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CLINICAL TRIAL STUDY

Nutritional Intervention in Chronic Fatigue Syndrome and Fibromyalgia (CFS/FMS) A Unique Porcine Serum Polypeptide Nutritional Supplement

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Abstract:

Background:

Clinical experience suggested that a unique porcine serum polypeptide extract, used in hospitals for people with severe malnutrition, serendipitously resulted in a dramatic improvement in many fibromyalgia cases.

Aims:

The study aims to determine the effectiveness of a unique polypeptide serum extract in improving the symptoms of CFS and fibromyalgia (CFS/FMS).

Methods:

An open-label prospective study of 43 people with CFS or Fibromyalgia recruited worldwide.

Interventions:

Four 500 mg tablets twice daily for five weeks.

Outcome Measures:

Assessed baseline at five weeks of treatment using a VAS(1-10 points) rating energy, sleep, cognitive function, pain, overall well-being, anxiety, and digestive health, as well as the FIQR. The primary outcome measure was the pre- and post-treatment VAS composite score for the first five symptoms.

Results:

43 subjects completed the three-week treatment trial. 60.5% of subjects rated themselves as improved, with 18.6% rating themselves as much better.

In the 60.5% of subjects that rated themselves as improved, the significant average improvement was seen in all categories:
1. 69.4% increase in energy(p<.001)
2. 69.2% increase in overall well-being(<.001)
3. 53.8% improvement in sleep(<.001)
4. 60.5% improvement in mental clarity(<.001)
5. 37.9% decrease in pain(<.013)
6. 34.8% decrease in anxiety(<.001)
7. 54.6% improvement in digestive symptoms(<.001)
8. FIQR 59.2 to 39.3(<.001) In six individuals who also had pre- and post IgG antibody levels, total IgG increased by 13.8% on average, with similar improvements seen in the IgG 1-4 subsets.

Conclusion:

Recovery Factors® resulted in markedly improved energy, sleep, cognition, pain relief, calming, digestion and overall well-being in those with CFS/FMS.

Clinical Trial Registration Number: NCT04381793.

Keywords: Fibromyalgia, Chronic fatigue syndrome, Polypeptides, Immune deficiency, Pain, Pain relief.

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1. INTRODUCTION

Fibromyalgia (FMS), which currently affects about 2.1% of adults worldwide and an estimated three to six million Americans [1], and Chronic Fatigue Syndrome (CFS) are two overlapping and disabling syndromes. CFS affects more than one million people in the United States. There are tens of millions of people with similar fatiguing illnesses who do not fully meet the strict research definition of CFS [2]. Severe persistent fatigue, diffuse migratory pain, cognitive dysfunction, and disordered sleep are common symptoms reported by patients suffering from these syndromes, along with gastrointestinal symptoms and anxiety exacerbated by their illness.

Many of the problems seen in CFS/FMS may be associated with a decrease in tissue energy levels and altered energy metabolism. The consequences of dysfunctional energy metabolism frequently include pain from chronic muscle shortening [3], post-exertional malaise, and low exercise tolerance associated with decreased blood cell mass, cardiac output and stroke volumes [4, 5].

Adenosine triphosphate (ATP) levels have also been shown to be significantly higher in healthy *vs*. FMS patients [6]. In addition, it has been suggested that decreased energy production also results in hypothalamic dysfunction, which can result in disordered sleep, hormonal imbalances, and autonomic dysfunctions seen in these syndromes [7].

Small fiber neuropathy [8] and associated autonomic dysfunction [9] are also common in these conditions and have been associated with low levels of total IgG and IgG 1-4 antibody subtypes, leading to the successful use of intravenous gamma globulin in the treatment of small fiber neuropathy [10]. These antibody deficiencies are also commonly seen in people with CFS and fibromyalgia [11], confirmed in our clinical experience-especially low IgG 3 followed by low IgG 1.

It has been the author's (JT) clinical impression that small fiber neuropathy, dysautonomia, and IgG 1 and/or IgG 3 antibody deficiencies are all different faces of the same underlying process in people with CFS and fibromyalgia. In a number of refractory and severely disabling cases of CFS and fibromyalgia, IV gamma globulin has been clinically very helpful in those with this triad. Unfortunately, this treatment is quite expensive, difficult, and not available to most people suffering from these conditions.

In addition, numerous other factors contribute to the energy crisis seen in CFS and fibromyalgia. In the author's (JT) previously published RCT, optimizing energy levels using the S.H.I.N.E.® Protocol, which addresses sleep, hormonal optimization, infections, and nutritional support, resulted in the treatment group improving dramatically. This protocol resulted in an average 90% improvement in the quality of life ($p<.0001$ versus placebo) [7].

Previous research by our group showed that optimizing ATP production with Ribose 5 g three times daily improved energy to an average of 61% [12]. But this only addressed part of the needs in this patient population. It is suspected that people with fibromyalgia are often in a catabolic state, and research has shown that even in women with normal testosterone levels, giving low-dose anabolic bioidentical testosterone decreases fibromyalgia pain [13].

This raised the question of whether specific polypeptide nutritional support geared towards increasing anabolic metabolism, without the use of anabolic steroids, might also be helpful.

Quite by serendipity, it was found that a unique porcine serum polypeptide extract used in treating people hospitalized with malnutrition often improved fibromyalgia and a myriad of other symptoms and conditions. One of the authors (GM) obtained some of the supplements for use in his fibromyalgia population, observing dramatic improvement in a number of cases.

We, therefore, decided to do an initial open-label study to explore this further.

2. MATERIALS AND METHODS

2.1. Patient Enrollment

The author (JT) invited patients in his practice as well as readers of his newsletter (available at Vitality101.com) to join in this study. This initial study was limited to 60 people. Of those, 43 qualified for the study by meeting diagnostic criteria for CFS or fibromyalgia, received the supplement, and completed the pre and post-study questionnaires. No compensation was given for being in the study, except for supplying the supplement for free.

Being a pilot study, we were looking for a broad subject base. The study subjects were largely from North America, but also included five subjects from Europe and one from New Zealand.

2.2. Inclusion Criteria

(1) Subjects must meet the ACR 2010 (amended 2011) diagnostic criteria for fibromyalgia [14] or the CDC criteria for chronic fatigue syndrome [15].

(2) Subjects must be over 18 years of age and nonpregnant.

2.3. Exclusion Criteria

(1) Subjects cannot be on the blood thinner Coumadin.

(2) Subjects cannot have a history of pulmonary embolus or severe phlebitis.

(3) Subjects cannot have a history of severe and frequent natural product or nutrient sensitivities.

2.4. Outcome Measures

Primary outcome measures: A visual analog scale combining effects on energy, sleep, pain, cognitive function and overall well-being. The VAS questions asked were:

Please rate the following on a scale of 1 (near dead) to 10 (excellent)

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E-mail: FatigueDoc@gmail.com

A) How is your energy?

1 2 3 4 5 6 7 8 9 10

1= near dead and 10= excellent

B) How is your sleep?

1 2 3 4 5 6 7 8 9 10

1= no sleep and 10= 8 hours of sleep a night without waking

C) How severe is your achiness/pain? (1 is worst possible pain)

1 2 3 4 5 6 7 8 9 10

1= very severe pain and 10 = pain free

D) How is your overall sense of well-being?

1 2 3 4 5 6 7 8 9 10

1= near dead and 10= excellent

E) How is your mental clarity?

1 2 3 4 5 6 7 8 9 10

1= brain dead and 10= good clarity

Secondary outcome measures: Visual analog scales looking at:

1. Anxiety and lower digestive symptoms (gas, bloating, diarrhea, constipation). The questions asked were:

A) Rate your level of anxiety:

1 2 3 4 5 6 7 8 9 10

1= severe anxiety and 10= anxiety not a problem

B) Rate the severity of your digestive symptoms (gas, bloating, diarrhea, constipation):

1 2 3 4 5 6 7 8 9 10

1= severe problem and 10= digestion not a problem

2. Each subject's overall subjective feeling after taking the supplement (*i.e.*, much better, somewhat better, no change, somewhat worse, or much worse.

3. Revised Fibromyalgia Impact Questionnaire (FIQR) [16].

4. In a second nested study, those with documented low total IgG or IgG 1-4 subset antibody levels who chose to also enter that arm of the study had post-treatment antibody levels drawn after 10 weeks of treatment.

Study subjects were also asked to note if they experienced any adverse side effects. They were also asked in the prestudy questionnaire to note if they had any other health conditions.

2.5. Demographic Data (Table 1)

Patients could continue other current treatments in addition to the study supplement. They were asked not to take any other treatment changes during the study.

Table 1. Patient demographics.

n=43	
Subjects with CFS	40 (93%)
Subjects with FMS	37 (86%)
Subjects with CFS and FMS	34 (79%)
Duration of CFS or FMS	average 18 years (range 1-40 years)
Average Age (years)	58 years old
Age (Range)	34-75 years old
Male	n=7 (16.3%)
Female	n=36 (83.7%)

2.6. Study Design

The design (a prospective open, unblinded trial) and outcome measurement instruments were kept simple to improve compliance. All patients gave informed consent, and the study was approved by the Practitioner Alliance Network IRB (PAN study 2019-10).

2.7. Treatment

Treatment consisted of a unique proprietary polypeptide extract from porcine serum (Recovery Factors® from Recovery Nutraceuticals, www.RecoveryFactors.com). Recovery Factors is a complete profile serum-derived, porcine protein, extracted through proprietary extraction mechanisms targeting all 20 amino acids and iron. No lipids or glucose are extracted.

This has been used for over a decade in hospitals for treating severe malnutrition. Subjects were given the following dosing instructions:

Day 1-3: Take four tablets, three times a day (12 total tablets per day) for three days.

Day 4-5: If energy levels are improved, then continue the same dosage for day four and five. If no energy improvement, increase the dosage to five tablets, three times a day for day 4 and 5 (15 total tablets per day).

Day 6: Drop to four tablets twice per day (eight total tablets per day).

It is recommended to take the doses first thing in the morning on an empty stomach, and at around 3 p.m. in the afternoon.

Each subject was supplied with 360 tablets and instructed to complete the follow-up form when they had a few days of the supplement left.

2.8. Statistical Analysis

A total of 43 participants completed the pre- and post-treatment outcome measures. All continuous variables were assessed for normality using visual inspection of histograms. No missing data were present on the primary outcome measure.

To examine the change in the primary outcome, the VAS composite score, a two-tailed paired-sample t-test was conducted with the alpha level set to .05. Analyses of secondary outcomes were also conducted using paired samples t-tests to assess change on each of the seven VAS items and the FISQ total score. A Bonferroni correction was applied to adjust for multiple testing of secondary outcomes, with the alpha level set to .006 (.05/8). The above analyses were repeated within

the subsample of participants whose self-rating was "better" or "much better" at the end of treatment (n = 26). Effect sizes were calculated using Cohen's *d* for paired samples t-tests. Effect sizes are interpreted as follows: small: $d = 0.2$; medium: $d = 0.5$; large: $d = 0.8$.

Change in antibody levels across seven different markers (by immunoturbidimetric methodology for IgG total; by Immunologic methodology for IgG 1-4 subsets) was assessed in a subset of participants who underwent blood testing (n = 6). Paired samples t-tests were conducted. The conventional alpha level of .05 was maintained due to the small sample size and possible increased risk of a Type II error.

Supplementary analyses were conducted to examine characteristics associated with participants who self-reported improvement (n = 26) versus those who did not (n = 17). Independent samples t-tests and chi-square tests were used to compare groups on continuous and categorical variables, respectively. Continuous variables included age and duration of illness (in years), and categorical variables included gender (male, female) and the presence of at least one self-reported comorbid medical condition.

3. RESULTS

Statistical analysis for VAS and FIQR results are shown in Table **2**:

Antibody levels pre and post treatment are given in Table **3**. Tables **4**-**7** below gives the VAS and FIQR as percent changes.

Given the small sample sizes for these antibody analyses, the results above should be interpreted with caution. We have placed more emphasis on discussing the effect sizes and less so on the p-values because of the small sample size. Larger effect sizes are likely to be more clinically meaningful. However, we recommend considering the interpretation of larger effect sizes here with the caveat that these may not be reliable estimates due to small samples and larger standard errors in some cases. Nonetheless, some of these antibodies show large effect sizes (especially IgG1), and these findings are useful in generating hypotheses for future research.

3.1. Supplementary Analyses

There were no differences between participants who self-reported improvement (n = 26) versus those who did not (n = 17) on age ($t = .85$, < = .402) and duration of illness ($t = 1.34$, < = .189). Additionally, no differences between groups on gender ($X^2 = 1.08$, < = .298) or rate of comorbid medical conditions ($X^2 = 0.17$, < = .896) were noted.

Table 2. Change from pre to post-treatment evaluated with paired sample t-tests.

	Total Group (n=43)				Subjects That Improved (n=26)			
Variable	Pre-tx Mean (SD)	Post-tx Mean (SD)	T statistic (p-value)	Effect size (*d*)	Pre-tx Mean (SD)	Post-tx Mean (SD)	T statistic (p-value)	Effect size (*d*)
VAS 1. Energy	3.4 (1.1)	5.5 (2.0)	-7.38 (<.001)	1.1	3.7 (1.0)	6.2 (1.9)	-6.64 (>.001)	1.3
VAS 2. Slee<	4.7 (1.9)	6.0 (2.0)	-3.35 (.002)	0.5	4.5 (1.8)	6.8 (1.7)	-6.45 (>.001)	1.2
VAS 3. Pain*	4.6 (2.1)	5.8 (2.0)	-2.26 (.029)	0.4	4.4 (1.9)	6.0 (2.1)	-2.67 (>.013)	0.5
VAS 4. Cognition	4.7 (1.8)	6.8 (1.9)	-5.97 (<.001)	0.9	4.7 (1.5)	7.4 (1.7)	-5.39 (>.001)	1.1
VAS 5. Well-being	3.7 (1.2)	5.7 (2.0)	-5.43 (<.001)	0.8	3.8 (1.3)	6.4 (1.8)	-5.05 (>.001)	1.0
VAS total 1-5	21.2 (5.5)	29.7 (6.9)	-6.05 (<.001)	0.9	21.0 (5.7)	32.9 (6.3)	-6.15 (>.001)	1.2
VAS 6. Calmness	4.9 (2.2)	6.7 (2.1)	-4.82 (<.001)	0.7	4.6 (2.6)	7.0 (2.1)	-4.90 (>.001)	1.0
VAS 7. Digestion	4.2 (2.3)	5.9 (2.7)	-4.05 (<.001)	0.6	4.6 (2.3)	7.1 (2.1)	-4.67 (>.001)	0.9
FIQR total	61.1 (14.7)	46.7 (16.1)	5.64 (<.001)	0.9	59.0 (16.6)	39.3 (14.8)	5.46 (>.001)	1.1

* denotes effects that did not survive a Bonferroni correction.

Table 3. Change in antibody levels (all in mg/dl) from pre- to post-treatment with paired samples t-tests.

Variable	Pre-tx Mean (SD)	Post-tx Mean (SD)	t statistic (p-value)	Effect Size (*d*)
IgG[a]	830.5 (182.7)	944.8 (223.3)	-4.22 (.008)	1.7
IgA[b]	217.0 (101.2)	251.5 (105.0)	-2.61 (.080)	1.3
IgM[b]	63.3 (28.2)	79.3 (42.8)	-2.11 (.125)	1.1
IgG1[a]	470.5 (138.0)	531.0 (143.7)	-8.31 (<.001)	3.4
IgG2[a]	215.7 (54.6)	223.2 (63.3)	-1.31 (.248)	0.5
IgG3[a]	30.3 (34.1)	33.7 (38.1)	-1.85 (.123)	0.8
IgG4[a]	23.3 (15.8)	25.7 (18.3)	-0.94 (.402)	0.4

Note.[a]N = 6; [b]N = 4

Table 4. Descriptive statistics for supplementary analyses.

Variable	Self-Reported Improvement (n = 26)	Self-Reported No Improvement (n = 17)
Age, mean (SD)	56.9 (11.0)	59.8 (11.0)
Duration of illness in years, mean (SD)	16.4 (9.5)	20.5 (13.0)
Gender, % male (n)	11.5 (3)	23.5 (4)
Comorbid medical condition	80.8 (21)	82.4 (14)

Table 5. Subject self rating after treatment.

n=43	
Much Better	8 (18.6%)
Better	18 (41.9%)
No Change	14 (32.5%)
Worse	3 (7%)
Much Worse	0 (0%)

Table 6. VAS and FIQR scores as percent change from baseline.

	Total Group (n=43) AVERAGE			The 60% of Subjects that Improved (n=26)		
Domain (VAS 0-10)	Pre Rx	Post Rx	Improvement	Pre Rx	Post Rx	Improvement
1. ENERGY	3.3	5.5	66.7%	3.6	6.1	69.4%
2. SLEE<	4.7	6.0	27.7%	4.42	6.8	53.8%
3. PAIN	4.6	5.8	26.1%	4.38	6.04	37.9%
4. COGNITION	4.7	6.8	44.7%	4.58	7.35	60.5%
5. WELL-BEING	3.7	5.7	54%	3.77	6.38	69.2%
6. Total 1-5	21	29.8	41.9%	20.75	32.67	57.5%
7. CALMNESS	4.9	6.7	36.7%	4.88	6.58	34.8%
8. DIGESTION	4.2	5.9	40.5%	4.58	7.08	54.6%
9. FIQR	61	47	23%	59.15	39.31	33.5%

VAS visual analog scale (1-10, with higher numbers showing clinical improvement): pre-Rx-before treatment: Post Rx – after treatment: FIQR-Revised Fibromyalgia Impact Questionnaire (lower numbers show clinical improvement)

Table 7. Average antibody titers and percent increase pre-and post-treatment.

Antibody (mg/dL)	n=	Pretreatment	Posttreatment	Percent Increase
Total IgG	6	830.5	944.8	13.8%
Total IgM	4	63.25	79.25	25.3%
Total IgA	4	217	251	15.7%
Total IgG 1	6	470.5	531.0	12.9%
Total IgG 2	6	215.7	223.2	3.5%
Total IgG 3	6	30.0	33.7	12.3%
Total IgG 4	6	23.3	25.7	10.3%

As CFS and fibromyalgia represent a mix of numerous different conditions, there is no single treatment that everybody responds to. Therefore, it is important to also note the degree of effect on those who are responders. Due to this, we have also calculated that subgroup separately.

3.2. Changes in Antibody Levels as "Percent Change"

A group of six subjects who had either low total IgG or a low level on their IgG 1-4 participated in a separate analysis of pre-and post-treatment antibody levels. For one subject, only partial results were available.

3.3. Adverse Effects

Overall, the treatment was very well tolerated. Eight people noted mild side effects. One subject felt "irritable when in traffic" and one noted that they felt "fidgety." Four people noted mild gas or loose stool and one had nausea. One person noted worsening fatigue. All the above is generally resolved by simply lowering the dose. One person noted that the bedtime dose worsened insomnia, and this resolved by moving the second dose to 2 p.m..

4. DISCUSSION

This study offers a potentially powerful new tool for treating people with chronic fatigue syndrome and fibromyalgia. It is very promising that this safe and low-cost treatment was able to significantly improve patients' clinical outcomes, with subjects in the overall group reporting an average 54% increase in overall well-being. This increased to an average 69% improvement in overall well-being in the 60% of subjects who improved with treatment. Having treated countless thousands of people with fibromyalgia, the authors find this to be remarkable for a single-agent response.

The mechanism of action is still unclear. But as the late Prof. Janet Travell MD, the White House physician for President Kennedy and the world's leading expert on myofascial pain noted, it is often important to simply first observe what is actually occurring. And then see if one can understand why.

This is a situation that we often find in medicine. Where the clinical observation of efficacy is made before understanding the mechanism, and that is what is occurring here.

A growing body of clinical experience, as well as this study, shows that this unique form of nutritional support results in often dramatic clinical improvement in 60% of those with CFS and fibromyalgia, usually within one month.

So what do we know?

(1) Clinical experience with tens of thousands of people suffering from severe malnutrition has shown the supplement results in dramatic improvement.

(2) The supplement contains a mix of polypeptides. But that the effect is far greater than simply giving a similar amount of amino acids

(3) Clinically, it has been found that total IgG and IgG 3 and less often IgG 1 are frequently low in CFS and fibromyalgia. We find this to be especially common in those with dysautonomia (orthostatic intolerance) and small fiber neuropathy. There is a good possibility that all three of these are simply different facets of the same process.

(4) Although we have only tested a small number of subjects in this study, it is interesting that these three antibodies went up about 13%, with an even greater increase of 25% in IgM. And that this increase correlated with clinical improvement. This raises the possibility of the supplement having a direct effect on improving immune function in this population. In my clinical experience, I have seen nothing else raise these antibodies this quickly and as effectively except for intravenous gamma globulin.

(5) The product is derived entirely from porcine blood components. It is predominantly a purified serum polypeptide nutritional support mix.

(6) As the earlier effects were seen in a malnourished population, there was the question of whether it was simply an effect of increased caloric support. The current population was not malnourished and had not shown this benefit from much larger amounts of amino acid supplementation, showing that these benefits are not simply from increased caloric intake.

There are several factors that we need to be looking at in the research going forward.

Although "protein" is a general term given to everything made from polypeptide structures, each is quite different in effect. By way of analogy, amino acids are like random words. This unique mix is like a book written from these words. How they are combined makes all the difference.

The porcine immunoglobulin portion of the immune system is, in many ways, remarkably similar to humans, which is one reason why pigs are often used in research on infections and immunity. But their very strong immune system is what allows them to wallow in the mud without getting sick. It is possible that this nutritional support conveys some of the immune benefits.

Decades of experience using this nutritional supplement for malnutrition have shown that it quite safely and effectively helps people recover, suggesting a significant anabolic effect.

Just a few leads to follow. So as research continues, we are left with Dr. Travell's observation. First, see what is, and then try to understand it.

Fortunately, research has advanced to the point where CFS and fibromyalgia can be very effectively treated. For example, ribose was shown to be associated with an average 61% increase in energy and a highly significant 37% increase in overall well-being.12 An RCT looking at the SHINE Protocol, Optimizing Sleep, Hormones, Immunity, Nutrition, and Exercise as able resulted in an average 90% increase in quality of life.7 This study adds one more unique effective approach to optimizing function in this very ill population.

This study has a number of weaknesses, the key ones being small size and lack of randomization and a control group. Our current plan is to conduct another larger open trial to gain a better understanding of these supplements effect, followed by doing a randomized double-blind placebo-controlled study.

In the interim, this study offers millions of people suffering from these devastating conditions good reason for hope and optimism.

CONCLUSION

A unique porcine serum polypeptide nutritional supplement (Recovery Factors® by Recovery Nutraceuticals) resulted in markedly improved energy levels, sleep, mental clarity, pain relief, calming, digestive symptom improvement and overall well-being in those with CFS and fibromyalgia. In those who also had low total IgG or IgG 1-4 subsets, a 13.8% average increase in total IgG was seen post-treatment.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Practitioner Alliance Network IRB, USA (PAN study 2019-10).

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research

procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

All patients participated on a voluntary basis and gave their informed consent.

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CONFLICT OF INTEREST

The authors declare no other conflict of interest, financial or otherwise.

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Declared none.

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