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Serum Levels of Carnitine in Chronic Fatigue Syndrome: Clinical Correlates

Key Words
Carnitine
Chronic fatigue syndrome
Fatigue

Abstract
Carnitine is essential for mitochondrial energy production. Disturbance in mitochondrial function may contribute to or cause the fatigue seen in chronic fatigue syndrome (CFS) patients. One previous investigation has reported decreased acylcarnitine levels in 38 CFS patients. We investigated 35 CFS patients (27 females and 8 males); our results indicate that CFS patients have statistically significantly lower serum total carnitine, free carnitine and acylcarnitine levels, not only lower acylcarnitine levels as previously reported. We also found a statistically significant correlation between serum levels of total and free carnitine and clinical symptomatology. Higher serum carnitine levels correlated with better functional capacity. These findings may be indicative of mitochondrial dysfunction, which may contribute to or cause symptoms of fatigue in CFS patients.

Introduction

Profound muscle fatigue, precipitated by minimal physical activity, is one of the major symptoms in chronic fatigue syndrome (CFS) patients [1]. In CFS there have been reports of excessive intramuscular acidification [2] and abnormal jitter in CFS with single-fiber electromyography [3] suggestive of abnormal muscle membrane function. However, other investigators have not found abnormalities in muscle fatigability and excitation-contraction coupling [1, 4].

In vitro tests have shown depressed muscle mitochondrial respiration in CFS, and patients have demonstrated reduced aerobic work capacity [5]. Mitochondrial palmitate oxidation has been reported to be reduced in CFS patients [6]. Intracellular concentration of adenosine triphosphate has been demonstrated to be reduced at peak exercise in CFS patients [7]. These results suggest a mitochondrial abnormality.

Recent investigations in Great Britain have shown that 70% of CFS patients have ultrastructurally abnormal muscle mitochondria [8–11]. These mitochondria have abnormal sizes, shapes and a peculiar infolding of the inner mitochondrial membrane, producing 'compartmentalization' of their internal structure. These structural abnormalities may be associated with deficits in mitochondrial energy production that may lead to fatigue.

Carnitine is essential in mitochondrial energy metabolism. It has two principal functions: (1) to transport long-chain fatty acids into the mitochondrion for β-oxidation; (2) to help regulate the intramitochondrial ratio of acetyl-coenzyme A to free acetyl-coenzym A [12]. Carnitine deficiency conditions may be primary, such as those associated with inborn errors of metabolism, or secondary, such as those associated with inadequate intake or those that are induced by medicines. Clinical symptoms of carnitine deficiency may include myopathy, cardiomyopathy and encephalopathy. In a study of 38 CFS patients, serum lev-

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els of acylcarnitine were found to be statistically decreased when compared to controls [13]. Free carnitine and total carnitine levels were found not to differ statistically from controls. Also, clinical correlations were noted between increases in acylcarnitine levels and improvement in fatigue symptoms [13].

The objective of our study was to determine whether indeed CFS patients have decreased serum carnitine levels and to investigate possible clinical correlates of these biochemical findings. Preliminary results of this investigation have been previously presented [14].

Materials and Methods

35 patients (27 females and 8 males; age range 16–67 years, median 40 years) were evaluated for CFS. They all underwent detailed reviews of their medical history and a thorough general physical and neurologic examination. All had routine blood tests performed, including complete blood count, chemistry screen (including glucose, electrolytes, calcium, magnesium, liver function tests and renal function tests), sedimentation rate, rheumatoid factor, ANA, T_3, T_4, TSH, CPK, HIV, hepatitis screen, RPR, B_{12}, red blood cell folate and serum carnitine determinations. All patients had a urinalysis performed. All patients underwent chest X-rays and intradermal intermediate-strength PPD testing. When clinically indicated, selected patients had Lyme disease screen, head MRI scanning or polysomnography. All patients underwent detailed clinical evaluations including the Fatigue Severity Scale (FSS) [15], the Beck Depression Inventory [16], the Symptom Checklist 90-R (SCL–R-90) [17] and the CFS Impairment Index (CFS-II) which consists of physical and mental subsets. The CFS-II is presented in appendix 1 and is a modification of another CFS evaluation scale [18]. In no case was an alternate diagnosis made. All patients met the Centers for Disease Control criteria for the diagnosis of CFS [19].

At the time of phlebotomy, serum samples were immediately frozen and were courier-delivered to the Mayo Clinic laboratories for assays of total carnitine, free carnitine and acylcarnitine levels using radio-labeled enzymatic techniques [20, 21]. Our results were compared to Mayo Clinic laboratory normative data [20, 21] and to previously published results [13]. No patients were taking *L*-carnitine at the time of phlebotomy.

For statistical analysis, the two-tailed t test and Pearson's correlation coefficient were used. The data are presented as the mean ± 1 standard deviation of the mean. The carnitine levels are expressed in micromoles per liter.

Results

In comparison to normative Mayo Clinic data [20, 21], the total carnitine levels in both females and males ranged in the lower range of the normal, with 3 females and 1 male having levels that were below normal limits (fig. 1, 2). In comparison to the control group of females (n = 45), where the total carnitine level was 51.5 ± 11.6, our CFS female patient result was statistically significantly lower, 41.2 ± 9.5 ($p < 0.001$). Similar results were obtained in males, where the total carnitine level was 59.3 ± 11.9 in the control group (n = 40), and our CFS male patient result was statistically significantly lower, 49.9 ± 9.1 ($p < 0.05$).

In comparison to normative Mayo Clinic data [20, 21], free carnitine levels in both females and males also ranged in the lower normal range with 1 male having a result below normal limits (fig. 1, 2). In comparison to the control group of females (n = 45), where the free carnitine level was 40.1 ± 9.5, our CFS female patient result was statistically significantly lower, 32.1 ± 6.9 ($p < 0.01$). In comparison to the control group of males (n = 40), where the free carnitine level was 46.8 ± 10.0, our CFS male patient result was statistically significantly lower, 40.6 ± 8.9 ($p < 0.05$).

Figures 1, 2 also display our CFS patient results for acylcarnitine. The Mayo Clinic does not have normative data for acylcarnitine levels that can be used for statistical comparison.

In comparing our results to those previously published by Kuratsune et al. [13], acylcarnitine levels were statistically significantly lower in our CFS patients as compared to controls. Acylcarnitine levels in our CFS patients are plotted in comparison to the results of Kuratsune et al. in figures 3, 4. In comparison to the control group (n = 308), where acylcarnitine levels were 14.5 ± 4.6, our CFS patient results were statistically significantly lower, 9.0 ± 6.3 ($p < 0.00001$). There was no statistically significant difference in acylcarnitine levels between our patients (females or males) and the CFS patients of Kuratsune et al. Our results were 8.9 ± 7.0 for females and 9.3 ± 3.7 for males, in comparison to 8.4 ± 4.4 and 8.7 ± 3.3, respectively, as reported by Kuratsune et al.

In comparing our results to those of Kuratsune et al. [13], free carnitine levels were statistically significantly lower in our CFS patients as compared to controls and to the CFS patient results of Kuratsune et al. (fig. 5, 6). In comparing our CFS patients' free-carnitine results to the controls' results (n = 308) of Kuratsune et al., our result of 34.0 ± 8.1 is statistically significantly lower than the control value of 51.3 ± 12.1 ($p < 0.00001$). In comparing the free carnitine levels of our total CFS patient population (n = 35) to the levels of the corresponding group (n = 38) in the experiment of Kuratsune et al., our result of 34.0 ± 8.1 is statistically significantly lower (results of Kuratsune et al.: 49.8 ± 9.2; $p < 0.00001$). Separating our free carnitine results by sex, the result of our CFS female patients (n = 27), 32.1 ± 6.9, was statistically significantly lower

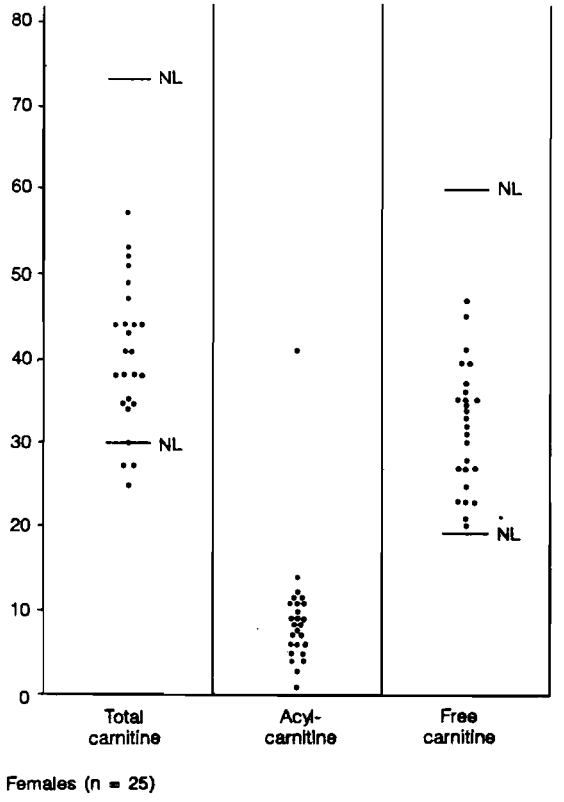


Fig. 1. Serum carnitine levels in our CFS female patients (n = 27). The units are micromoles per liter. The normative values are according to the Mayo Clinic where these assays were performed [20, 21]. Three patients had total carnitine levels that were below normal limits. For both total carnitine and free carnitine, our patient results are in the lower normal range. In comparison to normative Mayo Clinic data (n = 45) where the total carnitine level was 51.5 ± 11.6, our CFS female patient result was statistically significantly lower, 41.2 ± 9.5 ($p < 0.001$). In comparison to the control group of females (n = 45) where the free carnitine level was 40.1 + 9.5, our CFS female patient result was statistically significantly lower, 32.1 ± 6.9 ($p < 0.01$). There is no Mayo Clinic acylcarnitine normative data for statistical comparison. NL = Normal level.

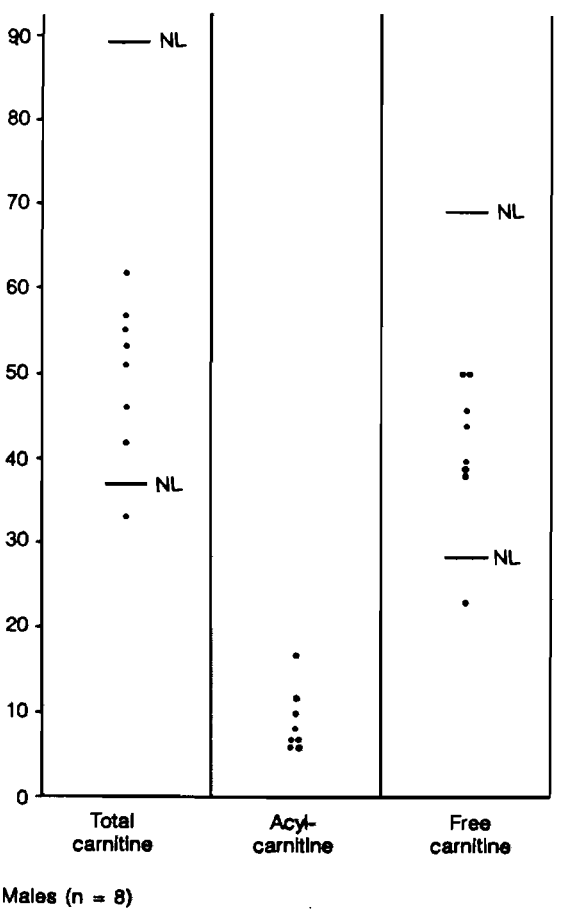


Fig. 2. Serum carnitine levels in our CFS male patients (n = 8). The units are micromoles per liter. The normative values are according to the Mayo Clinic where these assays were performed [20, 21]. One patient had a total carnitine level below normal limits, and another patient had a free carnitine level below normal limits. In comparison to the control group (n = 40) the total carnitine level in our CFS male patients, 59.3 ± 11.9, was statistically significantly lower, 49.9 ± 9.1 ($p < 0.05$). In comparison to the control group of males (n = 40) where the free carnitine level was 46.8 ± 10.0, our CFS male patient result was statistically significantly lower, 40.6 ± 8.9 ($p < 0.05$). There is no Mayo Clinic acylcarnitine normative data for statistical comparison. NL = Normal level.

than that of Kuratsune et al., 46.8 ± 8.2 (n = 19; $p < 0.00001$). The resuls of our CFS male patients 40.6 ± 8.9 (n = 8), was also statistically significantly lower than that of Kuratsune et al. 53.5 ± 8.5 (n = 19; $p = 0.002$).

In comparing our results to those of Kuratsune et al. [13], total carnitine levels were statistically significantly lower in our patients as compared to the levels of the controls and CFS patients of Kuratsune et al. Our total patients' (n = 35) total-carnitine result of 43.2 ± 9.9 was statistically significantly lower than that of the controls of Kuratsune et al. 65.8 ± 12.3 (n = 308; $p < 0.00001$). Likewise, our total CFS patient total carnitine result was statistically significantly lower than the CFS patients of Kuratsune et al. 58.7 ± 9.9 (n = 38; $p < 0.00001$).

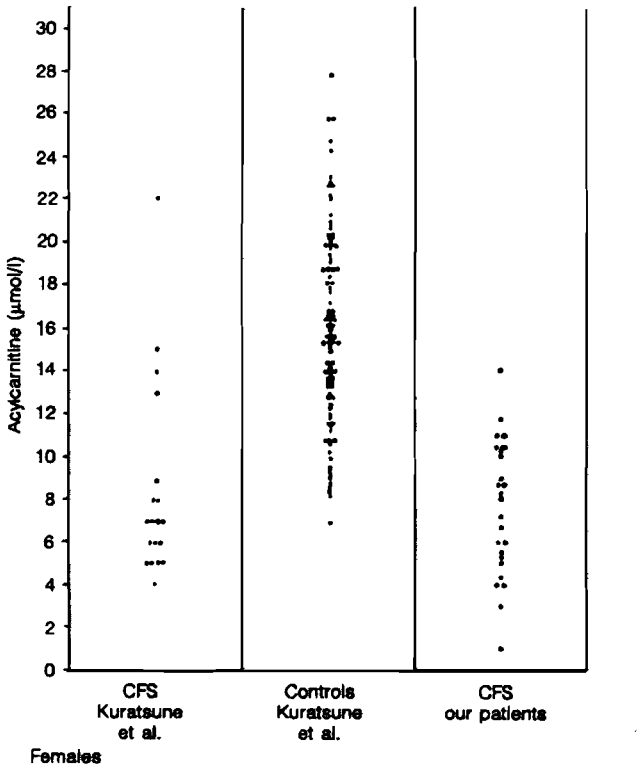


Fig. 3. Serum acylcarnitine levels in micromoles per liter for female CFS patients and controls. The first column displays the results from Kuratsune et al. et al. [13] for CFS patients (n = 19), the second column their results for controls (n = 131) and the third column those of our patients (n = 27). Our CFS female patients have statistically significantly lower acylcarnitine levels, 8.9 ± 7.0, as compared to the controls, 15.5 ± 4.4 ($p < 0.00001$), but there is no statistically significant difference between the results of our patients and those of the patients of Kuratsune et al. The data of Kuratsune et al. are presented with permission.

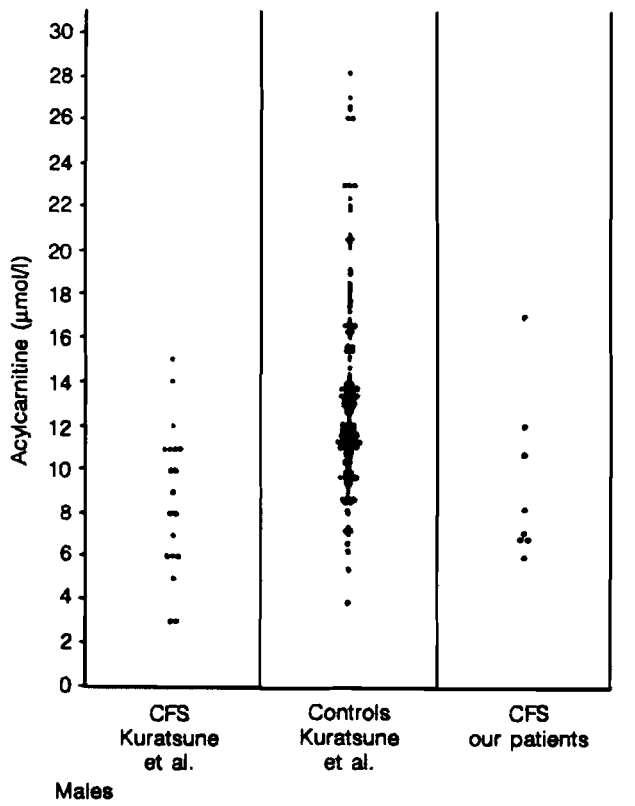


Fig. 4. Serum acylcarnitine levels in micromoles per liter for male CFS patients and controls. The first column displays results from Kuratsune et al. [13] for CFS patients (n = 19), the second column the results of the controls of Kuratsune et al. (n = 177) and the third column those of our patients (n = 8). Our CFS male patients have statistically significantly lower acylcarnitine levels, 9.3 ± 3.7, as compared to the controls, 13.4 ± 4.6 ($p < 0.00001$), but there is no statistically significant difference between the results of the patients in our study and those of the patients of Kuratsune et al. The data of Kuratsune et al. is presented with permission.

There was a statistically significant direct correlation between free carnitine levels and results from the CFS Impairment Index physical impairment subset (higher free carnitine levels correlated with better physical abilities; $r = 0.412$; $p < 0.05$). These results are illustrated in figure 7.

There was an inverse correlation between free carnitine levels and the FSS (higher free carnitine levels correlated with lower fatigue severity; $r = -0.496$; $p = 0.02$). These results are illustrated in figure 8. Also, there was an inverse correlation between total carnitine levels and the FSS (higher total carnitine levels correlated with lower fatigue severity; $r = -0.473$; $p = 0.02$). These results are illustrated in figure 9.

We did not find any statistically significant correlation between acylcarnitine levels and any of the clinical scales used.

Discussion

Our results confirm those of Kuratsune et al. [13] in that acylcarnitine levels are decreased in female and male CFS patients. Our observations extend the results of

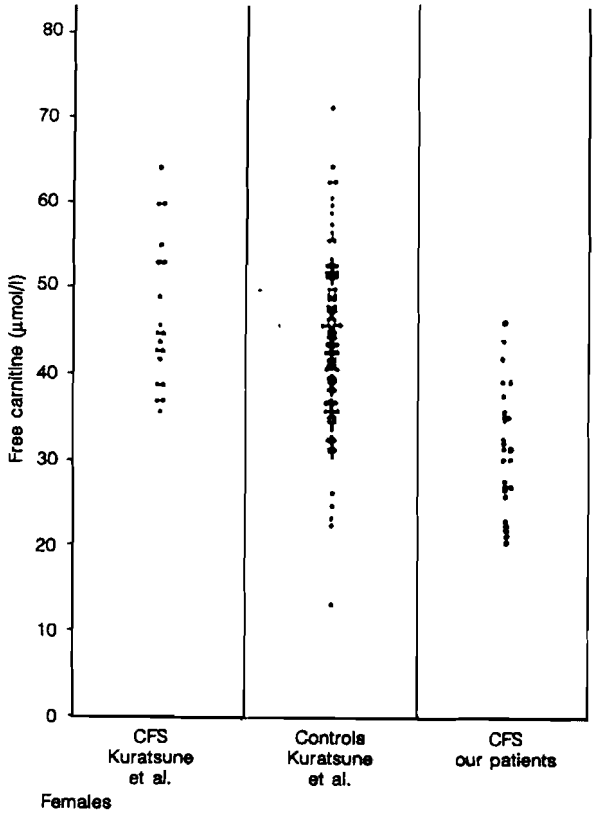


Fig. 5. Serum free carnitine levels in micromoles per liter for female CFS patients and controls. The first column displays results from Kuratsune et al. [13] for CFS patients (n = 19), the second column the results of their controls (n = 131) and the third column those of our patients (n = 27). Our CFS female patients have statistically significantly lower free carnitine levels, 32.1 ± 6.9, as compared to the controls, 43.6 ± 10.0 ($p < 0.00001$). Our CFS patients also have statistically significantly lower free carnitine levels as compared to the levels of patients as recorded by Kuratsune et al., 46.8 ± 8.2 ($p < 0.00001$). The data of Kuratsune et al. are presented with permission.

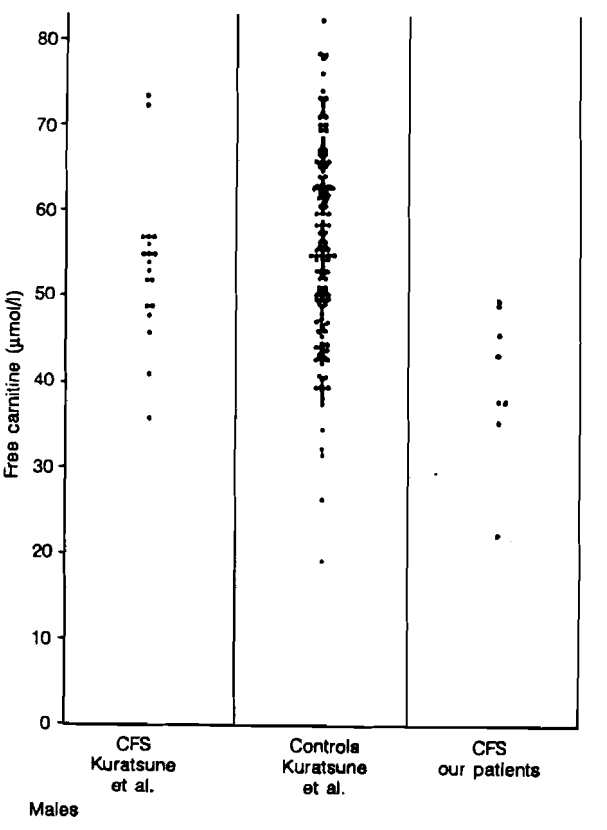


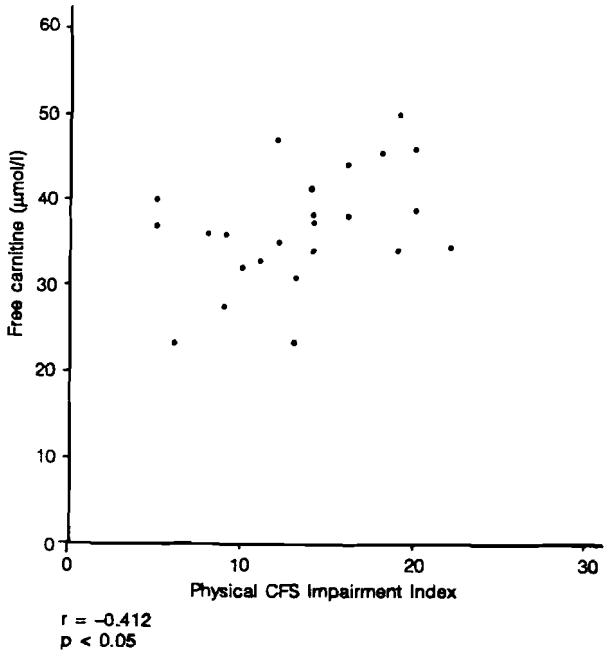
Fig. 6. Serum free carnitine levels in micromoles per liter for male CFS patients and controls. The first column displays results from Kuratsune et al. [13] for CFS patients (n = 19), the second column their results for controls (n = 177) and the third column the results of our patients (n = 8). Our CFS male patients have statistically significantly lower free carnitine levels, 40.6 ± 8.9, as compared to the controls 56.1 ± 10.7 ($p < 0.00001$). Our CFS patients also have statistically significantly lower free carnitine levels as compared to the levels of patients recorded by Kuratsune et al., 53.5 ± 8.5 ($p = 0.002$). The data of Kuratsune et al. is presented with permission.

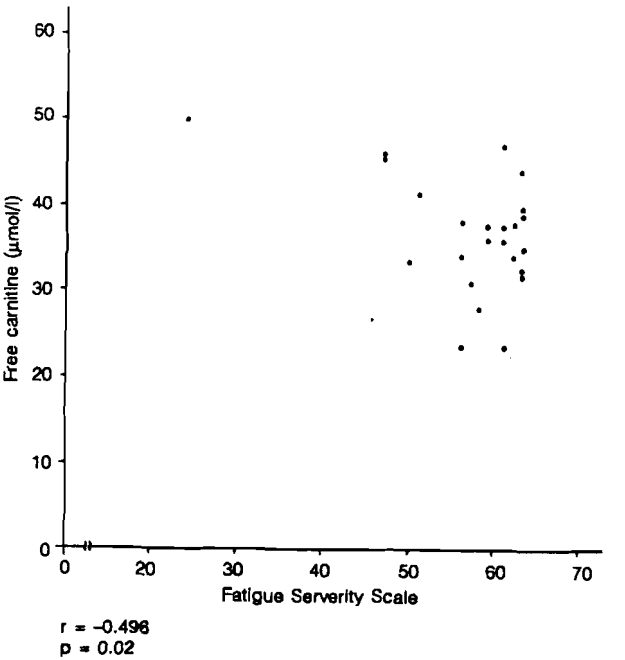
Kuratsune et al. further in that we also found statistically significantly decreased free carnitine and total carnitine levels in both male and female CFS patients in comparison to the normative data [20, 21] and to the control and CFS patient results of Kuratsune et al. [13].

It is important to note that our acylcarnitine results in CFS patients and those of Kuratsune et al. do not differ statistically. This result suggests that the diagnosis of CFS can be made reliably in different geographic areas and that different laboratory techniques in assaying carnitine levels can produce similar results.

Our observations also revealed a statistically significant correlation between free and total carnitine levels and clinical symptomatology. Higher carnitine levels were associated with less fatigue and better physical abilities. It would be of value to longitudinally study carnitine levels in comparison to patient clinical symptomatology.

The cause of the carnitine deficiency in CFS patients is not known. It is possible that carnitine may not be obtained or absorbed from food in sufficient amounts or that carnitine synthesis in the liver may be insufficient. Also, excessive excretion by the kidneys may be a factor.





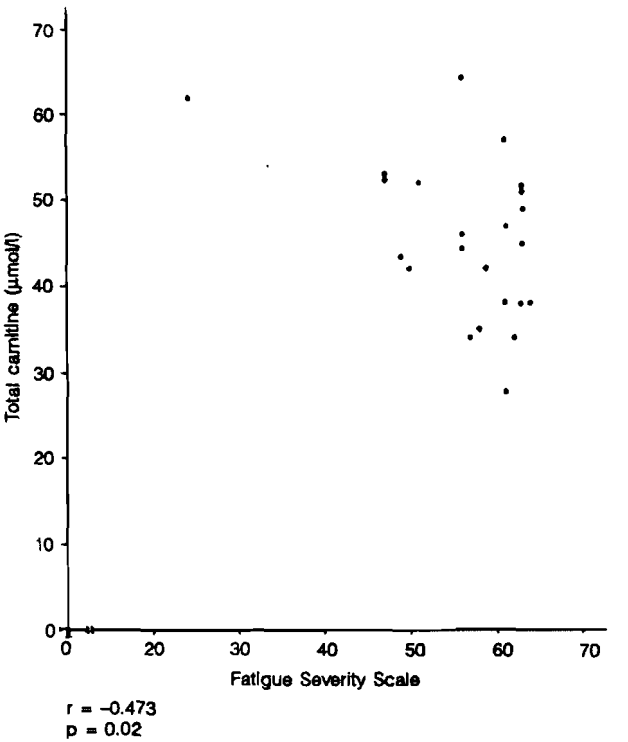


Fig. 7. Comparison of free carnitine levels in micromoles per liter to CFS Impairment Index physical subset scores in CFS patients. There was a statistically significant direct correlation between free carnitine levels and the CFS Impairment Index physical impairment subset (higher free carnitine levels correlated with better physical abilities, $r = 0.412$; $p = 0.02$).

Fig. 8. Comparison of free carnitine levels in micromoles per liter to the FSS in CFS patients. There was an inverse correlation between free carnitine levels and the FSS (higher free carnitine levels correlated with lower fatigue severity, $r = -0.496$; $p = 0.02$).

Fig. 9. Comparison of total carnitine levels in micromoles per liter to the FSS in CFS patients. There was an inverse correlation between total carnitine levels and the FSS (higher total carnitine levels correlated with lower fatigue severity, $r = -0.473$; $p < 0.05$).

Physical inactivity, which often accompanies CFS symptoms, appears not to be a cause of these findings since carnitine levels do not differ between controls and chronically bedridden patients [Kuratsune, pers. commun.]. Further investigations of dietary intake, carnitine metabolism and excretion in CFS patients are warranted.

Carnitine deficiency conditions can be treated with oral administration of *L*-carnitine. Our observations of decreased carnitine levels in CFS patients suggest that *L*-carnitine may be an appropriate treatment of CFS patients. *L*-carnitine has been shown to reduce the lethargy and fatigue in a number of different chronic neurologic diseases processes [23, 24]. Preliminary results have suggested clinical improvement in CFS patients with this treatment approach [24].

Acknowledgement

The authors wish to acknowledge the technical assistance provided by Ms. Ramute Plioplys.

Appendix 1

CFS Impairment Index

Choose a number that best indicates your physical and mental condition:

0 – complete disability
1 – severe impairment
2 – moderate impairment
3 – mild impairment
4 – minimal impairment
5 – no impairment

Physical parameters						
1. personal care	0	1	2	3	4	5
2. walking	0	1	2	3	4	5
3. working	0	1	2	3	4	5
4. sleeping	0	1	2	3	4	5
5. coordination	0	1	2	3	4	5
Mental parameters						
1. concentration	0	1	2	3	4	5
2. speech	0	1	2	3	4	5
3. memory	0	1	2	3	4	5
4. calculation	0	1	2	3	4	5
5. orientation	0	1	2	3	4	5

Physical: _____ Mental: _____ Total: _____

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