

Editorial: Clinical Relevance of Racial and Ethnic Differences in Sex Steroids

Racial/ethnic variations in physiological responses, enzyme activities, drug metabolism, and prevalence of diseases are well known. Such differences may be ascribed to genetic polymorphisms, environmental modifications, tissue receptivity and responsiveness, and circulating levels of hormones. Racial/ethnic differences in responsiveness to sex steroids have been a particularly rich area for investigation and have been associated with significant differences in the prevalence of risk factors for obesity and diabetes, osteoporosis, and prostate cancer in men as described by Rohrmann *et al.* (1) in this issue of the *Journal of Clinical Endocrinology and Metabolism*. These investigators reported differences in androgens and estrogen levels in men over the age of 20 yr in a population that is representative of the United States and differed from other earlier studies by the large number of subjects studied spanning a wide age range across the nation.

Racial/Ethnic Differences in Serum Androgens

Prior small studies have shown either no difference or slightly lower serum testosterone (T) and its 5 α -reduced metabolites in white *vs.* black men. Others have reported that the levels of 5 α -reduced androgens such as 5 α -dihydrotestosterone (DHT) or 5 α -androstenediol and its glucuronide (5 α -androstenediol G) levels in Asian men were lower compared with white or black men (see references in Refs. 1 and 2). In 2006 Litman *et al.* (2) published data in this *Journal* on serum androgen levels in 1899 men from the multiracial, multiethnic Boston Area Community Health (BACH) study. Their study population included a wide racial/ethnic distribution with more than 500 white, black, and Hispanic men belonging to each of the three largest racial/ethnic groups in the U.S. population. All samples were collected less than 4 h after waking, presumably in the morning. Adjusting for body mass index, cigarette and alcohol consumption, and other comorbid conditions that are known to affect serum androgens, they found no racial/ethnic differences in serum testosterone, bioavailable testosterone, dehydroepiandrosterone sulfate, and SHBG levels, but blacks had significantly higher serum DHT levels and DHT to T ratios than white and Hispanic men. These data from a population-based study supported prior suggestions that peripheral 5 α -reductase activity may be higher in black than other racial groups (3). Notably in this report, the authors measured the active metabolite DHT and not the inactive metabolite 5 α -androstenediol G.

Abbreviations: BACH, Boston Area Community Health; DHT, dihydrotestosterone; ER, estrogen receptor; NHANES III, National Center for Health Statistics III; T, testosterone.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

In the current issue of the *Journal*, Rohrmann *et al.* (1) measured not only morning serum androgens but also serum estradiol in a subset of men participating in the National Center for Health Statistics III (NHANES III) conducted in 1988–1994. After excluding other racial/ethnic groups, this subset of 1413 men consisted of 674 non-Hispanic whites, 363 non-Hispanic blacks, and 376 Mexican-Americans. Similar to the BACH study, the sex steroids were measured by the same electrochemiluminescence immunoassay system, whereas 5 α -reduced androgens were measured by a RIA. Several recent studies reported problems of these automated platform immunoassay systems when compared with methods based on mass spectrometry. These problems include accuracy in measuring serum T levels in the low range in hypogonadal men, women, and children. Nevertheless, these assay systems are reasonably accurate for quantitation of serum T in the adult male reference range (4–6) and may be acceptable in epidemiological surveys for adult men. Adjusting for age, smoking habits, alcohol consumption, physical activity, and adiposity (by body mass index or percent body fat), the investigators reported similar serum T levels in the three racial/ethnic groups. Mexican-Americans had the highest percent body fat, and after adjusting for percent body fat, Mexican-American men had higher serum T levels than the other two groups. SHBG levels were higher in blacks and lowest in Mexican-Americans; however, after adjusting for percent fat, the SHBG concentration was not significantly different among groups. These observations demonstrate the complicated interrelationships among T, obesity, adipocytes, adipokinins, and insulin sensitivity of the tissues. The authors conclude that serum T concentrations do not differ between white and black men. In contrast to earlier studies in which serum 5 α -reduced metabolites of T, DHT, and 5 α -androstenediol G were significantly higher in blacks than other racial groups (2, 3, 7), samples obtained from the younger men in the NHANES III study showed that white men had higher 5 α -androstenediol G levels, compared with blacks and Mexican-Americans. Increased 5 α -reductase activity as demonstrated by higher 5 α -reduced products had been suggested as a cause of the higher prevalence of prostate cancer in black men. 5 α -androstenediol G is not active in tissues and is converted from DHT by a pair of 3 α -hydroxysteroid dehydrogenases. The higher 5 α -androstenediol G found in white men in this study does not negate the importance of active androgens such as DHT and increased 5 α -reductase activity as a risk factor for development of prostate cancer.

Racial/Ethnic Differences in Serum Estradiol

Racial /ethnic variations in serum estradiol concentrations have not been reported in most population based studies. In this study by Rohrmann *et al.* (1), serum estradiol levels were

significantly different among the groups studied with blacks having significantly higher levels than whites or Mexican-Americans. The mean differences are relatively small (less than 6 pg/ml) but represent about 10% of the normal estradiol range found in men in that study. In a study of older men, serum concentrations of estradiol and free estradiol showed no racial/ethnic differences (8). Serum levels of estradiol are typically measured by immunoassay methods designed for measurement of higher levels in premenopausal women rather than men or postmenopausal women. Despite this fact, the Rohrmann study (1) did verify small coefficients of variation for estradiol at typical levels in men as well as levels found in premenopausal women. Careful studies on the accuracy and precision of low estradiol levels in postmenopausal women, children, and men measured by platform immunoassays, compared with mass spectrometry methods (9), have not been reported. Higher estradiol levels have been suggested as a possible causal factor for the higher bone mass (10) and increased risk of prostate cancer in black men (11). Until more sensitive estradiol assays are developed and validated for men, the value of serum estradiol in relation to racial/ethnic disease disparity has to be interpreted with caution.

Other Factors Influencing Serum Levels of Androgens or Estrogens

Dietary intake affects serum sex hormones levels (12–16). A low-fat diet decreases serum and urinary androgens, testosterone production rates, and lowers serum estradiol in healthy men. Thus, whereas the authors did consider smoking habit and alcohol consumption in their analyses, one of the most important environmental factors, nutrition, and dietary intake was not included in the covariates in the NHANES III study. Moreover, serum measurements of androgens are only a partial reflection of the production rates of these hormones in men. Despite reporting minimal significant differences in serum T concentrations, racial differences in testosterone production rates have been reported between Asian and white men when Asian men were studied in their country of origin. When the production rates are measured in acculturated Asians living in the United States, such differences disappeared (17, 18). Thus, the racial/ethnic differences reported in studies conducted in the United States such as the NHANES and BACH (1, 2) cannot be generalized to populations studied in their native country of origin.

Consideration of Hormone Actions at Target Tissues

With the understanding of the molecular mechanisms of steroid hormone action, it is clear that measuring serum hormones as indicators or predictors of physiological responses or disease processes may be an oversimplified assessment. First, the importance of the concentration of these sex hormones in the target organs cannot be ignored. A recent study reported no difference in prostatic T or DHT levels or DHT to T ratios between white and black men (19), suggesting that 5 α -reductase activity may not be higher in black men and cannot account for the higher prevalence of prostate cancer. Second, the conversion of T to DHT is irre-

versible, but the shuttle between DHT and the 5 α -androstanediols depends on the activity of the oxidase *vs.* reductase of the 3 α -hydroxysteroid dehydrogenases. A high oxidase activity will convert 5 α -androstanediol back to DHT, a potent ligand for the androgen receptor. Conversely, if the reductase activity is high, DHT will be converted to 5 α -androstanediol, a ligand with low affinity for the androgen receptor (19–21). There are also genetic polymorphisms of 5 α -reductase and the aromatase enzymes that have not been comprehensively studied. Third, the number of steroid receptors in the target tissues is in excess but the amount and specificity of coactivators and corepressors are different in different tissues. The variability of these molecular controllers of androgen and estrogen actions among racial/ethnic groups is unknown. Fourth, the length of CAG repeats on the first exon of the androgen receptor is known to be related to androgen receptor transcription activity and action. The length of the CAG repeats have recently been shown to be of clinical significance in relation to phenotypic features of androgen deficiency, bone mineral density, and lipid profiles (22–24). Ethnic variation in CAG repeats have been reported with blacks having the shortest and Asians the longest CAG repeat lengths (25). Fifth, the estrogen receptors (ER)- α and - β have tissue specificity, expression and activity. ER α is important for the actions of estrogens in bone, whereas ER β may be important in prostate growth and development (26–28).

In conclusion, many factors other than serum hormone levels influence the actions of androgen and estrogen actions in men. To understand fully the impact of racial/ethnic differences in sex hormones and their contribution to human health and disease, hormone metabolism, ligand interaction with receptor, receptor action, and enzyme and receptor gene polymorphisms must also be considered in future studies.

Christina Wang, Peter Christenson, and Ronald Swerdloff
Division of Endocrinology
Department of Medicine
Harbor-University of California
Los Angeles Medical Center
Los Angeles Biomedical Research Institute
Torrance, California 90509

Acknowledgments

Received May 15, 2007. Accepted May 16, 2007.

Address all correspondence and requests for reprints to: Christina Wang, M.D., General Clinical Research Center, Box 16, Harbor-UCLA Medical Center, 1000 Carson Street, Torrance, California 90509. E-mail: wang@labiomed.org.

References

1. Rohrmann S, Nelson WG, Rifai N, Brown TR, Dobs A, Kanarek N, Yager JD, Platz EA 2007 Serum estrogen, but not testosterone levels, differ between black and white men in a nationally representative sample of Americans. *J Clin Endocrinol Metab* 92:2519–2525
2. Litman HJ, Bhasin S, Link CL, Araujo AB, McKinlay JB 2006 Serum androgen levels in black, Hispanic, and white men. *J Clin Endocrinol Metab* 91:4326–4334
3. Ross RK, Bernstein L, Lobo RA, Shimizu H, Stanczyk FZ, Pike MC, Henderson BE 1992 5 α -reductase activity and risk of prostate cancer among Japanese and U.S. white and black males. *Lancet* 339:887–889
4. Sikaris K, McLachlan RI, Kazlauskas R, de Kretser D, Holden CA, Handelsman DJ 2005 Reproductive hormone reference intervals for healthy fertile

- young men: evaluation of automated platform assays. *J Clin Endocrinol Metab* 90:5928–5936
5. **Taieb J, Mathian B, Millot F, Patricot MC, Mathieu E, Queyrel N, Lacroix I, Somma-Delpero C, Boudou P** 2003 Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. *Clin Chem* 49:1381–1395
 6. **Wang C, Catlin DH, Demers LM, Starcevic B, Swerdloff RS** 2004 Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. *J Clin Endocrinol Metab* 89:534–543
 7. **Wu AH, Whittemore AS, Kolonel LN, John EM, Gallagher RP, West DW, Hankin J, The CZ, Dreon DM, Paffenbarger Jr RS** 1995 Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. *Cancer Epidemiol Biomarkers Prev* 4:735–741
 8. **Orwoll E, Lambert LC, Marshall LM, Phipps K, Blank J, Barrett-Connor E, Cauley J, Ensrud K, Cummings S** 2006 Testosterone and estradiol among older men. *J Clin Endocrinol Metab* 91:1336–1344
 9. **Nelson RE, Grebe SK, OKane DJ, Singh RJ** 2004 Liquid chromatography-tandem mass spectrometry assay for simultaneous measurement of estradiol and estrone in human plasma. *Clin Chem* 50:373–384
 10. **Khosla S, Bilezikian JP** 2003 The role of estrogens in men and androgens in women. *Endocrinol Metab Clin North Am* 32:195–218
 11. **Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ** 1996 Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* 88:1118–1126
 12. **Dorgan JF, Judd JT, Longcope C, Brown C, Schatzkin A, Clevidence BA, Campbell WS, Nair PP, Franz C, Kahle L, Taylor PR** 1996 Effects of dietary fat and fiber on plasma and urine androgens and estrogens in men: a controlled feeding study. *Am J Clin Nutr* 64:850–855
 13. **Hamalainen E, Adlercreutz H, Puska P, Pietinen P** 1984 Diet and serum sex hormones in healthy men. *J Steroid Biochem* 20:459–464
 14. **Heber D, Ashley JM, Leaf DA, Barnard RJ** 1991 Reduction of serum estradiol in postmenopausal women given free access to low-fat high-carbohydrate diet. *Nutrition* 7:137–139
 15. **Key TJ, Roe L, Thorogood M, Moore JW, Clark GM, Wang DY** 1990 Testosterone, sex hormone-binding globulin, calculated free testosterone, and oestradiol in male vegans and omnivores. *Br J Nutr* 64:111–119
 16. **Wang C, Catlin DH, Starcevic B, Heber D, Ambler C, Berman N, Lucas G, Leung A, Schramm K, Lee PW, Hull L, Swerdloff RS** 2005 Low-fat high-fiber diet decreased serum and urine androgens in men. *J Clin Endocrinol Metab* 90:3550–3559
 17. **Santner SJ, Albertson B, Zhang GY, Zhang GH, Santulli M, Wang C, Demers LM, Shackleton C, Santen RJ** 1998 Comparative rates of androgen production and metabolism in Caucasian and Chinese subjects. *J Clin Endocrinol Metab* 83:2104–2109
 18. **Wang C, Catlin DH, Starcevic B, Leung A, DiStefano E, Lucas G, Hull L, Swerdloff RS** 2004 Testosterone metabolic clearance and production rates determined by stable isotope dilution/tandem mass spectrometry in normal men: influence of ethnicity and age. *J Clin Endocrinol Metab* 89:2936–2941
 19. **Marks LS, Hess DL, Dorey FJ, Macairan ML** 2006 Prostatic tissue testosterone and dihydrotestosterone in African-American and white men. *Urology* 68:337–341
 20. **Bauman DR, Steckelbroeck S, Williams MV, Peehl DM, Penning TM** 2006 Identification of the major oxidative 3α -hydroxysteroid dehydrogenase in human prostate that converts 5α -androstane- $3\alpha,17\beta$ -diol to 5α -dihydrotestosterone: a potential therapeutic target for androgen-dependent disease. *Mol Endocrinol* 20:444–458
 21. **Penning TM, Bauman DR, Jin Y, Rizner TL** 2007 Identification of the molecular switch that regulates access of 5α -DHT to the androgen receptor. *Mol Cell Endocrinol* 265–266:77–82
 22. **Zitzmann M, Nieschlag E** 2003 The CAG repeat polymorphism within the androgen receptor gene and maleness. *Int J Androl* 26:76–83
 23. **Zitzmann M, Gromoll J, von Eckardstein A, Nieschlag E** 2003 The CAG repeat polymorphism in the androgen receptor gene modulates body fat mass and serum concentrations of leptin and insulin in men. *Diabetologia* 46:31–39
 24. **Zitzmann M, Depenbusch M, Gromoll J, Nieschlag E** 2004 X-chromosome inactivation patterns and androgen receptor functionality influence phenotype and social characteristics as well as pharmacogenetics of testosterone therapy in Klinefelter patients. *J Clin Endocrinol Metab* 89:6208–6217
 25. **Irvine RA, Yu MC, Ross RK, Coetzee GA** 1995 The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. *Cancer Res* 55:1937–1940
 26. **Gennari L, De Paola V, Merlotti D, Martini G, Nuti R** 2007 Steroid hormone receptor gene polymorphisms and osteoporosis: a pharmacogenomic review. *Expert Opin Pharmacother* 8:537–553
 27. **Carpenter KD, Korach KS** 2006 Potential biological functions emerging from the different estrogen receptors. *Ann NY Acad Sci* 1092:361–373
 28. **Ho SM, Leung YK, Chung I** 2006 Estrogens and antiestrogens as etiological factors and therapeutics for prostate cancer. *Ann NY Acad Sci* 1089:177–193

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.