

## Serum level of IGFBP3 and IGF1/IGFBP3 molar ratio in addition to PSA and single nucleotide polymorphism in PSA and CYP17 gene may contribute to early diagnostics of prostate cancer.

M. TAJTAKOVA<sup>1</sup>, A. PIDANICOVA<sup>1</sup>, L. VALANSKY<sup>2</sup>, LACHVAC<sup>2</sup>, V. NAGY<sup>2</sup>, M. SIVONOVA<sup>3</sup>, D. DOBROTA<sup>3</sup>, J. KLIMENT<sup>4</sup>, J. PETROVICOVA<sup>5</sup>

<sup>1</sup>1st Department of Internal Medicine, Faculty of Medicine, Safarikienis University, Košice, Trieda SNP 1, 040 66 Košice, Slovakia, e-mail: maria.tajtakova@upjs.sk, <sup>2</sup>Department of Urology, Faculty of Medicine, Safarikienis University, Košice, <sup>3</sup>Department of Medical Biochemistry, Comenius University, Jessenius Faculty of Medicine, Martin, Slovakia, <sup>4</sup>Department of Urology, Comenius University, Jessenius Faculty of Medicine, Martin, <sup>5</sup>Department of Medical Informatics, Faculty of Medicine, Safarikienis University, Košice, Slovakia.

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The aim of the paper is to determine whether IGF1, IGFBP3 and IGF1/IGFBP3 molar ratio in addition to PSA and one-nucleotide polymorphism in PSA and CYP17 gene might contribute to early diagnostics of prostate cancer (PCa). Serum level of PSA, IGF1 and IGFBP3 in the group of 158 individuals (92 PCa and 66 controls) was examined by RIA method and IGF1/IGFBP3 was calculated. PCR RLFP method was used to examine one-nucleotide polymorphism in PSA and CYP 17 gene. The results suggest that serum level of IGF1 over 95% CI did not increase relative risk of PCa development in overall group, not even regarding to particular investigated genotypes, not even if individuals with genotype AG+A1A1, AG+A1A2, GG+A1A1 and GG+A1A2 were evaluated. Serum level of IGFBP3 under 95% CI increased PCa relative risk in overall group ( $\chi^2 = 10,03$ ,  $p = 0,001$ , OR 3,12, 95% CI 1,44-6,93), as well as regarding to one-nucleotide polymorphism in individuals with PSA genotype AG ( $\chi^2 = 4,72$ ,  $p = 0,029$ , OR 2,87, 95% CI 01,09-7,49) and CYP 17 genotype A1A1 ( $\chi^2 = 3,76$ ,  $p = 0,052$ , OR 2,57, 95% CI 0,97-6,75). The association between frequencies of occurrence of PCa and higher IGF1/IGFBP3 molar ratio was not confirmed, nor for gene polymorphism in PSA and CYP17, however OR ( $\chi^2 = 1,58$ ,  $p = 0,208$ , OR 1,67, 95% CI 0,75-3,71) was more than 1, nor in combination AG+A1A1, AG+ A1A2. Serum level of IGFBP3 and IGF1/IGFBP3 molar ratio in addition to PSA and gene polymorphism in PSA and CYP17 gene might contribute to early diagnostics of PCa. Further research is needed to prove, whether serum level of IGFBP3 in addition to PSA determines the prognosis and progression of PCa.

*Key words.* Prostate cancer, insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), genetic polymorphisms

Prostate cancer (PCa) belongs to the most frequent malignant diseases in men over 50 years. The incidence of PCa has increased almost twice in Slovakia in the past 30 years [1, 2]. Risk factors associated with this disease are age, race, geographic factor, diet, environmental factors, circulating androgens and, regarding to family abundance, genetic predisposition, as well [3].

Examination of prostate specific antigen (PSA) is substantial for early diagnostics of PCa. PSA is considered the most important tumor marker for detection and follow-up of PCa, but low specificity is its disadvantage [4, 5].

PSA is a protein produced by epithelial cells of prostatic acini and ducts and its production and expression is mediated via androgen receptor by binding of androgens to androgen responsive

elements (ARE) in region of PSA gene. PSA is encoded by a gene localized at the chromosome 19. In the promoter ARE-I region at the -158 position from starting point of transcription, one-nucleotide polymorphism (A/G) was determined. It has been reported, this polymorphism is associated with higher PSA level and higher risk of PCa development [6, 7, 8].

The growth of prostatic cells is dependent upon the level of active testosterone, and thus monitoring the activity of genes involved in the regulation of testosterone synthesis might contribute to detection of individuals with increased risk of PCa. One of these genes, which is a member of Cytochrome P450 family, termed as CYP17A1, encodes steroid 17-alpha-hydroxylase and enable, with its lyase activity, synthesis of testosterone in testes [9, 10].

Tab.1. Investigated parameters in correlation with diagnose

Investigated parameters	PCA N = 93	CON N =78	P
Age in years	65,5 ± 8,2	60,7 ± 9,4	NS
BMI	27,4 ± 3,4	28,1 ± 3,6	NS
PSA ng/ml	16,8 ± 32,4	1,46 ± 1,4	0,01
IGF1 ng/ml	172,6 ± 61,8	171,1 ± 60,4	NS
IGFBP3 ng/ml	2195,2 ± 651,0	2527,1 ± 638,2	0,01
IGF1 /IGFBP3	0,078 ± 0,02	0,068 ± 0,02	0,01

Beside PSA and gene polymorphisms, other biomarkers are investigated to improve the diagnostics of PCa, the disease with increasing incidence nowadays.

Numerous studies have concerned the association between serum level of insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3) and IGF-1/IGFBP-3 molar ratio, but the results are somehow contradictory [11, 12, 13, 14, 15, 16, 17, 18].

### Patients and methods

In our previous study [16] presented at The Fourth International Congress of IGF and GRS Society in Genova, group of 93 PCa individuals and 44 healthy controls were examined and serum levels of PSA, IGF-1 and IGFBP-3 by RIA method were estimated. We confirmed significantly decreased level of IGFBP-3 and increased IGF-1/IGFBP-3 ratio in PCa group in compare with control group. There was no difference in IGF-1 level between both groups. Negative correlation between PSA and IGFBP-3, and positive correlation between PSA and IGF-1/IGFBP-3 molar ratio was observed, and in addition, positive correlation between PSA and IGF-1 in individuals with PCa and Gleason score over 6. More 38 healthy controls were added to the primary group afterwards, but the new results did not differ from early obtained ones (Table1).

Genetic polymorphisms in PSA and CYP17 gene were examined by PCR RLFP method in 92 PCa and 66 controls. Our group was involved into a bigger study of Sivoňová et al. [19] and no association between PSA polymorphism at the -158 position and the risk of PCa development was found. Regarding these results, we were interested in the relative risk of PCa development in correlation to IGF-1 and IGF-1/IGFBP-3 ratio over 95% CI and to IGFBP-3 under 95% CI of its normal range. In addition, we were questioning, whether the individuals with IGF-1 a IGF-1/IGFBP-3 over 95%CI a IGFBP-3 under 95%CI posses a higher risk of PCa development in correlation to gene polymorphism of PSA and CYP17 gene.

Serum levels of IGF-1, IGFBP-3 and IGF-1/IGFBP-3 were correlated to separate PSA and CYP 17 polymorphisms. Cor-

relation between investigated parameters and relative risk was evaluated by  $\chi^2$  test. In case of frequencies of occurrence lower than 5, Yates correction or Fisher exact test were used. Relative risk of PCa in correlation to serum IGF-1 level and IGF-1/IGFBP-3 ratio over 95% CI and IGFBP-3 under 95% CI, as well as in correlation to gene polymorphism in PSA and CYP17 gene were estimated.

### Results

In our study of 158 individuals (PCa 92, CON 66), regarding to polymorphism in PSA gene, genotype AA was observed in 27 individuals – 17,1% ( PCa 19, CON 8) AG in 79 – 50% (PCa 43, CON 36) and GG in 52 – 32,9 % (PCa 30, CON 22). In both groups most of investigated individuals showed AG and GG genotype. Regarding to polymorphism in CYP 17 gene, genotype A1A1 occurred in 54 individuals – 34,1% (PCa 36, CON 18), A1A2 in 79 - 50% (PCa 42, CON 37) and A2A2 in 25 – 15,8% (PCa 14, CON 11). In both groups the most individuals showed A1A1 and A1A2 genotype.

We did not confirm the association between PSA polymorphism at the – 158 position and PCa. However, regarding to CYP17 polymorphism, we observed increased PCa risk in individuals with genotype A1A1 ( $\chi^2 = 2,4$ ,  $p = 0,12$ , OR 1,71, 95% CI 0,86-3,39).

There was no difference in age (PCa 65,5 ± 8,2, CON 60,7 ± 9,4) or in BMI (PCa 27,4 ± 3,4, CON 25,1 ± 3,7) between both groups. Serum level of PSA was significantly higher in PCa group comparing to control group (16,8 ± 32,4/1,46 ± 1,4,  $p < 0,01$ ). In PCa group the highest serum level of PSA was observed in PSA genotype AA and in CYP17 genotype A1A1, but the differences were not statistically significant. Regarding to particular genotypes, we did not confirm any statistically significant differences in serum level of IGF-1, IGFBP-3 or IGF1/IGFBP3 ratio between both groups. The individuals with PCa and Gleason score more than 6 showed higher occurrence of PSA genotype AG and GG and CYP17 genotype A1A1 (Table 2, 3).

Tab.2. Investigated parameters and one-nucleotide polymorphism in PSA gene

Investigated parameters	PCa N= 92			P	CON N = 66			P
	AA N=19 (26,6%)	AG N=43 (46,7%)	GG N=30 (32,6%)		AA N=8 (12,1%)	AG N=36 (54,5%)	GG N=22 (33,3%)	
PSA ng/ml	33,9 ± 58,9	12,5 ± 17,2	12,1 ± 21,8	NS	1,60 ± 2,0	1,59 ± 1,4	1,60 ± 1,5	NS
IGF1 ng/ml	182,6 ± 68,5	173,6 ± 66,7	160,5 ± 44,8	NS	184,5 ± 78,6	158,3 ± 52,6	188,1 ± 70,9	NS
IGFBP3 ng/ml	2336,8 ± 701,2	2192,3 ± 692,7	2112,3 559,6±	NS	2782,5 ± 887,6	2492,8 ± 614,2	2396,4 ± 628	NS
IGF1/IGFBP3	0,079 ± 0,02	0,079 ± 0,02	0,076 ± 0,02	NS	0,065 ± 0,02	0,063 ± 0,01	0,078 ± 0,02	NS
Gleason score	< 6	> 6	> 6					

Tab.3. Investigated parameters and one-nucleotide polymorphism in CYP17 gene

Investigated parameters	PCa N= 92			P	CON N = 66			P
	A1A1 N=36 (39,1%)	A1A2 N=42 (45,6%)	A2A2 N=14 (15,2%)		A1A1 N=18 (27,3%)	A1A2 N=37 (56,1%)	A2A2 N=11 (16,6%)	
PSA ng/ml	23,8 ± 45,4	11,1 ± 18,5	19,4 ± 29,9	NS	1,65 ± 1,6	1,60 ± 1,5	1,50 ± 1,5	NS
IGF1 ng/ml	183,2 ± 76,9	169,9 ± 53,4	153,6 ± 35,2	NS	166,1 ± 60,6	173,3 ± 67,2	176,6 ± 56,6	NS
IGFBP3 ng/ml	2228,5 ± 632,4	2256,8 ± 744,1	2033,1 ± 449,1	NS	2550,0 ± 618,8	2464,1 ± 691,8	2513,6 ± 636	NS
IGF1/IGFBP3	0,078 ± 0,01	0,078 ± 0,02	0,076 ± 0,01	NS	0,065 ± 0,02	0,070 ± 0,02	0,068 ± 0,01	NS
Gleason score	> 6	< 6	< 6					

Serum level of IGF-1 over 95% CI did not increase the risk of PCa development neither in overall group, nor in subgroups of particular investigated genotypes, nor if individuals with genotype AG+A1A1, AG+A1A2, GG+A1A1 and GG+A1A2 were evaluated.

Serum level of IGFBP3 under 95% CI increased the risk of PCa development in overall group ( $\chi^2 = 10,03$ ,  $p = 0,001$ , OR 3,12, 95% CI 1,44-6,93), as well as regarding to one-nucleotide polymorphism in individuals with PSA genotype AG ( $\chi^2 = 4,72$ ,  $p = 0,029$ , OR 2,87, 95% CI 0,09-7,49) and CYP17 genotype A1A1 ( $\chi^2 = 3,76$ ,  $p = 0,052$ , OR 2,57, 95% CI 0,97-6,75). The association between frequencies of occurrence of PCa and higher IGF-1/IGFBP-3 ratio was not confirmed, not even when correlating for gene polymorphism in PSA and CYP17, however OR was over 1 ( $\chi^2 = 1,58$ ,  $p = 0,208$ , OR 1,67, 95% CI 0,75-3,71), and not even in combination with AG+A1A1, AG+A1A2.

## Discussion

Prostatic specific antigen is the most important tumor marker for early diagnostics of PCa nowadays. For its low

specificity, other biomarkers are investigated, that might be useful in early diagnostics of PCa. IGF-1 is primarily produced in liver, but can be synthesized in other tissues, including prostate. Bioactivity of IGF-1 is dependent on its interaction with IGF-1 receptor and is influenced by group of binding proteins (IGFBP1-6), which bind IGF-1 in circulation. It has been reported, that IGF-1 receptor is over-expressed in many malignant cells [14]. More than 90% of circulating IGF-1 is bound to IGFBP-3, the main binding protein. This peptide exerts antiproliferative and proapoptotic activities dependent on and independent of IGF-1 [20, 21, 22, 23, 24]. The levels of both proteins are varying with age and are under genetic control. In addition, PSA is an IGFBP-3 protease. It cleaves IGFBP-3 [7, 25], what results in an increase of free IGF-1 fraction in circulation.

IGF-1 acts as a growth factor via its IGF receptor stimulates growth, proliferation, migration and inhibits apoptosis of normal and malignant cells. It induces neovascularisation and cell adhesion and motility [23].

Contrary to study by Stattin et al. [5] and Rowlands et al. [24], however, consistently with studies by Aksoy et al. [11],

Severi et al. [24], Borugian et al. [13], Sciarra et al. [25] we did not confirm increased serum level of IGF1 in individuals with PCa. Similar to Severi et al. [24] findings, the risk of PCa did not increase even for serum level of IGF1 over 95% CI of normal range. In contrast to study by Stattin et al. [5] and Severi et al. [24], where the increased serum level of IGFBP-3 was associated with PCa, in our study the significantly decreased IGFBP-3 levels in PCa group compared to control group were found. Our findings are consistent with Aksoy et al. [11] and Meinbach et al. [15]. Serum level of IGFBP-3 under 95% CI and IGF-1/IGFBP-3 ratio over 95% CI increased PCa risk in our study, but this was not observed by Severi et al. [24].

In addition, relations between PCa and gene polymorphism in PSA gene have been investigated in some studies. It has been reported, that G allele and GG genotype are associated with higher risk of PCa development and with higher Gleason score in PCa [26,27]. In some other studies this association was not confirmed [19, 28, 29].

The association between CYP 17 gene and risk of PCa has also been reported, however the conclusions are inconsistent [26, 30, 31, 32, 33]. In our study, the serum level of IGF-1 over 95% CI did not increase the risk of PCa development, not even if individuals with genotype AG+A1A1, AG+A1A2, GG+A1A1 and GG+A1A2 were evaluated. Serum level of IGFBP3 under 95% CI increased risk of PCa development in all over group, as well as regarding to particular investigated genotypes, and this was the most strongly pronounced in PSA genotype AG and CYP17 genotype A1A1. The association between frequencies of occurrence of PCa and higher IGF-1/IGFBP-3 ratio was not confirmed, nor for gene polymorphism in PSA and CYP gene, however OR was higher than 1, mainly in individuals with PSA genotype AG and in combination AG+A1A2.

In conclusion, serum level of IGF/1, IGFBP-3 [34] and IGF-1/IGFBP-3 molar ratio as well as other biomarkers in addition to PSA and gene polymorphism in PSA and CYP17 gene might contribute to early diagnostics of PCa. Further research is needed to prove, whether the serum level of IGFBP-3 in addition to PSA determines the prognosis and progression of PCa. Serum level of IGFBP-3 and IGF-1/IGFBP-3 molar ratio in addition to PSA and one-nucleotide polymorphism in PSA and CYP17 gene may contribute to early diagnostics of prostate cancer.

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