Male Health

LETTER TO THE EDITOR

Relationships between biological aging and male reproductive monitors

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Dear Editor,

Advanced paternal age affects testicular function, reproductive hormones, and sperm parameters, but it is unclear whether chronological age or biological age exercises a greater sway on reproductive function. Thus, the authors carried out this prospective, multicenter, observational study, in which sperm concentration; motility and morphology; ejaculated volume; testicular volume; and the blood concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone (T) were related to chronological and biological age.[1]

The study was authorized by the Institutional Review Board (IRB) of Gynepro Medical Team. Patient recruitment began on January 2, 2015, and ended on November 30, 2017. A power analysis was carried out to estimate the number of observations needed to have a reliable chance of detecting the effect sought; the power (π) of our tests used $\pi = 0.90$ as a standard for adequacy;[2] an online sample-size calculator was used: http://www.sample-size.net/correlation-sample-size/.

All asymptomatic fertile males over 40 years of age who presented at the outpatient clinics of the authors requesting an andrological checkup were invited to participate in the study; they were a part of the existing andrological clinic cohort.

The exclusion criteria were the presence of any ejaculation disorder (42 patients), clinical varicocele (38 patients), previous genital surgery/trauma (15 patients), ongoing medical treatment (any type of antibiotic use, antitumoral treatments, nonsteroidal anti-inflammatory drugs, gonadotropins, and steroids; 12 patients), and any previous treatment for couple infertility (28 patients).

Clinical history collection and physical examination were carried out on each patient. Biological age was assessed using the Aging Males' Symptoms Scale Score (AMSSS) (Italian version),[3] the Charlson Comorbidity Index (CCI),[4] and the body adiposity index (BAI).[5] Testicular volume (TV) was assessed and measured using an automated formula provided by the ultrasound machine: TV = width × height × depth × 10^{-3} × 0.523.[6] The FSH, LH, and T levels were assessed using the same methods and reference values in Bologna and Varese.[6] Semen volume, sperm concentration, motility, and morphology were also assessed for each patient in two consecutive sperm analyses according to the World Health organization (WHO).[7]

The importance of the relationships regarding the CCI, the BAI, and the AMSSS and age with respect to reproductive monitors were assessed using multiple regression analysis. Each patient delivered two semen samples; thus, the analysis was corrected for the number (two) of sperm samples with Bonferroni correction to guard against the bias of repeated testing effects (*i.e.*, because each regression was computed twice). There were five assumptions of linear regression, and all were fulfilled: absence of any multicollinearity, linearity, statistical independence of the errors, homoscedasticity, and normality of the error distribution.[2] Two hundred and fifty-four patients were eligible for participation in the study. Twenty patients refused to participate in the study and 14 patients dropped out for unknown reasons; thus, 220 patients were assessed. Their characteristics were as following median (range): age (year) = 49.0 (40.3–63.4), BAI = 26.5 (22.0–30.1), CCI = 1.0 (0.0–4.0), AMSSS = 42.0 (17.5–70.3), left testicular volume (cm^3) = 16.0 (10.5–20.0), right testicular volume (cm^3): 17.0 (11.1–20.0), FSH (mIU ml^{-1}) = 7.7 (2.1–56.3), LH (mIU ml^{-1}) = 6.6 (1.5–48.7), prolactin = 8.4 (4.7–38.9), T (ng ml^{-1}) = 4.9 (2.9–18.2), ejaculated volume (ml, 1st sample) = 2.5 (1.0–7.5), sperm concentration (10^6 ml^{-1}, 1st sample) = 38.5 (15.1–110.3), progressive motile sperm (%, 1st sample) = 46.3 (21.2–85.2), typical forms (%, 1st sample) = 10.4 (6.0–21.2), ejaculated volume (ml, 2nd sample) = 2.7 (1.0–8.0), sperm concentration (10^6 ml-1) (2nd sample) = 42.2 (16.3–120.4), progressive motile sperm (%, 2nd sample) = 50.0 (22.3–88.4), and typical forms (%, 2nd sample) = 9.1 (6.3–22.4). The results of the multivariate analysis are presented analytically in **Table 1**. The same results are briefly indicated in decreasing order of their importance in influencing the reproductive monitors: AMSSS, BAI, CCI, and, finally, chronological age. These relationships were positive in the case of FSH and LH whereas they were negative in the other cases (left/right testicular volume, sperm volume, testosterone, sperm concentration, motility, and morphology). The results in the present study indicated that clinical monitors of reproduction were strongly influenced by the monitors of biological age (CCI, AMSSS, and BAI) in patients over 40 years of age whereas the importance of chronological age was lower.

The final pathways of biological aging are programmed cell death (apoptosis) or permanent cell-cycle arrest (cellular senescence).[1] These data explain the relationship between the AMSSS and sperm count and testicular volume (90% of testicular volume is made up of gametes).[1] The AMSSS assesses the symptoms of aging, independently of those which are disease related; it was developed in response to the lack of standardized scales which

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Table 1: Results of multiple regression analyses which define the relationships between follicle-stimulating hormone, luteinizing hormone, total testosterone, ejaculated volume, sperm concentration, motility or morphology, and left and right testicular volume and the chronological age, the Charlson Comorbidity Index, the Aging Males' Symptoms Scale Score, and the body adiposity index

Relationship	Level of intersection of the Y axis	Regression coefficients	Significance of each regression coefficient of the dependent variables	
			Determining factors (t)	P
Relationships A				
Independent variable				
Age	8.176			
Dependent variables				
FSH		6.287	21.199	0.009
LH		8.001	21.210	0.009
T		−5.334	18.221	0.010
VOL		−6.445	20.300	0.009
C		−8.443	20.004	0.009
Sperm MOT		−7.336	21.000	0.009
Sperm MOR		−8.667	22.008	0.009
Relationships B				
LTV		−6.334	19.010	0.010
RTV	−6.009	18.922	0.010	
Dependent variables				
FSH		35.767	36.200	<0.001
LH		14.770	37.180	<0.001
T		−16.551	19.567	0.010
VOL		−17.553	18.001	0.010
C		−21.553	22.856	0.008
Sperm MOT		−31.433	22.402	0.008
Sperm MOR		−34.540	22.520	0.008
LTV		−18.435	22.110	0.009
RTV		−17.009	22.122	0.009
Relationships C				
Independent variable				
AMSSS	4.500			
Dependent variables				
FSH		25.333	29.200	0.005
LH		17.140	27.401	0.006
T		−15.667	18.989	0.009
VOL		−15.117	23.300	0.008
C		−18.443	29.433	0.005
Sperm MOT		−31.223	27.011	0.006
Sperm MOR		−28.667	29.120	0.005
LTV		−16.334	20.010	0.009
RTV		−16.009	18.922	0.010
Relationships D				
Independent variable				
BAI	12.500			
Dependent variables				
FSH		26.287	30.509	0.004
LH		28.301	29.516	0.005
T		−18.009	21.165	0.009
VOL		−17.221	24.009	0.008
C		−19.223	22.001	0.009
Sperm MOT		−26.667	24.000	0.008
Sperm MOR		−29.134	27.904	0.006
LTV		−26.338	21.010	0.009
RTV		−26.129	21.922	0.009

FSH reference value: 1.5–12.4 mIU ml^{-1}; LH reference value: 1.8–12.0 mUI ml^{-1}; T reference value: 240–950 ng dl^{-1}; left/RTV reference value: >14 ml. *t*: *t* statistics. Relationships A: relationships between age and FSH, LH, T, VOL, C, MOT or MOR, and left and RTV. Relationships B: relationships between CCI and FSH, LH, T, VOL, C, MOT or MOR, and left and RTV. Relationships C: relationships between AMSSS and FSH, LH, T, VOL, C, MOT or MOR, and left and RTV. Relationships D: relationships between BAI and FSH, LH, T, VOL, C, MOT or MOR, and left and RTV. FSH: follicle-stimulating hormone; LH: luteinizing hormone; T: total testosterone; C: sperm concentration; VOL: ejaculated volume; MOT: motility; MOR: morphology; RTV: right testicular volume; LTV: left testicular volume; BAI: body adiposity index; AMSSS: Aging Males' Symptoms Scale Score

measure the severity of aging symptoms and their impact on the quality of life.[8]

Elevated BAI increases reactive oxygen species (ROS) in human fluids and affects the production of testosterone via a chronic inflammatory status which leads to biological senescence.[9] An increase in FSH and LH with increasing age is consistent with the decline in testosterone. This knowledge legitimizes gonadotropin increase with aging. Reactive oxygen species induces subtle changes in intracellular signaling pathways with the result of prostatic function (*i.e.*, secretion) impairment. The final result is a decrease in the sperm volume.[9] Actually, the BAI is linked to aging well (*i.e.*, biological age).[9] The CCI affects reproductive monitors as well. In fact, comorbidities are linked to aging and to an increase in biological age.[10]

The strength of this manuscript lies in the marked distinction between chronological age and biological age. The major limitation of this study is the lack of standardized scales for measuring the severity of chronological aging. To overcome this bias as much as possible, three scales (AMSSS, BAI, and CCI) linked to biological aging were used. These data allowed us to conclude that biological age should be considered as well as chronological age when we are counseling prospective fathers over 40 years of age.

AUTHOR CONTRIBUTIONS

GC conceived the study, prepared the research protocol, studied 170 patients, wrote the manuscript, and analyzed the data. FS studied 150 patients, revised the research protocol, and edited the manuscript. Both authors have read and approved the final manuscript.

COMPETING INTERESTS

Both authors declared no competing interests.

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