GENETIC TESTING AND MOLECULAR BIOMARKERS
Volume 17, Number 4, 2013

Pp. 1–7
DOI: 10.1089/gtmb.2012.0398

Is There Any Association Between the Ser326Cys Polymorphism of the 8-Oxoguanine Glycosylase 1 (*OGG1*) Gene and Risk of Colon Polyp and Abnormal Glucose Tolerance in Acromegaly Patients?

Ayhan Zengi,[1] Muammer Karadeniz,[2] Vildan Bozok Cetintas,[3] Ece Harman,[4] Aslı Tetik,[3] Mehmet Orman,[5] Zuhal Eroglu,[3] Sevki Cetinkalp,[6] Ahmet Gokhan Ozgen,[6] Fusun Saygili,[6] and Candeger Yilmaz[6]

Aim: Evidence arising from experimental studies indicates an association between increased levels of the growth hormone/insulin-like growth factor 1 and oxidative stress. The association of the Ser326Cys polymorphism in the 8-oxoguanine glycosylase (*OGG1*) gene with a colon carcinoma and diabetes mellitus has been examined. The aim of the study was to compare the genotypic distribution of *OGG1* Ser326Cys between acromegaly patients and nonacromegalic subjects and to explore whether this polymorphism is associated with a colon polyp risk and abnormal glucose tolerance. *Methods:* We examined 98 acromegaly patients, and 99 healthy subjects who can be compared in terms of age and gender. All participants were evaluated by anthropometric and biochemical measurements. Also, a 75-g oral glucose test and colonoscopy was applied to the patients. Genomic DNA was isolated from peripheral blood leucocytes and the genotype was assessed by melting temperature analyses after using a real-time polymerase chain reaction protocol. *Results:* Colon polyps were detected in 13 (30.2%) of 43 patients who underwent the colonoscopy. Except for diastolic blood pressure, clinical and biochemical characteristics were similar between the patients diagnosed with and without a colon polyp. A higher proportion of acromegaly patients had the Ser326Ser genotype when compared to the control group ($p=0.007$). Genotypes were similar between the patients with a normal glucose tolerance and an abnormal glucose tolerance ($p=0.774$). The frequency of the Cys allele was significantly higher in patients with polyps than those without a polyp (38.5% vs. 18.3%) ($p=0.029$). *Conclusion:* Our results suggest that the Cys allele may influence the colon polyp risk in acromegaly patients. Large-scale studies with acromegaly patients are required to show whether being a carrier of the Cys allele is associated with the risk of a colorectal polyp.

Introduction

ACROMEGALY IS A rare disorder characterized by excessive levels of a circulating growth hormone (GH) and its tissue mediator, the insulin-like growth factor 1 (IGF-1). Acromegaly patients have high mortality rates due to cardio/cerebrovascular, respiratory, and metabolic comorbidities and, in some studies, malignancy (Melmed, 2009; Sherlock *et al.*, 2010) when compared to age- and gender-matched healthy subjects. It is accepted that acromegaly is associated with an increased risk of colorectal neoplasia (Cairns *et al.*, 2010). *In vitro* studies, animal models, and the data of nonacromegalic patients with colon cancer have been suggested the role of GH/IGF-1 in the development and/or progression of colon neoplasia in acromegaly patients (Loeper and Ezzat, 2008). Repeated colonoscopic screening of acromegaly patients demonstrated a high prevalence of new adenomatous and hyperplastic colonic polyps, dependent on both the occurrence of previous polyps and persistently elevated IGF-1 levels (Dworakowska *et al.*, 2010). Nevertheless, most of the studies fail to demonstrate associations between serum GH/IGF-1 levels and the presence of colorectal neoplasia in

[1]Department of Endocrinology and Metabolism, Isparta Public Hospital, Isparta, Turkey.
[2]Department of Endocrinology, Health Application and Research Center, Sifa University, Izmir, Turkey.
[3]Department of Medical Biology, Ege University Medical School, Izmir, Turkey.
[4]Department of Endocrinology and Metabolism, Izmir Education and Research Hospital, Izmir, Turkey.
[5]Department of Biostatistic, Ege University Medical School, Izmir, Turkey.
[6]Division of Endocrinology and Metabolism, Department of Internal Medicine, Ege University Medical School, Izmir, Turkey.

acromegalic patients (Clayton *et al.*, 2010). These negative results may arise from some methodological limitations and other pathogenetic mechanisms. Recently, it was suggested that endocrine mechanisms as well as genetic and/or epigenetic alterations may affect neoplasia or cancer risk in acromegaly patients (Loeper and Ezzat, 2008; Clayton *et al.*, 2010).

The prevalence of diabetes mellitus (DM) is also higher in the patients with acromegaly than in the general population (Mestron *et al.*, 2004). Metabolic effects of the GH on adipose tissue, liver, and skeletal muscles are more complicated. Animal models and human studies indicated that the GH may directly or indirectly affect the substrate metabolism via IGF-1 or antagonism of insulin action (Vijayakumar *et al.*, 2010). A GH-induced increase in free fatty acid flux from adipose tissue leads to an insulin resistance at the level of the liver or periphery, resulting in hyperinsulinemia. As long as a compensatory hyperfunction of pancreatic beta cells counterbalances reduced insulin sensitivity, normoglycemia is sustained. An impaired glucose tolerance (IGT) occurs when insulin secretion is impaired, and is followed by diabetes (Chanson *et al.*, 2009). Insulin and IGFs have significant homology and interact with differing affinity with their cognate receptors, which belong to the family of receptor tyrosine kinases (Vijayakumar *et al.*, 2010). Although GH-mediated induction of insulin resistance is well documented, the role of the supraphysiological concentration of IGF-I on insulin resistance has not been completely understood yet (Fukuoka *et al.*, 2010; Vijayakumar *et al.*, 2010).

Oxidative stress is a condition in which cells are subjected to excessive amounts of reactive oxygen species (ROS) as a result of a general increase in ROS generation, a depression of the antioxidant system, or both (Bayraktutan, 2002; Roberts and Sindhu, 2009). ROS react with cellular macromolecules, including proteins, lipids, and DNA. Oxidative stress plays a role in the pathogenesis or progression of several disorders, such as cancer, DM, atherosclerosis, hypertension, and other insulin resistance-related manifestations. Some authors have examined the relationship between excess GH/IGF-1 and oxidative stress in an animal model (Brown-Borg *et al.*, 2002; Andersson *et al.*, 2006; Fukuoka *et al.*, 2010). In acromegalic subjects, higher levels of thiobarbituric acid reactive substances and 8-hydroxy-2-deoxyguanosine (8-OHdG) have been detected (Nishizawa *et al.*, 2012). 8-oxoguanine (8oxoG) and 8-OHdG are biomarkers of oxidative DNA damage produced by mutagenic or carcinogenic reactive-free radicals resulting in G:C to T:A transversions. DNA damage induced by chemical agents, smoking, and diet can initiate many cancers, especially colorectal cancer. There is a complex DNA repair system to maintain the integrity of the genome from DNA damage. One of the members of this system is human 8-oxoguanine glycosylase (OGG1), which is a DNA repair enzyme responsible for excising the 8-OHdG from damaged DNA. Several single-nucleotide polymorphisms (SNPs) and somatic mutations have been determined in a human *OGG1* gene and investigated as a candidate gene for many types of tumors. Among these, Ser326Cys is a common SNP. Data indicated that the Cys326 has a lower ability for preventing the mutagenesis by 8-OHdG than Ser326 *in vivo* in human cells (Yamane *et al.*, 2004). Although no association could be revealed between the *OGG1* Ser326Cys polymorphism and the risk of colorectal cancer in a meta-analysis (Zhang *et al.*, 2011), several studies in different ethnic groups have indicated the existence of a relationship (Moreno *et al.*, 2006; Pardini *et al.*, 2008; Obtulowicz *et al.*, 2010). Obtulowicz *et al.* (2010) have reported that oxidative stress occurs in patients with a colorectal carcinoma and benign adenoma. They have found an association between the *OGG1* Cys/Cys genotype and colorectal carcinoma, but not a colon adenoma. The association of this polymorphism with insulin sensitivity and type 2 DM (T2DM) has been also examined by some authors. Most of them have suggested that the Cys allele was related to a decreased insulin sensitivity and/or the development of T2DM (Wang *et al.*, 2006; Daimon *et al.*, 2009; Sun *et al.*, 2010; Thameem *et al.*, 2010). The objective of our study was to assess the distribution of the *OGG1* Ser326Cys genotype in acromegaly patients and whether it is related to some comorbidities in acromegaly, especially colon polyps and abnormal glucose tolerance.

Materials and Methods

Study protocol

We included 98 acromegaly patients consecutively admitted from January 2007 through February 2010 to the Endocrinology and Metabolism outpatient clinic of the Ege University Hospital and 99 healthy control subjects. The study protocol was approved by the Ethics Committee of the Ege University Hospital, and written informed consent was taken from all subjects before participating in the study. Baseline characteristics of the patients were reviewed retrospectively. Acromegaly was diagnosed based on the medical history, clinical examination, failure of suppression of serum GH concentrations below 1 μg/L after 75-g oral glucose load and fasting plasma IGF-1 concentrations above the normal ranges for sex and age, and histopathological examination. Age at the time of diagnosis, gender, duration of the disease, treatment options for acromegaly (surgery, radiotherapy, stereotactic radiosurgery, somatostatin analog, and dopamine receptor agonist), and other clinical data were recorded. Control subjects were recruited from the hospital staff and persons admitted to the outpatient clinic of the Ege University Hospital for a routine health check-up. All of them were found to be free from acute or chronic infections, known ischemic heart disease, peripheral vascular disease, hypertension, dyslipidemia, and any other serious medical problems. Patients and controls were then further evaluated by physical examination, anthropometric measurements, and appropriate laboratory tests. Their body weights and heights were measured and the body mass index (BMI) was calculated as body weight/height^2 and expressed in kg/m^2. The waist circumference was measured according to a standard procedure described earlier (Daniel *et al.*, 1999). Blood pressure was recorded as the last of two measurements with the subjects seated using a sphygmomanometer. Colonoscopic screening was applied by the Olympus colonoscope to the patients accepting the colonoscopy. After an overnight fast, biochemical measurements and oral glucose tolerance test (OGTT) were performed. The serum GH concentration was measured by the chemiluminescent immunometric assay (Immulite 1000), and the plasma IGF-1 concentration was measured by the immunoradiometric assay (DSL-2800). The serum concentration of high-sensitivity c-reactive protein was determined by the immunonephelometric assay; serum total, low density lipoprotein and high density lipoprotein cholesterol, triglyceride,

and glucose levels were measured by an Olympus AU 2700 automated analyzer (Toshiba). Peripheral venous blood samples for genomic DNA were drawn from an antecubital vein into ethylenediaminetetraacetic acid-containing tubes and stored at −20°C until use.

Genotyping

Total genomic DNA was extracted from whole blood by using a Magna Pure LC DNA isolation kit (Roche Applied Science) in accordance with the protocol provided by the manufacturer. A real-time polymerase chain reaction (PCR) method was optimized by using a LightCycler 2.0 instrument (Roche Applied Science) for identifying the *OGG1* Ser326Cys alleles of each study participant. For this purpose, 0.5-μM specific primers and a 0.2-μM simple probe (Tib Molbiol) were used in combination with the LightCycler FastStart DNA Master Hybridization Probes kit (Roche Applied Science). About 1.5 mM $MgCl_2$, a 2.5 U GC-rich PCR buffer (Roche Applied Science), and 50 nmol genomic DNA were added to a 10 μL reaction mix (forward primer: 5′-CCCAACACTGTC ACTAGTCTCA-3′, reverse primer: 5′-TTGGGGAATTTCTT TGTCCA-3′, simple probe: 5′-CGCCAATCCCGCCAXITGC TCAG-PH). Following a denaturation step at 94°C for 10 min, DNA was amplified in 45 PCR cycles (94°C for 5 s; 51°C for 8 s; 72°C for 15 s). The melting analysis was set at 95°C for 20 s, 40°C for 20 s, and 85°C 0 s with a ramp rate of 0.2 in a continuous acquisition mode following a cooling step at 40°C for 30 s. While the wild-type genotype was identified by a melting amplicon at 62.5°C, the heterozygote genotype was determined at 62.5°C and 55.5°C, whereas the homozygote polymorphic genotype was at 55.5°C.

Statistical analysis

Statistical analyses were performed by using the SPSS 18.0. Variables were checked by using visual (probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test) for determining whether they were normally distributed. When the normality test was passed, the unpaired *t*-test was used for comparing the patients and the controls for each variable. The Mann–Whitney U test was used for non-normally distributed variables. Descriptive analyses were presented using means and standard deviations for normally distributed variables. Non-normally distributed data were expressed as the median ± interquartile range (IQR). The chi-square test was used for assessing the deviation from the Hardy–Weinberg equilibrium of genotype frequencies. The differences in genotype distribution between different groups were assessed by a logistic regression analysis. A *p*-value of less than 0.05 was accepted as statistically significant.

Result

Baseline characteristics of 98 acromegaly patients (46 female and 52 male) and 99 control subjects (58 female and 41 male) are summarized in Table 1. As demonstrated, the two groups were comparable with respect to gender, age, and smoking habit. Acromegaly patients had a significantly higher BMI, systolic and diastolic blood pressure, fasting and postprandial glucose, and triglyceride levels than the control group.

In the patient group, the mean age at the diagnosis was 43 ± 11.2 years and the median duration of the disease was 48 months (IQR: 89, minimum: 1, maximum: 360). The median size of the pituitary adenoma at the time of diagnosis was 15 mm (IQR: 12, minimum: 4, maximum: 45). According to applied treatment options, the classification of the patients is presented in Table 2. The number of pituitary surgeries was one in 73 patients, two in 8 patients, three in 2 patients. Sixteen patients had a controlled disease based on the last consensus criteria for acromegaly cure (Giustina *et al.*, 2010). Eleven (11.2%) patients received the thyroid hormone and glucocorticoid replacement therapy due to pituitary deficiency. DM, IGT, and impaired fasting glucose (IFG) were detected in 36 (36.7%), 7 (7.1%), and 14 (14.3%) patients, respectively. Forty-nine (50%) patients had hypertension. Thirty-one (31.6%) and 33 (33.7%) patients were under treatment for DM

TABLE 1. BASELINE CHARACTERISTICS OF ACROMEGALY PATIENTS AND CONTROL GROUP

	Acromegaly group	*Control group*	
	Mean ± SD	*Mean ± SD*	p *Value*
Gender, F/M	46/52	58/41	0.117
Age (years)	49.4 ± 10.8	48.8 ± 9.7	0.654
Smoke/nonsmoke	24/74	14/85	0.066
BMI (kg/m^2)	29.8 ± 4.8	27.2 ± 4.7	0.001
Waist circumference (cm)	97 ± 11.7	93 ± 11.4	0.058
Systolic BP (mmHg)	134 ± 25.4	117 ± 13.3	<0.001
Diastolic BP (mmHg)	84 ± 14.7	73 ± 8.2	<0.001
GH (μg/L)[a]	1.4–3.1	—	
IGF-1 (ng/mL)[a]	489–602	—	
Fasting glucose (mg/dL)	110 ± 31.3	91 ± 8.9	<0.001
Postprandial glucose (mg/dL)	126 ± 48.6	101 ± 18.7	0.001
HOMA-IR	2.0 ± 1.2	1.7 ± 0.9	0.250
Total cholesterol (mg/dL)	194 ± 38.7	193 ± 22.9	0.683
Triglyceride (mg/dL)	131 ± 73.7	106 ± 42.6	0.007
HDL-cholesterol (mg/dL)	53 ± 13.2	54 ± 12.4	0.176
LDL-cholesterol (mg/dL)	113 ± 36.6	118 ± 19.5	0.234
hs-CRP (mg/dL)	0.061–0.145	—	
Fibrinogen (mg/dL)	451 ± 101.0	—	

[a]Median – interquartile range (IQR).

SD, standard deviation; BMI, body mass index; BP, blood pressure; GH, growth hormone; IGF-1, insulin-like growth factor 1; HOMA-IR, Homeostasis model assessment of insulin resistance; HDL, high density lipoprotein; LDL, low density lipoprotein; hs-CRP, high-sensitivity c-reactive protein.

TABLE 2. THE CLASSIFICATION OF THE PATIENTS ACCORDING TO TREATMENT OPTIONS OF ACROMEGALY

Treatment option	n *(%)*
Newly diagnosed	1 (1)
Only surgery	28 (28.6)
Surgery + SSA (alone or with DA)	41 (41.8)
Surgery + radiotherapy	4 (4.1)
Surgery + stereotactic radiosurgery	1 (1)
Only SSAs	14 (14.3%)
Surgery + stereotactic radiosurgery + SSA (alone or with DA)	6 (6.1)
Surgery + radiotherapy + SSA (alone/or with DA)	3 (3.1%)

SSA, somatostatin analog; DA, dopamine receptor agonist.

TABLE 3. CLINICAL AND BIOCHEMICAL PARAMETERS OF ACROMEGALY PATIENTS WITH AND WITHOUT POLYP

	Acromegaly patients with polyp	*Acromegaly patients without polyp*	
	n: 13	n: 30	p *Value*
Gender, F/M	6/7	15/15	0.817
Age (years)	52.9±9.3	48.2±12.4	0.230
Smoke/nonsmoke	2/11	4/26	0.858
Cure for acromegaly	2	5	0.881
Duration of acromegaly (months)[a]	48–77	59–81	0.434
Diameter of pituitary adenoma at diagnosis (mm)	15.4±7.4	17.2±7.3	0.565
BMI (kg/m^2)	28.9±3.8	29.3±4.4	0.799
Waist circumference (cm)	95.9±11.9	93.0±10.4	0.466
Systolic BP (mmHg)	140±20.9	127±17.7	0.060
Diastolic BP (mmHg)	92±11.5	78±11	0.001
GH (μg/L)[a]	1.1–5.6	1.5–5.6	0.634
IGF-1 (ng/mL)	628.5±329.1	579.0±347.2	0.667
Fasting glucose (mg/dL)[a]	105±33.1	110±27.8	0.590
Postprandial glucose (mg/dL)[a]	121–74	100–50	0.462
HOMA-IR	1.3±0.7	1.9±1.2	0.266
Total cholesterol (mg/dL)	194±24.8	195±44.8	0.907
Triglyceride (mg/dL)[a]	110–47	132–56	0.923
HDL-cholesterol (mg/dL)	56±13.2	52±12.3	0.368
LDL-cholesterol (mg/dL)	117±25.9	118±39.1	0.945
hs-CRP (mg/dL)[a]	0.064–0.228	0.059–0.310	0.799
Fibrinogen (mg/dL)	488±62.1	451±121.9	0.425

Normally distributed data are presented as mean±SD.
[a]Non-normally distributed data are presented as median-IQR.

and hypertension, respectively. Forty-three patients (21 female, 22 male) accepted and underwent the colonoscopy. Colon polyps were detected in 13 patients (30.2%). The mean polyp size was 7.5±6.0 (range: 2–25) mm and the total polyp number was 23. Polyps were detected in the rectosigmoid (44.3%), transverse colon (21.5%), descending colon (21.5%), ascending colon (8.5%), and splenic flexure (4.2%). According to histopathological findings, distributions of the polyps were 12 (52.3%) tubular, 1 (4.3%) tubulovillous, 1 (4.3%) villous, 1 (4.3%) carcinoma insutu, 1 (4.3%) adenocarcinoma, 6 (26.2%) hyperplastic, and 1 (4.3%) inflammatory. Except for diastolic blood pressure, clinical and biochemical features were similar between the patients with and without polyps (Table 3). The patients with polyps had a significantly higher diastolic blood pressure ($p=0.001$).

Genotypic data in the acromegaly patients and control group were consistent with the Hardy–Weinberg equilibrium. Distribution of *OGG1* haplotypes and genotypes for the two groups is presented in Table 4. A higher proportion of acromegaly patients possessed the Ser326Ser genotype when compared to the control group ($p=0.007$). In the patient group, there was no statistically significant difference between the genotypes and anthropometric, clinical, and metabolic parameters as shown in Table 5. Genotype distribution in the patients with a normal glucose tolerance (NGT) and an abnormal glucose tolerance (DM, IGT, and IFG) was similar ($p=0.774$) (Table 6). *OGG1* haplotype and genotype distribution of the patients who underwent colonoscopy are also shown in Table 7. Genotype distribution in acromegaly patients with polyps was different from those without polyps, but it was not statistically significant ($p=0.093$). The frequency of the Cys allele was significantly higher in patients with polyps than those without polyps (38.5% vs. 18.3%) ($p=0.029$). When compared in terms of age, gender, and smoking habit, the presence of the Cys allele was related to the risk of the colon polyp as seen in Table 8 ($p=0.034$, odds ratio 5.029, 95% confidence interval 1.129–22.413).

TABLE 4. DISTRIBUTION OF *OGG1* HAPLOTYPES AND GENOTYPES IN ACROMEGALY PATIENTS AND CONTROL GROUP

	Acromegaly group	*Control group*			
	n: 98	n: 99	*OR*	*95% CI*	p-*Value*
Genotype					
Ser/Ser	55 (56.1%)	34 (34.3%)		R	0.007
Ser/Cys	37 (37.8%)	52 (52.5%)	0.440	0.241–0.802	0.007
Cys/Cys	6 (6.1%)	13 (13.1%)	0.285	0.099–0.882	0.020
Haplotype					
Ser	147 (75%)	120 (60.6%)			
Cys	49 (25%)	78 (39.4%)			

OGG1, 8-oxoguanine glycosylase 1; OD, odds ratio; CI, confidence interval; R, reference.

TABLE 5. CLINICAL AND BIOCHEMICAL PARAMETERS BETWEEN *OGG1* SER326CYS GENOTYPES IN ACROMEGALY PATIENTS

	Ser/Ser	*Ser/Cys*	*Cys/Cys*	p *Value*
BMI (kg/m^2)	30.0±4.6	29.7±5.4	28.4±4.8	0.743
Waist circumference (cm)	98.6±11.9	95.1±11.9	91.4±7.4	0.251
Systolic BP (mmHg)	134±23.4	138±27.9	117±24.2	0.161
Diastolic BP (mmHg)	82±13.9	88±15.4	80±16.7	0.226
GH (μg/L)[a]	1.4–2.6	1.3–4.5	2.2–4.5	0.812
IGF-1 (ng/mL)	554±370	551±292	544±197	0.998
Fasting glucose (mg/dL)	111±31.8	110±33.4	105±11.2	0.906
Postprandial glucose (mg/dL)[a]	122–64	97–68	115–41	0.079
HOMA-IR	2.2±1.5	1.6±0.7	2.4±0.6	0.199
Total cholesterol (mg/dL)	194±41.8	196±34.4	187±38.7	0.859
Triglyceride (mg/dL)[a]	125–65	104–53	94–75	0.056
HDL-cholesterol (mg/dL)	51±12.5	56±14.1	52±13.6	0.209
LDL-cholesterol (mg/dL)	113±39.0	117±30.9	86.5±41.7	0.168

[a]Median-interquartile range (IQR).

Discussion

Like other DNA repair genes, the contribution of the *OGG1* Ser326Cys polymorphism in the development of the colorectal carcinoma in the general population is controversial. No association between this polymorphism and colorectal carcinoma risk has been revealed in a meta-analysis of 12 studies (Zhang *et al.*, 2011). On the other hand, Moreno *et al.* (2006) have reported that the Ser326Cys variant of the *OGG1* was convincingly associated to a moderately increased risk of colorectal cancer. Obtulowicz *et al.* (2010) have also found a relation between the *OGG1* Cys326Cys genotype and colorectal carcinoma. A higher frequency of Cys/Cys homozygotes has been detected in the patients with the colorectal carcinoma than in the benign adenoma or control group. The effect of the *OGG1* Ser326Cys polymorphism on the 8-oxoGua excision rate has been also seen in the group of colorectal carcinoma. It has been found that Cys homozygotes were related to a decreased 8-oxoGua excision rate in comparison with Ser homozygotes. Another study reporting a negative result for the relation between the Ser326Cys polymorphism and colorectal cancer has suggested that the Cys genotype may alter the impact of some environmental factors on colon cancer development (Kim *et al.*, 2003). Pardini *et al.* (2008) have investigated the role of nine SNPs in eight DNA repair genes on the risk of colorectal cancer and showed an increased risk in smokers homozygous for the variant allele of the *OGG1* Ser326Cys polymorphism. They have recommended the exploration of gene–gene and gene–environmental interactions in a larger sample size with sufficient statistical power according to their results. In a study from Turkey, the *OGG1* variant genotype carrier was not found to be correlated with the increased risk of cancer progression (Engin *et al.*, 2010).

There is only a limited number of studies examining the effect of the *OGG1* Ser326Cys polymorphism on colon polyp risk in the literature. Although evidence of oxidative stress was observed in both colorectal carcinoma and benign adenoma patients, no relation between the genotype and benign adenoma could be shown (Obtulowicz *et al.*, 2010). No association has been found with the risk of adenomas in Norwegian cohort (Hansen *et al.*, 2005).

To our knowledge, there are no data related to the *OGG1* Ser326Cys polymorphism and colon polyp risk in acromegaly patients. In our study, we found that the frequency of the Cys allele is higher in acromegaly patients with colon polyps than in those without polyps. It has been well known that the Cys allele has a lower ability to prevent mutagenesis by 8-OHdG than Ser326 *in vivo* in human cells. Indeed, carriers of the Cys allele among acromegaly patients may be prone to the development of colorectal neoplasia. However, there is a need for large-scale studies to verify whether this hypothesis is valid.

In our study, the genotype distribution of *OGG1* Ser326Cys in the acromegaly group was found to be different from the

TABLE 6. DISTRIBUTION OF *OGG1* GENOTYPE IN THE PATIENTS WITH NORMAL GLUCOSE TOLERANCE AND ABNORMAL GLUCOSE TOLERANCE (DIABETES MELLITUS, IMPAIRED GLUCOSE TOLERANCE, IMPAIRED FASTING GLUCOSE)

n (%)	*Ser/Ser*	*Ser/Cys*	*Cys/Cys*	p *Value*
Patients with NGT	22 (53.7%)	17 (41.5%)	2 (4.9%)	0.774
Patients with abnormal glucose tolerance	33 (57.9%)	20 (35.1%)	4 (7.0%)	

NGT, normal glucose tolerance.

TABLE 7. DISTRIBUTION OF *OGG1* HAPLOTYPES AND GENOTYPES IN ACROMEGALY PATIENTS WITH AND WITHOUT COLON POLYP

	Acromegaly patients with polyp	*Acromegaly patients without polyp*	
	n: *13*	n: *30*	p *Value*
Genotype			0.093
Ser/Ser	4 (30.8%)	20 (66.7%)	
Ser/Cys	8 (61.5%)	9 (30.0%)	
Cys/Cys	1 (7.7%)	1 (3.3%)	
Haplotype			0.029
Ser	16 (61.5%)	49 (81.7%)	
Cys	10 (38.5%)	11 (18.3%)	

TABLE 8. STATISTIC OF CYS ALLELE AND OTHER FACTORS FOR THE RISK OF COLON POLYP

	Odds ratio 95% CI	*Lower limit*	*Upper limit*	p *Value*
Cys allele	5.029	1.129	22.413	0.034
Age	1.053	0.980	1.132	0.158
Gender	1.265	0.285	5.614	0.757
Smoking	0.495	0.045	5.429	0.565

healthy control group. However, no relation was detected between clinical and biochemical parameters and the genotype. Some patients were under medication for DM, hypertension, and acromegaly when they were included in the study. So, this condition may be a limiting factor to reveal any relation between the phenotypic features and the genotype. On the other hand, all patients receiving oral antidiabetic agents and/or insulin therapy have predetermined DM. Except for them, other patients whose results of OGGT were classified according to ADA criteria (American Diabetes Association, 2005) were not under medication for DM. Nevertheless, we could not determine any difference in genotypic distribution between acromegaly patients with NGT and those with an abnormal glucose tolerance. It has been shown that the Cys/Cys variant was associated with a significant decrease in insulin sensitivity in normal glucose tolerant subjects (Wang *et al.*, 2006). In some studies, a relationship between the polymorphism and the T2DM was reported in Japanese (Daimon *et al.*, 2009), Chinese (Sun *et al.*, 2010), and Mexican American (Thameem *et al.*, 2010) populations. Daimon *et al.* (2009) showed that genotypes with the Cys allele were significantly associated with diabetes. Similarly, a significant association was reported by Thameem *et al.* (2010) between the Ser326Cys polymorphism and T2DM in a Mexican American cohort. On the contrary, Kasznicki *et al.* (2009) have revealed no association in a small sample size of Polish type 2 diabetic patients. Whether the *OGG1* Ser326Cys polymorphism has a possible effect on the development of DM in acromegaly patients is not known. We did not obtain any result suggesting that the polymorphism may be related to glucose metabolism in acromegaly patients.

Acromegaly is commonly accompanied with the comorbidities that are relevant with oxidative stress, such as cardiovascular disease and metabolic disorders. Evidence of oxidative DNA damage has been detected in patients with atherosclerosis and DM (Andreassi, 2003; Wu *et al.*, 2004). Moreover, experimental studies have called attention to the association between excess GH/IGF-1 and oxidative stress during the last decade. It has been shown that the GH and IGF-1 might decrease the ability of the mouse hepatocyte to counter the oxidative stress (Brown-Borg *et al.*, 2002). In a transgenic mice model, endothelial dysfunction initially caused by increased oxidative stress was found to be associated with GH overexpression (Andersson *et al.*, 2006). It has been reported that the IGF-1 inhibits the insulin activity in the cultured adipocytes via ROS production (Fukuoka *et al.*, 2010). Evidence from GH transgenic rats and acromegalic humans have indicated an association between increased levels of IGF-1 and enhanced oxidative stress (Nishizawa *et al.*, 2012).

In the light of this information, it could be expected that the ratio of Cys allele carriers having a lower activity than the Ser allele in the prevention of the mutagenesis formed by 8-OGdG would be higher compared with Ser326 among acromegaly patients. However, the fact that we detected higher Ser/Ser genotype ratios in acromegaly patients than healthy controls may seem to be a controversial finding. It may suggest that the effects of excess GH/IGF-1 are the most important in the pathogenesis of acromegaly comorbidities. At the same time, the polymorphism of *OGG1* Ser326Cys may play a role in the development or the progression of the comorbidities, especially colon neoplasia.

In conclusion, our study demonstrated that the genotypic distribution of *OGG1* Ser326Cys in acromegaly patients is different from healthy controls. However, the effect of this polymorphism on acromegaly patients could not be explained sufficiently. A higher proportion of the Cys allele carrier was detected in the acromegaly patients with colorectal polyps. In the literature, there are only limited data examining the association between the polymorphism of *OGG1* Ser326Cys and the colorectal polyp in the general population. Further, large-scale studies are required to show whether being a carrier of the Cys allele leads to susceptibility of acromegaly patients to the development of colorectal polyps.

Acknowledgments

We are grateful to Biologist Gunes Yalıcı, Biologist Duygu Subay, and all technicians of Nail Tartaroglu Endocrinology and Metabolism Laboratory for their technical assistance.

Author Disclosure Statement

No potential conflict of interests relevant to this article was reported.

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Address correspondence to:
Ayhan Zengi, MD
Department of Endocrinology and Metabolism
Isparta Public Hospital
Isparta 32200
Turkey

E-mail: aliyezengi@yahoo.com