

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/237098111>

Vitamin D deficiency in myotonic dystrophy type 1

Article in *Journal of Neurology* · June 2013

DOI: 10.1007/s00415-013-6984-1 · Source: PubMed

CITATIONS

5

READS

123

10 authors, including:



Chiara Terracciano

University of Rome Tor Vergata

46 PUBLICATIONS 392 CITATIONS

SEE PROFILE



Maria Morello

University of Rome Tor Vergata

29 PUBLICATIONS 751 CITATIONS

SEE PROFILE



Giovanni Antonini

Sapienza University of Rome

162 PUBLICATIONS 2,025 CITATIONS

SEE PROFILE



Roberto Massa

University of Rome Tor Vergata

118 PUBLICATIONS 1,101 CITATIONS

SEE PROFILE

Vitamin D deficiency in myotonic dystrophy type 1

**Chiara Terracciano, Emanuele Rastelli,
Maria Morello, Monica Celi, Elisabetta
Bucci, Giovanni Antonini, Ottavia
Porzio, et al.**

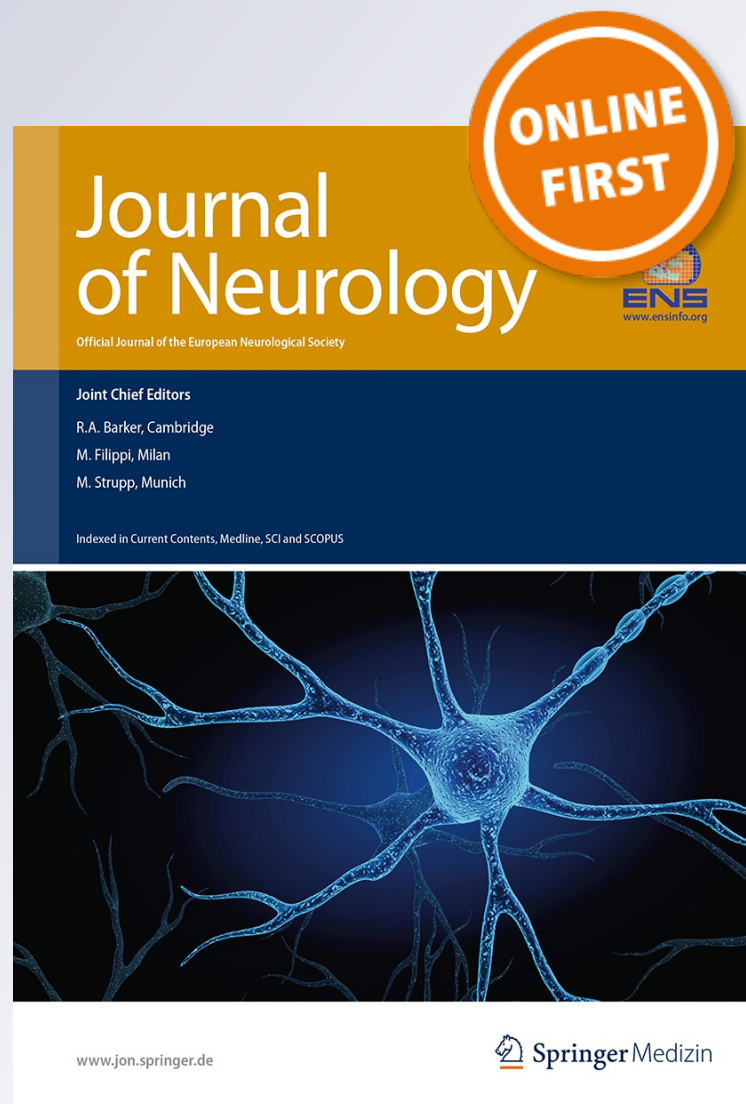
Journal of Neurology

Official Journal of the European
Neurological Society

ISSN 0340-5354

J Neurol

DOI 10.1007/s00415-013-6984-1



Your article is protected by copyright and all rights are held exclusively by Springer-Verlag Berlin Heidelberg. This e-offprint is for personal use only and shall not be self-archived in electronic repositories. If you wish to self-archive your article, please use the accepted manuscript version for posting on your own website. You may further deposit the accepted manuscript version in any repository, provided it is only made publicly available 12 months after official publication or later and provided acknowledgement is given to the original source of publication and a link is inserted to the published article on Springer's website. The link must be accompanied by the following text: "The final publication is available at link.springer.com".

Vitamin D deficiency in myotonic dystrophy type 1

Chiara Terracciano · Emanuele Rastelli · Maria Morello ·
Monica Celi · Elisabetta Bucci · Giovanni Antonini · Ottavia Porzio ·
Umberto Tarantino · Rossella Zenobi · Roberto Massa

Received: 17 April 2013 / Revised: 23 May 2013 / Accepted: 25 May 2013
© Springer-Verlag Berlin Heidelberg 2013

Abstract Myotonic dystrophy type 1 (DM1) is a multi-systemic disorder affecting, among others, the endocrine system, with derangement of steroid hormones functions. Vitamin D is a steroid recognized for its role in calcium homeostasis. In addition, vitamin D influences muscle metabolism by genomic and non-genomic actions, including stimulation of the insulin-like-growth-factor 1 (IGF1), a major regulator of muscle trophism. To verify the presence of vitamin D deficit in DM1 and its possible consequences, serum 25-hydroxyvitamin D (25(OH)D), calcium, parathormone (PTH), and IGF1 levels were measured in 32 DM1 patients and in 32 age-matched controls. Bone mineral density (BMD) and proximal muscle strength were also measured by DXA and a handheld dynamometer, respectively. In DM1 patients, 25(OH)D levels were reduced compared to controls, and a significant decrease of IGF1 was also found. 25(OH)D

levels inversely correlated with CTG expansion size, while IGF1 levels and muscle strength directly correlated with levels of 25(OH)D lower than 20 and 10 ng/ml, respectively. A significantly higher percentage of DM1 patients presented hyperparathyroidism as compared to controls. Calcium levels and BMD were comparable between the two groups. Oral administration of cholecalciferol in 11 DM1 patients with severe vitamin D deficiency induced a normal increase of circulating 25(OH)D, ruling out defects in intestinal absorption or hepatic hydroxylation. DM1 patients show a reduction of circulating 25(OH)D, which correlates with genotype and may influence IGF1 levels and proximal muscle strength. Oral supplementation with vitamin D should be considered in DM1 and might mitigate muscle weakness.

Keywords Myotonic dystrophy type 1 · Vitamin D · IGF1 · Parathormone · Muscle strength · CTG repeat expansion

C. Terracciano (✉) · E. Rastelli · R. Massa
Neuromuscular Center, Division of Neurology, Department of
Systems Medicine, Tor Vergata University, Via Montpellier 1,
00133 Rome, Italy
e-mail: chiara.terracciano@uniroma2.it

C. Terracciano · R. Massa
Fondazione Santa Lucia IRCCS, Rome, Italy

M. Morello · O. Porzio · R. Zenobi
Department of Experimental Medicine and Surgery, Tor Vergata
University, Rome, Italy

M. Celi · U. Tarantino
Department of Clinical Sciences and Translational Medicine,
Tor Vergata University, Rome, Italy

E. Bucci · G. Antonini
Department Nesmos, Faculty of Medicine and Psychology, La
Sapienza University, Rome, Italy

Introduction

Myotonic dystrophy type 1 (DM1) is the most common adult form of muscular dystrophy, caused by a CTG expansion in the 3' untranslated region of *DMPK* gene on chromosome 19. DM1 is a multi-systemic disorder affecting skeletal muscle, with myotonia and prominent muscle weakness and atrophy, as well as eye, heart, endocrine, and central nervous systems. Abnormal levels of steroid hormones, such as testosterone and DHEA have been reported in DM1 [1–3]. Moreover, recent studies showed that in DM1 patients there is an increased risk of calcium metabolism disorders such as hyperparathyroidism that seem to correlate with CTG expansion size [1].

Vitamin D is a steroid hormone produced in the skin, through the conversion of 7-dehydrocholesterol into pre-vitamin D₃ under the action of ultraviolet-B radiation. In the skin, pre-vitamin D₃ is converted to vitamin D₃ (cholecalciferol) before its subsequent conversion to 25-hydroxyvitamin D [25(OH)D] in the liver. Current routine laboratory methods detect levels of circulating 25(OH)D. Further hydroxylation of 25(OH)D to its active form, 1,25 hydroxyvitamin D (1,25(OH)₂D), occurs in the kidney [4].

It is well known that vitamin D, in conjunction with parathyroid hormone (PTH), plays a critical role in calcium homeostasis [5]. Moreover, vitamin D status has been described to influence muscle strength, performance, and mass, exerting both an indirect action via regulation of calcium and phosphate metabolism, and a direct effect through its receptor VDR, present in many human tissues, including skeletal muscle [6]. Vitamin D receptor has genomic and non-genomic effects, all promoting muscle differentiation and proliferation. Interestingly, one of its genomic actions is through the stimulation of the insulin-like growth factor-1 (IGF1) axis [7]; accordingly, vitamin D administration in children with vitamin D deficiency resulted in an increase of circulating levels of IGF-1 [8].

The aim of our study was to evaluate 25(OH)D levels and their relationships with CTG expansion size, IGF1, PTH, calcium, bone mineral density (BMD), and muscular impairment in a cohort of adult DM1 patients.

Patients and methods

Thirty-two patients with adult-onset DM1 were studied: 16 premenopausal women and 16 men, mean age 41 years (29–53 years) and 32 age-matched normal subjects: 14 men and 18 premenopausal women, mean age 42 years (24–55 years). Diagnosis of DM1 was confirmed in all patients by means of molecular analysis as previously described [9]. Only patients with musculoskeletal symptoms, implying a Muscular Impairment Rating Scale (MIRS) score ≥ 2 , but self-sufficient in daily activity and controls with low sun exposure (indoor workers) were selected. None of the patients reported pathological bone fractures, but two had suffered from traumatic fractures due to falls at least 1 year prior to being recruited for this study. Hepatic or renal insufficiency and vitamin D supplementation were considered exclusion criteria. The patients were informed about the experimental procedures and signed an informed consent form before participating in the study. The study was approved by Tor Vergata University Ethics Committee.

Serum 25-hydroxyvitamin D [25(OH)D], PTH, calcium, and IGF1 levels were quantified by routine clinical

laboratory methods (Vista, Centaur and Immulite Siemens Healthcare Diagnostic, Milan, Italy). To avoid seasonal variability, 25(OH)D levels in DM1 and controls were measured during the same season.

Quantitative muscle testing (QMT) was performed with a handheld dynamometer (Citec, Haren, The Netherlands) assessing isometric force in two proximal muscle groups of the upper and lower extremities in patients and controls: shoulder abductors for upper limbs and hip flexors for lower limbs. We chose to assess strength in proximal muscles, which are more sensitive to vitamin D deficiency [6]. QMT was performed by the same examiner in all subjects and repeated three times in order to overcome the possible effect of myotonia. The best performance on the weakest side per each muscle group was considered, according to the manufacturer's instructions. Bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry (DXA) measured at the femoral neck on the non-dominant side, as previously described [10].

Standard statistical procedure was used to calculate mean and standard error (SE) of age, CTG_(n...), 25(OH)D, PTH and IGF1 levels, and of QMT and BMD values. The significance of the differences in 25(OH)D, PTH, and IGF1 levels between DM1 and controls was evaluated by Student's *t* test. Correlation analysis was performed using the Pearson product moment correlation test; *p* values lower than 0.05 and 0.01 were considered significant and highly significant, respectively.

Results

It is generally accepted that 25(OH)D levels of 20–30 ng/ml represent insufficiency, whereas levels below 20 and 10 ng/ml represent deficiency and severe deficiency, respectively [7, 11]. Our results showed that vitamin D values were not statistically different between males and females among DM1 and normal subjects. In DM1 patients, 25(OH)D levels showed a highly significant ($p < 0.001$) reduction, with a mean value of 16.3 ± 9.3 ng/ml compared to controls (30.4 ± 17.1 ng/ml). About 38 % of DM1 patients had levels of 25(OH)D lower than 10 ng/ml, representing severe deficiency, and 34 % had a 25(OH)D deficiency with values between 10 and 20 ng/ml (Fig. 1). No correlation between age and 25(OH)D was observed either in DM1 or control subjects. On the other hand, 25(OH)D levels inversely correlated with CTG expansion size (correlation coefficient $r = -0.5$, $p < 0.05$) (Fig. 2).

Calcium levels were normal in DM1 patients with all values within the normal range (n.v. 8.8–10.2 mg/dl). Parathyroid hormone levels showed a pathological increase (higher than 72 pg/ml) in 20 % of patients and 10 % of

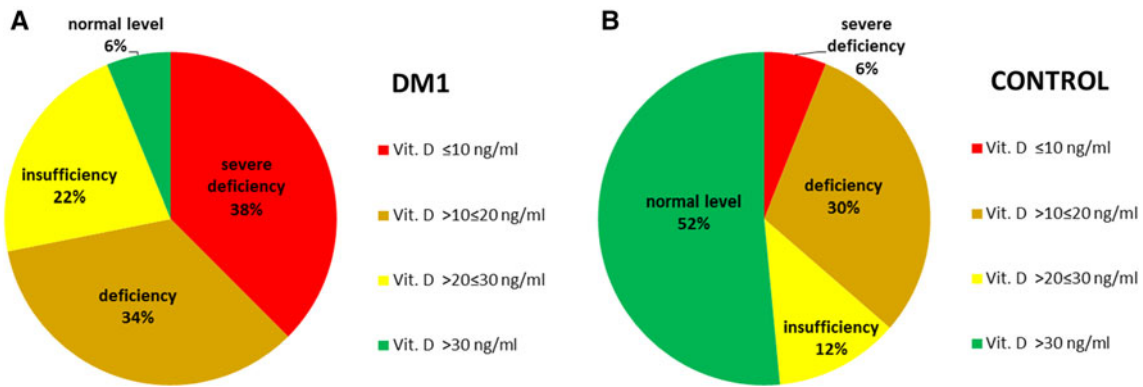


Fig. 1 Prevalence of DM1 (a) and normal subjects (b) with different degrees of vitamin D deficit

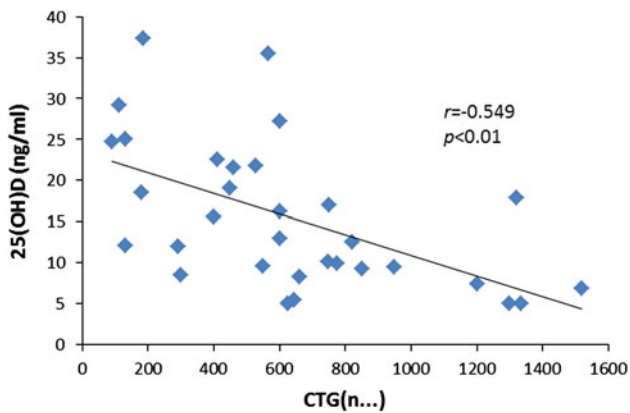


Fig. 2 Linear regression graph showing an inverse correlation between vitamin D levels and CTG expansion size in DM1

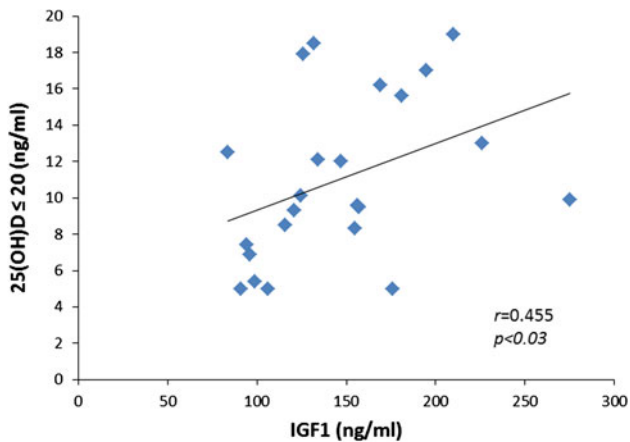


Fig. 3 Linear regression graph showing a direct correlation between vitamin D and IGF1 blood levels in the “deficiency” and “severe deficiency” (vitamin D ≤ 20 ng/ml) subgroups of DM1

controls ($p = 0.005$). The apparently high prevalence of hyperparathyroidism (HPT) in healthy subjects might be secondary to the high percentage of individuals with low 25(OH)D values, which is in accordance with data on Italian general population [12]. In our DM1 population,

IGF1 was reduced compared to controls ($p < 0.05$), with mean values of 138.2 ± 9.6 ng/ml and 180.8 ± 9.9 ng/ml, respectively; indeed, six out of 32 patients (19 %) as opposed to one out of 32 controls had an IGF1 value lower than reference value for age and sex [13].

BMD values/T-score were indicative of osteopenia in a similar percentage of patients (22 %) and normal subjects (24 %). Muscle strength, expressed in Newtons (N), was reduced in DM1 patients both in shoulder abductors (86 ± 7.0 N in DM1 and 166 ± 22.9 N in controls, $p < 0.001$) and hip flexors (129 ± 12.5 N in DM1 and 210 ± 12.1 N in controls, $p < 0.05$).

In order to detect alterations related to the pathological levels of 25(OH)D found in our DM1 population, we divided patients into three subgroups on the basis of their 25(OH)D levels: insufficiency (< 30 ng/ml), deficiency (10–20 ng/ml), and severe deficiency (< 10 ng/ml). Interestingly, in patients with deficiency or severe deficiency of 25(OH)D, a fair direct correlation between 25(OH)D and IGF1 was found ($r = 0.46$, $p < 0.05$) (Fig. 3), whereas in the severe deficiency subgroup a strong direct correlation between 25(OH)D levels and strength measured in shoulder abductors was detected ($r = 0.77$, $p < 0.01$) (Fig. 4). For the other muscle group tested, no significant correlation was found with 25(OH)D levels ($r = 0.53$, $p = 0.07$), although the lowest performances were observed in patients with severe 25(OH)D deficiency. In addition, PTH values showed a trend to increase proportionally to the vitamin D decrease, but no significant correlation was observed. Similarly, BMD values were lower in patients with low levels of 25(OH)D, although again no significant correlation was observed (Table 1). In an attempt to understand if the low 25(OH)D levels detected in our DM1 patients were due to an altered cutaneous transformation of the pre-vitamin D3 in cholecalciferol or to an impaired intestinal absorption or liver hydroxylation of vitamin D, we orally administered 25,000 UI of cholecalciferol in 11 DM1 patients with severe vitamin D deficiency and in ten

healthy controls. One week after administration, we detected the same increase of circulating 25(OH)D in patients and controls (about 20 % in both populations). This result suggests that in DM1 the intestinal absorption of vitamin D and its hepatic hydroxylation are not impaired.

Discussion

Our study shows that 25(OH)D is markedly reduced in DM1 patients, with a high prevalence of severe deficiency, and this seems to be related to the CTG expansion length.

On the other hand, calcium homeostasis, evaluated by calcium and PTH dosage, and BMD evaluation, appears to be only marginally influenced by this 25(OH)D reduction. In spite of normal calcium levels, DM1 patients presented higher levels of PTH than normal controls, especially in the

severe deficiency subgroup. Increased PTH levels have been reported in DM1, and interpreted as primary HPT [1], however our data show that in this disease, HPT is more likely secondary to vitamin D deficiency. The observed changes in PTH levels in DM1 were probably insufficient to induce bone mineral loss since BMD values were similar in DM1 and control subjects.

In accordance with previous reports [14], we detected low levels of IGF1 in our DM1 population. IGF1 is a peptide hormone similar to insulin that is considered one of the major muscle growth factors. Human recombinant IGF1 has been proposed as a therapeutic tool for muscle weakness in DM1 [14]. Vitamin D has been described to condition IGF1 by a genomic effect and probably values below a putative threshold have to be reached in order to cause a relevant change in circulating IGF1 levels. A significant direct correlation between 25(OH)D and IGF1 levels was found in patients with a 25(OH)D deficiency or severe deficiency. Similarly, Soliman et al. [8] demonstrated a direct correlation between 25(OH)D and IGF1 levels, before and after administration of vitamin D, in children with rickets, a disease caused by a severe 25(OH)D deficit. The 25(OH)D-related IGF1 reduction found in DM1 might partially influence muscle metabolism and performance in those patients, although direct non-genomic effects of vitamin D on skeletal muscle mediated by its receptor should be also considered. Further studies on larger cohorts of patients are needed to confirm this finding.

According to our results, severe 25(OH)D deficiency seems to affect muscle strength in proximal muscles in DM1 patients. This is in accordance with the preferential sensitivity of proximal muscles seen in rickets-associated myopathy [6, 15, 16].

Cholecalciferol is mainly produced by the cutaneous conversion of 7-dehydrocholesterol, and partially absorbed with diet, then it undergoes hydroxylation to 25(OH)D in the liver, the form of vitamin D usually measured in the blood [4]. Therefore, reduced levels of 25(OH)D in DM1

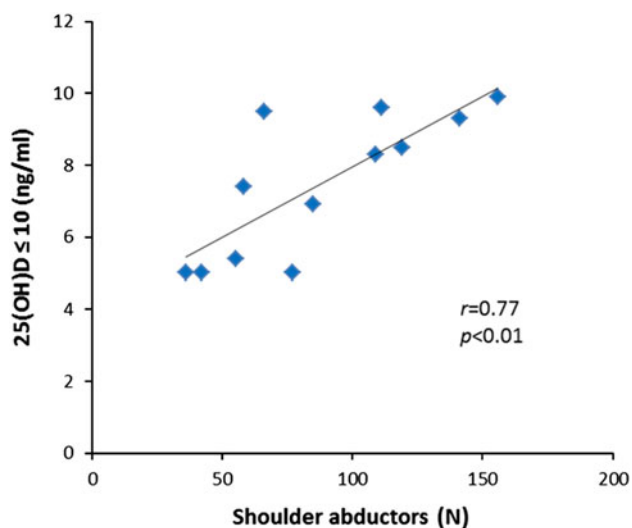


Fig. 4 Linear regression graph showing a direct correlation between vitamin D levels and shoulder abductors strength in the “severe deficiency” (vitamin D ≤ 10 ng/ml) subgroup of DM1

Table 1 Laboratory and instrumental data in DM1 patients stratified for vitamin D levels

	Vitamin D ≤ 10 (ng/ml)	Vitamin D > 10 ≤ 20 (ng/ml)	Vitamin D > 20 ≤ 30 (ng/ml)
Patients	12	11	7
CTG (n...)	893 ± 107	573 ± 102	373 ± 71
VIT.D (ng/ml)	7.5 ± 0.57	15.1 ± 0.96	27.3 ± 2.25
IGF1 (ng/ml)	138.6 ± 15.70	145.8 ± 13.23	146.0 ± 24.59
PTH (pg/ml)	71.7 ± 9.89	42.2 ± 5.49	39.8 ± 6.73
Calcium (mg/dl)	9.5 ± 0.14	9.3 ± 0.14	9.45 ± 0.26
Shoulder abductors (N)	84.0 ± 11.28	86.7 ± 11.27	93.3 ± 15.91
Hip flexors (N)	122.8 ± 23.15	124.9 ± 14.50	140.0 ± 26.75
BMD (g/cm ²)	0.931 ± 0.05	1.017 ± 0.04	1.043 ± 0.04

Values are mean ± SE

patients could be due to an insufficient cutaneous synthesis, to an altered gastro-intestinal absorption or to an abnormal hepatic hydroxylation of vitamin D. Our data on 25(OH)D-deficient patients administered with oral cholecalciferol showed a normal increase of circulating 25(OH)D, ruling out malabsorption and liver dysfunction and making an impaired cutaneous pre-vitamin D₃ transformation the main candidate mechanism of vitamin D deficiency found in DM1. Skin changes, such as baldness and epithelial tumors, are common in DM1 [17, 18], sustaining the hypothesis that cutaneous alterations might be responsible for 25(OH)D deficiency in this disease. Further studies are required to clarify the exact mechanisms underlying vitamin D deficiency in DM1.

In conclusion, DM1 patients show a significant reduction of 25(OH)D blood levels, and this is correlated with the severity of genotype and seems to influence the circulating levels of IGF1 and proximal muscle strength. The 25(OH)D reduction in DM1 could be due to an impaired skin production of cholecalciferol rather than a defective liver hydroxylation. Vitamin D administration has been described to improve physical performance in elderly subjects [19, 20]. Therefore, vitamin D supplementation should be considered in DM1 patients to prevent endocrine and bone modification due to vitamin D deficit, and in the attempt to increase IGF1 levels and to ameliorate muscle performance.

Acknowledgments This work was supported by R.S.A 2009 and ASI Grant # I/R/337/02 to RM.

Conflicts of interest On behalf of all authors, the corresponding author states that there are no conflict of interest.

Ethical standard This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

References

1. Ørngreen MC, Arlien-Søborg P, Duno M, Hertz JM, Vissing J (2012) Endocrine function in 97 patients with myotonic dystrophy type 1. *J Neurol* 259:912–920
2. Johansson A, Andrew R, Forsberg H, Cederquist K, Walker BR, Olsson T (2001) Glucocorticoid metabolism and adrenocortical reactivity to ACTH in myotonic dystrophy. *J Clin Endocrinol Metab* 86:4276–4283
3. Antonini G, Clemenzi A, Bucci E et al (2011) Hypogonadism in DM1 and its relationship to erectile dysfunction. *J Neurol* 58:1247–1253
4. Christakos S, Ajibade DV, Dhawan P, Fechner AJ, Mady LJ (2011) Vitamin D: metabolism. *Rheum Dis Clin North Am* 38:1–11
5. Raisz LG (2005) Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J Clin Invest* 115:3318–3325
6. Ceglia L, Harris SS (2012) Vitamin D and its role in skeletal muscle. *Calcif Tissue Int* 92:151–162
7. Hamilton B (2010) Vitamin D and human skeletal muscle. *Scand J Med Sci Sports* 20:182–190
8. Soliman AT, Al Khalaf F, Alhemaidi N, Al Ali M, Al Zyouid M, Yakoot K (2008) Linear growth in relation to the circulating concentrations of insulin-like growth factor I, parathyroid hormone, and 25-hydroxy vitamin D in children with nutritional rickets before and after treatment: endocrine adaptation to vitamin D deficiency. *Metabolism* 57:95–102
9. Salehi LB, Bonifazi E, Stasio ED et al (2007) Risk prediction for clinical phenotype in myotonic dystrophy type 1: data from 2,650 patients. *Genet Test* 11:84–90
10. Terracciano C, Celi M, Lecce D, Baldi J, Rastelli E, Lena E, Massa R, Tarantino U (2013) Differential features of muscle fiber atrophy in osteoporosis and osteoarthritis. *Osteoporos Int* 24:1095–1100
11. Holick MF (2007) Vitamin D deficiency. *N Engl J Med* 357:266–281
12. Romagnoli E, Caravella P, Scarnecchia L, Martinez P, Minisola S (1999) Hypovitaminosis D in an Italian population of healthy subjects and hospitalized patients. *Br J Nutr* 81:133–137
13. Mayo Foundation For Medical Education And Research (accessed 01/07/2013) <http://www.mayomedicallaboratories.com/test-catalog/print/15867>
14. Heatwole CR, Eichinger KJ, Friedman DI et al (2011) Open-label trial of recombinant human insulin-like growth factor 1/recombinant human insulin-like growth factor binding protein 3 in myotonic dystrophy type 1. *Arch Neurol* 68:37–44
15. Bischoff-Ferrari HA (2012) Relevance of vitamin D in muscle health. *Rev Endocr Metab Disord* 13:71–77
16. Fluss J, Kern I, de Coulon G, Gonzalez E, Chehade H (2012) Vitamin D deficiency: A forgotten treatable cause of motor delay and proximal myopathy. *Brain Dev Epub ahead of print pii: S0387-7604(12)00303-8*
17. Geh JL, Moss AL (1999) Multiple pilomatrixomata and myotonic dystrophy: a familial association. *Br J Plast Surg* 52:143–145
18. Harper PS (1989) *Myotonic Dystrophy*, 2nd edn. Saunders, London
19. Lagari V, Gómez-Marín O, Levis S (2013) The role of vitamin D in improving physical performance in the elderly. *J Bone Miner Res* doi: [10.1002/jbmr.1949](https://doi.org/10.1002/jbmr.1949) [Epub ahead of print]
20. Toffanello ED, Perissinotto E, Sergi G et al (2012) Vitamin D and physical performance in elderly subjects: the Pro.V.A study. *PLoS One*. 7:e34950. doi: [10.1371/journal.pone.0034950](https://doi.org/10.1371/journal.pone.0034950) [Epub ahead of print]