Original Research

Thigh Muscle Stiffness Assessed With Magnetic Resonance Elastography in Hyperthyroid Patients Before and After Medical Treatment

Sabine F. Bensamoun, PhD,[1] Stacie I. Ringleb, PhD,[1] Qingshan Chen, MS,[1] Richard L. Ehman, MD,[2] Kai-Nan An, PhD,[1] and Michael Brennan, MD[3*]

Purpose: To measure the stiffness of the vastus medialis (VM) in hyperthyroid patients before and after treatment.

Materials and Methods: A total of five healthy euthyroid patients and five hyperthyroid patients were tested using magnetic resonance elastography (MRE), which involves the induction of shear waves in the thigh muscles using a pneumatic driver at 90 Hz.

Results: Among the pretreatment hyperthyroid cohort a lower stiffness was found when the muscle was relaxed (2.11 ± 0.61 kPa) compared the stiffness following treatment of hyperthyroidism (5.52 ± 1.52 kPa), which was accompanied by an improvement in the contractile function of the VM. Pretreatment muscle stiffness was also less than that of age matched healthy volunteers (4.56 ± 0.40 kPa). The behavior of the waves was sensitive to the stage of this myopathy and to the amount of free thyroxine (FT4).

Conclusion: The MRE technique provides a new tool to gain new insights into pathophysiology of thyroid associated and other muscle diseases and their response to treatment.

Key words: magnetic resonance elastography; hyperthyroidism; muscle stiffness; myopathy; Graves' disease
J. Magn. Reson. Imaging 2007;26:708–713.

GRAVES' DISEASE is a common cause of hyperthyroidism and leads to variety of clinical symptoms, including skeletal muscle weakness that may be quite profound but which is reversible following correction of hyperthyroidism. Thyroid hormone exerts numerous biochemical influences on skeletal muscle (1) but the precise cause of muscle weakness in hyperthyroidism remains unclear. Skeletal muscle disorders can be evaluated by electromyography (EMG) which can be noninvasive (i.e., surface) or invasive (i.e., fine wire or needle). However EMG examination shows little or no change in patients with hyperthyroidism inducing myopathy (1). While muscle specific serum enzymes (aldolase, creatine kinase) are within the normal range, skeletal muscle atrophy occurs in hyperthyroidism but the severity of muscle weakness far exceeds that which can be accounted for by the relatively mild degree of muscle volume loss. This suggests a qualitative defect in the efficiency of skeletal muscle contraction (2,3). Hyperthyroidism also induces significant changes in the myosin composition of muscle resulting in a switch from slow myosin heavy chain (MHC) isoforms to fast twitch MHC isoforms (3,4).

Magnetic resonance elastography (MRE) is a noninvasive technique capable of quantifying the mechanical properties and imaging the entire spatial distribution of muscle elasticity in vivo (5,6). The stiffness of the soft tissue can be estimated from the displacement of shear waves inside the muscle. MRE technique has previously been used to evaluate patients with lower extremity neuromuscular dysfunction such as that encountered in poliomyelitis and traumatic paraplegia (7). Significant differences in tibialis anterior and gastrocnemius muscle stiffness were found between healthy volunteers and patients with such neuromuscular diseases.

The purpose of the present study was to apply the MRE technique to hyperthyroid patients before and after treatment to: 1) assess muscle stiffness in overtly hyperthyroid patients and follow the effects of the treatment on this parameter; 2) improve our understanding of the changes in proximal muscle stiffness at rest and

[1]Biomechanics Laboratory, Division of Orthopedic Research, Mayo Clinic, College of Medicine, Rochester, Minnesota, USA.
[2]Department of Radiology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA.
[3]Division of Endocrinology, Endocrine Research Unit, Mayo Clinic College of Medicine, Rochester, Minnesota, USA.
Contract grant sponsor: National Institute of Health (NIH); Contract grant numbers: EB00812; EB001981; CA91959; HD07447.
*Address reprint requests to: M.D.B., M.D., Division of Endocrinology, Endocrine Research Unit, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905.
E-mail: brennan.michael@mayo.edu
Received June 14, 2006; Accepted June 1, 2007.
DOI 10.1002/jmri.21073
Published online in Wiley InterScience (www.interscience.wiley.com).

during a contraction; and 3) shed further light on the pathogenesis of hyperthyroid myopathy.

MATERIALS AND METHODS

Patients

Hyperthyroid patients were identified in the Endocrinology Clinic and were recruited for the study. Graves' disease occurs in all age groups with peaks in the fifth and seventh decades of life, as was observed in patients from Olmsted County, MN (8). The majority of patients in this study were in their fifth decade and all patients were age- and sex-matched with euthyroid controls. A total of five healthy volunteers (four females and one male, mean age 53.8 ± 1.16 years, range 50–57 years) and five hyperthyroid patients (three females and one male, mean age 52.5 ± 1.48 years, range 50–57 years; and one younger female aged 27 years) participated in this MRE study. There is a significant female preponderance because hyperthyroidism (Graves' disease) is more common in women.

The study was approved by the Institutional Review Board and written informed consent was obtained. Hyperthyroid patients were recruited in the thyroid clinic. The diagnosis of Graves' disease was confirmed by clinical assessment together with blood test results that showed a suppressed serum thyrotropin (TSH) and elevated levels of serum free thyroxine (FT4) and triiodothyronine (T3).

Each patient underwent a MRE examination of the thigh while in the hyperthyroid state. Subsequently, all patients underwent treatment of hyperthyroidism that consisted of the administration of radioactive iodine. All patients were rendered hypothyroid over a three-month period and were then commenced on levothyroxine replacement therapy to restore serum TSH to normal. MRE studies of the thigh muscle were repeated after the patients had been rendered euthyroid for a period of three months. All patients were retested at least three months following the initiation of levothyroxine replacement therapy.

Experimental Setup

The volunteers lay supine in a 1.5T General Electric Signa MRI machine. The right leg was placed in a positioning device (9). An adjustable device maintained the shoulders in a fixed position and the right knee was positioned in 30° of flexion. The right foot was placed on a footplate and secured with Velcro straps. The footplate was composed of two MR compatible loads cells (Interface, Scottsdale AZ, USA), one to measure the horizontal forces and one to measure the vertical forces. A custom-made LABVIEW (National Instruments, Austin, TX, USA) program recorded the forces and gave the volunteer visual feedback to ensure the desired force was maintained. The MRE tests were conducted in the relaxed position (no contraction), 10% of maximum voluntary contraction (MVC), and 20% of MVC.

Longitudinal and transversal waves were applied to the thigh muscles with a pneumatic driver positioned on the thigh one-third of the distance from the patellar tendon to the greater trochanter. Only the shear (or transversal) waves were tracking and measured inside the muscle due to their small wavelengths, as compared to the higher wavelength produced by the longitudinal waves. The pneumatic driver consisted of a remote pressure driver (i.e., a large active loudspeaker) connected to a long hose. A smaller silicone tube was wrapped around the patient's thigh and connected to the remote pressure driver (9). This system created a time-varying pressure wave, which caused the tube around the thigh to expand or contract with the remote driver at 90 Hz. A custom-made Helmholtz surface receive coil was placed around the thigh for data acquisition.

Two-Dimensional (2D) Gradient Echo MRE

A gradient echo (GRE) MRI sequence was used to obtain the axial image of the thigh muscle. An oblique scan plane was selected on the medial side of the axial image to visualize the vastus medialis (VM). The MRE pulse sequence including a motion-encoding gradient oscillating at the same frequency as the driver (90 Hz) was applied to image the displacement of the shear waves. MRE images were collected at four time offsets (phase offsets) between the start of the motion and the motion-encoding gradients that were evenly spaced over one period of the motion to image the wave propagation over time. The flip angle was 45° and the field of view was 24 × 24 cm. The acquisition matrix was 256 × 64, which was interpolated to 256 × 256. The TR was 275 msec and the TE corresponded to the minimum time allowing for motion encoding (approximately 19 msec). The acquisition time was two minutes and 30 seconds at 90 Hz. This procedure was repeated when the hyperthyroid patients were tested after treatment.

2D Image Processing and Data Analysis

A profile was drawn along the direction of the wave propagation in the VM muscle (Fig. 1). The wavelengths were manually measured for each thigh muscle and the average value (obtained over the four offsets) was recorded. Treating the muscle as a linearly elastic (due to the small displacement of the wave), locally homogeneous, isotropic and incompressible material, the shear modulus (μ) can be calculated with the following Eq. [1] (9):

$$\mu = \rho f^2 \lambda^2 \tag{1}$$

where ρ is the muscle density ($\approx$1000 kg/m^3), f is the frequency (Hz) of the prescribed shear wave, and λ (m) is the measured wavelength.

Equation [1] is a simplification of the muscle behavior. The estimation of the muscle properties is affected by the complex geometry of the muscle, the boundary conditions, and the muscle's anisotropy and viscoelasticity. These conditions are being considered in the development of future inversion algorithms (10).

Statistical Analysis

A Kolmogorov-Smirnov test was performed with the Statgraphics 5.0 software (Sigma Plus, MD, USA) to

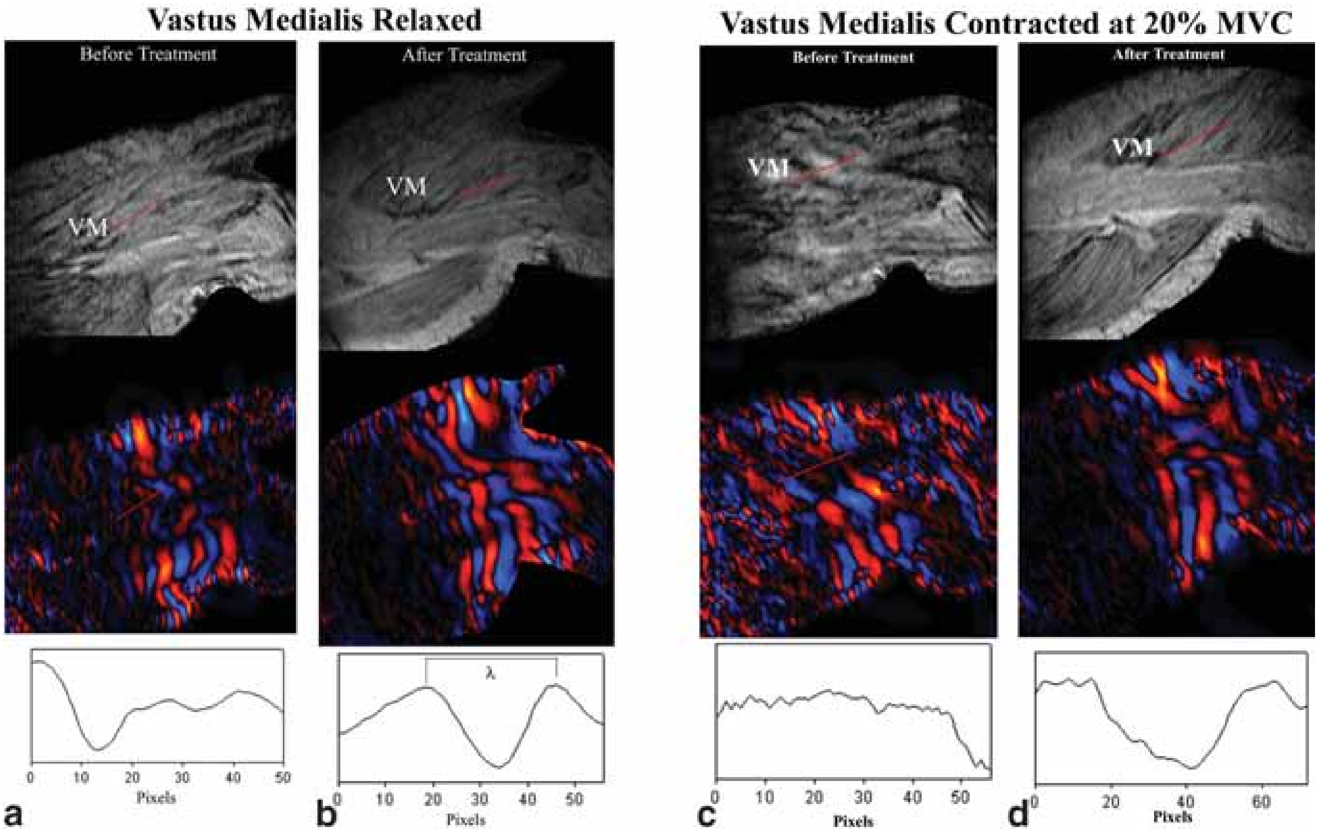

Figure 1. The first row shows the MRI anatomy of the VM muscle in a relaxed and contracted (20% MVC) state for patient #3 before and after treatment. The second row shows the propagation of the shear waves inside VM muscle. A red profile was drawn along the propagation of the shear waves and the same profile was represented on the MRI acquisition. **a**: MRI before treatment. **b**: MRI after treatment. **c**: Sheer wave propagation before treatment. **d**: Sheer wave propagation following treatment.

compare the VM stiffness between the healthy and hyperthyroid patients before treatment (**$P < 0.05$, *$P < 0.1$). A Wilcoxon pairs test was also performed with Statgraphics 5.0 to compare the VM stiffness before and after treatment (**$P < 0.05$, *$P < 0.1$; **, statistical differences in VM stiffness between healthy and hyperthyroid before treatment; *, statistical difference following treatment).

RESULTS

Body Mass Index and Thyroid Hormone Levels

The body mass index (BMI) was measured as the ratio between the weight and the square height of the patient. The BMI measured for the healthy volunteers (26.12 ± 1.66 kg/m^2) and hyperthyroid patients (25.54 ± 2.07 kg/m^2) before treatment were in the same range. After treatment hyperthyroid patients showed a 14% increase in the BMI (29.05 ± 1.92 kg/m^2) when the patients reached a euthyroid state. Table 1 shows the FT4 and the serum TSH measured for all the hyperthyroid patients. All patients had biochemical confirmation of hyperthyroidism, showing suppressed serum TSH and elevated serum FT4 and or T3. One patient (#4) had a free T4 that was at the upper part of the normal range but had a serum T3 that was elevated. This patient (#4) had milder disease both clinically and

Table 1
Five Patients Were Tested in a Hyperthyroid State, Four of Whom Were Restudied Following a Five- to Six-Month Interval*

			Pretreatment hyperthyroid state		Posttreatment euthyroid state			Healthy cohort		
Patients	Sex	Age (years)	FT4 (normal: 0.8–1.8 ng/dL)	TSH (normal: 0.3–5.0 mIU/liter)	FT4 (normal: 0.8–1.8 ng/dL)	TSH (normal: 0.3-5 mIU/liter)	Interval following treatment/months	Patients	Sex	Age (years)
#1	F	50	3.99	<0.010	1.2	4.6	6	# 1	F	50
#2	F	50	4.33	<0.010	–	–	–	# 2	F	54
#3	F	57	3.9	<0.010	–	3.9	5	# 3	F	57
#4	M	53	1.8	<0.010	0.9	1.8	5	# 4	M	53
#5	F	27	8.2	<0.010	1.1	1.5	6	# 5	F	28

*Five age-matched healthy patients are also represented.
F = female, M = male.

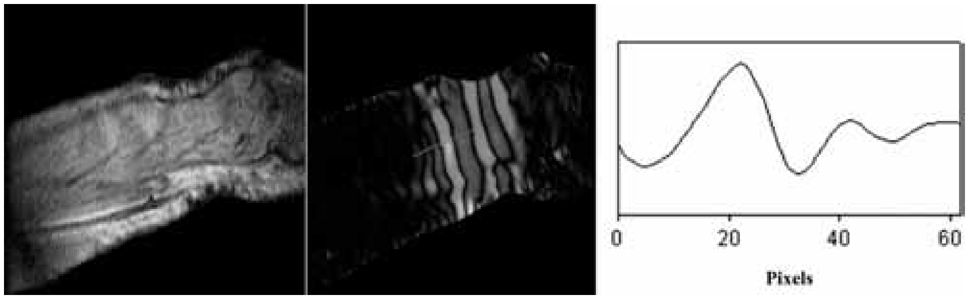

Figure 2. Propagation of the shear waves inside the VM muscle of a healthy volunteer.

biochemically than the remainder of the cohort. It is difficult to precisely date the onset of hyperthyroidism particularly among those over the age of 40 years as they tend to have fewer adrenergically mediated and therefore more recognizable symptoms compared to younger patients. We estimate, however, that the probable duration of hyperthyroidism prior to diagnosis and treatment in patients #1, #2, #3, and #5 was 12, six, six, and two months, respectively, while patient #4 was essentially asymptomatic. All the healthy volunteers had documented normal serum TSH levels.

VM Stiffness Measured Before and After Treatment

Figure 1 shows the propagation of the shear waves inside the relaxed and contracted VM of patient #3 before and after six months of treatment. Patient #3 was chosen as a representative hyperthyroid patient from our patient group because the amount of FT4 (= 3.9 ng/dL) was the median value of FT4 in our patient population and the TSH level (<0.010 mIU/liter) was the same as the rest of the patient population.

In a relaxed state, the shear wavelength before treatment was shorter (Fig. 1a) for the patients than the healthy group (Fig. 2). This observation was quantified and a significantly (**$P < 0.05$) lower stiffness was found for the patient (2.11 ± 0.61 kPa) before treatment than the age matched healthy volunteers (4.56 ± 0.40 kPa). Moreover, it was observed that the propagation of the shear waves were quite often located in the superficial part of the hyperthyroid VM while they propagated in the central portion of the muscle for healthy VM. After treatment, when the patients reach a euthyroid level, the shear wavelength was longer (Fig. 1b), thus increasing the stiffness significantly (*$P < 0.1$) to 5.52 ±1.52 kPa. The propagation of the shear waves were deeper inside the VM muscle in the euthyroid state and their propagation was clearly observed. The stiffness of the VM muscle after treatment was in the same range as the healthy patients (4.56 ± 0.40 kPa).

In a contracted state and before treatment, it was impossible to observe the propagation of shear waves inside the VM muscle (Fig. 1c) and therefore it was not possible to measure the stiffness (Fig. 3). The behavior of the shear waves showed a low signal-to-noise ratio (SNR) and did not lend themselves to wavelength measurement. After treatment, the shear waves were clearly propagated inside the VM (Fig. 1d) and the measured stiffnesses at 10% MVC and 20% MVC were 4.92 ±1.28 kPa and 7.46 ±1.89 kPa, respectively. Even after treatment, the euthyroid patients (N = 3) still showed an inferior stiffness than those of the healthy (N = 4) patients, who had a stiffnesses at 10% MVC and 20% MVC of 11.16 ± 3.56 kPa and 9.40 ± 1.05 kPa, respectively.

Figure 3 summarizes the trend of the stiffness measured for hyperthyroid patients before and after treatment. It is interesting to compare the behavior of the stiffness between patient #5 who had a more severe degree of hyperthyroidism (patient #5: FT4 = 8.2 ng/dL and TSH < 0.010 mIU/liter) and patient #4 who had mild hyperthyroidism, of which he was asymptomatic, and only modestly elevated levels of serum T3 and a borderline elevation of serum FT4 (patient #4: FT4 = 1.8 ng/dL, T3 = 193 [normal T3 range: 80–180 ng/dL],

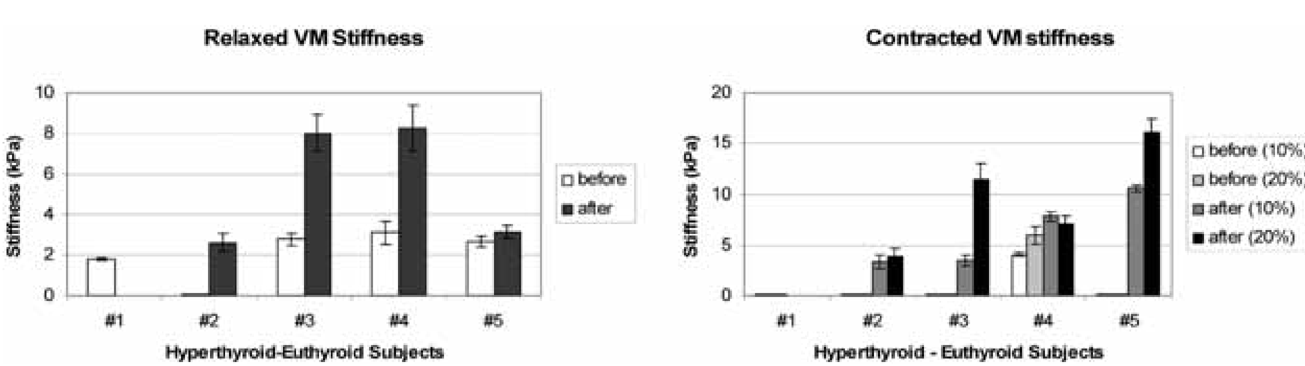

Figure 3. Behavior of the stiffness measured inside the relaxed and contracted VM muscle before and after treatment. (Note: no data was represented for patient #1 after treatment due to the unavailability of this patient).

and TSH < 0.010 mIU/liter). Patient #4 had a VM increase of 5.13 kPa of the stiffness after treatment, while the patient with a FT4 level of 8.2 ng/dL (age = 27 years) only had an increase of 0.44 kPa.

In a contracted state and before treatment, it was impossible to visualize the shear waves for the more severe degrees of hyperthyroidism (patient #5) while it was possible for the less severe disease. However, after treatment a greater increase in stiffness from 10% to 20% MVC (10% MVC: 10.55 kPa, 20% MVC: 16.08 kPa) was measured for the more severe hyperthyroid patients than for those who were less thyrotoxic (10% MVC: 7.88 kPa, 20% MVC: 7.08 kPa). We assume that the level of FT4 may contribute to these differences in stiffness, but we should also consider the age factor: younger age (27 years old) for patient #5 compared to patient #4 (53 years old); which influences the muscle stiffness. However, in a population of 18 healthy volunteers (range 22–28 years old), we found the mean stiffness was 5.07 ± 0.63 kPa at 10% MVC and 6.59 ± 0.68 kPa at 20% MVC. Additionally, for the older healthy age-matched volunteers, the mean VM stiffness was 11.16 ± 3.56 kPa for 10% MVC and 9.40 ± 1.05 kPa for 20% MVC, which is larger than the stiffness in the younger volunteers. Therefore, it is more probable that the pretreatment level of FT4 affected the stiffness measurements in patient #5, and that age is probably not the reason for these differences.

DISCUSSION

The purpose of this study was to measure the stiffness of the VM of hyperthyroid patients (Grave's disease) before and after treatment using a MRE technique. This study was focused on the feasibility and the sensitivity of the MRE technique to detect changes in muscle properties in hyperthyroid patients both before and following treatment. Muscle shear stiffness is one of the mechanical parameters, which not only is important for the force transmission within the muscle, and thus the function, but also is critical to the cellular responses in muscle repair and remodeling due to the mechanobiology. Noninvasive assessment of the tissue stiffness has thus been one of the challenges in the scientific field.

This present work is the first to use the propagation of the shear waves inside the VM to estimate its stiffness in a pathologic condition. Other studies (11,12) assessed muscle strength in hyperthyroid patients before and after treatment using isokinetic dynamometer. Celsing et al's (11) study found an increase of muscle strength after treatment ranged from 25% to 41% for concentric and isometric tests and from 19% to 35% for eccentric tests. Usually, the response to treatment for hyperthyroid myopathy showed an improvement of the muscle strength (13–15). Our MRE technique performed on the VM muscle showed an increase of the stiffness after treatment. It is important to note that while our assumptions led to some limitations, we are still able to see differences between muscle affected by pathology and healthy muscle. Therefore, MRE is sensitive to the changes in muscle caused by disease. In a previous study, it was found that muscles with a higher number of fast twitch fibers showed a faster increase in stiffness than slower twitch muscle fibers (9). It has also been shown that hyperthyroid patients have an increase in their percentage of fast twitch fibers (4). Therefore, these data suggest that after treatment, the increase in stiffness may reflect muscle fiber transformation.

The behavior of the shear waves defined by the wavelength and the quality of the shear wave propagation (low SNR or clear) was sensitive to the stage (before or after treatment) of the hyperthyroidism. Before treatment when the patients were asked to contract their muscles the propagation of the shear waves was observed with a low SNR. The precise cause of this may reflect in part changes in muscle composition (4) or the myriad changes in muscle biochemistry that occur in this condition.

In addition to the stage of hyperthyroidism, we found that muscle stiffness determined by MRE was also sensitive to the severity of hyperthyroidism as defined by the degree of elevation of free thyroid hormones in the serum. The limited cohort size combined with the acknowledged difficulty in precisely determining the duration of hyperthyroidism prevents a meaningful attempt to correlate the MRE findings with duration of hyperthyroidism.

An advantage of the MRE technique is that it allows for interrogation of isolated muscle (in this study VM) as compared to the dynamometry technique, which is only capable of assessing groups of muscles (e.g., the quadriceps). Isolated muscles weakness or changes in the mechanical properties could be masked by a global measure of a group of muscles. It is interesting to notice that the stiffness of the VM in a contracted state, when the patients reach a euthyroid level, still presents an inferior stiffness to the control group, suggesting a residual defect in muscle function following correction of hyperthyroidism. A finding consistent with that observed in dynamometer studies in this condition (16). This may point to the need for additional therapy to fully restore muscle function to normal following the correction of hyperthyroidism. Furthermore, previous studies point to the extreme sensitivity of skeletal muscle strength and mass to even mild perturbations in thyroid function (17). The sensitivity provided by MRE interrogation of individual muscles when correlated with biochemical assessment may shed further light on the pathogenesis of weakness in this condition. Further experience with the technique and an increased sample size may inform clinical decision making regarding the need for thyroid directed treatment in patients with mild, so-called subclinical hyperthyroidism (18–20).

The underlying mechanism for muscle weakness in Graves disease has yet to be fully determined it is clear from prior studies that it reflects both quantitative (muscle atrophy) and qualitative (decreased strength per unit of muscle volume) with the latter predominating. This may be considered, therefore, as a decrease in muscle efficiency that increases in severity in parallel with the severity of hyperthyroidism. While patients generally do not report muscle weakness per se, they often report exercise induced muscle fatigue that may be reflective of observed changes in muscle stiffness. Muscle strength and endurance depend on many factors such as the distribution of fiber types and properties as well as the organization of the extracellular matrix. The precise mechanism and relationship between the structure and function has yet to be studied. The stiffness measurement provides additional useful information for solving this important scientific question in the future.

REFERENCES

1. Klein I, Ojamaa K. Thyroid (neuro)myopathy. Lancet 2000;19:614.
2. Zurcher RM, Horber FF, Grunig BE, Frey FJ. Effect of thyroid dysfunction on thigh muscle efficiency. J Clin Endocrinol Metab 1989;69:1082–1086.
3. Celsing F, Blomstrand E, Melichna J, et al. Effect of hyperthyroidism on fibre-type composition, fibre area, glycogen content and enzyme activity in human skeletal muscle. Clin Physiol 1986;6: 171–181.
4. Brennan MD, Coenen-Schimke JM, Bigelow ML, Nair KS. Changes in skeletal muscle protein metabolism and myosin heavy chain isoform messenger ribonucleic acid abundance after treatment of hyperthyroidism. J Clin Endocrinol Metab 2006;91:4650–4656.
5. Muthupillai R, Lomas DJ, Rossman PJ, Greenleaf JF, Manduca A, Ehman RL. Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. Science 1995;269:1854–1857.
6. Sack I, Bernarding J, Braun J. Analysis of wave patterns in MR elastography of skeletal muscle using coupled harmonic oscillator simulations. Magn Reson Imaging 2002;20:95–104.
7. Jenkyn TR, Ehman RL, An KN. Noninvasive muscle tension measurement using the novel technique of magnetic resonance elastography (MRE). J Biomech 2003;36:1917–1921.
8. Bartley GB, Fatourechi V, Kadrmass EF, et al. The incidence of Graves' ophthalmopathy in Olmsted County Minnesota. Am J Ophthalmol 1995;120:511–517.
9. Bensamoun SF, Ringleb SI, Littrell L, et al. Determination of thigh muscle stiffness using magnetic resonance elastography. Magn Reson Imaging 2006;23:242–247.
10. Romano AJ, Abraham PB, Rossman PJ, Bucaro JA, Ehman RL. Determination and analysis of guided wave propagation using magnetic resonance elastography. Magn Reson Med 2005;54: 893–900.
11. Celsing F, Westing SH, Adamson U, Ekblom B. Muscle strength in hyperthyroid patients before and after medical treatment. Clin Physiol 1990;10:545–550.
12. Zürcher RM, Horber FF, Grunig BE, Frey FJ. Effect of thyroid dysfunction on thigh muscle efficiency. J Clin Endocrinol Metab 1989;69:1082–1086.
13. Norrelund H, Moller N. Muscle mass and function in thyrotoxic patients before and during medical treatment Clin Endocrinol 1999;51:693–699.
14. Da Nobrega AC, Vaisman M, De Araujo CG. Skeletal muscle function and body composition of patients with hyperthyroidism. Med Sci Sports Exerc 1997;29:175–180.
15. Olson BR, Klein I, Benner R, Burdett R, Trzepacz P, Levey GS. Hyperthyroid myopathy and the response to treatment. Thyroid 1991;1:137–141.
16. Epstein FH. Mechanisms of disease. N Engl J Med 2001;344:501–509.
17. Brennan MD, Powell C, Kaufman KR, Sun PC, Bahn RS, Nair KS. The impact of overt and subclinical hyperthyroidism on skeletal muscle. Thyroid 2006;16:375–380.
18. Col NF, Surks MI, Daniels GH. Subclinical thyroid disease: clinical applications. JAMA 2004;14:239–243.
19. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. Am Heart J 2001;142:838–842.
20. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004;14:228–238.