

Biochemical Factors Involved in the Unfavorable Evolution of Prostate Cancer

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Frequent association of depressive disorder with clinical manifestations in prostate cancer patients raises problems with therapeutic response and adherence to treatment. Androgen deprivation therapies exacerbate depression and cause somatic adverse reactions, mainly represented by obesity, anemia, osteoporosis, muscle atrophy, gynecomastia. Depressive disorders correlate with activation of the hypothalamic-pituitary-adrenal axis (HPA), which induces high cortisol levels. The structural similarity between cortisol and testosterone suggests possible associations with their side effects. Decreased testosterone levels amplify the risk of developing or exacerbating depressive disorders. It is important the early identification of sexual identity and body perception disorders, as well as the interdisciplinary assessment of cognitive status and depression. The direct relationship between elevated PSA and testosterone levels and high depression scores suggests the unfavorable evolution of non-metastatic prostate cancer. It is necessary to evaluate depression from the diagnosis of prostate cancer as well as its dynamic monitoring. Therapeutic resistance raises the issue of early oncologic therapeutic switch and the combination of pharmacological and non-pharmacological antidepressant therapies.

Keywords: prostate cancer; androgen deprivation, depression, cognitive deficiency

Prostate cancer has an incidence of 7.1% globally, with over 1.2 million new cases reported in 2018. This oncological diagnosis is second in men after lung cancer. [1] Increased incidence of prostate cancer in the elderly, with a maximum for age group 75-79 years [2, 3], and frequent association of depressive disorder with clinical manifestations, in approximately 1 in 6 cases [4], is a research premise regarding the medium and long term evolution of these patients. The association between depressive disorder and prostate cancer is reported in numerous studies [5], and the depression may occur before its oncological diagnosis or subsequent thereto.

In the case of depression prior to the oncological diagnosis, psychotropic substance therapy may determine increased level of prolactin, which is associated with pro-oncological mechanisms, namely prostate cancer in men and breast cancer in women [6-8]. Pharmacologically induced hyperprolactinemia may be caused by: typical (haloperidol, chlorpromazine, thioridazine), and atypical antipsychotics (risperidone, amisulpride, molindone, zotepine), tricyclic antidepressants (amitriptyline, desipramine, fluvoxamine), SSRI (sertraline, fluoxetine, paroxetine), MAO inhibitors (pargyline, clorgyline), other psychotropic drugs (buspirone, alprazolam) [9].

Depression in patients with non-metastatic prostate cancer is associated with suicidal risk [10], which may be amplified by the distress generated by changes in the perception of one's body image (especially after gynecomastia), and by the appearance of sexual dysfunction. [11]

Prostate cancer therapeutic strategies include in the first line androgen hormone deprivation therapy (ADT), by surgical or chemical techniques, with the subsequent use of estrogenic therapies. This approach was first described in 1941 by Huggins and Hodges, who noted that after surgical castration and use of estrogenic therapies, the development of prostate cancer was improved [12, 13].

Decreased testosterone levels amplify the risk of developing or exacerbating depressive disorders [14-16]. The risk for depression caused by low testosterone level is amplified in the elderly, irrespective of the oncological pathology [17].

The current conception regarding the neurobiology of the depressive disorder is represented by the multisystemic model, correlated with the activation of hypothalamic-pituitary-adrenal (HPA) axis. High levels of cortisol amplify proinflammatory mechanisms, disrupt immunity and induce endothelial dysfunctions, with a secondary increase

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in the risk for oncological diseases and cardiovascular disease [18].

Also, the somatic effects of androgen deprivation are recognized, mainly represented by obesity, anemia, osteoporosis, muscle atrophy, gynecomastia and the onset of depressive disorders [19]. These factors favor the increased risk for diabetes, high blood pressure, metabolic syndrome, coronary heart disease and stroke. There is a real vicious circle because androgen deprivation therapies favor depression, somatic symptoms amplify depression, and both favor the risk for severe somatic adverse effects, which can be anticipated by the presence of cardiometabolic syndrome and dysmetabolic markers.

Chemically, cortisol and testosterone have a nearly identical tetracyclic terpenoid structure [20]. Cortisol is represented by the formula $C_{21}H_{30}O_5$ and testosterone with $C_{19}H_{28}O_2$ [21, 22]. From biochemical point of view, both molecules are grouped in the steroid hormone category. It is important to know the chemical structure of therapeutic molecules and steroid structures, as the structural similarity between cortisol and testosterone as well as the variations in the number of C, H, and O atoms, suggest possible associations with their side effects. Even though cortisol and its derivatives are largely used in many pathologies [23] side effects may significantly influence the therapeutic response, the evolution of disease and the quality of life of the patient.

Experimental part

Our retrospective study was performed on a group of 27 patients with non-metastatic prostate cancer confirmed by histopathological examination and by prostate specific antigen biological marker (PSA). The selected patients did not have metastases at diagnosis or at the time of evaluation. Treatment administered for neoplastic disease consisted of pharmacological androgen deprivation therapy (ADT). This therapeutic option was preferred because it is less psycho-traumatic than the surgical method.

After a 6-month interval of pharmacological ADT treatment, the relationship existing between the intensity of the depressive disorder assessed with Hamilton scale and the cognitive deficit, measured using the MMSE scale, was followed. At the same time, the levels of biological markers, PSA and serum testosterone were determined. Patients who had depressive disorder diagnosed previously the neoplastic disease were excluded from the analysis.

There were evaluated the social stress factors and the identification of potential major psycho-traumatic factors (widowhood, loss of life partner), socio-cultural level (low, medium, high) and socio-material condition (retired, rural or urban background). Psychostress factors are associated with increased activity of the HPA axis.

Out of the total group, 25 patients responded to ADT therapy (Table 1) and 2 cases had therapeutic resistance, with increased PSA and testosterone values (Table 2).

Table 1
DATA FROM PATIENTS WHO RESPONDED FAVORABLY TO ADT THERAPY

Patient no.	Age group (years)	Residence area	Studies	Marital status	Workplace	PSA (ng/ml)	Testosterone (ng/ml)	Hamilton	MMSE
1	50 – 59	U	H	M	R	0.458	0.051	20	22
2		U	S	M	E	0.534	0.323	23	22
3		R	E	D	U	0.012	0.062	22	23
4	60 – 69	U	E	D	R	0.002	0.147	17	19
5		U	S	W	R	0.832	0.087	19	20
6		R	E	M	R	0.200	0.900	18	20
7		R	S	D	R	0.626	0.054	18	22
8		U	E	M	R	0.002	0.277	20	19
9		U	S	M	R	0.148	0.025	20	20
10		U	H	D	E	0.281	0.745	21	19
11		R	S	M	U	0.337	0.045	19	20
12	over 70	U	H	M	R	0.042	0.186	17	16
13		U	S	D	R	0.176	0.052	16	17
14		R	E	W	R	0.049	0.025	14	16
15		U	S	D	E	0.002	0.328	16	18
16		U	E	W	R	0.041	0.204	18	18
17		R	E	W	R	0.651	0.050	15	19
18		R	E	W	U	0.029	0.138	15	17
19		U	H	M	R	0.002	0.268	14	18
20		U	S	W	R	0.532	0.078	16	20
21		U	S	W	R	0.804	0.042	16	15
22		U	S	D	R	0.025	0.184	17	16
23		R	E	M	R	0.002	0.050	18	17
24		R	S	W	R	0.026	0.368	16	17
25		R	S	W	R	0.465	0.092	15	18

Table 2
DATA FROM PATIENTS WHO DID NOT RESPOND FAVORABLY TO ADT THERAPY

Patient no.	Age group (years)	Residence area	Studies	Marital status	Workplace	PSA (ng/ml)	Testosterone (ng/ml)	Hamilton	MMSE
26	60 – 69	U	H	M	R	6.2	2.99	19	20
27	60 – 69	U	H	M	E	5.7	3.57	22	21

Caption: Residence environment: U-urban, R-rural; Studies: E-elementary, S-secondary, H-higher; Marital status: M-Married, D-divorced, W-widowed; Workplace: R-retired, E-employed, U-unemployed

The socio-demographic data of the patients with favorable evolution showed an increased distribution for the urban area (60%) compared to the rural area (40%). Most patients are retired (76%), but 3 of them (12%) do not have a job. 64% of the cases do not have family support, being divorced or widowed.

The average PSA value for the whole subgroup with favorable evolution was 0.25112 ng/mL with the standard deviation = 0.2788. The reference values for total PSA depend on the age group of patients: under 40 years old, ≤ 2.0 ng/mL; 40-49 years old, ≤ 2.5 ng/mL; 50-59 years old, ≤ 3.5 ng/mL; 60-69 years old, ≤ 4.5 ng/mL; 70-79 years old, ≤ 6.5 ng/mL; over 80 years old, ≤ 7.2 ng/mL. [24] All values were below 1 ng/mL, indicating a good therapeutic response.

For testosterone the average value was 0.19124 ng/ml and the standard deviation = 0.21809. All values were below the minimum limit of normal value range for testosterone (2.4-9.5 ng/mL) [24].

In the age group 50-59 years, the average Hamilton score was 21.6666667 with the standard deviation 1.52753, and the average MMSE score was 22.33 with the standard deviation 0.57735. The age group 60-69 years had the average Hamilton score 18.625 with the standard deviation 1.40789 and the average MMSE score 19.875 with the standard deviation 0.99103. In the age group over 70 years, the average Hamilton score was 15.9285714 with the standard deviation 1.26881, while the average MMSE score was 17.2857143 with the standard deviation 1.32599.

Interpretation of the results of Hamilton scale is based on scores: 0-7 normal; 8-13 mild depression; 14-18 moderate depression; 19-22 severe depression; over 23 very severe depression [25].

Based on the scores of MMSE scale, a patient may be without cognitive deficit (25-30), with MCI syndrome (21-24), moderate cognitive deficit (10-20) or severe cognitive deficit (0-9) [26].

The two patients who did not respond to androgen blocking therapy had PSA above age-appropriate normal value of 4.5 ng/mL and high scores of Hamilton scale, for severe depression, similar to patients in the 50-59 age group. Both patients are from urban area, with higher education, married.

Results and discussions

The data obtained confirm the relationship existing between the decrease of testosterone levels and depression, confirming the existing data in the literature [27] which show that deprivation therapy in non-metastatic prostate cancer is associated with depression, anxiety, emotional tension, irritability, hostility and explosive manifestations. These symptoms are worn out during the evolution of the therapy with castration inhibitors, being

replaced by an apatho-abulic, anhedonic depression and with a chronic fatigability syndrome, also accompanied by the somatic effects of androgenic blockade (anemia, muscle atrophy, osteoporosis). Osteoporosis, chronic pain or repeated fractures are risk factors for the depression amplification [28].

Our study highlighted an increase in depressive disorders in patients in the age group of 50-59 years, being relevant the sexual dysfunction represented by decreased libido and erectile dysfunction. Obesity and gynecomastia, both side effects of ADT medication, generate dysmorphic perception for patients. This sexual identification disorder, which is part of the body dysmorphic disorder, can also amplify depression and aberrant sexual behaviors and causes a major decrease in adherence and compliance to the treatment (Fig. 1).

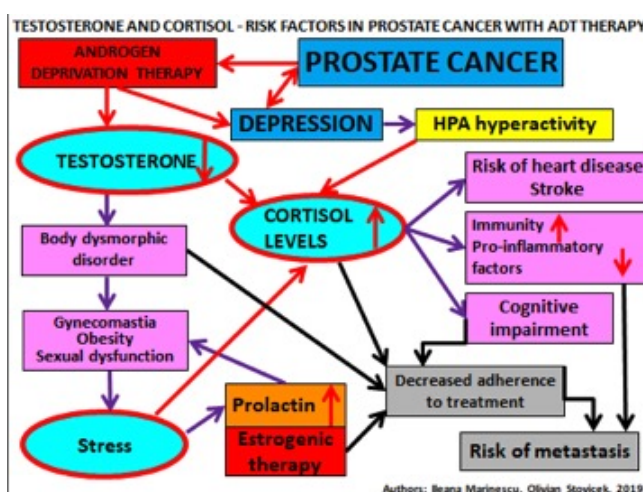


Fig. 1 Testosterone and cortisol - risk factors in prostate cancer with ADT therapy

The presence of sexual identity disorders and depression, irrespective of the adherence to ADT treatment, are evolutionary risk factors. As a result of androgenic deprivation, body image impairment, associated with decreased quality in the life of patients [29] and changes in brain metabolic activity, involved in the impaired mood, verbal memory and visual-spatial performance may occur [30]. The most important metabolic changes in the brain are decreased glucose metabolism and increase of oxidative stress in the: cerebellum (inducer of cognitive dysmetria), posterior cingulate cortex (correlated with aggressive impulsive behavior), medial thalamus, (cognitive dysfunction) and left parietal and temporal cortex (MCI syndrome, major cognitive dysfunction, aphasia-apraxo-agnosic syndrome). In this context, special monitoring of this group of patients is required [31, 32], with the possibility of occurring risk behaviors (hetero or

self-aggressive) or cognitive dysfunctions of neurodegenerative, dementia or mixed type [33].

In older age, ADT therapy significantly increases the risk for Alzheimer's disease, compared to the general population, also discussing the potential neuroprotective role of testosterone in cognitive structures. Neurodegenerative cognitive dysfunction is also potentiated by decreased BDNF levels [34, 35], a phenomenon correlated with decreased neurogenesis, synaptogenesis and neuroprotection [35,36].

At the same time, by increasing the endothelial dysfunction caused by oxidative stress is translated into depression, the cognitive deficit progresses rapidly, especially in the case of altered cerebral small vessels [36, 37].

The cognitive dysfunction highlighted in the analyzed group was present in all patients, being more intense in the age group 60-69 years, wearing the characteristic of MCI syndrome, and strongly expressed in patients over 70 years old. From the point of view of the neurobiochemical mechanisms involved in the cognitive deterioration following the androgenic blockade, a complex neurobiological and neurobiochemical model is highlighted (fig. 2).

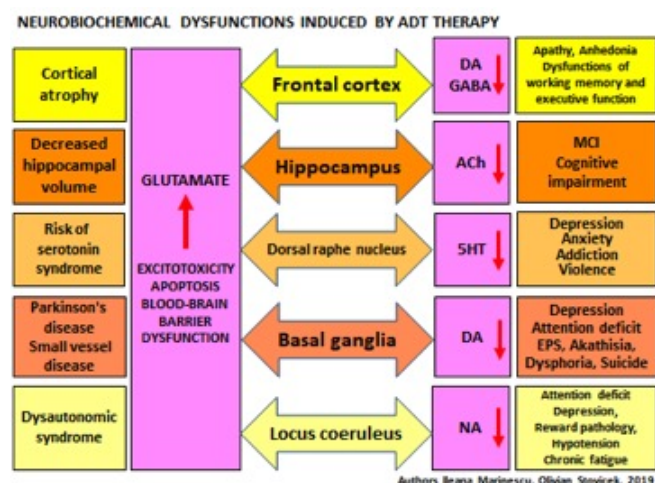


Fig. 2. Neurobiochemical dysfunctions induced by ADT therapy
Caption: DA - dopaminergic system; ACh - cholinergic system; 5HT - serotoninergic system; NA - noradrenergic system.

The blood-brain barrier dysfunction induced by glutamate growth, following androgen deprivation, may be an important marker of the risk of brain metastasis in prostate cancer. This risk is amplified by the persistence of depressive symptomatology and by the lack of objective therapeutic response by maintaining high PSA and testosterone values, as was the case in the 2 patients who did not respond to androgen blocking therapy. In these cases we suspect the existence of an undiagnosed depression, prior to the oncological diagnosis, which evolved independently from ADT treatment. This aspect suggests the emergence of the oncological therapeutic resistance, which is why an interdisciplinary assessment should be performed when initiating ADT therapy. The presence of depression prior to the oncological diagnosis suggests the avoidance of androgen blocking therapies.

Therapeutic guidelines for non-metastatic prostate cancer consider the ADT therapy a first-line therapy. The studies performed by the cancer specialists correlate this type of therapy with the favorable evolution in the vast majority of cases, with a survival rate of over 5 years, in a proportion of about 98%, for all stages [38]. The death of patients with prostate cancer most often occurs from non-

oncological disorders induced by ADT therapy, the most important being cardiovascular [39].

Therapeutic resistance is favored by depression and raises the issue of early oncologic therapeutic switch and the combination of pharmacological and non-pharmacological antidepressant therapies. The direct relationship between elevated PSA and testosterone values and high depression scores suggests unfavorable evolution. It is necessary to evaluate depression from the diagnosis of prostate cancer as well as its dynamic monitoring.

Conclusions

In oncological practice, the favorable evolution is correlated with the low level of PSA, while the transdisciplinary approach, which includes a psychiatrist and a clinical psychopharmacologist, highlights the importance of managing depressive disorders and cognitive dysfunctions, induced by ADT therapy. It is important to identify early the sexual identity and body perception disorders.

It may be suggested the opportunity for interdisciplinary assessments of cognitive status and depression, considered by us as potential risk factors for the unfavorable evolution of non-metastatic prostate cancer. The limits of the study are represented by the relatively small group and by the incompleteness of the biological markers regarding the dysmetabolic and inflammatory processes. Theoretical models presented above can provide the premises for further research on neurobiochemical, neuroimaging and psychosocial models that can approve or disprove these data.

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