Contractile properties of type I and type II skeletal muscle fibres are altered in aged men undergoing androgen deprivation therapy

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Prostate cancer (PrCa) is the most commonly diagnosed malignancy in men, and the second most common cause of cancer mortality. Increasing numbers of men with PrCa are receiving androgen deprivation therapy (ADT) which leads to profound decline in serum testosterone levels in order to suppress tumour growth. Although ADT has improved the survival of PrCa patients, its survival benefits are offset partly by its adverse effects on quality of life, including loss of muscle strength which cannot be explained solely by loss of muscle mass (Girard, Marino & Cannon, 2014).

The present study examined the contractile apparatus properties of mechanically-skinned fibres obtained from fresh biopsies of the *vastus lateralis* muscle in eight PrCa patients (68 ± 5 yr) undergoing ADT for at least 3 months, and ten age-matched healthy control males (70 ± 5 yr). More specifically, we assessed whether there were any differences between the two groups in regards to the specific force and Ca^{2+}-sensitivity in type I and type II fibres, and the effects of reversible oxidative modification. Individual mechanically-skinned muscle fibres were exposed to a sequence of heavily buffered solutions at progressively higher free [Ca^{2+}] to determine their force-Ca^{2+} relationship. To examine whether reversible oxidative modification of the contractile proteins occurs with ADT, some skinned fibres were treated for 5 min with 10 mM DTT, a potent reducing agent. Finally, a subset of type II fibres were subjected to S-glutathionylation by successive treatments with 2,2′-dithiodipyridine (DTDP) and glutathione (GSH). Western blotting was used to determine fibre type.

The Ca^{2+}-sensitivity in type I and type II fibres of PrCa patients with testosterone deprivation decreased by 0.05 and 0.04 pCa unit, respectively, compared to control subjects. In type I fibres of patients undergoing ADT, specific force was reduced by ~13% relative to that in type I fibres of control subjects, whereas in type II fibres there was no significant difference. DTT treatment significantly increased the specific force by ~2 and ~3% in type I and type II fibres, respectively, of the ADT group, with no effect in either fibre types of the control group. S-glutathionylation of fast troponin I (TnIf) markedly increased the Ca^{2+}-sensitivity of the contractile apparatus in type II fibres, but the increase was not significantly different between the groups (+0.140 and +0.136 pCa unit increases in ADT and Control, respectively). The findings suggest that testosterone deprivation can worsen the negative impact of ageing on contractile properties by reducing (i) the Ca^{2+}-sensitivity in both type I and type II fibres and (ii) the maximum specific force in type I fibres. All these differences could be expected to have adverse effects on muscle performance, and may be significant contributory factors to muscle weakness seen in patients undergoing ADT.

Girard D, Marino FE, Cannon J. (2014). Evidence for reduced neuromuscular function in men with a history of androgen deprivation therapy for prostate cancer. *Clin Physiol Funct Imaging* **34**, 209-217.