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Is Estradiol a Biomarker of Type 2 Diabetes Risk in Postmenopausal Women?

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COMMENTARY

Cross-sectional studies have suggested an association between the main female hormone, 17β-estradiol (E2), and the risk of type 2 diabetes (T2D) in postmenopausal women (1,2). Even prospective studies have found that among postmenopausal women not using hormone therapy, higher circulating levels of total and free E2 were strongly and prospectively associated with increased long-term risk of T2D, independently of adiposity or insulin resistance (3,4).

In this issue of *Diabetes*, Muka et al. (5) examine the association among sex hormone–binding globulin (SHBG)—a protein that binds and carries E2 in the blood and limits its bioavailability—sex hormones, and T2D risk in a large population-based sample of healthy postmenopausal women who were free of T2D at baseline, with a median follow-up of 11 years. They report that lower levels of SHBG (which translate into higher bioavailable E2) and higher concentrations of total E2 are associated with increased risk of T2D, independently of established risk factors, including BMI and insulin resistance. In contrast, they observed no association between testosterone and T2D risk. Their findings are reinforced by a systematic meta-analysis of 13 studies with 14,902 participants who included 1,912 case subjects with T2D, confirming that lower SHBG and increased total E2 are robust risk markers of T2D in postmenopausal women.

Of course, one limitation of this study is the lack of reliability of the immuno-based steroid assays used. Mass spectrometry is clearly the most reliable technology available for steroid assays, especially in postmenopausal women with low E2 levels (6). However, the generalizability of the finding makes it unlikely that the results were an assay artifact.

This study raises new questions regarding the pathogenesis of T2D in women. The obvious first one is whether circulating E2 is instrumental in predisposing postmenopausal women to T2D. The answer is probably no, as large randomized controlled trials have consistently shown decreased T2D incidence in women assigned to menopausal treatment with estrogens (7–9). In addition, the accumulation of decades of mechanistic studies in preclinical models conclusively demonstrated that therapeutic doses of E2 and other estrogens improve glucose homeostasis (10). A false perception exists that estrogens impair carbohydrate metabolism. This belief stems from old studies using high doses of oral contraceptives, which produced glucose intolerance in women (11). Indeed, no beneficial effect of estrogens on glucose homeostasis is observed outside a narrow therapeutic or physiological window (12,13), and high doses of oral estrogens or high serum concentrations of endogenous E2, such as are seen during pregnancy or in transsexuals, produce insulin resistance (10). This was not the case in the current study, which focused on untreated postmenopausal women with low circulating E2 concentrations. Furthermore, no association between E2 and T2D has been found in premenopausal women, who exhibit higher circulating E2 concentrations. Finally, and consistent with a beneficial role for endogenous E2 in glucose homeostasis in women, a prospective cohort study with a follow-up of 11 years concluded that early menopause—leading to more prolonged E2 deficiency—is associated with a greater risk of T2D (14).

The remaining question is whether increased E2 is a new indirect biomarker of a pathological process predisposing postmenopausal women to T2D. A fundamental concept in the interpretation of relationships between circulating E2 levels and disease in epidemiological studies is that, unlike in premenopausal women, E2 does not function as a circulating hormone in postmenopausal women because its ovarian production is suppressed. Rather, in postmenopausal women E2 is produced locally in extraovarian tissues such as breast, brain, adipose

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tissue, muscle, and bone from circulating sources of adrenal androgens, mainly dehydroepiandrosterone, which is converted to androstenedione, which in turn undergoes aromatization to estrone (E1) (15). In fact, nearly the only means of E2 production after menopause is E1 formation. E2 is produced locally in extraovarian tissues and acts locally as a paracrine and intracrine factor (16). E2 is also inactivated in the same cells where its synthesis takes place before being released as inactive (Fig. 1). Therefore, it is difficult to see how one can readily equate circulating levels of E2 to the concentrations that are present in target cells and thus to E2 action in those cells. In postmenopausal women, circulating E2 is not the driver of estrogen action; there is little physiological relationship between serum E2 concentrations (free or total) and cellular estrogen output. The consequence of this biological paradigm is that the association between higher circulating E2 and T2D in postmenopausal women is unlikely to reflect causality between increased E2 signaling and the development of T2D. Rather, E2 concentrations may reflect a leakage from increased local E2 biosynthesis or decreased E2 elimination from extraovarian sites as a compensatory adaptive mechanism (Fig. 1).

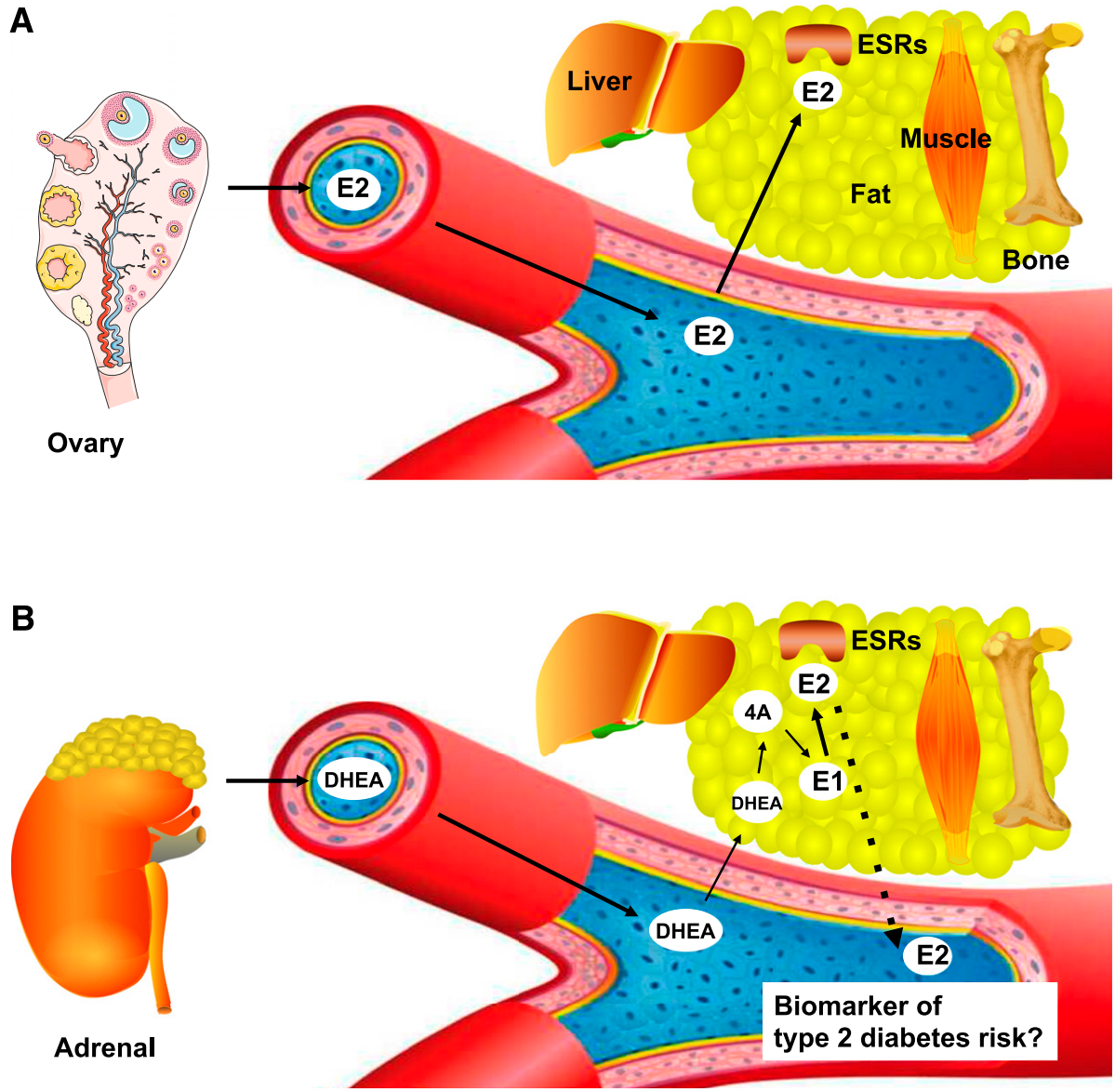

Figure 1—Schematic representation of the origin of E2 in women. *A:* In premenopausal women, E2 is produced by the ovary and acts as a circulating hormone. Therefore, circulating E2 is the driver of E2 action in peripheral tissues. *B:* In postmenopausal women, ovarian E2 production is abolished. E2 is synthesized locally in extraovarian tissues from an adrenal source of dehydroepiandrosterone (DHEA) and androstenedione (4A). The local precursor of E2 is E1 after aromatization from 4A. E2 is synthesized, acts, and is metabolized locally, and therefore circulating E2 is not a driver of E2 action. E2 could be a indirect biomarker of T2D risk in postmenopausal women. ESR, estrogen receptor.

Because E2 favors metabolic homeostasis (10), high E2 concentrations may also reflect a form of estrogen resistance as a biomarker for the pathological process that predisposes to T2D. In fact, there is an elevation in circulating E2 in clinical situations of estrogen resistance (17), just as there is an increase in circulating insulin in insulin resistance. Current standard measurement of serum E2 levels poorly reflects cellular E2 concentrations, biosynthesis, catabolism, and elimination. Studies are needed to develop novels assays that will provide accurate measures of cellular estrogen biosynthesis and sensitivity and that will be informative in epidemiological studies associating E2 with chronic diseases.

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