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Genetic Polymorphisms of INS, INSR and IRS-1 Genes Are Not Associated with Polycystic Ovary Syndrome in Croatian Women

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A B S T R A C T

Obesity and insulin resistance is a common finding in patients with polycystic ovary syndrome (PCOS). Significant number of PCOS women experience insulin resistance that is irrespective of the degree of obesity suggesting possible genetic basis. Therefore, several polymorphisms of the genes encoding for the insulin (INS), insulin receptor (INSR) or insulin receptor substrates (IRS) involved in postreceptor signaling have been explored for their association with abnormal sensitivity to insulin in PCOS. The aim of the present study was to determine whether selected polymorphisms of INS, INSR and IRS-1 are associated with the development of PCOS as well as with increased insulin resistance in Croatian women with PCOS. The study enrolled 150 women with PCOS and 175 control women. The diagnosis of PCOS was based on Rotterdam consensus criteria. Each subject underwent an evaluation of body mass index (BMI), hirsutism, acne and menstrual cycle abnormalities as well as follicular stimulating hormone (FSH), luteinizing hormone (LH), total and free testosterone, androstendione, dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG), fasting glucose and fasting insulin. Insulin resistance (IR) was quantified using the homeostatic model assessment of IR (HOMA-IR). Molecular analyses for the genetic polymorphisms were preformed. There was a significant difference in clinical and biochemical characteristics of the studied groups except for BMI and fasting glucose levels. No significant differences were observed in the genotype and allele distribution of the VNTR INS, C/T INSR, Gly792Arg IRS-1 polymorphisms between cases and controls. Moreover, no association was found between VNTR INS, C/T INSR and Gly792Arg IRS-1 polymorphism and parameters of insulin resistance in PCOS patients. In conclusion, our data does not support an association between VNTR INS, C/T INSR and Gly792Arg IRS-1 polymorphism and susceptibility to PCOS or insulin resistance in Croatian women with PCOS.

***Key words**: polycystic ovary syndrome, VNTR INS, C/T INSR, Gly792Arg IRS-1, insulin resistance*

Introduction

Obesity and insulin resistance is a common finding in patients with PCOS. The mechanism that induces insulin resistance in PCOS is not fully understood[1,2]. Significant number of PCOS women experience insulin resistance that is irrespective of the degree of obesity suggesting possible genetic basis. Therefore, several polymorphisms of the genes encoding for the insulin (INS), insulin receptor (INSR) or insulin receptor substrates (IRS) involved in postreceptor signaling have been explored for their association with abnormal sensitivity to insulin in PCOS[3–5].

Variable number tandem repeat (VNTR) is a minisatellite element which lies 5' to the insulin gene (INS)[6,7]. This highly polymorphic locus modifies insulin transcription *in vitro* therefore may contribute to altered insulin secretion in PCOS patients[8]. Waterworth et al. were first

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to report that the PCOS phenotypes were associated with the category III alleles at the INS VNTR-locus[9] but subsequent studies in women with PCOS from other ethnic backgrounds produced conflicting and inconsistent results[10–15]. There is also evidence that the interaction of obesity and the III/III INS VNTR genotype might be a risk factor for the development of PCOS[10].

Insulin receptor gene (INSR) is composed of 22 exons. The tyrosine kinase domain mutations (exons 17–21) are associated with severe insulin resistance and hyperinsulinemia[16]. Several studies reported that the common polymorphism involving substitution of C to T in the INSR gene (His-1058 C / T in exon 17) is associated with PCOS especially in interaction with BMI[3,17–20].

Insulin receptor substrate-1 (IRS-1) is the first substrate in the insulin signaling pathway[21]. The most common IRS-1 polymorphic variant, a Gly to Arg change at codon 972 (G972A) modifies and impairs insulin-stimulated signals contributing to insulin resistance[3,22–24]. The association between this polymorphism and the risk of PCOS has been observed in studies from different ethnic backgrounds[3,4]. There is also evidence that PCOS patients with Gly792Arg – polymorphism have a higher BMI, higher insulin resistance and elevated fasting insulin compared with patients with normal BMI and matched controls[22,24,25].

The aim of the present study was to determine whether selected polymorphisms of INS, INSR and IRS-1 are associated with the development of PCOS as well as with increased insulin resistance in Croatian women with PCOS.

Subjects and Methods

Subjects

A total of 150 PCOS patients were enrolled in the study with mean age of 26.7±5.9 (mean ± SD). The cohort was published in part previously[26]. The diagnosis of PCOS was made according to the Rotterdam consensus criteria, which are based on the presence of two out of three traits including oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound scanning[27]. The menstrual irregularities were defined as the presence of amenorrhea or oligomenorrhea. Hyperandrogenism was assessed by the presence of hirsutism and/or acne and/or by elevated androgen levels (serum total testosterone (TT)> 2.5 nmol/L or free testosterone (FT)>30 pmol/L). Hirsutism was defined by Ferriman-Gallwey index score>8 (FG>8)[28]. Other endocrinopathies and related disorders were ruled out by measuring basal serum 17-hydroxyprogesterone (17-OHP), prolactin (PRL) and thyroid stimulated hormone (TSH) levels.

The control group consisted of 175 healthy volunteers aged 29.1±4.7 years before entering in vitro fertilisation (IVF) programme due to male factor infertility. They had no menstrual cycle irregularities, no clinical or biochemical hyperandrogenism, no PCO findings on ultrasound, no history of endocrinological or autoimmune disorders and no surgery to the pelvic region. The patients discontinued medication (including hormonal contraceptives) for at least six months prior to enrolment to study.

All patients were observed in the early follicular phase of the menstrual cycle (day 3–5) or randomly in amenorrhoeic patients. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Transvaginal ultrasound (TVUS) was done to diagnose PCO according to the Rotterdam criteria[27]. Blood samples were drawn for the measurement of luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone (TT), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEAS), androstendione (A), fasting serum glucose and fasting insulin. Free testosterone (FT) was calculated from TT and SHBG as previously published[29] using a web-based calculator (http://www.issam.ch/freetesto.htm). Insulin resistance (IR) was quantified using the homeostatic model assessment of IR (HOMA-IR) (fasting insulin (mU/L) x fasting glucose (mmol/L)) / 22.5). Whole blood samples were obtained for genetic analysis.

The study protocol No. 04-1116-2006 was approved by the University of Zagreb Medical School Ethics Committee. Informed written consent was obtained from all women enrolled in the study.

Biochemical Analysis

Serum LH, FSH, SHBG, TT, DHEAS and A levels were measured. Serum LH, FSH, and TT concentrations were determined by chemiluminescent immunometric assays using LH – Vitros, FSH – Vitros, and Testosterone – Vitros, respectively (Ortho Clinical Diagnostics, Johnson&Johnson, Rochester, NY, USA). Serum SHBG, DHEAS and A levels were measured using chemiluminescent immunometric assays (SHBG – Immulite, DHEAS – Immulite and Androstendione-Immulite, respectively) (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA). The intra-assay and inter-assay coefficients of variation ranged between 1.5 and 7.9%. The plasma glucose level (Glc) was determined by the UV-photometric hexokinase method and the serum insulin (Ins) level by chemiluminescent immunometric assay using Insulin-Immulite, respectively (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA).

Genomic DNA was isolated from whole blood using FlexiGene Kit (Qiagen GmbH, Hilden, Germany) following the manufacturer´s protocol. Genotyping for rs1801278 (Gly972Arg in the IRS1 gene) and rs1799817 (C10923T in the INSR gene) was performed with real-time PCR allelic discrimination on 7900HT system using C__2384392_20 and C__8356128_1_assays, respectively (Applied Biosystems, Foster City, CA) following the manufacturer´s protocol. Genotyping of the INS VNTR was performed indirectly by analysing its surrogate marker, the –23*HphI* A>T polymorphism of the INS gene. In Europeans, the –23 T alleles have been found to be in complete linkage disequilibrium with INS VNTR class I alleles and the –23 A alleles have been found to be in

complete linkage disequilibrium with INS VNTR class III alleles[30]. The appropriate Custom TaqMan® SNP Genotyping Assay (Applied Biosystems, Foster City, CA) was used, containing unlabelled target-specific primers (F: 5´-GGG CAC CTG GCC TTC AG-3´, R: 5´-CCA TGG CAG AAG GAC AGT GA-3´), TaqMan® MGB VIC dye-labelled probe for detection of *HphI* T alleles (5´-CCT GCC TGT CTC CCA GA-3´) and TaqMan® MGB 6-FAM dye--labelled probe for detection of *HphI* A alleles 5´-CTG CCT GTC ACC CAG A-3´.

Genotype analysis was conducted at the Department of Obstetrics and Gynaecology, Division of Medical Genetics, University Medical Centre Ljubljana.

Statistical Analysis

In a comparison of the clinical and hormonal parameters the categorical variables were described by percentages, and the continuous as mean ± standard deviation. We used the independent Student's t-test to compare the values of the means between cases and controls, while differences in categorical characteristics were assessed using χ^2-test. Statistical analysis of the differences in genotype frequencies was performed using χ^2-test. Differences in clinical and biochemical parameters according to the genotype of the PCOS patients were assessed using the Mann-Whitney *U* test or Kruskal-Wallis test for the continuous, and χ^2-test for the categorical variables. Results were described as medians (interquartile ranges) or percentages. All statistical analysis were done using the SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL, USA). A p-value<0.05 was considered statistically significant.

Results

Clinical and biochemical characteristics of patients

The clinical and hormonal characteristics of the groups studied are presented in the Table 1. As expected according to Rotterdam consensus criteria PCOS patients presented with higher mean serum levels of LH, TT, FT and HOMA–IR, whereas the mean serum SHBG and FSH levels were significantly lower than in the control group. The PCOS patients had higher BMI, and a significantly higher frequency of hirsutism than controls. (Table 1)

TABLE 1
COMPARISON OF CLINICAL AND HORMONAL PARAMETERS IN THE PCOS AND CONTROL PATIENTS

	PCOS (N=150)	Control (N=175)	p-value[1]
Age (years)	26.7±5.9	29.1±4.7	0.001
BMI (kg/m^2)	23.4±4.2	22.4±3.3	0.019
BMI<25 (kg/m^2) (%)	77.0	89.3	0.004
FSH (IU/L)	3.9±1.9	5.1±1.4	<0.001
LH (IU/L)	8.9±5.9	3.2±1.2	<0.001
TT (nmol/L)	2.3±0.9	1.2±0.4	<0.001
FT (pmol/L)	42.6±23.2	14.7±6.3	<0.001
A (nmol/L)	11.1±4.9	7.1±3.8	<0.001
DHEAS (μmol/L)	6.5±2.7	4.9±1.9	<0.001
SHBG (nmol/L)	35.9±21.5	53.9±33.8	<0.001
HOMA-IR	2.3±2.8	1.3±0.5	<0.001
HOMA-IR > 2.5	22.4	2.8	<0.001
Oligo/amenorrhea (%)	90.1	0.0	<0.001
Hirsutism (%)	74.8	12.8	<0.001
Acne (%)	52.3	19.3	<0.001

BMI: body mass index; FSH: follicle stimulating hormone; LH: luteinizing hormone; TT: total testosterone; FT: free testosterone; A: androstendione; DHEAS: dehydroepiandrosterone sulphate; SHBG: sex hormone binding globulin; HOMA-IR: homeostatic model assessment of insulin resistance
[1] Students' t-test was used for continuous and χ^2-test for categorical variables

Allelic and genotypic frequencies of INS VNTR, INSR His 1058 C/T and IRS-1 Gyl972Arg polymorphisms in PCOS patients and controls

The allele and genotype distributions of the INS VNTR, INSR His 1058 C/T and *IRS-1* Gyl972Arg polymorphism for both PCOS and control group were consistent with the Hardy-Weinberg equilibrium and are presented in Table 2.

We found no significant difference in the distribution of category III INS-VNTR and category I INS-VNTR alleles between the groups studied (p=0.325, Table 2). Category II INS-VNTR allele was not present in our studied population. Patients with PCOS were frequent carriers of homozygous category III INS-VNTR genotype compared to the control group; however, this difference was not significant (Table 2).

Frequency distribution of T allele, and C allele of the INSR His 1058 C/T polymorphism was not different between the groups investigated (p=0.810, Table 2). There was also similar distribution of different genotypes between the groups, although the C/C genotype presented more frequently in the control group. Because of the low frequency of T/T genotype, for further analysis we divided the genotypes into two categories: C/C and C/T+ T/T.

The Arg allele of the IRS-1 Gyl972Arg polymorphism was frequently more present in the control group compared to PCOS group, but this finding was not significant (p=0.186, Table 2). The distribution of various alleles and genotypes was comparable between the groups as it is presented in Table 2. Because of the low frequency of Arg/Arg genotype, for further analysis we divided the genotypes into two groups: Gly/Gly and Gly/Arg+Arg/ Arg.

Influence of INS VNTR, INSR His 1058 C/T and IRS-1 Gyl972Arg polymorphisms on BMI, fasting insulin and HOMA-IR levels

We found no significant influence of INS VNTR, INSR His 1058 C/T and IRS-1 Gyl972Arg genotype concerning BMI, fasting serum insulin levels and insulin sensitivity in our studied group of PCOS patients as indicated in Table 3.

Discussion and Conclusion

The association of the INS VNTR, the INSR His 1058 C/T and the IRS-1 Gyl972Arg polymorphisms with PCOS have been studied in different populations but the results observed are conflicting and inconsistent[3,4,7,10–15,17,18,20–25,30]. To our knowledge this is the first study to explore this association in Croatian population of women with PCOS.

The PCOS patients tended to have a higher frequency of homozygous category III INS VNTR alleles compared to controls, although allele distribution was not significantly different between the groups, indicating that the VNTR INS polymorphism is not the major determinant of the PCOS (Table 1). This is concurrent with the observation of some previous studies in the Czech, Spanish, English, Finish and Chinese population with PCOS[1,11–13].

Additionally, we assessed the influence of INS VNTR polymorphism on insulin resistance in the PCOS and control group but found no significant association. This is in agreement with findings of Vankova et al. in Czech patients with PCOS[13]. Altered insulin sensitivity is probably the result of simultaneous interaction of different environmental and genetic factors[31–36]. Ferk et al. observed that the interaction of INS VNTR genotype with obesity might be a risk factor for the development of PCOS in Slovenian PCOS patients[10]. This interaction was not confirmed in our study however our results may have been biased by a small number of patients with BMI>25 kg/m^2.

We observed significantly lower frequency of T allele, and homozygous T/T genotype than previously reported[3]. The distribution of the polymorphic His 1058 C/T INSR alleles was equivalent between PCOS and the control group therefore we assume that this polymorphism is not significantly associated with the development of PCOS in Croatian PCOS patients. This is in agreement with the findings of two previous published studies in Turkish and Korean population[19,37]. The positive association between this polymorphism and PCOS was fre-

TABLE 2
GENOTYPE DISTRIBUTION OF INS VNTR, INSR HIS 1058 C/T AND IRS-1 GYL972ARG POLYMORPHISMS IN THE PCOS PATIENTS AND CONTROLS

Gene	Genotype	PCOS N=150	Controls N=170	p[1]
VNTR				
	III/III	55.1%	50.2%	0.561
	I/III	38.8%	42.1%	
	I/I	6.1%	7.7%	
	Allele frequency			
	III alleles (2N)	74.5%	71.3%	0.325
	I alleles (2N)	25.5%	28.7%	
INS				
	C/C	63.2%	65.9%	0.631
	C/T	34.2%	30.2%	
	T/T	2.6%	3.9%	
	Allele frequency			
	C allele (2N)	80.3%	81.0%	0.810
	T allele (2N)	19.7%	19.0%	
IRS-1				
	Gly/Gly	87.5%	83.6%	0.506
	Gly/Arg	11.8%	14.7%	
	Arg/Arg	0.7%	1.7%	
	Allele frequency			
	Gly allele (2N)	93.7%	91.0%	0.186
	Arg allele (2N)	6.3%	9.0%	

[1] χ^2-test

TABLE 3
BMI, INSULIN AND HOMA-IR VALUES ACCORDING TO INS VNTR, INSR HIS 1058 C/T AND IRS-1 GYL972ARG GENOTYPE IN THE PCOS PATIENTS

	INS VNTR genotype			p[1]	INSR His 1058 C/T genotype		p[2]	IRS-1 Gyl972Arg genotype		p[2]
	III/III N=83	I/III N=58	I/I N=9		C/C N=95	C/T+T/T N=55		Gly/Gly N=132	Gly/Arg + Arg/Arg N=18	
BMI (kg/m^2)	22.2 (20.9–24.1)	22.1 (20.7–24.7)	23.6 (21.5–24.8)	0.712	22.4 (21.0–25.2)	21.9 (20.9–24.5)	0.614	22.4 (21.0–24.8)	21.8 (20.7–24.8)	0.315
BMI >25 (kg/m^2) (%)	18.6	22.9	23.1	0.744	26.0	17.9	0.319	21.1	15.8	0.423
Fasting insulin (mIU/L)	8.9 (7.4–10.9)	8.7 (6.2–11.8)	8.2 (6.7–9.7)	0.916	8.6 (6.1–13.3)	8,8 (7.1–10.4)	0.966	8.7 (6.2–11,7)	9.0 (5.7–11.4)	0.800
HOMA-IR	1.7 (1.3–2.5)	1.6 (1.1–2.3)	1.5 (1.2–1.9)	0.894	1.6 (1.0–2.5)	1.7 (1.2–2.2)	0.953	1.7 (1.1–2.3)	1.7 (1.2–2.3)	0.861
HOMA-IR >2.5 (%)	19.7	25.8	20.0	0.680	26.0	16.1	0.166	22.6	21.1	0.883

BMI: body mass index; HOMA – IR: homeostatic model assessment of insulin resistance; [1] Kruskal-Wallis test continuous variables, χ^2-test categorical variable; [2] Mann–Whitney *U* test continuous variables, χ^2 -test categorical variable

quently observed in lean PCOS patients[17,20,21]. Siegel et al.[21] reported higher frequency of T allele in PCOS patients with BMI <27 kg/m^2 while Chen et al. confirmed these results in lean PCOS patients from China[17]. The major limitation of these two studies is lack of information on association of this polymorphism with insulin resistance while altered insulin sensitivity is considered to have strong genetic origin in lean PCOS patients[31]. Mukherjee et al. found preferential expression of C/T INSR genotype in lean group of PCOS patients from India (BMI < 23 kg/m^2)[20]. Carriers of this polymorphism also presented with higher values of fasting insulin and HOMA-IR[20]. Although women with PCOS in our studied group were generally lean we recorded no association of C/T-INSR gene polymorphism with parameters of insulin resistance.

We observed no significant difference in the distribution of Gly972Arg IRS-1 alleles between PCOS group and controls. This is concurrent with observations reported from Chilean, Spanish and Taiwan population[25,38,39]. Previously conducted studies also reported that insulin-resistant women with PCOS are frequently carriers of polymorphic Arg allele which directs to conclusion that this polymorphism may be associated with the development of insulin resistance in PCOS[22,24,25,39]. In contrast to these observations we found higher frequency of Arg allele in the control group however overall frequency of this polymorphic allele was very low. The results of aforementioned studies were included in a recently published metaanalysis of Ioannidis et al. that cumulatively confirmed the considerable association of IRS-1 polymorphism with the risk of developing PCOS but this association is primarily mediated by increasing the levels of fasting insulin[3]. We found no difference in fasting serum insulin levels between the carriers of different Gly872Arg genotypes. This may be the result of a very low incidence of this polymorphism in our population studied.

In conclusion, the VNTR INS, C/T INSR,Gly792Arg IRS-1 polymorphisms are not likely candidates for PCOS development in Croatian population. Moreover, these polymorphisms are not associated with increased parameters of insulin resistance in women with PCOS.

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POLIMORFIZMI GENA ZA INS, INSR I IRS-1 NISU POVEZANI SA SINDROMOM POLICISTIČNIH JAJNIKA U HRVATSKOJ POPULACIJI PCOS BOLESNICA

S A Ž E T A K

Povišena tjelesna težina i inzulinska rezistencija često su udruženi sa sindromom policističnih jajnika. Velik broj bolesnica s PCOS-om ima inzulinsku rezistenciju neovisno o povišenoj tjelesnoj težini što govori u prilog genskoj uvjetovanosti. Do sada je istraživana genska podloga u polimorfizmima gena koji kodiraju za inzulin (INS), inzulinski receptor (INSR), ali i gena za inzulinske receptorske supstrate (IRS) koji imaju ključnu ulogu u usmjeravanju postreceptorskog signala. Istraživana je njihova povezanost sa inzulinskom rezistencijom kod PCOS bolesnica. Cilj ovog istraživanja bio je istražiti povezanost genskih polimorfizama: VNTR INS, C/T INSR, Gly792Arg i IRS-1 sa nastankom PCOS-a te sa parametrima inzulinske rezistencije u hrvatskoj populaciji bolesnica s PCOS-om. U studiju smo uključili 150 PCOS bolesnica i 175 kontrola. Dijagnozu smo postavili na temelju konsenzusa u Rotterdamu. Svakoj ispitanici izmjeren je ITM, stupanj hirzutizma i akni te ocijenjen poremećaj ciklusa. Određene su serumske vrijednosti FSH, LH, ukupnog i slobodnog testosterona, DHEAS-a, androstendiona, SHBG-a te glukoze i inzulina na tašte. Inzulinska rezistencija izračunana je koristeći HOMA-IR (homeostatic model assessment of IR). Provedene su molekularne genske analize za određivanje genskih polimorfizama. Našli smo značajnu razliku u većini kliničkih i biokemijskih karakteristika između istraživanih skupina osim za ITM i glukoze na tašte. Nismo našli značajnu razliku u raspodjeli alela i genotipova polimorfizama VNTR INS, C/T INSR i Gly792Arg IRS-1 između istraživane i kontrolne skupine kao niti utjecaj navedenih polimorfizama na parametre inzulinske rezistencije u PCOS bolesnica. U zaključku, naši rezultati ne podupiru ranije opisanu povezanost VNTR INS, C/T INSR i Gly792Arg IRS-1 sa razvojem PCOS-a odnosno sa inzulinskom rezistencijom u Hrvatskoj populaciji bolesnica sa PCOS-om.