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Study of Carcinoma Embryonic Antigen (CEA) and its Relationship to TSH Polymorphisms in Patients with Thyroid Gland Dysfunction.

Sawsan Hassan Kadhum
Babylon Technical Institute, Al-Furat Al-Awsat Technical University, Iraq
E-mail: dr.mohamadsabri@yahoo.com

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ABSTRACT
In this study, 145 patients with different thyroid dysfunctions were included. All the patients have undergone for measuring thyroid hormone (T3, T4 & TSH). These patients are put in five groups, in the first group, which include 38 patients who have hyperthyroidism, the second group includes 58 patients who have hypothyroidism, the third group includes 31 patients who have Euthyroid with normal thyroid hormones levels, the fourth group includes 5 patients only who have low levels of thyroid hormones, and the last group includes 13 patients who have a high levels of TSH with normal level of T3 & T4. All samples are obtained before treatment. All serum samples are subjected to estimate the levels of CEA. The results of this study showed that CEA is increased at high levels in patients of group 2 & group 5 who have high levels of TSH. However, some patients when the treatment is given, CEA levels return to the normal. This will give an indicator that CEA is not biomarker for malignancy but it is a biomarker for the high TSH levels associated with two groups (two and five). Single nucleotide polymorphism was studied for $_{D1a}$ gene to show the variation between TSH & CEA levels in patients with thyroid dysfunction .The study was found that the genotype is C/C allele which gives absolute relationship between TSH concentration and CEA levels in both patients and control groups and to the less extent in heterozygous allele C/T.

Keywords: CEA, TSH, SNPs, Thyroid hormones

Correspondence:
Sawsan Hassan Kadhum
Babylon Technical Institute, Al – Furat Al – Aswat Technical University, Iraq
E-mail: dr.mohamadsabri@yahoo.com

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INTRODUCTION

Carcinoma embryonic antigen (CEA) is a glycoprotein present in normal mucosal cells. CEA is tumor marker that increases in many cases of cancer. (1).

In certain diseases, it was shown that this marker is increased but does not express on malignancy such as its elevation in case of hypothyroidism (2). It was seen that most cases of hyperthyroidism have normal values of CEA but this marker is high in the serum of patients with hypothyroidism (3), so it may be correlated with the increasing of thyroid stimulating hormone (TSH) (4).

Besides in patients with thyroid gland dysfunction, three hormones should be considered T_3, T_4 and TSH and all these hormones may play a role in assessment the function of this gland(5).The relationship between CEA and hypothyroidism was studied by Amino et.al, (1981) who found that any elevation in TSH may give rise to the increasing in CEA levels. (6).

To date, little information has been available regarding the presence of functionally relevant polymorphisms in the thyroid hormone pathway genes except the study done by (5) who focused on some genes responsible for expression and suppression of TSH and TSHR.

Single nucleotide polymorphisms (SNPs) was found to have a role in increasing of TSH concentration in the serum of patients with thyroid dysfunction particularly at D_{1a} gene. (7). RFLP analysis showed that this gene gives three important genotype C/C, C/T and T/T when specific restriction endonuclease is used.(8).These alleles may have direct role in making the TSH level being high or low. (5, 7)

These variants in $_{D1a}$ gene may be used to show their effect on CEA levels in consistent with TSH concentrations in patients and control group. So, The aim of this study is to estimate the levels thyroid hormones and CEA in different cases of thyroid dysfunction and study the SNPs for D_{1a} gene for TSH and its relationship with CEA concentrations in patients and control group.

MATERIAL AND METHODS

Patients

Patients with thyroid dysfunction (145 patients) were undergone in this study who admitting to Al-Hayat private lab in Hilla – Iraq . Also 20 healthy individuals were also subjected as control group ethical approval was taken verbly from the patients themselves or from their families.

BIOCHEMICAL PARAMETERS

T3 & T4 and TSH are measured I patient's serum samples , which are provided from bio-mereux company (France) by using mini-Vidus instrument The normal range for T_3 is (o.92 – 2.33) T_4 is (60–120) nmol/L and for TSH : (0.25 – 5.0) µIu/ml .

CEA is measured by kits provided by Afias-6 (France). The normal value for this marker is ranging from (2.5–5.0) µg/ml.

Single nucleotide polymorphisms (SNPs) was done for the TSH gene(D_{1a}) by using PCR technique. DNA extraction was carried out for whole blood samples by using Qiagene Kit and for PCR the primer as mentioned by (8) where forward primer 5 $^{/}$(GAACTTGATGTGAAGGCTGGA)3$^{/}$ and reversed 5$^{/}$(TAACCTCAGCTGGGAGTTGTTT)3$^{/}$, at a size 565 bp .

The conditions of PCR are as mentioned by (8) were the annealing temperature is 54^{o}C , initial denaturation is done by 94^{0}C and after PCR ,the product was digested by Bcl1 restriction enzyme to reveal the RFLP analysis in which the enzyme cut gives 2 bands (131 bp and 434 bp). All the experiments are carried out in Babylon medical college, under the supervision of the staff of molecular laboratory.

RESULTS AND DISCUSSION

In this study, the patients are divided into 5 groups according to the levels of thyroid hormones (T3, T4 & TSH) in the plasma of 145 patients under study .

Table (1) showed that group I (28 patients) have high level of T3 & T4 with low levels of TSH, this group is significantly considered the patients with hyperthyroidism.

The second group (38 groups) have low levels of T3 and T4 with high levels of TSH (Hypothyroidism) whereas the patients with Euthyroids showed normal levels of thyroid hormone, as seen in shape III. On the other hand group IV (5 patients) showed how levels in all thyroid hormones, but the last group (13 patients) showed only TSH is high.

Table 1: Distribution of patients according to thyroid hormones levels

Thyroid hormones	No. Patients	T3	T4	TSH
Group 1	28	high	High	Low
Group11	58	Low	Low	High
Group 111	31	Normal	Normal	Normal
Group 1V	5	Low	Low	Low
Group V	3	normal	Normal	High
Total	145			

High T3 (3.04 ± 0.62) significance (P < 0.05) Low T3: 0.71 ± 0.16
High T4 (140 ± 8.5) signification Low T4: 49.3 ± 8.4
High TSH (7.76 ± 1.44) Low TSH: 0.16 ± 0.04

For all these groups, carcino-embryonic antigen (CEA) was measured. it was found that CEA is significantly increased in patients with group II and group Vas shown in table (2) and it seems from these data that CEA elevation correlates mainly with the high levels of TSH regardless what the case of thyroid dysfunction was ,which correlate the results obtained by (6 & 9).

Table 2: CEA levels among patient's groups

CEA level	Group I	Group II	Group III	Group IV	Group V
CEA level Mean value	1.71± 0.9	10.07± 2.2	1.67± 1.0	3.9 ± 1.8	6.44 ± 2.05

Normal value of CEA (2.5 – 5.0) µg / L (P value< 0.05)

On the other hand, It was noticed that the level of CEA is decreased in the group no.1 which has low level of TSH. However control group was found to have normal levels of both thyroid hormones & CEA.

It was showed that a decreased hepatic clearance of CEA seemed to be the most likely explanation for the observed high CEA concentrations in patients with Hypothyroidism (5, 10). The exact mechanism underlying the elevated levels of CEA in patients with hypothyroidism is still not fully understood.

So, CEA elevation in hypothyroidism may correlate with decrease in the rate of degradation of CEA itself. (11)

It can be concluded that CEA is considered as biomarker for high levels of TSH in the plasma regardless on the presence of hypothyroidism or not.

The study of variation in CEA levels should be considered particularly single nucleotide polymorphisms to show the relationship between CEA polymorphisms with TSH genes polymorphisms and to investigation which SNPs types correlate between both markers in thyroid dysfunction.

In distinct experiments to show the relationship between TSH levels and the presence of single nucleotide polymorphisms (C/T) at a locus presence at D_{1a} gene in the chromosome no.1 of human genome (11).

After DNA extraction by using whole blood, and the DNA is then amplified by PCR techniques. The product after cutting showed that C/C allele homozygous appears at a position 565-without cutting and T/T allele homozygous appears with two bands 434 & 131 bp whereas heterozygous alleles (C/T) appears as three bands 565 , 434 , 131 bp .

Among 145 patients, only those patients (89 patients) belonging to group I, II & V were included in this experiment.

It was seen that 44 patients carry the genotype C/C whereas 30 patients carry the genotype T/T and the rest (15 patients) carry the genotype C/T. Most patients with T/T reveals high level of TSH and some of patients with heterozygous C/T reveals intermediate levels of TSH (some of them high levels and the others low levels) but all the patients carry C/C gives low levels of TSH who are classified within group I .

Allele frequency is calculated, C allele was found to be 57.8 % and for T allele 42.2 %. Although C allele is more predominant than T allele but has no role in an increasing of TSH levels. One notice should be considered that group (31 subjects) is considered as control group because all thyroid hormone levels were normal, also 58 subjects were considered at this study as control group to become, the number of this group 89 healthy subjects.

However, for control group, 64 subjects have the genotype CT heterozygous allele and 11 subjects with a genotype CC and the rest (14 subjects) with a genotype TT.

Allele frequency for C allele was 48.3% whereas for T alleles 51.7%. The results showed no differences between C and T alleles frequencies in control group when compared with patients as shown in table (3).

Table 3: Genotyping and allele frequency for D_1 gene for TSH hormone

Genotype / Subjects	CC	CT	TT	Allele frequency
Patients (89)	44	30	15	C = 57.8 T = 42.2
Control (89)	11	64	14	C = 51.7 T = 48.3

According to the data above most patients with group (1) have the genotype CC is more frequent while in group (II) TT genotypes is more frequent. As mentioned by peeters et.al, (8), the genotype CC will cause increasing in T3 and T3/T4 ratio but has no effect on TSH levels while this study confirmed that TT genotype may have a role in elevation of the levels of TSH in patients with thyroid dysfunction. So, When the result of variation for TSH engaged with CEA levels , all the patients with TT alleles gave high levels of CEA which is consistent with the high levels of TSH, whereas the patients with CC alleles has no effect on the levels of CEA .

Moreover, the patients with heterozygous alleles (CT) gave little variations in the amount of CEA when compared with the level of TSH .This results may be

Consistent with the study of (12 & 13) who infer that little information is available about the relation of heterozygous alleles to the TSH levels.

Besides, Also, some studies indicate that $_{D1a}$ gene polymorphisms are strongly associated with T_3 polymorphisms. (6, 8, 13).

there is no previous studies indicate the presence of relationship between CEA and TSH at molecular level through the presence of the same SNPs at CC allele for D1a gene which has a role in controlling thyroid hormones function.

CONCLUSION

The present study is concluded that genetic polymorphisms in the D1 gene for TSH expression may be not significantly associated with CEA levels in patients except In those with the genotype CC.

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