GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of August 9 - 13, 2021

SPOTLIGHT: Got Diabetes? Eat More Fiber

- High Protein Diet Led to 100% Pre-Diabetes Remission
- Will Drinking Milk Make My Prostate Bumpy?
- Got Zinc? Good for Children's Diarrhea!

Got Diabetes? Eat More Fiber

Dietary Fibre and Whole Grains in Diabetes Management: Systematic Review and Meta-Analysis

Reynolds AN, Akerman AP, Mann J. Dietary fibre and whole grains in diabetes management: systematic review and meta-analyses. *PLoS Med*. 2020 ;17(3):e1003053. Published 2020 Mar 6. doi:10.1371/journal.pmed.1003053

KEY TAKEAWAY: Increasing fiber intake to 35 g per day decreases mortality, improves glycemic control, and improves cardiovascular risk factors (CVRF) in patients with type 1 or 2 diabetes and pre-diabetes.

STUDY DESIGN: Meta-analysis and systematic review of 42 controlled trials (CTs) and two prospective cohort studies (CSs)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to heterogeneity)

BRIEF BACKGROUND INFORMATION: Our culture advocates for low-carbohydrate diets as the ideal for diabetics, however not all carbohydrates are equal in nutritional value. This meta-analysis aims to add to the growing evidence that fiber-rich, complex carbohydrates are important in diabetic care.

PATIENTS: Adults with type 1 or 2 diabetes or pre-diabetes

INTERVENTION: Increased daily fiber

CONTROL: Standard baseline daily fiber

OUTCOME: Mortality, glycemic control, and other CVRF

METHODS (BRIEF DESCRIPTION):

- Description of participants:
  - CTs: 1,789 type 1 & 2 diabetics and pre-diabetics, on various treatments, many of whom were non-insulin-dependent diabetics (NIDD), from various geographic areas
  - CSs: 8,300 type 1 & 2 diabetics (insulin-dependent and NIID) from 22 European countries
- Treatment intervention:
  - CTs: Intervention groups received increased daily fiber ranging from 1 g to 45 g
  - CSs: Participants stratified into multiple groups of increasing fiber, with baseline fiber intake of 19 g/d vs increased fiber intake of 35 g/d
- Measurements of outcomes:
  - CTs: Glycemic control and CVRF measured with before-and-after labs and clinical data

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD:

- CTs: Majority 1.5–3 months
- CSs: Mortality rates measured an average of 8.8 years after obtaining baseline data

RESULTS:

Increased fiber intake compared to usual fiber intake is associated with the following:

- Lower all-cause mortality (2 trials, N=8,300; RR 0.35; 95% CI, 0.35–0.86; I^2=0%)
- Lower levels of:
  - HbA1c (33 trials, N=1,553; MD –2.0; 95% CI, –3.3 to –0.71; I^2=99%)
  - Fasting plasma glucose (34 trials, N=1,807; MD –0.56; 95% CI, –0.73 to –0.38; I^2=99%)
  - Total cholesterol (27 trials, N=1,267; MD –0.34; 95% CI, –0.46 to –0.22; I^2=98%)
  - LDL cholesterol (21 trials, N=1,071; MD –0.17; 95% CI, –0.27 to –0.08; I^2=96%)
  - Triglycerides (28 trials, N=1,468; MD –0.16; 95% CI, –0.23 to –0.09; I^2=98%)
  - Body weight (18 trials, N=877; MD –0.56; 95% CI, –0.98 to –0.13; I^2=98%)
  - BMI (14 trials, N=763; MD –0.36; 95% CI, –0.55 to –0.16; I^2=97%)
  - C-reactive protein (7 trials, N=433; MD –2.8; 95% CI, –4.5 to –1.1; I^2=97%)
  - Fasting plasma insulin (19 trials, N=947; MD –2.0; 95% CI, –2.9 to –1.1; I^2=96%)
  - Insulin resistance (9 trials, N=581; MD –1.2; 95% CI, –1.7 to –0.76; I^2=99.7%)
- Higher HDL cholesterol (25 trials, N=1,388; MD 0.04; 95% CI, 0.01–0.07; I^2=97%)
- Increased fiber intake did not affect blood pressure or cardiovascular mortality.

LIMITATIONS:

- High heterogeneity in CTs.
- CTs were short-term.
- Many studies were limited to European countries.
- Minimal discussion regarding potential digestive side effects of increased fiber.

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High Protein Diet Led to 100% Pre-Diabetes Remission

Remission of Pre-Diabetes to Normal Glucose Tolerance in Obese Adults with High Protein versus High Carbohydrate Diet: Randomized Controlled Trial

Stentz FB, Brewer A, Wan J, et al. Remission of pre-diabetes to normal glucose tolerance in obese adults with high protein versus high carbohydrate diet: randomized control trial. *BMJ Open Diabetes Research and Care*. 2016; 4:e000258. doi:10.1136/bmjdrc-2016-000258.

KEY TAKEAWAY: A patient consuming a high protein diet is more likely to enter remission for pre-diabetes compared to those consuming a high carbohydrate diet.
STUDY DESIGN: Prospective, randomized, controlled trial
LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and high dropout rate)

BRIEF BACKGROUND INFORMATION: Obesity and pre-diabetes have significant long-term health implications. Dietary advice given by clinicians can vary drastically. "Lifestyle changes and weight loss" are first line treatment recommendations for pre-diabetes and diabetes, but no specific recommendations are given.

PATIENTS: Adults with pre-diabetes
INTERVENTION: High protein diet (30% protein, 30% fat, 40% carbohydrate)
CONTROL: High carbohydrate diet (15% protein, 30% fat, 55% carbohydrate)
OUTCOME: Remission of pre-diabetes, markers of insulin sensitivity, cardiovascular risk factors, inflammatory cytokines, and changes in lean/fat mass

METHODS (BRIEF DESCRIPTION):

- 233 patients were screened with 178 providing consent and 38 meeting all inclusion criteria.
  - Inclusion Criteria: 20–50 years old, BMI >30 and <55, pre-diabetes diagnosis via fasting blood glucose and oral glucose tolerance test (OGTT)
  - Exclusion Criteria: Abnormal LFTs, elevated serum Cr, DM2 diagnosis, abnormal TSH, weight >350 pounds, elevated triglycerides or LDL-C, elevated systolic or diastolic blood pressure
- Insulin, lipids, inflammatory cytokines, DEXA, and anthropometrics measured at baseline.
- Randomized to a six month diet:
  - High protein diet: 18 participants with 6 dropping out
  - High carbohydrate diet: 20 participants with 8 dropping out
- Patients completed a food journal once a week.
- Caloric maintenance was calculated using resting metabolic rate (RMR) via indirect calorimetry.
  - Diets were initiated with 500 kilocalorie deficit from RMR.
  - If weight loss stalled for >2 weeks, an additional 200 kilocalories were subtracted.
- Pre-diabetes remission was defined as fasting BGL <100 mg/dL and OGTT <140 mg/dL at 5 months follow up.

INTERVENTION (# IN THE GROUP): 12
COMPARISON (# IN THE GROUP): 12

FOLLOW UP PERIOD: 6 months

RESULTS:

- At six months, a high protein diet led to greater pre-diabetes remission rates compared to a high carbohydrate diet (100% vs 33%; *P*=.001).
- HbA1c changes at six months were greater in the high protein diet compared to the high carbohydrate diet (0.54% vs 0.20%; *P*<.0001).
- Triglycerides at six months were lower in the high protein diet compared to the high carbohydrate diet (69 mg/dL vs 99 mg/dL; *P*=.04).
- Inflammatory cytokines were lower in the high protein diet compared to the high carbohydrate diet.
  - TNF-alpha: 3.8 pg/mL vs 9.6 pg/mL; *P*<.0001
  - IL-6: 4.6 pg/mL vs 6.8 pg/mL; *P*<.0001
- At six months there was no significant difference in BMI or weight loss percentage. However, lean mass increased 2.6% in the high protein group and decreased 3.0% in the high carbohydrate group.

LIMITATIONS:

- In a group at high risk for OSA (BMI >30), no data was collected on sleep quality or quantity.
- Both groups had "limited physical activity" at baseline. Exercise could further impact changes in fat/lean mass.
- Exclusion parameters limit the applicability to the general population.

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Will Drinking Milk Make My Prostate Bumpy?

Milk Consumption and Prostate Cancer: A Systematic Review and Meta-Analysis

Sargsyan A, Dubasi HB. Milk Consumption and Prostate Cancer: A Systematic Review [published online ahead of print, 2020 Jul 27]. *World J Mens Health*. 2020;10.5534/wjmh.200051. doi:10.5534/wjmh.200051

KEY TAKEAWAY: Milk consumption is most likely associated with an increased risk for prostate cancer. However, there are some studies that conflict with this conclusion. Providers should discuss limiting milk and dairy with patients at high risk for prostate cancer.

STUDY DESIGN: Systematic review of 20 studies (3 ecological studies, 7 prospective cohort, and 10 case controlled)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to poor quality of included studies)

BRIEF BACKGROUND INFORMATION: Milk and dairy products are important for providing calcium and vitamin D for good bone health and the prevention of osteoporosis. Some studies indicate a possible increased risk of prostate cancer with milk consumption. This systematic review evaluates this potential association.

PATIENTS: Males with varying risk of prostate cancer
INTERVENTION: Milk or dairy consumption
CONTROL: Limited or no milk/dairy consumption
OUTCOME: Prostate cancer

METHODS (BRIEF DESCRIPTION):

- Studies analyzed milk and dairy consumption's association with prostate cancer across more than 40 nations.
- Most studies included men older than 45 years of age.
  - Some studies included men with a higher risk of prostate cancer and compared them with controls.
- Included studies aimed to study the relationship between milk consumption and prostate cancer.
  - Studies were excluded if they examined the effect of plant-based milk products, were genomic studies, or if they included subjects unrelated to study population.
- The analysis was broken down into skim milk, low fat milk, and non-fat milk separately.

INTERVENTION (# IN THE GROUP): 12,185
COMPARISON (# IN THE GROUP): 6,865

FOLLOW UP PERIOD: Varied largely by study

RESULTS: Conflicting evidence is present on the association between consuming whole milk and the risk for prostate cancer.

- Skim Milk:
  - Four studies found a higher association between the consumption of skim milk and prostate cancer compared to no milk consumption.
    - One case control study found ≥3 vs 0 glasses/d increased the risk of prostate cancer (OR 1.8; 95% CI, 1.2–2.9).
  - Three studies found no association between skim milk consumption and risk for prostate cancer.
- Whole/High Fat Milk:
  - Seven studies found whole/high fat milk consumption was associated with an increased risk for prostate cancer.
    - One prospective cohort study found >4 servings/week vs ≤3 servings/month increased the risk of prostate cancer recurrence (HR 1.7, *P*-trend=0.04).
    - One case study reported an increased risk for aggressive prostate cancer (OR=1.7; 95% CI, 1.2–2.6).
  - Only one study reported no association between whole/high fat milk and prostate cancer.
- Skim or Whole Milk
  - Six studies found an association between milk/dairy consumption and the development of prostate cancer.
    - One case control study found an increased risk of prostate cancer with the consumption of milk or cheese (RR=2.5; 95%CI, 1.3–4.7).
  - One large population study in Sweden found an increased risk with consumption of fermented milk compared to subjects in lowest vs highest quintiles of consumption (HR 1.2; 95% CI, 1.0–1.3).
  - One case control study in Australia found a weak protective effect of dairy/milk consumption (OR 0.72; 95% CI, 0.54–0.98).

LIMITATIONS:

- Dairy products other than milk are considered in some studies.
- Studies did not evaluate the possible effect of estrogens on prostate cancer risk.

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Got Zinc? Good for Children's Diarrhea!

Lower-Dose Zinc for Childhood Diarrhea – A Randomized, Multicenter Trial

Dhingra U, Kisenge R, Sudfeld CR, et al. Lower-Dose Zinc for Childhood Diarrhea - A Randomized, Multicenter Trial. *N Engl J Med*. 2020; 383(13):1231–1241. doi:10.1056/NEJMoa1915905

KEY TAKEAWAY: Lower doses of zinc are not inferior to the standard high 20 mg for the treatment of diarrhea and is associated with less vomiting.

STUDY DESIGN: Multisite, double-blind randomized controlled trial

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Diarrhea in children in underdeveloped and developing countries remains a major public health problem. The World Health Organization recommends 20 mg of zinc supplementation which has been shown to reduce the duration and severity of diarrhea in children compared to placebo. However, the risk of vomiting after taking zinc was higher as compared to placebo. No previous studies have compared lower doses of zinc and its efficacy in reducing diarrhea, and if it is associated with a lower risk of vomiting.

PATIENTS: Children in India and Tanzania 6–59 months old who had diarrhea for less than 72 hours or dysentery INTERVENTION: Low dose zinc 5 mg or 10 mg once daily for 14 days

CONTROL: Recommended standard dose of 20 mg of zinc daily for 14 days in children with diarrhea (set by WHO and UNICEF)

OUTCOME: Duration of diarrhea, number of loose stools and vomiting after zinc administration

Secondary Outcomes: Diarrhea lasting more than 3 days, the number of tablets consumed, caregiver report of child, illness (including diarrhea, fever, and respiratory symptoms), and growth changes

METHODS (BRIEF DESCRIPTION):

- 4,500 children in India and Tanzania between 6 and 59 months old with diarrhea present for less than 72 hours of dysentery were included in the study.
- Each participant was randomly assigned equally to receive 5 mg, 10 mg, or 20 mg of zinc tablets for 14 days.
- Parents of participants were instructed to dissolve tablets in 5 to 10 mL of water or breast milk.
- Parents were asked to record daily in a diary the zinc dose given, the amount of stools per day, and the number of vomiting in less than 30 minutes.
- Blood samples were obtained from a randomly selected one third of participants at days 1 and 14, days 3 and 21, and days 7 and 30 after treatment was started.

INTERVENTION (# IN THE GROUP):

- 5 mg group: 1,504
- 10 mg group: 1,498

COMPARISON (# IN THE GROUP):

- 20 mg group: 1,498

FOLLOW UP PERIOD: 60 days

RESULTS:

- The margin for non-inferiority was 4 percentage points and was preset before the study.
- Primary Outcome: The percent of children who had diarrhea for more than 5 days after starting treatment between the three groups was similar and non-inferior which were 7.2%, 7.7%, 6.5% in the 5 mg and 10 mg and 20 mg respectively.
  - The risk difference between the 10 mg group was 1.2 percent points higher than the 20 mg group (upper boundary of one sided 98.75% CI, 3.3).
  - The risk in the 5 mg group was 0.7 percentage points higher than the 20 mg group (upper boundary of the one-sided 98.75% CI, 2.8).
  - Children in the 10 mg group had a 19% lower risk of vomiting in the first 30 minutes of zinc administration in comparison to the 20 mg group (RR 0.81; 97.5% CI, 0.67–0.96).
- Secondary outcomes:
  - The three groups had similar percentages of children with diarrhea, fever, or fast or difficult breathing.
  - Growth of the children during the 60 day follow up period and anthropometric statis was similar between the three groups.
  - Adherence to the intervention was high and similar in the three groups.

LIMITATIONS: Unknown vaccination status against rota virus and the etiology of the diarrhea

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