Muscle fibre type changes in hypothyroid myopathy

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SYNOPSIS Changes in muscle fibre type in hypothyroid myopathy were studied by serial percutaneous needle biopsy of vastus lateralis before and during treatment with L-thyroxine. A type II fibre atrophy and loss was found, which correlated with the clinical and biochemical evidence of a myopathy. The type II fibre atrophy was corrected by L-thyroxine but type II fibre loss was still apparent in severely myopathic patients up to two years after starting treatment. The pathogenesis and significance of type II fibre atrophy and loss are discussed in relation to prognosis.

More than 90% of patients with hypothyroidism have evidence of significant muscular involvement indicated by elevated serum creatine phosphokinase levels (CPK, adenosine 5' triphosphate-creatine phosphotransferase, EC 2.7.3.2, Graig and Smith, 1965; Griffiths, 1965). Clinical evidence of myopathy occurs in 30-80% of patients (Nickel, Frame, Bebin, Tourtellotte, Parker, and Hughes, 1961; Ozker, Schumacher, and Nelson, 1960). The main features are weakness, cramps, aching or painful muscles, sluggish movements, myoedema, and occasionally an increase in muscle bulk. Treatment with L-thyroxine leads to complete clinical recovery within two to six months in most cases, but in some the recovery may be delayed or incomplete.

Few pathological studies of muscle in hypothyroidism have been reported and these based on paraffin sections have indicated only minor changes (Ramsay, 1974). The relatively atraumatic procedure of percutaneous needle biopsy permitted serial study of muscle fibre type changes in a wider spectrum of patients than would be justifiable with conventional open biopsy techniques.

Patients and Methods

Six hypothyroid patients were studied by serial percutaneous needle biopsies of vastus lateralis before and during treatment with L-thyroxine for up to 24 months to establish the diagnosis and response to therapy. The evidence for a myopathy ranged from elevation of serum CPK alone to gross wasting and weakness of proximal muscle groups. The main clinical and biochemical features of these patients are shown in table I, together with the

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timing of the muscle biopsies in relation to the duration of treatment. Normal volunteers served as age and sex matched controls.

Using a modified Bergström needle (3 or 5 mm diameter) vastus lateralis was biopsied under local analgesia (5-8 ml of 1% lignocaine) through a 5 mm incision in the skin and deep fascia (Edwards, 1971). Specimens (30-60 mg wet weight) were allowed to relax in air at room temperature for 15 minutes, before snap freezing in isopentane cooled in liquid nitrogen. Cryostat sections were cut with the muscle orientated for cross sections, stained for myosin-ATPase pH 9.4 (Padykula and Herman, 1955; Hayashi and Freiman, 1966), and photographed. From the photographic prints ($\times 250$ magnification) the proportion of type I to type II fibres was determined and the diameters of 200 fibres were measured as the maximum distance across the lesser aspect of the muscle fibre (Brooke and Engel, 1969a, b).

Fig 1 Percentage of type I and type II fibres from individual hypothyroid patients before and during treatment with L-thyroxine together with values for controls of comparable age and sex.

Patient Number	Age (years)	Sex	Clinical Myopathy ¹	TSH ($\mu\text{U/ml}$)	T ₃ Uptake % normal (95-119)	T ₄ (nmol/l) (60-180)	CPK (IU/l) (5-80)	Muscle Biopsy (duration after treatment)	Muscle Fibre Percentage	
									Type I	Type II
1	62	M	+	160	145	5	847	Before treatment	77	23
								7 months	77.5	22.5
								15 months	67	33
								24 months	72	28
2	64	M	+	155.7	130	3	1045	Before treatment	74.5	25.5
								4 months	69	31
3	60	F	-	18.5	118	17	144	Before treatment	62	38
								9 months	65.5	34.5
4	50	F	-	47.7	116	47	108	Before treatment	61	39
								7 months	58.5	41.5
5	63	F	+	50	112	57	523	Before treatment	63	37
								7 months	54	46
6	39	F	-	20.7	97	56	60	Before treatment	Unsatisfactory for measurement	Unsatisfactory for measurement
								5 months	58.5	41.5

Table I Clinical, biochemical, and histochemical data in patients with hypothyroid myopathy

¹All the patients showed the clinical features of hypothyroidism.

+ Proximal muscle weakness

- Normal muscle strength

TSH = thyroid stimulating hormone; T₃ uptake = tri-iodothyronine resin uptake test; T₄ = serum thyroxine; CPK = creatine phosphokinase

Results

The percentages of type I and type II fibres before and during treatment are shown in fig 1 together with the values for controls. Statistical analysis of fibre type frequency using the Mann-Whitney U test showed a significantly lower percentage of type II fibres in the untreated hypothyroid group ($P < 0.02$). The extent of these changes was directly related to the degree of hypothyroidism, as judged clinically and biochemically, and to the serum level

of CPK (table I). After treatment with L-thyroxine for periods from four to 24 months fibre type ratios tended towards normal (fig 1) although a significantly lower percentage of type II fibres persisted ($P < 0.02$).

The diameters of type I and type II fibres from the hypothyroid patients and controls are shown in figure 2. Patients 3, 4, and 5 show an increase in the proportion of smaller type II fibres before treatment. Significant type II fibre atrophy ($P < 0.01$) was confirmed in hypothyroid females (patients 3, 4

Patient Number	Type I Median Diameters (μ)			Type II Median Diameters (μ)		
	Male Hypothyroid Patients		Male Controls	Male Hypothyroid Patients		Male Controls
	A	B		A	B	
1	54.6	69.7	46.5 55.1 69.1 53.5 67.6	60.8	60.0	58 53.8 61.9 62.9 67.6
2	68.6	57.8	53.6 60.0	53	56.5	57.6 71.8
	Female Hypothyroid Patients		Female Controls	Female Hypothyroid Patients		Female Controls
	A	B		A	B	
3	56.8	65.0	50.3	29.3	46.7	52
4	42.7	51.7	51.7	34.7	42.1	46.4
5	60.1	53.1	50.6	32.2	53.6	59.5
6	Unsatisfactory for measurement	44.9	58.6 56.4	Unsatisfactory for measurement	45	54.7 53.1

Table II Median diameters of type I and type II fibres in hypothyroid male and female patients before and during treatment with L-thyroxine, together with control values

A = before treatment; B = during treatment with L-thyroxine

Fig 2 Distribution of fibre diameter for type I and type II fibres before and during treatment with L-thyroxine in hypothyroid patients. $\bar{x}$ = Mean and extreme range of control values.

and 5) using the Mann-Whitney U test applied to median fibre diameters (table II), but no significant differences from normal were demonstrated after treatment or in male type II fibres or type I fibres from either sex before or after treatment.

Discussion

Increased serum CPK levels, electromyographic changes, light and electron microscopic study indicate that hypothyroidism is associated principally with a myopathic rather than a neuropathic muscle weakness (Ramsay, 1974), but it is possible that the elevation of serum CPK is not entirely due to skeletal muscle damage since cardiac muscle is also affected (Griffiths, 1965). Light microscopic studies of muscle from hypothyroid patients have generally shown areas of focal necrosis, some variability in the size of muscle fibres, and evidence of regeneration, but serial quantitative studies to determine the effect of treatment have not previously been described.

The observed alteration in the ratio of type I to type II fibres could be explained by a selective atrophy and loss of type II fibres, increase of type I fibres, conversion of type II fibres to type I fibres or any combination of these three factors. Significant type II atrophy (smaller fibre diameter) was found only in the less severely hypothyroid patients (patients 3, 4, and 5) whereas type II fibre loss (fewer fibres) while present in all patients, was most marked in those severely myopathic (patients 1 and 2). This suggests progression from selective atrophy to loss of type II fibres with increasing severity of hypothyroidism and myopathy. It is known that type II fibres predominate in normal proximal muscle (Johnson, Polgar, Weightman, and Appleton, 1973); the observation of type II fibre loss proportional to the severity of hypothyroidism might therefore explain the characteristic pattern of proximal weakness in hypothyroid myopathy.

Selective atrophy of type II fibres is a common abnormality previously reported in collagen vascular disease (Engel, 1965), severe rheumatoid disease (Dubowitz and Brooke, 1973), Cushing's syndrome (Pleasure, Walsh, and Engel, 1970), Parkinson's disease (Edström, 1970a, b), and in association with pyramidal tract lesions (Brooke and Engel, 1969a, b; Edström, 1970a). It has been suggested that type II atrophy simply represents disuse of the muscle (Dubowitz and Brooke, 1973). However, prolonged immobilization of injured knee joints leads to a selective atrophy of type I fibres in quadriceps (Edström, 1970b). It is unlikely, therefore, that disuse atrophy is a satisfactory explanation of the type II fibre atrophy and loss found in hypo-

thyroid patients. Other possible aetiological mechanisms have been considered to explain the muscle involvement in hypothyroidism: mucopolysaccharide deposition in muscle (Nickel *et al*, 1961; Aström, Kugelberg, and Müller, 1961), myofibre damage induced by hypothermia (Lambert, Underdahl, Beckett, and Mederos, 1951) and autoimmune myositis (Fessel and Raas, 1968). No evidence for these processes was found in this material and an explanation of the selective fibre type atrophy and loss should be sought in the metabolic defect.

Histochemical methods show that type II muscle fibres are richer in myophosphorylase than type I which conversely are richer in oxidative enzymes associated with mitochondrial respiration (Dubowitz and Pearce, 1960). Type II fibres are thought, therefore, to derive their supply of adenosine triphosphate from glycogenolysis, glycolysis, and oxidative respiration, whereas type I fibres depend more heavily on mitochondrial respiration. Thyroxine is known to facilitate the stimulation of adenylcyclase by adrenaline leading to activation of phosphorylase and glycogen breakdown. Lack of thyroxine may thus lead to impairment of glycogen utilization in muscle, resulting in muscle fibre damage with a selective atrophy and loss of type II fibres, which owing to their greater dependence on glycogenolysis, and glycolysis for energy supplies, would be most affected.

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