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Does Levothyroxine Improve Exercise Capacity in Patients with Thyroid Disease?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

OBJECTIVE: The objective of this selective EBM review is to determine whether or not levothyroxine improves exercise capacity in patients with thyroid disease.

SUDY DESIGN: Review of three English language primary studies published in peer-reviewed journals in 2000, 2005, and 2009

DATA SOURCES: Two randomized control trials and one clinical trial comparing leveothyroxine to euthryroid were found using Medline, and PubMed databases.

OUTCOMES MEASURED: Each of the three studies measured heart rate and blood pressure before during, and after exercise in patients to determine the effect levothyroxine has on both heart rate and blood pressure

RESULTS: One RCT found that submaximal cardiopulmonary exercise performance improved after six months of TSH normalization. The second RCT found that with careful tailoring of TSH-suppressive therapy there is improvement in exercise performance. The controlled clinical trial found that restoring a patient to normal TSH levels does not produce significant changes in substrate response to exercise.

CONCLUSIONS: The results demonstrate that the studies do not agree on the effects of levothyroxine or euthyroid on exercise capacity.

KEYWORDS: Hypothyroidism, exercise capacity, levothyroxine

INTRODUCTION

Hypothyroidism is a condition in which the thyroid gland doesn't produce enough thyroid hormone, where thyroid stimulating hormone (TSH) is greater than normal, and the thyroid hormone (T4) levels are decreased. Thyroid hormones stimulate metabolic activities in most bodily tissues and when levels decrease, metabolism slows.[1] Major targets for thyroid hormones are the heart and skeletal muscle. Therefore, hypothyroidism can lead to weaker heart muscle, causing decreased cardiac output and contractility, bradycardia, and an increase in vascular resistance.[2] This can ultimately lead to a negative impact on an individual's quality of life.

It is estimated that 10 million Americans (approximately 1% of the US population) are diagnosed with hypothyroidism.[1,3] Higher rates of hypothyroidism have been diagnosed in women and in individuals over the age of 50.[1] Although the annual cost or number of healthcare visits is not available for the US, in Germany, data shows that iodine-deficiency hypothyroidism costs approximately 1 billion dollars annually and inpatient care accounts for nearly $250 million a year.[4]

There are several different causes of hypothyroidism. Iodine deficiency is the most common cause of hypothyroidism worldwide. The most common form found in the US is Autoimmune thyroiditis (Hashimoto's disease), which can be associated with a goiter and results in gradual loss of thyroid function. Hashimoto's disease has a mean incidence of 4/1,000F and 1/1,000M. Congenital hypothyroidism is caused by thyroid gland dysgenesis, is present in 1/4,000 newborns and can either be transient or permanent.[1]

Thyroid hormone is produced in the thyroid gland using iodine. Thyroxine (T4) and triiodothyronine (T3) are the two most important hormones. In the blood, all hormones are

converted into T3, the active hormone that affects the metabolism of cells. Since hypothyroidism can affect many different body systems, many individuals seek medical care due to the effects of hypothyroidism before they are even diagnosed. Individuals will often experience: fatigue, lethargy, anorexia, constipation, depression, menstrual changes, muscle stiffness, cold intolerance, dry skin, memory impairment. Definitive treatment for individuals with hypothyroidism is through the use of daily medication. Standard treatment is Levothyroxine (Synthroid), a form of T4. The dosage of levothyroxine is based between1.0-1.7 mcg/kg/day. Second line treatments include: Cytomel (Liothyronine), a form T3, and Armour thyroid, a T3/T4 combination.[1] Since hypothyroidism affects metabolism, it consequently affects skeletal muscle, cardiac function, and exercise capacity (maximal physical exertion) in individuals. When taking levothyroxine, the T4 hormone that is naturally produced in the body is replaced. This allows the body to function with normal hormone levels, ultimately decreasing the physical, cardiac and vascular effects of hypothyroidism within the body. In the three reviewed studies, decreased exercise capacity is evaluated through heart rate (HR) and blood pressure (BP), along with other factors. Being the standard treatment for hypothyroidism, levothyroxine may provide positive outcomes in regards to exercise capacity by helping to reverse the negative effects triggered by low thyroid hormone.

OBJECTIVE

The objective of this systematic review is to determine if levothyroxine is effective in increasing exercise capacity in subjects with thyroid disease.

METHODS

Studies for this systemic review were found using the key words: hypothyroidism, exercise capacity and levothyroxine. All studies were published in peer-reviewed journals in English. All literature searches were performed through Medline and PubMed. Inclusion criteria for the review were: POEM, randomized controlled trials and studies that were posted in 1996 or later. Exclusion criteria for the review included: drugs that could influence heart rate, blood pressure or thyroid function, except levothyroxine. The statistics used in the reviewed studies includes P-values, ANOVA, T-test, and Wilcoxon test.

Three studies (2 RCT, 1 clinical trial) were selected for this review and met the following criterion:1) The population of participants included male and/or female subjects receiving levothyroxine for thyroid disease; 2) Interventions used were levothyroxine either in a fixed dose or dosed to make an individual euthyroid; 3) Comparison groups in the study were euthyroid subjects compared to those taking levothyroxine and 4) Outcomes measured were blood pressure and/or heart rate. A summary of the design and results of the three studies is outlined in Table 1.

The study performed by Mainenti et al. was conducted in Rio de Janeiro, Brazil at the Federal University of Rio de Janeiro. Subjects were recruited from the outpatient Endocrine Clinic at the University. Inclusion criteria for the study included: untreated 30-60 years old with increased TSH >4.0 and Normal free T4 levels. Exclusion criteria used for the study were: subjects taking drugs that alter thyroid function, HR and/or BP, an individual diagnosed with cardiac diseases including atrial hypertension, and lastly problems that could interfere with walking. All subjects met the inclusion and exclusion criteria of the study and gave written consent that was approved by the ethics committee.[5]

The study performed by Caraccio et al. was conducted in Pisa, Italy at the University of Pisa School of Medicine. Individuals, aged 26-34, were recruited from the outpatient clinic with elevated TSH levels (>3.6 mlU/liter) and Hashimoto's thyroiditis which was verified with positive antithyroid peroxidase and antithyroid autoantibody titers. Exclusion criterion included: any parameters found outside of the given inclusion criteria for sex, age, BMI, body composition and subjects without Hashimoto's thyroiditis. Subjects had blood sampled and were evaluated for neurologic, cardiovascular, respiratory or other systemic diseases. The study protocol was approved by the ethics committee and all subjects signed and confirmed informed consent.[6]

The study performed by Mercuro et al. took place at the University of Cagliari in Cagliari, Italy. The inclusion criteria for this study included: individuals 26-65 years old, long term TSH-suppressive fixed dose levothyroxine therapy of 700-1575mcg for 2-20 years, a normal free T3 and suppressed TSH $\leq$ 0.1 mU/L. Exclusion criteria includes: subjects taking drugs for cardiovascular disease or any medications other than levothyroxine. All of the subjects were screened for cardiovascular disease or the concomitant use of other medications.[7]

Table 1: Demographics of included studies

Study	Design	Subjects	Age	Inclusion criteria	Exclusion criteria	W/D	Interventions
Mainenti et al.[5]; 2009	RCT	23	30-60	Untreated subjects; 30-60 yo; increased TSH >4.0, Normal free T4 levels	Drugs that could change thyroid fx, HR, BP; diagnosed cardiac ds, atrial HTN; problems that can interfere with walking	N/A	TSH normalized with levothyroxine
Caraccio et al.[6]; 2005	RCT	33	26-34	Increased TSH >3.6, normal free	Subjects that don't match control group	N/A	12mo levothyroxine replacement

				T3&4 levels; + Hashimoto's thyroiditis, + antithyroid peroxidase & antithyroid autoantibody titers	for sex, age, BMI, body composition; Pts with negative ds or antithyroid titers		to euthyroid
Mercuro et al.[7]; 2000	Clinical Trial	38	26-65	Long term therapy of 700-1575mcg X 2-20 years; normal free T3; suppressed TSH $\leq$ 0.1 mU/L	Cardiovascular ds; taking any drugs other than levothyroxine; No sympatholytic meds X 1yr	N/A	Levothyroxine at fixed dose of 1.8-4 mcg/kg

OUTCOMES MEASURED

The primary outcomes measured in the studies were HR and/or BP. The values were measured before, during, and after exercise in subjects to determine the effect that levothyroxine has on both HR and BP. In each of the three studies, subjects were monitored using an EKG during exercise from which they could determine the HR. In the Mainenti et al. study the BP was measured using the ausculatroy method before exercise and at three minute intervals during exercise.[5] In the Mercuro et al. study arterial BP was measured every three minutes of exercise and at the first, fifth and tenth minute of recovery using a mercury sphygmomanometer.[7]

Although the studies measured HR and/or BP, the studies also looked at other measurements. Mainenti et al. measured HR, oxygen uptake, minute ventilation and other cardiopulmonary parameters within the fifth minute of exercise to obtain sub-maximal exercise measurements.[5] Caraccio et al. measured HR, oxygen uptake (VO_2), and carbon dioxide output

during an incremental aerobic exercise test. At rest, every two minutes during the incremental aerobic exercise test, and during twenty minutes of recovery blood "glucose, lactate, pyruvate, free fatty acid, glycerol and B-hydroxybutyrate concentrations" were measured.[6] Mercuro et al. evaluated cardiac function through clinical, echocardiogram and ergometabolic means. The evaluation includes "intraventricular septum thickness, left ventricular posterior wall thickness, end-diastolic dimension and left ventricular mass index". "During the exercise portion of the study exercise tolerance (maximal tolerated workload), maximal VO_2, and anaerobic threshold" was evaluated in addition to heart rate.[7]

RESULTS

The results from the reviewed studies were presented as continuous data, which cannot be changed to data in the dichotomous form. Studies looked at HR and/or BP to help determine the effects that levothyroxine has on exercise metabolism by comparing control to treated subjects. Studies compared BP and/or HR at base line and then again at six months along with monitoring the values during exercise. With lower HR values during exercise the heart is working more efficiently and pumping more blood through the body with each beat. This means that at the same level of exercise, with a lower HR one is working less hard and pumping more blood to the tissues and organs in the body.[8] The same concept is used with BP during exercise. Blood pressure is a reflection of the resistance of blood flow through the arteries. If your BP is lower during exercise, the heart is working less to pump blood throughout the body. A lower HR and BP during exercise helps the body work more efficiently. With an elevated HR or BP during exercise one may experience: decreased ability to perform exercise routines, chest pain, palpitations, increased shortness of breath, increased fatigue, and headache.

Mainenti et al. reported HR of untreated subjects of 129 ± 17 bpm at baseline and 128 ± 17 bpm at six months vs 128 ±17 bpm at baseline and 121 ± 17 bpm at six month follow up for treated subjects. The p-value for HR was statistically significant with $p<0.05$. When compared before and at peak exercise, both systolic and diastolic blood pressure values were not significantly different from baseline to the six month follow-up. Systolic blood pressure (SBP) in untreated subjects at baseline was 142.7 ± 26.8 mmHg and 154.55 ± 23.9 mmHg at six months. For the treated subjects SBP was 145.5 ±17.9 mmHg and 142.3 ± 18.2 mmHg, respectfully. Prior to exercise, the mean BP was "116/79 mmHg vs 120/81 mmHg (untreated) and 122/80 mmHg vs 119/80 mmHg (treated)". At peak exercise, mean BP values were "159/90 mmHg vs 173/89 mmHg (untreated) and 158/87 mmHg vs 154/86 mmHg (treated)".[5] A summary of the results can be found in table 2.

Table 2: Summary of BP and HR as outline in the Mainenti et al. Study[5]

	Untreated Subjects (n = 12)		Treated Subjects (n = 11)	
	Baseline	6 months	Baseline	6 months
HR (bpm)	129 ± 17	128 ± 17	128 ±17	121 ± 17
SBP (mmHg)	142.7 ± 26.8	154.55 ± 23.9	145.5 ±17.9	142.3 ± 18.2
BP mean (prior to exercise)	116/79	120/81	122/80	119/80
BP mean (at peak exertion)	159/90	173/89	158/87	154/86

The p-value was statistically significant with <0.05

Caraccio et al. reported that euthyroid subjects experienced a higher HR as the workload increased compared to their control counterparts. This data was found to be statistically significant with $P<0.03$. Resting HR in untreated subjects was 85 ± 3 bpm vs 78 ± 4 bpm for

control subjects ((table 3). Following twenty minutes of exercise, the subjects HR was about 170 bpm vs 145 bpm for the control group. Resting HR in treated subjects was 78 ± 3 bpm (baseline) vs 79 ± 3 bpm (six months), whereas HR in placebo subjects was 85 ± 2 bpm vs 89 ± 3 bpm respectfully.[6] In follow up studies, there were no substantial differences observed between the placebo and active treatment for HR values.

Table 3: Summary of gathered HR data in the Caraccio et al. study[6]

	Untreated Subjects	Control Subjects
Resting HR (bpm)	85 ± 3	78 ± 4
Exercise HR (min 10)	~145	~130
Exercise HR (min 20)	~170	~145

Data was significant with P<0.03

Mercuro et al. reported a slightly higher HR in the experimental group compared to the control group, with p<0.01. Resting HR was 88 ± 17 bpm in subjects vs 88 ± 8 bpm in the control group. At peak exercise, HR was 96 ± 6.9 bpm and 95 ± 2 bpm respectfully. SBP was 133 ± 25 bpm and 114 ± 10 bpm respectfully and 183 ± 18 bpm and 179 ± 14 bpm respectfully. In regards to BP, P<0.05.[7] This data is represented in table 4.

Table 4: Mercuro et al. table of results summary[7]

	Treated Subjects (n=9)	Control Subjects (n=9)
Resting HR (bpm)	88 ± 7	88 ± 8
Peak Exercise HR	96 ± 6.9	95 ± 2
Resting SBP (mmHg)	133 ± 35	114 ± 10
Peak SBP (mmHg)	183 ± 18	179 ± 14

p<0.01

Mainenti et al. trial looked at treated and untreated experimental groups compared the results between baseline and six month follow up.[5] The Caraccio et al. trial studied treated subjects vs placebo both at baseline and then six month after treatment.[6] Finally, the Mercuro et al. study compared the experimental group and then the control group.[7] All three studies were without adverse affects, and therefore numbers needed to harm could not be calculated.

During all three studies, subjects were monitored at baseline and then at the six month follow-up and all parameters were measured at several intervals during exercise. None of the studies reported any loss of participants or adverse effects during the study causing subjects to leave.

DISCUSSION

Hypothyroidism is a very common endocrine disorder, especially in older women. Thyroid hormone released from the thyroid gland works to control the metabolism in the body. When levels are low, all functions of metabolism are decreased. Levothyroixine is the treatment of choice for hypothyroidism since it replaces T4, which is then converted into T3, the active from of thyroid hormone.[1] Since thyroid hormone is used to directly replace the hormone that is absent in the body, it is thought that all effects of the metabolic disorder will be reversed.

The studies used participants that were being seen and some treated for sub-clinical hypothyroidism. The participants of the studies were not on any other medication or had any other physical ailments that would prohibit them from performing the exercise portion of the study. All placebo or controlled subjects were matched for age, sex, BMI, and body composition. The studies took baseline and six month follow-up measurements. In the three studies, blinding did not seem to be compromised.

The Mainenti et al. study showed that in subjects who had received levothyroxine treatment had a decrease in HR after the six months. In the same treated group, the study found that at peak exercise exertion, BP was lower than in the untreated group. With these results, it was shown that at submaximal exercise, treated subjects spent less energy than the untreated group.[5]

Caraccio et al. demonstrates that untreated subjects show increased HR levels when compared to euthyroid subjects at an equal exercise intensity. The study was not able to find significant changes in energy or response to exercise. Levothyroxine did not appear to correct the exercise impairment found in sub-clinical hypothyroidism during the course of the study.[6]

Mercuro et al. was able to show that HR in subjects was slightly higher than euthyroid individuals during exercise, but "careful adjustment of levothyroxine dose can reverse and almost completely normalize cardiopulmonary" function.[7]

CONCLUSIONS

Two of the three studies show that there is a statistical difference in exercise capacity between untreated and treated subjects and between baseline and the six month follow up. Since there is discrepancy between the three studies, it cannot be stated that there is added benefit, for exercise capacity, to treatment in those with subclinical hypothyroidism. Therefore, the evidence is equivocal in determining a conclusive answer to whether or not levothyroxine is effective in increasing exercise capacity in subjects with thyroid disease.

Even though there are many individuals diagnosed with hypothyroidism yearly, it is a health disparity that requires further attention. Since subjects are given T4 in the form of levothyroxine to treat their hypothyroidism, each subject could respond differently to the

treatment, causing discrepancy in the study result. Instead of having a set TSH level in future studies, it might be beneficial to titrate levothyroxine to symptomatic treatment and then perform exercise studies. This would increase the chance that each individual person would be receiving the correct amount of treatment for their body and not being based just on lab values.

If a study could be conducted on populations at high risk for the development of sub-clinical hypothyroidism before being diagnosed or treated, it might help determine if those who are more active in their youth have a higher probability of responding to medicine and, thus, be able to reverse the effects of hypothyroidism on the body.

Researchers may also consider whether Synthroid, the brand name of levothyroxine, affects subjects significantly different compared to the generic form. If this is the case, then one form could be prescribed more in situations where exercise capacity is decreased.

Since each of the three reviewed studies had a small subject population, it would be beneficial to gather a larger subject population to help provide more conclusive data in the future. Apart of the subject population for the studies should be a placebo group to help compare results. This was not done in the Mainenti et al. study.

In conclusion, long term and larger subject trials are needed to help determine if levothyroxine does have a positive benefit on exercise tolerance in those with hypothyroidism since the three reviewed studies in this case review yielded inconclusive results.

References

1. Jameson, JL, Weetman, AP. Chapter 335. Disorders of the Thyroid Gland. In Braunwald, E.; Fauci, A., Kasper, D., et al. *Harrison's Principles of Internal Medicine*. 17th edition. New York: McGraw Hill; 2008.
2. Klein, I, et al. Cardiovascular effects of hypothyroidism. UpToDate 19.3. UpToDate Marking Professional, 2011. http://www.uptodate.com/contents/cardiovascular-effects-of-hypothyroidism. Accessed December 11, 2011
3. Fitzgerald, PA. Chapter 26. Endocrine Disorders. In McPhee, S.; Papadakis, M. *Current Medical Diagnosis and Treatment 2011*. 50th edition. New York: McGraw Hill; 2011
4. Kahaly, GJ, Dietlein M. Cost estimation of thyroid disorders in Germany. *Thyroid*. 2002;12:909- 914. http://ceecis.org/iodine/04a_consequences/04_cost/IDD%20costs%20Germany.pdf. Accessed December 11, 2011
5. Mainenti MR, Vigario PS, Teixeira PF, Maia MD, Oliveira FP, Vaisman M. Effect of levothyroxine replacement on exercise performance in subclinical hypothyroidism. *J Endocrinol Invest*. 2009;32(5):470-473.
6. Caraccio N, Natali A, Sironi A, et al. Muscle metabolism and exercise tolerance in subclinical hypothyroidism: a controlled trial of levothyroxine. *J Clin Endocrinol Metab*. 2005;90(7):4057-4062.
7. Mercuro G, Panzuto MG, Bina A, et al. Cardiac function, physical exercise capacity, and quality of life during long-term thyrotropin-suppressive therapy with levothyroxine: effect of individual dose tailoring. *J Clin Endocrinol Metab*. 2000;85(1):159-164.

8. Simon, Harvey MD. Exercise – Exercise's Effects on the Heart. University of Maryland Medical Center (UMMC), 2011. http://www.umm.edu/patiented/articles/what_ effects_of_exercise_on_heart_circulation_000029_3.htm. Accessed May 30, 2012