DNA Repair in Polycystic Ovary Syndrome and Genomic Instability

Introduction

Polycystic ovary syndrome (PCOS), characterized by menstrual irregularity, hyperandrogenism and polycystic ovaries, is an endocrine-induced pathology commonly seen in women of reproductive age (Battaglia et al., 2008). PCOS is influenced both by genetic and environmental factors (Urbanek et al., 2013), and more than 50 candidate genes with PCOS susceptibility have been identified. Some of these genes have been reported to play a key role in the pathogenesis of the syndrome (Menke et al., 2007; Celik et al., 2010).

PCOS is accompanied by such metabolic diseases as long-term obesity (Hoeger., 2001) insulin resistance (Cotrozzii et al., 1983), type 2 diabetes mellitus (Legro et al., 1999) premature arteriosclerosis (Talbott et al., 2000; Urbanek et al., 2013). Reactive oxygen species (ROS) are known to increase in these diseases (Dasanu et al., 2011). ROS levels above the threshold lead to an increase in oxidative stress, deterioration in proteins and lipids, and errors in nucleic acids (Marnett 2000; Cooke et al., 2003; Olinski et al., 2007). It has been also reported in previous studies that women with PCOS have an increased risk of cancer and genomic instability due to the increased oxidative stress and reduced antioxidant capacity (Yesilada et al., 2006; Hamurcu et al., 2010; Harris et al., 2010).

DNA damage is repaired in the cell by several mechanisms. The base excision repair (BER) pathway is the frontline mechanism in the repair of minor lesions caused by base modifications, methylation agents and small attachments as well as in the removal of oxidized DNA bases (Sancar et al., 2004; Tudek 2007). The nucleotide excision repair (NER) pathway is responsible for repairing pyrimidine dimers caused by UV light and other environmental carcinogens as well as lesions, such as photoproducts and other major chemical attachments (Goode et al., 2002; Sancar and Reardon 2004).

The Investigation of Polymorphisms in DNA Repair Genes (XRCC1, APE1 and XPD) in Women with Polycystic Ovary Syndrome

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Abstract

Background: PCOS was reported to arise from the interaction of genetic and environmental factors. Some studies reported that women with PCOS have DNA damage and chromosome breakage. Such studies bring to mind the genes that are involved in DNA repairing. At present, several DNA repair genes and, as products of these genes, certain polymorphisms that alter the activity of proteins are known in the literature. The aim of this dissertation is to study the genomic instability that have been reported in PCOS cases along with the relationship between XRCC1 Arg194Trp, XRCC1 Arg399Gln, APE1 Asp148Glu, and XPD Lys751Gln polymorphisms in order to contribute to the pathogenesis of PCOS. Methods: Polymorphisms in DNA repair genes have been associated with the increased risk of various diseases and could also be related to the etiology of PCOS. Therefore, we conducted a study including 114 women with PCOS and 91 controls. These polymorphisms were determined by quantitative real time PCR and melting curve analysis using LightCycler. Results: Comparing the control groups at the end of the study, the results have not shown any statistically significant difference as far as XRCC1 Arg194Trp, XRCC1 Arg399Gln, and XPD Lys751Gln polymorphisms are concerned. However, there were notable differences between the groups in terms of APE1 Asp148Glu polymorphism. Associated with this condition, it has been noted that both mutant allele (Glu) frequency (37.72 % in the study group; 19.23% in the control group, p=0.0001) and homozygous mutant genotype (Glu/Glu) frequency (%12.28 in the study group; %6.60 in the control group, p=0.015) have been higher in the study group.

Keywords: XRCC1- APE1- XPD- Polycystic ovary syndrome- gynecological cancers

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Introduction

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X-ray repair cross-complementing group 1 (XRCC1) and apurinic/apyrimidinic endonuclease (APE1) are key genes in the BER pathway. XRCC1 gene product is encoded by the gene region localized in 19q13.2 (Stern et al., 2001). XRCC1 is associated with several BER enzymes, such as DNA glycosylase, APE1, DNA polymerase β and DNA ligase III (Vidal et al., 2001; Attar et al., 2010).

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APE1 gene product, encoded by the gene region localized in 14q11.2-q12, consists of 4 introns and 5 exons, and it encodes a 318 amino acid protein with the weight of 35 kDa (Abbotts et al., 2010). APE1 is also known as APE, APEX, HAP1 and REF-1 (Wood et al., 2001; Zhong et al., 2016). APE1 is of critical significance in the BER pathway. APE1 is a multifunctional protein. It is not only responsible for the repair of the AP regions, but it also functions as an oxidation-reduction factor (Sharma et al., 2007; Martin 2008). It serves as a transcriptional coactivator for several transcription factors (Zhong et al., 2016). However, it has been shown to be closely associated with cellular apoptosis (Sharma et al., 2007). Asp148Glu (1349T> G) is the most oft-studied variant of APE1, and it is the non-synonymous coding variant of the region that transforms aspartic acid in the 5th exon into glutamic acid (Hadi et al., 2000; Mashayekhi et al., 2016).

Xeroderma pigmentosum complementation group D (XPD) gene product is encoded by the gene region localized in 13.3 region of the q arm of chromosome 19. XPD has an ATP-dependent 5′→3′ DNA helicase activity. It is known to be involved in the dissociation of the DNA double strand during the operation of the NER mechanism (Benhamou et al., 2002).

Genetic variation in DNA repair genes can affect the activity of DNA repair enzymes, thereby changing the DNA repair capacity. In this study, APE1 (Asp148Glu), the XRCC1 (Arg194Trp and Arg399Gln) and XPD (Lys751Gln) polymorphisms, reported to show instability in PCOS cases by various previous studies, were investigated.

Material and Methods

Study groups

The study group consisted of 114 women who were diagnosed with PCOS (as per the 2003 Rotterdam criteria) at Inonu University Turgut Ozal Medical Center Outpatient Clinic of Obstetrics and Gynecology and 91 healthy women. Our study was approved by the local ethics committee. The protocol followed was consistent with the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects). Accordingly, blood samples were taken into EDTA tubes on the third day of the menstrual period. The patient group consisted of women between 18-40 years of age who were diagnosed with PCOS and did not receive hormones or steroids treatment in the last six months due to hirsutism, or any other reasons. The median age of the patient group was 30.09 years. The control group consisted of women between 18-40 years of age who had no diseases, and they did not receive any medication in the last six months. The median age of the patient group was 31.51 years.

Genomic DNA extraction

Genomic DNA was isolated from peripheral blood leukocytes by using High Pure PCR Template Preparation Kit (Roche Diagnostics GmbH, Mannheim, Germany), according to manufacturer’s instructions and stored at -20 °C until analysis.
of variant alleles for all four studied polymorphisms in our control population (Table 1) were similar to those reported previously (Vural et al., 2009; Cincin et al., 2012; Sobczuk et al., 2012).

The frequencies of variant alleles for the XRCC1 Arg194Trp, XRCC1 Arg399Gln, APE1 Asp148Glu and XPD Lys751Gln polymorphisms in our control population were 7.15%, 36.81%, 19.23% and 48.90% respectively (Table 1). The frequencies of Arg/Arg genotype and Trp/Trp genotype for XRCC1 Arg194Trp were 85.71% and 0% in controls and 86.84% and 0.88% in women with PCOS. The frequencies of Arg/Arg genotype and Gln/Gln genotype for XRCC1 Arg399Gln were 39.56% and 13.19% in controls and 46.49% and 12.28% in women with PCOS. There was no difference between women with PCOS and controls in terms of XRCC1 Arg194Trp and XRCC1 Arg399Gln genotypes (OR= 1.15, 95% CI= 0.57-2.32, p= 0.69 for XRCC1 Arg194Trp and OR= 1.14, 95% CI= 0.87-1.48, p= 0.32 for XRCC1 Arg399Gln). The frequency of variant alleles for XRCC1 Arg194Trp and XRCC1 Arg399Gln in the study population were 7.02% and 32.90% respectively and similar to controls.

With regard to APE1 Asp148Glu polymorphism, the frequencies of Asp/Glu and Glu/Glu genotypes were significantly increased in women with PCOS compared to control group (50.88% versus 25.27%; and 12.28% versus 6.60%, respectively). Also, carriers of the Glu allele (Asp/Glu+Glu/Glu) were increased in women with PCOS (OR= 3.60, 95% CI= 2.08-6.30, p= 0.0001). Likewise the frequencies of variant allele Glu (37.72%) were significantly increased in PCOS group (OR= 2.54, 95% CI= 1.61 -4.01, p= 0.0001).

The frequencies of heterozygous genotype (Lys/Gln) and homozygous variant genotype (Gln/Gln) for XPD Lys751Gln polymorphism in controls were 47.25%, 25.28% and in women with PCOS were 47.37%, 23.69%.

In this study, no statistically significant differences were found in genotype or allele distributions of XPD Lys751Gln polymorphism between women with PCOS and controls (Table 1).

### Discussion

Many polymorphisms in DNA repair genes are known to affect the function of the protein products of these genes. The relationship between polymorphisms and the frequencies of Asp/Glu and Glu/Glu genotypes were significantly increased in women with PCOS compared to control group (50.88% versus 25.27%; and 12.28% versus 6.60%, respectively). Also, carriers of the Glu allele (Asp/Glu+Glu/Glu) were increased in women with PCOS (OR= 3.60, 95% CI= 2.08-6.30, p= 0.0001). Likewise the frequencies of variant allele Glu (37.72%) were significantly increased in PCOS group (OR= 2.54, 95% CI= 1.61 -4.01, p= 0.0001).

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### Table 1. Distribution of Genotypes and Allele Frequencies in Control Group and Women with Polycystic Ovary Syndrome (PCOS)

| Polymorphisms | Controls n (%) | PCOS n (%) | X² | p value | OR (95% CI) |
|---------------|----------------|------------|----|---------|-------------|
| **XRCC1 Arg194Trp** | | | | | |
| Arg/Arg | 78 (85.71) | 99 (86.84) | Reference |
| Arg/Trp | 13 (14.29) | 14 (12.28) | 0.15 | 0.69 | 1.15 (0.57 - 2.32) |
| Trp/Trp | 0 | 1 (0.88) | - | 1.00 | 0.55 (0.49 - 0.69) |
| Arg/Trp+Trp/Trp | 13 (7.15) | 15 (7.02) | 0.05 | 0.81 | 1.10 (0.72 - 1.51) |
| Arg allele frequency | 169 (92.85) | 212 (92.98) | Reference |
| Trp allele frequency | 13 (7.15) | 16 (7.02) | 0.02 | 0.96 | 1.01 (0.71 - 1.41) |
| **XRCC1 Arg399Gln** | | | | | |
| Arg/Arg | 36 (39.56) | 53 (46.49) | Reference |
| Arg/Gln | 43 (47.25) | 47 (41.23) | 0.97 | 0.32 | 1.14 (0.87 - 1.48) |
| Gln/Gln | 12 (13.19) | 14 (12.28) | 0.27 | 0.60 | 1.10 (0.74 - 1.64) |
| Arg/Gln+Gln/Gln | 67 (36.81) | 75 (32.90) | 1.00 | 0.31 | 1.12 (0.89 - 1.40) |
| Arg allele frequency | 115 (63.19) | 153 (67.10) | Reference |
| Gln allele frequency | 67 (36.81) | 75 (32.90) | 0.69 | 0.41 | 1.08 (0.89 - 1.30) |
| **APE1 Asp148Glu** | | | | | |
| Asp/Asp | 62 (68.13) | 42 (36.84) | Reference |
| Asp/Glu | 23 (25.27) | 58 (50.88) | 17.87 | 0.0001 | 2.09 (1.43 - 3.07) |
| Glu/Glu | 6 (6.60) | 14 (12.28) | 5.94 | 0.015 | 3.44 (1.22 - 9.68) |
| Asp/Glu+Glu/Glu | 35 (19.23) | 86 (37.72) | 21.47 | 0.0001 | 3.60 (2.08 - 6.30) |
| Asp allele frequency | 147 (80.77) | 142 (62.28) | Reference |
| Glu allele frequency | 35 (19.23) | 86 (37.72) | 16.63 | 0.0001 | 2.54 (1.61 - 4.01) |
| **XPD Lys751Gln** | | | | | |
| Lys/Lys | 25 (27.47) | 33 (28.94) | Reference |
| Lys/Gln | 43 (47.25) | 54 (47.37) | 0.02 | 0.88 | 1.02 (0.76 - 1.36) |
| Gln/Gln | 23 (25.28) | 27 (23.69) | 0.09 | 0.76 | 1.05 (0.75 - 1.48) |
| Lys/Gln+Gln/Gln | 89 (48.90) | 108 (47.37) | 0.07 | 0.78 | 1.03 (0.80 -1.34) |
| Lys allele frequency | 93 (51.00) | 120 (52.63) | 0.02 | 0.86 - 1.22 |
| Gln allele frequency | 89 (48.90) | 108 (47.37) | 0.09 | 0.75 | 1.02 (0.86 - 1.22) |

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in genes involved in the DNA repair systems and genomic instability has been reported in many recent studies (Lei et al., 2002; Chanvaivit et al., 2007; Guven et al., 2007; Da Silva et al., 2013). In this study, the common polymorphisms in three different DNA repair genes (XRCC1 Arg194Trp, XRCC1 Arg399Gln, APE1 Asp148Glu, and XPD Lys751Gln) in PCOS women, which have been reported by previous studies to show genomic instability and susceptibility to certain cancer types were investigated, and the results were compared with the control group.

XRCC1, a key protein involved in single strand breaks and the BER pathway, is known to be responsible for the repair of the errors caused by free radicals, ionizing radiation and alkylating agents (Stern et al., 2001; Sancar et al., 2004). The polymorphisms of Arg194Trp and Arg399Gln in the coding region of this gene are reported to affect the BER pathway in several previous studies. It is also noted in the same studies that variant alleles and homozygous variant genotype frequencies increase in some patient groups, particularly in those with various cancer types, compared to the control groups (Benhamou et al., 2002; Abbasoglu et al., 2009). In our study, there was no difference between PCOS women and the control groups in terms of Arg194Trp Arg399Gln polymorphisms of XRCC1 (Table 1).

It is reported that the expression of APE1 gene, which plays a key role in the removal of faulty base, is induced in such damaging stress conditions as UV and ROS, and the endonuclease activity increases (Tell et al., 2005). It is reported in a study conducted on APE1 Asp148Glu polymorphism that sensitivity to ionizing radiation increases in carriers of the Glu allele (Hu et al., 2001). In our study, both the Glu/Glu genotype (12.28%) and Glu allele frequencies (37.72%) regarding APE1 Asp148Glu polymorphism were found to be higher in PCOS women than the control group (6.60% and 19.23% respectively) (p <0.05). In contrast, the Asp/Asp genotype and Asp allele frequencies were found to be higher in the control group (%68.13, 80.77% respectively) than PCOS women (%36.84, 62.28% respectively) (p <0.05) (Table 1). This result is compatible with genomic instability data reported in women with PCOS and determined by increased ROS and reduced antioxidant activity and some other methods (Yesilada et al., 2006; Moran et al., 2008; Sekar et al., 2015). There are also several studies conducted on the relationship between APE1 polymorphism and cancer (Gu et al., 2009; Gu et al., 2011; AlMutairi et al., 2015; Zhong et al., 2016). The relationship between PCOS and endometrial cancer was first reported in 1949, and the relationship between obesity, one of the clinical symptoms of PCOS and endometrial cancer, is also commonly reported in the literature (Gadducci et al., 2005). It has been reported that the frequency of Glu allele carriers in the endometrial cancer group is higher than the control group, and that patients carrying Glu allele have an increased risk of endometrial cancer (Cincin et al., 2012).

XPD protein is involved in the normal transcription initiation and the NER. The mutations in the XPD gene cause disorders in DNA repair and transcription as well as abnormal apoptosis responses (Schaeffer et al., 1994; Coin et al., 1999). Glu allele was reported to be associated with poor DNA repair capacity in a study conducted on XPD Lys751Gln polymorphism (Shi et al., 2004). In our study, no statistical differences were observed between PCOS women and the control group in terms of Lys751Gln XPD polymorphism.

Several researches conducted on chromosome aberrations, micronuclei frequency (MN), sister chromatid exchange (SCE) and 8-hydroxydeoxyguanosine in PCOS women have reported that the number of MN and SCE increase in PCOS women, (Yesilada et al., 2006; Moran et al., 2008; Hamurcu et al., 2010). To the best of our knowledge, our study is the first research conducted on four different polymorphisms in three different DNA repair genes (XRCC1 Arg194Trp, XRCC1 Arg399Gln, APE1 Asp148Glu, and XPD Lys751Gln) with a key role in the BER and NER pathways. When the data obtained from PCOS women and the control group was compared, the only difference we observed was in terms of APE1 Asp148Glu polymorphism. The current study conducted with a relatively small population can help us have a better understanding of the relationship between PCOS and genomic instability, provided its scope is expanded to cover other DNA repair genes and different polymorphisms.

Conflicts of interest
The authors have no conflicts of interest to declare.

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