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Serum testosterone and its binding globulin during senescence

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Abstract

***Purpose**: The aim of this work is to analyze age-related changes in providing tissues with steroid hormones (androgens [A], mainly testosterone [T]) by means of specific steroid transport protein of the blood (testosterone-binding globulin, [TeBG]) and to propose new informative approach for reliable early diagnostics of impending hypogonadism in elderly men.*

***Methods:** Methods are analytical.*

***Results and conclusions**: Authors develop new approach for assessment of age-related physiological changes in supply of steroids (in particular T) by specific transporting them testosterone-binding globulin (TeBG). This work substantiates the following statements: a) existing common beliefs about circulating A (including 'exchangeable' and 'free' testosterone levels – [T_{exch}], [T_{free}]) do not match their true state of affairs concerning presence, interaction, interchange and transmission of A into target cells; b) blood pool of 'TeBG-T-TeBG'-complex should correctly be called the 'functional T-dimer' (FTD); c) venous blood FTD-content 'mirrors' the 'potentially active' (bioavailable) testosterone molecules conc. ([T_{act}]) in arterial blood (i. e. which capable to be transferred into target cells from capillaries, [T_{act}] = [FTD]); d) age-dependent rise in circulation of 'non-functional' TeBG-molecules ($TeBG_{nf}$) caused by accumulation with age the 'senescence factor' which inhibits needed FTD-formation; e) [FTD]-measurements can be useful for early diagnosis of impending hypogonadism in elderly men.*

***Keywords:** senescence; testosterone; testosterone binding globulin*

***Abbreviations:** A: androgen(s); conc.: concentration (e. g. [A]: conc. of substance 'A'); ABP (SHBG, TeBG): androgen (sex hormone, testosterone) binding protein (globulin); AC: adenylate cyclase; ADAM: 'A'-deficiency in the aging men, known as TD (testosterone deficiency accompanied by erectile dysfunction); AR: androgen receptor; B_{max}: (calculated in Scatchard plot) conc. of 'A'-specific binding sites (on TeBGs); CN: capillary network; DHT: 5α-dihydrotestosterone; FAI: free androgens index; [FTD]: functional T-dimer of TeBG; [^{3}H]-A: tritium-labeled A; K_a: equilibrium T⇄TeBG-association constant; KS: 17-ketosteroids; MF, OF: monomerization and oligomerization factors; PM: external plasmatic membrane of cell; PMAR: AR anchored on PM; RIA: radioimmunoassay; R_{TeBG}: receptor for TeBG on target cell external PM; [T] ([T_{total}], [T_t]): total concentration of T in blood; [T_{act}], [T_{exch}], [T_{free}]: concentrations of bioactive, exchangeable and protein nonbound T-fractions in blood; [T_{sp}]: specific conc. of T (calculated per 1 cm^3 of inhaled air); [$TeBG_{total}$], [$TeBG_t$]: total conc. of TeBG in blood; [$TeBG_{nf}$]: conc. of nonfunctional TeBGs; η_{Hill}: the value of cooperativity between subunits in TeBGs-complex for A-binding; VCL: vital capacity of lungs; V_R: the volume of inhaled air (consumed at rest in one breathing cycle).*

Introduction

The human senescence is associated with appreciable endocrine changes [1-3] – in the case under consideration during aging the concentration of testosterone ([T]) in circulation decreases [4,5], but of the testosterone binding globulin ([TeBG]) increases [6-8]. In humans, TeBG (he is sex hormone-binding globulin, SHBG) transports the biologically important steroids (androgens , A; estrogens, E) and regulates the access of these hormones to their targets tissues; monomer of TeBG has an extended shape and can be modeled as a cylinder with a length and diameter of 23 nm and 3 nm, respectively (two monomers assemble head to head with the steroid-binding site located in the center of the rod-like particle); also TeBG has specific binding sites for divalent cations – calcium and zinc (Zn-binding to a site at the entrance of the steroid-binding pocket reduces its affinity for E, while having no impact on the A-binding) [9].

Serum [TeBG]-values, determined by different methods are higher than of [T] , but TeBG 'grasps' only 65÷88 % of T and transports the hormone in forms of different complexes: monomer ('TeBG-T'), homodimer ('T-TeBG-TeBG-T'), heterodimer ('TeBG-T-TeBG') [7, 10-14]. 2÷5 % of T compose the free it form ([T_{free}], protein nonbound), while 10÷30 % of T is transported by albumin (ALB) and others nonspecific binders (thus due to low hormone affinity – capable of exchange [T_{exch}]) [15,16]). Supposedly, ALB binds only the T that is displaced from TeBG by a special regulatory modulator [13,17]. Now for many researcher it is became clear – [T_{free}] may not be enough to satisfy needs for testosterone in tissues at work (e. g. in the constantly beating heart), especially when they require the maximum supply of anabolic androgens and oxygen [7]. Respectively, those publications that theorize about working organs as consumers of only protein unbound testosterone [T_{free}] often are rechecked [18, 38].

The inaccuracy to estimate an available T in a circulation by the free androgen index (FAI ='[T]/[TeBG]') noted earlier [3,7]. Let us clarify this idea. So adult men venous T-range is 11÷33 nM ($[T]_{mean}$=22 nM) at TeBG of 17÷71 nM ($[TeBG]_{mean}$=44 nM) [19]. Hence, FAI [%]=(22:44) × 100 % = 50 % – the value entirely compliant with the results of Nindl studies [20], which showed that consumption of T by target tissues leads to a noticeable decrease in its total concentration (referring to [T] in the venous blood compared with [T] a in the arterial blood), and the 'magnitude' of this arterial-venous difference = FAI. It is more correct to consider FAI to be an index of the hormone possible for targeted 'release' from above-mentioned complexes and capable for transfer into cells through R_{TeBG} located on PM [21-23]. Therefore, FAI equals to the total 'percent quota' of biologically active hormone (T_{act}) [7,19]. Taking into account that after puberty a personal senescence is considered a 'sluggish pathology' and the above stated, we analyze the relevant data requested from the most objective works [6,7,19,23] aiming to find new approaches for reliable early diagnostics of impending hypogonadism in elderly men.

Results and discussion

According to contemporary concept [19,24] let's outline in context from reliable sources the events' sequence in human 'venous↔arterial' circulation concerning physiology of the TeBG conformations. First of all, venous blood during the passage through the testes and the reticular zone of the adrenal glands has received saturation with androgens, so forming 'TeBG-T'-complexes. Further cardinal events take place in lung CN – synthesized by alveolar cells regulatory 'oligomerization' factor (OF) and inhaled O_2 synergistically promote 'TeBG-T' conversion into its homodimers [7,19,25]: 2 'TeBG-T' → 'T-TeBG-TeBG-T' (as evidenced by the values of the Hill coefficient {η_{Hill}} changed from 1.2 to 1.8÷2.0 [7,12,13,23]). In some cases take place even tetramerization of 'TeBG-T' into $(TeBG+T)_4$-complex (evidenced by η_{Hill} of ≥2.2) [19]. For instance, intrinsic hemoglobin tetramers' η_{Hill} of O_2 binding equals to 2.8 [7]. Lung cells are also significant consumers of the anabolic [7]. The reason for the TeBGs' dimers and tetramers formation is that each subsequent attachment of the T-ligand is facilitated and accelerated [7,22]. Applying by analogy of how 2,3-diphosphogycerate acts on the hemoglobin tetramer, one can imagine that physiological restructuring and function of TeBG's-forms are initiated by special modulators [7,13,19,25]. Previously we substantiated that formed in lungs homodimeric complex of 'T-TeBG-TeBG-T' is an 'androgen providing key', because its concentration determinates the amount of T_{act} in arterial blood [7,19,24]. It is also hardly rightly justified to agree with that TeBG somehow manages to release T into blood plasma to make the so called 'T_{free}' because steroid solubility is very poor in the aquatic environment [26]. Besides, the isolated 'freed steroid' could dissolve for a long time in plasma membranes on the surface of target cells (obviously this does not correspond to rational T-exploitation as a signaling molecule) [13,17]. More 'wisely' to assume the 'relay-race' transfer of T that occurs by 'hand to hand' doings (which eliminate losses) [7,19]. Therefore we guess: rational usage of TeBG includes several stages: a) $TeBG_2$ is 'seized' from blood by its 'recognition system' (R_{TeBG}, specialized receptors of 174 kDa) on PM [21,22,27]; b) TeBG activates adenylate cyclase [22] or G-proteins [28,29]; and c) the assembly 'hands over' T-molecules to enzymatic machinery (thereunto for providing the 'T→DHT' reaction and further delivering DHT to PMAR, i. e. to the ARs on PM [16,17,30-32]. This can be done due to the special commands of signaling regulatory molecules (secreted by target cells [from those of them who currently need A]) – so T-molecules from the homodimeric $(TeBG+T)_2$-complex transferred to them who 'requested' it during the passage of arterial blood in the CN – capillary network of tissues and 'newly formed' venous blood becomes the carrier of the heterodimeric 'TeBG-T-TeBG'-complexes, called FTD (functional T-dimer) [7, 19, 24]. That is why the [FTD]-values in venous blood equals to the concentration of 'active' testosterone molecules ($[T_{act}]$) of arterial blood. Such a turn of events may resemble a 'hinge mechanism' for 'hand-to-hand'-transfer of hormone molecules with its intermediate goal – PMAR [7,12,16,23]. So the heterodimer 'TeBG-T-TeBG' may be rightly considered a basic complex because it circulate in venous blood until another one passage through hormone-producing adrenals and testes, that leads to next saturation of TeBGs with androgen ligands and MF-adjustable TeBGs transformation into monomers: T + 'TeBG-T-TeBG' → 2 'TeBG-T' as evidenced by the values of the Hill coefficient (η_{Hill} changed from 2.0 to 1.0÷1.2 [7, 19]). Thus the TeBG-interconversions ensure the tissues supply with up to 50 % of the total amount of A 'entering' the arterial blood. Correspondingly, at maximum 'withdrawal' only half of the initial pool of T in arterial blood (from the lungs) after targeted tissues delivery can return into the venous blood (contained already in a heterodimeric complex 'TeBG-T-TeBG'). This explains why the [TeBG-T-TeBG] in veins is a 'mirror' of the available T amount ($[T_{act}]$) – capable for consumption through capillary net by tissues from arterial blood [19].

Regarding what was said, it is of interest to analyze the experimental data of the relevant works [6,7,19,24] from the standpoint of the FTD-'behavior' during aging of men (see Table).

Graphs, plotted by the Table data in Figures 1 and 2, illustrates the senescence-related changes of [TeBG], [T] and other studied characteristics of men blood after their puberty in the period up to 100 yr, that is, until very old (expressed as a % of 20-30 yr as a controls).

Our previous studies of [^{3}H]-DHT binding by TeBG of in the venous blood of men [7,19,24] showed that at the age of 25 yr: $K_a=3.8\times10^9$ M^{-1}, $B_{max}=71.6\times10^{-9}$ M, $\eta_{Hill}=1.4$ with [FTD]=35.8×10^{-9} M; and at the age of 60 yr : $K_a=2.3\times10^9$ M^{-1}, $B_{max}=109.0\times10^{-9}$ M, $\eta_{Hill}=1.1$ with [FTD]=19.5×10^{-9} M.

These parameters are in good agreement with the data outlined above, showing that the aging process in men is accompanied by a big decline in the formation of FTD (Figure 2, line *2*) and cooperativity (↓ η_{Hill}) of TeBG's subunits. While the homodimers' formation is reduced, RIA reveals the increase in the total number

Table 1: *Age dynamics of men physiological parameters related to androgenic regulation*

Age, years*	VCL***			$\frac{[T_{total}]}{[T_{free}]}$ of blood plasma*, nM	$\frac{[TeBG_{total}]*\#}{[FTD]}$ of blood plasma, nM	[TeBGnf] ♫ in plasma of blood , nM	T_{free} per 1 cm^3 of air inhaled at rest, pM	T_{sp} , T_t per 1 cm^3 of air inhaled at rest, pM
	VR ,** cm^3	per 1 m^2 of body surface area						
		% V iR	Δ					
20÷24	520÷500	100→96	4.1	23.97 0.43	~35.5 [100%] 21÷24 (100%)	~11.5 [100%]	—	—
25÷34		~90.17	5.73##				0.83	46###
35÷44	470÷490	~86.07	4.1	23.14 0.36	~40.1 [113%] ~22.5 (93.8%)	~17.6 [153.0%]	0.72	46
45÷54	~460	~81.86	4.21	21.02 0.31	44.6 [125.6%] ~21.0 (87.5%)	~23.6 [205.2%]	0.67	46
55÷64	~420	~76.36	5.5	19.49 0.29	45.5 [128.2%] ~19.5 (81.3%)	~26.0 [226.1%]	0.69	46
65÷74	390÷395	~67.38	8.98##	18.15 0.24	48.7 [137.2%] ~18.0 (75.0%)	~30.7 [267.0%]	0.61	46
75÷84	~360	~60.48	6.90##	16.32 0.21	51.0 [143.7%] ~16.0 (75.0%)	~35.0 [304.3%]	0.58	45
85÷100	~340	~56.24	4.24	13.05 0.19	65.9 [185.6%] ~13.0 (66.7%)	~52.9 [460.0%]	0.56	38

* From [6]: # RIA of [SHBG] (sex hormone binding globulin) = [TeBGtotal] and T = FTD (authors' note).
♫ Nonfunctional TeBG-dimer in arterial blood: [TeBGnf] = [TeBGtotal] – [FTD].
** VR: the volume of inhaled (consumed at rest in one breathing cycle) air [24,33].
***VCL: vital capacity of lungs, according to [34,35]: as a man grows up to 20 yr of age, an increase in VCL occurs, however, in the subsequent years of life, its value gradually decreases.
Temporarily increasing Δ-values (100 % – % of V iR) – 'metabolic activation' indicator.
Calculation algorithm: 23.97 nM : 520 cm^3 = 0.046 nM/cm^3 = 46 pM/cm^3 .

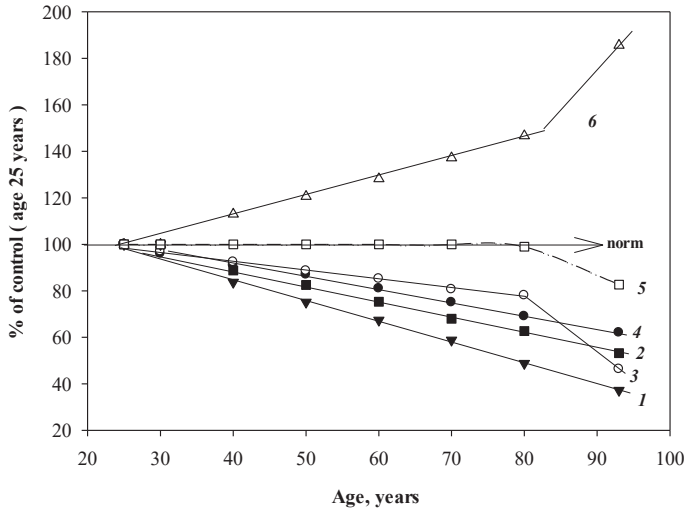

Figure 1*. Men age-dependent dynamics of some characteristics*
Designations: 1 – [T_{free}]; 2 – [T_{total}]; 3 – [T_{act}]= ; 4 – VCL; 5 – T_{sp} ; 6 – [$TeBG_t$].

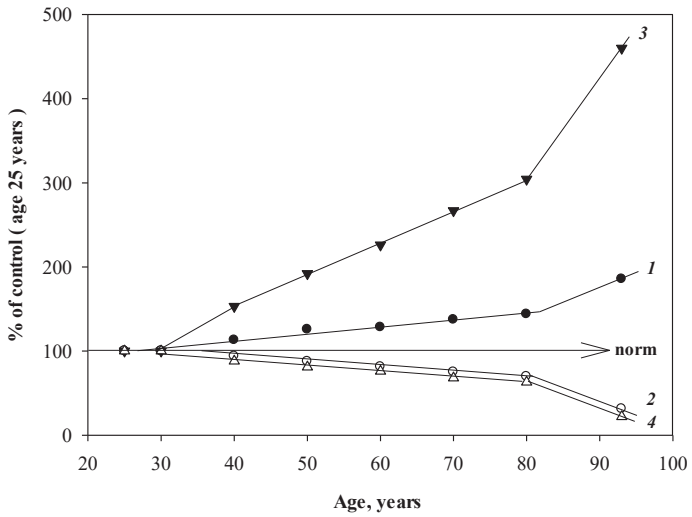

Figure 2*: Men age-dependent dynamics of TeBG-'varieties' in circulation*
Designations: 1 – [$TeBG_{total}$]; 2 – [FTD]; 3 – [$TeBG_{nf}$]; 4 – [FAI].

of TeBG molecules ($TeBG_t$ – see Figure 2, line *1*) and especially non-functional (T-devoid) designated $TeBG_{nf}$ in the Table.

Graphs (Figures 1 and 2 plotted by table data) illustrates the age-related changes of [TeBG], [T] and other studied characteristics of men (after their puberty in the age period up to 100 yr, expressed as a % of control (indicators at 20-30 yr age).

The $[T_t]$ in venous blood after men puberty is gradually diminished (see line *2* in Figure 1) from ~24.0 nM. If measured concentration of 'active' testosterone ($[T_{act}]$ = [FTD]) decreases in men blood to ≤13 nM this indicates some andro-dysfunction, what also can be found by our method [19, 24]. To do this, one need to have at hand a sheet of graph paper, where the age of the patient is plotted on the abscissa axis (in decades [divisions for 10 years]), and on the ordinate axis – 1) the TeBG-concentration concentration in venous serum (≈[FTD]) and 2) the vital capacity of the lungs air inhaled at rest): from ~ 520÷500 cm^3 at the age of 25-30 yr to ~360÷340 cm^3 at the age of 75-100 yr [33-35] (V_R in the table [520 cm^3 → 340 cm^3] and see line *4* in Figure 1). Next step – venous blood [FTD] should be taken equal to the $[T_t]$ measured by RIA-kit [19]. Dividing the [FTD] by the V_R, one obtain the specific $[T_{act}]$ (denoted T_{sp}) and we compare it with normal values (which in healthy men is ~46 pM per 1 cm^3 of air inhaled at rest). If the determined $[T_{sp}]$ is below 45 pM per cm^3 of V_R, the diagnosis reads the development of hypogonadism (ADAM or TD [36,37]) because the overcoming of the 'critical threshold'.

Figure 2 (lines ***1***, ***2***) presents the age dynamics of [FTD] compared with $[TeBG_{total}]$. The actual results indicate that from the age of 25 yr, [FTD]-values steadily decrease, whereas the $[TeBG_{total}]$-values increase from 35.5 nM to 51.0 nM (by the age of 80 yr). Thus [FTD]-loss strongly correlates with senescence (so even may be one of its causes, 'resonating' with the fall of the T-syntheses intensity of in Leydig testicular cells and in the reticular zone of adrenals).

Also one can see in parallel how the decrease in serum testosterone [T] is accompanied by the dramatic accumulation of $[TeBG_{nf}]$ ('free' of T) in the circulatory (line *3* in Figure 2).

Taking into account that venous [FTD] = arterial $[T_{act}]$ [19], we analyzed tissues' consumption of T (its arterial-venous concentrations' difference) at different ages (Table). In parallel we examined age-dependent volumes of the air quietly inhaled in one respiratory cycle and compare relevant endocrine parameters. This approach based on the data that point on generation of arterial T_{act} pool due to TeBG-homodimers' formation in the lungs alveolar capillary network (ACN) [7,19]. We calculated (please see Table) the age indices of [T] standardized to the volume of air inhaled at rest. As follows from these data, the men T-values per V_R-unit provide a normalized specific amount of their entry into the arterial blood and practically do not change with age (Figure 1, line *5*). The exception is the period from 85- to 100 years of men life, when fall of $[T_{free}]$ in the venous blood occurs [6]. At the same time, if calculated per volume of air inhaled by the lungs, the $[T_{free}]$-value decreases from 85- to 100-years of men life only by 33 % (please see Table data).

The dynamics of $[T_{free}]$ in arterial blood strongly correlates with [FTD] and FAI – to the 100-yr they decreased is approximately the same (by 46 % and 40 %, respectively, when calculated per one respiratory cycle, i. e., within the error of the methods for their determination). This result confirms conclusions made earlier [7,13,19]: lungs are the 'initial target' for steroid hormones and one of the main 'mediators' of the endocrine system, because the inhaled air volume 'regulates' the level of testosterone that can be released for target consumption in other tissues from arterial blood. Thus it's became clear how important in practice to have healthy lung tissue function, since it maximizes the lifespan of a person.

Another important aspect should also be touched upon: it is known that during senescence the number of cells and the weight of muscles' tissues decrease – old people can have ≤70 % of that ones at 25-30 yr [34]. Therefore (taking into account this ~30 % of myocytes' miss [19, 24]), the specific amount of T_{sp} taken by muscle tissue from arterial blood during aging from 30- to 80 years can increase from 46- to ~60 pM per cm^3 of V_R, and the phenomenon possibly provides some 'compensation' by increase of T-anabolic effect on the remaining target cells. In the periods of 20-30 yr ad 75-80 yr anabolism activation noted (accompanied by the growth of body hair and elevated urinary excretion of T-metabolites – 17-KS: dehydroepiandrosterone, etiocholanolone, androstenedione, androsterone, epiandrosterone) [2,24]. Also the >75 yr age period accounts for the greatest loss of functional cells while the specific T-level (per 1 cm^3 inhaled at rest) in arterial blood is kept constant [24]. The lowering of [FTD] can promote the retention of T in the blood, so, due to the feedback mechanism, inhibits the production of hypothalamus releasing factors, which leads to a drop in secretion of gonadotropins by the pituitary gland. These events cause decrease of T-synthesis in the testicular Leydig cells and in the reticular adrenal cortex (evidenced by the graphs shown in Figures 1 and 2).

Conclusions

Summing up, it should be pointed out that venous blood FTDs after saturation with T converted to 'T-TeBG-TeBG-T' complexes of arterial blood – only these ones are capable of transfer up to 50 % of their T-hormone for consumption to organs in capillaries, which occurs through the special receptor 'tuned' to the TeBG (R_{TeBG}, 174 kDa) on the plasma membranes of target cells. Supposedly, the transfer is regulated by 'injections' into CN from target cells of the aforementioned modulator, which also blocks reverse T-binding. As for the synthesis of the factor that inhibits the FTD-formation – it is 'switched' on (at the 'genetic level') immediately after the end of puberty and already in the period from 20-25 yr of age is noticeably manifested by a diminution of [FTD] in the circulation.

Based on the carried analyzes we assert the following:

1. the complex of 'TeBG-T-TeBG' is essentially a functional

T-dimer (FTD) i. e. a 'key' in mechanism of androgenic provision, because its blood concentration is determinative for the amount of biologically active androgen-molecules transferred to target cells;

2. the [FTD]-values in venous blood 'mirror' the concentration levels of 'active' testosterone molecules ([T_{act}]) in arterial blood, which by the by a 'hinge mechanism' can be released in the capillary network for 'hand-to-hand'-transfer of androgen-molecules on cell plasma membrane anchored TeBGs' receptors and further on plasma membrane anchored androgen receptors;

3. an age-related quantitative decline of functional dimeric TeBG-complexes ([FTD]) and a parallel increase in number of nonfunctional T-devoid $TeBG_{free}$ are caused by an unidentified inhibitor of androgen binding that accumulates in circulation during human senescence;

4. the specific concentration of testosterone in the arterial blood of adult men does not depend on age (from 25 to 85 years old) and is maintained at [~46 pM] per 1 cm^3 of air inhaled at rest (notwithstanding decreases in basal metabolism, muscle weight and sexual activity).

5. '[FTD]/V_R' value is [T_{act}]-indicator that can be used to predict hypogonadism or its predisposition in elderly men.

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