GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of July 17 - 21, 2023

SPOTLIGHT: The Bionic Pancreas - Is the Future Here for Type I Diabetes?

- Chronic Kidney Disease: SGLT2 Inhibitors for Cardiorenal Benefits
- Mediterranean Diet v. Cognitive Decline in Hispanics/Latinos
- Can You Predict the Future of Achilles and Patellar Tendon Pain in Runners with Ultrasound?

The Bionic Pancreas: Is the Future Here for Type I Diabetes?

Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes

Bionic Pancreas Research Group, Russell SJ, Beck RW, et al. Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. *N Engl J Med*. 2022;387(13):1161-1172. doi:10.1056/NEJMoa2205225

KEY TAKEAWAY: Use of a Bionic Pancreas in type 1 diabetes results in improved glycemic control over 13 weeks as compared to standard care (treatment-as-usual).

STUDY DESIGN: 13-week, multicenter, randomized, parallel-group, unblinded study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Only 20% of type 1 diabetics presently meet the A1C goal of <7%. Currently, available products for insulin delivery include hybrid closed-loop systems, which are only partially automated and require some active management/participation by the user (i.e., input of basal rate, carb counting, "warm-up" period). The Bionic Pancreas works more autonomously, needing only the user's body weight to determine dose decisions with subsequent automation of insulin delivery.

PATIENTS: Type 1 diabetics, 6–79 years old

INTERVENTION: Bionic pancreas

CONTROL: Current standard care ("SC") for DM (including unblinded, real-time continuous glucose monitoring)

PRIMARY OUTCOME: Change in A1C at 13 weeks phrase Secondary outcome: Percentage of time with hypoglycemia

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: Diagnosis of type 1 DM, age 6–79 years, use of insulin for ≥1 year.
  - Exclusion Criteria: Numerous, including personal history of hemoglobinopathy, cystic fibrosis, any pancreatic disease, or an intention to adjust diabetes regimen in the coming three months.
  - Randomized 2:2:1 –
    - Bionic Pancreas (as part or lispro)
    - Bionic Pancreas (fast acting; not included in this report)
    - Standard of care group
- Intervention: iLet Bionic Pancreas (BP)
  - Dexcom 6 continuous glucose monitor
  - Embedded insulin dose algorithms initiated upon entry of body weight (including basal, correctional, and meal announcement doses which incorporate user qualitative assessment of carbohydrate content)
  - The Inset I infusion set to accomplish insulin infusion
  - Insulin doses administered by BP were determined by algorithms without user modification.
- The standard care group continued the pre-trial method of insulin delivery under the guidance of their own provider with the addition of unblinded, real-time CGM.
- Follow-up visits were done at four, two, six, 10, and 13 weeks.
- Primary Outcome: Change in A1C from the time of randomization to follow-up points at six weeks and 13 weeks.
  - Key Secondary Outcome: Percentage of time that glucose level as measured by continuous monitor was below 54 mg/dL (prespecified noninferiority limit for this outcome was 1 percentage point).
  - Other secondary outcomes were also collected from CGM.

INTERVENTION (# IN THE GROUP): 219

COMPARISON (# IN THE GROUP): 107

FOLLOW-UP PERIOD: 13 weeks

RESULTS:

Primary Outcome –

- The BP group saw a greater mean reduction in A1C at 13 weeks compared to the standard care group (Mean difference –0.5%; 95% CI, –0.6 to –0.3).
- There was an average drop in A1C of 0.6% for the intervention group vs 0.0% for the control group.

Secondary Outcome –

- Key Secondary Outcome: The BP was non-inferior to standard care based at 13 weeks for hypoglycemia (Mean difference 0.0%; 95% CI, –0.1 to 0.04).
- Subjects with BP vs. standard care had the following outcomes:

- Lower mean glucose levels by 16 mg/dL (95% CI, –19 to –12 mg/dL)
- 11% greater time within the glucose range of 70–180 mg/dL (95% CI, 9–13)
- 10% less time with glucose above 180 mg/dL (95% CI, –12 to –8)
- 5% less time with glucose level >250 mg/dL (95% CI, –6.6 to –3.6)
- Less overall glucose variability vs standard care, with a glucose-level standard deviation of –7mg/dL (95% CI, –8 to –5)
- No significant difference was found for the percentage of time with glucose level <70 mg/dL.

LIMITATIONS:

- Infrequent measurement of baseline hypoglycemia impeded the ability to determine if the BP reduced the risk and severity of hypoglycemic events.
- Approaches to managing and reporting hyperglycemia and ketosis differed between the two groups.
- A commonly used single type of infusion set was used in the bionic-pancreas group, which may have added to the incidence of infusion-set failures.
- There was a greater number of unscheduled contacts in the bionic-pancreas group compared to the SC group (inherent to design as the latter group followed their usual care guidelines under the guidance of their own provider).
- Funding provided by the National Institute of Diabetes and Digestive and Kidney Diseases, but possible bias with two authors involved in the trial's oversight as Beta Bionics employees and shareholders.

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Chronic Kidney Disease: SGLT2 Inhibitors for Cardiorenal Benefits

Empagliflozin in Patients with Chronic Kidney Disease
The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2023;388(2):117-127. doi:10.1056/NEJMoa2204233

KEY TAKEAWAY: Daily empagliflozin significantly reduces the progression of chronic kidney disease (CKD) or death from cardiovascular causes, and hospitalizations from any causes among a wide range of patients with CKD.

STUDY DESIGN: Multicenter, randomized double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: CKD often leads to the development of kidney failure that requires dialysis or kidney transplantation. Prior evidence shows the benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors in slowing the progression of CKD in patients with diabetic kidney disease. However, limited evidence indicates the effects of SGLT2 inhibitors in a broader range of the CKD population. This study examines the effects of SGLT2 inhibitors on kidney disease progression in a wide range of patients with CKD.

PATIENTS: Adult patients with CKD

INTERVENTION: Empagliflozin

CONTROL: Placebo

PRIMARY OUTCOME: Progression of CKD or cardiovascular death

Secondary Outcome: First and sequent hospitalizations for any cause, or heart failure or death from cardiovascular causes

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: At a screening visit, adults with either a race-adjusted estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml/minute/1.73 m^2 or with an eGFR of at least 45 but less than 90 ml/minute/1.73 m^2 plus a urinary albumin-creatinine ratio >200 mg/day.
  - Patients had a mean age of 63.8 years old, with 33% female and 58% White, and were recruited from 241 centers in 8 countries.
- There was a brief run-in period of 8–12 weeks with a once-daily placebo to ensure eligible participants' compliance with treatment.
- After the run-in period, patients were randomly assigned to receive a seven-month supply of either empagliflozin (10 mg daily) or a matching placebo (film-coated tablet).
- CKD progression was defined as end-stage kidney disease, initiation of dialysis or kidney replacement therapy, or decrease in eGFR of at least 40% from baseline. It was assessed at two consecutive scheduled follow-up visits.
  - Follow-up visits were conducted at two and six months and every six months until the end of the trial.

INTERVENTION (# IN THE GROUP): 3,304

COMPARISON (# IN THE GROUP): 3,305

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- Empagliflozin significantly reduced the progression of CKD or cardiovascular death compared to placebo (13.1% vs 16.9%, respectively; hazard ratio [HR] 0.72; 95% CI, 0.64–0.82; NNT=26).

Secondary Outcome –

- Empagliflozin was significantly more likely to decrease rates of first and subsequent hospitalizations from any cause than placebo (24.8% vs 29%, respectively; hazard ratio [HR] 0.86; 95% CI, 0.78–0.95; NNT=23).
- There was no significant difference in the rates of hospitalizations for heart failure or death from cardiovascular causes between the two groups.

LIMITATIONS:

- There were fewer than expected cardiovascular events reported that reduced statistical power.

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Mediterranean Diet v. Cognitive Decline in Hispanics/Latinos

Association of Mediterranean Diet with Cognitive Decline Among Diverse Hispanic or Latino Adults from the Hispanic Community Health Study/Study of Latinos

Moustafa B, Trifan G, Isasi CR, et al. Association of Mediterranean Diet with Cognitive Decline Among Diverse Hispanic or Latino Adults from the Hispanic Community Health Study/Study of Latinos. *JAMA Netw Open*. 2022;5(7):e2221982. Published 2022 Jul 1. doi:10.1001/jamanetworkopen.2022.21982

KEY TAKEAWAY: Higher adherence to the Mediterranean diet is associated with better cognitive performance and decreased seven-year learning and memory decline in Hispanic/Latino adults.

STUDY DESIGN: Secondary analysis of two prospective cohort studies

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: Cognitive decline or impairment has a large impact on society. Hispanics and Latinos are a growing ethnicity in the United States, and present with cognitive impairments like dementia. They are underrepresented in cognitive studies, and studies have shown an association between culturally tailored Mediterranean diets and decreased cognitive decline.

PATIENTS: Hispanic/Latino adults

INTERVENTION: High or moderate adherence to a Mediterranean diet

CONTROL: Low adherence to a Mediterranean diet

PRIMARY OUTCOME: Cognitive decline

METHODS (BRIEF DESCRIPTION):

- Adults 18–74 years old living in the US (Chicago, Bronx, Miami, and San Diego) who were followed for three years (n=6321).
  - Sociodemographic variables (age, sex, household income, education level, US-born v. not US-born, preferred language, health insurance availability, smoking history, and stroke history) were accounted for or taken into consideration.
- Data was obtained from Study of Latinos-Investigation of Neurocognitive Aging (SOL-INCA; October 2015–March 2018) and an ancillary study of Hispanic Community Health Study-Study of Latinos (HCHS-SOL; March 2008–June 2011).
- Dietary recall and neurocognitive assessments were performed in both groups.
  - For dietary recall, one point was awarded for each beneficial part of the diet (i.e., fruits/vegetables), and one point was deducted for each detrimental part (i.e., alcohol, monounsaturated fat).
  - Original MDS (Mediterranean diet score) and modified MDS were used with the point system described above.
- Adherence was defined as:
  - High: 7–9 points
  - Moderate: 5–6 points
  - Low: 0–4 points
- Four neurocognitive tests were administered:
  - Brief Spanish-English Verbal Learning Test Sum
  - B-SEVLT Recall (delayed verbal episodic and memory test)
  - Word fluency for speech production
  - Digit Symbol Substitution Test
- For the beta coefficient, data closer to +1 there indicates a stronger correlation, 0 indicates no correlation, and –1 indicates an inverse correlation.

INTERVENTION (# IN THE GROUP): 4,209

COMPARISON (# IN THE GROUP): 2,112

FOLLOW-UP PERIOD: Seven years

RESULTS:

- At visit one, high vs low adherence groups were associated with:
  - Brief Spanish-English verbal learning test sum increased (β=0.11; 95% CI, 0.020–0.20)
  - Delayed verbal episodic and memory increased (β=0.16; 95% CI, 0.070–0.25)
  - Global cognition increased (β=0.10; 95% CI, 0.040–0.16)
- Comparison of cognitive change in high vs low adherence groups between visits one and two:
  - Brief Spanish-English verbal learning test sum increased (β=0.12; 95% CI, 0.050–0.20)
  - Delayed verbal episodic and memory increased (β=0.14; 95% CI, 0.050–0.23).

- Higher adherence to the Mediterranean diet was associated with increased global cognitive performance and decreased seven-year memory/learning decline in a sample of middle-aged/elderly Hispanic/Latino US population:
    - Global cognition no effect (β=0.11; 95% CI, 0.050–0.16)
    - Brief Spanish-English verbal learning test sum slow decrease (β=0.18; 95% CI, 0.050–0.20)
    - Delayed verbal episodic and memory slow decrease (β=0.21; 95% CI, 0.050–0.23)

LIMITATIONS:

- Recall bias was noted in the study as participants did not remember all the food items that they ate.
- Only four neurocognitive tests were performed, and more or other tests could have changed the results.
- The original MDS did not account for the refined grains that Hispanics/Latinos consume so a modified MDS was performed (per the article, the results remained unchanged).

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Can You Predict the Future of Achilles and Patellar Tendon Pain in Runners with Ultrasound?

Sonographic Screening of Distance Runners for the Development of Future Achilles and Patellar Tendon Pain

Cushman DM, Petrin Z, Cummings K, Eby SF, English J, Teramoto M. Sonographic Screening of Distance Runners for the Development of Future Achilles and Patellar Tendon Pain. *Clin J Sport Med*. 2022;32(5):493-500. doi:10.1097/JSM.0000000000000984

KEY TAKEAWAY: Ultrasound findings of abnormalities in the tendons of the Achilles and Patella are associated with the development of pain in those tendons within one year of a marathon or half marathon runner.

STUDY DESIGN: Prospective Cohort Study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Patellar and Achilles tendinopathies can cause inhibition for return to sports for athletes. 30% of individuals with patellar tendinopathies are unable to return to full sport participation within six months. In some populations, this causes retirement in over 50% of athletes. Achilles tendinopathies have an overall incidence of 10% in runners. Ultrasound-guided screenings could be available to predict pain or problems that can develop with these tendons in the future based on abnormalities seen upon the exam.

PATIENTS: Asymptomatic Adult Runners

INTERVENTION: Ultrasonographic Imaging of Achilles and patellar tendons for pathology before racing

CONTROL: Pain within one year following the race

PRIMARY OUTCOME: Relative risk of pain given a prior abnormal sonographic finding in the Achilles and patellar tendon

Secondary Outcome: Women were found to have a lower risk of developing pain

METHODS (BRIEF DESCRIPTION):

- 18-year-old or older runners were recruited for this study via a booth at the prerace in the 2019 Salt Lake City Marathon or half marathon.
  - The ages in the study were 36.2 yrs (+/- 12 yrs).
  - 166 runners were scanned, however only 138 runners ended up being included in the study as 28 did not respond to the two-day post-race email survey.
  - All participants were screened via ultrasound before the race. The athletes that had surgery or previously known damage to their Achilles or patellar tendons were excluded from the study.
- The ultrasound images were divided into normal and abnormal tendon images.
  - The abnormal were then subcategorized into:
    1) Focal hypoechogenic
    2) Paratenon blurring
    3) Tendon calcifications
    4) Presence of osteophytes at the enthesis
    5) Tendon thickening
- Participants were all followed for one year via e-mail to fill out a survey regarding the presence of pain in their Achilles or Patellar tendon.
  - The pain scale was rated 1-10.
  - Surveys were self-reported by the 138 runners immediately after the race, one month, three months, six months, and one year after the race.
  - Statistical analyses were then performed.

INTERVENTION (# IN THE GROUP): Not Applicable

COMPARISON (# IN THE GROUP): Not Applicable

FOLLOW-UP PERIOD: Immediately after the race, one-, three-, six-, and 12-months post-race

RESULTS:

Primary Outcome –

- There was a 2.6-fold increased risk of developing pain in runners with an abnormality of the Achilles tendon on ultrasound (HR 2.6; 95% CI, 1.4–4.8).
- There was a 1.6-fold increased risk of developing pain in runners with an abnormality of the patellar tendon on ultrasound (HR 1.67; 95% CI, 1.0–2.7).
- Developing pain over the year with regards to the Achilles tendon had a PPV (34%) and NPV (87%).
- Developing pain over the year with regards to the Patellar tendon had a PPV (23%) and NPV (85%).

Secondary Outcome –

- There was no significant relationship between the type of ultrasound abnormality found in the tendon and developing pain in the tendons (i.e., Achilles and Patellar).
- Survey response rates:
  - Immediately after the race (100%)
  - One month after the race (96%)

    - Three months after the race (93%)
    - Six months after the race (89%)
    - 12 months after the race (81%)
- Women were less likely to develop pain in the Achilles tendon (HR 0.40; 95% CI, 0.18–0.080).

LIMITATIONS:

- The only ultrasounds of the tendons (i.e., Achilles and Patellar) were performed before the race, and no images were taken immediately after, one-, three-, six-, or 12-months post-race.
- Tendon neovascularization evaluation was not performed in this study. Tendon neovascularization has been previously studied to be a good predictor of developing pain in Achilles tendons in the future.
- Pain in the Achilles and patellar tendons were all self-reported.
- A detailed description of the runners' training regimens was not ascertained.
- Bias in the study could be caused by runners who signed up for the evaluation due to previous patellar or Achilles injuries.
- With regards to patellar tendon ultrasound findings and pain, there actually may not be a clinically significant effect as the CI was close to 1.0.

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