

but also on the implications for their sexual partners. In addition to males and their parents, physicians should acknowledge that responsibility and support vaccination of males. And health insurers have a responsibility to provide reimbursement for HPV vaccination in males.

Mark A. Goldstein, M.D.

MassGeneral Hospital for Children  
Boston, MA 02114  
mgoldstein@partners.org

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## Age, Renal Tubular Phosphate Reabsorption, and Serum Phosphate Levels in Adults

**TO THE EDITOR:** A relation between age and serum phosphate levels in adults has been recognized since 1969.<sup>1</sup> We used data from the Gubbio Population Study to analyze serum phosphate levels and renal phosphate handling in relation to age in 2107 men and 2560 women (age range, 18 to 97 years).<sup>2</sup> Information concerning medical history and diet was collected by questionnaire. Overnight urine samples were obtained for analysis of albuminuria and markers of protein and salt intake. Early-morning samples of blood and urine were collected under fasting conditions to examine renal tubular function. Renal tubular phosphate handling was assessed as the ratio of the maximum rate of tubular phosphate reabsorption to the glomerular filtration rate (TmP:GFR).<sup>3</sup> Laboratory analyses were performed with the use of an autoanalyzer, with an intraassay error of less than 5% for serum variables and of less than 10% for urinary variables.

Among men, serum phosphate levels declined with age almost linearly (Fig. 1, top graph). Serum phosphate levels in women under the age of 45 years overlapped with those in men and then increased between the ages of 45 and 54 years before progressively declining from 55 years. The age-associated decline in serum phosphate levels was not associated with hypocalcemia and hypocalciuria, nor with indexes of protein and salt intake (not shown). The increase in serum phosphate levels in women between the ages of 45 and 54 years was probably not related to age itself, but rather to menstrual status, since serum phosphate levels were higher in 97 menopausal women under 50 years of age (mean age, 44.8 years) than in 67 menstruating women 50 years of age or older (mean age, 51.6 years) (3.61 mg per deciliter [1.17 mmol per liter] and 3.45 mg per decili-

ter [1.11 mmol per liter], respectively;  $P=0.04$ ). In both sexes, the decrease in the TmP:GFR ratio with age was similar to that in serum phosphate levels (Fig. 1, bottom graph).

Thus, in adults, serum phosphate levels decline with age, except for a transient increase during the perimenopausal period in women.<sup>4</sup> The age-associated decline in serum phosphate levels reflects changes in tubular phosphate reabsorption, which, in turn, might be explained by age-dependent changes in tubular phosphate handling or in its hormonal modulators (e.g., parathyroid hormone, phosphatonins, and growth hormone). The lack of association between the decrease in serum phosphate levels with hypocalcemia or hypocalciuria does not support a role for hyperparathyroidism caused by vitamin D deficiency. A possible mechanism might be the age-dependent decrease in growth-factor secretion and related stimulation of phosphate reabsorption.<sup>5</sup> The practical implication is that phosphate-depleting disorders might induce hypophosphatemia more readily in older persons because the tubular capacity for phosphate reabsorption and the level of serum phosphate before the development of such disorders are already diminished. For parallel reasons, disorders causing increases in serum phosphate levels should more readily induce hyperphosphatemia in younger persons.

Massimo Cirillo, M.D.

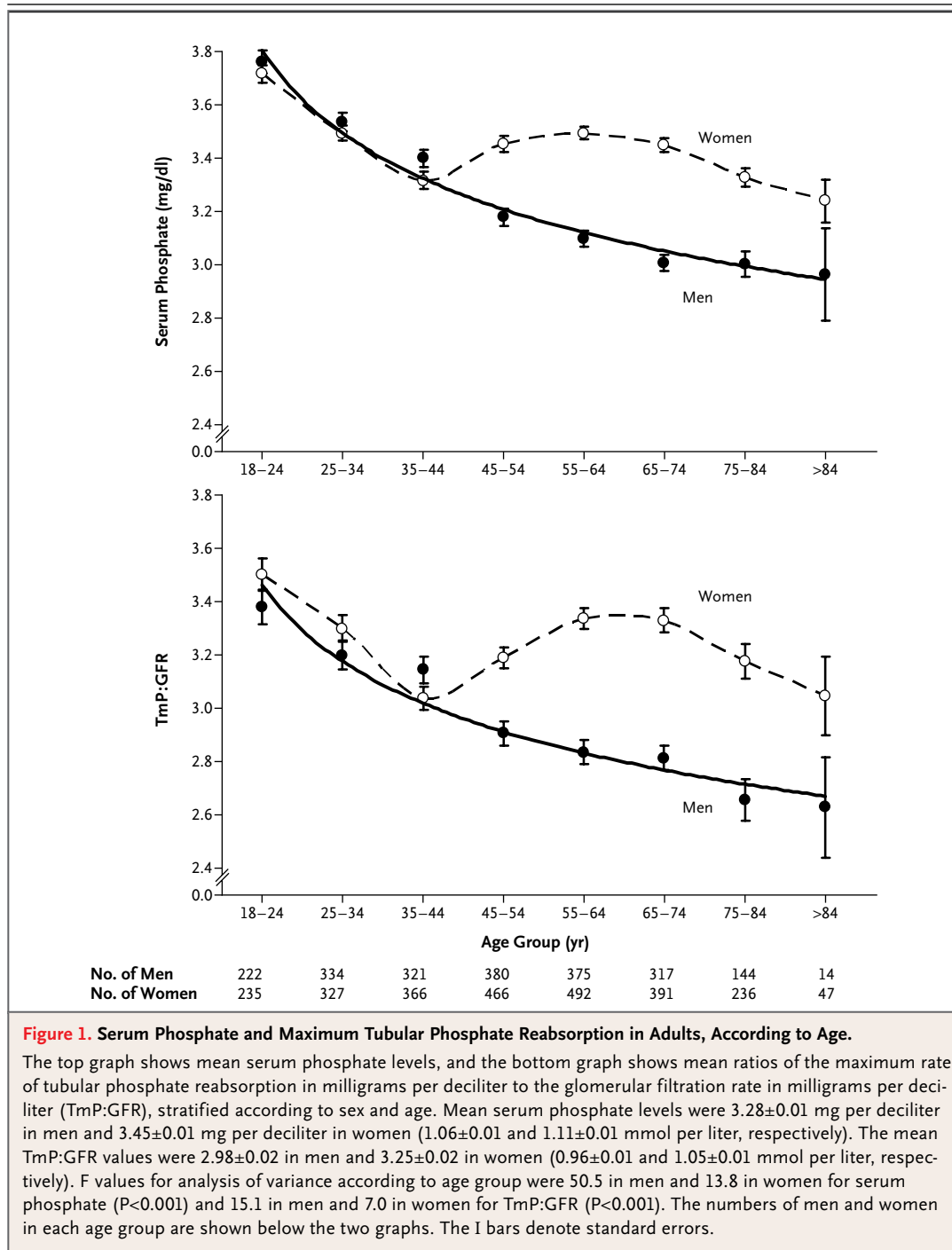
Second University of Naples  
80131 Naples, Italy  
massimo.cirillo@unina2.it

Carolina Ciacci, M.D.

Federico II University  
80131 Naples, Italy

Natale G. De Santo, M.D.

Second University of Naples  
80131 Naples, Italy



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## The Hepatopulmonary Syndrome

**TO THE EDITOR:** In their review of the hepatopulmonary syndrome, Rodríguez-Roisin and Krowka (May 29 issue)<sup>1</sup> provide a pathophysiological explanation of the symptoms of this syndrome, but they downplay the importance of the history and physical examination in making the diagnosis, stating that there are no signs, symptoms, or hallmarks of the hepatopulmonary syndrome on physical examination. We disagree. Platypnea (the opposite of orthopnea) not only is a common symptom, but also is almost diagnostic in itself in a patient with cirrhosis. Many patients with the hepatopulmonary syndrome also have cyanosis and clubbing, an unusual combination in cirrhosis.

We believe that the combination of known cirrhosis, platypnea, and orthodeoxia that is correctable with oxygen supplementation is absolutely diagnostic. The clinical examination and simple laboratory tests have a critical role in making this diagnosis. Thus, we question the need for expensive scans, since intracardiac shunting can be ruled out if the hypoxemia is responsive to oxygen.

Recognition of platypnea is a practical issue for care. Health care workers almost instinctively try to make patients with dyspnea sit up, but they should learn to let these persons lie down.

Cameron N. Ghent, M.D.

Mark A. Levstik, M.D.

Paul J. Marotta, M.D.

London Health Sciences Centre  
London, ON N6A 3R9, Canada  
ghent1@on.aibn.com

1. Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome — a liver-induced lung vascular disorder. *N Engl J Med* 2008;358:2378-87.

**TO THE EDITOR:** Rodríguez-Roisin and Krowka mention that an alveolar–arterial oxygen gradient of 15 mm Hg or more is one of the diagnostic criteria for defective oxygenation in the hepatopulmonary syndrome. In some earlier studies, the threshold of 20 mm Hg was used.<sup>1,2</sup> Since the

gradient increases with age, it may be more accurate to compare patients' gradients with those that are corrected for their age (the corrected alveolar–arterial oxygen gradient =  $10 + 0.43 \times [\text{age} - 20]$ ).<sup>3</sup> In a healthy 40-year-old person, the corrected alveolar–arterial oxygen gradient is 18.6 mm Hg, which is already above the lower threshold. In our analysis involving 96 patients on the waiting list for liver transplantation, 40 of the patients (42%) had an alveolar–arterial oxygen gradient above 20 mm Hg.<sup>4</sup> If the lower threshold were used, the number of patients would increase to 58 (60%). The hepatopulmonary syndrome was diagnosed in 23 patients (24%), but with a lower threshold, it would have been diagnosed in 33 patients (34%). Therefore, the use of a lower threshold for the alveolar–arterial oxygen gradient, without taking age into consideration, may lead to an overestimation of the incidence of the hepatopulmonary syndrome.

Cezary Szmigielski, M.D., Ph.D.

Rafal Krenke, M.D., Ph.D.

Grzegorz Styczynski, M.D., Ph.D.

Medical University of Warsaw  
02-097 Warsaw, Poland  
grzegorz.styczynski@amwaw.edu.pl

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**TO THE EDITOR:** Rodríguez-Roisin and Krowka state that contrast-enhanced transthoracic echocardiography cannot distinguish discrete arteriovenous malformations from intracardiac shunt. This technique can, in fact, discern three levels of shunting: atrial septal defect, ventricular septal defect with Eisenmenger's syndrome, and pulmonary arteriovenous malformations.<sup>1</sup> In the pres-