Alteration of insulin sensitivity by sex hormones during the menstrual cycle

It is well established that insulin resistance and impaired insulin secretion are two major prerequisites in the development of type 2 diabetes. Given the growing global epidemic of obesity, it is expected that the number of people with insulin resistance will expand exponentially. To maintain glucose homeostasis, insulin action, reflected by insulin sensitivity measured *in vivo*, is regulated by a well organized, but complicated, hierarchical mechanism. In this regard, many studies have shown that environmental factors might have a great influence on insulin sensitivity and these issues are further complicated when interaction between genes and the environment is taken into consideration[1].

Additionally, a number of studies have shown that the degree of insulin sensitivity is also influenced by many biological factors, in particular, hormone alterations, which might account for the diurnal changes of insulin sensitivity in normal and diabetic individuals or involve the occurrence of the dawn phenomenon. Extensive studies were carried out to determine how sex hormones harness insulin sensitivity or predispose humans to the development of diabetes[2]. In a recent article, obtained from The BioCycle Study, Yeung *et al.*[3] reported that, in a group of relatively healthy premenopausal women, insulin resistance, expressed by homeostasis model assessment for insulin resistance (HOMA-IR), changed slightly, but significantly, during the normal menstrual cycle. Specifically, HOMA-IR rose from 1.35 in the midfollicular phase to 1.59 (with a magnitude of increase of 17.8%) during the early luteal phase and decreased to 1.55 (by 14.8%) in the late luteal phase. These changes were positively associated with levels of estradiol and progesterone, but negatively associated with follicle stimulating hormone (FSH) and sex hormone binding globin (SHBG). In addition to findings from previous studies showing the impact of menstrual cycle variability on insulin sensitivity, this BioCycle Study enrolled the greatest number of healthy women (n = 257) and had the most frequent visits (eight visits during a cycle period), designed to monitor women at peak fertility. Thus, the findings from this study, which has overcome the shortages of previous inconsistent reports, should be reliable. However, concerns were raised as to how accurate HOMA-IR is in capturing the degree of insulin resistance[4]. It will be of great value, although difficult, to use more precise measures of insulin resistance, such as the glucose clamp study, in those studied participants.

The physiological effects of circulating estradiol and progesterone levels on insulin resistance in premenopausal women might be distinct from pharmacological applications in postmenopausal women. The present author and others have shown that oral contraceptive pills might decrease insulin resistance and increase cardiovascular risk in young women, whereas transdermal use of estrogen might prevent these untoward effects[5]. It is postulated that estrogen-induced increases in glucocorticoid activity might account for these unwanted effects. In addition, the influence of long-term use of estrogen might be different from that of short-term use, with the former preserving insulin secretion and maintaining glucose homeostasis.

In this article, the finding that alterations of HOMA-IR primarily reflected changes in fasting insulin levels and not fasting glucose levels[3] is not unexpected, given the tight regulation of insulin secretion during alterations of insulin sensitivity in healthy individuals. One of the limitations of the study by Yeung *et al.*[3] was the lack of measurement of testosterone, which was reported to be associated with insulin resistance, although the use of SHBG in this study might partially reflect the bioavailability and action of testosterone. In addition, the association between HOMA-IR and SHBG became insignificant after adjustment of body mass index (BMI), showing that these associations might be mediated through adiposity in the studied population.

Finally, although the alterations of insulin resistance during the menstrual cycle might be considered as minor, caution should be taken when recruiting premenopausal women to serve as study volunteers, especially when comparing changes of insulin resistance before and after certain interventional trials.

Wayne H-H Sheu*
Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, and School of Medicine, National Yang-Ming University, Taipei, Taiwan

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*Corresponding author. Wayne H-H Sheu
Tel.: +886-4-23741300 Fax: +886-4-23741318
E-mail address: whhsheu@vghtc.gov.tw
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