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## Muscle MRI in Duchenne and Becker muscular dystrophy

Wokke, B.H.A.

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**Author:** Wokke, Beatrijs Henriette Aleid

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Conclusion and general discussion

# Chapter 7



## CONCLUSION AND GENERAL DISCUSSION

In the last decade the interest in MRI and MRS studies in DMD patients, and to a lesser extent in BMD patients, has increased substantially. The ability to quantitatively assess various aspects of the affected muscle makes MRI and MRS potentially useful tools in the assessment of disease severity and progression. The development of future therapies for DMD patients has made such tools of increasing importance. So far the focus of many studies has been on the pattern in which the muscles are affected, the quantification of the fatty infiltration in the muscle and its relation with muscle strength and function and the relation with age [98, 101, 102, 104-106, 109, 140, 225]. Additionally some studies have described techniques to evaluate oedema in muscle and others applied proton and phosphorous MRS to study muscle metabolites [103, 108, 111-115, 225]. As DMD and BMD are the most common muscle diseases with a limb-girdle pattern of weakness, and genetic testing is readily available, MRI and MRS are generally not necessary to reach a diagnosis. However, MR techniques could contribute to the evaluation of disease progression and future therapies.

In terms of disease progression, a striking feature in dystrophinopathy patients is the progressive decline of muscle function and muscle tissue. The muscles show increasing amounts of fatty infiltration, although not all muscles become affected at the same moment or at the same rate. Our studies, and those of others, have shown that MRI can be used to quantify the fatty infiltration in multiple muscles and that these values are compatible with clinical features. We have shown that quantification of the fatty infiltration is more sensitive to subtle changes and shows less variability than semi-quantitative, visual scoring methods. Additionally we have shown that in DMD patients and in a homogeneous group of BMD patients, fatty infiltration increases with age and correlates with muscle function. A drawback of the use of fatty infiltration as outcome parameter is that fat is often regarded as an 'end-point' of the disease process and has so far not been shown to be reversible. Additionally, therapies currently under development aim to slow disease progression, rather than reverse pathology. Therefore evaluating the rate at which muscles become fat infiltrated could be a useful outcome parameter. If strength of muscle tissue were to improve, even with unchanged amounts of fatty infiltrated muscle, parameters such as the specific strength, described in chapter 2 would be useful to evaluate such effects.

As outcome parameter the muscle T2 relaxation time as indicator of oedema/inflammation in the muscle is more likely to be reversible in DMD patients than parameters such as the fatty infiltration [226]. In this thesis we described that the muscle T2 relaxation times in DMD patients were increased, while no such increase was found in BMD patients. This suggests that increased muscle T2 relaxation times as indicator of inflammation/oedema are associated with the severity of the muscle damage. If so, the

T2 relaxation time could be a valuable outcome parameter. Unfortunately, increased levels of fatty infiltration complicate consistent measurement of T2 relaxation times in dystrophic muscle, as the T2 relaxation time of lipids is much longer than the skeletal muscle water T2 relaxation time. A possible method to overcome this problem is by using fat suppression. However, complete fat saturation is technically very complicated to achieve [227]. Separate assessment of the water and lipid signal would be another method to overcome this problem. This remains technically challenging in the whole muscle, but the recently described tri-exponential model, which can be used to assess both the T2 relaxation time independent of the fatty infiltration and to quantify the fat fraction is a promising alternative [183, 228]. As previous studies have suggested changes of the muscle energy metabolism we studied the phosphorous metabolism in muscles of BMD patients. We established that in BMD patients there was an increase in PDE/ATP ratio, before an increase in fat levels became apparent. As such the PDE/ATP ratio could also be a useful parameter to assess muscle damage in early stages of the disease in BMD patients, but possibly also in DMD patients.

Other, so far not yet implemented in DMD or BMD patients, MR techniques could potentially also be of value as outcome parameters. Such techniques include diffusion tensor imaging for the assessment of the muscle fibre architecture and arterial-spin labelling for the evaluation of the tissue perfusion [229].

So far little is known of the value of the discussed methods in terms of therapy assessment, since it is uncertain to what extent there will be changes in the muscle with appropriate therapy and how this will vary between differently affected muscles. Nevertheless, as MR techniques can be used to assess different properties of the muscle it is likely that MRI and MRS can contribute in the evaluation of disease progression. Currently clinical trials use outcome measures such as the 6-minute walking test as outcome parameter. Although the relation between muscle strength and muscle tissue obtained with MRI has been shown to be significantly lower in DMD patients only one study so far has shown a relation between the mean fat fraction and ambulation in these patients [230]. However, it is likely that functional benefits of therapeutic approaches take longer to become apparent than subtle changes such as a decreased inflammatory response or increase in strength of the muscle tissue. Therefore finding a method which can be used to quantify both the fatty infiltration and muscle T2 relaxation time while accounting for the fat, especially when combined with the quantitative strength measurements, could provide a detailed overview of ongoing damage and muscle regeneration in the various stages of follow-up and as such could be a promising outcome parameter.



