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The Influence of Diet and Exercise on the Physical Health of Affected Individuals with VCP Disease

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Abstract: While there is no curative treatment for the Inclusion body myopathy, Paget disease of bone and/ or frontotemporal dementia (IBMPFD) disorder, it is worthwhile to investigate alternate therapies that may slow the progression of the disease and improve the quality of life in this patient population. Therefore, this study aims to evaluate the impact of diet and exercise changes on the Quality of Life questionnaire. We assessed data from the questionnaire in 30 individuals (mean age 50.86 years; range 27-65 years; 16 Males, 14 Females) that participated in the clinical study of Valosin Containing Protein (VCP) disease. Eleven affected individuals consumed a high fat/sugar diet and 15 low fat/sugar diet of 4.09±0.25 and 1.53±0.13 servings/day respectively. Eleven individuals reported not exercising and 12 reported moderate exercise of 2.44±0.74 hours/week. In this cohort we found significantly higher mean physical health domain score for all those who exercised ($P=.02$) and surprisingly in those who had a high fat/sugar diet ($P=.01$). In the high fat/sugar diet group there was a significantly greater ability to walk; greater perceived muscle strength in arms and legs ($P=.03$; $P=.02$ and $P=.02$ respectively). Therefore lifestyle changes with exercise training and a higher fat/ sugar diet may have a beneficial effect in affected individuals with VCP disease. Nevertheless, larger studies with further research are needed to confirm these preliminary studies before making clinical practice recommendations.

Keywords: IBMPFD, inclusion body myopathy, valosin-containing protein, diet, exercise.

INTRODUCTION

Inclusion body myopathy, Paget disease of bone and/or early-onset frontotemporal dementia (IBMPFD OMIM; 167320) is an autosomal dominant, adult-onset, progressive ultimately fatal neuromuscular disorder caused by mutations in the *valosin-containing protein* (VCP/p97) gene located on chromosome 9 [1,2]. VCP gene is an AAA+-ATPase chaperone protein in the ubiquitin-proteasome degradation pathways [3] and is also associated with various cellular functions including DNA damage repair, golgi reassembly, biogenesis of organelles, membrane integrity, cell signaling, cell division and apoptosis [4]. IBMPFD is an underdiagnosed disease that has been reported in >60 families worldwide, mainly from the United States and Europe. There is a considerable intra and inter familial phenotypic variability. Approximately 90% of affected individuals develop the myopathy in their thirties-forties; 50% develop Paget disease of bone (PDB) typically in their thirties [2,5] and 30% develop frontotemporal dementia in their mid-fifties. Affected individuals typically die from cardiac or respiratory failure in their forties-sixties or earlier [2,5]. Less common phenotypic features include cardiomyopathy, hepatic stenosis, cataracts, sensory motor axonal neuropathy, pyramidal

tract dysfunction, sphincter disturbance, sensorineural hearing loss, and amyotrophic lateral sclerosis (ALS) like features [6-10].

The diagnosis is typically made based on the presence of proximal myopathy, rimmed vacuoles and ubiquitin and TDP-43 positive inclusions in muscle, and typically the co-existence of PDB, frontotemporal dementia (FTD) or ALS [2,5,11-13]. PDB is responsive to treatment with bisphosphonates [14, 15], but there are currently no treatments for the other features.

Researchers have long been involved in exploring effective treatment options to prevent the muscle deterioration and neurodegeneration in diverse neuromuscular diseases. A number of clinical trials and studies in animal models have reported the benefits of dietary and exercise interventions in various neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, autism, multiple sclerosis ALS and epilepsies [16-19]. The ketogenic diet is an established treatment for epilepsy [20, 21] for many years. The antiepileptogenic effect of ketogenic diet on kialis acid administered rodents was discovered by Noh *et al.* (2008) [22].

In this study, we investigated the effects of lifestyle modifications including fat/sugar in the diet and exercise training in improving the physical health and quality of life in affected individuals with VCP disease using the VCP health related Quality of Life (VCP QoL)

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measures. These measures identify the physical and mental health perceptions comprising of health risks, functional status and socioeconomic status. QoL measures are typically used to determine the risk factors, the burden of disease, disease progression and to monitor the effectiveness of interventions helping in making changes to health policies and legislations at community and national level.

METHODS AND MATERIALS

Study Population

Individuals recruited for this study were previously consented to the ongoing genetic and natural history study in families with familial inclusion body myopathy, Paget disease and FTD. The study was approved by the Institutional Review Board of the University of California, Irvine (UC Irvine IRB Number #2008-6279). Individuals over age 18 years and who carried the VCP mutation were eligible in the study.

From our database a total of 30 affected individuals completed the VCPQoL questionnaire. Of these, 23 completed the exercise component and 26 completed the diet component of the questionnaire. The sociodemographics of the 30 affected individuals can be seen in Table 1.

VCP Quality of Life (VCPQoL) Questionnaire

The VCPQoL used for VCP disease incorporated questions from the 36-item short-form health survey (SF-36), The Behavioral Risk Factor Surveillance System (BRFSS-CDC) and Inclusion body myositis functional rating scale (IBMFRS) [23-25]. The BRFSS survey conducted by CDC staff annually is a state level, telephone survey consisting of the core component (the fixed core, rotating core, and emerging core); optional modules, and state-added questions. It collects data on chronic conditions, preventive health services [26,27]. The IBMFRS is a 10 point valid, reliable and a sensitive measure to assess the disease severity over a period of study [28]. This instrument consists of seventy-eight self-administered questions split up into three subscales: mental, physical and general health reflecting the overall health of an individual. The sum of all subscales range from 0- 212, calculated by grading 53 questions from minimum of 0 points to a maximum of 4 points. The physical health subscale maximum score is 84, calculated by grading 21 questions. The first section asks the participants to provide general demographic information including name, date of birth, age, mailing address, name of diagnosis, age at diagnosis, gender, and VCP mutation status. Included in the QoL questionnaire was a series of 10 questions relating to diet, smoking and alcohol use related habits. The questionnaires on the diet

Table 1: Population Characteristics

Total Number who completed the questionnaire	30/90 (33.3%)	
Average age	50.87 yrs. (range 27-65 yrs.)	
Gender	16 Females	
	14 Males	
Ethnicity	All Caucasian	
Mutation Status	All mutation positive	
Myopathy	29	
Paget's Disease of bone	8	
Frontotemporal dementia	3	
	N (%)	Mean ± SEM (servings/day)
Number to complete diet questionnaire	26	
· High calorie intake	11 (42.3%)	4.09 ± 0.25
· Low calorie intake	15 (57.6%)	1.53 ± 0.13
		(hours/week)
Number to complete physical activity questionnaire	23	
· Moderate Exercise	12 (52.2%)	2.44 ± 0.74
· No exercise	11 (47.8%)	0 ± 0

included the information regarding the amount of fat/oil, and sugar servings per day. The questionnaire on the exercise portion included information on the intensity and duration of weekly exercise. If exercise or a high fat/sugar diet increase physical health and overall quality of life, then the individuals should receive higher scores for both the physical health domain score and the total VCPQoL score.

Our study concentrated on the VCPQoL physical health domain. Four specific questions were analyzed directly from the physical health domain: ability to walk, ability to run and jump, muscle strength in arms and muscle strength in legs. The questions regarding ability are scored at which a higher score (Score 4) indicates greater ability. The muscle strength in the arms and legs was graded on Scale 0-4 where Score 4 was no weakness and Score 0 was inability to use arms or legs.

Diet Questionnaire

Information on the high fat and high carbohydrate QoL diet questionnaire was obtained by wording such as “In a typical weekday, how often do you eat one

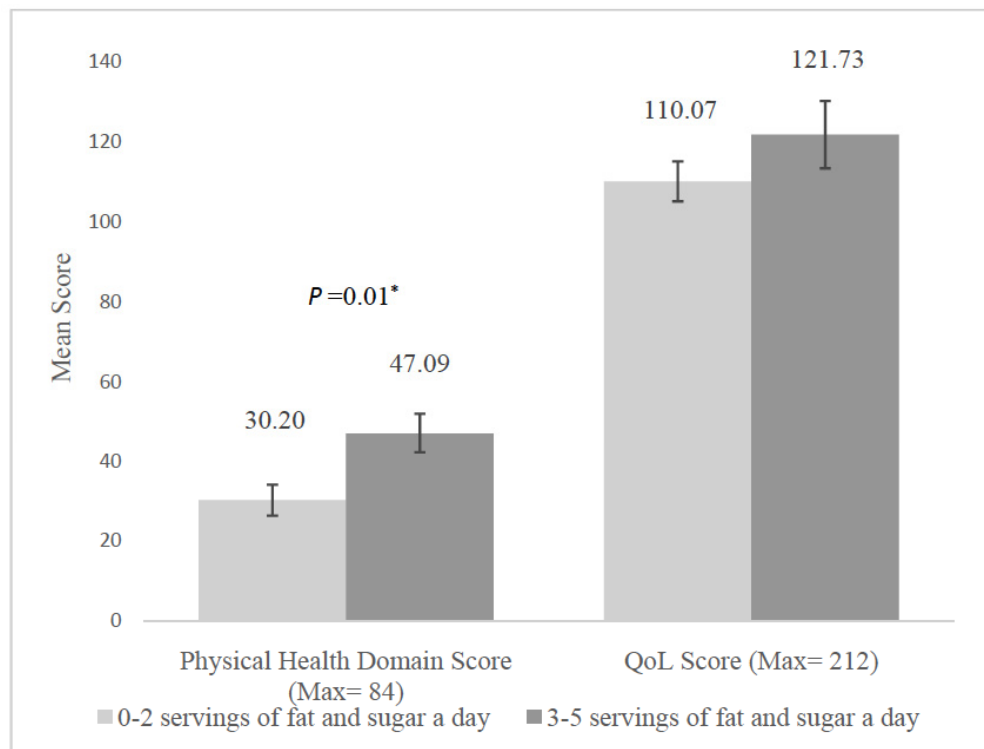
serving of sweets, fats and oil? (1 serving= 1 teaspoon butter or margarine, 12oz soda, 1 teaspoon sugar, 1 tablespoon salad dressing, 1 teaspoon jam/jelly)” and there was a choice between 0-5+ servings. Affected individuals were split into two groups of either lower intake or higher intake of fat and sugar. Lower intake was classified as 0-2 servings per day and higher intake was classified as 3-5 servings per day.

Exercise Questionnaire

Exercise was measured in the QoL Questionnaire in two separate questions pertaining to the amount of moderate and vigorous hours of exercise per week. Moderate exercise was classified as “brisk walking, bicycling, vacuuming, or gardening” while vigorous exercise is classified as “running, aerobics, strenuous sports, heavy yard work”. The “total hours of exercise” of moderate and vigorous exercise was also analyzed.

Data Analysis

The results of all the questionnaires were entered into the statistical software package SPSS 21.0 (IBM SPSS; International Business Machines, IBM



The standard error of mean bars is seen.

* *P*-value is significant ($P < 0.05$)

Figure 1: The corresponding mean physical health domain and total quality of life scores in high and low fat/sugar intake groups with VCP disease.

Corporation, Chicago, IL, USA). Items for each of the diet and exercise portions were summed and means for each were calculated. Where an individual had completed the diet and exercise portions of the questionnaire and independent samples t-test was used to detect any significant change. Statistical significance was set at $P < .05$.

RESULTS

Participants

Of the 90 affected individuals in the database, 30 (33.3%) returned the completed diet and/or exercise portion of the questionnaire. Their mean age was 50.87 years (range 27-65 years), 16 were females and 14 males. Among these individuals the majority 29/30 (96.6%) had myopathy, 8 (26.6%) had Paget's disease of bone and 3 (10%) had frontotemporal dementia. Of the total 30 affected individuals, 23 completed the exercise component and 26 completed the diet component of the questionnaire.

Fat/Sugar Diet and VCPQoL Score

Of the 26 affected individuals who completed diet questionnaire, a total of 11 consumed high fat/sugar diet of 4.09 ± 0.25 servings per day and 15 consumed low fat/sugar diet of 1.53 ± 0.13 servings per day (Table 1). As shown in Figure 1, there was a significant difference between affected individuals who consumed high fat/sugar diet when compared to the ones on low fat/sugar diet with regard to physical health domain score ($P = .01$). However, there was no significant difference in the total mean QoL score ($P = .21$). There was an improved ability to walk and perceived muscle strength in arms and in legs in the higher fat/sugar diet group ($P = .03$, $P = .02$ and $P = .02$ respectively) (Table 2).

Exercise and VCPQoL Score

Of the 23 affected individuals who completed the exercise questionnaire, 12 affected individuals exercised at moderate exercise of 2.44 ± 0.74 hours/week and only three reported periods of vigorous exercise of 0.21 ± 0.16 hours/week (Table 1). As shown in Figure 2, although the individuals who exercised had a significantly higher physical health domain score than those who did not exercise ($P = .02$) there was no significant difference in the total mean QoL score ($P = .08$). There was a trend of improved ability to walk in those who exercised but this was not statistically significant ($P = .07$) (Table 2). There was no significant differences in the ability to run/ jump, muscle strength in arms and legs in the exercise versus non-exercise groups ($P = .31$, $P = .67$ and $P = .56$ respectively).

DISCUSSION

It was interesting to note that the high fat/sugar diet group and exercise group individuals performed better in the physical health domain. The ability to walk, muscle strength in arms and legs was significantly better for the high fat/ sugar group. This was consistent with the mouse model studies that we have reported previously [29] and other studies. Llewellyn *et al.* (2003) [29] discovered that homozygote VCP^{R155H/R155H} mice lifespan greatly increased from 21 days to >10 months when the pregnant heterozygous mice were fed on the high fat diet for three months. The VCP^{R155H/R155H} homozygous mice only survive 21 days when on a normal chow diet. The mice showed decreased expression of histological markers of myopathy including ubiquitin, P62/SQSTM1, LC3 I/II and TDP-43. A number of other studies have reviewed the effect of high fat/ ketogenic diet/ high fat/sugar diet in diverse neurological disorders including Alzheimer's disease, Parkinson's disease, ALS and epilepsy

Table 2: Independent Samples T-Test and P Values for Physical Health Domain Variables in Diet and Exercise Subgroups

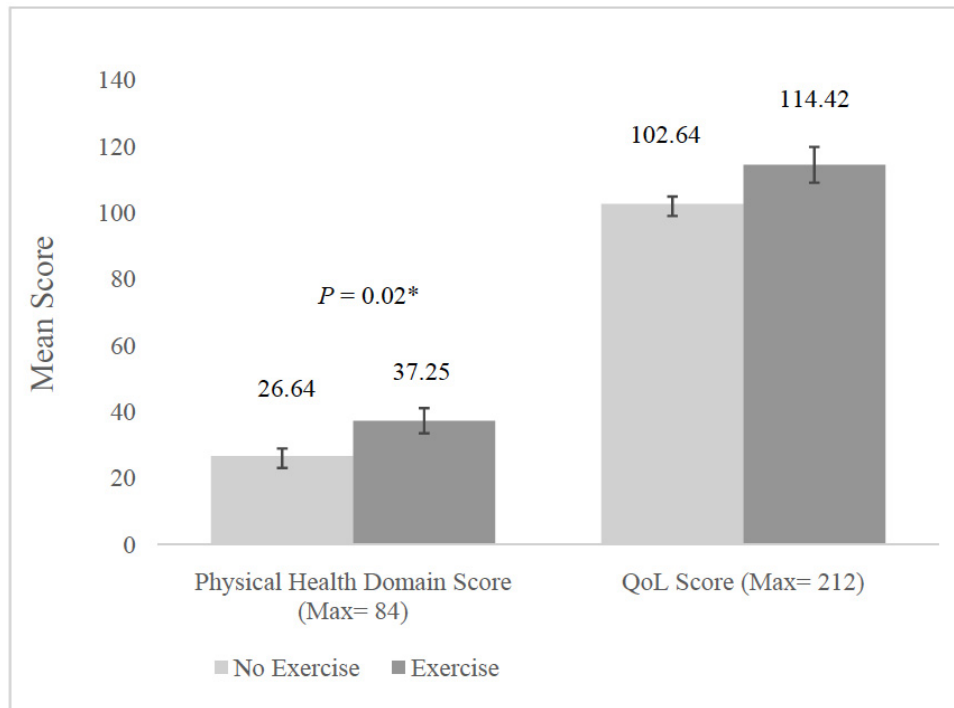
Scale (0-4)	Fat and Sugar diet intake (servings/day)		P value*	Exercise		P value*
	High (n=11)	Low (n=15)		Yes (n=12)	No (n=11)	
Ability to walk	3.20 ± 0.78	2.20 ± 1.20	0.03 [#]	2.83 ± 0.83	2.09 ± 1.04	0.07
Ability to run or jump	1.27 ± 0.90	1.07 ± 0.70	0.51	1.0 ± 0	0.90 ± 0.30	0.34
Muscle strength in arms	2.90 ± 0.87	1.80 ± 1.20	0.02 [#]	2.08 ± 1.16	1.90 ± 0.70	0.67
Muscle strength in legs	2.36 ± 1.02	1.40 ± 0.98	0.02 [#]	1.66 ± 0.88	1.45 ± 0.82	0.55

Data are expressed as mean ± standard deviation.

Scale (0-4): 0 is worst and 4 is best.

*P-value for the test of the null hypothesis of zero mean change.

[#]P-value < 0.05 (statistically significant).



The standard error of mean bars is present.

* P -value is significant ($P < 0.05$)

Figure 2: The corresponding mean physical health domain and total quality of life scores in exercise and no exercise groups with VCP disease.

[16,18,19]. The randomized phase 2 clinical trial by Wills *et al.* (2014) [19] in 20 affected individuals with ALS reported significantly fewer serious adverse events, tolerability, deaths, and disease progression in those individuals fed on a high-carbohydrate hypercaloric tube-fed diet compared to high-fat hypercaloric tube-fed diet and isocaloric tube-fed diet. The prospective study by O'Reilly *et al.* (2013) [30] determined if Amyotrophic Lateral Sclerosis (ALS) risk varies according to body mass index (BMI) captured up to three decades earlier. Compared to individuals with normal BMIs, ALS rates were significantly lower among the overweight and obese. Although mitochondrial myopathy is distinctly different, hereditary inclusion body myopathy (HIBM) is shown to have impaired mitochondria [31]. The benefit of high-fat diets with muscle degradation disorders on human subjects has not been well studied. Hancock *et al.* (2008) support that high-fat diets increased skeletal muscle mitochondria in rats [32]. A ketogenic diet has been supported to slow the progression of mitochondrial myopathy in mice [33]. A study conducted by Schrauwen *et al.* (2001) regarding high-fat diets had results supporting a significant increase in skeletal muscle expression of uncoupler proteins UPC2 and

UPC3 that are responsible for releasing the energy in the form of heat instead of ATP production [34]. This could be a mechanism of relieving stress on the mitochondria and may be one of the many possible reasons of why high-fat diets slow down the progression of muscle degradation in HIBM.

Our study showed that there was an increase in the physical health domain score in affected individuals that exercised suggesting that exercise slows the progression of symptoms impacting physical health. There were no perceived differences in the ability to walk, run, jump, muscle strength in arms and legs in the exercise versus non-exercise groups. Nalbandian *et al.* (2012) found correlation between exercise and slowed progression of symptoms in VCP^{R155H/+} mice running uphill. However, not all types of exercise were considered beneficial since increased muscle degeneration was found with the downhill running of mice [35]. A wealth of information points to training exercise platforms as a key intervention for prevention and treatment in neurodegenerative diseases in patients. Alexanderson *et al.* (2005) [36] did a clinical study on different exercise intensities with subjects affected with idiopathic inclusion body myopathy and

claimed that particularly intensive muscle training may reduce muscle degradation Sveen *et al.* (2008) reported that endurance training showed improvement in fitness and strength by 13-40% in patients with Becker muscular dystrophy (BMD) [37]. A further study by this group found that resistance training increased the muscle strength and endurance in some of the muscles in patients with limb girdle and BMD [38]. The positive effects of aerobic training in muscle performance in patients with mitochondrial myopathies have been previously demonstrated in several studies [39-42].

A limitation of our study was the relatively small sample size of 30 completing the questionnaire. A challenge in rare genetic diseases, such as VCP disease is to obtain a large sample size. The QoL questionnaire was extensive and the overall time required to finish the survey may have been a burden. This is a self-reported survey posing a challenge in getting accurate and unbiased answers for the questions regarding exercise and fat-sugar intake. We have made this our first step in bridging findings from the mice in the lab to affected individuals in VCP disease.

In conclusion, this study had some interesting findings some of which were unexpected. While the QoL questionnaire was suggestive that moderate exercise and a high fat/sugar diet slowed the progression of symptoms impacting physical health, larger studies are indicated before deriving conclusions from these correlations.

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CONFLICTS OF INTEREST

No conflicts of interest.

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