ALCOHOLIC MYOPATHY

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INTRODUCTION
Alcohol has been an integral part of man's social history since antiquity. After the art of distillation was rediscovered in the Middle Ages, alchemists found, in ethanol, a cure for every illness, a tradition that still continues in this age with the Gaelic name for whisky (uísquebaigh, meaning ‘water of life’). In more recent times researchers have wondered why the enzyme alcohol dehydrogenase, which converts ethanol to its major metabolite, acetaldehyde, exists in the body if alcohol has no physiological role.

Though ‘alcohol’ is a generic name, in practice it usually means ‘ethyl alcohol’ or ‘ethanol’ (C₂H₅OH). Other aliphatic alcohols include methyl alcohol (methanol) and isopropyl alcohol, both of which are used as industrial solvents, are occasionally implicated in accidental human poisoning and have no reported direct effect on skeletal muscles. Skeletal muscle rigidity secondary to basal ganglia injury that is partially levodopa-responsive is, however, known to occur following methanol poisoning.¹

CLINICAL FEATURES OF ALCOHOLIC MYOPATHY
There are two distinct types of alcoholic myopathy: an acute, painful condition with swelling of affected muscles both in the arms and the legs and a chronic, painless myopathy affecting the proximal limb girdle muscles with wasting.² ³

Both forms of alcoholic myopathy are due to the direct toxic effects of ethanol and its principal metabolite, acetaldehyde, on skeletal muscles. Indeed, ethanol is the most commonly encountered neurotoxin and is incriminated as the commonest cause of acute myoglobinuria in medical practice.⁴

Acute alcoholic myopathy
Attacks of acute alcoholic myopathy usually occur after binge drinking² and a previous period of fasting or caloric deprivation is considered to be a predisposing factor. This acute form develops over hours to days and affected patients are typically men. Proximal muscles are most severely involved but the distribution of weakness may be asymmetrical or multifocal; muscle enzymes, including serum creatine kinase (CK), are invariably raised. Most patients will also have myoglobinuria or other evidence of acute rhabdomyolysis, hence this form of myopathy is also known as ‘alcoholic rhabdomyolytic myopathy’ (ARM). This acute disorder is always painful; the patient experiences conspicuous muscle cramps and there is tenderness and swelling of the affected muscles. The clinical picture may be confused with venous thrombophlebitis when muscle involvement is asymmetric⁵ and, rarely, dysphagia can also occur. ARM may be associated with signs of acute liver injury (acute alcoholic hepatitis) and congestive cardiac failure. Electromyography (EMG) shows profuse fibrillations and myopathic changes similar to acute polymyositis. Attacks of ARM may recur on a number of occasions following alcoholic binges.

Following its original description by Hed et al. in 1962,¹ acute alcoholic myopathy is now known to present with variable severity, ranging from transient asymptomatic rises in serum CK and myoglobin levels to a more fulminant rhabdomyolysis, myoglobinuria and renal failure.⁶ ⁷ It has been recently suggested that magnetic resonance (MR) imaging of thigh and leg muscles may be useful in the evaluation of alcoholic myopathy, mainly in predicting the onset of rhabdomyolysis.⁴ Alcoholic patients with a recent history of rhabdomyolysis have been shown, by ³¹P nuclear spectroscopic MR, to have evidence of a metabolic myopathy during aerobic exercise, with a greater utilisation of muscle phosphocreatinine and reduced adenosine triphosphate (ATP) turnover.⁹

Acute alcohol intoxication can also lead to secondary skeletal muscle injury as a result of focal trauma (crush injury), seizures (from rhabdomyolysis), delirium tremens and electrolyte or metabolic dysfunction. Another type of secondary acute alcoholic myopathy is an ischaemic myopathy which develops as a result of focal compression of buttock, leg or shoulder muscles. This occurs in an inebriated alcoholic lying for a prolonged period on the affected muscles, immobile and insensate. Rarely, acute painless myopathy has also been seen after alcohol intake where the cause of myopathy was hypokalemia provoked by alcohol;¹⁰ ¹¹ Severe degrees of hypokalemia (<2 mmol/L) may also develop in an alcoholic due to vomiting and/or diarrhoea in the course of a prolonged drinking bout, giving rise to an acute, painless proximal myopathy. Hypomagnesemia precipitating subacute myopathy and hypocalcaemia in alcoholic patients is also reported.¹²

Chronic alcoholic myopathy
Ekblom et al., in 1964, first drew attention to the syndrome of painless progressive wasting of pelvic and shoulder girdle muscles in chronic alcoholic myopathy.¹³ It is a more common disorder than the acute form of alcoholic myopathy, and is an under-recognised complication of ethanol abuse which evolves over weeks to months.¹ Clinically, symptomatic chronic alcoholic myopathy usually presents with proximal limb girdle weakness, wasting, normal or minimally raised muscle enzymes and EMG evidence of a chronic muscle disease. Patients also usually have other stigmata of chronic alcoholism, i.e. polyneuropathy, cardiomyopathy or liver cirrhosis. The myopathy of a chronic alcoholic is typically painless, though some patients may complain of muscle

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cramps. In some cases, an elevation of serum aldolase may be a more sensitive marker than serum CK. In one study of 100 male alcoholic patients, 44 had alcoholic myopathy and 24 (55%) of these patients had clinical symptoms of myopathy. 15 (35%) had proximal muscle atrophy, 27 (60%) had increased serum muscle enzymes and 37 (80%) had significantly decreased muscle strength by myometric measurement. Most patients with chronic alcoholicism show evidence of a skeletal myopathy often associated with a similar disease affecting heart muscle as well (alcoholic cardiomyopathy). 14,15 A polyneuropathy coexists in many patients which is responsible for any distal, less. 18 There is also a greater risk of chronic alcoholic skeletal and cardiomyopathy. 7,18,19 Ethanol is toxic to striated muscle and may play a synergistic role. The presence of B-complex deficiencies is responsible for any distal, less. 18 The biochemical pathways of chronic alcohol-induced muscle damage are equally unclear, despite data to show that malnourishment, 23 hypokalemia 34 or hypophosphatemia 35 are primary events in its pathogenesis.

PATHOGENESIS OF ALCOHOLIC MYOPATHY
Experimental and animal models
Skeletal muscle has been shown to be damaged by alcohol administration to well-nourished volunteers. 24 Experimental alcoholic myopathy can be induced in rats by a combination of prolonged alcohol intake (mean 15.3 g ethanol/kg/day for up to ten weeks) and a short fast, 25 the predominant histological finding being type IIB fibre atrophy. Biochemically the activity of glycolytic enzymes was depressed and mean mitochondrial respiratory rates were lower. 29 In another acute study, rats were given single boluses of ethanol and rates of protein synthesis were examined 2.5 hours later. 26 The results suggested defective synthesis of skeletal muscle protein. In another experimental model in rats, 27 ethanol caused acute elevation in serum CK of muscle origin. In vitro studies on isolated actomyosin preparations obtained from skeletal muscles of alcohol-fed baboons and volunteers have shown reduced ATPase activity, reduced sarcolemmal calcium uptake and diminished contractility of actomyosin. 28

Mechanism of muscle injury by ethanol
The precise mechanism of acute muscle injury caused by alcohol intoxication is unknown but present evidence favours a direct toxic effect of alcohol on muscle cells. It is possible that ethanol dissolves into the plasma membrane of skeletal muscle cells, 29 altering their sarcolemmal transport mechanism, transmembrane ion fluxes, 10,12 receptor-effector coupling, 13 calcium sequestration and actin-myosin interaction. 28 The biochemical pathways of chronic alcohol-induced muscle damage are equally unclear, despite data to show that malnourishment, 23 hypokalemia 34 or hypophosphatemia 35 are primary events in its pathogenesis. Long-term exposure to ethanol produces lasting changes in cellular membranes, 32,33 leading to alterations in sarcolemmal fluidity, configuration and membrane pump (Na+/K+-ATPase) activity. 3 A number of other mechanisms for muscle cell injury due to ethanol have been proposed, including alteration of sarcolemmal permeability leading to disturbances of sodium-potassium transport and reduced uptake of intracellular calcium by the sarcoplasmic reticulum, 2 carbonic anhydrase, 24 glycogen depletion, 27 accumulation of lipids within the muscle, 15,19 oxidation induced by free radicals, 40 sustained decrease in muscle MnA content, 41 reduced fractional rate of skeletal muscle protein synthesis 36 and intramuscular neuropathy 45 as a part of chronic alcoholic polyneuropathy.

Acetaldehyde, the product of alcohol dehydrogenase activity, reacts with many cellular proteins to form acetyldehyde-protein derivatives (adducts) that are themselves cytotoxic and which may also provoke immune response. 44 Despite having relatively high circulating cortisol concentrations, myopathy in chronic alcoholics is not thought to be due to hypercortisolemia (pseudo-Cushing’s syndrome). 45 Though data from animal experiments suggest that acute rhabdomyolysis may arise from a superimposed
mitochondrial failure, mitochon
drial studies in human alcoholics indicate that chronic myopathy is not associated with a deficiency of mitochondrial energy supply.

The precise mechanism that transforms a reversible type of muscle injury caused by alcohol into an irreversible, permanent muscle damage caused by alcohol has never been understood. Changes in the sarcoplasmic membrane and intracellular calcium transport both in the skeletal and cardiac muscles may act as the primary events for developing chronic atrophic myopathy. It has been shown experimentally that, following long-term exposure to alcohol, cells adapt by increasing the concentration and activity of voltage-dependent calcium channels. The calcium channel-blocker verapamil prevented the development of ethanol-induced muscle abnormalities in an experimental model of alcoholic cardiomyopathy. The cellular signal transduction system responsible for regulating intracellular second messenger system (cyclic adenosine monophosphate or cAMP) is another major target of ethanol, both in the short and long term. In the short term, ethanol increases the production of receptor-dependent cAMP, but long-term exposure reduces its level. This is called heterologous desensitisation of cAMP production and has been confirmed by measuring lymphocytic cAMP concentrations in chronic alcoholics. Heterologous desensitisation induces changes in the secondary messenger system function and could be expected to lead to inappropriate cell signalling in response to various circulating hormones and chemical messengers.

**MUSCLE PATHOLOGY IN ALCOHOLIC MYOPATHY**

**Aute alcoholic myopathy**

Muscle biopsy usually shows polyfocal areas of sterile necrosis with selective vulnerability of type I muscle fibres (defined by their low myosin adenosine triphosphatase activity). (Figure 1.) Mild mononuclear infiltration may be present and there may be areas of regenerating muscle fibres.

**Chronic alcoholic myopathy**

Selective type II fibre atrophy (defined by their high myosin adenosine triphosphatase activity) is characteristic of chronic alcoholic myopathy. This is, however, non-specific since type II fibre atrophy has been associated with a variety of unrelated muscle diseases such as inactivity, caloric malnutrition, systemic diseases, cirrhosis, steroid therapy, denervation and metabolic myopathies (e.g. hypothyroidism and osteomalacia). Approximately 30–50% of patients with chronic alcoholic myopathy have a reduction of type II fibre size, often selective for fibre type IIB, whereas type I fibres are relatively unaffected. The selective injury to type IIB muscle fibres may be reversible. Table 1 shows the current histological criteria used to classify alcoholic myopathy in the absence of other causes. (Figure 2.)

**TABLE 1**

<table>
<thead>
<tr>
<th>Mild myopathy:</th>
<th>Scattered myocytolysis or at least four of the following criteria:</th>
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<tbody>
<tr>
<td></td>
<td>Fibre atrophy</td>
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<td></td>
<td>Inflammation</td>
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<tr>
<td></td>
<td>Fibre regeneration</td>
</tr>
<tr>
<td></td>
<td>Fibre size variability</td>
</tr>
<tr>
<td></td>
<td>Internal nuclei&gt; 10% of fibres</td>
</tr>
<tr>
<td></td>
<td>Moth eaten fibres&gt; 10% of fibres</td>
</tr>
<tr>
<td></td>
<td>Subsarcolemmal deposition of 10% of fibres</td>
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<tr>
<td></td>
<td>Type I fibre predominance</td>
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<tr>
<td></td>
<td>Fat deposition in endomysia</td>
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<td></td>
<td>Tubular aggregates</td>
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| Moderate myopathy: | Scattered myocytolysis and at least three of the previous criteria. |
| Severe myopathy: | Myocytolyis in up to 5% of fibres. |
include dilatation of the sarcoplasmic reticulum, enlarged and distorted mitochondria and increased fat. In a study of 48 human muscle biopsies from patients with alcoholic myopathy, increased glycogen and reduced pyruvate kinase activity were noted before the first histological signs of myopathy appeared; when histological evidence of myopathy was present, glycogen levels fell. A Additional abnormalities occasionally found in the muscle biopsy are the presence of tubular aggregates and evidence of hypokalemic vacuolar myopathy. Histological changes of neurogenic features (fibre type grouping) may be present in biopsies from proximal muscles (quadriceps muscle) indicating denervation due to possible intramuscular neuropathy contributing to muscle atrophy and weakness.

Correlation between clinical and pathological evidence of myopathy There is no consistent correlation between clinical symptoms, nutritional status and histological evidence of myopathy in chronic alcoholics. Type II fibre atrophy is frequently seen in the skeletal muscle biopsies of chronic alcoholics without any evidence of symptomatic myopathy. In their study of 151 inpatients with a history of chronic heavy alcohol intake (>100 g per day for at least three years) and not selected for muscle symptoms, Martin et al. found no clear relationship between muscular skeletal symptoms and muscle biopsy histology. Twenty three patients had raised serum CK, 92 (60%) patients had histological evidence of chronic myopathy with type II fibre atrophy and five patients (7%) had evidence of acute myopathy. In a recent study of muscle biopsy in 100 chronic alcoholics, type II fibre atrophy was found in only one-third of patients (selective for type II B in 23 cases) even though 61 of these 100 patients had evidence of skeletal myopathy, 26 cases had alcoholic cardiomyopathy, 23 patients were found to have peripheral neuropathy and 12 had cirrhosis. Thus the presence of type II fibre atrophy in the skeletal muscle histology of chronic alcoholics appeared to be entirely non-specific, although patients who had both symptomatic myopathy and type II fibre atrophy in muscle biopsies had a significantly higher total lifetime dose of ethanol (31.7±17 kg/kg body weight), showed a higher incidence of peripheral neuropathy and had evidence of significantly lower anthropometric parameters of caloric nutrition (% of ideal weight, perimeter of non-dominant arm and lean body mass).

INVESTIGATIONS FOR ALCOHOLIC MYOPATHY

There is a good enough correlation between clinical symptoms, the presence of atrophic limb girdle myopathy and decreased muscle strength to allow a clinical diagnosis of chronic alcoholic myopathy to be made in most patients with an appropriate history of alcohol consumption and without a family history of muscle disease. Since peripheral neuropathy, cardiomyopathy and liver cirrhosis commonly co-exist in patients with chronic alcoholic myopathy, patients should be screened for evidence of other alcohol-induced organ-specific injuries. Based on current evidence, we do not recommend muscle biopsy as a diagnostic tool in the evaluation of alcoholic myopathy unless metabolic or inflammatory myopathy is a differential diagnosis (Table 2). The recommended investigations for suspected alcoholic myopathy are given in Table 3.

ALCOHOL AND FATIGUE

In small doses, alcohol lessens the appreciation of fatigue and increases the ability for muscular work, probably because it acts as a CNS stimulant. At larger doses, alcohol causes CNS depression and diminishes the amount of muscular work that may be accomplished.

In acute alcohol intoxications, the severity of central nervous system (CNS) symptoms is typically greater when the blood alcohol concentration is rising rather than falling (Mellanby effect) and is presumably caused by alterations in specific neurotransmitters and neuronal function. Alcoholic blackouts typically tend to occur during short-term consumption of large amounts of alcohol in otherwise healthy individuals. It has been proposed that alcoholic blackouts result from a disorder of central serotonergic...
neurotransmission, since plasma levels of the serotonin precursor, tryptophan, are decreased in patients with a history of blackouts due to ethanol intoxication, and a trial of the serotonin reuptake inhibitor zimelidine has shown improvement in memory function in moderately intoxicated subjects. Most patients with well-defined chronic fatigue syndrome (CFS) are unable to tolerate even the smallest amount of alcohol, and experience blackouts and conspicuous deterioration of their fatigue symptoms. Alcohol intolerance is so characteristic of CFS that most patients are forced to stop drinking socially. Alcohol intolerance in CFS patients is probably a marker of a serotonin supersensitivity that has been well documented in neuroendocrine tests (e.g. buspirone-stimulated prolactin release). In a comparative study of dynamic muscle function tests and histomorphometry, basal lactate levels were found to be higher in patients with chronic alcohol abuse in comparison to the CFS patients. Muscle biopsy in CFS patients usually do not show type II fibre atrophy.

**TREATMENT OF ALCOHOLIC MYOPATHY**

There is no specific treatment for alcohol-induced muscle disease. As a general rule, abstinence from alcohol is associated with gradual improvement of myopathy in most, but not all, patients with chronic alcoholic myopathy whereas continued ethanol abuse will result in clinical deterioration; supplementation of protein, B-complex vitamins (especially folate) and minerals is advisable. The outcome is more favourable in acute alcoholic myopathy although full recovery may take several months.

**Early treatment should be instituted for acute renal failure complicating ARM. Specific treatment will be required in patients for any associated cardiomyopathy, cirrhosis or chronic pancreatitis. Changing the drinking habit and lifestyle are priorities that need to be strongly emphasised and patients should be referred to the local alcohol rehabilitation unit for counselling.**

**CONCLUSION**

Alcoholic myopathy is probably more under-recognised than uncommon in clinical practice, and most patients with chronic alcoholic myopathy will also have evidence of associated peripheral neuropathy and cardiomyopathy. The definitive mechanism of alcoholic myopathy is unknown, however it is clear that altered cellular permeability and intracellular signalling may lead to a number of changes within the muscle cells in the presence of alcohol that could effectively reduce the substrates for cellular energy and suppress muscle protein synthesis. Alcohol abstinence is the only proven way to recover from muscle weakness though, in some cases, abstinence may only prevent further progression of alcoholic myopathy.

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**TABLE 2**

Differential diagnosis of proximal weakness in an alcoholic.

**Acute/subacute onset:**
- Necrotising polymyopathy with rhabdomyolysis
- Muscle compression (ischaemic myopathy)
- Drug induced myopathy (e.g. ‘statin’ group of drugs)
- Toxic myopathy (e.g. alcohol)
- Malignant hyperthermia
- Muscle infarction
- Crush injury

**Metabolic myopathy:**
- Hypokalaemia
- Hypophosphataemia
- Hereditary disorders of muscle glycolysis (e.g. McArdle's disease)

**Paroxysmal myoglobinuria (Meyer-Betz and related diseases)**

**Acute polymyositis**

**Atypical presentation of Guillain-Barré syndrome**

**Eosinophilia-myalgia syndrome**

**Chronic:**

**Metabolic (hypocalcaemia, hypophosphataemia)**

**Endocrine (hypothyroid)**

**Drug/toxin induced**

**Malignant syndromes (e.g. Lambert-Eaton)**

**Peripheral neuropathy (e.g. diabetes, CIDP)**

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**TABLE 3**

Investigations for suspected alcoholic myopathy.

<table>
<thead>
<tr>
<th>All cases</th>
<th>Acute cases</th>
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<tbody>
<tr>
<td>Full blood count and MCV</td>
<td>As above, plus:</td>
</tr>
<tr>
<td>ESR and CRP</td>
<td>Serum myoglobin</td>
</tr>
<tr>
<td>U &amp; Es, glucose</td>
<td>Plasma bicarbonate and H⁺</td>
</tr>
<tr>
<td>Serum CK, aldolase, LDH</td>
<td>Blood gases</td>
</tr>
<tr>
<td>Liver function tests (total protein, albumin, ALT, AST, gGT)</td>
<td>Periodic serum U &amp; Es, creatinine</td>
</tr>
<tr>
<td>Calcium profile (Ca, P, alkaline phosphatase)</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>Thyroid function test (TSH)</td>
<td>Urine Na⁺</td>
</tr>
<tr>
<td>Urine for myoglobin</td>
<td>Monitor: blood pressure, heart rate, temperature and 24-hour urine output</td>
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<tr>
<td>Stool for occult blood</td>
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<tr>
<td>ECG</td>
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<tr>
<td>Chest X-ray</td>
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<tr>
<td>EMG &amp; nerve conduction studies</td>
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</table>

**Optional:**

- Serum folate, Vitamins B₁ and B₁₂
- Serum ferritin
- Serum magnesium and 1,25 Vit D
- Echocardiography
- Abdominal ultrasound
- CT scan of head
- Muscle biopsy
- Psychiatric assessment
ACKNOWLEDGEMENTS

We are indebted to Dr M astaglia for providing us with the photomicrographs of the muscle histology. Dr Chaudhuri is supported by the Wellcome Trust at the University of Glasgow.

REFERENCES


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- Royal College of Paediatrics & Child Health
  RCPE Joint Symposium
  Disease Surveillance for the 21st Century
  5 November 1999

- Dundee Symposium
  17 November 1999

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  24 November 1999

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  Spring 2000

- Geriatric Medicine
  5 May 2000

- RCPE / Royal Pharmaceutical Society of Great Britain Joint Symposium
  Appropriate Antibiotic Prescribing
  16 June 2000

- RCPE / Royal College of Paediatrics & Child Health Joint Symposium
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  28 September 2000

- Respiratory Medicine
  1 November 2000

- 40th St. Andrew’s Day Festival Symposium
  Cardiology
  30 November – 1 December 2000