Scientific Research Publishing

Health, 2019, 11, 1331-1337
https://www.scirp.org/journal/health
ISSN Online: 1949-5005
ISSN Print: 1949-4998

Smoking, ACP_1 and Infertility in Subjects with Varicocele

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How to cite this paper: Neri, A., Banci, M., Pietropolli, A., Gloria-Bottini, F. and Magrini, A. (2019) Smoking, ACP_1 and Infertility in Subjects with Varicocele. *Health*, **11**, 1331-1337.
https://doi.org/10.4236/health.2019.1110102

Received: August 11, 2019
Accepted: October 13, 2019
Published: October 16, 2019

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Abstract

Several studies suggest that smoking may have detrimental effect on seminal parameters and that genetic polymorphisms may influence this effect. In the present paper we have examined the relationship between ACP_1 genotypes and the association of smoking and infertility in a sample of men with varicocele. 126 subjects with varicocele were studied. ACP_1 genotype was determined by DNA analysis and statistical analyses were performed by SPSS software. In general there is a protective action of low activity *A/*B genotype against infertility that is much more marked in smokers than in non-smokers. If confirmed in other clinical settings, determinations of ACP_1 genotype could have practical importance to evaluate the risk of infertility in smokers with varicocele.

Keywords

Smoking, ACP_1, Varicocele, Infertility, Genetic Polymorphism

1. Introduction

Many studies have been made on the relationship between male fertility and smoking but the results are contradictory. At least 1 or 2 studies are proposed to explain. Smoking may affect the quality of sperm having detrimental effect on fertility.

Among various effects underlined, smoking interferes with DNA methylation that is significantly correlated with sperm parameters while the life of seminal leukocytes is doubtful [1] [2] [3]. Nicotine could damage sperm through nicotinic receptors. The damage of sperm chromatin condensation and sperm viability depends on the number of cigarettes smoked per day and on the duration of

smoking [4] [5]. Aryanpur, comparing smokers with non-smokers, has shown that active cigarette consumption, even if in small amount, decreases sperm concentration while no significant correlation has been found with morphology or motility [6]. As de Jong did not find differences for cigarette smoking and alcohol intake between subfertile and fertile men concluded that cigarette smoking and alcohol intake would not influence significantly sperm parameters [7]. Smoking is associated also to an increase of psychological anxiety and depression [8].

The interaction between some genes and smoking would help to predict body cancer [9] [10] [11].

In the present paper we have examined the possible interactions between infertility due to smoking and ACP_1 genotypes.

Acid Phosphatase locus 1 (ACP_1)

ACP_1 (Acid Phosphatase locus 1) is a polymorphic enzyme with three codominant alleles (*A, *B and *C) at an autosomal locus that encodes the cytosolic Low Molecular Weight Protein Tyrosine Phosphatase (cLMWPTP). ACP_1 has six genotypes with enzymatic activity decreasing in the order *C/*C > *B/*C > *A/*C ~ *B/*B > *A/*B > *A/*A. The genotypes *A/*A and *A/*B have low activity while the genotypes *B/*B, *A/*C, *B/*C and *C/*C have medium-high activity. The enzyme is composed by two isoforms F and S with different quantities among genotypes (See **Table 1**). Two biological substrates have been proposed for cLMWPTP activity: flavin mononucleotide (FMN) and phosphorylated tyrosine residues. Catalyzing the conversion of FMN to riboflavin, the enzyme may regulate the concentration of FAD (flavin adenine dinucleotide), flavo-enzyme activity and energy metabolism. As a phosphotyrosine-phosphatase, cLMWPTP may have an important role in modulating the glycolytic rate through the control of insulin receptor activity and of band 3 protein (BPP) phosphorylation [12] [13] [14]. ACP_1 is able to dephospsphorylate Platelet Derived Growth Factor (PDGF) receptor [15]. PDGF is important for embryonic and postnatal development of male gonad [16] [17] [18] [19]. Deficiency of PDGF is associated with spermatogenic impairment [20].

Based on the effect of PDGF on spermatogenesis and on the effect of cLMWPTP on PDGF receptors we would expect a relative protection against infertility in

Table 1. F and S isozyme concentations in relation to the ACP_1 genotype. The quantities of enzyme are given per ml of packed red cells.

Total quantity of F (μg/ml RBC)	Total quantity of S (μg/ml RBC)	F/S ratio
*B/*B 16.4	*C/*C 20.6	*B/*B 4.2
*A/*B 12.0	*A/*C 12.7	*A/*B 3.6
*B/*C 11.3	*B/*C 12.1	*A/*A 2.4
*A/*A 7.9	*B/*B 3.9	*B/*C 0.9
*A/*C 7.5	*A/*B 3.4	*A/*C 0.6
*C/*C 5.7	*A/*A 3.3	*C/*C 0.3

subjects carrying ACP_1 genotypes with low activity and a greater susceptibility to infertility in subjects with ACP_1 genotypes with high activity. Indeed, in this regard, in a recent study we have observed that *B/*C genotype with high activity is associated with impairment of spermatic parameters in subjects with varicocele [21].

Brief outline of the content

Smoking may affect the quality of sperm having detrimental effect on fertility. Genetic polymorphisms may influence this effect. We have examined the possible interactions between infertility due to smoking and ACP_1 genotypes. ACP_1*A/*B genotype with low enzymatic activity shows a protective effect against infertility in smokers.

2. Material and Methods

We have studied 160 subjects admitted consecutively to the outpatients in Department of Infertility at the University of Rome La Sapienza. Specific inclusion criteria and exclusion criteria for patients need to be provided.

In these patients was performed a Color Doppler ultrasonography in 66 infertile men with a mean age of 37.6 years to detect intrascrotal abnormalities. 4.5% of these patients have been diagnosed with varicocele.

A couple was classified as infertile if was unable to conceive after one year of regular intercourse with the intent to conceive. Part of these patients have been included in previous studies [17] [18] [19]. Does this situation have a significant impact on the results of this study? It should be clearly stated in the text.

Statistical analyses were carried out by the software Statistical Package for the Social Sciences (SPSS).

All patients examined gave informed consent to participate in the study that was approved by the Council of Department. Specific time needs to be provided.

ACP_1 genotypes were determined by DNA analysis as previously described [16]. Statistical analyses were performed by commercial software (SPSS).

3. Results

Table 2 shows the proportion of infertile men in relation to smoking. No significat association is observed.

Table 3 shows the proportion of infertile men in relatioin to ACP_1 activity. The proportion of *A/*B genotype (low activity) is lower in infertile than in fertile men while the proportion of *C carriers (high activity) is the opposite, higher in infertile than in fertile.

In Table 4 is reported the proportion of ACP_1 genotypes in relation to smoking/non-smoking and fertility/infertility. In smoking men the proporion of *A/*B genotype is much lower in infertile than in fertile men. This difference has been examined more in details in Table 5. A similar analysis for *B/*C genotype is meaningless because of low number of subjects with this genotype. The analysis in Table 4 indicates that the protective action of *A/*B against infertility is much more marked and statistically significant in smokers than in non-smokers.

Table 2. Proportion (%) of infertile men in relation to smoking.

	Smoking	
	Yes	No
Proportion of infertile men	43.2%	47.6%
Total number	44	82
Chi-square test of independence	P = 0.294	

Table 3. Proportion of infertile men in relation to ACP_1 activity.

	Fertile	Infertile
ACP_1*A/*B (low activity)	44.0%	29.5%
ACP_1 *C carriers (*C/*C,*B/*C, *A/*C) (high activity)	2.7%	13.1%
Other ACP_1 genotypes	53.3%	57.4%
Total n	68	58
Chi square test of independence	P = 0.112	

Table 4. Percent proportion of infertile men in relation to ACP_1 genotype and smoking.

	Smoking		Non-Smoking	
	Fertile	Infertile	Fertile	Infertile
ACP_1				
*A/*A	4.0%	15.0%	11.6%	10.3%
*B/*B	36.0%	55.0%	46.5%	41.0%
*A/*B	56.0%	25.0%	39.5%	30.8%
*A/*C and *B/*C	4.0%	5.0%	2.3%	17.9%
Total n	25	19	43	39

Table 5. Percent proportion of infertile men in relation to ACP1*A/*B genotype and smoking.

	Smoking		Non-smoking	
	Fertile	Infertile	Fertile	Infertile
ACP_1*A/*B	56%	25%	39.5%	30.8%
Total n	25	20	43	39
Chi-square test of independence	P = 0.036		P = 0.407	

4. Discussion

The present study suggests a relationship between ACP_1 activity and susceptibility to infertility in men with varicocele. The proportion of *A/*B genotype (low activity) is higher in fertile than in infertile men. *A/*B genotype shows a protective effect against infertility that is more marked and statistically significant in smoking subjects.

Considering the whole sample there is no significant effect of smoking on susceptibility to infertility: this effect emerges when considering ACP_1 genotype the proportion of subjects with *A/*B genotype is 26.3% in infertile versus 56.0% in fertile men, in other ACP_1 genotypes the pattern is reversed and is 73.7% in infertile versus 44.0% in fertile men.

Among ACP_1 genotypes with low enzymatic activity, only *A/*B shows a protective effect against infertility in smokers. *A/*A genotype that has also low activity does not manifest this effect. This could be connected to the difference between the relative concentration of F and S isoforms. The two isoforms show different biochemical properties and it has been suggested that have also different functions in the cell. As far as we know, however, this problem has not been adequately investigated.

The limitation of our study is represented from the relatively low number of subjects examined. If confirmed in other clinical settings, our results could have practical importance to evaluate the risk of infertility in smokers with varicocele.

5. Conclusion

As several studies suggest that genetic polymorphisms may influence the detrimental effect of smoking on seminal parameters, we have examined the relationship between ACP_1 genotypes and the association of smoking with infertility in a sample of men with varicocele. Among ACP_1 genotypes with low enzymatic activity, only *A/*B shows a protective effect against infertility in smokers. This could be connected to the difference between the relative concentration of F and S isoforms in ACP_1 genotypes that show different biochemical properties having probably different functions in the cell.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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