

Sex Differences in Diabetes, Heart Disease, and Beyond

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The Rancho Bernardo Study (RBS) [1] has had an important and lasting contribution to the literature addressing sex differences in cardiovascular disease and, in particular, how diabetes modifies these risks. It began as 1 of the 12 LRC (Lipid Research Clinic) prevalence study sites and was a unique cohort study in which 82% of a target population was enrolled, resulting in low selection bias. RBS was among the first cohort studies to focus on sex differences in the association of diabetes and cardiovascular disease and has had lasting effects on how we diagnose and perhaps manage women with diabetes. It was among the few studies at the time that focused on older persons; thus, it broke new ground in geriatric epidemiology as well.

RBS was the first cohort study to perform oral glucose tolerance tests to assess insulin resistance and diabetes. The study documented important differences between men and women in fasting glucose and impaired glucose tolerance, including a diabetes detection bias in women because a higher proportion of women than men had diabetes diagnosed only after an oral glucose tolerance test. In addition to finding a source of underdetection of diabetes in women, the RBS also documented a linear relationship in men with fasting glucose and heart disease mortality risk, but in women a threshold effect was found; an association between fasting glucose and coronary heart disease (CHD) mortality existed only after the fasting glucose level reached 100 mg/dl.

The RBS study also showed CHD mortality differences in men and women, thereby showing that the presence of diabetes eliminated cardioprotection in women. In their *JAMA* publication [2] on this topic that examined 14-year risk of fatal ischemic heart disease, the relative hazard associated with diabetes after adjustment for age and other risk factors was 1.9 in men and 3.3 in women. The RBS also measured endogenous sex hormones using the most sensitive and specific assays available at the time for total and bioavailable testosterone and estradiol. Although they did not find a direct relationship between sex hormones and CHD, they found evidence that perhaps the effect of changing hormones, particularly in a post-menopausal state in women was mediated through impaired glucose tolerance and diabetes. The relationships found were complex. The risk of diabetes was increased in men if their bioavailable testosterone was in the lowest quartile and in women if their bioavailable testosterone was in the highest quartile.

In addition, low levels of total testosterone were significantly associated with incident CHD events in the RBS women. Therefore, both low and high testosterone were associated with higher risk of CHD events in women, high bioavailable testosterone was associated with obesity,

diabetes, and metabolic syndrome components, whereas low total testosterone may have a different mechanism.

RBS is a very important cohort study in delineating differences in men and women in how diabetes modulates risk for CHD. It helped close gaps in knowledge of how diabetes eradicates cardioprotection in women. Observational studies, including the RBS, have been invaluable for testing hypotheses among “real women seen in practice,” who are often more representative than those selected for clinical trials, often representing a wider socioeconomic and ethnic distribution than that used in clinical trials. Moreover, such studies will include those who may be excluded from clinical trials, such as women with severe menopausal symptoms, who are typically excluded from clinical trials [3].

Whereas we have focused on the contributions the RBS has made in the area of sex differences in diabetes and cardiovascular disease, the study has made countless other contributions that are too great to mention here. As a sampler, most recently, the predictive role of biomarkers such as troponin and N-terminal pro-B-type natriuretic peptide have been studied in relation to dementia [4] and mortality [5], and factors such as abdominal obesity and kidney function have been examined in relation to progression of atherosclerosis measured by novel factors such as coronary calcification [6,7].

In 2009, in her 2009 Distinguished Scientist Lecture awarded by the American Heart Association, Dr. Barrett-Connor described how her simple addition of fasting glucose and information about diabetes to the LRC study in Rancho Bernardo shaped what was to become among the most pre-eminent studies examining sex differences in coronary heart disease and diabetes that would ultimately contribute greatly to awareness of the problems of diabetes and heart disease in women [8]. With the many investigators who have participated and continue to participate in exploring new hypotheses in the RBS, the future of the study, now in its fifth decade, continues to hold great promise.

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