GEMs of the Week

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What's in this week's issue?

Week of May 29 - June 2, 2023

SPOTLIGHT: One Pregnancy, Two Steps - The Sugar Test

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- IV Antihypertensives: Life Saver, or Heart Breaker?
- Novel β-Cell Peptide Therapy Shows Promise for Improved Glycemic Control in New-Onset DMI Patients

One Pregnancy, Two Steps: The Sugar Test

One-Step Compared with Two-Step Gestational Diabetes Screening and Pregnancy Outcomes: A Systematic Review and Meta-Analysis

Brady M, Hensel DM, Paul R, et al. One-Step Compared With Two-Step Gestational Diabetes Screening and Pregnancy Outcomes: A Systematic Review and Meta-analysis. *Obstet Gynecol*. 2022;140(5):712-723. doi:10.1097/AOG.0000000000004943

KEY TAKEAWAY: One-step compared with two-step gestational diabetes mellitus (GDM) testing results in no differences in the rate of large-for-gestational-age infants. It does, however, result in higher rates of a GDM diagnosis and treatment with medications and is associated with higher rates of neonatal intensive care unit admission and hypoglycemia. Two-step testing should continue to be the standard of care for GDM screening.

STUDY DESIGN: Systematic review and meta-analysis of four RCTs and 13 observational studies

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Gestational diabetes is associated with increased risks of large for gestational age (LGA) newborns, pre-eclampsia, cesarean birth, and development of type 2 diabetes later in life. At present, there is no universally accepted standard for screening or diagnosis of GDM, thus practitioners follow the guidance of their local medical organizations, which may be one-step or two-step GDM testing. This systematic review and meta-analysis assessed the short-term maternal and neonatal implications of one-step compared with two-step GDM testing using randomized controlled trials and observational studies.

PATIENTS: Pregnant patients without pre-existing diabetes

INTERVENTION: One-step GDM testing

CONTROL: Two-step GDM testing

PRIMARY OUTCOME: Maternal outcomes

Secondary Outcome: Neonatal outcomes

METHODS (BRIEF DESCRIPTION):

- Four RCTs and 13 observational studies published prior to September 2021 comparing International Association of Diabetes in Pregnancy Study Group Criteria (IADPSG) one-step and the Carpenter-Coustan (CC) two-step methods of GDM screening and diagnosis.
- Records were identified through the databases Ovid Medline, EMBASE, Scopus, Cochrane Central, and ClinicalTrials.gov.
- Maternal Outcomes: GDM diagnosis, GDM treatment, hypertensive disorders of pregnancy, primary cesarean delivery
- Neonatal outcomes: macrosomia, small for gestational age (SGA) infants, shoulder dystocia, NICU admission, preterm birth, respiratory distress syndrome (RDS), neonatal hypoglycemia, stillbirth, neonatal death
  - Secondary outcome definitions: macrosomia: >4,000 grams, SGA: <10th percentile
  - Neonatal hypoglycemia was defined as <40 g/dL at any time within 24 hours after birth.
- Seventeen studies with a total of 735,643 patients were included and analyzed with Downs and Black checklist to assess the quality of the studies, and pooled relative risks (RRs) were calculated with a 95% CI.
- Three versions of meta-analyses were developed: all studies, separated by design (RCT vs observational) and high-quality only.
- The authors found no evidence of study heterogeneity (I^2=0) or publication bias.

INTERVENTION (# IN THE GROUP): 12,520

COMPARISON (# IN THE GROUP): 12,446

FOLLOW-UP PERIOD: Not available

RESULTS:

- One-step testing did not influence the following outcomes compared to two-step testing (using RCT data only).
  - LGA neonates (relative risk [RR] 0.95; 95% CI, 0.88–1.04)
- One-step testing increased the following outcomes compared to two-step testing (using RCT data only).
  - Diagnosis of GDM (RR 2.1; 95% CI, 1.6–2.8; number needed to screen [NNS]=13)
  - Treatment with diabetes medications (RR 2.2; 95% CI, 1.2–4.5; NNS=31)
  - Neonatal intensive care unit admission (RR 1.2; 95% CI, 1.0–1.3; NNS=167)

    - Neonatal hypoglycemia (RR 1.2; 95% CI, 1.1–1.3; NNS=59)
- One-step testing increased the following outcomes compared to two-step testing (using RCT and high-quality scored observational studies; n=363,950).
    - LGA neonates (RR 0.97; 95% CI, 0.95–0.98)
    - Diagnosis of GDM (RR 2.1; 95% CI, 1.6–2.8)
    - Treatment with diabetes medications (RR 1.9; 95% CI, 1.4–2.5)
    - Neonatal intensive care unit admission (RR 1.1; 95% CI, 1.1–1.3)
    - Neonatal hypoglycemia (RR 1.3; 95% CI, 1.2–1.3)

LIMITATIONS:

- No long-term outcome assessment to determine the favorability of one-step or two-step GDM testing, which is critical in the framework of public health and course-of-life care.

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Freestyle Libre vs. POC Glucose Monitoring in Hospitalized Patients with Type 2 Diabetes Mellitus

Comparison of the FreeStyle Libre Pro Flash Continuous Glucose Monitoring (CGM) System and Point-of-Care Capillary Glucose Testing in Hospitalized Patients with Type 2 Diabetes Treated with Basal-Bolus Insulin Regimen

Galindo RJ, Migdal AL, Davis GM, et al. Comparison of the FreeStyle Libre Pro Flash Continuous Glucose Monitoring (CGM) System and Point-of-Care Capillary Glucose Testing in Hospitalized Patients with Type 2 Diabetes Treated with Basal-Bolus Insulin Regimen. *Diabetes Care*. 2020;43(11):2730-2735. doi:10.2337/dc19-2073

KEY TAKEAWAY: Continuous glucose monitoring (CGM) as compared to point of care (POC) glucose increases the ability to detect nocturnal hypoglycemia and hypoglycemia events.

STUDY DESIGN: Single site within-subject clinical study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: CGM is becoming a more widely used tool in the outpatient setting and has resulted in better glucose control among patients with insulin-dependent diabetes. Implementation of this method of glucose monitoring is not widely used in inpatient settings but may have similar benefits for hospitalized patients with type 2 diabetes.

PATIENTS: Non-critically ill hospitalized patients with type 2 DM receiving basal-bolus insulin

INTERVENTION: CGM

CONTROL: POC glucose testing

PRIMARY OUTCOME: Mean daily glucose levels, hypoglycemic events, nocturnal hypoglycemia

Secondary Outcome: Mean absolute relative difference (MARD) of glucose levels

METHODS (BRIEF DESCRIPTION):

- The study consisted of 134 hospitalized, non-critically ill patients with type 2 DM receiving basal-bolus insulin with glargine U300 and U100 plus glulisine insulin before meals.
- Inclusion criteria included adult patients >18 years admitted to the general medical or surgical services previously treated with diet, orals agent, or insulin with an admission blood glucose >140–400 mg/dL without evidence of ketoacidosis.
- Exclusion criteria included patients with type 1 diabetes, pregnant patients, patients receiving steroids, and patients with significant liver, kidney, or pancreatic impairment.
- The CGM method utilized was the Freestyle Libre Pro.
- Patients were monitored with both POC testing before meals and at bedtime and CGM during their hospital stay.
- Patients and study personnel were blinded to the results of the Freestyle Libre Pro. All data was downloaded after discharge.
- Each POC blood glucose was paired with the corresponding CGM value within five minutes and was used for accuracy analysis.
- Primary outcomes included differences in mean daily blood glucose by POC vs. CGM, hypoglycemic events (<70 mg/dL and <54 mg/dL blood glucose), and nocturnal hypoglycemia.
- Secondary aims included calculating the mean absolute relative difference (MARD) of glucose levels to determine the clinical accuracy of CGM vs. POC glucose monitoring.

INTERVENTION (# IN THE GROUP): 134

COMPARISON (# IN THE GROUP): 134

FOLLOW-UP PERIOD: Through hospital discharge (average 7-day length of stay)

RESULTS:

Primary Outcome –

- Overall mean daily glucose was significantly higher when measured by POC compared with CGM (189 vs 176 mg/dL; mean glucose difference 13 mg/dL; 95% CI, 8.3–17 mg/dL).
- POC had a higher detection rate of hypoglycemic events compared to CGM.
  - Blood glucose <70 mg/dL (56% vs 14%; *P*<.001)
  - Blood glucose <54 mg/dL (36% vs 4.1%; *P*<.001)
- CGM detected nocturnal hypoglycemia not detected by POC glucose monitoring.
  - Blood glucose <70 mg/dL: 41%
  - Blood glucose <54 mg/dL: 26%

Secondary Outcome –

- Clinical accuracy was acceptable when comparing POC with CGM (overall MARD percentage of 14.4%).

- FreeStyle Libre Pro was less accurate in the hypoglycemic range (<70 mg/dL) compared to POC.

LIMITATIONS:

- Relatively small study size.
- Consider the use of alternative glucose monitoring methods in future studies (e.g., Dexcom vs. serum glucose levels) to determine the reproducibility of this study.
- Low number of hypoglycemic events observed.

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IV Antihypertensives: Life Saver, or Heart Breaker?

Effect of Intravenous Antihypertensives on Outcomes of Severe Hypertension in Hospitalized Patients without Acute Target Organ Damage

Ghazi L, Li F, Simonov M, et al. Effect of intravenous antihypertensives on outcomes of severe hypertension in hospitalized patients without acute target organ damage. *J Hypertens*. 2023;41(2):288-294. doi:10.1097/HJH.0000000000003328

KEY TAKEAWAY: In adult patients admitted for non-hypertensive reasons who develop asymptomatic severe hypertension (HTN), treatment with intravenous (IV) antihypertensives is associated with an increased risk of myocardial injury.

STUDY DESIGN: Multi-hospital retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Approximately 10% of patients admitted to the hospital for reasons other than HTN develop severe range HTN (systolic >180 or diastolic >110 mmHg). Physicians caring for hospitalized patients are often tempted to ¬treat these blood pressures (BPs) despite a lack of symptoms or evidence of benefit in the absence of acute target organ damage. Previous studies have identified increased harms associated with the use of IV antihypertensives in asymptomatic patients but used more limited patient populations.

PATIENTS: Hospitalized patients with asymptomatic severe HTN and no target organ damage

INTERVENTION: IV antihypertensives

CONTROL: No treatment; oral antihypertensives

PRIMARY OUTCOME: Myocardial injury, stroke, AKI, inpatient death

Secondary Outcome: Comparison between IV and oral antihypertensives

METHODS (BRIEF DESCRIPTION):

- Researchers performed a retrospective records review of 20,383 non-intensive care hospitalized adults at multiple hospitals within a single health system who developed severe HTN without evidence of acute target organ damage.
- Researchers excluded ICU admissions, maternity ward admissions, and patients recently on vasopressors.
- Severe HTN was defined as systolic blood pressure >180 or diastolic blood pressure >110 mmHg.
- Groups were compared using overlap propensity score weighted COX models.
- 5% received IV antihypertensives and 79% received no treatment within three hours of developing severe HTN.
- IV drugs included were those on the hospital formulary: hydralazine, labetalol, metoprolol, and nicardipine. Dose and frequency were not reported.
- Outcomes were defined as follows:
  - Myocardial injury: troponin >99th percentile
  - Stroke: ICD-10 code and head CT or MRI evidence after severe HTN
  - AKI: defined as creatinine increase of >0.3 mg/dl within 48 hours or 1.5 times the lowest measured serum creatinine within the previous 7 days
  - Death: determined by EHR review

INTERVENTION (# IN THE GROUP): 1,059

COMPARISON (# IN THE GROUP): 16,204

FOLLOW-UP PERIOD: Single hospital admission

RESULTS:

Primary Outcome –

- Patients treated with IV antihypertensives were more likely to develop myocardial injury compared to those untreated (5.9% vs 3.6%; HR 1.5; 95% CI, 1.1–2.1).
- There was no difference in stroke, AKI, or death between the IV antihypertensive group vs the untreated group.
  - Stroke (0.7% vs 0.7%, respectively; HR 1.0; 95% CI, 0.5–2.2)
  - AKI (23% vs 18%, respectively; HR 1.1; 95% CI, 0.9–1.2)
  - Death (2.6% vs 1.3%, respectively; HR 1.1; 95% CI, 0.7–1.6)

Secondary Outcome –

- Patients treated with IV antihypertensives had a greater risk of myocardial injury compared to those treated with oral antihypertensives (HR 1.9; 95% CI, 1.1–3.2).
- In the unadjusted analysis, there was a higher risk of AKI and death in patients treated with IV

antihypertensives, but this difference was not present after overlap propensity weighting.
    - AKI (23% vs 18%, respectively; HR 0.7; 95% CI, 0.3–1.6)
    - Death (2.6% vs 1.3%, respectively; HR 0.9; 95% CI, 0.5–1.5).

LIMITATIONS:

- Unmeasured covariates may have affected decisions to treat with IV medications (i.e., patients deemed to require IV antihypertensives may be more likely to have a myocardial injury).
- This study does not define target organ damage, which could lead to heterogeneity in defining who qualifies for study participation.
- This was a nonrandomized study.

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Novel β-Cell Peptide Therapy Shows Promise for Improved Glycemic Control in New-Onset DMI Patients

Immune and Metabolic Effects of Antigen-Specific Immunotherapy Using Multiple β-Cell Peptides in Type 1 Diabetes

Liu YF, Powrie J, Arif S, et al. Immune and Metabolic Effects of Antigen-Specific Immunotherapy Using Multiple β-Cell Peptides in Type 1 Diabetes. *Diabetes*. 2022;71(4):722-732. doi:10.2337/db21-0728

KEY TAKEAWAY: Novel β -cell peptide treatments may increase C-peptide levels and improve glucose control in new-onset Diabetes Mellitus Type I (DMI).

STUDY DESIGN: Single-site, placebo-controlled, double-blind, randomized, phase-one study

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION:

Immunomodulation therapy in DMI patients is limited. This RCT shows promise for β-cell treatments in new-onset DMI patients to increase C-peptide levels, a marker of insulin secretion, which ultimately correlates to improved β-cell function and glucose control.

PATIENTS: Patients with DMI

INTERVENTION: β-cell auto antigen peptide therapy

CONTROL: Placebo

PRIMARY OUTCOME: Patient safety, drug tolerance

Secondary Outcome: Change in stimulated C-peptide levels, HbA1c, average insulin dose, change in T-cell biomarkers, islet-cell antibody function

METHODS (BRIEF DESCRIPTION):

- Subjects met the following inclusion criteria: new onset DMI <4 years, HLA-DRB1*0401 positive, presence of islet autoantibodies (GAD or IA/2 or ZNT8), meal stimulated C-peptide responses >0.2 pmol/mL
- Exclusion criteria included: Immunomodulatory conditions or therapies, pregnancy/breastfeeding.
- Treatments consisting of peptides derived from β-cell autoantigens were administered to participants every four weeks at three different doses.
    - For every six participants receiving a treatment there were two patients receiving placebo doses. Placebo and treatments were given over the course of 24 weeks with a subsequent 24-week follow-up.
- Statistical comparison performed of mean changes in stimulated C-peptide production, HbA1c, average daily insulin usage, T-cell biomarkers, and islet cell auto-antibodies using 95% CI cutoffs.

INTERVENTION (# IN THE GROUP):

- 10 mg: 8
- 100 mg: 6
- 500 mg: 6

COMPARISON (# IN THE GROUP): 6

FOLLOW-UP PERIOD: 24-week treatment with an additional 24-week follow-up period

RESULTS:

Primary Outcome –

- Treatment doses were well tolerated with no serious adverse events of anaphylaxis or symptoms of hypersensitivity reported.
- The most common adverse events reported were mild hypoglycemia and injection site skin reactions:
    - 270 mild hypoglycemic events were reported in 20 subjects who received drug treatment.
    - 84 mild hypoglycemic events in six patients who received placebo treatment.
    - Local skin reactions occurred in both placebo and drug treatment groups, in general, <50 mm in diameter and resolved by 90 min.

Secondary Outcome –

- β-Cell peptide treatments of 100 mg preserved C-peptide levels.
- There were no significant differences seen in A1c or insulin dose requirements among treatment groups.
- Populations of tolerant (immunosuppressive) CD4 T-cells increased with peptide dose up to 100 mg.

LIMITATIONS:

- Small sample size n=24.
- There is a high degree of interindividual variation in genetic profiles that correlate to transcriptional outcomes of regulatory T cells, their biomarkers, and auto-antibodies at a baseline.
- Such interindividual variation limits the power to detect differential expression between subjects.
- This variability also complicates the ability to identify reproducible and uniform enriched specific pathways targeted by the treatment, warranting large-scale studies.

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