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 5α -reduced metabolites in white vs. black men. Others have reported that the levels of 5α -reduced and rogens such as 5α -dihydrotestosterone (DHT) or 5α -androstanediol and its glucuronide (5-androstanediol 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 5α -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 5α -androstanediol G.

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 5α -reduced and rogens 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 5α -reduced metabolites of T, DHT, and 5α androstanediol 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-androstanediol G levels, compared with blacks and Mexican-Americans. Increased 5α -reductase activity as demonstrated by higher 5α -reduced products had been suggested as a cause of the higher prevalence of prostate cancer in black men. 5 α -androstanediol G is not active in tissues and is converted from DHT by a pair of 3α -hydroxysteroid dehydrogenases. The higher 5α -androstanediol G found in white men in this study does not negate the importance of active androgens such as DHT and increased 5α -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

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

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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 spectometry 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 NI-HANES 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 5α -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 5α -androstanediols depends on the activity of the oxidase vs. reductase of the 3α -hydroxysteroid dehydrogenases. A high oxidase activity will convert 5α -and rost and rost to DHT, a potent ligand for the androgen receptor. Conversely, if the reductase activity is high, DHT will be converted to 5α androstanediol, a ligand with low affinity for the androgen receptor (19–21). There are also genetic polymorphisms of 5α -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 $ER\beta$ 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.

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