The role of endurance exercise program inhyperthyroidism in relation to ACE genotype

Heshmat, H.* and Saad El Taib**

* Dep. of physiol. Fac. Of Med. Zagazig Univ.
** Dep. of Biol. SC. and Motion Rehab. Fac. Of PE, Zawia Univ.
Taibsaad2010@yahoo.com; Husseinheshmat43@hotmail.com

Abstract: Background : There are three widely recognized types of exercise: endurance, resistance and sprint. Endurance exercise is characterized by prolonged continuous or intermittently periods of contractile activity against low resistance. ACE gene polymorphisms has been associated with some metabolic disorders. **Purpose** : This study investigated the role of endurance exercise program in hyperthyroidism in relation to ACE genotype. **Methods** : Using PCR method the ACE was genotyped in ten hyperthyroid patients and ten control before and after 12 weeks of endurance exercise program, thyroid hormones and TSH were investigated using Elisa technique. **Results** : ACEDD (80%) and ID (20%) genotype were associated with hyperthyroidism, in control, ACEID (50%), ACEII (25%), ACEDD (25%). TSH decreased in hyperthyroidism with increased F. T_4, T_3, T. T_4, T_3. compared to control. After endurance training program TSH increased, while F.T_4, T_3 and TT$_4$, T_3 decreased in hyperthyroidism together with reduction in pulse rate and blood pressure .**Conclusion**: ACE genotype may have a pathogenic role in thyroid gland, Endurance exercise training might have a positive effect alone in treating hyperthyroid subjects. **Recommendation:** to use ACE genotype to evaluate hyperthyroidism, and TSH and thyroid hormones as indicators of the efficiency of endurance training program.

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1. Introduction

Thyroid hormones are essential for normal growth, development and metabolism. Hormone production by the thyroid gland is tightly regulated through the hypothalamic pituitary axis (Smith et al., 1990). They also added that thyroid disease is common, particularly in women, with a prevalence in the community of 3-5Y. Once diagnosed, thyroid disease is easily treated, with an excellent long-term outcome for most patients.

Guyton and Hall (2006) reported that the most important regulator of thyroid homeostasis is thyroid-stimulating hormone (TSH). This peptide hormone comprises a specific beta unit, which is required for binding to the TSH receptor, and an alpha subunit, which is common to the gonadotrophins, both subunits are required for bioactivity.

Hyperthyroidism is the symptom of an overactive thyroid gland follow logically from the actions of thyroid hormone, it is characterized by nervousness, weight loss, hyperphagia, heat intolerance, increased pulse pressure, a fine tremor of the fingers, sweating and a BMR from +10 to as high as + 100. The most common cause is graves disease, which accounts for 60 – 80% of the cases, This is an autoimmune disease, more common in women, in which antibodies to the TSH receptor stimulate the receptor. This produces marked T_4 and T3 and enlargement of the thyroid gland (goiter), TSH is low and exophtalmos occurs in 50% of patients (Barret et al., 2010).

The renin – angiotensin – aldosterone system : Renin is secreted in response to a fall in renal afferent arteriolar pressure or to a reduction in supply of Na^+ to the distal tubule. It convert angiotensinogen in plasma to angiotensin I (A_I), which in turn is converted to angiotensin II (A_{II}) by angiotensin converting enzyme (ACE). Both A_{II} and its metablolic product angiotensin III are pharmacologically active, and stimulate the release of aldosterone from the adrenal cortex, which promote Na^+reabsorption in exchange for urinary loss of H^+ or K^+ (El Shafei et al, 2011, Joshi etal 2011). Palvic et al., (2012) stated that ACE is an important regulator of blood pressure and cardiovascular homeostasis. Plasma levels of ACE depend on an insertion / deletion polymorphism in its gene.

El Taib (2012) reported that the thyroid gland hormones are so vital for many plysiological process in the human body but the biological effects of short term changes on the levels of these hormones due to physical effort is not totally understood until now. Some studies mentioned that physical efforts lead to an instant decline in T_3 and T_4 concentrations, where others mentioned that physical effort has no effect on these hormones. A third group mentioned that physical efforts raised the level of these hormones as a reaction of exercises. The disagreement between those studies leads to the necessary of performing further

researches trying to indentify this effect together with its action on ACE genotype.

Sports activity cause basic changes in the energy required for metabolism and to ensure the excess production in muscle and cardiac contraction due to physical exertion and the hormones working to accumulate energy in the physical activity are stress hormones including thyroid hormones or enzymes expressed by genes as ACE. (Heshmat et al., 2010), Burger (2004)

Inherited defects of thyroid hormone metabolism has been discussed by Dumistrescu and Refetoff (2011) They came to the conclusion that the only known inherited defect of intracellular thyroid hormone metabolism is caused by mutations in the SBP_2 gene affecting selenoprotein synthesis, among which the typical laboratory findings are high T_4, Low T_3, high r T_3, normal or slightly elevated serum TSH, decreased serum se and decreased selenoprotein levels and activity in serum and tissues. The clinical phenotype is complex; affected individuals may have delayed growth and puberty, and in severe cases failure to thrive, mental retardation, infertility and myopathy. SBP_2 defects could have as yet undetermined consequences and the identification of additional patients, and their long term follow up are important in further characterizing this recently described defect. So, we investigated the role of endurance exercise program, in hyperthroidism in relation to ACE genotype.

Methods

The study included 10 female thyroid patients (hyperthyroid) and 10 female control group. Their baseline characteristic are reported in

Table (1)

Variables	Thyroid patients (n=10)	Control (n=10)
Age,Y	35 ± 4	37 ± 5
Gender	Female	Female
Height, cm	162 ± 7	164 ± 9
BMI	23.4 ± 5.6	22.3 ± 4.5
Weight, Kg	63 ± 11	61 ± 12
Blood pressure mm/Hg	150/90	122/78
Pulse Rate count/min	88 ± 6	78 ± 7

Values M±SD significant P< 0.05

Venous blood was obtained from all participants for genomic DNA and ACE genotype, pulse rate, B/P, BMI. Thyroid function test (TSH, $F.T_{3,4,}$ T_{T3} T_4,) each participant underwent a medical history and Physical examination. The presence of Thyroid dysfunction was determined by lab test and clinical assessment.

Identification of ACE genotype

Genomic DNA was extracted, then DNA fragments were amplified by PCR, genotype was performed by Quiaxel. Including concentration and pulse rate, BP in each case of participants, diseased and control.

The main symptoms of hyperthyroidism in the examined patients of the study :

- a high state of excitability.
- intolerance to heat.
- increased sweating.
- weight loss.
- varying degrees of diarrhea.
- muscle weakness.
- extreme fatigue.
- nervousness.
- inability to sleep.
- tremors of the hands.
- some patient develop some degree of protrusion of the eyeballs (exophthalmos).
- some other patients with increased thyroid gland (Barret el al, 2010).

The PCR conditions were determined using a primer pair of sense 5-CTG GAG ACC ACT CCC ATC CTT TCT – 3 and antisense 5-GAT GTG GCC ATC TTC GTC AGA- 3. PCR amplification was carried out in a total volume of 25 ul containing 50ng template DNA, Hormone estimation was carried out using Elisa technique.

Endurance training program after Grandys (2008).

Statistical analysis: Genotypes among the patients and controls were obtained by direct enumeration based on PCR results.

3. Results

The results of hormones were reported as Means ± SD.

T test was also performed between two groups, significant resuls reported P< 0.05.

Table (2) comparison of the studied parameters in control and hyperthyroid groups.

Parameters / Groups	TSH m iu/L	F T_4 (pmol/L)	F T_3 (pmol/L)	T T_4 (mmol/L)	T. T_3 (mmol/L)
control n = 10	2.4±0.23	16.4±4.1	1.80±0.5	81±11.2	2.6+0.2
hyperthyroid patients n = 10	(*) 0.1±0.02	(*) 32.1±6.2	(*) 7.9±2.1	(*) 90±13.0	(*) 2.9±0.3

Values given as the mean + SD * Significant difference at P≤ 0.05

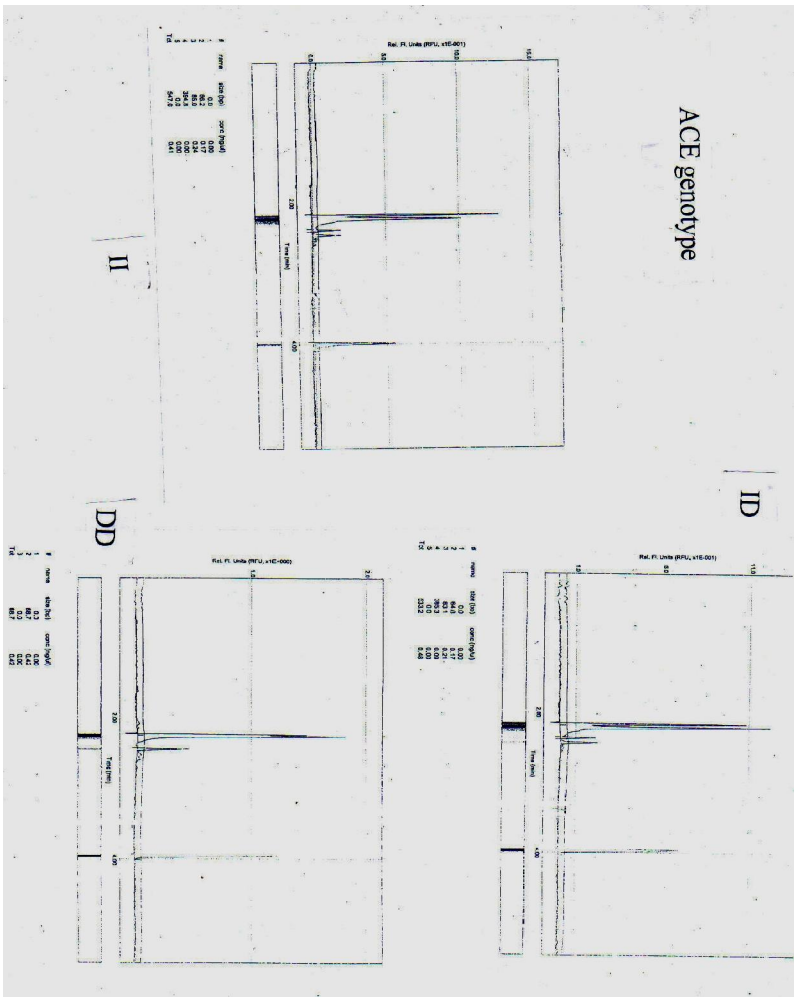

Table (3) comparison of the studied parameters in hyperthyroid group before and after endurance exercise program.

Parameter / Group	TSH miu/L	F T_4 (pmol/L)	F T_3 (pmol/L)	T T_u (mmol/L)	T. T_3 (mmol/L)
hyperthyroid before endurance exercise	0.1±0.02	32.1±6.2	7.90±2.1	90±13.0	2.9±0.3
hyperthyroid after endurance exercise	(*) 1.3±0.6	(*) 25.2±4.4	(*) 2.4±0.7	84±6.4	2.8±0.4

Values M ± SD Significant at P < 0.05

Table (4) Comparison of the pulse rate and blood pressure in hyperthyroid group before and after endurance exercise.

Parameter / Group	Pulse rate Count/min	Blood Pressure mm Hg
hyperthyroid before exercise	88 ± 6	150/90
hyperthyroid after exercise	82 ± 5 *	138/84*

Values M ± SD significant P < 0.05

Table (2) revealed a decreased TSH, and increased F.T_4, T_3, T_{T4}, T_3 in hyperthyroid subjects.

- The results indicated (table3) a decrease in T_{T3}, and T_{T4}, hormones after the endurance training program.
- TSH increased after endurance exrcise in hyperthyroid cases.
- The results also revealed a decreased T_{T3}, T_{T4}, after endurance physical effort.
- As for ACE genotype, the results indicated that the ACEDD and ACEID represents a major association with abnormalities of thyroid function and may have a pathogenic role in thyroid glands and needs to be addressed in future studies. In control group the ACE genotype recorded revealed ACEDD (25%) I/D (50%) ACEII (25%)

4. Discussion

TSH acts on thyroid metabolism through its stimulation of thyroid hormones at all stages such as iodine uptake, organization and coupling, it also enhances the release of stored thyroid hormones, and increases DNA content, RNA and translation of proteins together with stimulation of glycolysis and activates adipose tissue lipase to enhance the release of fatty acids (Chatlerjea and Rana Shinde, 2006) Yen (2001).

The data presented in table (2) indicated a low TSH concentration (0.1 mu/ L.)this result is in agreement with that of Smith el al (1990)

Mona Abou Zahra et al (2006) and Stockigt (1996). They reported that the measurement of TSH in a basal blood sample provides the single most sensitive, specific and reliable test of thyroid status. In case of hyperthyroidism TSH is below 0.1 m u/L. and a normal TSH excluded a primary thyroid disorder (Cooper, 2003).

As for $F.T_3$, $_{T4}$ and $T.T_3$ T_4, data presented in Table (2) indicated a higher level of both $F.T_3$ and T_4 and $T.T_3$, $T.T_4$. The measurement of thyroid hormones free or total provide the most reliable indication of thyroid status, as free and total T_3, T_4 can help assess the severity of thyroid disease and distinguish subclinical from overt disease. Smith et al (1990) reported that free thyroid hormone measurements correlate more closely with thyroid status than total hormone measurements , which are heavily influenced by changes in the concentration of thyroid hormone – binding proteins. Murray et al., (2009) stated that one half to two thirds of T3 and T4 in the body is in an extrathyroidal reservoir most of this circulates in bound form, bound to a specific binding protein, Thyroxine – binding globulin (TBG), is a glycoprotein with a molecular mass of 50 KDa, binds T_4 and T_3 and has the capacity to bind 20 ug/ed of plasma. Under normal circumstances. TBG, binds nearly all of the T_4 and T_3 plasma, and it binds T4 with greater affinity than T3. Thus, in spite of the great differences in total amount, the free fraction of T_3 approximates that of T_4 and given that T_3 is intrinsically more active than T_4, most biologic activity is attributed to T_3, T BG does not bind to other hormones. (Guyton and Hall, 2006 Dayan 2001)

From the conversion of Angiotens in I into angiotensim II by ACE. La Churie et al. (1995) stated that contracting with the lack of relation between ACE gene polymorphism and blood pressure level, a large case – control study has shown that the deletion marker allele of the ACE gene was associated with an increased risk of myocardial infarction. While, Ohishi, (1993) identified that the Dallele has been associated with growth of vascular smooth muscle at the site of coronary angioplasty and human cardiac hypertrophy in response to exercise (Montgomery et al., 1997). Kumar et al., (2012) investigated seven polymorphisms including ACE gene and essential hypertension and found a possible contribution of ACE and Nos in the complex etiology of hypertension As for ACE genotype, the results indicated 80% ACEDD, 20% in case of ACEID with a higher Blood pressure in case of ACEDD compared to ACEID genotype. In case of the control group they have normal blood pressure and ACEDD 25%, ACEID 50%, ACEII 25% This was also reported by Jalil et al (2004) . Heshmat et al., (2010).

Andreas (1997) stated that ACE is a key component of the renin angiotensin system thought to be important in the pathogenesis of hypertension and other cardiovascular disease, Tiret el al., (1992) recorded that the Dallele of ACE genes is characterized by higher ACE in the blood. Hashimoto et al (2001) reported that the increase in blood pressure noticed in subjects having ACEDD might results. After an exercise training program of low intensity endurance exercise for 3 months, there was an elevated TSH concentration together with decreased level of F,T3, T4 and T. T3, T4 (Table 3) .

The exercise training program induced a positive effect on thyroid hormone parameters in hyperthyroid patients, the positive effect of endurance exercise might be due to decreased stresses on the patients and hence a relaxation of muscles of blood vessels which induced a higher stimulation on pituitary and thyroid glands, with the end results a positive effect and higher metabolic action. Fricker et al. (2003) and Wiesli et al (2003) reported that thyroid dysfunction is associated with changes is cystatin C which can be used as marker for thyroid patients due to direct thyroid hormones upon it.

The decreased thyroid hormones and elevated TSH concentration was noted after exercise in many studies such Malik (2011), Maha et al (2011), Mohamed et al (2009). Grandys et al (2008), Figen et al (2005), Loucks et al (1993). They stated that the decreased $F.T_3$ might be caused due to R T_3 formation which act as a brake if the body needs lesser energy, which direct the thyroid gland to synthesize more reverse T_3 (R T_3) than T_4 .

Table (4) revealed that endurance exercise training induced a significant decrease in pulse counts and blood pressure, which indicated a better fitness state to the hyperthyroid patients. It was also noted that there was an association with the occurrence of hypertension and hyperthyroid patients and the prevalence of ACE genotype DD and ID. This was in accordance with Wu et al (2011) and Siklar et al (2011).

Conclusion

1- ACEDD, ID genotypes predominate hyperthyroidism and may have a pathogenic role in thyroid gland.

2- TSH decrease is the main lab test of hyperthyroidism.
3- Endurance training might have a positive effect alone or together with antithyroid drugs in treating hyperthyroidism

Recommendation

To use ACE genotype to evaluate hyperthyroidism, and thyroid hormones as indicators of training efficiency.

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