OBSERVATIONS

Sex Differences in Insulin Dose and Postprandial Glucose as BMI Increases in Patients With Type 2 Diabetes

In a recent review by Geer and Shen (1), using the PubMed database and the references cited in these reports, men were reported to have more lean mass and women to have higher adiposity. Men were also found to have more visceral and hepatic adipose tissue, whereas women had more peripheral or subcutaneous adipose tissue. The researchers concluded that these differences, as well as differences in sex hormones and adipokines, may contribute to a more insulin-sensitive environment in women than in men. When they normalized to kilograms of lean body mass, men and women had similar resting energy expenditure, but physical energy expenditure was more closely related to percent body fat in men than in women. Greater amounts of visceral and hepatic adipose tissue, in conjunction with the lack of a possible protective effect of estrogen, may be related to higher insulin resistance in men compared with women.

However, sex-specific comparisons of efficacy and safety are rarely included in the development and reporting of clinical trials in type 2 diabetic subjects. We performed a post hoc analysis (2) and examined sex differences in efficacy and safety parameters within groups of patients on lispro mixtures twice a day ($n = 319$) or three times a day ($n = 344$) or three times a day in conjunction with a basal bolus therapy using glargine as the basal insulin ($n = 184$), or using NPH insulin alone ($n = 355$), or glargine alone ($n = 203$). An integrated database (Eli Lilly and Company) was evaluated for the clinical trials that were at least 12 weeks in duration and included only insulin-using type 2 diabetic subjects (± oral agents). Six such trials were identified and used for this analysis. ANOVA or ANCOVA and χ^2 tests were used to analyze continuous and categorical variables, respectively. The ANOVA or ANCOVA model included effects for baseline, sex, sulfonylurea use (when applicable), duration of diabetes, and sex by linear BMI interaction. Hypoglycemia was analyzed with a negative binomial model. The end point values were defined using the last-observation-carried-forward approach.

At end point, with increasing baseline BMI, the 2-h postprandial glucose and insulin dose were significantly different in women versus men, although change in A1C was not significantly different. Women had a lower end point 2-h postprandial glucose after lunch and dinner than men (8.08 ± 0.19 vs. 8.66 ± 0.18 mmol/l, $P = 0.028$ and 8.55 ± 0.21 vs. 9.14 ± 0.21 mmol/l, $P = 0.046$, respectively). Weight gain was also greater in women than men (1.45 ± 0.23 vs. 0.21 ± 0.29 kg, $P = 0.005$), while women on twice-daily lispro mixtures had less hypoglycemia (0.56 ± 0.10 vs. 0.87 ± 0.11 episodes $\cdot$ pt^{-1} $\cdot$ 30d^{-1}, $P = 0.035$; the glargine-alone group also showed this response 1.06 ± 0.19 vs. 1.64 ± 0.21 episodes $\cdot$ pt^{-1} $\cdot$ 30d^{-1}, $P = 0.042$). Of note, in the basal bolus group when the thrice-daily lispro was combined with glargine, no significant differences between the sexes in any variables were observed.

In conclusion, sex differences in response to insulin therapy in type 2 diabetic subjects appear to exist and may have implications for the safety, efficacy, and optimal utilization of insulin therapy. Thus, sex differences should be explored and considered in future clinical trial design and analyses in diabetes (1–3).

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