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Original Study

Endocrinology of Aging From a Muscle Function Point of View: Results From the Toledo Study for Healthy Aging

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A B S T R A C T

Introduction: Aging is a process that involves a reduction in muscle strength and anabolic hormone concentrations, which impacts significantly on health.
Aim: To study the hormone/total strength (H/TS) ratio as a proxy of anabolic insensitivity status in elders, and its relationship with disability, hospitalization, and mortality risk.
Design: A total of 1462 persons aged ≥65 years from the Toledo Study of Healthy Aging participated in this study. Serum concentrations of insulin like growth factor 1, total and free testosterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and 17β-estradiol were measured. Total maximal voluntary isometric strength was obtained (handgrip, shoulder, hip, and knee) using standardized techniques and equipment. Physical activity was recorded by physical activity scale for the elderly questionnaire. Associations of the H/TS ratio with hospitalization and mortality were assessed using logistic regression models, and participants stratified into quartiles for each H/TS ratio.
Results: In women, all individual ratio H/TS models showed a strong to moderate increased risk for death and hospitalization. In men, all models revealed a significant positive association of the ratio H/TS with mortality rate but not for hospitalization ($P < .01$). Participants who have 2 or more H/TS ratios in the worst quartile increased the risk of hospitalization and mortality at least by 2-fold.
Conclusions: We demonstrate the main role that muscle function plays in the relationship between the hormonal status and hospitalization and mortality risk; this could be taken into consideration as a way to classify patients for hormonal therapy.

Aging naturally implies loss of skeletal muscle mass (termed as sarcopenia) and muscle strength, and an increase in the proportion of fat mass.[1,2] These changes are known to be dependent to some extent on hormones and are related to the impairment of physical functions and mobility and loss of independence and increases the risk of institutionalization and mortality in older adults.[3] However, elderly people who regularly exercise show much better health standards.[4]

In the last decade, there is incremental evidence that skeletal muscle exerts a pivotal role as an endocrine organ.[5] This hypothesis is based on the idea that muscle contraction triggers a cross talk between muscle and other tissues (ie, liver, bone, fat, circulatory system) resulting in

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improvements in glucose metabolism, fatty acid oxidation, endothelial function, and bone apposition, among other general effects.[6] Moreover, contraction of the skeletal muscle elicited by exercise is known to promote anabolic actions through several signaling pathways that lead to protein synthesis and hypertrophy, more specifically the ones mediated by insulin like growth factor 1 (IGF-1), growth hormone (GH), androgens (total and free testosterone; TT and FT), and to a lesser extentestrogens (E_2).[7] Thus, muscle mass and function, expressed as the ability to generate strength, may be considered as good estimators of a person's anabolic level, as well as indicators of health status.[8] In that sense, a recent study published by Srikanthan et al[9] highlights the survival predication ability of relative muscle mass in older adults.

During the aging process, it is observed that the systemic concentrations of this anabolic hormones decrease gradually, reaching a status of a "multiple hormonal dysregulation," rather than a deficit in a single hormone.[10,11] This state is associated to poor health outcomes.[10,12,13] Interestingly, the relationship among systemic anabolic hormones concentration and/or mortality, physical performance, and frailty is not always constant, especially when IGF-1, TT, dehydroepiandrosterone (DHEA), and E_2 are taken into consideration individually. First, there is a different direction in the association between hormone concentration and health events among studies. For example, reports from the Toledo Study for Healthy Aging (TSHA) show a negative association among systemic levels of both TT and FT and frailty in men,[12] and conversely, a positive association among E_2 levels and frailty in postmenopausal women.[14] Second, several reports show inconsistencies in the hormone dose-effect relationship. Such an effect has also been observed in the association between anabolic hormones and physical performance,[15–17] as well as a U-shaped risk between E_2, dehydroepiandrosterone sulfate (DHEAS), and IGF-1 levels and mortality.[13,18,19] Third, there are clinical inconsistencies too. Although hormonal dysregulation increases mortality in patients suffering from heart failure or frailty, hormone supplementation is linked to increased health status complications and death.[17] These evidences question the belief that states the more anabolic hormone level, the better health status.

Taking into consideration current knowledge, we consider that muscle mass and/or function (strength) can help to better understand the relationship between anabolic hormone levels and health events, allowing, on the other hand, to better select potential persons to receive hormonal therapy. Therefore, we aimed to develop a functional mortality and hospitalization predictor model. This model includes measurements of representative hormones implied in aging (FT, TT, DHEA, DHEAS, IGF-1, and E_2) and physical activity levels, using data from the TSHA. We hypothesize that muscle strength modulates the association of these anabolic hormones with mortality and/or hospitalization incidence in elders.

Methods

Study Sample

We selected all participants assessed for strength, physical activity, and available blood samples from the TSHA, a Spanish population-based prospective cohort study involving men and women over 65 years of age. This study aims at investigating the determinants of frailty in the elderly. Full methodology has been described previously.[14,20] Briefly, data collection was performed in 3 stages. At baseline, participants were interviewed at home by trained psychologists, where sociodemographic information, social support, limitations in activities of daily living, health-related quality of life, physical activity, diet, alcohol use, and depressive symptoms were recorded. In addition, an extensive neuropsychological evaluation was performed for each participant. In the second stage, 3 nurses completed an in-house examination. Information regarding blood pressure, anthropometrics, ankle-brachial index, electrocardiogram, spirometry, and physical performance tests (upper and lower extremities strength, walk speed, balance, and sit and stand from a chair) was obtained. In the third stage, the participants went to their health center where a blood sample was taken while fasting. There were no clinical or functional statistically significant differences between the phases.[20]

Initially, of the 2488 persons recruited for the TSHA (56% women), we selected those who had undergone the nursing evaluation (1966 men and women). After exclusion of persons who did not perform any of the 4 strength measurements (78 men and 123 women), those who did not provide a blood sample for hormonal determinations (165 men and 186 women), those who showed inaccurate hormonal determinations (7 men and 8 women), and those who were taking medication known to affect systemic hormone levels (2 women and 35 men), we finally obtained a sample composed of 1362 participants (57% women). Because of sample limitations, IGF-1 was measured on 533 men and 662 women. Study participants gave a signed informed consent, and the study protocol was approved by the Clinical Research Ethics Committee of the Complejo Hospitalario de Toledo (Spain).

Anthropometrics and Questionnaires

Height was measured to the nearest millimeter using a portable stadiometer (Medizintechnikseit 1890; KaWe, Asperg, Germany) and weight was measured with a precision scale (Seca 884 floor scale; Seca, Asperg, Germany). Individuals removed shoes, socks, and heavy clothes prior to weighing. Body mass index was calculated as weight divided by height^2 (kg/m^2). For quantification of comorbidities a questionnaire version of the Charlson comorbidity index was used.[21] This tool has previously been validated for population-based studies to estimate the risk of death and includes several medical conditions (ie, myocardial infarction, cardiovascular disease, diabetes, hypertension, dementia, renal disease, tumour, etc).

Muscle Strength

Maximal voluntary isometric strength was measured for shoulder abduction, knee extension, and hip flexion in all participants using a Manual Muscle Test System (Lafayette Instruments Company. Lafayette, IN) and a hydraulic dynamometer (Jamar Preston, Jackson, MI) for hand grip. All measurements were gathered using international standard procedures.[22,23] Briefly, during 6 seconds, participants were encouraged to exert the highest strength against a fixed manual dynamometer in the lowest time. The best of 3 attempts, allowing 1-minute rest between measurements, was considered as the maximal voluntary isometric strength (kg), which was determined as the highest value of the force produced.

Hormonal Determinations

Blood samples were collected between 8 AM and 9 AM while fasting. Samples were centrifuged, and serum fraction was taken to the laboratory within 2 hours, using containers at a temperature between 2°C and 4°C, then divided in aliquots and finally stored at −80°C.

Enzyme-linked immunosorbent assay (ELISA) techniques in a Dynex DS2 Automated ELISA System (Dynex Technologies, Inc, Chantilly, VA) were used to measure serum concentrations of TT and FT (DRG testosterone, and DRG FT ELISA kits). Total E_2, IGF-1, DHEA, and DHEAS were measured with a sensitive direct radioimmunoassay (Spectria Kit; Orion Diagnostica, Espoo, Finland; DRG Diagnosis, Marburg, Germany; 1776 Kit; DRG Instruments GmbH, Marburg, Germany, and 1538 Kit; DRG Instruments GmbH. respectively).

The lower end sensitivities were 0.083 ng/mL for TT, 0.06 pg/mL for FT, 9.5 pmol/L for E_2, 9 pg/mL for DHEA, 1.7 μg/100 mL for DHEAS, and 0.25 ng/mL for IGF-1, respectively. The intra- and interassay coefficients of variation were 3.34%–4.16% and 4.73%–9.94% for TT, <10%

and <10% for FT 5% and 9.7% for E_2, 3.5% and 7.6% for DHEA. 8.2% and 9.6% for DHEAS, and 9.6% and 10.4% for IGF-1, respectively. Values of TT and FT lower than the sensitivity threshold were given the value of this threshold in statistical analysis.

Total Mortality and Hospitalization

Data on all-cause mortality were obtained using information from the Spanish National Mortality Database and through follow-up interviews by telephone. Individuals who died and the date of death were identified. Data on hospitalization was collected from the regional health system database. Participants were followed up during a mean time period of 5.5 (range: 0.3–6.8) years for all-cause mortality and 3.5 (range: 0.3–4.8) years for hospitalization.

Statistics

Total muscle strength was analyzed as a summation of each individual strength value (handgrip, shoulder, hip, and knee). The associations of vital status and hospitalization with the logarithm of hormone level and the logarithm of each hormone ratio (hormone levels divided by total muscle strength) were assessed using logistic regression models, including age, physical activity scale for the elderly, waist and hip perimeters and Charlson index as possible confounders, for each sex. All analyses were carried out with the Statistical Package R for windows v 2.15.2 (Vienna, Austria; http://www.r-project.org). Data are presented as mean values ± standard deviation unless otherwise stated. Significance level was set at a P value of $< .05$.

Logistic Regression Models

Six functional models to associate the 6 measured hormones and absolute muscle strength with mortality and hospitalization were calculated according to each hormone measured and separated by sex. The functional model assumes that the hormonal levels depend partially on the total strength (TS) score. Then, using the properties of the logarithms, we can split the association in terms of the ratio hormone divided by the total strength (H/TS), or derive both the global effect of the hormone or the TS alone from the estimated model using the formula depicted below:

$$\beta_1 Ln\left(\frac{H}{TS}\right) + \beta_2 Ln(H) \leftrightarrow \beta_1 Ln(H) - \beta_1 Ln(TS) + \beta_2 Ln(H) \leftrightarrow (\beta_1 + \beta_2) Ln(H) - \beta_1 Ln(TS)$$

Odds ratios and confidence intervals were calculated for each estimated parameter (hormone, H/TS) and derived parameter (TS and global effect).

Results

Study Population

Overall, 1462 participants (57% women) were included in our analysis. Table 1 displays general descriptive values of all the measured variables in the study population. From the entire study population, according to body mass index scales, 42% of the participants were overweight and 42% were obese, 17% had diabetes, 50% were hypertensive, 13% had a cardiovascular event, 5% had a cerebrovascular accident, and 6% had cancer. The accumulated incidence of 5.5 years mortality was 20% in men and 13% in women, whereas 33% of men and 25% of women were hospitalized in the same period of time (congregate mortality and/or hospitalization was 53% and 38% for men and women, respectively). There were significant differences by sex between dead and alive participants in total and regional strength (Table 1).

Hormonal Level and Total Strength Relation with All-Cause Mortality and Hospitalization in Elder Men and Women

Results regarding the logistic regression for the hormonal models are detailed in Table 2. Overall, the functional models revealed that the

Table 1
Descriptive Sociodemographic and Anthropometric Characteristics, Strength, and Hormone Concentration of the Participants Stratified by Sex and Survival Status

	Women			Men		
	Alive (n = 704)	Dead (n = 92)	*P*	Alive (n = 456)	Dead (n = 110)	*P*
	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)	
Age (years)	74.0 (70.0–77.0)	81.0 (77.0–85.8)	<.001	74.0 (70.0–77.0)	78.0 (75.0–83.0)	<.001
BMI (kg/m^2)	29.7 (26.8–33.1)	30.3 (25.9–33.4)	.756	28.3 (25.8–30.8)	27.1 (24.9–30.8)	<.05
Hip perimeter (cm)	109.0 (102–116)	110.0 (102–119)	.418	104.5 (100–110)	104.0 (99.8–110)	.678
Waist perimeter (cm)	98.0 (91–106)	99.5 (92–109)	.183	102.0 (97–110)	102.0 (94–109)	.313
Total muscle strength (kg)	53.8 (42.2–71.4)	34.2 (28.9–45.3)	<.001	85.4 (68.2–106.9)	65.7 (49.7–84.8)	<.001
Grip strength (kg)	18.0 (14.0–21.0)	12.0 (8.0–16.0)	<.001	30.0 (25.0–36.0)	24.0 (19.0–29.0)	<.001
Shoulder strength (kg)	10.4 (7.5–14.3)	6.5 (4.8–8.5)	<.001	17.8 (13.1–24.4)	13.0 (9.3–17.8)	<.001
Hip strength (kg)	14.5 (10.1–20.5)	8.8 (6.4–13.0)	<.001	21.5 (15.5–26)	16.2 (12.0–22.5)	<.001
Knee strength (kg)	10.3 (6.9–16.2)	6.0 (3.5–8.4)	<.001	15.1 (10.0–21.2)	10.8 (6.4–15.4)	<.001
PASE (TS)	67.1 (50–95.7)	25.0 (2.9–52.9)	<.001	71.1 (30.4–107.4)	33.1 (8.6–75.7)	<.001
IGF-1 (ng/mL)	105.0 (70.0–147.6)	85.1 (52.5–137.0)	.093	105.0 (72.5–156.7)	101.4 (69.2–152.6)	.120
FT (pg/mL)	0.4 (0.1–0.9)	0.3 (0.1–0.9)	.418	6.0 (4.0–9.2)	6.3 (3.5–9.6)	.586
TT (ng/mL)	0.4 (0.2–0.7)	0.4 (0.2–0.6)	.213	4.4 (3.4–5.8)	4.1 (3.2–5.8)	.180
DHEA	5.5 (4.0–9.5)	5.0 (3.0–8.0)	.251	5.0 (3.5–8.0)	4.0 (3.0–7.0)	<.05
DHEAS (pg/mL)	57.3 (31.0–116.0)	49.0 (28.1–108.5)	.483	90.5 (50–182)	77.0 (30.8–156.6)	<.05
E_2 (pmol/L)	20.4 (13.9–30.0)	18.8 (14.7–30.5)	.985	33.9 (24.8–47.7)	33.5 (21.1–43.9)	.127
Education level (%)			.094			.541
<Primary school	86.2	94.3		81.7	87.3	
Primary school	8.6	3.8		7.0	5.6	
>Primary school	5.2	1.9		11.2	7.1	
Charlson index (%)			<.05			<.01
0	47.5	37.4		50.0	38.1	
1 or 2	38.1	43.0		39.2	46.0	
3 or 4	10.4	10.3		7.2	9.5	
>4	4.0	9.3		3.6	6.3	

BMI, body mass index; E_2, 17β-estradiol; IQR, interquartile range; PASE, physical activity scale for the elderly.

Table 2
Logistic Regression Models for Death and Hospitalization in Elderly Women and Men Regarding the Ratio H/TS and Hormone Concentration

	Women				Men			
	Death		Hospitalization		Death		Hospitalization	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Ratio								
DHEA/TS	4.28 (2.41–7.61)	<.001	2.35 (1.60- 3.45)	<.001	2.70 (1.64–4.44)	<.001	1.28 (0.84–1.96)	.250
DHEAS/TS	4.27 (2.41–7.58)	<.001	2.35 (1.60–3.45)	<.001	2.67 (1.62–4.40)	<.001	1.26 (0.82–1.93)	.290
E_2/TS	4.32 (2.43–7.68)	<.001	2.35 (1.58–3.48)	<.001	2.65 (1.61–4.35)	<.001	1.31 (0.86–2.01)	.214
IGF-1/TS	3.36 (1.83–6.18)	<.001	1.90 (1.28–2.82)	<.01	2.86 (1.67–4.90)	<.001	1.11 (0.73–1.67)	.631
FT/TS	4.61 (2.50–8.52)	<.001	2.13 (1.42–3.20)	<.001	2.89 (1.71–4.89)	<.001	1.17 (0.76–1.81)	.473
TT/TS	4.26 (2.36–7.71)	<.001	2.26 (1.53–3.33)	<.001	2.71 (1.61–4.55)	<.001	1.11 (0.72–1.72)	.624
Hormone concentration								
DHEA	0.24 (0.13–0.46)	<.001	0.43 (0.28–0.66)	<.001	0.36 (0.20–0.63)	<.001	0.59 (0.36–0.97)	.038
DHEAS	0.23 (0.12–0.41)	<.001	0.45 (0.30–0.68)	<.001	0.36 (0.21–0.60)	<.001	0.79 (0.51–1.23)	.300
E_2	0.28 (0.14–0.54)	<.001	0.52 (0.33–0.84)	<.01	0.33 (0.18–0.60)	<.001	1.01 (0.61–1.68)	.971
IGF-1	0.30 (0.15–0.58)	<.001	0.51 (0.32–0.81)	<.01	0.39 (0.21–0.73)	<.01	0.76 (0.47–1.23)	.264
TL	0.23 (0.12–0.43)	<.001	0.46 (0.31–0.70)	<.001	0.35 (0.20–0.60)	<.001	0.88 (0.56–1.38)	.573
TT	0.20 (0.10–0.38)	<.001	0.37 (0.24–0.56)	<.001	0.33 (0.19–0.56)	<.001	0.88 (0.56–1.38)	.577

CI, confidence intervals; E_2, 17β-estradiol; OR, odds ratio.
The cut-off points for the highest hormone concentration quartiles in women were IGF-1 ≥146, FT ≥ 0.93, TT ≥0.66, E2 ≥30.1, DHEA ≥9, and DHEAS ≥116; and for men were IGF-1 ≥156, FT ≥9.21, TT ≥5.76, E_2 ≥46.74, DHEA ≥8, and DHEAS ≥176. The cut-off points for the highest ratio hormone concentration/TS quartiles in women were IGF-1/TS ≥3.12, FT/TS ≥0.023, TT/TS ≥0.013, E_2/TS ≥0.71, DHEA/TS ≥0.213, and DHEAS/TS ≥2.90; and in men were IGF-1/TS ≥2.08, FT/TS ≥0.14, TT/TS ≥0.08, E_2/TS ≥0.65, DHEA/TS ≥0.11, and DHEAS/TS ≥2.63. Model adjusted by age, PASE, hip and waist perimeters, and Charlson index for each sex.

risk of death or hospitalization is in close relationship with the equilibrium between the hormonal level and strength. Specifically when the ratio H/TS is disrupted (by increasing the hormonal level for a given strength, or decreasing TS for a given hormonal level), the risk of death or hospitalization increases significantly (Table 2). In women, all individual ratio H/TS models showed a strong to moderate increased risk for death and hospitalization ($P < .01$). Similarly, in men, all models revealed a significant positive association of the ratio H/TS with mortality rate but not for hospitalization ($P < .05$). On the other hand, the hormone concentration alone followed an inverse fashion in women (ie, there was a significant negative association between each hormone and death and/or hospitalization). In men, this association was significant for mortality rate but not for hospitalization. However, there was a protective effect of DHEA levels over hospitalization risk in men ($P < .05$, Table 2).

Cause of H/TS Ratio on All-Cause Mortality and Hospitalization in Elder Men and Women

Table 3 displays the relative effect of harboring one to 6 of the worst [ie, highest, H/TS ratios quartiles of each measured hormone (DHEA, DHEAS, E_2, IGF-1, FT, and TT)] on mortality and hospitalization risks taking 0 and 1 as reference.

Overall, this statistical model shows that having more ratios in the worst quartile results in an increased risk of hospitalization and death. Specifically, women who have 2 or more ratios in the worst quartile have a significantly higher risk (∼2-fold) of hospitalization and death. Furthermore, when women had more than 3 ratios in the worst quartiles, death and hospitalization risk increased by 3- or 4-fold ($P < .01$). However, when men are in the same situation neither the death nor the hospitalization risk are increased significantly, and only when men have more than 3 ratios in the worst quartile they increase the risk of death by 3-fold (Table 3).

Discussion

The main finding of this study relies on the development of a functional model that relates hormonal levels and muscle strength with hospitalization and mortality risk in elders. This demonstrates the main role that muscle function plays in the relationship between the hormonal status and the hospitalization and death probability, which is often overlooked in the literature. Moreover, this model can

Table 3
Logistic Regression Models for Death and Hospitalization in Elderly Women and Men Regarding the Ratio H/TS and Hormone Concentration Regarding the Corresponding Worst Quartile Classification

	Women				Men			
	Death		Hospitalization		Death		Hospitalization	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Ratio								
Score = 0 or 1	Ref.		Ref.		Ref.		Ref.	
Score = 2 or 3	2.16 (1.06–4.40)	<.05	1.76 (1.04–2.99)	<.05	1.73 (0.9–3.33)	.103	1.20 (0.72–2.02)	.483
Score >3	4.61 (1.72–12.37)	<.01	2.64 (1.28–5.43)	<.01	3.02 (1.24–7.36)	<.05	0.81 (0.38–1.71)	.575
Hormone concentration								
Score = 0 or 1	Ref.		Ref.		Ref.		Ref.	
Score = 2 or 3	0.42 (0.19–0.92)	<.05	0.69 (0.41–1.17)	.174	0.73 (0.38–1.4)	.337	0.94 (0.58–1.54)	.815
Score >3	0.35 (0.1–1.25)	.105	0.67 (0.29–1.55)	.352	0.56 (0.16–1.95)	.362	0.96 (0.4–2.35)	.936

CI, confidence intervals; E_2, 17β-estradiol; OR, odds ratio.
The model shows the relative effect of harboring any of the worst H/TS ratios quartiles or hormone concentrations quartiles on mortality and hospitalization risks. Score = 0 or 1: none or 1 ratio/hormone in the highest quartile, reference; score = 2 or 3: 2 or 3 ratios/hormone in the highest quartile; Score = 3 or 4: 3 or 4 ratio/hormone in the highest quartile. Women highest hormone concentration quartiles: IGF-1 ≥146, FT ≥0.93, TT ≥0.66, E_2 ≥30.1, DHEA ≥9, and DHEAS ≥16. Men highest hormone concentration quartiles: IGF-1 ≥156, FT ≥9.21, TT ≥5.76, E_2 ≥46.74, DHEA ≥8, and DHEAS ≥176. Women highest ratio hormone concentration/TS quartiles: IGF-1/TS ≥3.12, FT/TS ≥0.023, and TT/TS ≥0.013, E_2/TS ≥0.71, DHEA/TS ≥0.213, and DHEAS/TS≥2.90. Men highest ratio hormone concentration/TS quartiles: IGF-1/TS ≥2.08, FT/TS ≥ 0.14, TT/TS ≥0.08, E_2/TS ≥ 0.65, DHEA/TS ≥0.11, and DHEAS/TS ≥2.63. Model adjusted by age, PASE, hip and waist perimeters, and Charlson index for each sex.

be taken into consideration as a way to correctly classify patients considered for hormonal therapy.

General theory of aging states that there is a progressive decline in hormonal anabolism with aging. This results in a deregulation that affects multiple systems (ie, somatopause [decrease in GH by the pituitary gland and IGF-1 from the liver]; menopause and andropause [decreased E_2 from the ovaries and testosterone from the testicles]; and adrenopause [decreased production of DHEA and DHEAS from the suprarenal glands]).[24] This central dysregulation, explains (in part) the progressive loss of muscle mass and increase in fat mass that occurs with aging.[25–27] However, the relationship among low hormonal concentrations and poor health outcomes is not always constant. Studies in aged populations show an unexplained U-shaped or J-shaped curve between hormonal levels and adverse health events.[13,18,19] The results obtained in this investigation evidence the main role that skeletal muscle function (expressed as the ability to generate force) exerts on hormone, death, and hospitalization relationships. Logistic regression models depicted in Tables 2 and 3 show that whenever the balance between force and hormonal concentrations is disrupted (disproportionate increase in the ratio between hormone level and force), both death and hospitalization probabilities are significantly increased.

Hormonal Dysregulation from a Muscle Function Point of View

Muscle mass balance is a complex coordinated interaction between (1) anabolic signals activated by insulin, IGF-1, GH, and androgens, and (2) catabolism, which is stimulated by glucocorticoids, reactive oxygen species, and proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, interleukin-6, and interferon-γ. Furthermore, the inevitable reduction in skeletal muscle mass and associated loss of strength occurs even in the healthy elderly.[8] Thus, aging has also been related to the loss of functionality of several anabolic pathways in human skeletal muscle. Evidence of lower androgen receptor messenger RNA expression, as well as GH/IGF-1 messenger RNA expression and protein abundance in response to a training stimulus is seen in aged skeletal muscle.[28–30] The downregulation in the pathways governing muscle growth in aged skeletal muscle suggests a local insensitivity to the action of those hormones, as has been reported before.[31,32] Thus, a disproportionate rise in systemic anabolic hormone concentrations would be the key to detect a local receptor-like insensitivity, as has been demonstrated with leptin in relation to the amount of muscle leptin receptors mediated signaling.[33] In consequence, a highly deteriorated muscle signaling, at the receptor amount or downstream at signaling level, would imply higher systemic hormonal concentrations necessary to maintain muscle mass balance.

It is important to notice that muscle maximal voluntary contraction and force production better predict physical dependence and mortality than muscle size[34]; highlighting neuromuscular control of movement, which is significantly affected by age, as another major player in relation to muscle mass and contractile function quality.[35] Moreover, anabolic actions in skeletal muscle are also mediated by muscle surface mechanoreceptors, which are able to translate neuromuscular mechanical actions into discrete signaling pathways.[36] Accordingly, the functional model can help to identify persons with peripheral dysregulation. The hormonal term (Ln [IGF-1^i]), independent of force, expresses intrinsic and protector effect of the hormone and assesses the impact in the probability of death and hospitalization derived from the level of hormone age-related decline. The other term (Ln [IGF-1/TS]; hormone level conditioned to force) could be considered as an indirect estimator of muscular insensitivity to hormonal action.

Functional Models and the Importance of Strength Measurements to Predict the Association of Hormone Levels with Hospitalization and/or Mortality

Many epidemiologic studies associating age-related decline in hormone levels with mortality lead to the hypothesis that hormone supplementation (DHEAS, testosterone, E_2, GH) may induce beneficial effects on functional outcomes (physical fitness) and changes in body composition, especially increasing muscle mass.[37–39] For example, restoring testosterone to youthful levels is shown to increase synthesis of myofibrillar proteins, total body cell mass, and muscle strength.[40] Unfortunately, there is a high risk of side effects with these treatments, including adverse cardiovascular events and prostate hypertrophy.[41] To deal with the potential failure of sex hormone replacement treatment, the correct selection of potential candidates is essential. Some authors point to other factors such as the correct selection of route of administration and dosage, type of interventions (intermittent vs continuous), the use of selective androgen receptor modulators, and the combination with nutritional supplementation and exercise.[42] Our study can help to identify persons whose peripheral anabolic function is disturbed in whom treatment with exercise interventions are mandatory.

More than a refined model to forecast health events, where muscle strength is the main component, our study provides a new approach to understanding the relationship between anabolic hormones and health events and help to explain the U-shaped curve of adverse health events. Moreover, the study identified participants in whom the hormonal supplementation could have a poor or bad effect because receptor and postreceptor fields are disturbed. These participants with high H/TS ratio could improve with exercise intervention.

This study has some strengths. First, data source is a population study with an elevated number of patients where muscle strength was measured in upper and lower extremities. Second, the models are controlled for important confounders as physical activity levels. However, the study has some weaknesses. First, the hormone level and strength were measured at the same time; therefore, we cannot establish a causal explanation between them. Second, muscle function is not only the expression of muscle strength; important aspects such as neural (central) activation, fatigability, and motor control are also implicated. Furthermore, the magnitude of importance of each aspect may be muscle specific and, therefore, TS is only an indirect estimator of muscle function.

With our study, we aimed to better classify patients according to their muscle function together with their sex-hormone levels rather than hormone levels alone. Taking into consideration muscle function (strength measurements) will allow the clinician to indirectly check the local anabolic status to identify potential insensitivity to the action of the hormones, which would, on the other hand, produce an adverse effect if supplemented.

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