Magnesium (Mg) and ATP Abnormalities Correlate with Weakness in Chronic Alcoholic Myopathy

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INTRODUCTION: Chronic alcoholic myopathy has been estimated to affect between 40% to 60% of chronic alcohol dependent individuals and is associated with decreased muscle strength, fatigue, and pain. Alcoholic myopathy can be determined by biopsy to identify atrophy of type II fibers[1], and more recently, by non-invasive P-31 MRS to detect low levels of ATP and PCr and decreased PCr/Pi ratios during exercise and recovery [2]. Chronic alcohol consumption is also associated with magnesium (Mg) depletion. Mg is an essential cation required for all enzymatic reactions involving ATP, particularly the Krebs cycle which provides ATP necessary for muscle contraction [3]. Mg deficiency is known to produces neuromuscular symptoms of weakness, fatigue and abnormal EMG. Intracellular Mg levels are difficult to determine using the clinical measurement of serum Mg. In this investigation, P-31 MRS is utilized to detect deficits in levels of free and ATP-bound magnesium (MgATP) in the muscles of chronic alcoholics patients.

METHODS: P-31 MRS spectra of the quadriceps muscles were acquired from 10 chronic alcohol dependent patients and 12 normal subjects. ATP levels were quantitatively determined during rest, 2 levels of graded exercise, and recovery, as previously described [4]. Concentrations of free Mg^{2+} and MgATP complex were determined from spectroscopic data by calculating the chemical shifts of the β-phosphate peak of ATP [5]. Patients were divided into two subgroups based on their ATP concentrations at 25% MVC exercise. Alcoholic subjects with ATP levels 2 or more standard deviations below mean values for normal subjects were classified as myopathic alcoholics. Patients whose ATP levels fell within 2 standard deviations of controls made up the amyopathic group.

RESULTS: **Alcohol dependent patients** had levels of total Mg, β-ATP, and MgATP that were 20% lower than control values at rest ($P < 0.03$). At 50% MVC exercise and during the recovery period, these deficits increased to approximately 25% ($P < 0.008$ and < 0.03, respectively) (Table 1). During 50% MVC exercise or recovery, free Mg^{2+} levels were 30% lower in alcoholic patients ($P < 0.02$) and percent free ATP was approximately 23% higher ($P < 0.03$). **Myopathic alcoholics** had decreased levels of total Mg, β-ATP, and MgATP that were approximately 30% lower than controls at rest ($P < 0.0007$). During the stress of exercise at 50% MVC, these deficits increased to 37% below control values ($P < 0.0002$) and during the recovery period remained 38% below normal ($P < 0.001$). During exercise at 50% MVC or recovery, free Mg^{2+} was 34% lower in myopathic patients ($P < 0.05$) and percent free ATP was 28% higher ($P < 0.04$). **Amyopathic alcoholics** showed slightly lower levels of total Mg, β-ATP, and MgATP compared to control subjects, but these differences were not statistically significant at any stage of the protocol. Free Mg^{2+} values were decreased but only differed significantly at 50% MVC exercise ($P < 0.03$). **Comparison of the 2 alcoholic groups** demonstrated that total Mg, β-ATP, and MgATP levels were 30-35% lower in the myopathic group of alcoholics as compared to the amyopathic subjects throughout the protocol ($0.004 < P < 0.03$). Free Mg^{2+} levels were lower in myopathic patients and percent free ATP was higher, but the differences lacked statistical significance.

DISCUSSION: For myopathic patients, abnormally low concentrations of ATP, enzymatically-active MgATP, and free Mg^{2+} conceivably contributed to muscle weakness and fatigue, particularly during heavy exercise. Since MgATP is in equilibrium with intracellular free Mg^{2+}, it has been proposed that low ATP levels could result from decreased free Mg^{2+}. Low levels of free Mg^{2+} also affect the equilibrium constant of creatine phosphokinase [6]. This results in increased levels of ADP, which in turn down regulate mitochondrial ATP production. Adequate levels of free Mg^{2+} are also necessary for regulating ATP-dependent ion channels for K^+, Na^+, and Ca^{2+} transport [7]. Insufficient levels of cytosolic Mg^{2+} could lead to "channelopathy," in which faulty ion channels allow mitochondria to become overridden with inflowing Ca^{2+}, thus impairing energy production [8]. Myopathic patients had greater levels of percent free ATP than controls throughout the protocol. During exercise and recovery, relative increases in this inactive fraction of ATP correlated negatively with decreases in free Mg^{2+}. Thus, deficits in Mg and increases in free ATP represent compounding factors in muscle dysfunction. For amyopathic patients, their metabolic parameters, with minor exceptions, resembled those of control subjects. As a broader observation, decreased Mg levels may also impact other complications associated with chronic alcoholism such as cardiovascular disease, hypertension, cirrhosis, and pancreatitis.

In summary, low levels of free Mg^{2+} and MgATP correlate with the weakness and fatigue in myopathic alcoholic patients. MRS data suggest a significant role of Mg in the pathophysiology of alcoholic myopathy.

Table 1. Abnormalities in Mg and ATP concentrations at 50% MVC exercise (mmol/kg ± SE).

Subjects	Mg (free)	Mg (total)	% Mg free	β-ATP	MgATP	% ATP free
Controls (n=12)	0.81 ± 0.08	5.68 ± 0.28	14.2 ± 1.2	5.22 ± 0.25	4.87 ± 0.24	6.8 ± 0.7
Patients (n=10)	0.56 ± 0.03	4.23 ± 0.32	13.7 ± 1.0	4.02 ± 0.33	3.67 ± 0.31	8.9 ± 0.6
Myopathics (n=6)	0.54 ± 0.06	3.59 ± 0.21	15.1 ± 1.2	3.36 ± 0.18	3.05 ± 0.18	9.3 ± 0.9
Amyopathics (n=4)	0.59 ± 0.02	5.19 ± 0.40	11.7 ± 1.0	5.01 ± 0.44	4.59 ± 0.40	8.2 ± 0.3
P-values						
Controls vs. Patients	0.02	0.003	NS	0.008	0.006	0.03
Controls vs. Myopathics	0.05	0.0002	NS	0.0002	0.0002	0.04
Controls vs. Amyopathics	0.03	NS	NS	NS	NS	NS
Myopathics vs. Amyopathics	NS	0.005	NS	0.004	0.004	NS

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