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Effects of Vitamin D Supplementation on Muscle Function in Graves' Disease Patients
Running Title: Vitamin D Supplementation in Graves' Disease

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ABSTRACT

Background: Lack of vitamin D and Graves' disease are linked to the decrement in quality of life (QoL) and weakening of the muscle groups. The goal of study report was to discover at the possible advantages of vitamin D supplementation for the improvement of thyroid-related QoL and muscle function in GD patients.

Methods: A single-blinded randomized controlled trial was conducted at King Abdullah Hospital in Mansehra Hospital in Abbottabad. The trial was carried out from January 1, 2021, to January 1, 2022. This study was carried out on 48 participants recruited via the envelop method of simple random sampling technique who had been diagnosed with Graves' disease. The participants were divided into two groups n=24 in each group. In summation to standard ATD, Groups received either a placebo or received 70 µg (2800 IU) of vitamin D daily. We measured muscular function and isometric strength at baseline, at three, and nine months, whereas QoL was measured at baseline and 9 months. Data was analyzed using SPSS. Paired sample t-test was run for within-group analysis whereas an independent sample t-test was applied for between-group comparison. Statistics were deemed significant when P <0.05.

Results: From baseline to the three- and nine-month follow-ups, both groups showed significant gains in hand grip strength, elbow flexion and extension, and knee flexion and extension at 60° and 90° angles (p=0.001). Comparison between group showed an increased mean difference with p <0.001 from baseline to 9 months. For Quality of Life the results were significantly improved in vitamin D group for Goiter Symptoms (p=0.045), Hypothyroid Symptoms (p=0.027), Tiredness (0.032), Emotional Susceptibility (p=0.011), and Social and Work Impact respectively (p=0.034).

Conclusion: Vitamin D supplementation appears to enhance muscle function and thyroid-related quality of life (QoL) in patients with Graves' disease. It significantly improves muscle strength compared to placebo.

Keywords: Graves' Disease, Muscle Strength, Range of Motion, Vitamin D.

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INTRODUCTION

Hyperthyroidism is defined by low amounts of thyroid-stimulating hormone (TSH) and high levels of thyroid hormone within the body[1]. Graves' disease is the leading cause of this disorder especially in the West with an incidence rate of 20 cases/100,000 persons[2,3]. After the identification of this thyroid-stimulating factor as an IgG antibody, a thyroid-stimulating factor that did not belong to thyrotropin was found in the serum of individuals with Graves' hyperthyroidism. It is now apparent that these thyroid-stimulating antibodies, which attach to and trigger the thyrotropin receptor on thyroid cells, are the cause of Graves' hyperthyroidism[4]. Graves' disease is an autoimmune condition primarily affecting the thyroid gland. Autoantibodies to the thyroid-stimulating hormone receptor (TSHR) function as agonists and generate excessive thyroid hormone discharge, which frees the thyroid gland from pituitary regulation resulting in Graves' hyperthyroidism[5].Thyroid hormones exert widespread effects on various bodily systems, resulting to a wide variety of Graves' disease (GD) signs and symptoms that have a substantial impact on general health. Tremors, increased heat sensitivity, inadvertent weight loss an enlarged thyroid gland, irregular menstrual cycles, low libido or erectile dysfunction, exhaustion, increased frequency of bowel movements, palpitations, and other symptoms are typical manifestations[6]. Anti-thyroid drug treatments help patients with Graves' hyperthyroidism return to normal, whereas some individuals experience a relapse of hyperthyroidism after discontinuing the medication. As a consequence, many individuals undergo ablation therapy and develop hypothyroidism following thyroid ablation with radioiodine, surgery, or after a brief or prolonged remission[7].

One important site of action for thyroid hormone action is skeletal muscle. These hormones are essential in controlling numerous aspects of the biochemistry of muscle cells, including the composition of myosin heavy chains, protein metabolism, control of myofibrillar and calcium regulatory proteins, and energy metabolism[8]. Skeletal muscle mass and function are clinically significantly altered in both overt hypothyroidism and hyperthyroidism. Proximal limb muscles are frequently noticeably weaker in people with overt hyperthyroidism (OH), which is defined by decreased serum thyrotropin (TSH) and high free thyroxine (FT4) levels. Research has shown that OH correction leads to significant gains in strength and muscular growth, however β-blockade therapy alone can also improve strength to some extent[9]. People with Graves' disease (GD) frequently experience symptoms such difficulty focusing, memory problems, emotional instability, irritability, sleeplessness, restlessness, sadness, and anxiety during the early stages of the condition. Several prospective studies have demonstrated that the emotional and cognitive symptoms that are present at the beginning of the disease usually go away after the euthyroid state is reached. However, results from prospective studies conducted in Sweden and Denmark have shown that the reduction in quality of life continues over months and years, even in the case of protracted periods of euthyroidism[10]. Vitamin D has been demonstrated to play a function in bone homeostasis and calcium metabolism. It has been established more recently that vitamin D modulates both innate and adaptive immunity. Several autoimmune conditions, such as type 1 diabetes mellitus (T1DM), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and multiple sclerosis (MS), have a documented association with vitamin D insufficiency[11]. Numerous lines of evidence suggest that vitamin D affects the structure and function of muscles. Research on a variety of populations has demonstrated a correlation between decreasing muscle strength and lower levels of 25(OH)D[12]. Observational studies have shown a connection between low levels of vitamin D and weakened muscles, as well as a loss in athletic performance[13]. Hence, the study is aimed to identify the effects of vitamin D supplementation on muscle function and quality of life in individuals with graves' disease.

METHODS

The Belmont Report for Human Subjects' recommendations have been implemented in this investigation. Everyone who participated in the study enjoyed complete autonomy, and their privacy was safeguarded. The study acquired ethical approval was taken from Frontier Medical and Dental Collage Ethical Review Committee (ERC # 3387). A single blinded randomized controlled trial registered in Clinical Trial Registry (NCT06451016). This study was being carried out at King Abdullah Hospital Mansehra Hospital Abbottabad. Duration of the study was between 1-January-2021 to 1-January-2022.

A total of 48 patients recently diagnosed with GD were recruited via envelop method of simple random sampling technique based on the selection

criteria. Written informed consent was obtained from all patient's after explaining the study purpose, procedure, risk and benefits, and confidentiality was maintained throughout the study. Patients, who ranged in age from 18 to 40years, were first diagnosed with GD and were either starting or about to start anti-thyroid medication (ATD) as their preferred course of treatment were included in this study. Individuals with chronic granulomatous disease, hypercalcemia (ionized calcium > 1.40 mmol/l), poor renal function (eGFR < 45 ml/min), or the presence of malignant disease were excluded from the study. Pregnant females or people with low immune strength were also excluded.[14-15]

Patients were randomly divided into Vitamin D supplementation group and placebo group. Standard ATD was provided to both groups for nine months. Patients were allocated in two groups, both the groups were given interventions for nine months of a matching placebo, given as a single daily tablet during mealtime, or with 70 mcg/day (equal to 2800 IU) of cholecalciferol. According to local practice guidelines, all subjects received conventional treatment with ATDs. During baseline, three-month, and nine-month clinical examinations, blood was drawn, isometric muscular strength was evaluated, muscle function tests were performed, and postural stability was measured. Measurements of body composition were obtained at baseline and after nine months. The Physical Activity Scale (PAS) questionnaire was used to assess the participants' levels of physical activity at each research visit. The ThyPRO-39 questionnaire was used to measure health-related quality of life (QoL) at baseline, six weeks, and three, six, and nine months. At baseline, three months, and nine months, more data on drugs, comorbidities, sociodemographic, and musculoskeletal symptoms were gathered. Additional questionnaires were sent to non-respondents after five and ten days, or sent by postal after one and two weeks.

An adjustable dynamometer chair which has a good degree of dependability with correlation values ranging from 0.87 to 0.96 was used to measure muscle strength. Through hand grip, elbow extension and flexion at a fixed position of 90 degrees, and knee extension and flexion at fixed angles of 60 and 90 degrees, the maximal voluntary isometric muscular strength (measured in Newton) and maximum force output (measured in Newton/second) were assessed. Quality of life was measured using Thy Pro-Quality of Life at baseline and after 9 months.

The data was analyzed using SPSS version 23. Demographic information was collected using measures of central tendency and variance, i.e. mean and standard deviation (SD). The Skewness and kurtosis test was applied to identify the normality of data. The data was normally distributed, so an independent sample t-test was run for between-group analysis at baseline, third, and ninth months. P <0.05 was considered statistically significant for muscle strength whereas for quality of life, the test was run at baseline and 9 months.

RESULTS

A total of 48 patients were recruited in the study which were randomly divided into two of the treatment groups n=24 in each group. Demographic details are mentioned in table 1.

Table 1: Showing Demographic Details in Both Groups

Variables		Vitamin D group (n=24)	Placebo Group (n=24)	p-value (<0.05)
Gender	**Male**	8 (33.33%)	7 (29.17%)	0.23
	Female	16 (66.67%)	17 (70.83%)	
Age, years		34.12±4.3	32.8±15	0.01
Body mass index (kg/m²)		24.92±24	26.81±1.34	0.01
Time since diagnosis, days		15±7	21±5	0.02

t-test was applied

Table 2 presents the quantitative changes in muscle strength in patients with Graves' disease who received conventional ATD treatment in addition to either vitamin D supplementation or a placebo from baseline to 3 months and baseline to 9 months using a paired t test. The factors that were looked at included hand grip strength, elbow flexion and extension, knee flexion at 60° and

90°, and knee extension at 60° and 90°. Results showed significant changes from baseline to three-month and ninth-month follow-up in both groups. However, the difference from baseline to three months and ninth month was more significant (p<0.001) in the group who received ATD along with vitamin D supplementation.

Table 2: Muscle Strength at Baseline, Third and Ninth Month

Variables	Vitamin D group			P-value	Placebo Group			P-value
	3 months vs. baseline MD (95% CI)	P-value	9 months vs. baseline MD (95% CI)		3 months vs. baseline MD (95% CI)	P-value	9 months vs. baseline MD (95% CI)	
Hand Grip	1.9 (1.2, 1.6)	0.001	2.1 (3.2, 4.2)	0.001	1.0 (-0.8, 2.8)	0.001	2.0 (0.3, 1.7)	0.001
Elbow Flexion	1.7 (0.5, 1.1)	0.001	1.9 (2.1, 3.9)	0.001	0.7 (-0.6, 2.0)	0.001	1.5 (-0.2, 1.2)	0.001
Elbow Extension	1.1 (-0.3, 1.0)	0.001	1.4 (1.0, 2.6)	0.001	0.5 (-1.0, 2.0)	0.001	1.3 (-0.5, 1.1)	0.001
Knee Flexion 60°	1.5 (1.8, 2.0)	0.001	2.2 (3.7, 4.5)	0.001	0.9 (-0.6, 2.4)	0.001	1.8 (-0.1, 1.7)	0.001
Knee Flexion 90°	1.1 (1.4, 1.7)	0.001	1.8 (2.9, 3.5)	0.001	0.8 (-0.7, 2.3)	0.001	1.6 (-0.2, 1.4)	0.001
Knee Extension 60°	0.9 (0.8, 1.3)	0.001	2.3 (1.8, 5.4)	0.001	0.4 (-0.9, 1.7)	0.001	1.3 (-0.3, 1.9)	0.001
Knee Extension 90°	1.0(1.0, 1.8)	0.001	1.8 (2.5, 3.1)	0.001	0.6 (-0.5, 1.7)	0.001	1.2 (-0.2, 1.6)	0.001
MD, Mean Difference; CI, Confidence Interval, Paired t test for within group analysis								

Table 3 shows between-group comparison of muscle strength analyzed via an independent sample t-test. At 3 months, the Vitamin D group exhibited significantly larger increases in hand grip strength (mean difference: 0.9, $p < 0.001$) and elbow flexion (mean difference: 1.0) compared to the placebo. Although to a lesser extent, improvements were also observed in knee flexion, knee extension, and elbow extension across a variety of angles.

The groups' differences increased over nine months, with the vitamin D group continuing to demonstrate gains in knee flexion and extension measurements, elbow flexion (mean difference: 1.1), and hand grip strength (mean difference: 1.1, $p < 0.001$).

Table 3: Between-Group Comparison of Muscle Strength

Variables	3 months MD (Vitamin D vs. Placebo) (95% CI)	P-value	9 months MD (Vitamin D vs. Placebo) (95% CI)	P-value
Hand Grip	0.9 (0.6, 1.3)	<0.001	1.1 (0.7, 1.5)	<0.001
Elbow Flexion	1.0 (0.7, 1.5)		1.1 (0.8, 1.6)	
Elbow Extension	0.6 (0.1, 1.2)		0.8 (0.2, 1.4)	
Knee Flexion 60°	0.6 (0.2, 1.1)		0.8 (0.4, 1.4)	
Knee Flexion 90°	0.3 (-0.1, 0.8)		0.7 (0.2, 1.3)	

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Knee Extension 60°	0.5 (0.0, 1.1)		1.0 (0.5, 1.6)	
Knee Extension 90°	0.4 (-0.1, 1.0)		0.6 (0.1, 1.2)	
MD, Mean Difference; CI, Confidence Interval; Independent t-test for between-group analysis				

Table 4 provides the Thy Pro Quality of Life scores for both the Vitamin D and Placebo groups at baseline (pre-intervention) and at the ninth month (post-intervention) analyze via paired sample t test. Both groups exhibited improvements in a number of categories, however the Vitamin D group generally experienced more notable decreases in the intensity of their symptoms.

Significant reductions in goiter symptoms (mean drop from 14.5 to 10.5, $p < 0.05$), hypothyroid symptoms, fatigue, cognitive complaints, and emotional vulnerability were noted in the vitamin D group. Interestingly, the overall impact on quality of life decreased from 9.8 to 6.7.

Table 4: Thy Pro Quality of Life at Baseline and Ninth Month

Domain	Vitamin D Group (Pre: Mean ± SD)	Vitamin D Group (Post: Mean ± SD)	P-value	Placebo Group (Pre: Mean ± SD)	Placebo Group (Post: Mean ± SD)	P-value
Goiter Symptoms	14.5 ± 4.0	10.5 ± 3.2	<0.05	14.8 ± 4.2	12.8 ± 3.7	<0.05
Hyperthyroid Symptoms	10.2 ± 3.4	8.7 ± 2.9		10.4 ± 3.3	9.6 ± 3.1	
Hypothyroid Symptoms	15.0 ± 4.5	11.3 ± 3.4		15.3 ± 4.7	14.2 ± 4.0	
Tiredness	16.0 ± 4.5	12.1 ± 4.2		16.3 ± 4.8	14.5 ± 4.5	
Cognitive Complaints	12.1 ± 3.9	9.8 ± 3.1		12.4 ± 4.2	11.5 ± 3.8	
Emotional Susceptibility	14.1 ± 3.8	10.0 ± 2.5		14.3 ± 4.0	13.2 ± 3.0	
Social and Work Impact	10.8 ± 3.7	7.9 ± 2.6		11.0 ± 3.9	10.4 ± 3.5	
Cosmetic Concerns	10.1 ± 3.3	8.5 ± 2.9		10.3 ± 3.5	9.3 ± 3.2	
Overall Quality of Life	9.8 ± 3.5	6.7 ± 2.8		10.1 ± 3.7	9.1 ± 3.1	
SD, Standard Deviation, Paired t-test for within-group analysis						

The Thy Pro-Quality of Life scores between the Vitamin D and Placebo groups following the intervention are compared via independent sample t-test.

In comparison to the placebo group, the vitamin D group exhibited significantly improved results in a number of domains. For instance, the vitamin D group experienced significantly less goitre symptoms (10.5 ± 3.2) than the placebo group (12.8 ± 3.7, $p = 0.045$). Similarly, there were substantial decreases in emotional susceptibility ($p = 0.011$), fatigue ($p = 0.032$), hypothyroid symptoms ($p = 0.027$), social and work effect ($p = 0.034$), and overall quality of life ($p = 0.022$) in the vitamin D group.

The two groups did not vary statistically in terms of hyperthyroid symptoms, cognitive problems, or cosmetic issues.

Table 5: Between-group comparison of Thy Pro Quality of life

Domain	Vitamin D Group (Mean ± SD)	Placebo Group (Mean ± SD)	P-value
Goiter Symptoms	10.5 ± 3.2	12.8 ± 3.7	0.045
Hyperthyroid Symptoms	8.7 ± 2.9	9.6 ± 3.1	0.108
Hypothyroid Symptoms	11.3 ± 3.4	14.2 ± 4.0	0.027
Tiredness	12.1 ± 4.2	14.5 ± 4.5	0.032
Cognitive Complaints	9.8 ± 3.1	11.5 ± 3.8	0.065
Emotional Susceptibility	10.0 ± 2.5	13.2 ± 3.0	0.011
Social and Work Impact	7.9 ± 2.6	10.4 ± 3.5	0.034
Cosmetic Concerns	8.5 ± 2.9	9.3 ± 3.2	0.087
Overall Quality of Life	6.7 ± 2.8	9.1 ± 3.1	0.022
SD, Standard Deviation; Independent t-test for between-group analysis			

Graves' disease presents a significant clinical challenge due to its complex pathophysiology and diverse array of symptoms[16-17].Musculoskeletal symptoms are among the most important of these, affecting the afflicted person's functional abilities and quality of life[18-19] .The purpose of this randomized clinical trial was to evaluate the effects of vitamin D supplementation on the quality of life and muscular function in people with Graves' disease, a group that is frequently affected by weak muscles and decreased athletic performance.

The study's findings are encouraging regarding the possible advantages of vitamin D supplementation in people with Graves' illness, the study's findings are encouraging. There were notable improvements in the muscle strength of both the vitamin D supplementation group and the placebo group from baseline to the three- and nine-month follow-ups in terms of hand grip, elbow flexion and extension, and knee flexion and extension at different angles. But as compared to the placebo group, vitamin D supplementation showed a noticeably bigger improvement in terms of muscle strength boost. These results imply that vitamin D treatment may improve muscle performance in Graves' disease patients, thereby lessening the characteristic muscle weakness of the illness[20-21].

The gains in muscle strength that have been seen after taking vitamin D supplements are consistent with earlier studies that have shown the importance of vitamin D for the health of skeletal muscles. In a study conducted on Vitamin D Level in Graves' Disease and Effect of Vitamin D Supplements on Associated Autoimmunity showed that Low Vitamin D levels have been associated with increased Thyrotropin receptor antibody titers in GD patients, and vitamin D therapy was found to lower thyroid autoantibodies, suggesting a possible link between vitamin D deficiency and increased thyroid autoimmunity[22] .Low vitamin D levels have been linked in numerous studies to both muscle weakness and a decline in sports performance[23]. Skeletal muscle tissue has vitamin D receptors, suggesting a direct mechanism by which vitamin D may affect muscle function[24-25]. Furthermore, it has been demonstrated that vitamin D controls the composition of muscle fibers, protein synthesis, and calcium homeostasis—all of which are vital factors in determining the strength and function of muscles.

Interestingly, the current study's findings on increases in muscle strength were noted in conjunction with standard antithyroid medication treatment, highlighting the possible additional benefits of vitamin D supplementation in enhancing muscle function in Graves' disease patients. This synergistic method, which focuses on combining dietary treatment protocol with the traditional method of pharmaceutical therapy, has considered to be a comprehensive approach to reduce the many signs of Graves' disease and improving overall patient outcomes.

Although the results of our study are not demotivat-

ing but few limitations cannot be ignored. The conclusions drawn may not be able to cover a large aspect or cannot be generalized as the sample size is small. Also, due to the duration which was short, it would have been feasible if a long term follow-up was made to investigate the sustaining of the muscular function improvements that were noted. Moreover, large dosages of vitamin D might have some effects which may have been labelled as unfavorable consequences including hypercalcemia, which were not assessed in this study.

CONCLUSION

In summary, vitamin D supplementation might be a vital additional treatment for improving overall wellbeing and muscular health in this targeted population. More studies with large sample sizes, along with standard longer follow-up periods, and a rigorous evaluation of possible side effects are indeed necessary to clarify the function of vitamin D in the treatment of Graves' illness.

RECOMMENDATIONS

In order to adopt a comprehensive approach, health care provision will be addressed diversely and accordingly thus enhancing both therapeutic outcomes and quality of life.

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CONFLICT OF INTEREST

There was no conflict of interest.

ETHICAL APPROVAL

Ethical approval from Frontier Medical and Dental College Ethical Review Committee (ERC # 3387).

AUTHOR'S CONTRIBUTION

SS, SR, and **MT** participated in the study design, data collection, drafting, and critical review. **SAK, SK, SB,** performed data collection, and analysis and wrote the description of the results, and wrote the Discus-sion **SS, SR, SK**, and **SB** participated in the finalization of the article. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

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