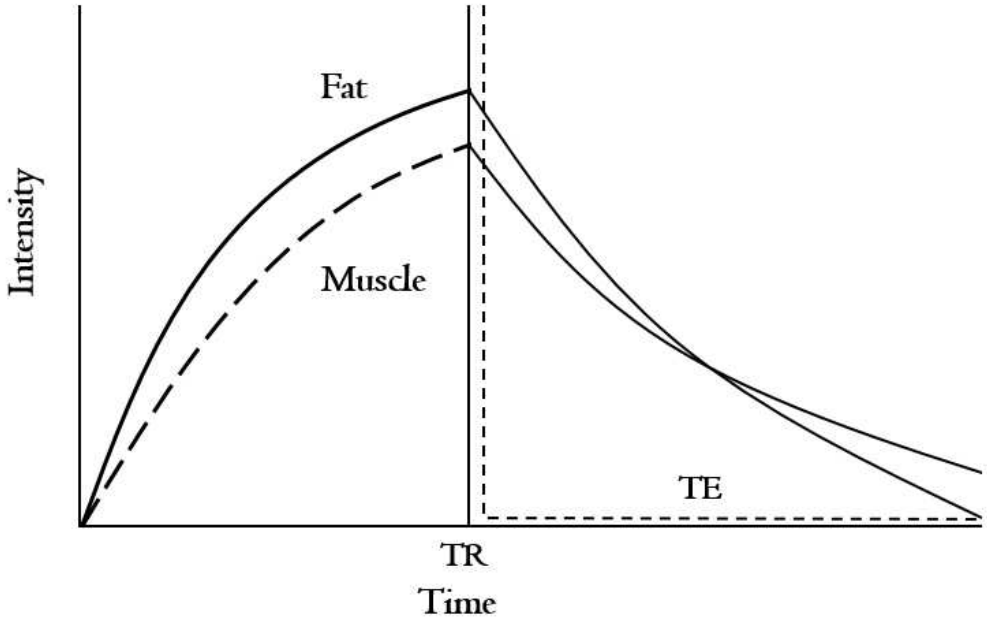

Figure 2. The example of T_2 decay curve of fat and muscle (TR: repetition time, TE: echo time).

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que (Arpan et al, 2013; Kim et al, 2010) (Figure 2). Fleckenstein in 1989 found a relationship between muscle activity and subsequent increase in T_2 relaxation time (Fleckenstein et al, 1989). After physical exercise, T_2 relaxation time was increased and lasted for a short time. An exercise-induced increase in T_2 relaxation time does not usually last long if the physical exercise was not intense and/or not repeated. If the increase in T_2 relaxation time is prolonged, it might represent muscle inflammation or edema (Shellock et al, 1991). In the study of Mathur, T_2 relaxation time was increased and lasted for 2 days after eccentric exercise in mdx mice, an animal model for DMD widely used in pre-clinical settings (Mathur et al, 2011). It is well known that muscle is more susceptible to damage (including inflammation and edema) during eccentric exercise or intensive exercise (Lovering and Brooks, 2014; Petrof et al, 1993). Intensive muscle contraction leads to muscle damage due to an absence of the dystrophin protein, which provides structural integrity and stability to muscle membrane. The sensitivity of the T_2-weighted MR technique for the differentiation of muscle damage makes it very useful in follow up on disease progression.

Pathological changes in muscle, including inflammation or edema, might be more clearly detectable with short-tau inversion recovery (STIR) imaging (Beltran et al, 2015; Tasca et al, 2012) (Figure 3). In young boys with DMD, the edema or inflammation is often presented without any fatty infiltration. The STIR technique increases the sensi-

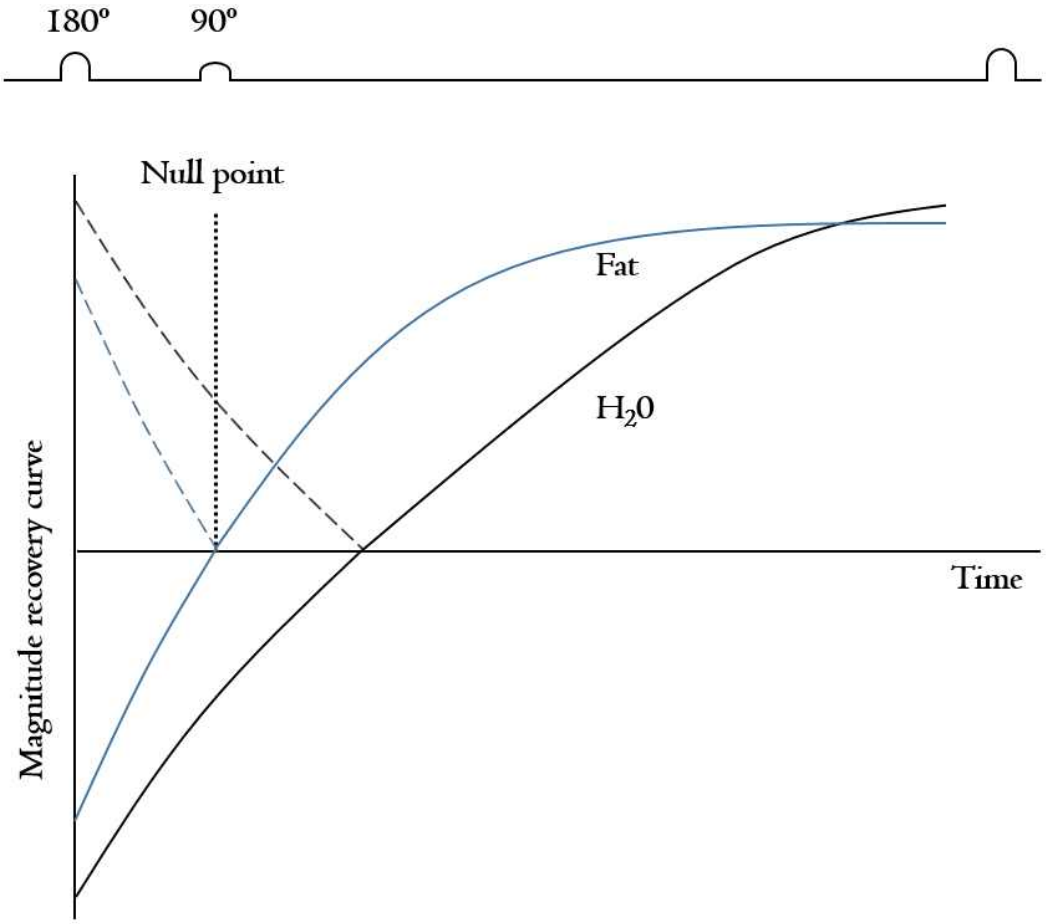

Figure 3. Magnititude T_1 curve in the short tau inversion recovery (STIR) technique.

tivity of measurement of extracellular water content suggesting presence of edema and inflammation. Marden found signal abnormalities from skeletal muscle appearing to be normal muscle on T_1-weighted images using the STIR technique in two boys with DMD (Marden et al, 2005). Additionally, the STIR technique makes it easy to discriminate between fat and muscle by suppressing the signal from fatty tissue so that the examiner can exactly segment muscle CSAmax.

Recently, even lipid fraction and metabolic change in skeletal muscle have been measured by magnetic resonance spectroscopy (MRS) in conjunction with MRI (Felber et al, 2000; Lott et al, 2014; Torriani et al, 2012). As mentioned above, it is often difficult to diagnose young boys with DMD or discover progression of the disease with conventional MRI. A recent study by Forbes reported higher lipid fraction, measured by MRS, in soleus and vastus lateralis muscles in young boys with DMD when compared with controls (Forbes et al, 2014). In Forbes' study, MRS proved a very sensitive tool in determining lipid fraction because it can provide MR signals from water and lipid separately and precisely. Additionally, MRS has been used to study skeletal metabolism in DMD. Metabolic changes such as glycolytic substrate glucose, glutamine, and glycolytic product lactate were significantly lower in those with DMD compared to controls (Sharma et al, 2003). Thus, MRS can be more powerful for evaluating patients with DMD when used in conjunction with MRI.

Conclusion

DMD is a life-threatening disease and worsens more quickly than other muscular dystrophies. There have been several clinical trials so far, but there is no current cure. Only glucocorticosteroids have been accepted as a pharmaceutical agent which can slow down symptoms of disease progression such as skeletal muscle degeneration and loss of muscle tone. Physical exercise with early medication, unless intensive eccentric exercise, can very helpful to maintain functional activity and muscle strength. Since muscle damage in boys with DMD begins before functional declines, detecting changes in muscle is of the utmost importance so that physical therapy can begin as early as possible. MRI and/or MRS measurements have proven effective in detecting muscle damage even in the early stages of DMD.

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