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# Study of the Role of Adiponectin Gene Polymorphism in Patients with Thyroid Disorders

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## ABSTRACT

**Background:** Both hypo & hyperthyroidism are associated with some morbidity & mortality. Adiponectin is a fat cell-derived hormone that protect against atherosclerotic cardiovascular diseases through its enhancing effect on insulin sensitivity. Clinical studies investigating serum adiponectin levels in patients with hypothyroidism and hyperthyroidism have reported conflicting results.

**Objective:** The study aimed to study the role of adiponectin gene polymorphism in patients with thyroid disorders either hypothyroidism or hyperthyroidism. Also, the relation of adiponectin gene polymorphism with obesity and DM.

**Patients and Methods:** Cross sectional study was conducted on one hundred and fifty cases that were classified into hypothyroid group and hyperthyroid group. History, examination and investigation (adiponectin gene) was done.

**Results:** In current study within hypothyroid & hyperthyroid group, there was non-significant relation between gene polymorphism and either total T3, free T3, free T4 or TSH. There was statistically non-significant relation between associated diabetes and either gene or allele polymorphism among patients within hypothyroid group and hyperthyroid group. There was statistically non-significant relation between patient BMI and either gene or allele polymorphism among patients within hypothyroid group and hyperthyroid group.

**Conclusion:** There was no role of adiponectin gene polymorphism and either total T3, free T3, free T4 or TSH. In addition, there was no role of adiponectin gene polymorphism and either obesity and DM.

**Keywords:** Total T3, free T3, T4, TSH, Adiponectin, Polymorphism.

## INTRODUCTION

Both hypo & hyperthyroidism are associated with cardiovascular morbidity & mortality. Adiponectin is a fat cell-derived hormone that protect against atherosclerotic cardiovascular diseases through its enhancing effect on insulin sensitivity. Adiponectin is a peptide produced exclusively in adipose tissue. It plays an important role in the regulation of a variety of processes, ranging from energy homeostasis, lipid metabolism and insulin sensitivity to inflammation and atherosclerosis [(1)].

Clinical studies investigating serum adiponectin levels in patients with hypothyroidism and hyperthyroidism have reported conflicting results. While, various studies have demonstrated higher adiponectin levels in hyperthyroid or hypothyroid patients [(2)]. Other reports found no differences in the adiponectin levels in individuals with thyroid dysfunction [(3)].

The adiponectin is expressed in adipose tissue exclusively. The encoded protein circulates in the plasma and is involved with metabolic and hormonal processes**.** Gene sequence analysis of human adiponectin discovered numerous allele single-nucleotide polymorphisms (SNPs) of adiponectin in the general population. In addition, there are many SNP polymorphism types, which are related to coronary heart diseases (CHD) [(4)]. Genetic variations in the human adiponectin gene have recently been reported to be associated with the risk of obesity, insulin resistance, T2D, and high levels of low-density lipoprotein cholesterol [(5)]. In contrast, **Menzaghi *et al.*** [(6)] found no association with obesity or type 2 diabetes. Genetic association studies of ACDC gene in T2D and /or obesity have been well reported. Two SNPs, 45G15G (T/G) and +276G/T, respectively, in exon 2 and intron 2 of the ACDC gene are found to be significantly associated with T2D patients [(7)].

This is the first study to assess adiponectin gene polymorphism in patients with thyroid disorder either hypo or hyperthyroidism. Adiponectin gene polymorphism was reported as non-significant marker in detecting thyroid dysfunctions. Adiponectin gene polymorphism G 276T was reported to be not increased or decreased in patients with hypothyroidism and hyperthyroidism.

The study aimed to study the role of adiponectin gene polymorphism in patients with thyroid disorders either hypothyroidism or hyperthyroidism. Also, the relation of adiponectin gene polymorphism with obesity and DM.

This cross sectional study was conducted in Outpatient Endocrine Clinic and Internal Medicine Department in association with the Medical Biochemistry Department, Zagazig University Hospital. It included 150 patients, 75 patients of hypothyroidism (group 1) and 75 patients of hyperthyroidism (group 2) during period from August





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2018 to January 2019. Patients' age ranged from 20 to 60 years. Pregnant women, elderly patients and patients with liver cell failure or renal failure were excluded.

**Ethical considerations:**

**Approval of Ethical Committee in Faculty of Medicine, Zagazig University** and informed consents were obtained from cases participating in this study after informing them about the steps of study.

**Participants were subjected to the following:**

- **Full history taking** (age and sex).
- **Anthropometrics measures including:** BMI, the formula of BMI is weight in kilograms divided by height in squared meters. The standard weight status categories associated with BMI ranges for adults are shown in the following table**.**

**Table (1):** Standard weight categories associated with BMI ranges

| ♦ BMI | ♦ Weight Status |
|---|---|
| ♦ Below 18.5 | ♦ Underweight |
| ♦ 18.5 – 24.9 | ♦ Normal |
| ♦ 25.0 – 29.9 | ♦ Overweight |
| ♦ 30.0 and above | ♦ Obese |

- **Laboratory investigation:**

They were all done according to the methods applied in the clinical pathology and laboratories of Zagazig University Hospitals and include:

1. Fasting, 2 hour postprandial blood glucose level.
2. Serum level of total T3, free T3, free T4 and TSH.
3. Determinationof adiponectin gene by PCR amplification:

Genomic DNA extraction and analysis for determination of adiponectin genotype by detecting nucleotide variation at position 276 of adiponectin gene was done using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP).

**Determination of adiponectin 276G > T polymorphism by PCR-based restriction fragment length polymorphism:**

Genomic DNA analysis for identification of adiponectin gene polymorphism at position G276 T was done using polymerase chain reaction PCR followed by restriction fragment length polymorphism RFLP technique.

***Statistical analysis***

The data were coded, entered and processed in computer using statistical package for social science (SPSS version 18). The results were represented in tabular and diagrammatic forms then interpreted. Mean, standard deviation, range, frequency and percentage were used as descriptive statistics.

Chi-Square test $X^2$ was used to test the association variables for categorical data. Students't-test was used to assess the statistical significance of the difference between two population means in a study involving independent samples. ANOVA (F test) was used for normal quantitative variables to compare between more than two groups. Post Hoc test (LSD) was used for pairwise comparisons. P value was considered significant as the following: * $P > 0.05$: Non significant* $P \leq 0.05$: Significant.

**RESULTS**

- There was statistically non-significant difference between the studied groups regarding age or gender (Table 2).
- There was statistically significant difference between the studied groups regarding BMI and waist circumference (both were significantly higher among hypothyroid group) (Table 3).
- **Table (4) and figure (1)** showed that there was statistically non-significant difference between the studied groups regarding genotype. GG genotype increased in hyperthyroid group (49.3%) than in hypothyroid group (41.3%). While, GT genotype increased in hypothyroid group (49.3%) than in hyperthyroid group (34.7%). TT genotype increased in hyperthyroid group (16%) than in hypothyroid group (9.3%). In allele distribution, the frequency of G allele was (66%) in hypothyroid group and (66.7%) in hyperthyroid group. While, the T allele increased in hypothyroid group (34%) than in hyperthyroid group (33.3%).
- There was statistically non-significant relation between patient BMI and either gene or allele polymorphism among patients within hypothyroid group (Table 5).
- There was statistically non-significant relation between patient BMI and either gene or allele polymorphism among patients within hyperthyroid group (Table 6).
- There was statistically non-significant relation between associated diabetes and either gene or allele polymorphism among patients within hypothyroid group (Table 7).
- There was statistically non-significant relation between associated diabetes and either gene or allele polymorphism among patients within hyperthyroid group (Table 8).
- Within hypothyroid group, there was statistically non-significant relation between gene polymorphism and either total T3, free T3, free T4 or TSH (Table 9).
- Within hyperthyroid group, there was statistically significant relation between gene polymorphism and TSH. On LSD comparison, the difference was significant between GG and GT groups. Within

hyperthyroid group, there was statistically non-significant relation between gene polymorphism and either total T3, free T3, or free T4 (Table 10).

**Table (2):** Comparison of the studied groups according to demographic characteristics

| **Demographic characteristics** | **Groups** | | Test | |
|---|---|---|---|---|
| | **Hypothyroid group** | **Hyperthyroid group** | $\chi^2$/t | p |
| | **N=75** | **N=75** | | |
| **Gender**:<br>Female (%)<br>Male (%) | <br>27 (36)<br>48 (64) | <br>23 (30.7)<br>52 (69.3) | 0.48 | 0.488 |
| **Age (years)**<br>Mean ± SD<br>Range | <br>41.23 ± 7.15<br>26 – 55 | <br>41.56 ± 7.85<br>26 – 54 | -0.272 | 0.7786 |

t independent sample t test

**Table (3):** Comparison of the studied groups according to anthropometric measures

| **Anthropometric measures** | **Groups** | | | | Test | |
|---|---|---|---|---|---|---|
| | **Hypothyroid group** | | **Hyperthyroid group** | | t | p |
| | Mean ± SD | **Range** | Mean ± SD | **Range** | | |
| **BMI (kg/m$^2$)** | 26.92 ± 3.49 | 19 - 36 | 25.49 ± 4.29 | 19 – 35 | 2.236 | 0.027* |
| **Waist circumference** | 99.23 ± 15.95 | 71 – 127 | 91.31 ± 14.92 | 72 – 115 | 3.14 | 0.002* |

t independent sample t test *p<0.05 is statistically significant

**Table (4):** Comparison of the studied groups according to adiponectin genotype

| | **Groups** | | **Test** | | COR (95% CI) |
|---|---|---|---|---|---|
| | **Hypothyroid group** | **Hyperthyroid group** | **$\chi^2$/t** | **p** | |
| | **N=75 (%)** | **N=75 (%)** | | | |
| **Genotype**<br>GG<br>GT<br>TT | <br>31 (41.3)<br>37 (49.3)<br>7 (9.3) | <br>37 (49.3)<br>26 (34.7)<br>12 (16) | 0.014 | 0.906 | <br><br>1.7(0.85 – 3.39)<br>0.7(0.24 – 1.98) |
| **Alleles:**<br>G<br>T | <br>99 (66)<br>51 (34) | <br>100 (66.7)<br>50 (33.3) | 0.015 | 0.903 | <br><br>1.03(0.64 – 1.66) |

COR crude odds ratio CI confidence interval.

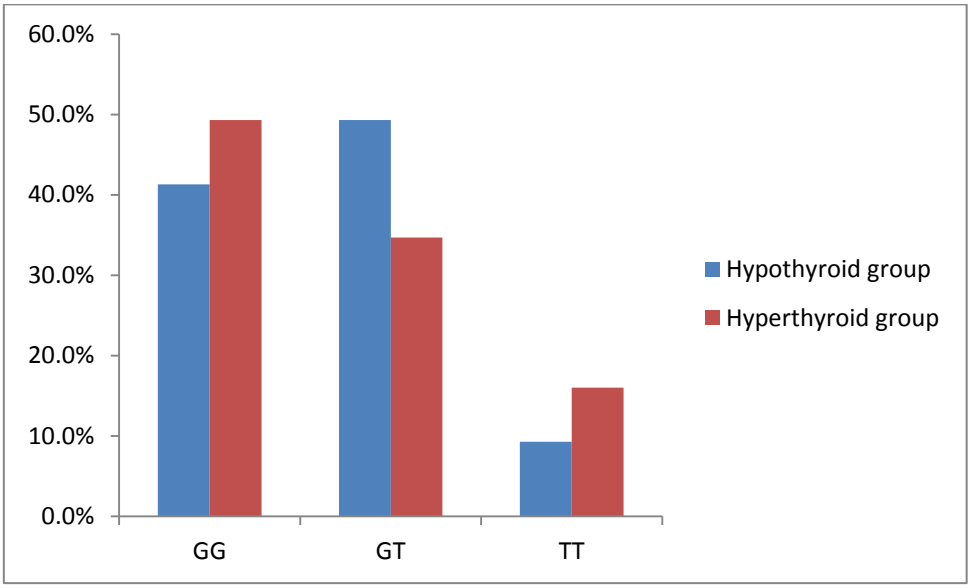


**Figure (1):** combined bar chart showing comparison of the studied groups according to adiponectin genotype

**Table (5):** Relation between genotype and BMI among patients with hypothyroidism

| | BMI | | | Test | |
|---|---|---|---|---|---|
| | Normal weight | Overweight | Obese | $\chi^2$ | p |
| | N=21(%) | N=34(%) | N=20 (%) | | |
| **Genotype** | | | | | |
| GG | 7 (33.3) | 16 (57.1) | 8 (40) | | |
| GT | 10 (47.6) | 15 (41.1) | 12 (60) | 5.264 | 0.271 |
| TT | 4 (19) | 3 (8.8) | 0 (0) | | |
| **Alleles:** | N=42 | N=68 | N=40 | | |
| G | 24 (57.1) | 47 (69.1) | 28 (70) | 2.048 | 0.359 |
| T | 18 (42.9) | 21 (30.9) | 12 (30) | | |

**Table (6):** Relation between genotype and BMI among patients with hyperthyroidism

| | BMI | | | Test | |
|---|---|---|---|---|---|
| | Normal weight | Overweight | Obese | $\chi^2$ | p |
| | N=38 (%) | N=27(%) | N=10(%) | | |
| **Genotype** | | | | | |
| GG | 15 (39.5) | 14 (51.9) | 8 (80) | | |
| GT | 18 (47.4) | 7 (26.9) | 1 (10) | 5.264 | 0.271 |
| TT | 5 (13.2) | 6 (22.2) | 1 (10) | | |
| **Alleles:** | N=76 | N=54 | N=20 | | |
| G | 48 (63.2) | 35 (64.8) | 17 (85) | 3.529 | 0.171 |
| T | 28 (36.8) | 19 (35.2) | 3 (15) | | |

**Table (7):** Relation between genotype and presence of associated diabetes among patients with hypothyroidism

| | Diabetes | | Test | |
|---|---|---|---|---|
| | Yes | No | $\chi^2$ | p |
| | N=42 (%) | N=33 (%) | | |
| **Genotype** | | | | |
| GG | 19 (45.2) | 12 (36.4) | 0.041 | 0.839 |
| GT | 18 (42.9) | 19 (57.6) | | |
| TT | 5 (11.9) | 2 (6.1) | | |
| **Alleles:** | | | | |
| G | 56 (66.7) | 43 (65.2) | 0.039 | 0.846 |
| T | 28 (33.3) | 23 (34.8) | | |

**Table (8):** Relation between genotype and gender of the studied patients with hyperthyroidism

| | Diabetes | | Test | |
|---|---|---|---|---|
| | Yes | No | $\chi^2$ | p |
| | N=23 (%) | N=52 (%) | | |
| **Genotype** | | | | |
| GG | 17 (54.8) | 20 (45.5) | 0.278 | 0.598 |
| GT | 9 (29) | 17 (38.6) | | |
| TT | 5 (16.1) | 7 (15.9) | | |
| **Alleles:** | | | | |
| G | 43 (69.4) | 57 (64.8) | 0.344 | 0.558 |
| T | 19 (30.6) | 31 (35.2) | | |

**Table (9):** Relation between genotype polymorphism and thyroid profile among the studied patients among hypothyroid group

| Parameters | Genotype | | | Test | |
|---|---|---|---|---|---|
| | GG | GT | TT | F | p |
| | Mean ± SD | Mean ± SD | Mean ± SD | | |
| **Total T3 (ng/dL)** | 1.17 ± 0.34 | 1.16 ± 0.32 | 1.02 ± 0.15 | 0.688 | 0.506 |
| **Free T4 (ng/dL)** | 0.94 ± 0.26 | 0.92 ± 0.21 | 1.11 ± 0.35 | 0.931 | 0.399 |
| **TSH** | 6.56 ±1.98 | 6.97 ± 1.97 | 6.19 ±1.3 | 0.675 | 0.512 |
| **Free T3 (ng/dL)** | 0.59 ± 0.16 | 0.5 ± 0.01 | 0.4 ± 0.01 | 1.978 | 0.372 |

F One way ANOVA

**Table (10):** Relation between genotype polymorphism and thyroid profile among the studied patients among hypothyroid group

| Parameters | Genotype | | | Test | |
|---|---|---|---|---|---|
| | GG | GT | TT | F | p |
| | Mean ± SD | Mean ± SD | Mean ± SD | | |
| **Total T3 (ng/dL)** | 2.77±0.52 | 2.92 ± 0.47 | 3.03 ± 0.15 | 1.718 | 0.187 |
| **Free T4 (ng/dL)** | 2.32 ± 0.47 | 2.18 ± 0.36 | 2.35 ± 0.26 | 1.118 | 0.333 |
| **TSH** | 0.2 ± 0.05 [1,2] | 0.15 ± 0.05[1,2] | 0.17 ± 0.07 | 5.873 | 0.003* |
| **Free T3 (ng/dL)** | 3.35 ± 0.61 | 3.04 ± 0.43 | 3.47 ± 0.41 | 2.093 | 0.131 |

F One way ANOVA

## DISCUSSION

In current study, within **hypothyroid** & **hyperthyroid** group, there was non-significant relation between gene polymorphism and either total T3, free T3, free T4 or TSH. On the other hand, a pronounced association between the wild type TT and TSH in obese and strong association has been perceived with reference to T4 in wild type TT as reported by **Jayanthi *et al.*** [(8)]**.** These results point to relationship of Hypothalamus-Anterior Pituitary-Thyroid axis, and gene polymorphism. Another different results was reported by **Rajendran *et al.*** [(9)] who found an associations concerning TSH in TT & TG

Our study showed that there was statistically non-significant relation between genotype regarding presence of abnormally over weight, gender or associated diabetes in hypothyroid group. T allele polymorphism decreased risk of overweight and obesity (OR=0.6 and 0.57) respectively. Also T polymorphism was associated with absence of diabetes (OR=0.93). Male gender was associated with higher risk of T allele polymorphism (OR=1.56). In addition, in hyperthyroid group, there was statistically non-significant relation between genotype regarding presence of abnormally high weight, gender or associated diabetes. T allele polymorphism decreased risk of overweight and obesity (OR=0.93 and 0.3) respectively. Moreover, T polymorphism was associated with absence of diabetes (OR=0.81). Male gender was not associated with higher risk of T allele polymorphism (OR=0.6). Some studies agree with our finding like those of **Xita *et al.*** [(10)] who revealed that the 276T allele did not have any association to obesity and found to be protective for insulin resistance and the G/G genotype of SNP276 had a higher risk of insulin resistance. Another study revealed data like our results, was published by **Zadeh and Zarghami** [(11)] who could not find any significant difference or association in genotype and allele frequnencies of SNP276 to obesity. Opposing to our findings, **Moushira *et al.*** [(12)] showed that the risk of obesity was associated with the presence of T allele and TT genotype. **Mackawy *et al.*** [(13)] published data showing that T allele and TT genotypes of 276G>T SNP were associated with higher risk of obesity, lower plasma adiponectin, insulin resistance and higher parameters of metabolic syndrome and type 2 DM.

Some studies in contrast with our finding like **Yang *et al.*** [(14)] and **Melistas *et al.*** [(15)] noticed that subjects having the SNP276 T containing genotypes (TT or GT) suffered from central obesity and they had the greatest risk of being diabetic. They confirmed the correlation between the T allele and obesity. Moreover, those with T allele had great risk of being hyperglycemic than those carrying G allele, which play a protective role against the development of overweight and obesity.

Another study revealed data like our results where **Lee *et al.*** [(16)] suggested that ADIPOQ 276 SNP was not associated with T2DM or insulin resistance in Korean subjects. Several studies in Swedish, French, American, Japanese, Chinese and Romanian Caucasian populations did not detect any association of this SNP267 with T2DM [(17)]**.**

In current study, there was statistically non-significant relation between associated diabetes and either gene or allele polymorphism among patients within hypothyroid group and hyperthyroid group. Our findings are similar to those reported in the American, Fenland, and Korean populations as they reported that the T allele of ADIPOQ might confer protection from T2DM [(18)]**.** Moreover, results of **Szopa *et al.*** [(19)] revealed decreased T2DM risk in carriers of the T allele indicating that this allele was a protective factor for T2DM in a Polish population. In addition, **Lee *et al.*** [(16)] suggested that ADIPOQ SNP was not associated

with T2DM in Korean subjects. The contrast is found in the study of **Hara *et al.* [20]** who suggested that ADIPOQ SNP was significantly associated with T2DM in Japanese population.

In current study, although T allele polymorphism decreased risk of overweight and obesity respectively, there was statistically non-significant relation between patients' BMI and either gene or allele polymorphism among patients within hypothyroid group and hyperthyroid group. Therefore, the absence of association does not necessarily indicate a lack of effect because body composition changes may be conferred by a collection of variants rather than a single one. The current study is in line with **Khabour *et al.* [21]**study who examined the effect of single nucleotide (SNPs) polymorphisms in the ADIPOQ gene SNPs (I146T and G276T) on BMI of young adult women and showed no association with BMI groups. Meanwhile, **Filippi *et al.* [22]** reported that T/T genotype was more frequent in lean than obese Italians. It appears that polymorphism may not affect BMI in healthy individuals and may be related to BMI only in specific populations.

## CONCLUSION

This study concluded that adiponectin gene polymorphism is not associated with either total T3, free T3, free T4 or TSH.

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