GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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Family Physicians Inquiries Network

What's in this week's issue?

Week of March 7 - 11, 2022

SPOTLIGHT: COVID-19 mRNA Vaccine Responsiveness in Pregnant and Lactating Women

- Semaglutide Sweeter Than Sitagliptin in Reducing Glycated Hemoglobin
- Does Metformin Reduce Mortality Rates in Prediabetes?

COVID-19 mRNA Vaccine Responsiveness in Pregnant and Lactating Women

Immunogenicity of COVID-19 mRNA Vaccines in Pregnant and Lactating Women

Collier AY, McMahan K, Yu J, et al. Immunogenicity of COVID-19 mRNA Vaccines in Pregnant and Lactating Women. *JAMA*. 2021;325(23):2370-2380. doi:10.1001/jama.2021.7563

KEY TAKEAWAY: COVID-19 mRNA vaccines induced CD4 and CD8 T-cell responses, binding, neutralizing, and nonneutralizing antibody responses against SARS-CoV-2 in pregnant, nonpregnant and lactating women. Infant cord blood and breast milk also demonstrated binding and neutralizing antibody responses. Titers against some variants were reduced, however, T-cell responses were maintained. Patient-oriented outcomes were not assessed.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: Pregnant women with COVID-19 are not only at increased risk for needing intensive care and death, but also preterm birth or stillbirth. Information is limited regarding responsiveness and safety of the vaccine in the pregnant and lactating population. This study examines the responsiveness of the COVID vaccine in this population.

PATIENTS: Pregnant and lactating women

INTERVENTION: COVID-19 vaccination

CONTROL: Unvaccinated women with confirmed SARS-CoV-2 infection

OUTCOME: Immune responses

METHODS (BRIEF DESCRIPTION):

- Nonpregnant, pregnant, and lactating women 18–45 years old who had received a COVID-19 vaccine between December 2020 and March 2021 or were infected with SARS-CoV-2 and confirmed from April 2020 to March 26, 2021 were included.
- Samples from a hospital-wide, data and tissue biorepository were used.
- Infant cord blood was sampled at delivery. Maternal blood and breast milk samples were taken near each vaccine dose and between 2 and 8 weeks following second dose of the COVID-19 vaccine.
- Receptor Binding Domain (RBD) responses of the SARS-CoV-2 was studied by ELISA. SARS-CoV-2 neutralization titers were compared to virus controls and antibody dependent cellular phagocytosis, complement deposition, and neutrophil phagocytosis were all examined by bead-based assays.

INTERVENTION (# IN THE GROUP): 103

COMPARISON (# IN THE GROUP): 28

FOLLOW UP PERIOD: March 18, 2020 – August 22, 2020

RESULTS:

- Compared to pre-vaccination baseline (28), median RBD-IgG binding antibody titers were higher in pregnant (27,601), lactating (23,497), and nonpregnant (37,839) women after the second vaccine dose.
- At delivery, maternal median serum RBD IgG binding antibody titers were lower (14,953) in relation to cord blood (19,873).
- After vaccination, the median serum IgG binding antibody titer was higher (25,055) than after infection (1,593).
- Median IgG titer in breast milk was lower (97) in vaccinated individuals compared to those infected (203).
- After vaccination, the median serum IgA-binding antibodies were higher (820) compared to after infection (152).
- Breast milk IgA binding antibody median was lower (25) following vaccination then those samples taken following infection (1,940).
- Spike-specific IFN-y production by CD4 T cells and CD8 T cells were similar in nonpregnant, pregnant, and lactating women.
- Serum RBD IgG binding antibody responses were similar against wildtype but were lower for variants in all samples.
- Median neutralizing antibody titers were as much as 6-fold lower for variants than for wild type in lactating, pregnant, and nonpregnant women.
- There was no difference in T-cell responses across variants.

LIMITATIONS:

- No conclusions regarding vaccine safety and tolerability can be made due to small sample size.
- Patient-oriented outcomes were not assessed.
- Cannot assume any difference in findings between groups are causal, especially as statistical analysis was not conducted.
- Generalizability of the findings are limited given the sample of women were willing to be

vaccinated.

- No conclusion regarding stability of the immune response can be drawn from these results due to the short follow up period.

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Semaglutide Sweeter Than Sitagliptin in Reducing Glycated Hemoglobin

Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults with Type 2 Diabetes Uncontrolled with Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial

Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults with Type 2 Diabetes Uncontrolled with Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. *JAMA*. 2019; 321(15):1466–80.

KEY TAKEAWAY: Oral semaglutide (7 or 14 mg daily) is more effective than sitagliptin in reducing glycated hemoglobin and body mass in patients with type II diabetes mellitus uncontrolled with metformin alone or with metformin and a sulfonylurea.

STUDY DESIGN: Double-blind double-dummy randomized active-controlled parallel-group phase 3a trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: GLP-1 receptor agonists are diabetic medications traditionally administered subcutaneously in patients with type II diabetes to maintain euglycemia and are associated with reduced glycated hemoglobin and body mass. This study investigates the efficacy of an oral formulation of semaglutide (a GLP-1RA) as compared to oral sitagliptin (a DPP-4 inhibitor) on glycated hemoglobin and body mass.

PATIENTS: Type II diabetics on metformin with or without sulfonylurea

INTERVENTION: Semaglutide

CONTROL: Sitagliptin

OUTCOME: Glycated hemoglobin

Secondary Outcomes: Body weight, fasting plasma glucose, BMI, waist circumference

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: Type II diabetes mellitus with a glycated hemoglobin between 7.0 and 10.5 and be on a stable dose of metformin with or without sulfonylurea
- Exclusion Criteria: Renal impairment, proliferative retinopathy/maculopathy, other diabetic/weight loss medication usage, or a history of pancreatitis
- Each patient was randomly assigned to 3, 7, or 14 mg/d oral semaglutide or 100 mg/d oral sitagliptin.
- Participants were instructed to take pills fasting in the morning.
- Semaglutide dosage began at 3 mg/d.
  - After 4 weeks this was increased to 7 mg/d for the 7 and 14 mg/d groups.
  - After an additional 4 weeks this was increased to 14 mg/d for the 14 mg/d group.
- All participants in the sitagliptin arm received 100 mg/d throughout the trial
- All patients continued their pretrial stable dosage of metformin with or without sulfonylurea.

INTERVENTION (# IN THE GROUP):

- Semaglutide 3 mg/d: 466
- Semaglutide 7 mg/d: 465
- Semaglutide 14 mg/d: 465

COMPARISON (# IN THE GROUP): 467

FOLLOW UP PERIOD: 78 weeks

RESULTS:

Primary Outcomes –

- Semaglutide 7 and 14 mg/d reduced glycated hemoglobin more than sitagliptin 100 mg/d when comparing baseline to 26 weeks.
  - 7 mg/d: mean difference [MD] –0.3% (95% CI, –0.4% to –0.1%)
  - 14 mg/d: MD –0.5% (95% CI, –0.6% to –0.4%)
  - These greater reductions were maintained at 56 and 78 weeks.
- Semaglutide 3 mg/d was inferior to sitagliptin 100 mg/d in reducing glycated hemoglobin at week 26 as compared to baseline.

Secondary Outcomes –

- Semaglutide 7 and 14 mg/d reduced weight compared sitagliptin 100 mg/d when comparing baseline to 26 weeks.
  - 7 mg/d: estimated difference –1.6 kg (95% CI, –2.0 to –1.1)
  - 14 mg/d: estimated difference –2.5 kg (95% CI, –3.0 to –2.0)
- Semaglutide 3, 7, and 14 mg/d reduced body mass compared to sitagliptin 100 mg/d at 78 weeks.
  - 3 mg/d: MD –0.8 kg (95% CI, –1.5 to –0.1)
  - 7 mg/d: MD –1.7 kg (95% CI, –2.3 to –1.0)
  - 14 mg/d: MD –2.1 kg (95% CI, –2.8 to –1.5)

LIMITATIONS:

- African Americans were underrepresented in the study.
- Many patients discontinued treatment due to

intolerable side effects such as nausea.

- Patient adherence to treatment was not monitored.
- Patients included in the study only had mildly uncontrolled type II diabetes as denoted by the mean baseline glycated hemoglobin 8.3%.
- This study was sponsored by the pharmaceutical manufacturer.

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Does Metformin Reduce Mortality Rates in Prediabetes?

Effect of Metformin and Lifestyle Interventions on Mortality in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study

Lee CG, Heckman-Stoddard B, Dabelea D, et al. Effect of Metformin and Lifestyle Interventions on Mortality in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. *Diabetes Care*. 2021;44(12):2775-2782. doi:10.2337/dc21-1046

KEY TAKEAWAY: Neither metformin or lifestyle modification reduced all-cause mortality in adults at high risk for type II diabetes.

STUDY DESIGN: Multisite, double blind randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Metformin and lifestyle modification can prevent diabetes, but it is less clear if they decrease all-cause, cancer or cardiovascular (CV) mortality. Animal models and observational studies suggest these interventions may lower mortality rates, however, randomized clinical trials are lacking.

PATIENTS: Prediabetic adults >25 years old

INTERVENTION: Lifestyle modification or metformin 850 mg oral twice daily

CONTROL: Placebo tablet oral twice daily

OUTCOME: All-cause, cancer, and cardiovascular disease (CVD) mortality rates

METHODS (BRIEF DESCRIPTION):

- Adults at 27 U.S. sites were enrolled from 1996 to 1999.
- Patient Demographics: Mean age 51+ 11 years and body mass index (BMI) 34 +6.7 kg/m2, 55% White, 32% male, 41% former/current smokers, 29% had hypertension, 69% had hyperlipidemia
  - Inclusion Criteria: (BMI) >24 kg/m2 (> 22 for Asian Americans), fasting plasma glucose 95–125 mg/dL, and 2-hour glucose 140–199 mg/dL after a 75-gram oral glucose load
  - Exclusion: significant CV/renal disease, cancer, hepatitis, conditions likely to decrease life span or increase risk of the interventions; post-bridge period: worsening glucose >140 mg/dL or hemoglobin A1C >7%
- The three study arms from enrollment to July 1, 2001 were:
  - Lifestyle: goal of >150 min physical activity weekly and 7% weight loss
  - Metformin 850 mg twice a day with standard diet/exercise recommendations
  - Placebo twice a day with standard diet/exercise recommendations
- 2002 bridge period offered all participants group lifestyle intervention.
- 2,779 participants continued lifestyle or metformin intervention (open label).
- Secondary data analysis was performed with rigorous adjudication of causes to evaluate all-cause, cancer and CVD mortality up to December 31, 2018.
  - Blinded adjudication committee used medical records, questionnaires, death certificates and the National Death Index cause of death codes to assign cause of mortality, demographics, and lifestyle factors.

INTERVENTION (# IN THE GROUP):

- Lifestyle: 1,079
- Metformin: 1,073

COMPARISON (# IN THE GROUP): 1,073

FOLLOW UP PERIOD: 21 years

RESULTS:

- Lifestyle and metformin interventions did not affect mortality compared to placebo.
- Lifestyle Interventions:
  - All-Cause Mortality: 7.4/1,000 person-years (Hazard Ratio [HR] 1.0; 95% CI, 0.81–1.3)
  - Cancer-Related Mortality: 2.8/1,000 person-years (HR 1.1; 95% CI, 0.74–1.6)
  - CVD-Related Mortality: 2.3/1,000 person-years (HR 1.2; 95% CI, 0.77–1.81)
- Metformin Interventions:
  - All-Cause Mortality: 7.1/1,000 person-years (HR 0.99; 95% CI, 0.79–1.3)
  - Cancer-Related Mortality: 2.7/1,000 person-years (HR 1.0; 95% CI, 0.72–1.52)
  - CVD-Related Mortality: 2.1/1,000 person-years (HR 1.1; 95% CI, 0.7–1.7)

LIMITATIONS:

- Relatively healthy study population with lower mortality rates than other studies and possibly confounded by improved CV risk factors in the U.S. driven by advances in health care.
- Drop-in metformin use may not have been fully accounted for in multivariable adjustment.
- Lifestyle sessions given to all participants may

have negated that specific intervention to draw long-term conclusions.

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