as playing a key role in reproductive regulation, specifically as a modulator of gonadotropin-releasing hormone secretion [Topaloglu AK et al. *Nat Genet*. 2009]. The aim of this study [NCT01872078], presented by Jyothis T. George, PhD, University of Oxford, Oxford, United Kingdom, was to assess the effect of the NKB receptor antagonist, AZD4901, on LH secretion and testosterone levels in women with PCOS.

A total of 67 women with PCOS were randomized to receive AZD4901 20, 40, or 80 mg/day, or placebo for 28 days. All of the patients had a clinical diagnosis of PCOS with polycystic ovarian morphology, free testosterone (>0.85 upper limit of normal), and oligomenorrhea. The patients had intensive LH and testosterone sampling at baseline (day –1), day 7, and day 28. The primary end point was the change in 8-hour LH area under the curve (AUC) between baseline and day 7. The secondary end points were the change in total testosterone levels from baseline to days 7 and 28 and in LH pulse frequency at days 7 and 28.

The LH AUC was 67.4 ± 1.6 IU/L*h at baseline and 36 ± 2.3 IU/L*h at day 7 in the AZD4901 80-mg group compared with 61.1 ± 1.9 IU/L*h at baseline and 69.8 ± 1.7 IU/L*h at day 7 in the placebo group (a 52% reduction relative to placebo, adjusted for baseline; 95% CI, 30% to 67%; $P = .0003$). LH pulse frequency was 5.8 ± 2.1 pulses/8 hours at baseline and 3.7 ± 2.1 pulses/8 hours at day 7 in the AZD4901 80-mg group compared with 7.2 ± 2.3 pulses/8 hours at baseline and 6.8 ± 2.6 pulses/8 hours at day 7 in the placebo group, an adjusted mean change of –3.55 pulses/8 hours vs placebo ($P < .0001$).

Total testosterone levels were 2.2 ± 1.3 nmol/L at baseline and 1.6 ± 1.5 nmol/L at day 7 in the AZD4901 80-mg group compared with 1.5 ± 1.7 nmol/L at baseline and 1.6 ± 1.9 nmol/L at day 7 in the placebo group (a 29% adjusted reduction relative to placebo; 95% CI, 14% to 41%; $P = .0006$). At day 28, testosterone was reduced by 17% in the AZD4901 80-mg group.

A post hoc analysis in the anovulatory patients, defined as patients with serum P≥6 ng/mL throughout the study, showed that LH AUC was reduced in the ADZ4901 80-mg group by 46% at day 7 ($P = .0004$) and by 35% at day 28 ($P = .0203$); LH pulse frequency was –3.9 pulses/8 hours at day 7 ($P < .0001$) and –1.89 pulses/8 hours at day 28 ($P = .0205$); and testosterone was reduced by 27% at day 7 ($P = .0005$) and by 20% at day 28 ($P = .0111$) compared with placebo.

After 7 days of treatment with AZD4901 80 mg, women with PCOS had significant reductions in LH, LH pulse frequency, and total testosterone. These effects persisted for 28 days in nonovulating women. AZD4901 was safe and well tolerated. Longer-duration studies are needed to further evaluate its therapeutic potential, including metabolic responses.

Improvements in Diabetes Control Similar in Patients Who Undergo LAGB or Intensive Management

Written by Jill Shuman

Because of advances in both the surgical and nonsurgical treatment of obesity in adults with type 2 diabetes mellitus (T2DM), there is increasing controversy regarding the best treatment algorithm for patients who are obese with T2DM.

The SLIMM-T2D study [NCT01073020] was a 1-year pragmatic randomized trial within a single hospital setting. The trial was designed to compare clinical outcomes between patients who are obese with T2DM who underwent laparoscopic adjustable gastric band surgery (LAGB) or Roux-en-Y gastric bypass (RYGB) and those who participated in Why WAIT, a nonsurgical intensive diabetes and weight loss intervention. Why WAIT incorporated intensive diet, exercise, education, and drug modification using a multidisciplinary approach that included a dietitian, a psychologist, a diabetes educator, an exercise physiologist, and a physician who prescribed medications considered weight neutral. Patients in the Why WAIT intervention received 2 hours of instruction per week and individualized exercise training for the first 12 weeks, with monthly one-on-one support visits for the remainder of the 1-year follow-up.

The primary end point was the number of patients with fasting blood sugar < 126 mg/dL and HbA_{1c} < 6.5% at 1 year. Secondary end points included measurement of metabolic and cardiovascular risk factors.

Data from the RYGB arm of the trial were previously published [Halperin F et al. *JAMA Surg*. 2014] and showed that, compared with medical management, RYGB produced sustained and statistically significant improvements in HbA_{1c} and fasting glucose ($P = .03$), as

Table 1. Baseline Patient Characteristics

Mean age, y	51 ± 10
Mean weight, kg	109 ± 15
Body mass index, kg/m^2	36.5 ± 3.7
Duration of type 2 diabetes mellitus, y	9 ± 5
HbA_{1c}, %	8.2 ± 1.2
Percentage on insulin	40

well as greater weight loss and reduction in cardiometabolic risk factors at 1 year.

Donald C. Simonson, MD, MPH, ScD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented data from the LAGB arm of SLIMM-T2D. Forty patients were randomized to either LAGB (n = 18; 9 men, 9 women) or medical management (n = 22; 13 men, 9 women), with 12 months of follow-up. Other baseline characteristics are outlined in Table 1.

At 12 months, there was no significant difference between the 2 groups in the primary end point of $HbA_{1c} < 6.5\%$ and fasting blood sugar < 126 mg/dL ($P = .46$). There was also no significant difference in the number of patients who met all 3 treatment goals prescribed by the American Diabetes Association ($HbA_{1c} < 7.0\%$, low-density lipoprotein < 100 mg/dL, systolic blood pressure < 130 mm Hg; $P = .77$). However, patients in the LAGB group lost significantly more weight than their Why WAIT counterparts (–13.5 ± 1.7 kg vs –8.5 ± 1.6 kg; $P < 0.05$).

In conclusion, among patients who are obese with T2DM, weight loss was significantly greater in the LAGB group. There were no significant differences in biochemical measures associated with either LAGB or an intensive weight and exercise management program. Programs similar to Why WAIT may be a plausible option for patients who are not good candidates for LAGB or who choose not to undergo the procedure.

Calcium Supplementation and Hyperabsorption Lead to Hypercalcemia and Hypercalciuria

Written by Toni Rizzo

Approximately 50% of women in the United States take calcium and vitamin D supplements [Centers for Disease Control and Prevention. http://www.cdc.gov/nchs/data/databriefs/db61.pdf. Accessed March 12, 2015]. From 1988 to 2002, vitamin D use increased from 50% to 56%, and from 1988 to 2006, calcium use increased from 28% to 61% in women aged > 60 years. Around this same time, the prevalence of kidney stones in the United States has increased from about 1 in 20 persons to 1 in 11 persons [Scales CD et al. *Eur Urol*. 2012]. Additionally, the Women's Health Initiative study found an increased risk of kidney stones with the use of vitamin D 400 IU/d plus calcium 2100 mg/d [Jackson RD et al. *N Engl J Med*. 2006].

Until now there have been no studies on the effect of different doses of vitamin D and calcium supplementation on hypercalcemia and hypercalciuria. Two double-blinded randomized trials by Vinod Yalamanchili, MD, Creighton University School of Medicine, Omaha, Nebraska, USA, and his group assessed the effect of vitamin D and calcium supplementation on serum 25-hydroxyvitamin D and serum and urine calcium levels in older (age range, 57–90 years) and young (age range, 25–45 years) women with vitamin D insufficiency. A total of 163 white and 110 black older women were randomized to vitamin D_3 400, 800, 1600, 2400, 3200, 4000, or 4800 IU/d or placebo. The young women (113 white, 79 black) were randomized to vitamin D_3 400, 800, 1600, or 2400 IU/d or placebo. All groups received calcium supplementation. Calcium intake was estimated from 7-day diaries. The average daily calcium supplementation was 580 mg in the elderly women and 450 mg in the young women.

Hypercalcemia occurred in 11% of the elderly white women, 2.5% of the elderly black women, and 1% of the young white and black women. Hypercalciuria was present in 36% of the elderly white women, 25% of elderly black women, 27% of young white women, and 21% of young black women. There was no dose-response relationship between hypercalcemia or hypercalciuria and the vitamin D dose.

Receiver operating characteristic curves (specificity 90%) showed that women with a baseline 24-hour urine calcium > 132 mg were more likely to develop hypercalciuria > 300 mg. Women with a baseline 24-hour urine calcium > 180 mg had a 20-fold increased risk of developing hypercalciuria > 300 mg. Baseline urine calcium was < 300 mg in 66%, 300 to 400 mg in 20%, and > 400 mg in 13% of the women.

Women with hypercalciuria > 400 mg (n = 19) or 300 to 400 mg (n = 28) had a significantly higher mean 24-hour calcium ($P < .0001$), baseline 1,25-dihydroxyvitamin D ($P = .008$), and higher baseline calcium absorption ($P = .032$) compared with women with hypercalciuria < 300 mg or 300 to 400 mg. Further, women with hypercalciuria > 400 mg were also significantly younger ($P = .0005$) than those with hypercalciuria < 300 mg or 300 to 400 mg.

This study showed that hypercalcemia and hypercalciuria are not associated with the vitamin D dose, but more likely related to calcium supplementation and calcium hyperabsorption. Based on the study results and the number of women taking calcium and vitamin D supplements, the investigators estimated that approximately 15 million women on supplements have periodic hypercalcemia and may be at increased risk for kidney stones. Women with hyperabsorption (24-hour urine calcium > 132 mg) do not need calcium or vitamin D supplementation.