Aaron Baum, PhD
Mark D. Schwartz, MD

Author Affiliations: Department of Health System Design and Global Health, Icahn School of Medicine at Mount Sinai, New York, New York (Baum); Department of Population Health, New York University School of Medicine, New York (Schwartz).

Corresponding Author: Aaron Baum, PhD, Department of Health System Design and Global Health, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029 (aaron.baum@mssm.edu).

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Divergence in Timing and Magnitude of Testosterone Levels Between Male and Female Youths

Data on testosterone levels in children and adolescents segregated by sex are scarce and based on convenience samples or assays with limited sensitivity and accuracy. Such data would be useful in evaluating children with pubertal or androgen disorders and dichotomizing male and female youths participating in sport. Thus, we analyzed the timing of the onset and magnitude of the divergence in testosterone in youths aged 6 to 20 years by sex using a highly accurate assay.

Methods | Testosterone concentrations from separate cohorts of male and female youths collected during 2 periods of the National Health and Nutrition Examination Survey (NHANES; 2013-2014 and 2015-2016) were pooled into 1 data set for analyses. Briefly, NHANES uses a multistage probability design to randomly sample US residents from all 50 states. The overall response rate in the 2 data collection cycles was 70.4% in youths, and 80% of those responders elected to participate in the collection of biospecimens for testosterone analyses. All procedures accessed public, deidentified information and did not require ethical review as determined by the Mayo Clinic Institutional Review Board.

As described previously,[1] testosterone was quantified via isotope dilution liquid chromatography tandem mass spectrometry, which demonstrates a broad analytical measurement range (0.75-1400 ng/dL), excellent precision across a wide range (<3% coefficient of variation) and high accuracy (−0.7% mean bias for a 2-year period), confirmed using reference materials from the National Institute for Standards and Technology.

Full factorial analysis of variance was used to examine the change in testosterone concentration from ages 6 to 20 years by sex, focusing on the age of divergence of testosterone and the overlap at the extremes. Two-tailed post hoc analyses (Scheffe test) were used to test for differences between pairs with Bonferroni-corrected P values ($P < .025$). For all other analyses, significance was determined at $P < .05$. All analyses were performed with R software, version 3.4.2 (R Foundation).

Results | The data set included 4495 youth samples—2293 male and 2202 female—with diverse racial representation including Hispanic (36%), white (26.6%), black (23.0%), Asian (8.8%), and multiracial (6.1%). No statistical differences of race (effects or interactions) were noted.

The median testosterone concentration increased for female youths from age 6 to 20 years from 2.4 ng/dL to 29.5 ng/dL ($P < .001$), with a plateau beginning at age 14 years (**Table**). Over the same age range, the median testosterone concentration increased considerably more for male youths compared with female youths (age × sex; $P < .001$), from 1.9 ng/dL at age 6 years to 516 ng/dL at age 20 years ($P < .001$), with a plateau beginning at age 17 years. Testosterone concentration was not different between the sexes from age 6 to 10 years; however, male youths had greater testosterone concentrations than female youths from age 11 to 20 years (**Figure**).

Among youths aged 12 years or older, there was no overlap of the interquartile range of testosterone between male and female youths. After cessation of the age-related increase in testosterone for female youths (at 14 years), there was an intersection of testosterone concentration distributions between the lowest (first) percentile of male youths and the uppermost (99th) percentile of female youths (≥100 ng/dL), which includes 8 of 949 samples (<1%) for female youths.

Discussion | These data demonstrated the following: (1) the sex-related divergence of testosterone initiated at 11 years of age on average; (2) clear and distinct distributions of serum testosterone between the sexes after 11 years of age; and (3) the distribution of testosterone within male youths was much larger in magnitude and spread than the distribution of testosterone within female youths. At the population level, serum testosterone created a clear dichotomy between male and female youths, and the presented age-adjusted distributions may be useful in evaluation of pubertal and androgenic disorders in youths.

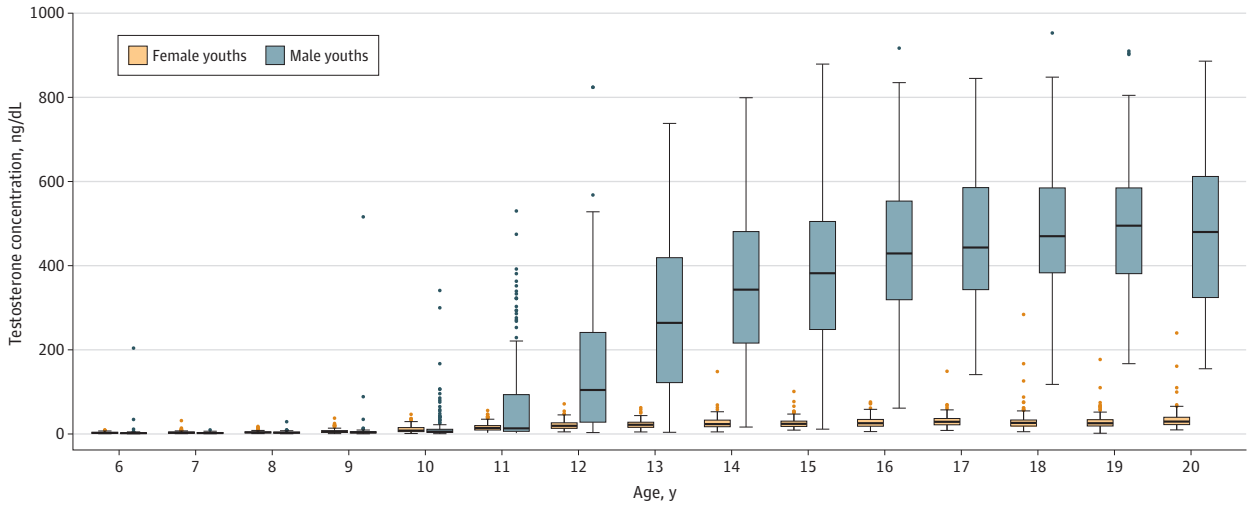
A testosterone value of 100 ng/dL distinctly separated the sexes with minimal overlap, which may have broad implications for athletic competition, as serum testosterone has been demonstrated to be strongly associated with sex differences in athletic performance.[2,3] Potential testosterone thresholds for eligibility in sports may need to be adjusted based on further information on outliers and direction of error accepted.

Table. Age-Adjusted Testosterone Concentration Percentiles

	Male youths						Female youths						
		Testosterone concentration, median, ng/dL, by percentile						Testosterone concentration, median, ng/dL, by percentile					
Age, y	No.	5th	25th	50th	75th	95th	No.	5th	25th	50th	75th	95th	*P* value[a]
6	157	0.5	1.1	1.9	2.7	4.9	166	0.8	1.6	2.4	4.0	6.5	.64
7	187	0.5	1.4	2.2	3.5	5.4	144	1.2	2.1	3.0	4.2	8.4	.16
8	171	1.2	2.0	3.0	4.4	7.6	158	1.3	2.6	3.7	5.0	9.4	.17
9	161	1.1	2.3	3.7	5.4	9.1	161	1.7	3.4	5.3	7.9	18.6	.66
10	177	1.8	3.7	5.6	11.2	76.1	168	3.0	5.5	8.0	15.2	26.2	.35
11	171	3.1	6.2	13.3	95.7	327	185	4.9	9.4	14.2	20.0	38.5	<.001
12	148	7.9	27.5	105	250	497	144	7.1	13.3	19.5	26.6	40.3	<.001
13	157	16.4	121	264	424	620	127	8.0	15.7	21.9	27.9	42.8	<.001
14	165	64.0	216	343	482	699	157	9.5	17.1	23.4	33.0	47.0	<.001
15	158	140	246	382	506	745	133	12.1	17.9	24.1	30.5	51.4	<.001
16	151	149	319	429	554	695	178	11.4	18.3	25.5	34.6	56.5	<.001
17	140	220	343	443	589	779	131	13.0	21.6	28.9	36.9	56.8	<.001
18	142	265	380	470	587	737	145	12.1	18.6	26.3	33.2	62.0	<.001
19	120	235	381	496	595	804	125	10.9	18.8	25.4	34.0	65.0	<.001
20	88	188	326	516	632	862	80	10.2	21.8	29.5	40.0	98.1	<.001

[a] Comparing male youths vs female youths at the 50th percentile.

Figure. Total Testosterone Concentrations of the US Population Aged 6 to 20 Years



The horizontal line in the middle of each box indicates the median; top and bottom borders, 75th and 25th percentiles; whiskers above and below the box, 90th and 10th percentiles; and circles beyond the whiskers, outliers beyond the 90th or 10th percentiles.

These analyses were limited by a lack of information on pubertal stages and history of androgenic disorders and by self- or parental report of male/female sex.

Jonathon W. Senefeld, PhD
Doriane Lambelet Coleman, JD
Patrick W. Johnson
Rickey E. Carter, PhD
Andrew J. Clayburn
Michael J. Joyner, MD

Author Affiliations: Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota (Senefeld, Clayburn, Joyner); Duke University School of Law, Durham, North Carolina (Lambelet Coleman); Department of Health Sciences Research, Mayo Clinic, Jacksonville, Florida (Johnson, Carter).

Corresponding Author: Jonathon W. Senefeld, PhD, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (senefeld.jonathon@mayo.edu).

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Supervision: Lambelet Coleman, Joyner.

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COMMENT & RESPONSE

Stress Ulcer Prophylaxis for ICU Patients

To the Editor The trial comparing proton pump inhibitors and histamine-2 receptor blockers for stress ulcer prophylaxis in patients in the intensive care unit (ICU) receiving mechanical ventilation[1] found that even though proton pump inhibitors were more effective in reducing the risk of gastrointestinal bleeding, there was no significant difference between proton pump inhibitors and histamine-2 receptor blockers in relation to 90-day all-cause mortality, *Clostridioides difficile* infection, or ICU and hospital lengths of stay. The study indirectly measured the effect of gastric acid suppression on the stated outcomes. The conclusion requires that all proton pump inhibitors be uniformly effective.

However, the data show great differences in the relative potency of proton pump inhibitors in terms of suppression of gastric acidity.[2] The most commonly used proton pump inhibitor in this and most other similar studies was pantoprazole,[1,3] which is the least effective proton pump inhibitor in terms of gastric acid suppression (40 mg of pantoprazole is similar in potency to approximately 9 mg of omeprazole).[3] Because of the low potency of pantoprazole, the potential benefits and harms related to acid suppression cannot be representative of all proton pump inhibitors. The concept that proton pump inhibitors are interchangeable is incorrect.

The unanswered questions regarding acid suppression in stress ulcer prophylaxis are whether the benefits of acid suppression and reduced gastrointestinal bleeding are outweighed by potential harms such as increased length of stay, morbidity (eg, infections), or all-cause mortality. In this study, weak acid suppression produced weak benefits.

It may be time to test the relative benefits and risks of highly effective acid suppression using one of the more potent proton pump inhibitors, such as esomeprazole or rabeprazole.[2] A negative result would obviate further trials, whereas a positive result would prompt the search for the minimal reliably effective dose and duration of therapy. Studies with the least potent proton pump inhibitors cannot be used to impute the risks and benefits of acid suppression for an entire class of drug.

Aylin Tansel, MD, MPH
David Y. Graham, MD

Author Affiliations: Division of Gastroenterology and Hepatology, Medical University of South Carolina, Charleston (Tansel); Department of Medicine, Baylor College of Medicine, Houston, Texas (Graham).

Corresponding Author: Aylin Tansel, MD, MPH, Division of Gastroenterology and Hepatology, Medical University of South Carolina, 30 Courtenay Dr, STB Ste 249, MSC 702, Charleston, SC 29425 (atansel@gmail.com).

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To the Editor In the study on the effect of stress ulcer prophylaxis with proton pump inhibitors vs histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation,[1] no restriction was imposed on the regimen of histamine-2 receptor blockers or proton pump inhibitors, and the dosing regimen was not reported. Ranitidine, which was the major histamine-2 receptor blocker used across the various study sites, is a small molecule that undergoes renal elimination primarily and has a short half-life and low protein binding. For ICU patients who often display augmented clearance or require continuous renal replacement therapy, whether the usual dose of ranitidine (50 mg every 6-8 hours administered intravenously or 150 mg twice daily enterally) provides an adequate serum concentration to confer protection against stress ulcer is unknown.

Moreover, being a competitive inhibitor means that the effect of gastric acid suppression correlates with serum concentration.[2] Bolus dosing of ranitidine may lead to fluctuations in serum concentration and hence fluctuation of gastric pH, which could compromise its protective effect against upper gastrointestinal tract bleeding. In contrast, proton pump inhibitors are highly protein bound and primarily undergo hepatic metabolism. They also have an additional advantage for being irreversible inhibitors of the $H^+/K+$-adenosine triphosphatase system in the parietal cells, so the effects of proton pump inhibitors last until the regeneration of new proton pumps in the parietal cells regardless of fluctuation in the serum concentration.[3]

Studies have shown ranitidine to be more effective in increasing gastric pH compared with proton pump inhibitors after single or double doses.[4] It might be worthwhile to explore the comparability of adequately dosed continuous infusion of histamine-2 receptor blockers vs proton pump inhibitors. Continuous infusion of histamine-2 receptor blockers maintains a steady serum concentration and hence a constant effect on gastric acid suppression compared with