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Association of the T45G and G276T polymorphisms in the adiponectin gene with PCOS: A meta-analysis

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Adiponectin is the most abundant adipocytokine in human body and may play a role in the pathogenesis of polycystic ovary syndrome (PCOS). To clarify the conflicting data in the literature concerning the association between PCOS and two polymorphisms of the adiponectin gene, T45G and G276T, a meta-analysis was performed in this study. Literature search was conducted through PubMed, EMBASE and other relevant studies. Pooled odds ratios (OR) were estimated using fixed-effects (FE) models in codominant, recessive and dominant models. Sensitivity analysis was performed by excluding invalid studies. Eight articles investigated the T45G polymorphism in PCOS, and five publications are associated with the G276T polymorphism in PCOS. Significant associations of adiponectin T45G polymorphism with PCOS were found in codominant (FEM: OR = 1.36, 95% CI: 1.12–1.65), recessive (FEM: OR = 2.02, 95% CI: 1.17–3.47) or dominant models (FEM: OR = 1.33, 95% CI: 1.06–1.67). For adiponectin G276T polymorphism, the OR and 95% CI are 0.81 (0.68, 0.98), 0.74 (0.51, 1.09) and 0.78 (0.61, 0.99) in codominant, dominant and recessive models, respectively. This study provides positive evidence for a causal relationship between the adiponectin gene and PCOS which needs to be further confirmed by further studies.

Keywords: Adiponectin, polymorphism, polycystic ovary syndrome, meta-analysis

Introduction
Polycystic ovary syndrome (PCOS) is one of the most common heterogeneous endocrine disorders, which affect 5–10% of women in reproductive age and is considered as one of the leading causes of female infertility [1]. It is characterized by biochemical and clinical hyperandrogenism, polycystic ovaries on ultrasound and oligo-ovulation or anovulation. Besides, PCOS frequently accompanies with metabolic abnormality such as insulin resistance (IR) and obesity which predisposes women with PCOS to type 2 diabetes [2] (DM2) and cardiovascular disease [3].

Various genetic markers, which involved in steroidogenesis, insulin resistance, metabolic syndrome and proinflammatory genotypes, have been implicated in the predisposition to PCOS, such as CYP17, insulin receptor gene (INSR) and TNF-α [4]. However, none of above variants has conclusively been associated with the syndrome. Adiponectin is a protein expressed exclusively by adipocytes and known to exert insulin sensitizing, anti-atherogenic and anti-inflammatory actions [5–7]. This circulating protein stimulates glucose uptake and fatty acid oxidation [8]. Hypoadiponectinemia has been reported to be associated with increased cardiovascular disease, worse vascular function, and poor lipid profiles [9–11]. Besides, low level of adiponectin was also investigated in obesity [12] and DM2 [13]. Recently adiponectin was shown decreased in PCOS patients [14], indicating the possible role of adiponectin in the etiopathogenesis of PCOS development and metabolic dysfunction.

Two single nucleotide polymorphisms, T45G in exon 2 and G276T in intron 2 of the adiponectin gene, both with high frequencies in all populations, have been reported to be associated with the high risk of obesity, IR and DM2 [15–18]. However, others did not find convincing association between these two particular loci with obesity or DM2 [19–21]. Similarly, in the past years several studies have explored the possible association of T45G and G276T polymorphisms with the risk of PCOS, but no consensus was reached [22–29].

In this study, a comprehensive literature search and subsequent meta-analysis was performed for a better understanding of the susceptibility of the adiponectin gene variation in the development of PCOS.

Materials and methods
Retrieval of published studies
A comprehensive electronic search of PubMed and EMBASE was conducted up until JUN 2010. The following key words or combination of term were used: ‘adiponectin’, ‘AIDPQ’, ‘polymorphism’ coupled with the term ‘polycystic ovary syndrome’ or ‘polycystic ovaries’. The electronic investigation was restricted to English literature and supplemented by the assessment of references of published studies. Studies were included in the analysis if: [1] They were case-control studies associated with adiponectin polymorphisms and PCOS; [2] Numbers of PCOS and control groups for each genotype should be reported or available data could be used. Contribution of the two SNPs to the development of PCOS and they provided adequate data to calculate the odds ratio (OR) comparing PCOS patients and healthy unrelated controls.

Data extraction and quality assessment
Following data were extracted from each study: first author, journal, year of publication, ethnicity of study population, allelic
and genotypic number of polymorphism, diagnosis criteria of PCOS, number of cases and controls. Whereas lacking the allelic and genotypic number, the two polymorphisms for cases and controls were calculated.

Statistical analysis
In this study, Hardy-Weinberg equilibrium for the two polymorphisms distribution was tested by Chi square analysis via stata 10. Software Review Manager 4.3 was used for meta-analysis. OR with the corresponding 95% CI was applied in all contrasts to detect the association of T45G and G276T polymorphisms in adiponectin gene with the risk of PCOS. Heterogeneity between studies was quantified using the Q-statistic; if P < 0.10, the heterogeneity was considered statistically significant [30]. The inconsistency index (I²) was also used to test the heterogeneity. This index is independent of the number of studies included in the meta-analysis. If I² < 25%, it was considered as absent of heterogeneity; if I² = 25–50%, as moderate heterogeneity and if I² > 50%, as large heterogeneity [31]. In case of large heterogeneity, random-effects models were more appropriate since they were usually more conservative. When heterogeneity was absent or moderate, random- and fixed-effects methods were coincided. Therefore, if I² < 50%, fixed-effects models were used for the meta-analysis. If I² > 50%, random-effects models were applied. To assess the publication bias and small-study bias, funnel plot of the data was applied. In addition, Begg’s test and Egger’s test was also used with software Stata 10 to detect publication bias and small-study bias. Sensitivity analysis was undertaken by removing the unreliable study deviated from Hardy–Weinberg equilibrium in the control group then performing meta-analysis again.

Comparison between allelic and genotypic frequencies in PCOS in the control group then performing meta-analysis again. This index is independent of the number of studies included in the meta-analysis. If I² < 25%, it was considered as absent of heterogeneity; if I² = 25–50%, as moderate heterogeneity and if I² > 50%, as large heterogeneity [31]. In case of large heterogeneity (I² > 50%), random-effects models were more appropriate since they were usually more conservative. When heterogeneity was absent or moderate, random- and fixed-effects methods were coincided. Therefore, if I² < 50%, fixed-effects models were used for the meta-analysis. If I² > 50%, random-effects models were applied. To assess the publication bias and small-study bias, funnel plot of the data was applied. In addition, Begg’s test and Egger’s test was also used with software Stata 10 to detect publication bias. Sensitivity analysis was undertaken by removing the unreliable study deviated from Hardy–Weinberg equilibrium in the control group then performing meta-analysis again.

In the eight studies used, four studies applied the ESHRE/ASRM criteria for the diagnosis of PCOS, two based on NIH criteria, one on NIH criteria and revised by ESHRE/ASRM criteria. In Heinonen’s study, PCOS patients were diagnosed by the observation of anovulation and polycystic ovaries on ultrasound, as well as exclusion of other reasons for anovulation and hyperandrogenism such as hypothyreosis, hypercortisolism and late onset of congenital adrenal hyperplasia. Due to the diversity nature of PCOS diagnosis, all eight studies using different criteria were included.

Table I. The studies included in the meta-analysis concerning the association of adiponectin T45G polymorphism with PCOS. The detailed genotypes per study are listed as also as the general characteristics of the study (country, year, Journal and issue).

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Total (con/cas)</th>
<th>GG (con/cas)</th>
<th>TG (con/cas)</th>
<th>TT (con/cas)</th>
<th>G (con/cas)</th>
<th>T (con/cas)</th>
<th>Year</th>
<th>Journal and issue</th>
</tr>
</thead>
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<tr>
<td>Panidis</td>
<td>Greece</td>
<td>100/132</td>
<td>2/7</td>
<td>17/33</td>
<td>81/92</td>
<td>21/47</td>
<td>179/217</td>
<td>2004</td>
<td>Hum Reprod</td>
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<tr>
<td>San Millan</td>
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<td>1/2</td>
<td>12/22</td>
<td>29/48</td>
<td>14/26</td>
<td>70/118</td>
<td>2004</td>
<td>J Clin Endocrinol Metab</td>
</tr>
<tr>
<td>Haap</td>
<td>Germany</td>
<td>542/53</td>
<td>16/7</td>
<td>112/8</td>
<td>414/38</td>
<td>144/22</td>
<td>940/84</td>
<td>2005</td>
<td>Exp Clin Endocrinol Diabetes</td>
</tr>
<tr>
<td>Heinonen</td>
<td>Finland</td>
<td>245/143</td>
<td>1/1</td>
<td>22/17</td>
<td>222/125</td>
<td>24/19</td>
<td>466/267</td>
<td>2005</td>
<td>Gynecol Endocri</td>
</tr>
<tr>
<td>Xita</td>
<td>Greece</td>
<td>140/100</td>
<td>4/0</td>
<td>30/23</td>
<td>106/77</td>
<td>38/23</td>
<td>242/177</td>
<td>2005</td>
<td>Clin Chem</td>
</tr>
<tr>
<td>Escobar-Morreale</td>
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<td>40/76</td>
<td>1/1</td>
<td>13/20</td>
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<td>15/22</td>
<td>65/130</td>
<td>2006</td>
<td>Hum Reprod</td>
</tr>
<tr>
<td>Zhang</td>
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<td>4/9</td>
<td>42/54</td>
<td>74/57</td>
<td>50/72</td>
<td>190/168</td>
<td>2008</td>
<td>Eur J Endocrinol</td>
</tr>
<tr>
<td>Demirici</td>
<td>Turkey</td>
<td>93/96</td>
<td>3/6</td>
<td>16/20</td>
<td>74/70</td>
<td>22/32</td>
<td>164/160</td>
<td>2010</td>
<td>Gynecol Endocri</td>
</tr>
</tbody>
</table>

Table II. The studies included in the meta-analysis concerning the association of adiponectin G276T polymorphism with PCOS. The detailed genotypes per study are listed as also as the general characteristics of the study (country, year, Journal and issue).

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Total (con/cas)</th>
<th>TT (con/cas)</th>
<th>GT (con/cas)</th>
<th>GG (con/cas)</th>
<th>T (con/cas)</th>
<th>G (con/cas)</th>
<th>Year</th>
<th>Journal and issue</th>
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<tr>
<td>San Millan</td>
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<td>Heinonen</td>
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<td>25/8</td>
<td>110/58</td>
<td>110/77</td>
<td>160/74</td>
<td>330/212</td>
<td>2005</td>
<td>Gynecol Endocri</td>
</tr>
<tr>
<td>Xita</td>
<td>Greece</td>
<td>140/100</td>
<td>15/12</td>
<td>73/49</td>
<td>52/39</td>
<td>103/73</td>
<td>177/127</td>
<td>2005</td>
<td>Clin Chem</td>
</tr>
<tr>
<td>Escobar-Morreale</td>
<td>Spain</td>
<td>40/76</td>
<td>4/7</td>
<td>21/39</td>
<td>15/30</td>
<td>29/53</td>
<td>51/99</td>
<td>2006</td>
<td>Hum Reprod</td>
</tr>
<tr>
<td>Zhang</td>
<td>China</td>
<td>120/120</td>
<td>29/18</td>
<td>50/46</td>
<td>41/56</td>
<td>108/82</td>
<td>132/158</td>
<td>2008</td>
<td>Eur J Endocrinol</td>
</tr>
</tbody>
</table>

Results
Comprehensive literature search
After the initial search nine published studies [22–29,32] which investigated the association of adiponectin polymorphisms with PCOS were found, 8/9 were about the T45G polymorphism and 5/8 also studied the G276T. One study about adiponectin polymorphism at −11,377 was also found which was excluded in our meta-analysis.

In the eight studies used, four studies applied the ESHRE/ASRM criteria for the diagnosis of PCOS, two based on NIH criteria, one on NIH criteria and revised by ESHRE/ASRM criteria. In Heinonen’s study, PCOS patients were diagnosed by the observation of anovulation and polycystic ovaries on ultrasound, as well as exclusion of other reasons for anovulation and hyperandrogenism such as hypothyreosis, hypercortisolism and late onset of congenital adrenal hyperplasia. Due to the diversity nature of PCOS diagnosis, all eight studies using different criteria were included.

All studies were cross-sectional case-control studies with sufficient data to calculate the possible relationship between the two polymorphisms and PCOS. All used studies were published in English.

The genotypes T45G included in the first meta-analysis were summarized in Table I, whereas G276T included in the second meta-analysis were shown in Table II.

Adiponectin T45G polymorphism
All eight used studies contain the report about the adiponectin T45G polymorphism, which in total recruited 792 cases and 1322 controls. The allele G was the mutational allele for T45G polymorphism. Furthermore, five of the studied groups reported only one subject carrying the GG genotype and Xita’s study reported

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no person carrying the GG genotype in 100 PCOS patients. The heterogeneity was absent (I² < 25%) in codominant, dominant and recessive models. Therefore, fixed-effects models were used for all comparisons. In dominant models the OR is 1.33 and 95% CI 1.06–1.67 (Figure 1). Statistical difference was found in both models (Table III).

Pooled measure was meta-analyzed repeatedly in codominant, dominant, and recessive models after excluding Haap's study which deviated from Hardy–Weinberg equilibrium in the control group. Then in dominant and codominant models statistical differences were also found (in codominant model, OR = 1.31, 95% CI: 1.06–1.62, in dominant model OR = 1.34, 95% CI: 1.05–1.71) but in recessive model there was no significant difference (OR = 1.54, 95% CI: 0.82–2.92).

Finally, funnel plot of the data showed that no obvious publication bias was detected in any of codominant, recessive and dominant models. Furthermore, by Begg’s and Egger’s test no evident publication bias was found (all P > 0.05).

**Adiponectin G276T polymorphism**

In eight included studies, five reported the association between G276T polymorphism and PCOS, which contained 511 cases and 587 controls (Table IV). The heterogeneity in dominant and recessive models was absent (I² < 25%), and in codominant model it was moderate (I² = 25.7%). So fixed-effects models were used for all comparisons. Statistical difference was found in codominant and dominant models (Figure 1) except in recessive model (Table IV). Funnel plot showed no obvious publication bias in codominant, recessive and dominant models. Furthermore, by Begg’s and Egger’s test no evident publication bias was found (all P > 0.05).

**Discussion**

In the present study, the relationship of two polymorphisms of the adiponectin gene, the T45G and G276T, with PCOS was assessed. Evidence supports that the T45G polymorphism was associated with the risk of PCOS. After excluding Haap’s study in which the control group deviates from Hardy–Weinberg equilibrium, T45G polymorphism was also associated with the risk of PCOS in codominant and dominant models. Concerning the adiponectin G276T polymorphism, this polymorphism was also associated with the risk of PCOS in codominant and dominant models. From the value of OR, it is found that with regards to T45G polymorphism people with GG or TG genotypes could be more predisposed to PCOS than those with TT genotype. Similarly, in terms of G276T polymorphism people with GG may be more predisposed than those with GT or TT.
Several studies demonstrated the T45G polymorphism of adiponectin gene could affect plasma adiponectin level [33,34]. The TT genotype was associated with higher serum adiponectin concentrations compared to GG and TG ones in healthy individuals [35]. In Demirci's study [29], it was also found PCOS patients carrying the GG or TG genotype have lower plasma adiponectin level than those carrying TT genotype. In Xita's study people with TG genotype also tended to have lower serum adiponectin concentrations [26]. For G276T polymorphism high adiponectin mRNA level has been found in visceral adipocytes people with GT or TT than those with GG genotype [36]. This notion consisted with the higher plasma adiponectin level in people with GT or TT genotype. In Panidis' studies serum adiponectin concentration was significantly lower in people with GG or GT genotype than in people TT [22]. A recent meta-analysis also demonstrated that people with PCOS have lower plasma adiponectin level than control groups [14]. All above results support that the two polymorphisms participate in pathogenesis of PCOS by affecting plasma adiponectin level.

Adiponectin can improve insulin sensitivity and hypoadiponectinemia may contribute to insulin resistance which has been regarded as part of the pathogenesis of PCOS. Recently numerous studies have shown that adiponectin affect the reproductive system through central effects on the hypothalamus-pituitary axis and peripheral effects on the ovary, uterus, or directly on the oocyte and embryo. Adiponectin and its receptors are expressed in human pituitary, and adiponectin is precisely localized in growth hormone, follicle-stimulating hormone, luteinizing hormone and thyroid-stimulating hormone-producing cells [37]. It has been demonstrated that adiponectin decreased LH secretion in pituitary gonadotropes in an AMPK-dependent manner [38]. Patients with PCOS often accompanied with high LH level and low adiponectin. It agrees with the fact that people with GG, TG (for T45G polymorphism) or GG (for G276T polymorphism) genotypes may have lower serum adiponectin level, resulting in up-graded luteinizing hormone level which associated with disordered steroidogenesis.

Adiponectin is expressed in rat and bovine ovaries, and precisely localized in oocyte, granulosa and theca cells [39,40]. In the cultured bovine theca cells, adiponectin attenuated IGF-I-induced LHR, CYP11A1, and CYP17A1 gene expression [41], so hypoadiponectinemia may induce more androgen secretion through its effects on the key enzymes in androgen synthesis which cause hyperandrogenism. This hyperandrogenism is one of the most common phenotypes of PCOS. Adiponectin exerts its function partially through binding to its membrane receptors, Adipo R1 and Adipo R2 expressed in human granulosa cells of pre-ovulatory follicles [42]. In human granulosa tumor cell line, cell proliferation was arrested and apoptosis was emerged [43]. IGF-induced granulosa proliferation could be enhanced by adiponectin in the cultured bovine granulosa cells [40]. Adiponectin has also been proved to be involved in the steroidogenesis of granulosa cells. In primary human granulosa cells, the secretion of progesterone and estradiol in response to insulin-like growth factor I (IGF-I) could be reinforced by human recombinant adiponectin, which was associated with an increase of p450 aromatase [44]. When adip R2 was knocked down, the lowered progesterone and estradiol levels in response to FSH and IGF-1 alone or in combination was observed in human granulosa tumor cell line [38]. Adiponectin can also act directly on granulosa cells, by rapidly inducing the expression of the two critical factors cyclooxygenase 2 (COX-2) and prostaglandin E (PGE) expression [37] during ovulation [42].

These polymorphisms may also be in linkage disequilibrium with some other functional genetic loci responsible for analteration in production of adiponectin or for the ability of adiponectin to polymerize, which affects its biological action [45]. Therefore, additional studies are needed to confirm the association of two polymorphisms with PCOS. Just the same as all meta-analyses, our results of this study should be considered with cautious. The analysis was performed on a relatively small number of retrospective case-control studies with few participants. Although the publication bias was denied by funnel plot, Egger's and Begg's test, the possibility of undetected bias cannot be absolutely excluded. In addition, only one of the examined studies was performed in non-Caucasian population, so the ethnicity effect was not adequately investigated. Further studies may be needed before a final conclusion to be drawn. Moreover, since adiponectin is a highly polymorphic molecule more studies are needed to address simultaneously the contribution of several polymorphisms in the form of haplotypes.

In conclusion, PCOS is a disease influenced by the interaction of genetic and environmental factors. The present study suggests that adiponectin polymorphisms at T45G and G276T have impact on the susceptibility to PCOS.

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References


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