Diabetes Care Summit

Virtual Conference

Friday, September 10, 2021

OU Health | Harold Hamm Diabetes Center

ADCES Association of Diabetes Care & Education Specialists

2021 HAROLD HAMM DIABETES CARE SUMMIT

September 10, 2021

VIRTUAL CONFERENCE

SYLLABUS CONTENT

HAROLD HAMM DIABETES CARE SUMMIT

Friday, September 10, 2021
Virtual Conference

8:00 a.m. **Welcome and Introductory Remarks**

8:10 – 9:10 a.m. **KEYNOTE** | ***Precision Medicine in Diabetes***
Rochelle Naylor, MD

9:10 – 9:15 a.m. **Break**

9:15 – 11:15 a.m. **CONCURRENT BREAKOUT SESSION I**

a. ***Cancer & Diabetes***
Itivrita Goyal, MD

b. ***Diabetes Technology Update***
Jonea Lim, MD
Christy Olson, MS, RDN, LD, CDCES

CONCURRENT BREAKOUT SESSION II

Diabetes Prevention and Intervention in Tribal Communities
Valarie Blue Bird Jernigan, DrPH, MPH
Michelle Dennison, PhD, RDN, LD, BC-ADM, CDCES

11:15 – 12:00 p.m. **LUNCH**

12:00 – 1:00 p.m. **KEYNOTE** | ***SARS-CoV-2, COVID-19 and Diabetes: A New Bidirectional Disease?***
Steven Kahn, MB, ChB

1:00 – 1:15 p.m. **Break**

1:15 – 3:15 p.m. **CONCURRENT BREAKOUT SESSION I**

Diabetes-Related Complications and Comorbidities in Youth
Jeanie Tryggestad, MD
Petter Bjornstad, MD
Rose Gubitosi-Klug, MD, PhD

CONCURRENT BREAKOUT SESSION II

a. ***Pharmacology Update***
Katherine O'Neal, PharmD, MBA, BCACP, CDCES, BCADM, AE-C, CLS, FADCES

b. ***The Role of Mental Health in Diabetes Care***
Kathryn Jeter, PhD

3:15 – 3:30 p.m. **Break**

3:30 – 4:30 p.m. **PLENARY SESSION** | ***An Overview of Nonalcoholic Fatty Liver Disease (NAFLD)***
Sirish Palle, MD

4:30 p.m. **Adjourn**

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PROGRAM INFORMATION

Course Overview

Co-sponsored by the Association of Diabetes Care & Education Specialists, the Harold Hamm Diabetes Care Summit is a one-day course that focuses on the management of the patient with diabetes. It is designed to address the unmet educational needs of the interprofessional health care team who have a diverse case mix that includes people with diabetes. The purpose of this conference is to promote excellence in care, and provide up-to-date information to enhance knowledge integral to the effective management of diabetes. This continuing education activity is needed because of the explosion of diabetes in our country. The number of persons with diabetes is expected to more than triple by 2050. According to the 2020 National Diabetes Statistics Report from the CDC, diabetes affects 34.2 million people of all ages, which is 10.5 percent of the US population. The Oklahoma State Department of Health also reports more than 14 percent prevalence of diabetes in Oklahoma among adults ages 18 and older. In 2021, Oklahoma ranks the fifth highest in diabetes mortality rate in the nation. Because of the size of this problem and the complexity of managing people with diabetes, this requires continuous training to the health care team in order to meet the needs of people with diabetes in our state and region. This course also combines best practice strategies and education through case studies and lectures.

Educational Objectives

At the end of this activity, the diabetes care team will indicate an increased knowledge of the current evidence-based guidelines and the strategies to create a person-centered treatment plan that considers co-conditions, culture, mental health, age, the person's ability to use technology and patient generated health data, and as possible, with a precision medicine approach.

Target Audience

Family Practice, Internal Medicine, General Practitioners, Endocrinologists, Pediatricians, APRNs, Registered Nurses, Registered Dietitians, Pharmacists, Certified Diabetes Educators, and other interprofessional health care providers.

PLANNING COMMITTEE

Jonea Lim, MD, Course Director
Associate Professor
Endocrinology and Diabetes Section
Harold Hamm Diabetes Center
University of Oklahoma College of Medicine

Niki Brooks, MSW, MHS, PA-C
Clinical Associate Professor
Physician Assistant Program
Oklahoma City University

Jodi Lavin-Tompkins MSN, RN, BC-ADM, CDCES
Director of Accreditation and Content
Association of Diabetes Care & Education Specialists

Emily Jones, PhD, RNC-OB, FAHA, FPCNA
Associate Professor
PhD Program Director
Fran and Earl Ziegler College of Nursing
University of Oklahoma College of Medicine

Christy Olson, MS, RDN, LD, CDCES
Dietitian and Diabetes Educator
OU Health Adult Diabetes & Endocrinology Clinic
Harold Hamm Diabetes Center
University of Oklahoma College of Medicine

Katherine O'Neal, PharmD, MBA, BCACP, CDCES, BC-ADM, AE-C, CLS, FADCES
Associate Professor
Ambulatory Care Degree Option, Co-Director
Department of Clinical and Administrative Sciences
University of Oklahoma College of Pharmacy
Adjunct Associate Professor, University of Oklahoma College of Medicine
Clinical Pharmacist, OU Physicians General Internal Medicine
Diplomate, Accreditation Council for Clinical Lipidology

Jeanie Tryggestad, MD
Associate Professor
Paul and Ruth Jonas Chair
Pediatric Diabetes and Endocrinology Section
Harold Hamm Diabetes Center-Children's
University of Oklahoma College of Medicine

SPEAKERS

Steven Kahn, MB, ChB –
Keynote Speaker
Leonard Wright and Marjorie Wright Chair
Professor, Division of Metabolism,
Endocrinology and Nutrition
Director, Diabetes Research Center
University of Washington and VA Puget
Sound Health Care System
Seattle, Washington

Rochelle Naylor, MD –
Keynote Speaker
Assistant Professor
Department of Pediatrics and Medicine
Section of Adult and Pediatric
Endocrinology, Diabetes, & Metabolism
The University of Chicago Medicine
Chicago, Illinois

Petter Bjornstad, MD
Assistant Professor
Department of Pediatrics and Medicine
Boettcher Investigator
School of Medicine
Univ. of Colorado Anschutz Medical Campus
Children's Hospital Colorado
Denver, Colorado

Michelle Dennison, PhD, RDN, LD, BC-ADM, CDCES
Director, Public Policy
Metabolic Care Center Grants Administrator
Oklahoma City Indian Clinic
Oklahoma City, Oklahoma

Itivrita Goyal, MD
Assistant Professor
Endocrinology and Diabetes Section
Harold Hamm Diabetes Center
Univ. of Oklahoma College of Medicine
Oklahoma City, Oklahoma

Rose Gubitosi-Klug, MD, PhD
Professor and Chief, Pediatric Endocrinology
William T. Dahms Professor of Pediatrics
Case Western Reserve University
Rainbow Babies and Children's Hospital
Cleveland, Ohio

Kathryn Jeter, PhD
Assistant Professor
Pediatric Diabetes and Endocrinology
Harold Hamm Diabetes Ctr- Children's
Univ. of Oklahoma College of Medicine
Oklahoma City, Oklahoma

Valarie Blue Bird Jernigan, DrPH, MPH
Professor of Rural Health
Director, Center for Indigenous Health
Research and Policy
Okla. State Univ. Center for Health Sciences
Tulsa, Oklahoma

Jonea Lim, MD
Associate Professor
Endocrinology and Diabetes Section
Harold Hamm Diabetes Center
Univ. of Oklahoma College of Medicine
Oklahoma City, Oklahoma

Christy Olson, MS, RDN, LD, CDCES
Dietitian and Diabetes Educator
OU Health Adult Diabetes & Endocrin. Clinic
Harold Hamm Diabetes Center
Univ. of Oklahoma College of Medicine
Oklahoma City, Oklahoma

Katherine S. O'Neal, PharmD, MBA, BCACP, CDCES, BC-ADM, AE-C, CLS, FADCES
Associate Professor
Dept. of Clinical and Administrative Sciences
Univ. of Oklahoma College of Pharmacy
Oklahoma City, Oklahoma

Sirish Palle, MD
Assistant Professor
Section of Pediatric Gastroenterology
Department of Pediatrics
Univ. of Oklahoma College of Medicine
Oklahoma City, Oklahoma

Jeanie Tryggestad, MD
Associate Professor
Pediatric Diabetes and Endocrinology
Harold Hamm Diabetes Center-Children's
Univ. of Oklahoma College of Medicine
Oklahoma City, Oklahoma

PLANNING COMMITTEE AND SPEAKER DISCLOSURES

In accordance with the ACCME Standards for Integrity and Independence, the Association of Diabetes Care & Education Specialists (ADCES) requires anyone in a position to affect or control continuing education content (e.g., authors, presenters, and program planners) to disclose all financial relationships with ineligible companies. It is the responsibility of ADCES to mitigate and disclose all relevant conflicts of interest. Disclosure of a relationship is not intended to suggest or condone bias in any presentation but is made to provide participants with information that might be of potential importance to their evaluation of the presentation.

Relevant disclosures (or lack thereof) among education activity planners and faculty are as follows:

Planning Committee:
Jeanie Tryggestad, MD – No conflicts of interest
Jonea Lim, MD – No conflicts of interest
Christy Olson, MS, RDN, LD, CDCES – No conflicts of interest
Katherine O'Neal, PharmD, MBA, BCACP, CDCES, BC-ADM, AE-C, CLS – No conflicts of interest
Emily Jones, PhD, RNC-OB, FAHA, FPCNA – No conflicts of interest
Niki Brooks, MSW, MHS, PA-C – No conflicts of interest
Jodi Lavin-Tompkins MSN, RN, BC-ADM, CDCES – No conflicts of interest

Speaker disclosures:
Jeanie Tryggestad, MD – No conflicts of interest
Jonea Lim, MD – No conflicts of interest
Christy Olson, MS, RDN, LD, CDCES – No conflicts of interest
Katherine O'Neal, PharmD, MBA, BCACP, CDCES, BC-ADM, AE-C, CLS, FADCES – No conflicts of interest
Petter Bjornstad, MD – Consultant: AstraZeneca, Bayer, Bristol-Meyer-Squibb, Boehringer-Ingelheim, Novo Nordisk, Eli Lilly, Horizon Pharma
Itivrita Goyal, MD – No conflicts of interest
Rose Gubitosi-Klug, MD, PhD – No conflicts of interest
Kathryn Jeter, PhD – No conflicts of interest
Valarie Blue Bird Jernigan, DrPH, MPH – No conflicts of interest
Michelle Dennison, PhD, RDN, LD, BC-ADM, CDCES – No conflicts of interest
Steven Kahn, MB, ChB - Consultant and Educational Events Speaker: Bayer, Casma Therapeutics, Eli Lilly, Intarcia, Merck, Novo Nordisk, Pfizer, Third Rock
Rochelle Naylor, MD – No conflicts of interest
Sirish Palle, MD – No conflicts of interest

Disclosure and Mitigation of Relevant Conflicts of Interest: All identified relevant conflicts of interest have been mitigated.

ACCREDITATION STATEMENTS

In support of improving patient care, this activity has been planned by Harold Hamm Diabetes Center and the Association of Diabetes Care & Education Specialists. The Association of Diabetes Care & Education Specialists is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

This activity was planned by and for the healthcare team, and learners will receive 7.0 Interprofessional Continuing Education (IPCE) credits for learning and change.

Accreditation Council for Pharmacy Education
The Universal Activity Number is JA4008258-9999-21-526-L01-P. This knowledge-based activity has been approved for 7.0 contact hour(s)

American Medical Association (AMA)
Association of Diabetes Care & Education Specialists designates this live activity for a maximum of 7.0 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

American Nurses Credentialing Center (ANCC)
Association of Diabetes Care & Education Specialists designates this activity for a maximum of 7.0 ANCC contact hours. This activity discusses 1.25 contact hours of pharmacotherapeutic content.

The Association of Diabetes Care & Education Specialists is approved by the California Board of Registered Nursing, Provider Number 10977, for 7.0 contact hours. RNs must retain this document for 4 years after the activity concludes.

The Association of Diabetes Care & Education Specialists has been authorized by the American Academy of PAs (AAPA) to award AAPA Category 1 CME credit for activities planned in accordance with AAPA CME Criteria. This activity is designated for 7.0 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation.

Commission on Dietetic Registration (CDR): CDR Credentialed Practitioners will receive 7.0 Continuing Professional Education units (CPEUs) for completion of this activity. Completion of this RD/DTR profession-specific or IPCE activity awards CPEUs (One IPCE credit = One CPEU). If the activity is dietetics-related but not targeted to RDs or DTRs, CPEUs may be claimed which are commensurate with participation in contact hours (One 60 minute hour = 1 CPEU). RDs and DTRs are to select activity type 102 in their Activity Log. Performance Indicator selection is at the learner's discretion.

Certified Diabetes Care and Education Specialists: To satisfy the requirements for renewal of certification for the Certification Board for Diabetes Care and Education (CBDCE), continuing education activities must be diabetes related and approved by a provider on the CBDCE list of Approved Providers (www.ncbde.org). CBDCE does not approve continuing education. The Association of Diabetes Care & Education Specialists is on the CBDCE list of Approved Providers.

Other Health Professionals
It is the responsibility of each participant to determine if the program meets the criteria for re-licensure or recertification for their discipline.

To Obtain a Statement of Continuing Education Credit:
To receive a statement of credit you must attend the entire conference. In order to receive a statement of credit, participants must complete and submit the conference evaluation. The evaluation will be emailed to participants on September 10, 2021. Once the evaluation has been completed and submitted, your statement of credit will be emailed to you. If you have any questions, please contact Katie Hoefling at Katie-Hoefling@ouhsc.edu

Accommodation Statement
The University of Oklahoma Health Sciences Center fully complies with the legal requirements of the ADA and the rules and regulations thereof. Please notify us if you have any special needs. Accommodations are available by contacting Katie Hoefling at Katie-Hoefling@ouhsc.edu

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Precision Medicine in Diabetes

Harold Hamm Diabetes Summit

Rochelle N. Naylor, MD
Assistant Professor of Pediatrics
Section of Adult and Pediatric Endocrinology, Diabetes and Metabolism

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Disclosure Statement

I have no financial interest of other relationship with any manufacturer/s of any commercial product/s which may be discussed at this activity.

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Objectives

- Provide an overview of the ADA's Precision Medicine in Diabetes consensus report
- Examine monogenic diabetes as a case study for precision medicine implementation
- Discuss approaches to applying precision medicine in polygenic forms of diabetes

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Diabetes Mellitus- The Scope of this Disease

- 463 million people worldwide have diabetes
- 10.5% of the US population (34.2 million people) have diabetes
- 34.5% of the US population (>88 million people) have prediabetes

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Diabetes Mellitus- The Cost of this Disease

$237 billion in direct medical cost

+

$90 billion in reduced productivity

$327 billion for diagnosed diabetes

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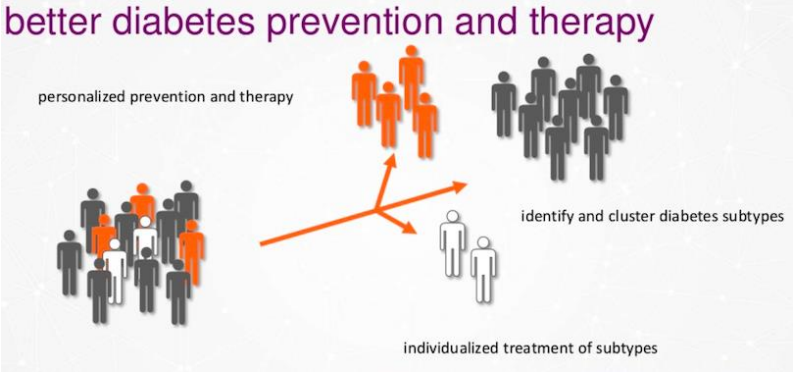
Diabetes Mellitus- Many Diseases

- Heterogeneous group of metabolic disorders characterized by sustained hyperglycemia



https://neo4j.com/blog/graphs-to-fight-diabetes/

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Precision Medicine in Diabetes Initiative

Precision Medicine in Diabetes Initiative

Precision Diabetes Medicine 2021 (PDM2021)

2019 Research Symposium

Overview

The American Diabetes Association (ADA) is establishing the Precision Medicine in Diabetes Taskforce that will, over the coming 5 years, formulate a consensus statement on precision diabetes medicine as well as initiate complementary activities.

- The overall objective is to improve diabetes care by realizing the promise of precision medicine for diabetes.
- Vision Statement- Through engagement of a broad group of stakeholder representatives, our vision is realizing a future of longer, healthier lives for people with diabetes, achieved by applying the appropriate treatment for the appropriate person at the appropriate time.

Wendy K. Chung et al. Dia Care 2020;43:1617-1635

What Precision Medicine Is…and Is Not

Precision medicine ≠ Personalized medicine

Diabetes Precision Medicine

- Precision diagnostics
- Precision therapeutics
- Precision prevention
- Precision prognostics
- Precision monitoring

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The Path to Precision Diabetes Medicine

• ***Precision diagnosis*** involves refining the characterization of the diabetes diagnosis for therapeutic optimization or to improve prognostic clarity using information about a person's unique biology, environment, and/or context.

○ Precision diagnostics may involve subclassifying the diagnosis into subtypes, such as is the case in MODY, or utilizing probabilistic algorithms that help refine a diagnosis without categorization.

○ Careful diagnosis is often necessary for successful precision therapy, whether for prevention or treatment. This is true where subgroup(s) of the population must be defined, within which targeted interventions will be applied, and also where one seeks to determine whether progression toward disease has been abated.

○ Precision diagnosis can be conceptualized as a pathway that moves through stages, rather than as a single step. The diagnostic stages include *1*) an evaluation of prevalence based on epidemiology, including age, or age at diagnosis of diabetes, sex, and ancestry; *2*) probability based on clinical features; and *3*) diagnostic tests that are interpreted in the light of *1*) and *2*). A diagnosis in precision medicine is a probability-based decision, typically made at a specific point in the natural history of a disease, and neither an absolute truth nor a permanent state.

Wendy K. Chung et al. Dia Care 2020;43:1617-1635

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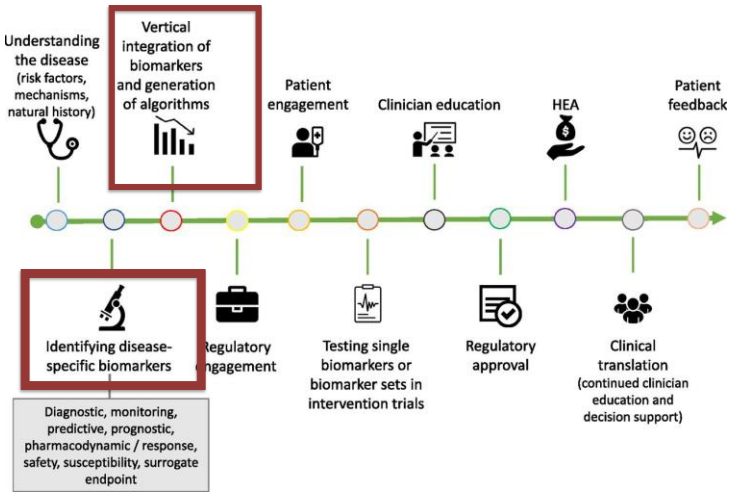
The Path to Precision Diabetes Medicine



Wendy K. Chung et al. Dia Care 2020;43:1617-1635

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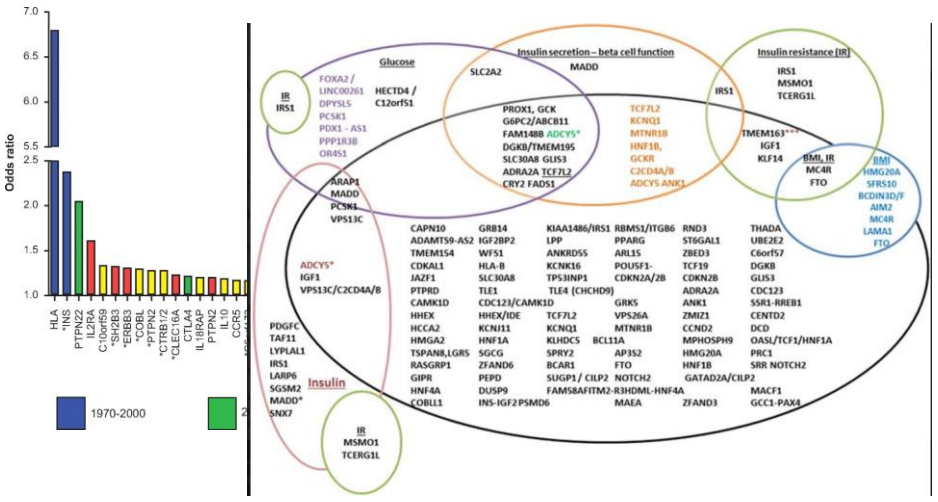
Incorporating Genetic Precision Medicine into Clinical Practice



Flemming Pociot, Beena Akolkar, Patrick Concannon, et al. Genetics of Type 1 Diabetes: What's Next? Diabetes Jul 2010, 59 (7) 1561-1571; **DOI:** 10.2337/db10-0076

Prasad RB, Groop L. Genetics of Type 2 Diabetes—Pitfalls and Possibilities. *Genes*. 2015; 6(1):87-123. https://doi.org/10.3390/genes6010087

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Monogenic Diabetes: Many Diseases of the Beta Cell

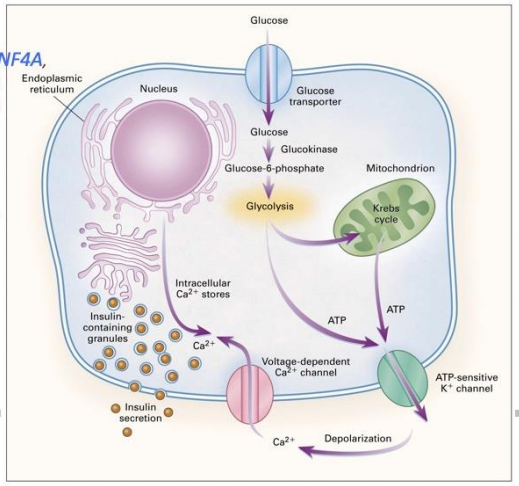
Genetic disorder of gene expression
HNF1A, HNF1B, HNF4A, PDX1, NEUROD1, GLIS3 PAX4, PAX6, NEUROG3, PTF1A, RFX6, GATA6, GATA4, MNX1, NKX2-2

Genetic disorder of ER stress
EIF2AK3, WFS1, WFS2, IER3IP1

Genetic disorder of insulin synthesis
INS

Epigenetic disorder of the beta cell
6q24, ZFP57

Genetic disorder of glucose transport
SLC2A2 (GLUT2)



Genetic disorder of glucose metabolism
GCK

Primary genetic disorder of auto-immunity
FOXP3, AIRE, SIRT1

Genetic disorder of the exocrine pancreas
CEL, CFTR

Genetic disorder of ion channels
KCNJ11, ABCC8

Genetic disorder of insulin secretion
SLC19A2 (Thiamine transporter-1)

Genetic disorder of tRNA methyl-transferase
TRMT10A

Monogenic Diabetes

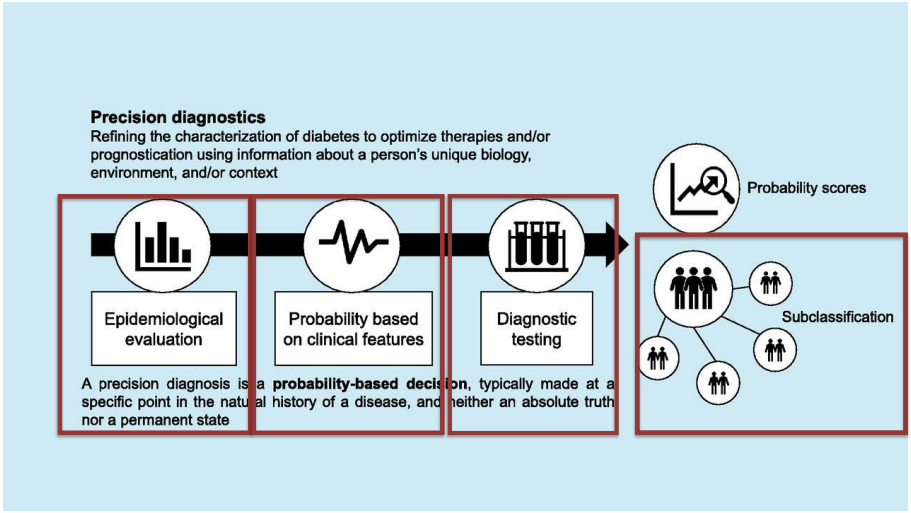
- 0.4% of all diabetes
- ~3.5% of all diabetes diagnosed under 30 years
- Due to highly penetrant mutations in genes that are important to beta cell function and may affect other parts of the body

Monogenic Diabetes

- Two main clinical phenotypes
- Neonatal diabetes- "Simple" phenotype
  - Do genetic testing for diagnosis <6 months of age (consider for 7-12 months of age)
  - Probe for details if someone says "I have had diabetes my whole life"
- Maturity-onset diabetes of the young (MODY)

Approaches to Diagnosing MODY

Monogenic Diabetes as a Model of Precision Medicine



Wendy K. Chung et al. Dia Care 2020;43:1617-1635

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Diabetes Mellitus- Many Diseases

Table 1. Features of the most frequent types of maturity-onset diabetes of the young (MODY) compared to common forms of diabetes.

Feature	Type 1 diabetes	Type 2 diabetes	GCK-MODY	HNF1A- and HNF4A-MODY
Typical age of onset (years)	10–30	>25	Fasting hyperglycaemia from birth	10–45
β-cell antibodies	>90% at diagnosis	Negative by definition	Rare	Rare
Diabetic ketoacidosis	Common	Rare	Not observed	Rare
Parental diabetes	10–15%	Common	Not always reported, but one parent has impaired fasting glucose (IFG) if tested	60–90%, depending on ascertainment criteria
C-peptide levels	Undetectable/low	Normal/high	Normal	Normal
Features of insulin resistance	Infrequent	Common	Infrequent	Infrequent
hsCRP levels	Normal	Often chronically elevated	Normal	Suppressed in HNF1A-MODY Normal in HNF4A-MODY
First-line treatment	Insulin	Metformin	Nil	Low-dose sulphonylurea

GCK = glucokinase; HNF1A = hepatocyte nuclear factor 1-alpha; HNF1β = hepatocyte nuclear factor 1-beta.

Katharine R Owen
Clinical Medicine Jun 2013, 13 (3) 278-281

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Useful Labs in Diabetes Classification

Pancreatic autoantibodies GAD65, islet cell antibodies (IA-2, ICA), insulin, Znt8	Negativity at diabetes onset should prompt consideration of MODY. Positive antibodies at or after diagnosis suggests type 1 diabetes, though exceptions occur.
C-peptide	Clearly positive C-peptide levels (≥0.60 ng/mL or 0.2 nmol/L)after 3-5 years duration of clinically diagnosed type 1 diabetes should prompt consideration of MODY.
Urine C-peptide creatinine ratio (UCPCR)	Useful after diabetes of >5 year's duration. UCPCR is higher in *HNF1A*-MODY and *HNF4A*-MODY compared to type 1 diabetes. UCPCR of ≥0.2 nmol/mmol should prompt consideration of MODY.
High sensitivity C-Reactive protein (hs-CRP)	Mean hs-CRP is consistently lower in *HNF1A*-MODY compared to other monogenic and polygenic forms of diabetes. hs-CRP <0.75 mg/L should prompt consideration of MODY.
HbA1c- useful when considering a diagnosis of *GCK*-MODY	Values consistent with *GCK*-MODY: 5.6–7.3% (38–56 mmol/mol) at ages </=40 years 5.9–7.6% (41-60 mmol/mol) at ages >40 years
MODY Probability Calculator	For use in estimating the likelihood of a MODY diagnosis in patients with diabetes onset before age 35 years. Developed in a European Caucasian cohort. diabetesgenes.org/content/mody-probability-calculator
Type 1 diabetes genetic risk score (T1D-GRS)	Discriminates T1DM from MODY and NDM T1D-GRS >50th T1D centile is indicative of T1DM (94% specificity, 50% sensitivity)

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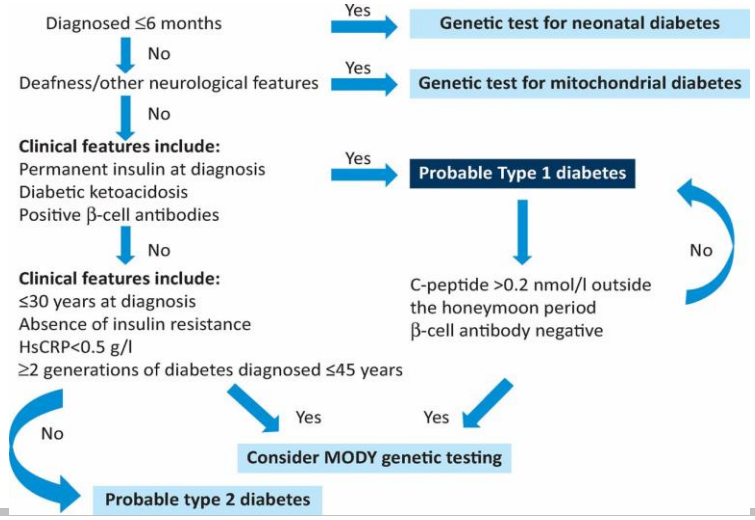
Precision Diagnostics in Diabetes



Katharine R Owen
Clinical Medicine Jun 2013, 13 (3) 278-281

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Diabetes Care Volume 40, August 2017 1017

Population-Based Assessment of a Biomarker-Based Screening Pathway to Aid Diagnosis of Monogenic Diabetes in Young-Onset Patients

Beverley M. Shields,[1,2] Maggie Shepherd,[1,2] Michelle Hudson,[1] Timothy J. McDonald,[1,3] Kevin Colclough,[4] Jaime Peters,[5] Bridget Knight,[1,2] Chris Hyde,[5] Sian Ellard,[1,4] Ewan R. Pearson,[6] and Andrew T. Hattersley,[1,2] on behalf of the UNITED study team

Diabetes Care 2017;40:1017–1025 | https://doi.org/10.2337/dc17-0224

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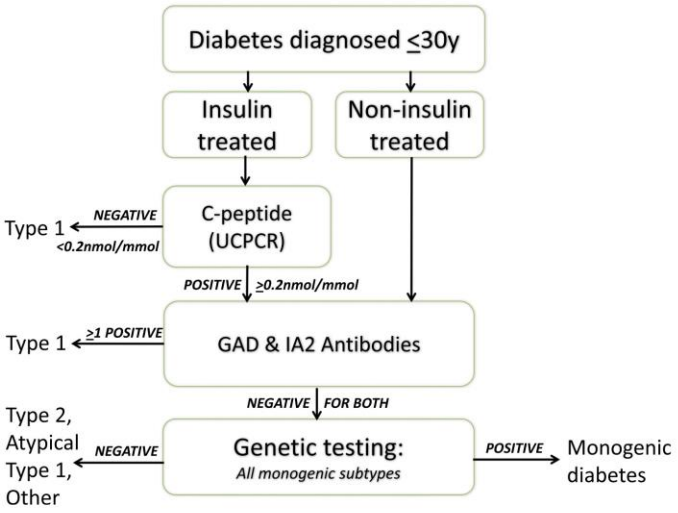

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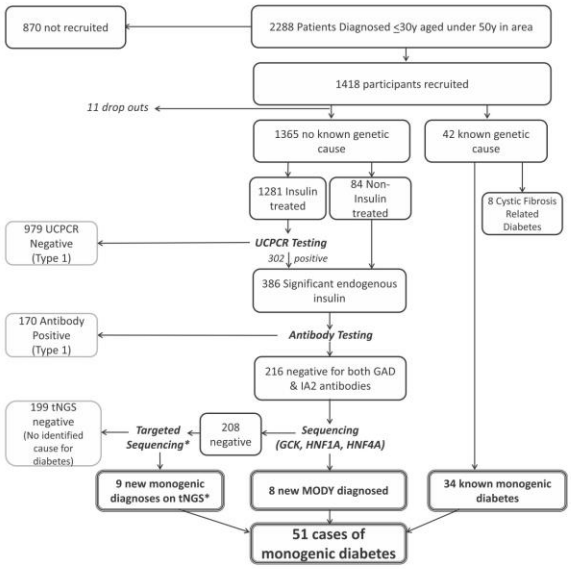

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Table 2—PPV and NPV values for the biomarker pathway, traditional MODY criteria (age at diagnosis younger than 25 years, non–insulin-treated, and parent affected with diabetes), and the MODY probability calculator (using a probability >25%, the pickup rate for the diagnostic laboratory)

	N	Prevalence of monogenic diabetes	PPV (%)	NPV (%)	Percentage of monogenic cases missed	Number needed to test
Biomarker pathway	1,407	3.6% (51/1,407)	20.0	99.91	0	5
Traditional MODY criteria	1,362	3.6% (49/1,362)	57.6	97.7	63	2
MODY probability calculator	1,347	3.3% (45/1,347)	40.4	98.3	55	3

Prevalence is the proportion of diagnosed monogenic diabetes, percentage of monogenic cases missed is the proportion of monogenic cases not picked up by the approach, and number needed to test is 1/PPV.

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Diabetes Care Volume 42, December 2019 2247

The Impact of Biomarker Screening and Cascade Genetic

Matthew S. GoodSmith,[1]
M. Reza Skandari,[2] Elbert S. Huang,[3] and
Rochelle N. Naylor[4]

RESULTS The strategy of biomarker screening and genetic testing was cost-saving as it increased average quality of life (+0.0052 QALY) and decreased costs (−$191) per simulated patient relative to the control arm. Adding cascade genetic testing increased quality-of-life benefits (+0.0081 QALY) and lowered costs further (−$735).

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Ordering Genetic Testing

Monogenic Diabetes Diabetes

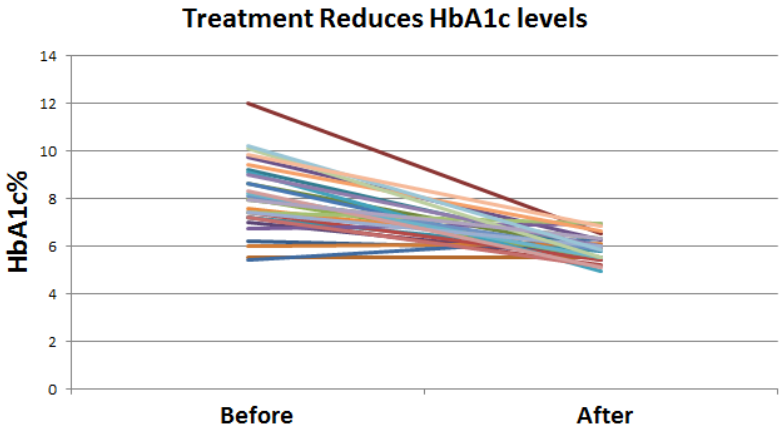
- CLIA-certified labs
  - Academic-based labs (e.g, The University of Chicago Genetics Services Lab), GeneDx, Athena Diagnostics, Invitae, LabCorp, Prevention Genetics, many others
- Get a prior authorization FIRST!
  - Don't forget co-pays
- Encourage patients to inquire about payment plans/assistance from the labs
- Get help interpreting the genetic test report if needed

monogenicdiabetes@uchicago.edu

MonogenicDiabetesRegistry.org

Precision Medicine in Monogenic Diabetes

Diabetes Control Improves After Transition to Sulfonylureas in K-ATP Related Neonatal Diabetes



Mean HbA1c: 8.1 ± 1.5 → 5.9 ± 0.4

P < 0.0001, n = 44

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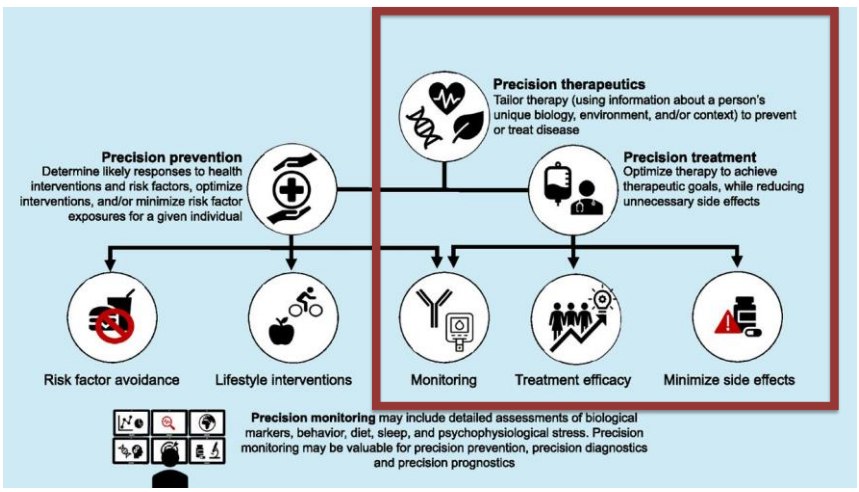
Monogenic Diabetes as a Model of Precision Medicine



Wendy K. Chung et al. Dia Care 2020;43:1617-1635

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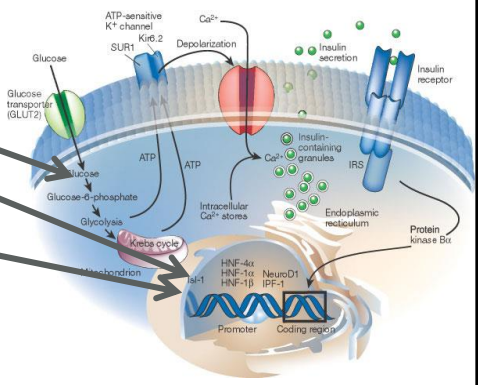
Management of the Common & Clinically Actionable forms of MODY

- GCK- MODY
- HNF1A-MODY
- HNF4A-MODY
- HNF1B-MODY



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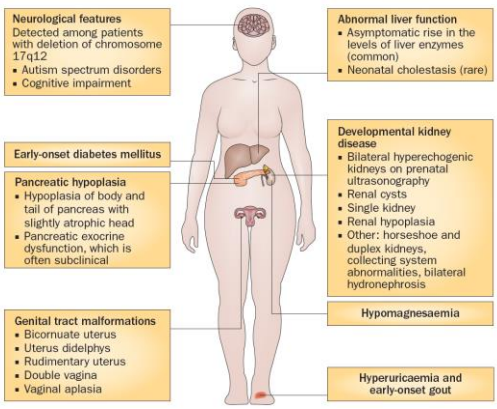
HNF1B-MODY

- <5% of MODY cases
- Approximately 30% will respond to sulfonylureas
- The majority of patients will require insulin treatment



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Clinically Actionable MODY

- MODY due to *HNF1A*, *HNF4A*, or*GCK* is **clinically actionable**
- Treatment is not needed for GCK-MODY and HbA1c doesn't change
  - Decreased costs, medical surveillance, exposure to adverse medication outcomes
- First-line therapy for HNF1A- and HNF4A-MODY is sulfonylureas
  - Decreased drug costs, decrease in HbA1c, expected decrease in diabetes-related complications

HNF1A-MODY and HNF4A-MODY

- HNF1A-MODY is the most common cause of MODY worldwide; HNF4A-MODY represents ~5% of all MODY cases
- Progressive defect in glucose-dependent insulin secretion resulting in young-onset diabetes
- At risk for diabetes-related microvascular and macrovascular, tied to glycemic control

HNF1A-MODY- Clinical presentation

- Low renal glucose threshold
- Large incremental increase between fasting and 2 hour glucose on OGTT (usually >90 mg/dL [5.0 mmol/L])
  - Can have normal fasting glucose even while HbA1c is abnormally high due to postprandial hyperglycemia
- Lower hsCRP levels (vs T2DM, T1DM, other MODY)
- Higher urinary c-peptide to creatinine ratio (vs T1DM)
- Normal/Increased HDL, but CV risk is higher than in non-affected first-degree relatives → Give statin therapy

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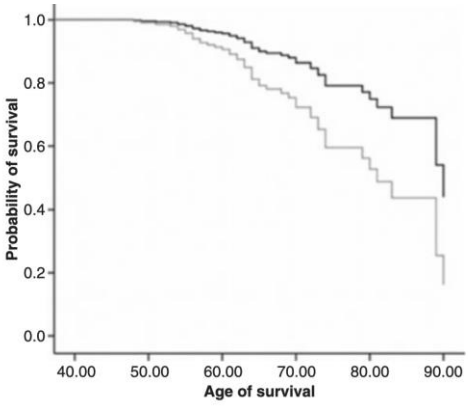
DIABETICMedicine
DOI: 10.1111/j.1464-5491.2009.02913.x

Original Article: Complications

Increased all-cause and cardiovascular mortality in monogenic diabetes as a result of mutations in the *HNF1A* gene

A. M. Steele*, B. M. Shields*, M. Shepherd*, S. Ellard*, A. T. Hattersley* and E. R. Pearson*†



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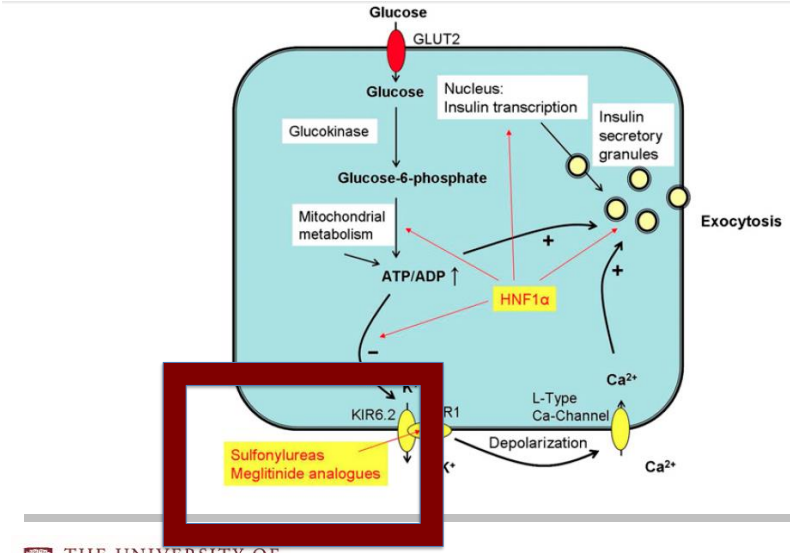
HNF4A-MODY

- Clinical presentations
  - Fetal macrosomia
  - Transient neonatal hypoglycemia
  - Diabetes presentation in adolescence or early adulthood
- Laboratory features
  - Possible low HDL, lipoprotein A1, A2

Precision medicine for HNF1A-MODY & HNF4A-MODY



Sensitivity to Sulfonylureas

- Transitioning from insulin to sulfonylureas is associated with stable or decreased HbA1c
  - 0.8-1.5% decrement demonstrated in HNF1A-MODY
  - Important implications for diabetes complications given strong relationship between HbA1c and likelihood of microvascular complications
  - Dedicated tertiary MODY clinic showed much lower complication rates in modern HNF1A-MODY cohort versus historical cohorts

DIABETICMedicine

DOI: 10.1111/dme.12992

Research: Genetics

Successful maintenance on sulphonylurea therapy and low diabetes complication rates in a HNF1A–MODY cohort

S. Bacon[1], M. P. Kyithar[1], S. R. Rizvi[1], E. Donnelly[1], A. McCarthy[1], M. Burke[1], K. Colclough[2], S. Ellard[2,3] and M. M. Byrne[1]

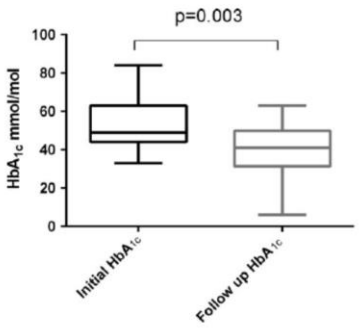


Table 3 Indication for alternative or additional agent to sulphonylurea therapy at median 84-month follow-up

Medication	Indication for alternative agent to sulphonylurea
Sulphonylurea + Basal insulin	Suboptimal glycaemic control; *n* = 5 Patient preference; *n* = 2
Sulphonylurea + Metformin	Weight gain; *n* = 3 Suboptimal glycaemic control; *n* = 2
Sulphonylurea + GLP–1 agonist	Weight gain
Sulphonylurea + DPP–4 inhibitor	Suboptimal glycaemic control
Insulin + metformin	Unable to tolerate sulphonylurea and weight gain
Diet alone	Good glycaemic control
Metformin only	Pre-pregnancy; *n* = 1 Weight gain; *n* = 4
Insulin (multiple daily injections)	Pre-pregnancy; *n* = 1 Contraindication to sulphonylurea therapy (renal impairment); *n* = 1 Patient preference; *n* = 2

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Sensitivity to Sulfonylureas

- Typically start with ¼- ½ pill for treatment, and escalate as needed
  - If you are using type 2 diabetes doses, then that is a sign of non-response
  - Durability varies
    - Weight gain increases the likelihood of sulfonylurea failure
- Meglitinides are an alternative treatment option if hypoglycemia is a problem

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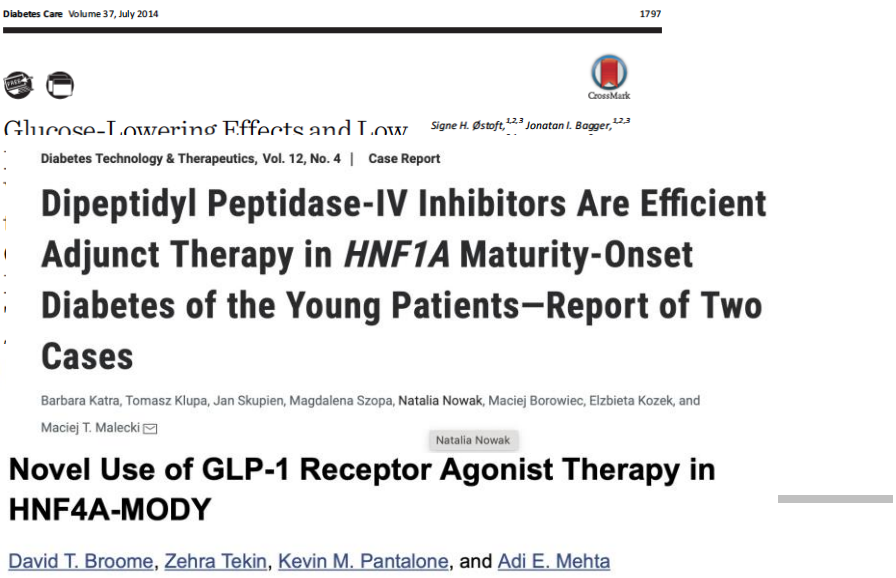
Augmentative/Alternative Therapy



Diabetes Care Volume 37, July 2014 1797

Glucose-Lowering Effects and Low ... Signe H. Østoft,[1,2,3] Jonatan I. Bagger,[1,2,3]

Diabetes Technology & Therapeutics, Vol. 12, No. 4 | Case Report

Dipeptidyl Peptidase-IV Inhibitors Are Efficient Adjunct Therapy in *HNF1A* Maturity-Onset Diabetes of the Young Patients—Report of Two Cases

Barbara Katra, Tomasz Klupa, Jan Skupien, Magdalena Szopa, **Natalia Nowak**, Maciej Borowiec, Elzbieta Kozek, and Maciej T. Malecki

Natalia Nowak

Novel Use of GLP-1 Receptor Agonist Therapy in HNF4A-MODY

David T. Broome, Zehra Tekin, Kevin M. Pantalone, and Adi E. Mehta

GCK-MODY

- Glucokinase catalyzes the first step in glucose metabolism
- Heterozygous inactivating mutations in *GCK* raise the set-point for glucose stimulated insulin release (GSIR) to 120-130 mg/dL
- Stable, mild fasting hyperglycemia

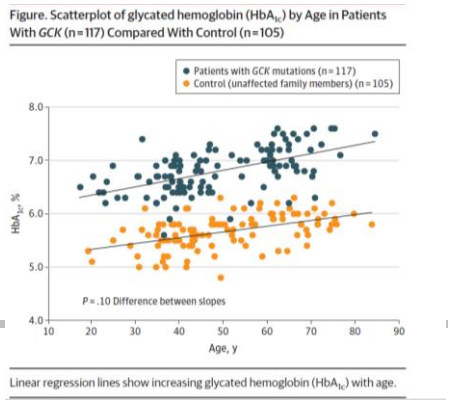


Figure. Scatterplot of glycated hemoglobin (HbA_{1c}) by Age in Patients With *GCK* (n = 117) Compared With Control (n = 105)

Linear regression lines show increasing glycated hemoglobin (HbA_{1c}) with age.

GCK-MODY

- Clinical presentations
  - Asymptomatic incidental finding, especially in children
  - GDM with continued hyperglycemia after delivery
- Laboratory features
  - Fasting glucose typically ranges from 99-144 mg/dL (5.5-8 mmol/L)
  - Small incremental increase between fasting and 2 hour glucose on OGTT (usually <65 mg/dL [3.6 mmol/L])
  - Hemoglobin A1c typically 5.6-7.8%

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Research

Original Investigation

Prevalence of Vascular Complications Among Patients With Glucokinase Mutations and Prolonged, Mild Hyperglycemia

Anna M. Steele, PhD; Beverley M. Shields, PhD; Kirsty J. Wensley, AdDip(Nursing); Kevin Colclough, BSc; Sian Ellard, PhD; Andrew T. Hattersley, DM

Both microvascular and macrovascular complications are rare in GCK-MODY

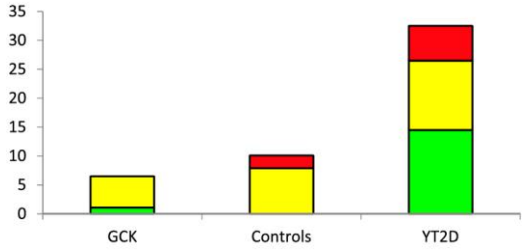

Figure 1—Prevalence of clinically significant microvascular (green) and clinically significant macrovascular (yellow) disease alone and combined microvascular and macrovascular disease combined (red) in patients with GCK-MODY (GCK), control subjects, and patients with young-onset type 2 diabetes (YT2D). Clinically significant microvascular disease, defined as greater than background retinopathy or persistent microalbuminuria or proteinuria; clinically significant macrovascular disease, defined as intermittent claudication, amputation, angina, myocardial infarction, or stroke.

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Precision medicine for GCK-MODY…

Is no medicine at all

(most of the time)

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Precision medicine for GCK-MODY

Diabetologia
DOI 10.1007/s00125-013-3075-x

SHORT COMMUNICATION

Cross-sectional and longitudinal studies suggest pharmacological treatment used in patients with glucokinase mutations does not alter glycaemia

Amanda Stride · Beverley Shields · Olivia Gill-Carey · Ali J. Chakera · Kevin Colclough · Sian Ellard · Andrew T. Hattersley

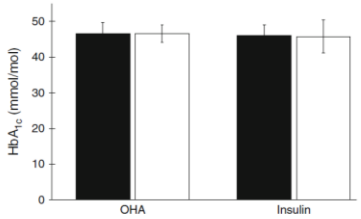

Fig. 1 Bar chart of mean HbA_{1c} for patients with GCK-MODY treated with either OHAs ($n=6$) or insulin ($n=10$). Black columns represent HbA_{1c} during treatment and white columns represent HbA_{1c} once treatment had stopped. Error bars represent 95% CIs. To convert values for HbA_{1c} in mmol/mol into %, add 2.15 and divide by 10.929 or use the conversion calculator at www.hba1c.nu/eng/

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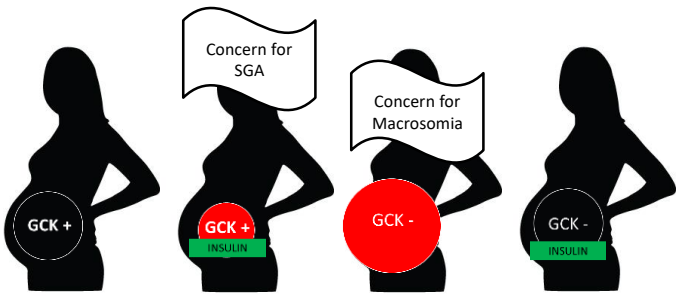
GCK-MODY in Pregnancy

- Outside of pregnancy → treatment unnecessary and ineffective
- In pregnancy → treatment based on fetal genotype



GCK-MODY Management in Pregnancy

- In pregnancy, treatment is based on fetal genotype

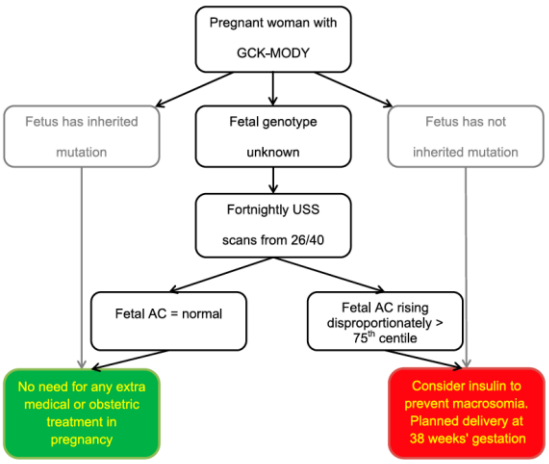


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Figure 3—Flow diagram for the management of GCK-MODY pregnancy. AC, abdominal circumference; USS, ultrasound scan.

GCK-MODY Outcomes in Pregnancy

- There are unresolved questions on maternal and fetal risks related to how GCK-MODY is managed
- The best management is still unclear

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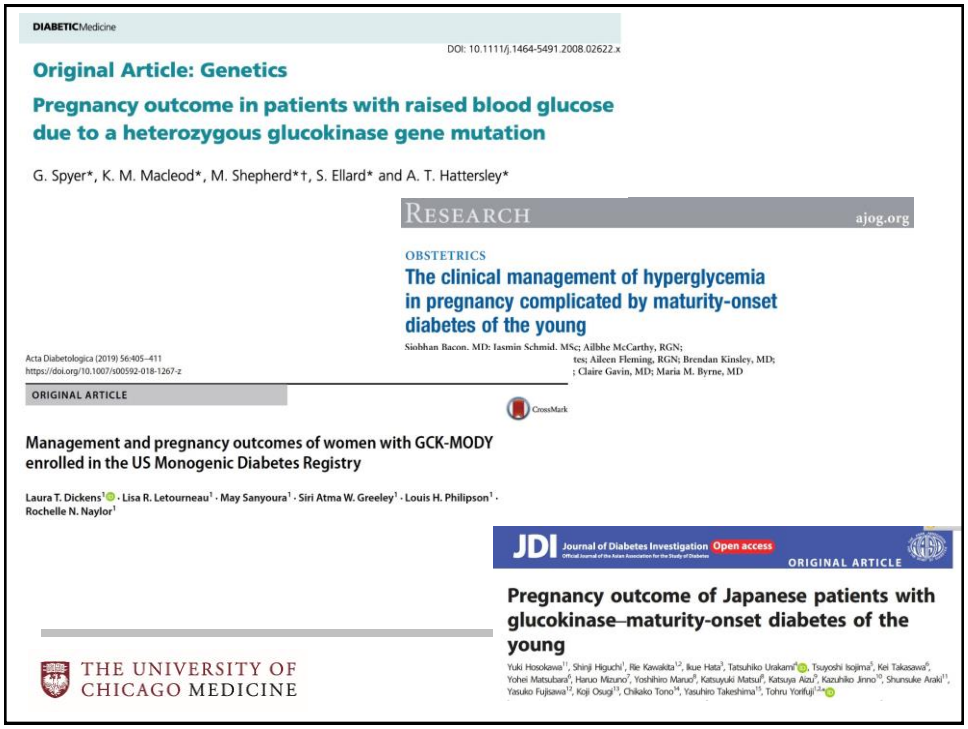

DIABETICMedicine

DOI: 10.1111/j.1464-5491.2008.02622.x

Original Article: Genetics

Pregnancy outcome in patients with raised blood glucose due to a heterozygous glucokinase gene mutation

G. Spyer*, K. M. Macleod*, M. Shepherd*†, S. Ellard* and A. T. Hattersley*

RESEARCH ajog.org

OBSTETRICS

The clinical management of hyperglycemia in pregnancy complicated by maturity-onset diabetes of the young

Siobhan Bacon, MD; Jasmin Schmid, MSc; Ailbhe McCarthy, RGN; tes; Aileen Fleming, RGN; Brendan Kinsley, MD; ; Claire Gavin, MD; Maria M. Byrne, MD

Acta Diabetologica (2019) 56:405–411
https://doi.org/10.1007/s00592-018-1267-z

ORIGINAL ARTICLE

CrossMark

Management and pregnancy outcomes of women with GCK-MODY enrolled in the US Monogenic Diabetes Registry

Laura T. Dickens[1] · Lisa R. Letourneau[1] · May Sanyoura[1] · Siri Atma W. Greeley[1] · Louis H. Philipson[1] · Rochelle N. Naylor[1]

JDI Journal of Diabetes Investigation Open access

ORIGINAL ARTICLE

Pregnancy outcome of Japanese patients with glucokinase–maturity-onset diabetes of the young

Yuki Hosokawa[1†], Shinji Higuchi[1], Rie Kawakita[1,2], Ikue Hata[3], Tatsuhiko Urakami[4], Tsuyoshi Isojima[5], Kei Takasawa[6], Yohei Matsubara[6], Haruo Mizuno[7], Yoshihiro Maruo[8], Katsuyuki Matsui[8], Katsuya Aizu[9], Kazuhiko Jinno[10], Shunsuke Araki[11], Yasuko Fujisawa[12], Koji Osugi[13], Chikako Tono[14], Yasuhiro Takeshima[15], Tohru Yorifuji[1,4]

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GCK-MODY Outcomes in Pregnancy: Neonatal Outcomes

Acta Diabetologica (2019) 56:405–411
https://doi.org/10.1007/s00592-018-1267-z

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GCK-MODY Outcomes in Pregnancy: Neonatal Outcomes

Table 1 Background information about survey respondents and pregnancies

Respondents	54
Pregnancies	128
Average age at pregnancy	29.9 years (range 17–41 years)
Average number of pregnancies	2.7 (range 1–6)
Hyperglycemia diagnosed before pregnancy	51 (40%)
GCK	18 (+2 suspected MODY)
Gestational diabetes	10
Type 1 diabetes	4
Type 2 diabetes or pre-diabetes	26
Caucasian race by self-report	48 (89%)

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Table 2 Management of known GCK-MODY

GCK diagnosis known before pregnancy	18/128 (14%)
Glucose-lowering medication prior to pregnancy	6 (33%)
Healthcare provider during pregnancy (respondents could select more than 1)	
Family physician	2 (11%)
General obstetrician	13 (72%)
High-risk obstetrician	11 (61%)
Endocrinologist	13 (72%)
Midwife	3 (17%)
Dietary changes recommended	10 (56%)
Treatment during pregnancy	
No medication	7 (39%)
Oral (glyburide)	1 (6%)
Insulin[a]	10 (56%)
Average timing of insulin initiation when started during pregnancy (weeks)	16.4 (range 5–32)
Pregnancy outcome	
Term birth	13 (72%)
Pre-term birth	3 (17%)
Currently pregnant	2 (11%)

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GCK-MODY Outcomes in Pregnancy: Neonatal Outcomes

Table 3 Fetal birth weight by genotype and maternal treatment

Infant genotype	Maternal treatment	Number of infants (full term)	Average birth weight (SD) for term infants (g)	*p* value	Average birth weight percentile (SD)[a] for all infants	*p* value
GCK +	Insulin	8 (7)	2967 (9330)		34 (27)	
	No treatment	15 (14)	3725 (568)	0.005	58 (33)	0.110
GCK −	Insulin	9 (5)	3757 (532)		84 (22)	
	No treatment	3 (2)	4023 (284)	0.489	90 (8)	0.530

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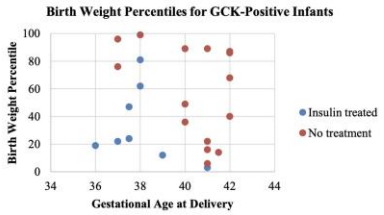
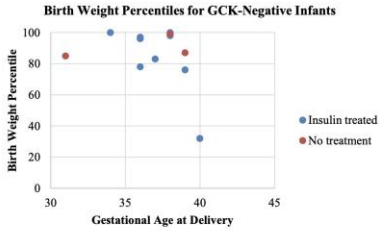
GCK-MODY Outcomes in Pregnancy: Neonatal Outcomes





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Cell-free fetal DNA for GCK-MODY

Clinical Chemistry 66:7
958-965 (2020)

Molecular Diagnostics and Genetics

Noninvasive Fetal Genotyping by Droplet Digital PCR to Identify Maternally Inherited Monogenic Diabetes Variants

Richard C. Caswell,[a,b] Tristan Snowsill,[c] Jayne A.L. Houghton,[a,b] Ali J. Chakera,[a,d] Maggie H. Shepherd,[a,e] Thomas W. Laver,[a] Bridget A. Knight,[a,e] David Wright,[f] Andrew T. Hattersley,[a,b] and Sian Ellard[a,b,*]

Sequencing cell-free fetal DNA in pregnant women with GCK-MODY: a proof-of-concept study

Soo Heon Kwak ✉, Camille E Powe, Se Song Jang, Michael J Callahan, Sarah N Bernstein, Seung Mi Lee, Sunyoung Kang, Kyong Soo Park, Hak C Jang, Jose C Florez ... Show more

The Journal of Clinical Endocrinology & Metabolism, dgab265,
https://doi.org/10.1210/clinem/dgab265
Published: 20 April 2021 **Article history ▾**

Monogenic Diabetes Clinical take home points

- Young-onset diabetes: Always consider MODY!
- Always get a PA before ordering genetic testing
  - monogenicdiabetes@uchicago.edu
    - For PA letters
    - Help interpreting reports
- Implement precision therapeutics:
  - HNF1A-MODY- Sulfonylureas and a statin
  - HNF4A-MODY- Sulfonylureas
  - GCK-MODY- No pharmacologic therapy and de-escalate diabetes care

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Applying Precision Medicine to Polygenic Forms of Diabetes

THE FUTURE

Diabetes Sub-Classification in Type 1 Diabetes

> Zhonghua Nei Ke Za Zhi. 2004 Mar;43(3):174-8.

[Subclassification of seronegative type 1 diabetic subjects with HLA-DQ genotypes]

[Article in Chinese]

Dong-mei Zhang [1], Zhi-guang Zhou, Chi Zhang, Gan Huang, Ping Jin, Jian-ping Wang, Jia-li Wei, Bai-ying Hu

Diabetes Sub-Classification in Type 2 Diabetes

From Wikipedia, the free encyclopedia. A **wastebasket diagnosis** or **trashcan diagnosis** is a vague **diagnosis** given to a patient or to medical records department for essentially non-medical reasons.

https://en.wikipedia.org › wiki › Wastebasket_diagnosis

Wastebasket diagnosis - Wikipedia

https://dictionary.cambridge.org/images/thumb/wastep_noun_002_40605_2.jpg?version=5.0.161

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Diabetes Sub-Classification in Type 2 Diabetes

frontiers in Genetics

New insights from monogenic diabetes for "common" type 2 diabetes

Divya Sri Priyanka Tallapragada, Seema Bhaskar, and Giriraj R. Chandak

wide association studies. The diagnosis of T2D can rather be considered "*waste basket diagnosis*"—not because there is *no-cause*, but because there is *no-one-cause*. The rate of

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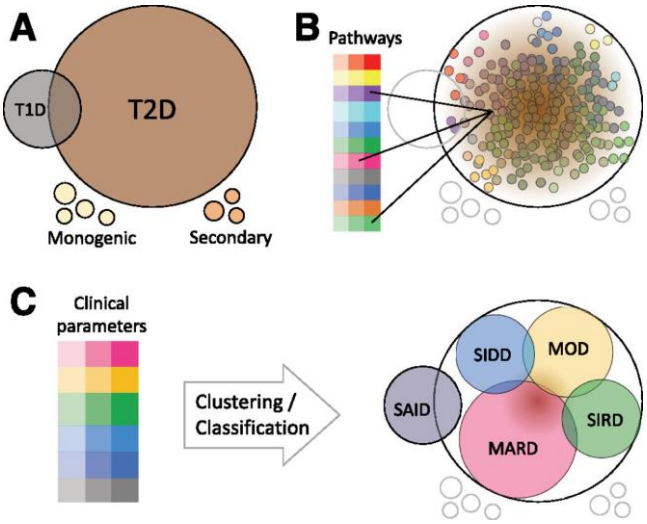
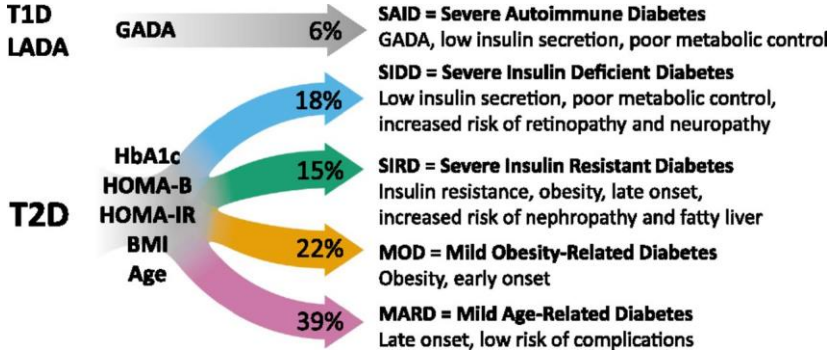
Schematic representations of diabetes classification and models of heterogeneity.



Emma Ahlqvist et al. Diabetes 2020;69:2086-2093

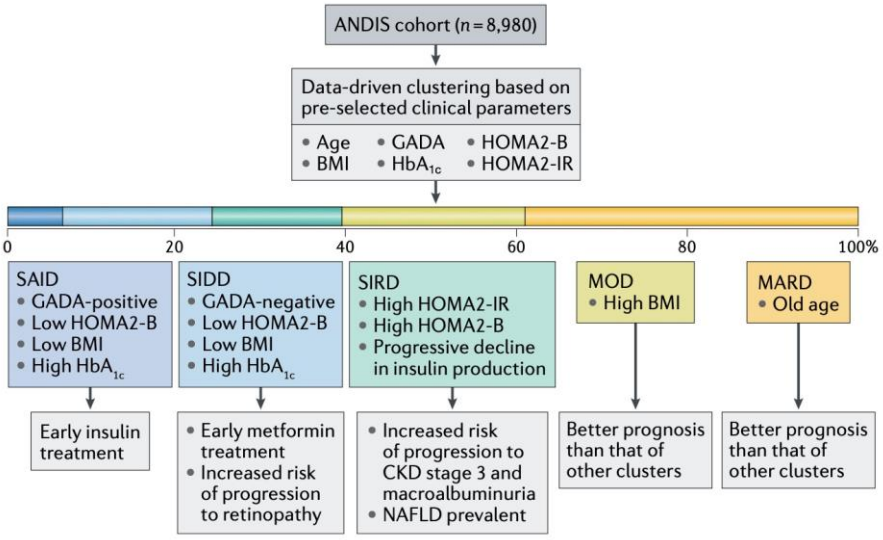
American Diabetes Association.

Novel diabetes subtype characteristics.



Emma Ahlqvist et al. Diabetes 2020;69:2086-2093

American Diabetes Association.



Applying Precision Medicine to Polygenic Forms of Diabetes

THE NOW

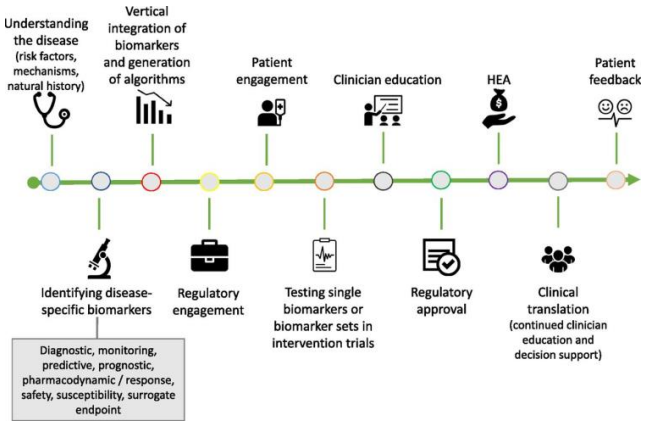
Applying a Precision Lens to Type 1 Diabetes

- Always use biomarkers
  - Antibody testing
  - C-peptide
- Do not ignore obesity
  - Discuss Metformin, lifestyle changes

Applying a Precision Lens to Type 2 Diabetes

- Always use biomarkers
  - Antibody testing
  - C-peptide
- Consider ancestry and how that impacts BMI assessment
- Use a step-wise approach to therapy considering options other than insulin as your second-line agent for appropriate clinical pictures

The Path to Precision Diabetes Medicine



Wendy K. Chung et al. Dia Care 2020;43:1617-1635

https://www.uhhospitals.org/Healthy-at-UH/articles/2020/04/5-things-to-know-about-kids-and-diabetes

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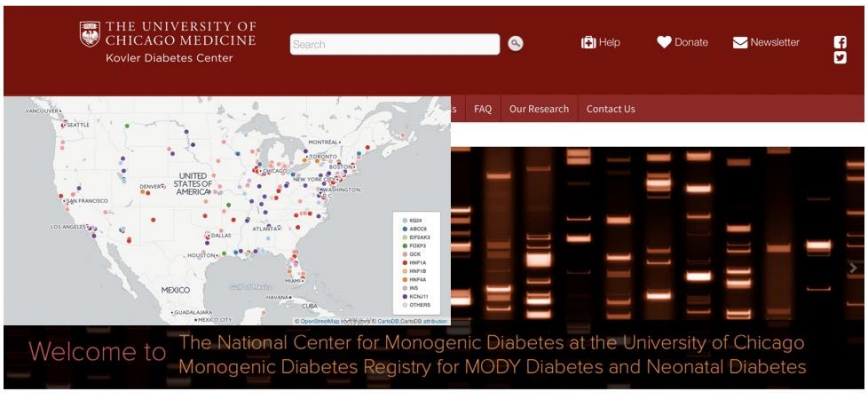
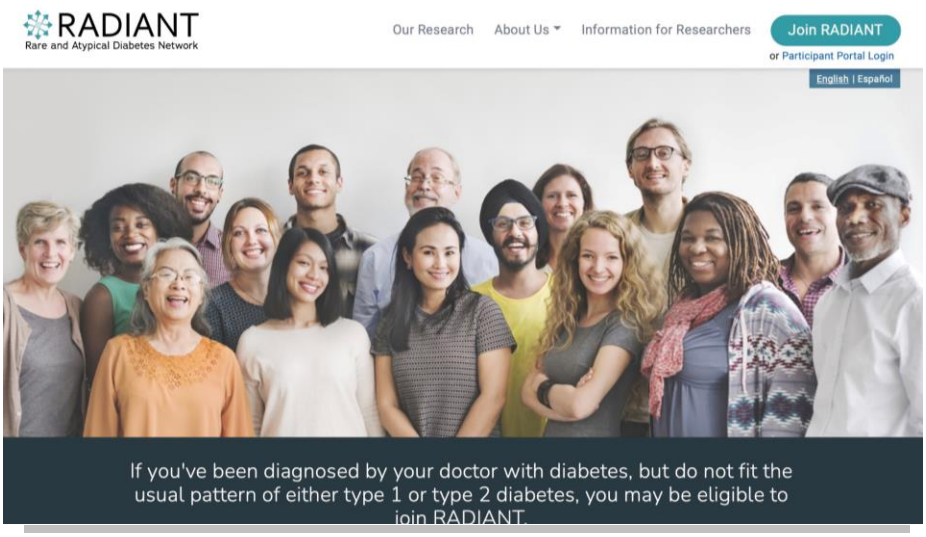


MonogenicDiabetesRegistry.org



Thank you for your attention

monogenicdiabetes@uchicago.edu

Diabetes Care Summit

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ADCES Association of Diabetes Care & Education Specialists

Breakout Session I:

- *Cancer & Diabetes*
- *Diabetes Technology Update*

Diabetes Care Summit

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ADCES Association of Diabetes Care & Education Specialists

Diabetes and Cancer

ITIVRITA GOYAL, MD
Assistant Professor of Medicine
Endocrinology, Diabetes, Metabolism
OUHSC

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DISCLOSURES

- None to disclose
- No conflicts of interest

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Objectives

1. Epidemiology
2. Interplay of diabetes mellitus and cancer
3. Chemotherapy/ Immunotherapy and new onset-diabetes
4. Management of diabetes in cancer
5. Diabetes management at end-of-life

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Cancer – 2nd
Diabetes – 12th

Leading causes of death worldwide
Incidence is increasing globally

Giovannucci et al., CA Cancer J Clin. 2010

INTRODUCTION

- Strong and consistent link b/w diabetes and cancer
- Share many common risk factors
- Diabetes a/w increased risk of many cancers and cancer mortality
- Diabetes and cancer have bidirectional relation
- Cancer survivors have a higher incidence of developing subsequent diabetes (reverse causality)

Citation: Garg et al., Diabetes Obesity and Metabolism. 2013
Lega et al., Endocrine Reviews. 2019

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Risk factors

- Non-modifiable risk factors:
  - Age
  - Sex
  - Ethnicity (differences in genetic factors and socioeconomic disparities)
- Modifiable risk factors
  - **Overweight, obesity and weight change**
  - Diet
  - Physical activity
  - Tobacco/Alcohol

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Obesity – strong risk factor

- Strong association b/w obesity, insulin resistance, T2DM and cancer risk
- Breast, colorectal, endometrium and pancreas: consistently a/w overweight and obesity
- In parallel with the obesity epidemic in adolescents and young adults; increasing frequency of incidence/ prevalence of T2D and colon cancers also in this population
- Visceral adiposity (more than BMI) a/w higher risk
- Weight loss and diabetes and cancer risk

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Critical question?

Association between diabetes and cancer:
Is it due to shared risk factors
or
Diabetes itself (directly by hyperglycemia or indirectly by insulin resistance) increases risk of cancers

Epidemiology associations

Obesity and cancer risk

- Endometrial
- Breast
- Colorectal

Account for >60%

- Others – esophageal, liver, pancreas, GB, ovarian and renal cancers

Diabetes and cancer risk

- Breast
- Colorectal
- Endometrial
- GB

Consistent relationship

- Kidney, pancreatic, HCC, gastric and thyroid - ?? bias

Citation: Lega et al., Endocrine Reviews. 2019

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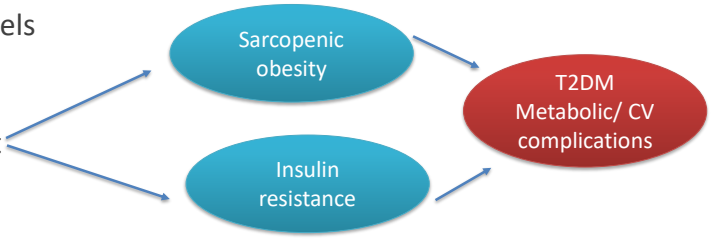
T2DM and prostate cancer

- Inverse relationship
  - Meta-analysis of 45 observational studies suggest that men with diabetes have a 14% lower risk of prostate cancer compared to men without diabetes
- Plausible explanations:
  - Lower levels of androgen levels
  - Decreased PSA levels
- Contrary, ADT used in treatment of prostate cancer



Citation: Bansal et al., Prostate Cancer Prostatic Dis. 2013
Kasper et al., Cancer Epidemiol Biomarkers Prev. 2006

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Potential Mechanisms of Obesity, Diabetes, and Cancer Risk

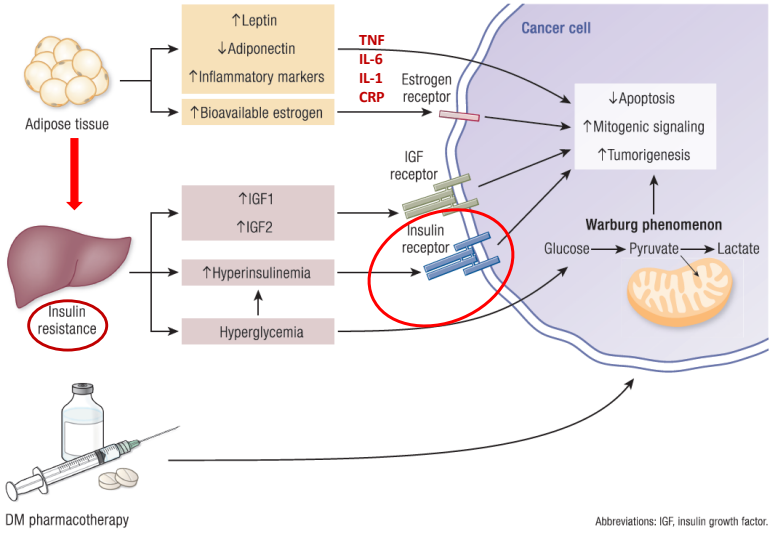

Figure 1. Main mechanisms and pathways between obesity, insulin resistance, and diabetes pharmacotherapy and cancer growth and progression.

Adapted from Lega et al., Diabetes, Obesity and Cancer. Endocrine Reviews. 2019

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Do anti-diabetes drugs cause cancer?

Metformin	• Anti-neoplastic effects in many preclinical and in-vitro studies • Reduced incidence of development of breast Ca and pancreatic Ca in 2 studies • Being investigated as adjuvant therapy for cancer now
Sulfonylureas	• Increased risk of developing solid tumors in some studies • Low numbers of cancers reported, evidence is weak
Thiazolidinediones	• Pioglitazone has been shown to increase risk of bladder cancer (weak association) • Use with caution in personal or family h/o bladder cancer
GLP1 based therapies (GLP1RA/DPP IV inh)	• GLP1RA a/w thyroid C-cell hyperplasia and MTC in rats, avoid use in h/o MTC or MEN-2 • Increased risk of pancreatic cancer - ??

Giovannucci et al., CA Cancer J Clin. 2010
Garg et al., Diabetes Obesity and Metabolism. 2013

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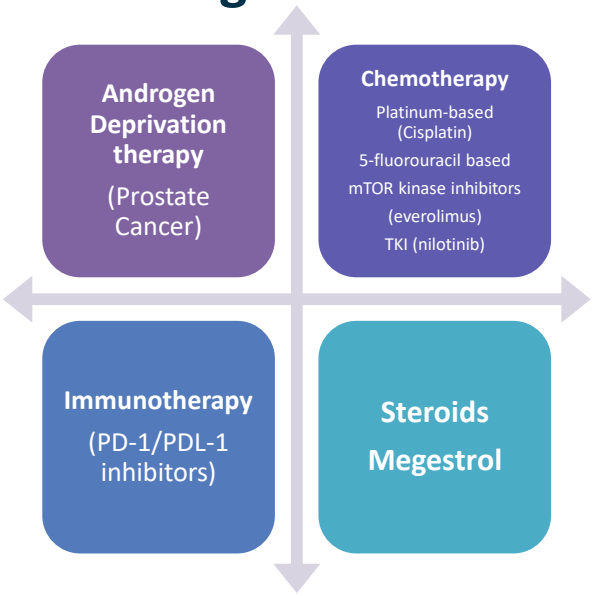
Do anti-cancer drugs cause diabetes?



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Late metabolic complications of cancer

- Survival rates for most cancers improved
- Cancer survivors (CSs) now have increased mortality from secondary neoplasms and CV disease
- Increasing evidence of metabolic syndrome seen in survivors of cancer
- Increased risk of DM (2-3.6 fold) in patients who underwent HCT compared to sibling donors
- CSs need long term follow up and appropriate screening

Citation: Gallo et al. Acta Diabetol. 2016
Lega et al., Endocrine Reviews. 2019

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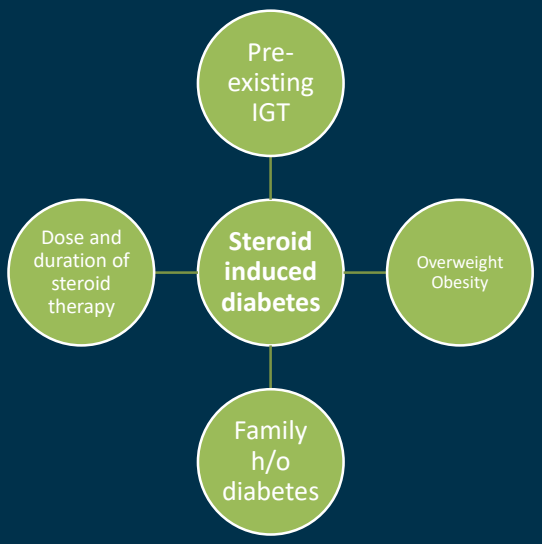

Risk factors for developing steroid-induced diabetes

Steroid induced diabetes

- Widely used in cancer patients, common in many treatment protocols
- Used in anti-emetic regimen, reduce edema, aid in nutrition and pain management
- Induce and exacerbate diabetes
- Fasting BG are often normal, more post prandial hyperglycemia, often severe
- Increase hepatic gluconeogenesis, increase insulin resistance and decrease insulin secretion
- Can resolve if temporary and low dose steroids used, but usually permanent

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Management

Prompt recognition	Proactive treatment
▪ Patient w/o h/o diabetes • A1c not reliable due to acute hyperglycemia • Screen before starting steroids • Capillary BG testing more reliable	▪ Flexible approach due to cyclical use of steroids ▪ Use of agents targeting post-prandial glucose required
▪ Patients with pre-existing diabetes • Educate patient, exacerbation of hyperglycemia on GC therapy • More frequent SMBG needed • Understanding the cyclical nature of GC therapy and escalating therapy during steroid use	▪ Use of short-acting sulfonylureas can be considered ▪ Once daily NPH/Levemir regimens ▪ Basal-bolus regimens; prandial short acting insulin given before meals ▪ Intensification of therapy (2-3 times) during GC use and simultaneously reduced once GC tapered or stopped.

Jacob et al., Management of diabetes in patients with cancer. Q J Med. 2015

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Immunotherapy/Immune Checkpoint Inhibitors (ICI)

CTLA-4 inhibitors	PD-1 inhibitors	PD-L1 inhibitors
• Ipilimumab (Ipi)	• Nivolumab • Pembrolizumab • Dostarlimab	• Atezolizumab • Avelumab • Druvalumab

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CTLA-4 inhibitors

Mechanism of action

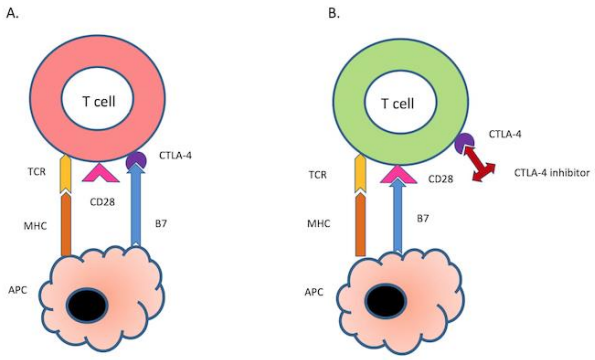

Fig. 1 (original): CTLA-4 inhibitors mechanism of action.

A. Inactivated T cell. Binding of B7 with CTLA-4 instead of CD28 keeps T cell inactivated by blocking co-stimulation.
B. Activated T cell. CTLA-4 inhibitors like Ipilimumab binds with CTLA-4 on T cells thereby releasing B7 to bind with CD28 for co-stimulating and activating T cells

TCR- T cell receptor; MHC- Major Histocompatibility Complex; APC- Antigen Presenting Cell; CTLA-4- Cytotoxic T-lymphocyte associated antigen-4

Engelhardt et al., *J Immunol.* 2006
Goyal et al., IJMR. In press

PD-1/PDL-1 inhibitors

Mechanism of action

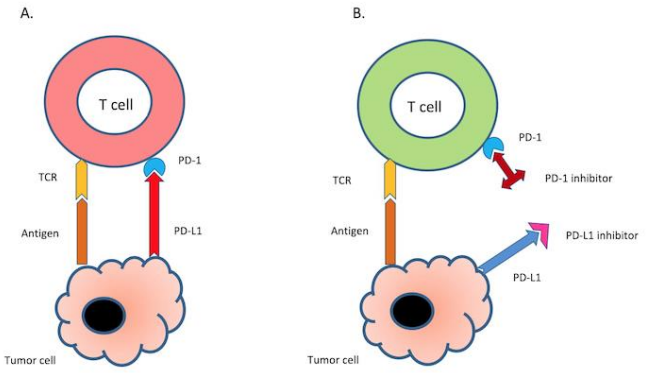

Fig. 2 (original): PD-1/PDL-1 inhibitors mechanism of action.

A. Inactivated T cell. Binding of PD-1 on T-cell with PD-L1 on tumor cell keeps T cell inactivated.
B. Activated T cell. Anti PD-1 or PD-L1 antibodies prevent binding of PD-1 with PD-L1 to keep T cell activated

TCR- T cell receptor; PD-1- Programmed Cell Death Protein -1; PD-L1- Programmed Death Ligand-1

Blank et al., Cancer Immunol Immunother. 2005
Goyal et al., IJMR. In press

New onset-diabetes

- Autoimmune diabetes or new onset diabetes from ICI therapy
- Autoimmune destruction of pancreatic β cells
- More common with PD-1/PD-L1 inhibitors with incidence ranging from 0-2%
- Majority develop within three months of starting ICI
- Many cases described in literature now

Citation: Barroso-Sousa et al., JAMA Oncol. 2018
de Filette et al., Horm Metab Res. 2019
Akturk et al., Diabet Med. 2019

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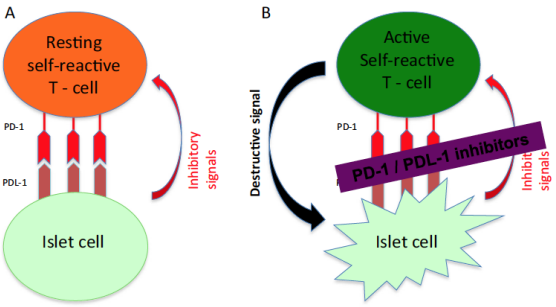

Citation: Hickmott et al., Target Oncology. 2017
Ansari et al., J Exp Med. 2003
Wang et al., Proc Natl Acad Sci. 2005
Kochupurakkal et al., PLoS One. 2014

Pathogenesis

- Considered to be autoimmune in nature
- PD-1/PD-L1 interaction in pancreatic cells is protective
- PD-1/PD-L1 inhibitors → expansion of autoreactive T cells → destruction of β cells
- Individuals with either **HLA-DR3-DQ2 or HLA-DR4-DQ8** haplotypes at higher risk

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Clinical presentation

- Timing of presentation variable
- Acute presentation: can present as severe hyperglycemia or DKA
- A1c not reliable
- Insulin and c-peptide levels undetectable, presence of diabetes-associated antibodies variable
- Diabetes-associated autoantibodies need not be present for diagnosis
- ICI-induced diabetes mellitus is almost always permanent

Citation: Hong et al., Front Endocrinol. 2020
Usui et al., J Thorac Oncol. 2017
Goyal et al., IJMR. 2021 (in press)

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How does it differ from T1D/LADA?

- Age of onset is later
- Rapid decline of C-peptide and sudden ß-cell failure
- Autoantibodies frequently testing negative

Citation: Tsang et al., J Clin Endocrinol Metab. 2019
Quandt et al., Clin Exp Immunol. 2020

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Management

Acute setting

DKA or severe hyperglycemia:

- Appropriate management with insulin infusion, intravenous fluids, and electrolyte monitoring
- Steroids not indicated in this condition

Chronic management

- Insulin therapy in a basal-bolus regimen
- Education on insulin use
- Recognition of hypo/ hyperglycemia

Routine monitoring on ICI use

- HbA1c and blood glucose should be tested before and during treatment with PD-1/PD-L1 inhibitors or
- When symptoms of diabetes develop

Call and refer to an endocrinologist immediately

Brahmer et al., Journal for ImmunoTherapy of Cancer. 2021
Goyal et al., IJMR. 2021 (in press)

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Barriers in treating cancer among diabetes

- Pre-existing renal, cardiac or neuropathic complications in long standing or poorly controlled DM
- Many chemotherapeutic agents known to exacerbate these complications
  - Cisplatin known to cause renal insufficiency
  - Anthracyclines – cardiotoxicity
  - Cisplatin, paclitaxel and vincristine - neurotoxic

Citation:

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Barriers in treating diabetes with cancer

- Altered renal function
- Hepatic impairment
- Variable dietary patterns
- Gastrointestinal disturbances
- Cyclical nature of chemotherapy
- Patient's position in oncological condition and prognosis

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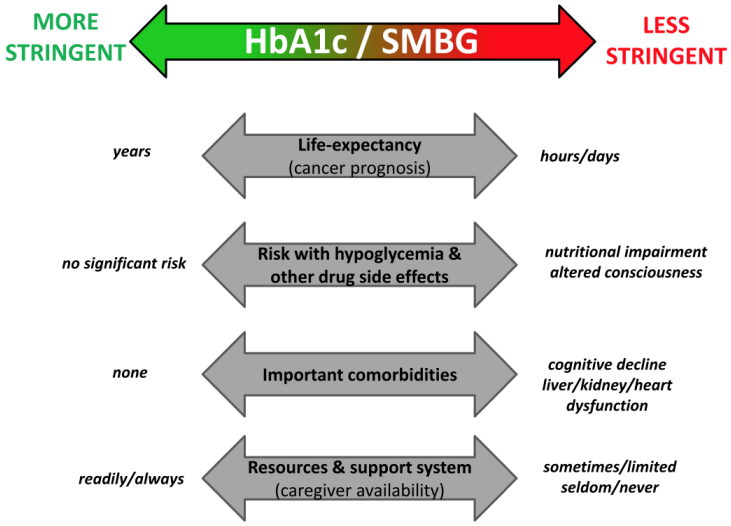
Glycemic targets



Adapted from: Gallo et al., Metabolism 2017
ADA. Glycemic goals. Sec 6, Standards of Medical care in diabetes 2021.

Choice of anti-diabetic agent

Drug class	Drugs	Advantages	Drawbacks	Contraindications
Biguanides	Metformin	Low cost Mild weight loss Oral pill	Abd bloating/ cramping Diarrhea Abd pain	Renal failure Liver failure (avoid in hepatic mets, HCC) Hold in acute illness, sepsis and when contrast-enhanced imaging is scheduled
Sulfonylureas	Glipizide Glimepiride Glyburide	Low cost Efficacious	**Hypoglycemia** (more pronounced with longer-acting) Weight gain	Renal failure Poor oral intake

Citation: ADA. Pharmacologic approaches to glycemic treatment. Sec 9, Standards of medical Care in Diabetes 2021.

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Drug class	Drugs	Advantages	Drawbacks	Contraindications
Meglitinides	Repaglinide Nateglinide	Shorter acting, useful in steroid induced postprandial hyperglycemia	Frequency of taking med Hypoglycemia Limited efficacy	Use with caution in hepatic and renal failure due to increased risk of hypoglycemia
TZDs	Pioglitazone	Low cost Efficacious Improve insulin resistance	Edema Bone fractures Weight gain Slow onset of action	Liver failure (but can be used in NAFLD) Congestive heart failure
Alpha glucosidase inhibitors	Acarbose	Useful for post-prandial hypoglycemia	Abd pain Flatulence Diarrhea Low efficacy	Intestinal obstruction (GI tumors) Severe renal failure (GFR<30)

Citation: ADA. Pharmacologic approaches to glycemic treatment. Sec 9, Standards of medical Care in Diabetes 2021.

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Drug class	Drugs	Advantages	Drawbacks	Contraindications
DPP-4 inhibitors	Sitagliptin Saxagliptin Linagliptin Alogliptin	Weight neutral Well tolerated	High cost Low potency ? Pancreatitis	Moderate to severe CKD and ESRD Heart failure (avoid use of saxagliptin)
GLP-1 receptor agonists	Liraglutide Dulaglutide Exenatide Semaglutide	Weight loss Once weekly injections CV and renal protective	**Nausea, vomiting**, abd pain Loss of appetite/ **anorexia** ? Pancreatitis Very high cost	Severe GI disease Anorexia/ cachexia Pancreatic cancers Previous h/o pancreatitis
SGLT-2 inhibitors	Canagliflozin Empagliflozin Dapagliflozin	Weight loss Highly effective CV and renal benefits	**Volume depletion** Dehydration, **AKI** Euglycemic DKA Genital infections High cost	Renal failure Increased risk of volume depletion

Citation: ADA. Pharmacologic approaches to glycemic treatment. Sec 9, Standards of medical Care in Diabetes 2021.

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Drug class	Drugs	Advantages	Drawbacks	Contraindications
Basal insulins/ Long acting insulins	Glargine U-100/U-300 Levemir Degludec NPH	- Universally effective - Anabolic effects - Flexible dosing - Safe with liver, renal or hepatic failure	Injection training	none
Short acting insulins	Aspart Lispro Faster aspart Lispro-aabc Regular insulin Inhaled insulin	- Universally effective - Anabolic effects - Flexible dosing - Post prandial hyperglycemia	- Injection training - Hypoglycemia - Weight gain - Patient reluctance to MDI - Requires patient/ caregiver education and involvement in care	none

Citation: ADA. Pharmacologic approaches to glycemic treatment. Sec 9, Standards of medical Care in Diabetes 2021.

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Case discussion

- 74 year old female with known h/o T2D, osteoporosis and diagnosed with pancreatic adenocarcinoma with mets to liver
- Previous chemo – Gemcitabine/ Abraxane
- Referred for diabetes management
- Current regimen:
  - Tresiba
  - Humalog with meals and correctional scale
  - Glipizide
- Previously on metformin, now stopped

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- Laboratory findings:
  - AST/ALT and bil wnl
  - GFR has been fluctuating b/w 43 - >60
- CT abd pelvis done in July 2021:
  - Slightly increasing pancreatic mass
  - No discretely measurable abnormality to correlate with previously seen liver lesions, no new or progressive lesions seen
- Started on new chemotherapy with 5FU and liposomal irinotecan, gets it as a 3 day infusion and also receives dexamethasone
- Daughter calls after infusion that blood sugars have been running high – what to do??

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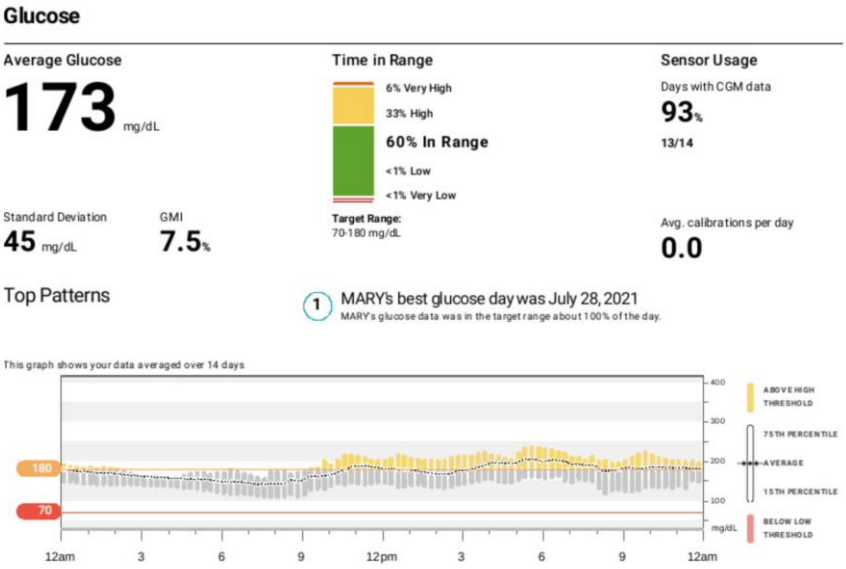
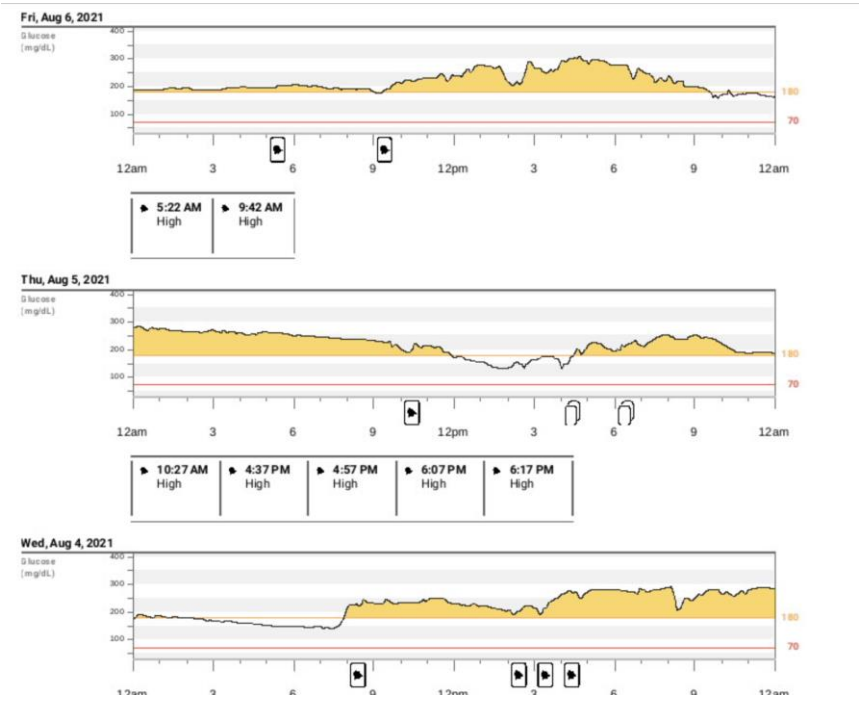
DEXCOM download




Fri, Aug 6, 2021
Glucose (mg/dL)
400
300
200
100
180
70
12am
3
6
9
12pm
3
6
9
12am
5:22 AM
High
9:42 AM
High
Thu, Aug 5, 2021
Glucose (mg/dL)
400
300
200
100
180
70
12am
3
6
9
12pm
3
6
9
12am
10:27 AM
High
4:37 PM
High
4:57 PM
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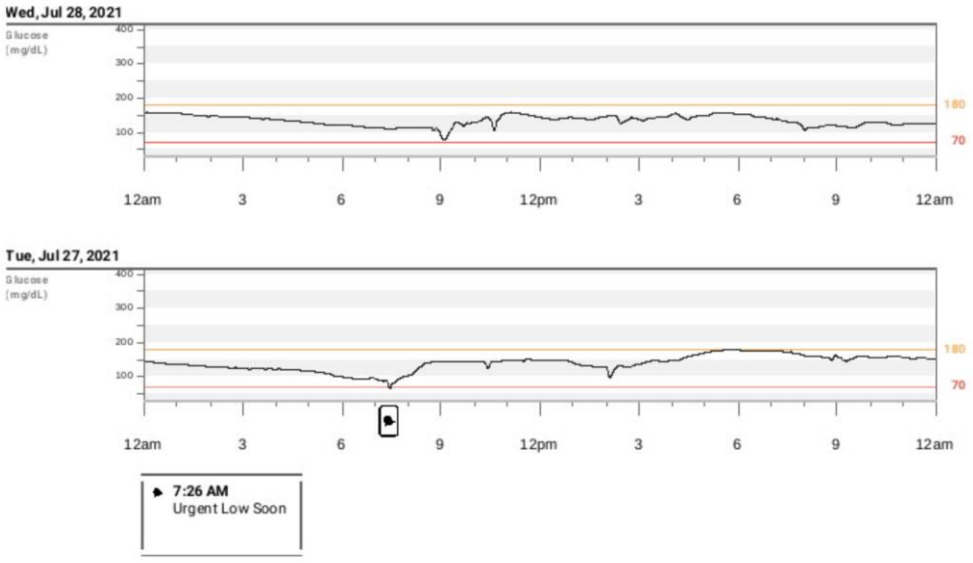
6:17 PM
High
Wed, Aug 4, 2021
Glucose (mg/dL)
400
300
200
100
180
70


Wed, Jul 28, 2021
Glucose (mg/dL)
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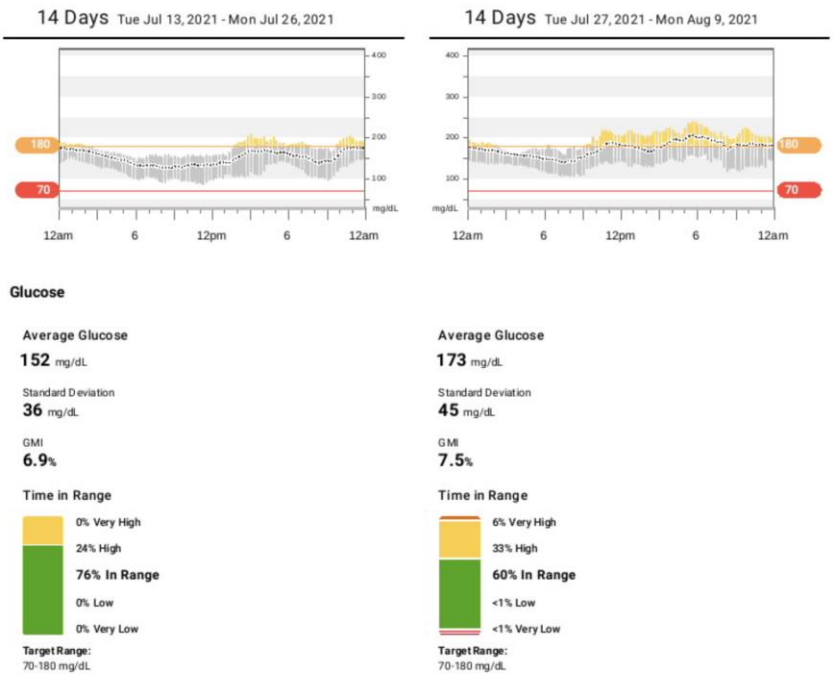
300
200
100
180
70
12am
3
6
9
12pm
3
6
9
12am
Tue, Jul 27, 2021
Glucose (mg/dL)
400
300
200
100
180
70
12am
3
6
9
12pm
3
6
9
12am
7:26 AM
Urgent Low Soon



Artificial nutrition

- Very commonly used in cancer patients for malnutrition; enteral or parenteral
- Cause acute exacerbations in hyperglycemia
- Use diabetes specific formulas
- Insulin therapy:
  - Regular insulin added to TPN (initial dose 1: 10 gm carb)
  - SQ basal/bolus regimens for enteral feeding
    - Basal options – once daily glargine or NPH/Levemir 2-3 doses
    - Bolus– Lispro every 4 hrs or regular every 6 hrs.

Citation: Psarakis. Diabetes Spectrum. 2006
ADA. Sec 15, Standards of Medical care in Diabetes. 2021

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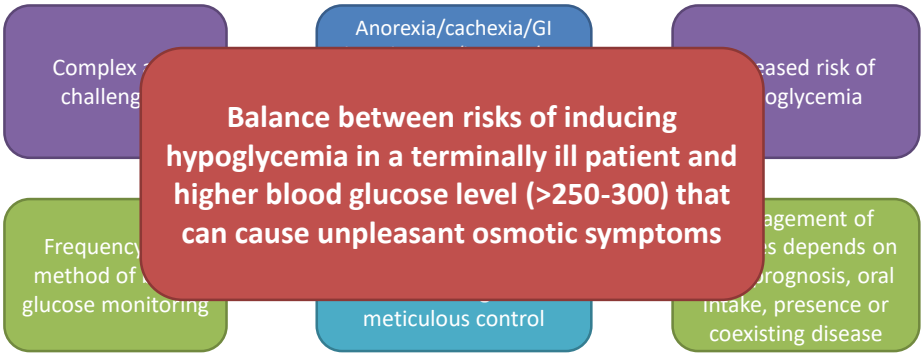
Diabetes management at end-of-life



Citation: King et al., Q J Med 2012
Pan Birmingham Cancer Network. Guideline for management of diabetes in palliative medicine
Diabetes UK. End of Life diabetes care – clinical care recommendations

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Treatment options

- T1D and T2D on insulin therapy
  - Reduce dose of prandial insulin due to reduced oral intake
  - Low dose basal insulin if required
  - Minimize number of injections/ day
- T2D on oral agents
  - Reduce dose of sulfonylureas
  - Use short acting agents (glinides) or DPP IV inh to cover meals
  - MTF should be stopped
  - Avoid use of SGLT-2 inh due to risk of dehydration

Citation: King et al., Q J Med 2012
ADA. Older Adults. Section 12. Standards of medical care in diabetes 2021. Diabetes Care. 2021

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Education for patients and caregivers

- Comprehensive education of SMBG, insulin injection devices, injection techniques
- Understanding the cyclical nature of chemotherapy and steroids and their effect on BG
  - Education and instructions to patient and caregivers on insulin dose titration
- Avoidance of/response to hypoglycemia

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Contact Information

Mailing Address
1000 N. Lincoln Blvd, Suite 2900
Oklahoma City, OK
73104

Email Address
Itivrita-Goyal@ouhsc.edu

Phone Number
405-271-3613

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ADCES Association of Diabetes Care & Education Specialists

Metrics Beyond A1c : Positioning Time in Range (TIR) in Diabetes Care

Jonea Lim, MD

Associate Professor, Section of Endocrinology

University of Oklahoma Health Sciences Center

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Pearls:

- Time in range (TIR) is a key metric in the quality of glucose control.
- Utility of A1c is enhanced when TIR is used to complement glycemic data measured by CGM.
- TIR correlates inversely with HbA1c (↑ **TIR** = ↓ **A1c**).
- Beginning evidence linking lower TIR to increased risk of long term diabetes complications.
- Different targets should be considered for older or higher-risk individuals, pediatric populations and pregnant women.

Advani, Diabetologia (2020) 63:242-252

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Assessment of Glycemic Control

- Conventional Glucose Metrics (Diabetes Control Complication Trial –DCCT, 1998)*
  Intensive glucose management involves:
  - Self-monitoring blood glucose (SMBG) four times per day
  - 3:00 AM blood glucose check weekly
  - A1c measurement every 90 days

- Modern use of continuous glucose monitoring (CGM) began in year 2000
  - Retrospective CGM (professional, masked to user at time of wear)
  - Real-time CGM (rtCGM, personal, unmasked)
  - Intermittent scan CGM (isCGM, "flash" CGM)
  - Type 1 DM: lowered A1c, shortened duration of time in hypoglycemia & reduction of in moderate to severe hypoglycemia.
  - Type 2 DM: lowering A1c without increasing frequency of hypoglycemia

*Advani, Diabetologia (2020) 63:242-252
Battelino and Associates, Diabetes Care (2019) Volume 42: 1593-1603

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Need for Metrics Beyond A1c

- A1C may not reflect the quality of glycemic control in the way of actionable insights with intra and inter day glucose variability. There is lack of information about acute hyperglycemic excursions.
- Accuracy of A1C can be affected by a range of physiologic or pathologic conditions such as chronic kidney disease, liver disease, hemoglobinopathies, blood loss or transfusions, and pregnancy.
- Utility of A1c is enhanced when TIR is used to complement to glycemic data measured by CGM

Battelino and Associates, Diabetes Care (2019) Volume 42: 1593-1603

The Fallacy of Average: How Using HbA_{1c} Alone to Assess Glycemic Control Can Be Misleading

Roy W. Beck,[1] Crystal G. Connor,[1] Deborah M. Mullen,[2] David M. Wesley,[2,3] and Richard M. Bergenstal[2]

Diabetes Care 2017;40:994–999 | https://doi.org/10.2337/dc17-0636

N = 387 participants from 3 randomized control trials
T1DM = 315
T2DM= 72
CGM device used was DEXCOM G4 to collect 13 weeks CGM data

- Relationship between A1c and CGM mean glucose correlation

The Fallacy of Average: How Using HbA_{1c} Alone to Assess Glycemic Control Can Be Misleading

Roy W. Beck,[1] Crystal G. Connor,[1] Deborah M. Mullen,[2] David M. Wesley,[2,3] and Richard M. Bergenstal[2]

Diabetes Care 2017;40:994–999 | https://doi.org/10.2337/dc17-0636

A1c Derived Average Glucose (ADAG), 2006-2007
13 days of CGM measurements
39 days of Fingerstick blood glucose (FSBG)
ADA & American Association of Clinical Chemistry
Strong correlation (r=0.92) to justify reporting both A1c results and estimated average glucose

Table 1—Range of mean glucose concentrations for observed HbA_{1c} levels in pooled data from three recent studies* and the ADAG study

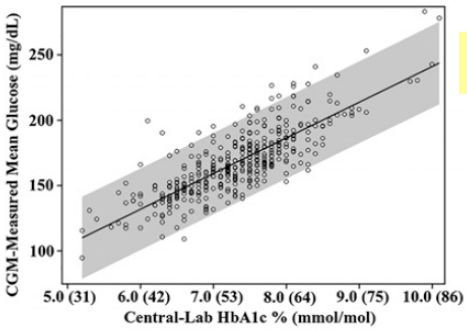
	Estimated mean glucose concentration (mg/dL) for a given HbA_{1c}, 95% CI†	
HbA_{1c}, % (mmol/mol)	Current study* (*N* = 387)	ADAG study (*N* = 507)
6 (42)	101–163	100–152
7 (53)	128–190	123–185
8 (64)	155–218	147–217
9 (75)	182–249	170–249
10 (86)	209–273	193–282

*The three studies from which data were obtained using the Dexcom G4 Platinum CGM System with an enhanced algorithm, software 505, pooled for the analyses herein are refs. 15, 16, and 28 (ClinicalTrials.gov identifiers NCT02282397, NCT02282397, and NCT02258373, respectively). †95% CI for a patient's mean glucose concentration for a measured HbA_{1c} level.

Table 6.1—Estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

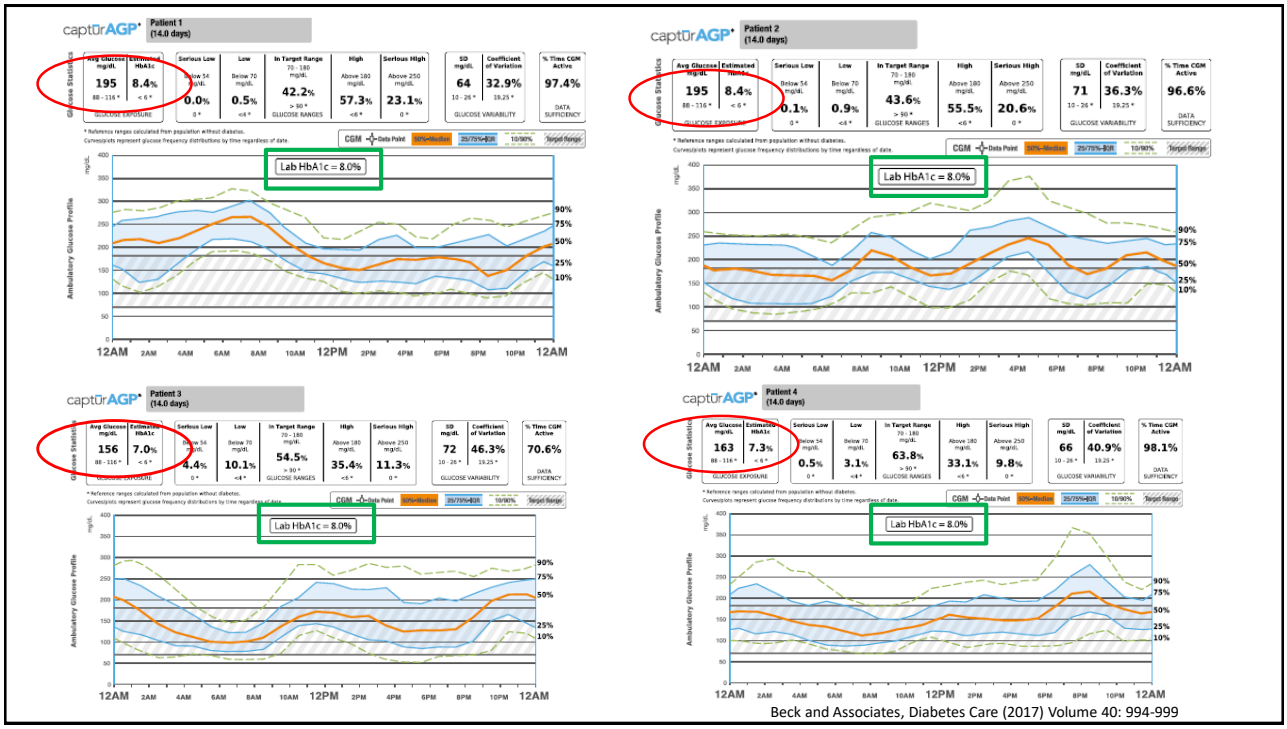
Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (6,7). Adapted from Nathan et al. (6).



Wide range of CGM-measured mean glucose concentration for a given A1c value

Figure 1—Plot of CGM-measured mean glucose concentration vs. laboratory-measured HbA_{1c}. The shaded area represents the 95% prediction interval (analogous to an individual CI) for a patient's mean glucose concentration for a measured HbA_{1c} level, demonstrating the wide range of mean glucose concentration values that are possible for any HbA_{1c} value.

Beck and Associates, Diabetes Care (2017) Volume 40: 994-999



Beck and Associates, Diabetes Care (2017) Volume 40: 994-999

The Fallacy of Average: How Using HbA_{1c} Alone to Assess Glycemic Control Can Be Misleading

Roy W. Beck,[1] Crystal G. Connor,[1] Deborah M. Mullen,[2] David M. Wesley,[2,3] and Richard M. Bergenstal[2]

Diabetes Care 2017;40:994–999 | https://doi.org/10.2337/dc17-0636

Summary of findings:

- Results are quite similar to ADAG study: wide range of measured mean glucose concentration for a given A1c value
- Estimating glycemic control by HbA1c alone may not be accurate for some patients.
- Mean glucose itself is an average, and different degrees of glycemic variability and many different glycemic patterns could produce similar mean glucose concentrations and similar HbA1c levels.

Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

Diabetes Care 2019;42:1593–1603 | https://doi.org/10.2337/dci19-0028

Table 2—Standardized CGM metrics for clinical care: 2019

1. Number of days CGM worn (recommend 14 days) (42,43)	
2. Percentage of time CGM is active (recommend 70% of data from 14 days) (41,42)	
3. Mean glucose	
4. Glucose management indicator (GMI) (75)	
5. Glycemic variability (%CV) target ≤36% (90)*	
6. Time above range (TAR): % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2
7. Time above range (TAR): % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1
8. Time in range (TIR): % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. Time below range (TBR): % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1
10. Time below range (TBR): % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2
Use of Ambulatory Glucose Profile (AGP) for CGM report	

CV, coefficient of variation. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas (45,90,91).

Core CGM metrics streamlined for use in clinical practice based on expert opinion of this international consensus group.

Of 14 core metrics, the panel selected 10 metrics that may be most useful in clinical practice.

70% use of CGM for 14 days correlates strongly with 3 months mean glucose, time in ranges metrics and hyperglycemia metrics.

Goal of effective and safe glucose control is to increase TIR while decreasing TBR.

Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

Diabetes Care 2019;42:1593–1603 | https://doi.org/10.2337/dci19-0028

Table 5—Estimate of A1C for a given TIR level based on type 1 diabetes and type 2 diabetes studies

Beck et al. (26) (n = 545 participants with type 1 diabetes)			Vigersky and McMahon (27) (n = 1,137 participants with type 1 or type 2 diabetes)	
TIR 70–180 mg/dL (3.9–10.0 mmol/L)	A1C, % (mmol/mol)	95% CI for predicted A1C values, %	TIR 70–180 mg/dL (3.9–10.0 mmol/L)	A1C, % (mmol/mol)
20%	9.4 (79)	(8.0, 10.7)	20%	10.6 (92)
30%	8.9 (74)	(7.6, 10.2)	30%	9.8 (84)
40%	8.4 (68)	(7.1, 9.7)	40%	9.0 (75)
50%	7.9 (63)	(6.6, 9.2)	50%	8.3 (67)
60%	7.4 (57)	(6.1, 8.8)	60%	7.5 (59)
70%	7.0 (53)	(5.6, 8.3)	70%	6.7 (50)
80%	6.5 (48)	(5.2, 7.8)	80%	5.9 (42)
90%	6.0 (42)	(4.7, 7.3)	90%	5.1 (32)
Every 10% increase in TIR = ~0.5% (5.5 mmol/mol) A1C reduction			Every 10% increase in TIR = ~0.8% (8.7 mmol/mol) A1C reduction	

The difference between findings from the two studies likely stems from differences in number of studies analyzed and subjects included (RCTs with subjects with type 1 diabetes vs. RCTs with subjects with type 1 or type 2 diabetes with CGM and SMBG).

Diabetologia (2020) 63:242–252
https://doi.org/10.1007/s00125-019-05027-0

REVIEW

Positioning time in range in diabetes management

Andrew Advani [1]

Received: 8 April 2019 / Accepted: 21 August 2019 / Published online: 7 November 2019

Time in range (TIR) is not synonymous to upper and lower limits of "normal" glucose values.

Choice of the upper and lower limits are partly pragmatic.

Outside pregnancy range, most DM1 are unable to spend most of the day between 70 to 140 mg/dl.

Upper limit of TIR (< 180) is aligned to recommended upper limit of post prandial glucose.

Lower limit of TIR (> 70) refers to the upper limit of definition of hypoglycemia, the point where counter regulatory hormone release generally begins.

Diabetologia (2020) 63:242–252
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REVIEW

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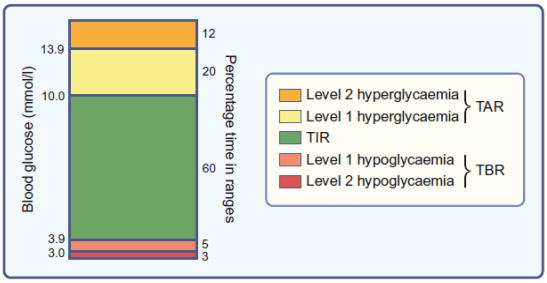

Time Above Range (TAR): subdivided into
> 180 (level 1) and > 250 (level 2)

Time Below Range (TBR) subdivided into
< 70 (level 1) and < 54 (level 2)

Subdivision is based on recent consensus recommendations as to the adverse consequences of glucose < 54 (decreased symptom awareness, increased risk of hypoglycemia and increased mortality risk) and glucose > 250 (increased risk of diabetes ketoacidosis, higher likelihood of long term complications).

Correlation between TIR with HbA1c

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 21, Number 2, 2019
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DOI: 10.1089/dia.2018.0310

DTT

ORIGINAL ARTICLE

The Relationship of Hemoglobin A1c to Time-in-Range in Patients with Diabetes

Robert A. Vigersky, MD and Chantal McMahon, PhD

The Relationships Between Time in Range, Hyperglycemia Metrics, and HbA1c

Journal of Diabetes Science and Technology
2019, Vol. 13(4) 614–626
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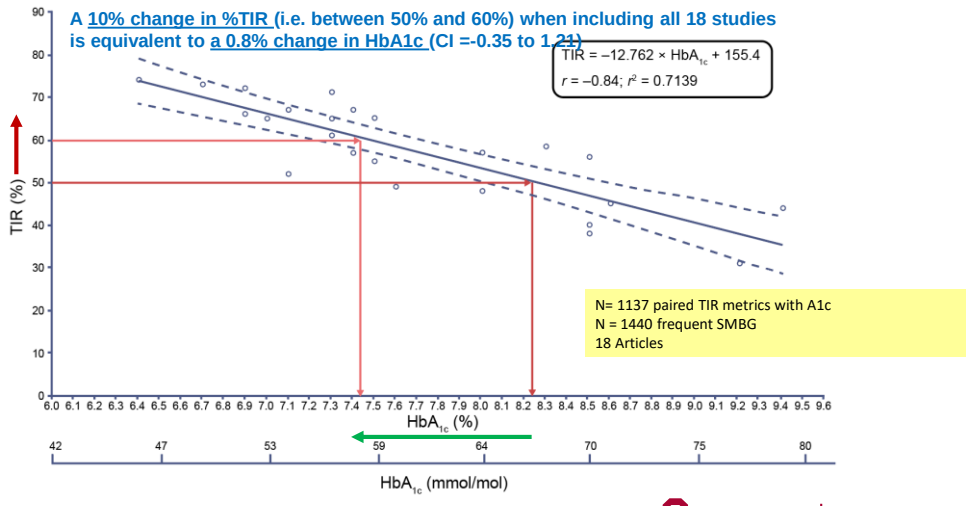
Roy W. Beck, MD, PhD[1], Richard M. Bergenstal, MD[2], Peiyao Cheng, PhD[1], Craig Kollman, PhD[1], Anders L. Carlson, MD[2], Mary L. Johnson[2], RN, CDE, and David Rodbard, MD[3]

The relationship between HbA_{1c} and per cent TIR derived using paired HbA_{1c} and TIR data from various clinical trials



Andrew Advani (2020) Diabetologia DOI 10.1007/s00125-019-05027-0

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DIABETES TECHNOLOGY & THERAPEUTICS
Volume 21, Number 2, 2019
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DTT

ORIGINAL ARTICLE

The Relationship of Hemoglobin A1c to Time-in-Range in Patients with Diabetes

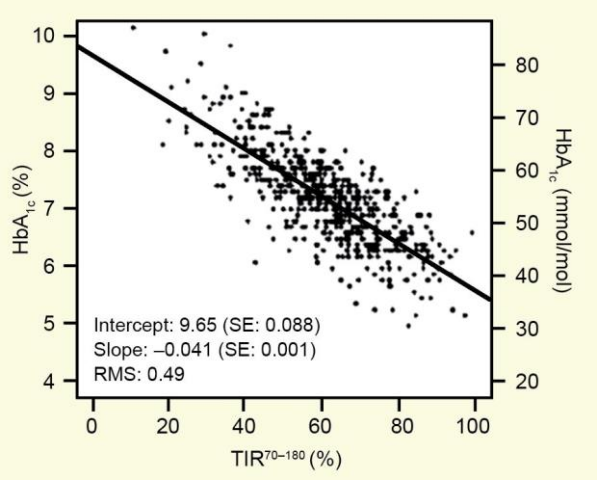
Robert A. Vigersky, MD and Chantal McMahon, PhD

TABLE 2. HEMOGLOBIN A1C IN % AND MMOL/MOL AT EACH DECILE OF TIME-IN-RANGE PER EQUATION IN THE FIGURE

Time-in-range	*HbA1c (%)*	*HbA1c (mmol/mol)*
0%	12.1	109
10%	11.4	101
20%	10.6	92
30%	9.8	84
40%	9.0	75
50%	8.3	67
60%	7.5	59
70%	6.7	50
80%	5.9	42
90%	5.1	32
100%	4.3	23

TIR correlates inversely with HbA1c (↑TIR =↓ **A1c**).

Variability in the relationship between TIR and HbA_{1c}



N= 545 adults with Type 1 DM
4 randomized control trials

The graph illustrates that whereas there is an inverse linear relationship between TIR and A1c, a wide range of HbA1c values may equate with any given TIR.

Andrew Advani (2020) Diabetologia DOI 10.1007/s00125-019-05027-0

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Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

Diabetes Care 2019;42:1593–1603 | https://doi.org/10.2337/dci19-0028

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Every 10% increase in TIR = ~0.5% (5.5 mmol/mol) A1C reduction			Every 10% increase in TIR = ~0.8% (8.7 mmol/mol) A1C reduction	

The difference between findings from the two studies likely stems from differences in number of studies analyzed and subjects included (RCTs with subjects with type 1 diabetes vs. RCTs with subjects with type 1 or type 2 diabetes with CGM and SMBG).

Battelino and Associates, Diabetes Care (2019) Volume 42: 1593-1603

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Beginning evidence linking lower TIR to increased risk of long term diabetes complications

Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes

Jingyi Lu,[1] Xiaojing Ma,[1] Jian Zhou,[1] Lei Zhang,[1] Yifei Mo,[1] Lingwen Ying,[1] Wei Lu,[1] Wei Zhu,[1] Yuqian Bao,[1] Robert A. Vigersky,[2,3] and Weiping Jia[1]

Diabetes Care 2018;41:2370–2376 | https://doi.org/10.2337/dc18-1131

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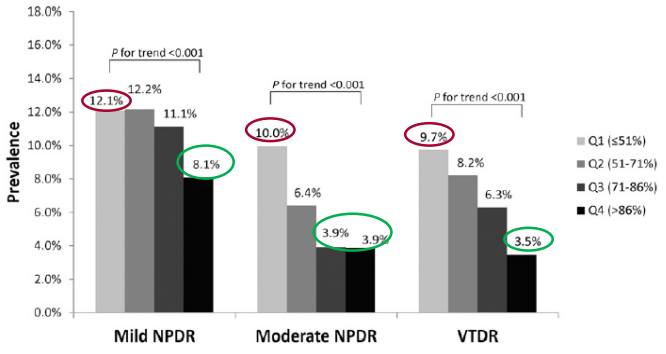

Figure 1—Prevalence of DR by severity, as a function of TIR quartile.

N = 3262 Adults with Type 2 DM
January 2005 to February 2012
Data from 72 hours CGM

Retinopathy graded according to international classification of Diabetic Retinopathy

Beginning evidence linking lower TIR to increased risk of long term diabetes complications

Metrics Derived from Continuous Glucose Monitoring (CGM)

Table 2—Standardized CGM metrics for clinical care: 2019	
1. Number of days CGM worn (recommend 14 days) (42,43)	
2. Percentage of time CGM is active (recommend 70% of data from 14 days) (41,42)	
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5. Glycemic variability (%CV) target ≤36% (90)*	
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9. Time below range (TBR): % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1
10. Time below range (TBR): % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2
Use of Ambulatory Glucose Profile (AGP) for CGM report	

CV, coefficient of variation. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas (45,90,91).

Battelino and Associates, Diabetes Care (2019) Volume 42: 1593-1603

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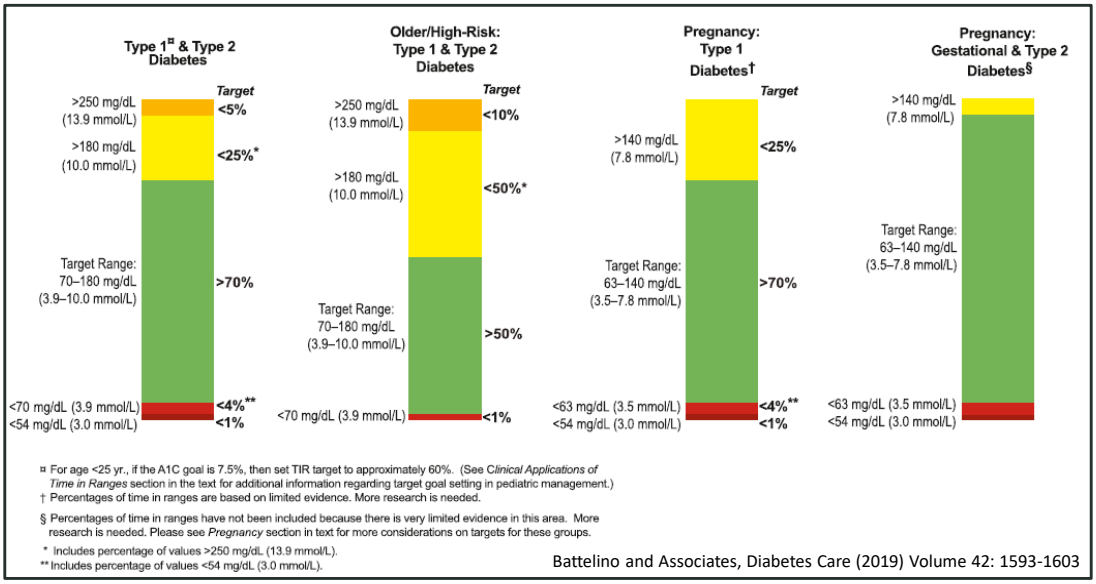
CGM –based Targets for Different Diabetes Populations



¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)
† Percentages of time in ranges are based on limited evidence. More research is needed.
§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.
* Includes percentage of values >250 mg/dL (13.9 mmol/L).
** Includes percentage of values <54 mg/dL (3.0 mmol/L).

Battelino and Associates, Diabetes Care (2019) Volume 42: 1593-1603

Different targets should be considered for older or higher-risk individuals, pediatric populations and pregnant women

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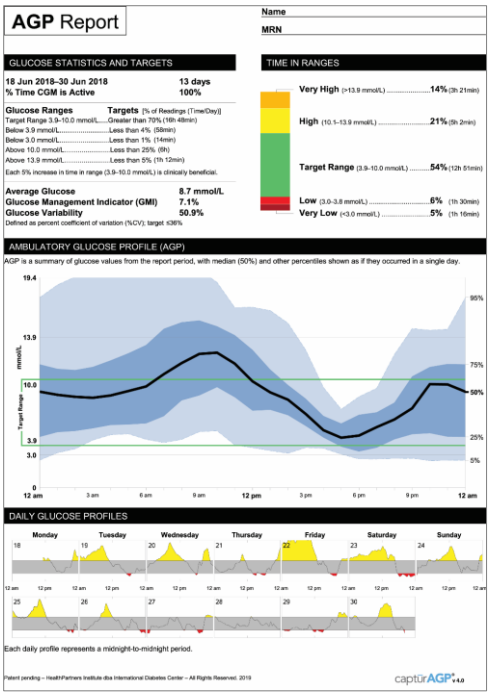
Ambulatory glucose profile (AGP) showing time in ranges as a stacked bar in the top right corner



Andrew Advani (2020) Diabetologia DOI 10.1007/s00125-019-05027-0 © 2019 International Diabetes Center at Park Nicollet, Minneapolis, MN. Used with permission. See AGPreport.org for more information

Take Home :

- Time in range (TIR) is a key metric in the quality of glucose control.
- Utility of A1c is enhanced when TIR is used to complement glycemic data measured by CGM.
- TIR correlates inversely with HbA1c (↑TIR =↓A1c).
- Beginning evidence linking lower TIR to increased risk of long term diabetes complications.
- Different targets should be considered for older or higher-risk individuals, pediatric populations and pregnant women.

Thank You!

Diabetes Care Summit

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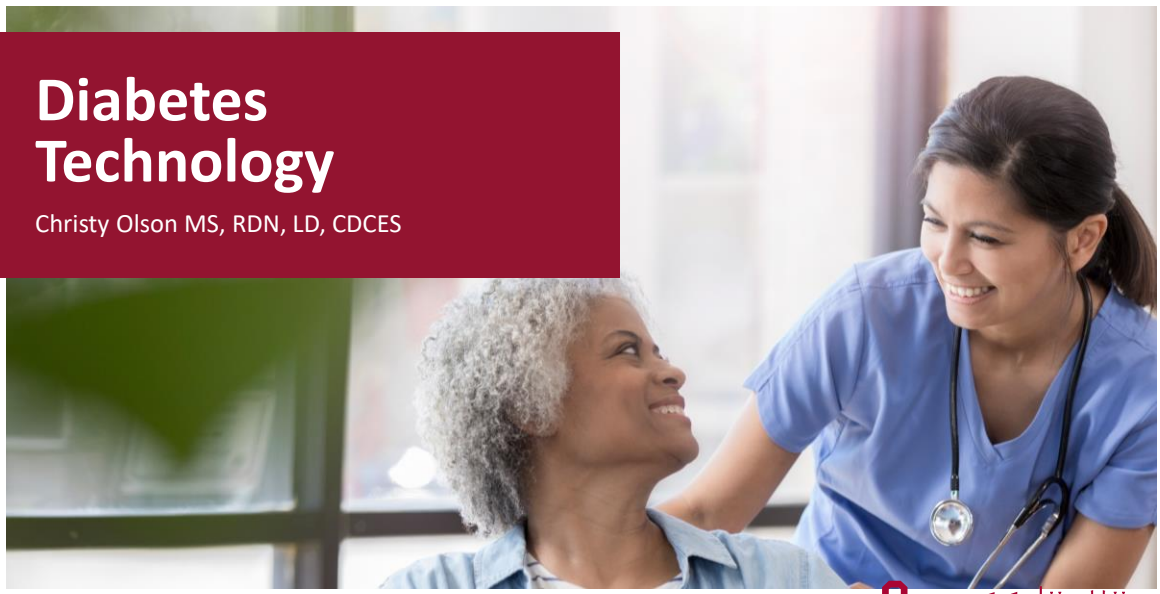
ADCES Association of Diabetes Care & Education Specialists

Diabetes Technology

Christy Olson MS, RDN, LD, CDCES



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Objectives

- Review FDA approved personal diabetes technologies
- Discuss appropriate patient candidates for diabetes technologies
- Review important aspects of device training
- Explain how to use device reports as a part of diabetes education

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Diabetes Technology

- Technology is rapidly changing, but there is no “one-size-fits-all” approach to technology use in people with diabetes
- Use of technology should be individualized based on a patient’s needs, desires, skill level, and availability of devices

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Personal Continuous Glucose Monitors (CGM)

FreeStyle Libre | Guardian Connect | Eversense | G6

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Krouse et al. *Reference Guide for Integrating Continuous Glucose Monitoring into Clinical Practice.* The Diabetes Educator. (2010) 42 (Suppl 1): 3S-20S

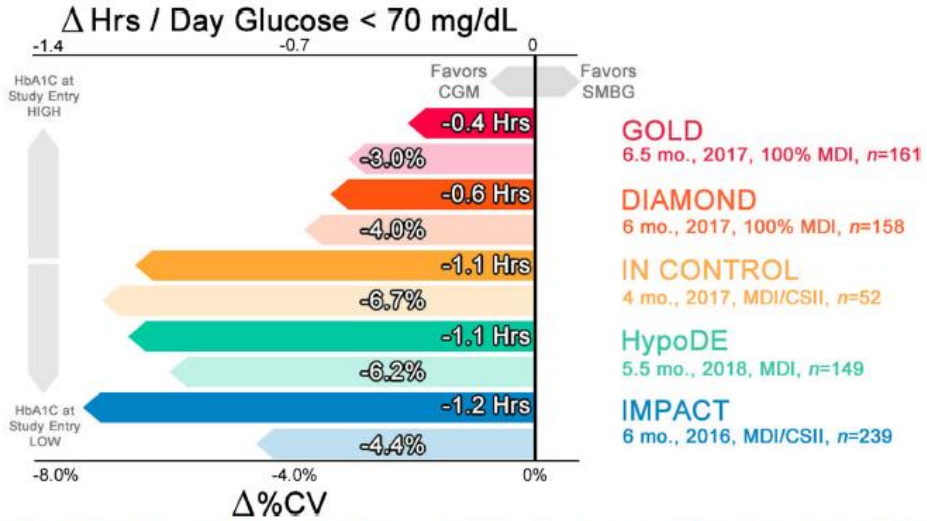

Fig. 3 Summary of recently published CGM trials demonstrating reduction in time spent with glucose < 70 mg/dL and %CV as compared with SMBG

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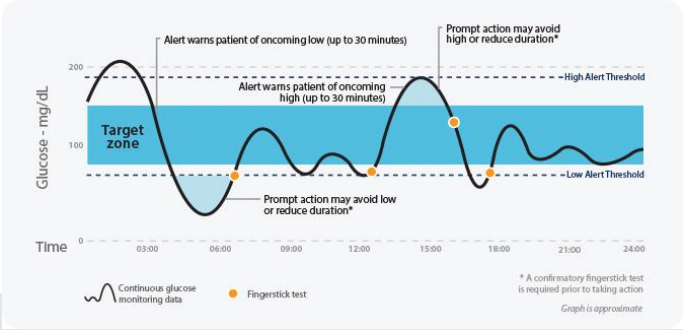
Martin et al. *Advanced Technology in the Management of Diabetes: Which Comes First- Continuous Glucose Monitor or Insulin Pump?* Current Diabetes Reports (2019) 19 (50).

CGM Use

- Provides trend information
- Provides direction & rate of change of glucose
- Provides alerts if glucose is traveling outside targets



http://professional.medtronicdiabetes.com/personal-cgm

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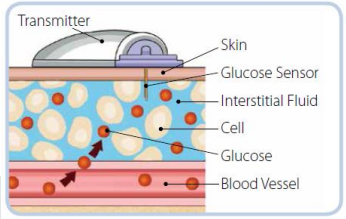
CGM Use

- CGM measures glucose in the interstitial fluid every 5 minutes
- Lag time of ~4-50 minutes between finger stick blood glucose & interstitial fluid. Rapid fluctuations in plasma glucose have been shown to accentuate this time lag.
- Blood glucose testing is still sometimes required
- Sensor information converted to a glucose value displayed on receiver, phone & or pump



http://professional.medtronicdiabetes.com/personal-cgm

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Medtronic Arrow	Dexcom Arrow	FreeStyle Libre Arrow	Trend Meaning	Glucose Value in 30 Minutes*
↑↑↑	↑↑	NA	Glucose is rising very quickly, >3 mg/dL/min	>90 mg/dL higher
↑↑	↑	↑	Glucose is rising quickly, 2–3 mg/dL/min (>2 mg/dL/min with FreeStyle Libre)	60–90 mg/dL higher (>60 mg/dL for FreeStyle Libre)
↑	↗	↗	Glucose is rising 1–2 mg/dL/min	30–60 mg/dL higher
No arrow	→	→	Glucose is changing slowly, <1 mg/dL/min	<30 mg/dL
↓	↘	↘	Glucose is falling 1–2 mg/dL/min	30–60 mg/dL lower
↓↓	↓	↓	Glucose is falling quickly, 2–3 mg/dL/min (>2 mg/dL/min with FreeStyle Libre)	60–90 mg/dL lower (>60 mg/dL for FreeStyle Libre)
↓↓↓	↓↓	NA	Glucose is falling very quickly, >3 mg/dL/min	>90 mg/dL lower

*Predicted 30-minute change in glucose is illustrative. NA, not applicable.

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Miller, E. M. *Using Continuous Glucose Monitoring in Clinical Practice.* Clinical Diabetes Journals (2020) 38 (5).

Attribute	Libre CGM	Libre 2 CGM	Dexcom G6	Medtronic	Eversense
Insulin pump integration	No	No	Tandem T-slim X2 insulin pump as Basal IQ and Control IQ, Smart Pen (In Pen)	Guardian 3; compatible with 630G/670G/770G insulin pumps Guardian Connect: Smart Pen (In Pen)	No
Maximum wear time	14 days	14 days	10 days	7 days	3 months
FDA approved sites	Back of arm	Back of arm	Abdomen Upper buttocks (ages 2-18 years)	Back of arm, abdomen	Back of arm
FDA approved ages (years)	18 and up	4 and up	2 and up	Guardian 3: 2 and up Guardian Connect: 7 and up	18 and up
Warm-up and calibration	1-hour warm up, No calibration	1-hour warm up, No calibration	2-hour warm up; No calibration	Up to 2-hour warm up, 2 calibrations per day + occasional diagnostic calibrations required	24-hour warm up and 4 calibrations within 6-36 hours at start up; then 2 calibrations per day
Interfering substances	Salicylic acid and Vitamin C	Vitamin C	Hydroxyurea	Acetaminophen, Hydroxyurea	Tetracycline
MARD (accuracy-the lower the better)	9.4%	9.4%	9.0% adults 7.7% pediatrics	9.64% with 3-4 calibrations per day; 10.55% with 1-2 calibrations per day	8.5%
FDA approved for insulin dosing	Yes	Yes	Yes	No	Yes

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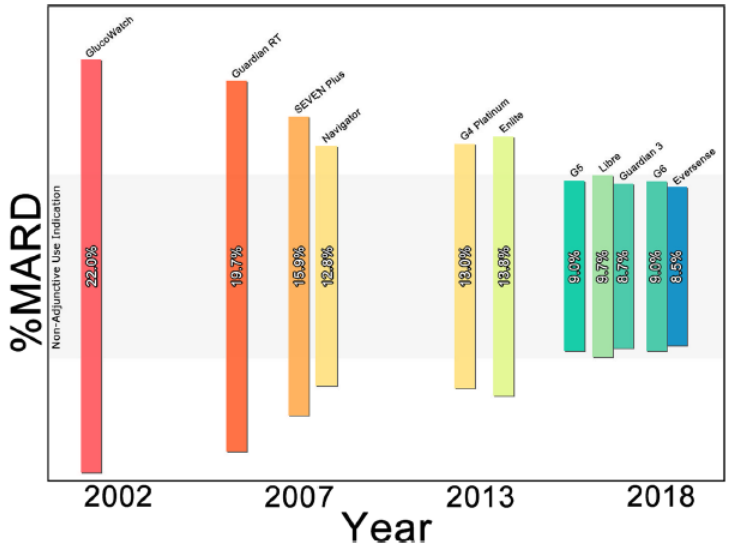
The Diabetes Care and Education Specialist's Role in Continuous Glucose Monitoring. ADCES Practice Paper. (March 2021)



The **mean absolute** relative **difference** (MARD) is currently the most common metric used to assess the performance of **CGM** systems. MARD is the average of the **absolute** error between all **CGM** values and matched **reference** values

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Martin et al. *Advanced Technology in the Management of Diabetes: Which Comes First- Continuous Glucose Monitor or Insulin Pump?* Current Diabetes Reports (2019) 19 (50)

Medtronic Guardian Connect (rtCGM)

- Adjunctive CGM
- FSBG calibration required 2-4 times daily
- Guardian Connect app on compatible iOS or android device
- 14-75 years
- 7 day sensor wear- abdomen or back of upper arms
- System can alert 10 to 60 min before high or low alert
- Links with Sugar IQ diabetes assistance app
- Carelink software

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Kruger et al. *Reference Guide for Integrating Continuous Glucose Monitoring into Clinical Practice*. The Diabetes Educator. (2019) 43 (Suppl 1): 3S-20S.

Dexcom G6 (rtCGM)

- Non-Adjunctive CGM
- No FSBG calibration
- 2 years and older
- 10 day sensor wear
- Sensor worn on abdomen for adults and abdomen or upper buttocks for ages 2-17
- Customizable glucose alerts
- Can use receiver or smart phone with Dexcom G6 mobile app
- Dexcom Clarity

Kruger et al. *Reference Guide for Integrating Continuous Glucose Monitoring into Clinical Practice*. The Diabetes Educator. (2019) 43 (Suppl 1): 3S-20S.

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Freestyle Libre (rtCGM)

- Non Adjunctive CGM
- No FSBG calibrations
- 18 years and older
- 14 day sensor wear
- No alarms
- Sensor worn on back of upper arm
- Must scan sensor every 8 hours to maintain a constant stream of data
- Can use receiver or smart phone with Libre View app to scan sensor

Kruger et al. *Reference Guide for Integrating Continuous Glucose Monitoring into Clinical Practice*. The Diabetes Educator. (2019) 43 (Suppl 1): 3S-20S.

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Freestyle Libre 2 (rtCGM)

- Non Adjunctive CGM
- 4 years and older
- Customizable glucose alarms
  - Optional Low or high glucose alerts
  - Signal loss alert
- Freestyle Libre 2 app now available for iOS

https://www.freestyle.abbott/us-en/products/freestyle-libre-2.html

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Eversense (rtCGM)

- Adjunctive CGM
- FSBG calibrations 2-4 times daily
- 18 years and older
- Implanted sensor- 90 day use
- Worn on back of upper arm
- Smart transmitter alerts

Kruger et al. *Reference Guide for Integrating Continuous Glucose Monitoring into Clinical Practice*. The Diabetes Educator. (2019) 43 (Suppl 1): 3S-20S.

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CGM Patient Training

- Sensor site selection and insertion of the sensor
- Attachment (and charging) of the transmitter to the sensor, if required
- Required taping/securing of the sensor/transmitter
- Connect of the transmitter to the receiver
- Difference between SG and BG
- Understanding CGM data and trends
- Calibration including timing, frequency and importance of accurate meter/finger stick technique if required

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The Diabetes Care and Education Specialist's Role in Continuous Glucose Monitoring. ADCES Practice Paper. (March 2021)

CGM Patient Training

- Setting and managing alerts including high alert, low alert, high snooze, low snooze, rise rate, fall rate, and predictive alerts
- Support with coping and problem solving related to individual behavioral issues that can improve management
- Possible interference of products ie acetaminophen, salicylic acid and high-doses vitamin C
- Education to prevent overcorrection of high glucose
- Sharing data
- Understanding CGM reports including the AGP and TIR

The Diabetes Care and Education Specialist's Role in Continuous Glucose Monitoring. ADCES Practice Paper. (March 2021)

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CGM Patient Training

D Download Data	• Key metrics, AGP, day by day or spaghetti graph • Start with global overview; what AGP, key metrics mean, ask what the person learned/what is going well with self-management
A Assess Safety	• Hypoglycemia- identify times below range, % time in hypoglycemia, # events • Interactive discussion: possible causes and solutions
T Time in Range	• Focus on the positive- identify days or times where time in range is highest • Interactive discussion: possible causes, solutions, and adjustments to self-management
A Areas to Improve	• Hyperglycemia- Identify times above range, % time in hyperglycemia, # events • Interactive discussion: possible causes, solutions, and adjustments to self-management
A Action Plan	• Develop collaboratively with the person with diabetes

The Diabetes Care and Education Specialist's Role in Continuous Glucose Monitoring. ADCES Practice Paper. (March 2021)

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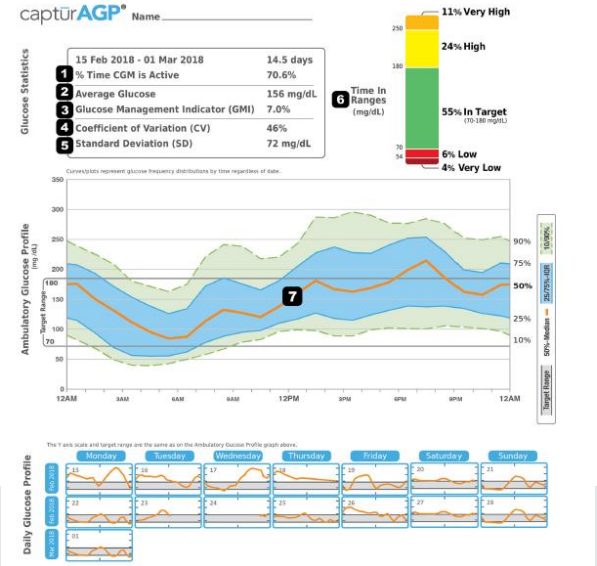
CGM Patient Training



Martin et al. *Advanced Technology in the Management of Diabetes: Which Comes First- Continuous Glucose Monitor or Insulin Pump?* Current Diabetes Reports (2019) 19 (50).

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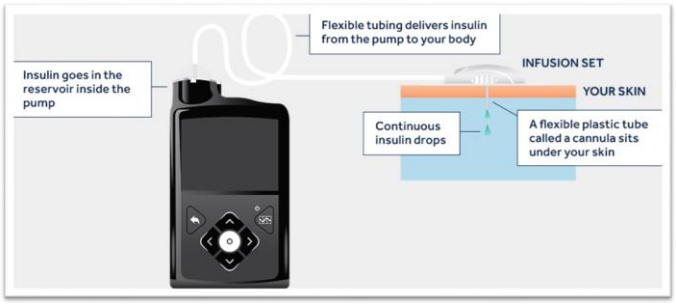
Insulin Pump Therapy (CSII)

- Continuous Subcutaneous Insulin Injection (CSII) insulin pump mimics the physiology of the pancreas
- Bolus insulin delivery
- Basal insulin delivery
- Reservoir filled with insulin
- Infusion set
- Worn 24 hours per day
- Delivers rapid-acting insulin



https://www.medtronicdiabetes.com/treatments/insulin-pump-therapy

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Adults & CSII

- CSII may be considered an option for all adults with type 1 DM, adults with type 2 DM on MDI, and other forms of diabetes resulting in insulin deficiency who are able to safely manage the device
- Sensor-augmented pump therapy with automatic low glucose suspend may be considered in adults with type 1 diabetes to prevent/mitigate episodes of hypoglycemia
- Automated insulin delivery systems may be considered in adults with type 1 diabetes to improve glucose control

Diabetes Technology: Standards of Medical Care in Diabetes- 2021. Diabetes Care (2021) 44 (Suppl. 1): S85-S99.

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Pump Candidates

- Realistic expectations of the capabilities of pump therapy
- Demonstration of independent diabetes management and knowledge of the basics of diabetes education
- Physical ability to view the pump screen and hear the arms along with dexterity skills
- Emotional stability and adequate emotional support
- Adequate insurance benefits or personal resources to afford the cost of the pump and supplies
- Ability to problem solve potential challenges with the pump
- Capacity to learn, practice and understand insulin pump therapy

Continuous Subcutaneous Insulin Infusion (CSII) Without and With Sensor Integration. ADCES Practice Paper. (March 2021)

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Pump Model Considerations

- Complexity of the pump relative to the user's abilities
- Water resistant
- Patch pump or pump with tubing
- Does it link to CGM?
- Does the pump respond to sensor data by adjusting basal rate? Correctional insulin? Suspend prior to low?
- Can the patient read the pump on-screen text or hear the pump alerts?
- Does the pump hold enough insulin to last the patient 2-3 days?
- Which brands are covered by the patients insurance?

Continuous Subcutaneous Insulin Infusion (CSII) Without and With Sensor Integration. ADCES Practice Paper. (March 2021)

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Omnipod

- Patch insulin pump
- No tubing
- 200 unit reservoir
- Pod includes cannula
- All programming done via DASH or Eros PDM
- Food data base
- Integrated Freestyle glucose meter (Eros)
- DASH connected with Bayer Contour glucose meter
- No CGM integration
- Approved for ages 2 and older

https://www.myomnipod.com/DASH_Update

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Tandem t-slim X2

- Sensor augmented pump (Basal IQ) or automated insulin delivery system (Control IQ)
- Displays data from Dexcom G6 CGM
- Pump with tubing
- Bright, full- color touchscreen
- Compact-thin dimensions
- Charges, no disposable batteries
- No linked BG meter
- 300 unit reservoir
- Approved for ages 6 and older

https://www.tandemdiabetes.com/products/t-slim-x2-insulin-pump

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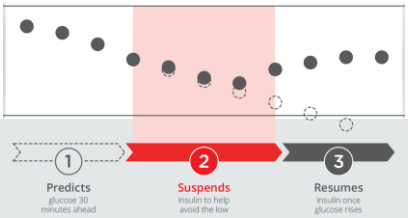
Tandem t-slim X2 with Basal IQ

- Predicts glucose levels 30 minutes ahead based on 3 of the last 4 consecutive CGM readings
- If the glucose level is predicted to be less than 80 mg/dL in 30 min., or if a CGM reading falls below 70 mg/dL, insulin delivery is suspended. Insulin delivery resumes as soon as sensor glucose values begin to rise
- Insulin may be suspended for a minimum of 5 minutes and a maximum of 2 hours within a 2.5-hour rolling window



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https://www.tandemdiabetes.com/products/t-slim-x2-insulin-pump

Tandem t-slim X2 with Control IQ

- Control IQ algorithm designed to increase time in range (70-180 mg/dl)
- Automatically adjusts basal insulin to prevent high or low glucose
- Delivers automatic correction boluses to bring down high glucose
- Layered on top of user's pump settings
- Uses Dexcom CGM values to predict glucose levels 30 minutes ahead and adjusts insulin accordingly
- Optional settings for sleep and exercise activities that adjust treatment ranges

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https://www.tandemdiabetes.com/products/t-slim-x2-insulin-pump/control-iq

Tandem t-slim X2 with Control IQ

180	Delivers	Delivers an automatic correction bolus if sensor glucose is predicted to be above 180 mg/dL
	Increases	Increases basal insulin delivery if sensor glucose is predicted to be above 160 mg/dL
160		
	Maintains	Maintains active Personal Profile settings
112.5		
	Decreases	Decreases basal insulin delivery if sensor glucose is predicted to be below 112.5 mg/dL
70 mg/dL		
	Stops	Stops basal insulin delivery if sensor glucose is predicted to be below 70 mg/dL

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https://www.tandemdiabetes.com/products/t-slim-x2-insulin-pump/control-iq

Medtronic 670G & 770G

- Sensor Augmented Pump with low glucose suspend or predictive low glucose suspend (Manual Mode) or Automated Insulin Delivery (Automode)
- Pump with tubing
- 300 unit reservoir
- Displays data from the Guardian Sensor 3 CGM
- 670G approved for ages 7 and older
- 770G approved for ages 2 and older
- Contour Next linked meter for 670G
- Accu-Check Guide linked meter for 770G

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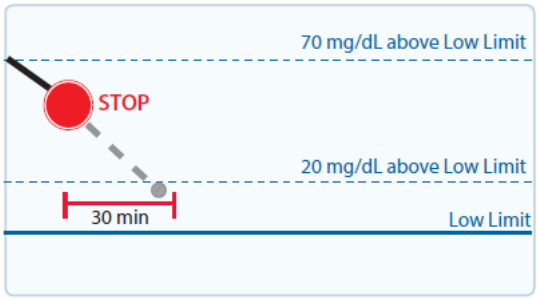
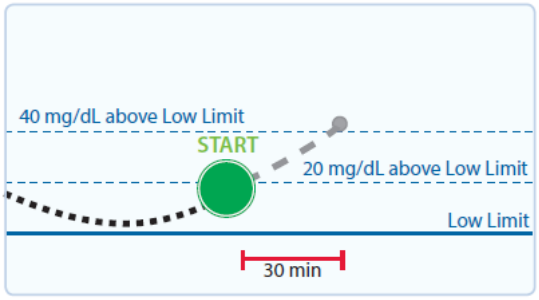
https://www.medtronicdiabetes.com/products/minimed-770g-insulin-pump-system

Medtronic 670G & 770G Suspend Before Low





https://professional.medtronicdiabetes.com/resources-download-library

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Medtronic 670G & 770G Automode

- Auto adjusts basal insulin every 5 min based on sensor glucose
- Fixed glucose target of 120 mg/dl but 150 mg/dl can be turned on for a temporary target
- Required user input includes carbohydrate amount for meals, and BGs to deliver correction bolus and to calibrate the sensor
- Pump will suggest a correction based on a blood glucose target of 150 mg/dL with a correction dose that is calculated by the algorithm every 24 hours
- Only modifiable parameters in Automode include active insulin time and the insulin to carbohydrate ratio

Weaver et al. *The Hybrid Closed Loop System: Evolution and Practical Applications.* Diabetes Technology & Therapeutics. (2018) 20 (Suppl 2): S2-16-S2-23.

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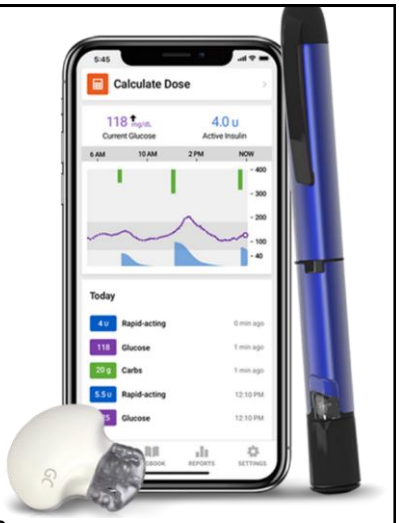
In Pen Smart Insulin Pen



- Blue tooth smart insulin pen-lasts one year
- Calculates insulin doses
- Syncs to an app that tracks each dose, when they were delivered, and active insulin time
- App compatible with iphone and android devices
- Temperature meter embedded inside
- Shares therapy data
- Integrates with Dexcom G6 and Guardian Connect CGM
- Compatible with Novolog, Humalog and Fiasp U-100 insulin cartridges

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https://www.medtronic.com/us-en/healthcare-professionals/therapies-procedures/diabetes.html

Contact Information

Mailing Address
Harold Hamm Diabetes Center
1000 N. Lincoln Blvd. Ste. 3400
OKC, OK 73104

Email Address
christine-olson@ouhsc.edu

Phone Number
(405) 271-1000

Diabetes Care Summit

OU Health | Harold Hamm Diabetes Center

ADCES Association of Diabetes Care & Education Specialists

Breakout Session II:

Diabetes Prevention and Intervention in Tribal Communities

DIABETES PREVENTION AND INTERVENTION IN TRIBAL COMMUNITIES

Presented to Harold Hamm Diabetes Care Summit

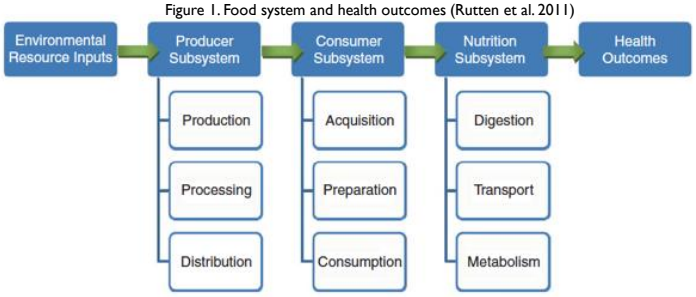
September 10, 2021

CENTER FOR
INDIGENOUS HEALTH
RESEARCH AND POLICY
OSU Center for Health Sciences

INTRODUCTION

- Professor of Rural Health, Oklahoma State University Center for Health Sciences
- Director, Center for Indigenous Health Research and Policy
  - Education and Training
  - Research and Evaluation
  - Dissemination

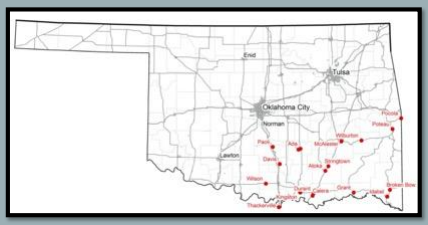
Figure 1. Food system and health outcomes (Rutten et al. 2011)



INTERVENTION SCIENCE WITH INDIGENOUS COMMUNITIES

- Use Community Based Participatory Research (CBPR) orientation to address diet-related health disparities (i.e. diabetes, hypertension, obesity) within Indigenous communities
- Food system interventions

THRIVE STUDY PURPOSE: TO INCREASE HEALTHY FOOD ACCESS BY IMPROVING TRIBAL CONVENIENCE STORES



Chickasaw Travel Stop, Ada, OK

Choctaw Travel Plaza, Broken Bow, OK

PRELIMINARY STUDIES: FOOD INSECURITY AND CHRONIC DISEASE AMONG NATIVES IN CHOCTAW AND CHICKASAW NATIONS

-Conducted cross sectional survey of 513 Natives

-Administered USDA 6-item short form Household Food Security Scale

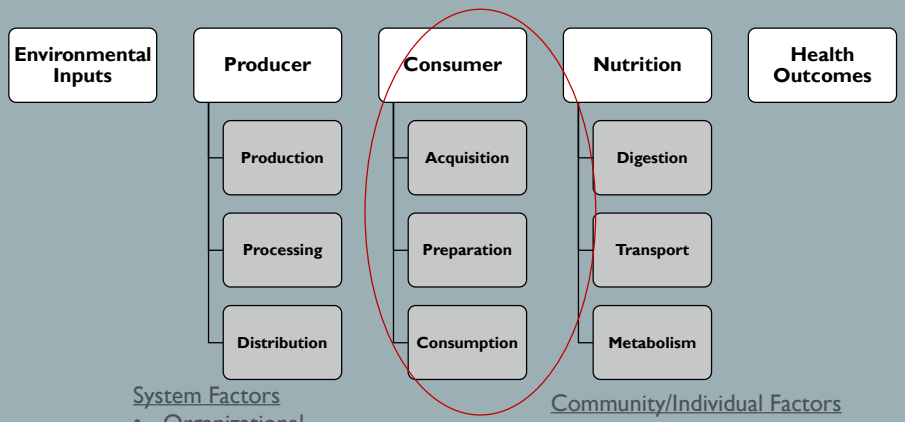
-58% of Natives surveyed were food insecure

-Among those who were food insecure, the prevalence of **diabetes** (27.3% vs 18.8%), **obesity** (60.7% vs 45.8%), and **hypertension** (52.5% vs 42.5%) was higher compared to those who were food secure, even after adjustment for age, gender, education, income, and study site

-More than 60% of Natives surveyed reported shopping for food at tribal convenience stores 3 or more times per week

Jernigan et al. "Food Insecurity and Chronic Diseases Among American Indians in Rural Oklahoma: The THRIVE Study", *American Journal of Public Health* 107, no. 3 (March 1, 2017): pp. 441-446.

FOOD SYSTEM CONCEPTUAL MODEL: THRIVE STUDY FOCUS



System Factors
- Organizational
- Financial
- Technological
- Regulatory/Policy

Community/Individual Factors
- Resources
- Awareness
- Access
- Skills

Rutten, L. F., Yaroch, A. L., & Story, M. (2011). Food systems and food security: a conceptual model for identifying food system deficiencies. *J of Hunger & Env Nut*, *6*(3), 239-246.

DESIGN AND METHODS

- Participatory research orientation
- Cluster control trial with eight stores (4 intervention/4 control)
- Longitudinal cohort study surveying Native shoppers (n= 1637) before and after the intervention
- Intervention strategies: **product, placement, promotion, and pricing**
  - Nation A: July 2016-April 2017 (9mos)
  - Nation B: June 2016-May 2017 (12mos)
- **Outcomes:**
  - Store: increased fruit/vegetable availability
    - store inventory and sales; nutrition environment measures scores
  - Individual: increased fruit/vegetable purchasing and intake
    - eating behaviors, self-efficacy, perceived nutrition environment, sociodemographics and exposure to intervention

Institute of Medicine. Committee on Prevention of Obesity in Children and Youth : Koplan JP, Liverman CT, Kraak VI, editors., Preventing Childhood Obesity: Health in the Balance. Washington, DC: National Academies Press; 2005

PHASE ONE: PRODUCT AVAILABILITY; BASELINE MEASURE OF STORE NUTRITION ENVIRONMENTS

Wetherill, M. et al.. (2018). Adaption and validation of the Nutrition Environment Measures Survey (NEMS) to assess tribal convenience stores in rural Oklahoma: the THRIVE study. *Health Promotion Practice;* E-pub head of print September 21, 2018.

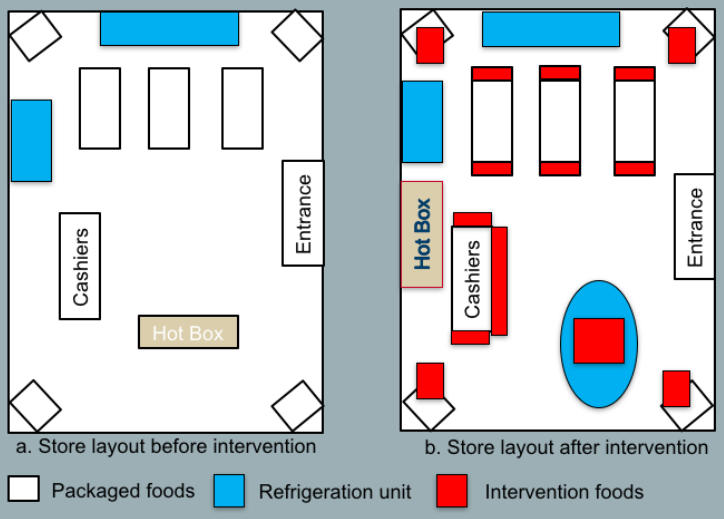
PHASE TWO: INTERVENTION STRATEGIES (PLACEMENT, PROMOTION, PRICING)

Jernigan, VB et al. (2018). Using Community-based Participatory Research to Develop Healthy Retail Strategies in Native American-Owned Convenience Stores: the THRIVE Study. *Preventive Medicine Reports.* Sep;(11):148-153. PMID: PMC6039850.

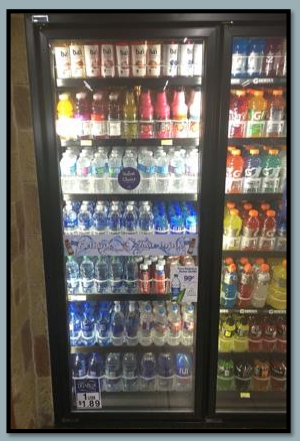
STRATEGY #1 PRODUCT

Choctaw Nation Salad and Wraps

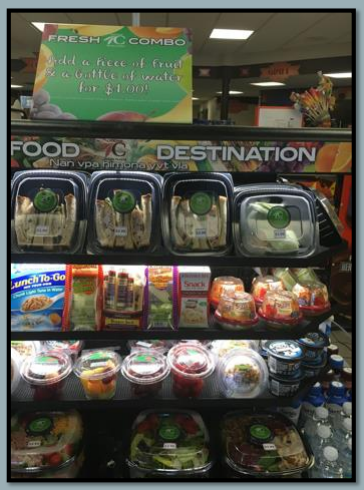
STRATEGY #2 PLACEMENT



STRATEGY #3 PROMOTION



STRATEGY #4 PRICE



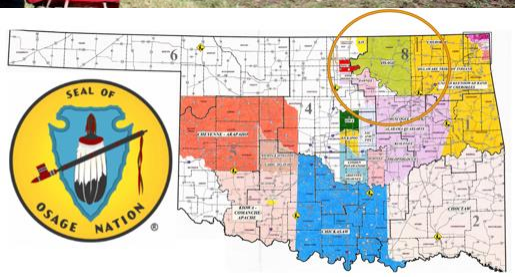
FINDINGS AND SUSTAINABILITY

-All of our findings have been published, with study outcomes published in the *American Journal of Public Health*

-To summarize, the intervention:

- -Increased healthy food options (perceived and objective NEMS measures)
- -Increased purchases of healthy foods
- **-Increased self-report of healthy food intake**
- -Like other studies that only target the environment, we did not see significant changes in ***overall*** dietary intake, **but we did change purchasing decisions, especially among those shopping more often**
- Resulted in important policy changes: distributors for both Nations expanded suppliers and options

Next steps: expand intervention strategies, include behavioral change and traditional foods focus, increase local food options



> "Finally, we have a way to do what we did 200 years ago...feed our own people."
>
> — Raymond Red Corn, Osage Nation Assistant Principal Chief

FRESH STUDY ORIGINS

CBPR Partnership with Osage Nation

Began 2 years before application for NIMHD grant award

Builds upon Bird Creek Farm Initiative and Osage Nation's vision to create a sustainable food system/ Indigenous food sovereignty

INDIGENOUS FOOD SOVEREIGNTY

- The right and responsibility of Indigenous people to healthy and culturally appropriate foods produced through traditional Indigenous practices[1]
- Supports communities in taking greater control over their food systems by increasing traditional and healthy food access and reducing dependence on packaged and fast foods[2]
- Mirrors public health efforts to address diet-related disparities through food system change in other populations

[1]Settee P, Shukla, S. *Indigenous Food Systems: Concepts, Cases, and Conversations.* Toronto Ontario: Canadian Scholars; 2020.
[2]Jernigan VBB. Addressing food security and food sovereignty in Native American communities. *Health and Social Issues of Native American Women.* 2012:113-132.

FRESH STUDY GOAL

- Develop a culturally relevant, multilevel, multicomponent farm-to-school intervention and evaluate its efficacy in increasing vegetable and fruit intake and reducing food insecurity, BMI, and blood pressure (adults only) among Osage families
- Create and disseminate a Web-based multimedia manual and documentary film and evaluate its effectiveness in increasing tribal readiness and capacity to improve Indigenous food environments

STUDY DESIGN, SETTING, AND OUTCOMES

- Study Design: Multi-level, multi-component wait-list controlled trial
- Setting: Early Childhood Education (ECE) centers in 4 communities, total of 9 ECEs
- Inclusion criteria: American Indian, with a child enrolled in one of the ECEs, aged 3-5, and no plans of moving within the next year
- Intervention from Jan 2018-Dec 2018
  - 2 communities randomized to intervention group (5 ECEs) - Received intervention in Spring 2018
  - 2 communities randomized to control group (4 ECEs) - Received intervention in Fall 2018
  - Total participants: 369 (176 parent/caregivers; 193 children aged 3-6)
- Primary Outcomes:
  - Increase fruit and vegetable willingness to try and intake in children
- Secondary Outcomes:
  - Reduce food insecurity, Body Mass Index (BMI), and blood pressure (BP) (adults only), and increase vegetable and fruit intake in adults

Community outcomes: Launch farm to feed children and inform policy

MULTI-LEVEL MULTI-COMPONENT INTERVENTION

Environment/ Policy
Bird Creek Farm

→

School/ Community
Curriculum
Staff Feeding Practices
Menu Changes

→

Family (Passive)
Weekly meal kits
Web-based parent curriculum
Monthly family nights

School/ Community

Family (Passive intervention)

<u>Children:</u>
15 week hands-on sensory gardening, cooking and cultural story-telling curriculum
Take home recipe kits

<u>Teachers:</u>
Curriculum tailoring and training workshops[1]
Classroom activities, supplies (books and snacks)
Garden beds at each site
Garden maintenance provided by farm

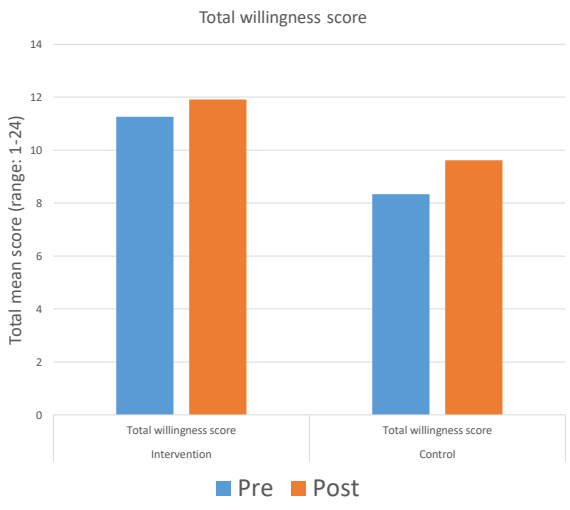
<u>Cooks:</u>
Best practice six-week cycle menu[2]
Best practice menu training[3]
Farm produce delivered fresh 2x per week

<u>Parents:</u>
12 weekly healthy eating videos
Four in person healthy eating, cooking, and food sovereignty meetings
Take-home meal kits from children
Cooking supplies

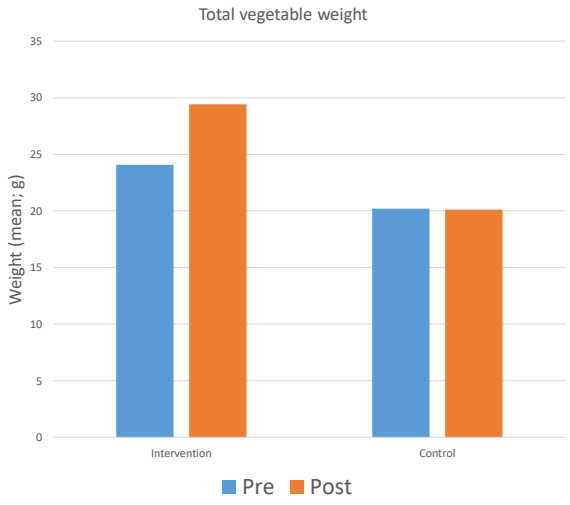
[1]Sisson, S, Jernigan, VB. (2019). The Development of Child and Adult Care Food Program Best-Practice Menu and Training for Native American Head Start Programs: the FRESH Study. *Preventive Medicine Reports*, 14(June). Article 100880.
[2]Sleet, K, Sisson, S, Jernigan, VB. (2020). The Impact of Responsive Feeding Practice Training on Teacher Feeding Behaviors in Tribal Early Care and Education: The FRESH Study. *Current Developments in Nutrition*, *4*(Supplement_1), 23-32.
[3]Sisson, S, Sleet, K, Rickman, R, Jernigan, VB. (2020). Impact of the 2017 Child and Adult Care Food Program Meal Pattern Requirement Change on Menu Quality in Tribal Early Care Environments: The FRESH Study. *Current Developments in Nutrition*, *4*(Supplement_1), 12-22.

DATA COLLECTION

- Classroom and child measures:
  - Child willingness to try and plate waste measures at baseline, mid point, and post intervention
  - Weekly program implementation surveys completed by teachers to assess fidelity to the intervention
  - Site visits by university staff
- Menu measures:
  - Weekly menus collected during produce drop-off with modifications noted
  - Weekly menu surveys administered to cooks
  - Analysis of menus in prior years to compare changes
- Parent measures:
  - 24-hour dietary recalls and surveys were administered before and after intervention by trained university staff either in-person or via telephone
  - Biometrics were completed before and after intervention by trained university staff



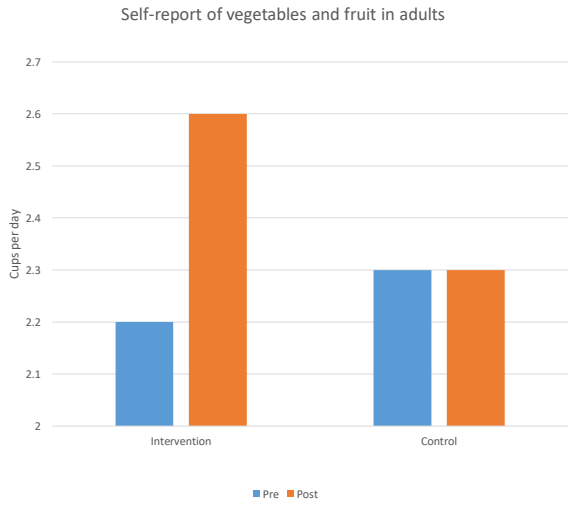
CHILD WILLINGNESS TO TRY



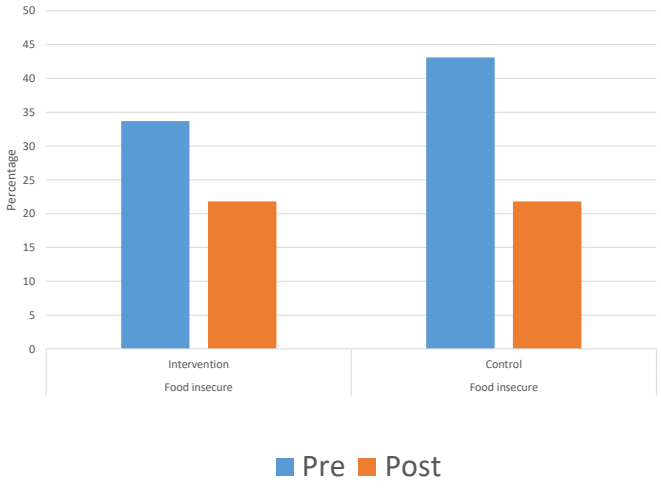
CHILD PLATE WASTE

	Overall (N=176)	Intervention (N=94)	Control (N=82)	P-value
Age, years, mean (SD)	33.2 (7.1)	34.0 (7.3)	32.2 (6.8)	0.11
Female, %	91.8	90.3	93.5	0.64
Native American, %	56.5	66.7	44.2	0.005
Education, %				0.08
Some high school	4.1	4.3	3.9	
High school graduate/GED	41.2	35.5	48.1	
Technical/Vocational school	30.6	28.0	33.8	
College graduate or higher	24.1	32.3	14.3	
Annual household income, %				0.09
≤ $15,000	15.0	16.2	13.3	
$15,001-30,000	25.6	18.3	34.5	
$30,001-50,000	30.5	24.7	40.0	
> $50,000	28.0	40.8	12.0	
Employed full or part time, %	67.1	75.3	57.2	
Marital status, %				0.94
Married	59.4	60.2	58.4	
Divorced/Separated	15.9	17.2	14.3	
Never married	14.7	12.9	16.9	
Partner/significant other	10.0	9.7	10.4	
Food assistance program participation, %				
Food Stamp benefits	10.8	12.8	8.5	0.47
Food Distribution benefits	2.3	2.1	2.4	1.0
Women, Infants, and Children	30.1	29.8	30.5	1.0

CAREGIVER FINDINGS: DEMOGRAPHICS



SELF-REPORTED VEGETABLES AND FRUIT AT BASELINE AND FOLLOW-UP IN CAREGIVERS (N=152)



SELF-REPORTED FOOD INSECURITY AT BASELINE AND FOLLOW-UP IN CAREGIVERS (N=152)

CAREGIVER FINDINGS CONT.

- Moderate and total physical activity were significantly higher among intervention group at follow-up compared to control
- Obesity and high blood pressure decreased slightly in intervention group from baseline to follow-up while increased in control though not significant

COMMUNITY OUTCOMES AND NEXT STEPS

- We achieved launch of BCF and its continued development
- Tripled active usage of acres and food production
- Used data to advocate for policy and BCF was expanded by Osage Nation Congress in 2019
- We developed and disseminated the study information through a PBS series called "Blood Sugar Rising," which premiered on PBS April 15, 2020
- We were featured in the journal *Nature* for our CBPR approach
- Next steps are CSA to expand food production

NIH National Institute on Minority Health and Health Disparities

(NIMHD Grant #) R01MD011266

Health and the American Indian

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www.okcic.com

Introduction

* Kaw/Osage
* Raised in Cheyenne and Arapaho Country
* Indian Health Service (IHS)-PCP
* Reside in Citizen Potawatomi Nation
* Work for Oklahoma City Indian Clinic (Urban Clinic)

Outline

1. What is an American Indian?
2. Health History and Status of American Indians
3. Indian Health Service System and Successes
4. Future of American Indian Health Care
5. Questions/Discussions

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What is an American Indian?

Native people of North America

- Native American (NA), Indigenous Peoples, First Nations, Alaska Natives(AN), American Indian (AI)
- Within U.S.-
  - 574 federally recognized tribes* (229-AK)
    - 39 federally recognized tribes in Oklahoma
  - 66 state-only recognized tribes

Tribal Sovereignty- decisions about tribes are made with their participation and consent.(Government to government relationship)

McGirt v. Oklahoma(2020)

**does not include Native Hawaiians*

https://www.bia.gov/frequently-asked-questions

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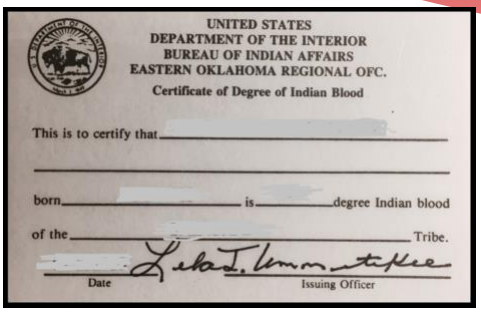
Certificate Degree of Indian Blood (CDIB)



UNITED STATES
DEPARTMENT OF THE INTERIOR
BUREAU OF INDIAN AFFAIRS
EASTERN OKLAHOMA REGIONAL OFC.

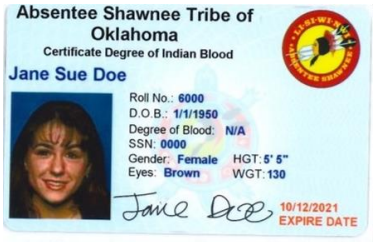
Certificate of Degree of Indian Blood

This is to certify that _____

born _____ is _____ degree Indian blood

of the _____ Tribe.

Date _____ Issuing Officer



Absentee Shawnee Tribe of Oklahoma

Certificate Degree of Indian Blood

Jane Sue Doe

Roll No.: 6000
D.O.B.: 1/1/1950
Degree of Blood: N/A
SSN: 0000
Gender: Female HGT: 5' 5"
Eyes: Brown WGT: 130

10/12/2021
EXPIRE DATE

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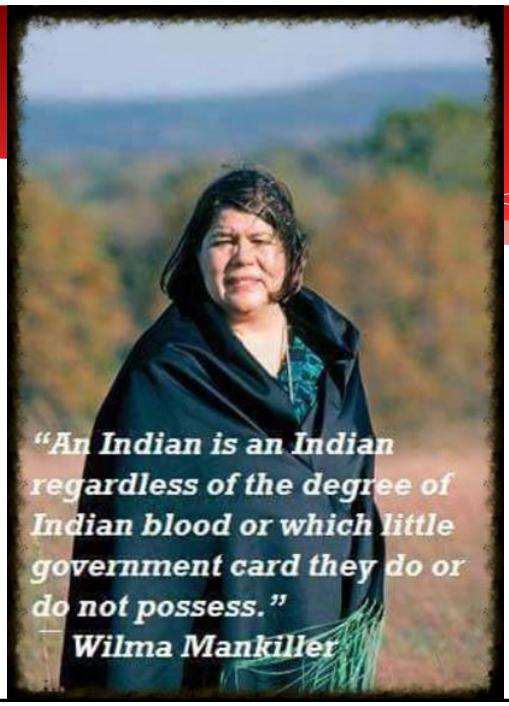

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What it is like to be Indian

Reservation:
https://www.youtube.com/watch?v=OOWUDM1GBhk
3:09

What it means to be Indian:
https://www.youtube.com/watch?v=J2HeHShGD7k
6:10

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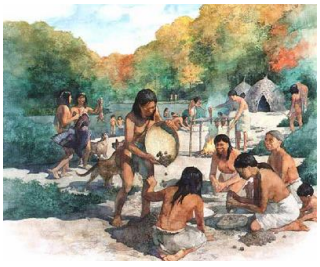
Pre-Colonialism

American Indians- Lived off Land

* Hunters, Gatherers, Gardeners
* High Fiber, High physical activity, lean protein



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Removal/Relocation/Reservation

- Eastern Tribes sent to Oklahoma
- Lifestyle
  - Diet (known game, fruits/vegetables)
    - Cultural tradition around geographic foods no longer available

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Health Consequences

- American Indians not prepared/familiar with OK area foods/game
  - Food rations 2x per month
    - (lard, flour, coffee, sugar, canned meat)
    - Created dependence (now known as commodities)
- Lower physical activity, fiber, high fat protein
- Total lifestyle loss
  - High physical, cultural, emotional, social trauma

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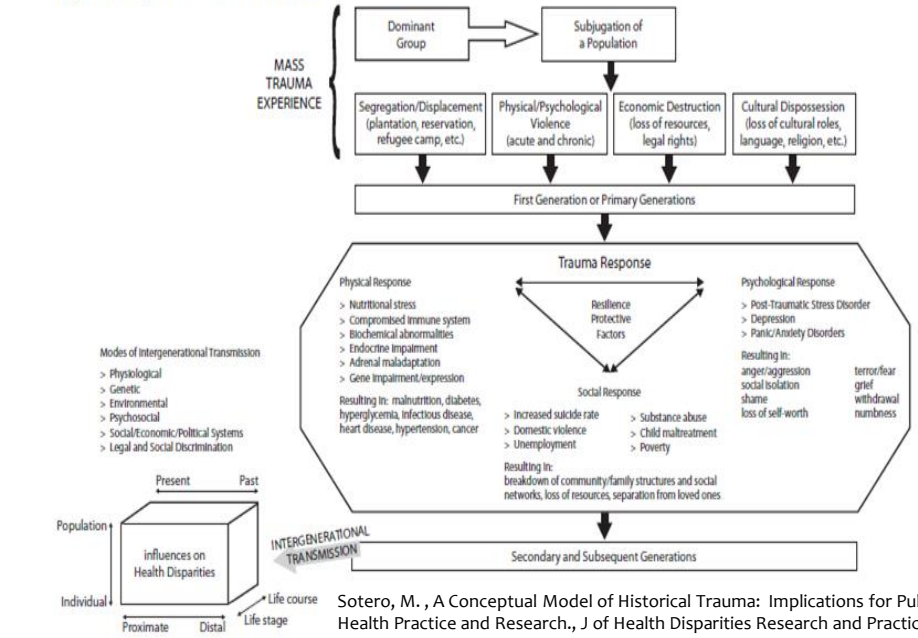
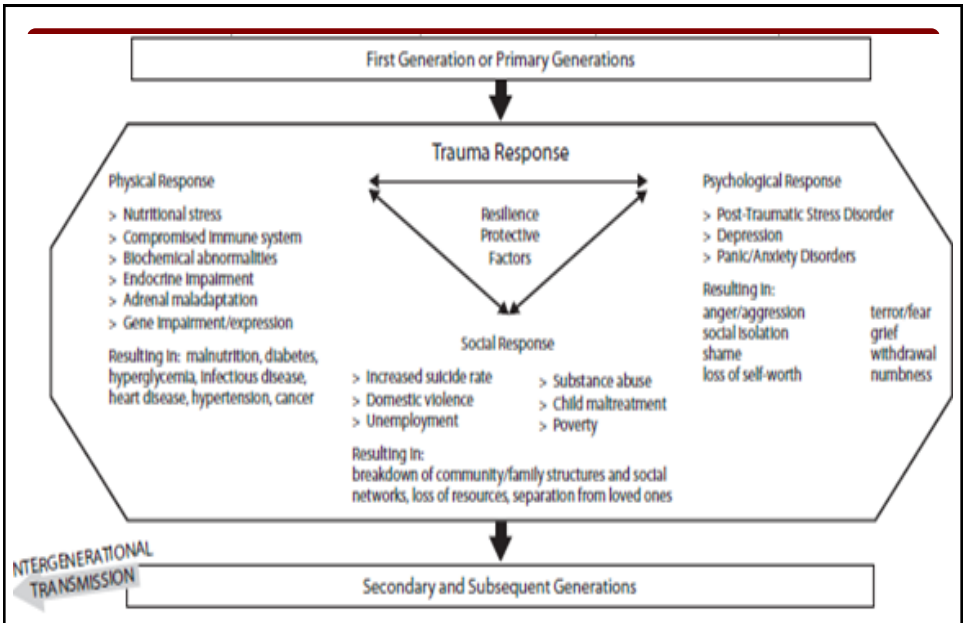
Historical Trauma Conceptual Model



Sotero, M. , A Conceptual Model of Historical Trauma: Implications for Public Health Practice and Research., J of Health Disparities Research and Practice Vol1, No1 pp93-108



Modes of Intergenerational Transmission: Physiological, Genetic, Environmental, Psychosocial, Social/Economic, Legal/Social Discrimination

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Modern Day Quality of Life

* Socio-Economic Conditions
  * lower end of SES scale
  * high HS drop-out and unemployement rates
  * often remote/rural
* Lifestyle
  * diet-high fat/processed foods (inexpensive)
  * exercise
  * tobacco
* Genetics

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AI/AN Health Disparities

Leading Causes of Death

* Heart Disease
* Cancer
* Diabetes
* Unintentional injuries

"Broad quality of life issues rooted in economic adversity and poor social conditions" (IHS) (genetic, lifestyle, environment)

i.e. Navajo Nation (COVID-19)

Life expectancy is 5.5 years less than general population

https://www.ihs.gov/newsroom/factsheets/disparities/#:~:text=These%20are%20broad%20quality%20of,deaths%20(2009%2D2011).

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Cardiometabolic Disease Statistics

- American Indian/Alaska Native *adolescents* are **30%** more likely than non-Hispanic white adolescents to be obese.[1]
- American Indian or Alaska Native *adults* are **50%** more likely to be obese than non-Hispanic whites.[1]
- CVD is leading cause of death in AI[2]
  a. 50% more likely to have CVD than caucasian
- AI have a greater chance of having DM than any other US racial group[3]

1. https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlid=40
2. https://www.ahajournals.org/doi/full/10.1161
3. https://www.cdc.gov/vitalsigns/aian-diabetes/index.html

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How is American Indian Health Addressed

* Private practices
* VA
* IHS*

*Required by Federal Law

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AI/AN Health Care System

Indian Health Care System (I/T/Us)

- I.H.S. Clinics/Hospitals
- Tribal Clinics/Hospitals
- Urban Clinics/Hospitals

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I.H.S. Service Areas

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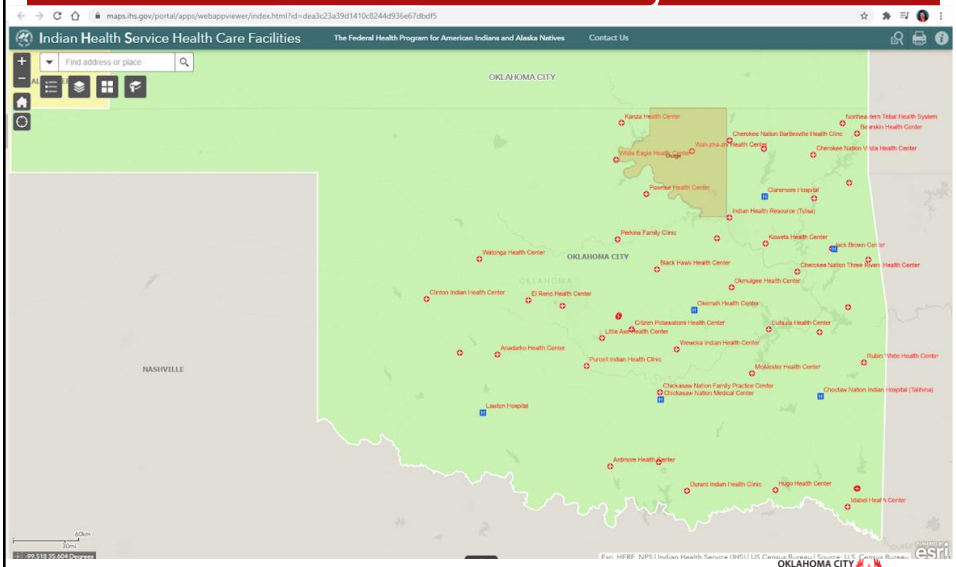
Indian Health Service System-OK



System Transformation

Circa 1975- basic services

Circa 2017- cutting edge service and technology

Indian Health Service System Services

Dependent on location/provider

Outpatient ⟹	Inpatient
Primary Care ⟹	Speciality Care
Basic Prevention ⟹	Robust
Preventive Services ⟹	
"Modern" Health Care	"Blended"
Health Care	

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Shining Star of Indian Health Care

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Special Diabetes Program for Indians (SDPI)

- Balanced Budget Act of 1997
  - $30 million per year (1998-2002)
  - $100 million per year (2001-2003)
  - $150 million per year (2004-present)
- Added Demonstration Projects (2004)
  - Diabetes Prevention
  - Healthy Heart
- Supports 301 programs in 35 states=>708,000 patients

Special Diabetes Program for Indians 2020 Report to Congress

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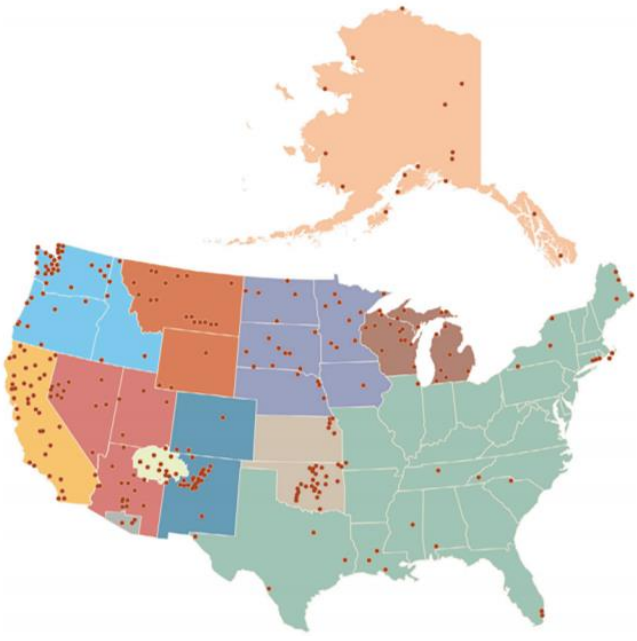

Special Diabetes Program for Indians 2020 Report to Congress

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SDPI Efforts

- Medications, strips, eyeglasses, shoes
- Staff
  - Education (RD, CPT, RN, MSW, CDE)
    - DSMT- diabetes education curriculum
    - DPP- Diabetes Prevention Program (MEDICAID)
    - Youth programs
      - afterschool programs, school break camps, evening/weekend events (PICS)
      - Native Youth Preventing Diabetes
    - Advocacy (Local, State and Federal)
      - Oklahoma Inter-Tribal Diabetes Coalition
      - OK State DM Caucus- legislation and regulation
      - ADCES, ADA

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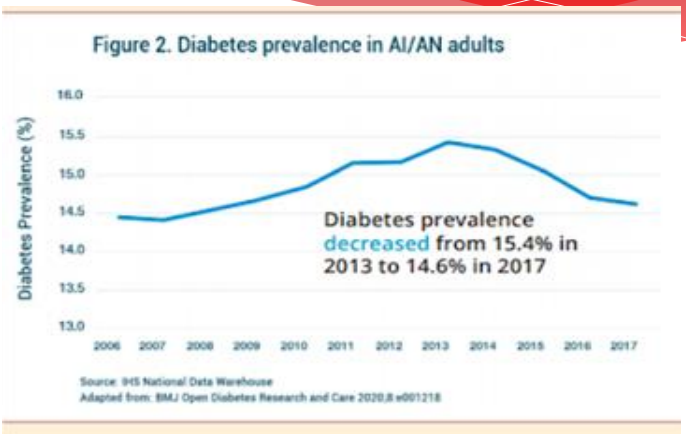
SDPI Successes- Diabetes Prevalence



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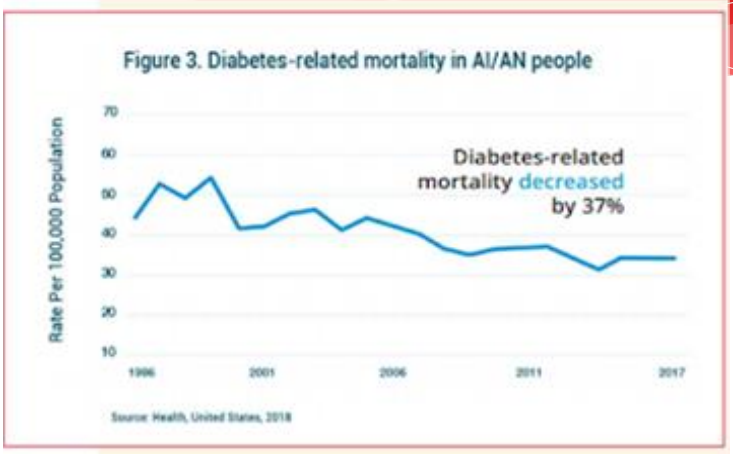
Special Diabetes Program for Indians 2020 Report to Congress

SDPI Successes- Diabetes Mortality



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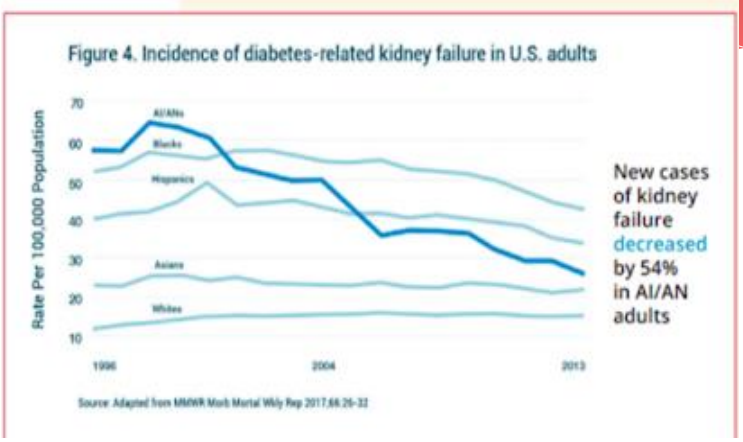
SDPI Successes- Diabetes-related kidney failure



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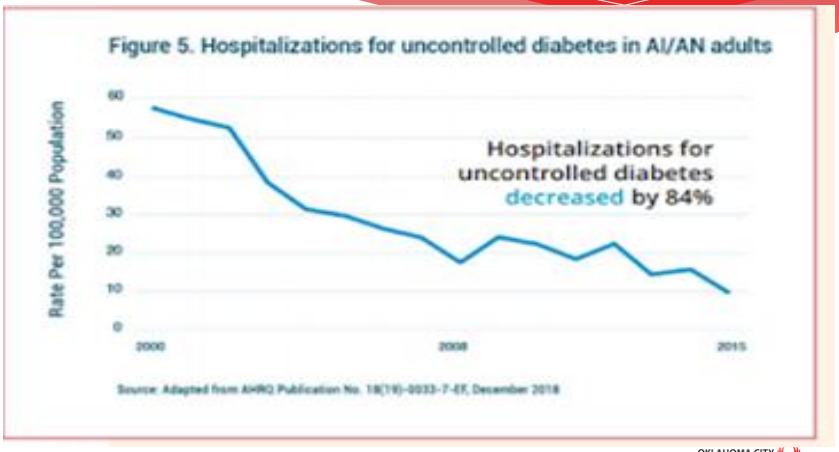
SDPI Successes- Diabetes Hospitalizations



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Cultural Bias and Transformation

Cultural Barriers in American Indian Health Care

* Two-way judgement
  * What an AI looks or acts like
* AI providers get better communication
* Younger generation more accepting

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INDIAN CLINIC www.okcic.com

AI Specific Cultural Barriers

* Female dominant (some tribes)
* Difference in social courtesies
  * Looking you in the eye
  * Not commenting on instruction
    * Sign as disrespect
* Spiritual Belief System
  * "white-man medicine"

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Moving Forward

Indian Health Service System Services

Dependent on location/provider

Outpatient ⟹	Inpatient
Primary Care ⟹	Speciality Care
Basic Prevention ⟹	Robust
Preventive Services ⟹	
"Modern" Health Care	"Blended"
Health Care	

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Muskogee Nation- Tulsa

Council Oak Comprehensive Health Care

-Specialty Care
-Inpatient Care
-Family Accomodations

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Tribal Investments in Communities

Reducing health disparities by:

* Investments in:
  * Socioeconomic Factors
    * Schools (facilities, internet, equipment, scholarships)
    * Roads/bridges
    * Housing
  * Lifestyle Factors
    * Drinking water
    * Access to healthy foods
    * Tobacco-free policies
  * Health
    * non- AI programming

Improving OK also improves tribes

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Moving Forward

- Decrease in Fatalism
- Self- empowerment
- Momentum for better health

Chickasaw Nation Bus

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Questions?

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Thank You

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HAROLD HAMM DIABETES CENTER
THE UNIVERSITY OF OKLAHOMA SM

Diabetes Care Summit
10 September 2021

SARS-CoV-2, COVID-19 and Diabetes: A New Bidirectional Disease?

Steven E. Kahn, M.B., Ch.B.
VA Puget Sound Health Care System
University of Washington
Seattle, WA

Dualities of Interest

Advisory Board, Consulting and Lectures

Bayer
Boehringer Ingelheim
Casma Therapeutics
Eli Lilly
Intarcia
Merck
Novo Nordisk
Pfizer
Third Rock Ventures

Outline

1. Considerations in the need to find answers to a new disease entity
2. Epidemiology of the disease
3. Hyperglycemia in COVID-19 – a “new” vs. “old” disease entity?
4. Response to medications in patients with diabetes – real or unreal?
5. Post-Acute Sequalae of COVID-19 (Long COVID)

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Some Words of Caution

1. Quality of peer review
2. Most studies are retrospective
3. Confounding by indication
4. Meta-analyses may count individuals more than once
5. Few or small randomized clinical trials (RCTs) of interventions

Outline

1. Considerations in the need to find answers to a new disease entity
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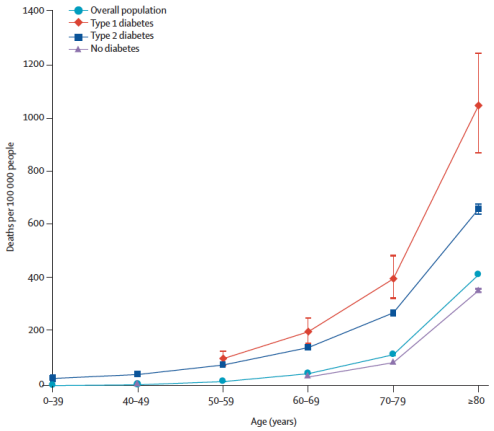
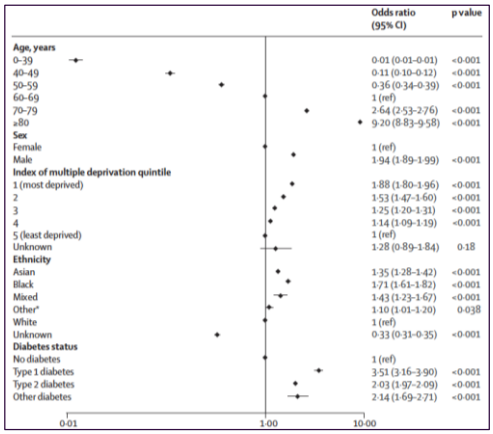
In-hospital Death for People with COVID-19 in England: March 1 to May 11, 2020

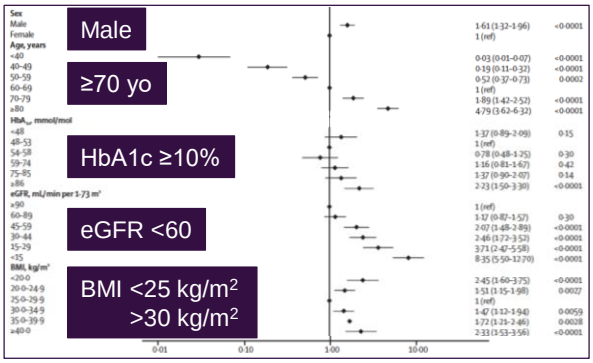




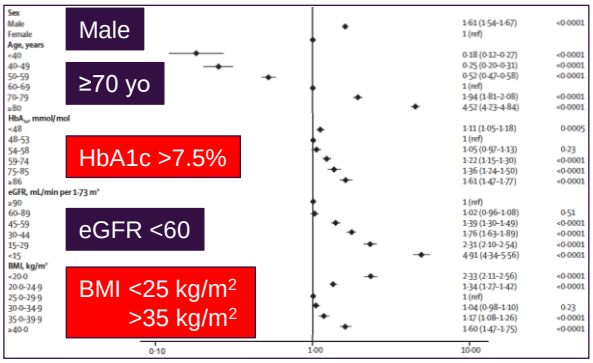
Barron E et al: Lancet Diabetes Endocrinol 8:813-822; 2020

Hazard Ratios for COVID-19 Related Death in People with Diabetes in England

Type 1 Diabetes
Deaths/Number: 464/264,390



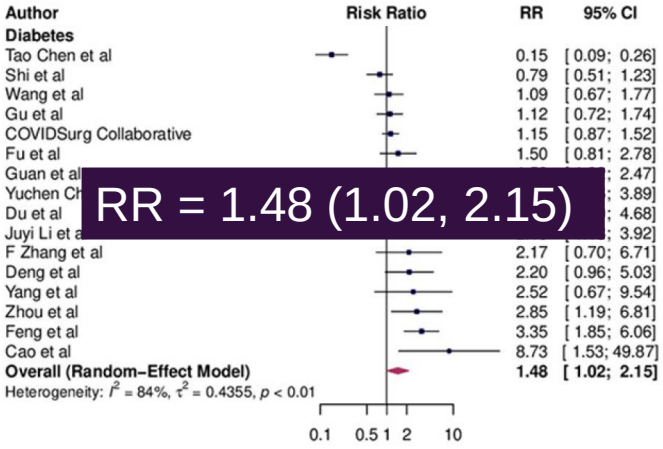
Type 2 Diabetes
Deaths/Number: 10,525/2,874,020



Holman N et al: Lancet Diabetes Endocrinol 8:823-833; 2020

March 1 to May 11, 2020

Association of Comorbid Diabetes and Mortality Risk from COVID-19



RR = 1.48 (1.02, 2.15)

Ssentongo P et al: PLoS ONE 15(8): e0238215; 2020

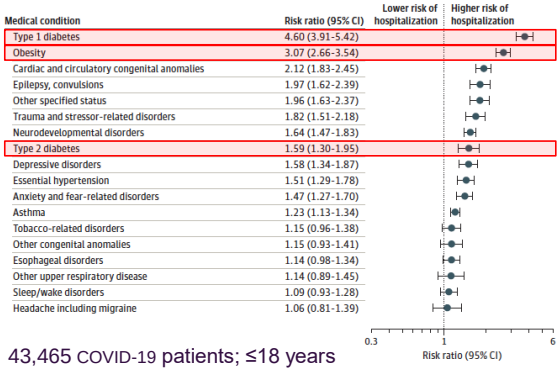
Association of Comorbid Conditions and Mortality Risk from COVID-19

Cardiovascular Disease	RR = 2.25 (1.60, 3.17)
Hypertension	RR = 1.82 (1.43, 2.32)
Cerebrovascular Disease	RR = 2.16 (0.97, 4.80)
Chronic Kidney Disease	RR = 3.25 (1.13, 9.28)
Congestive Heart Failure	RR = 2.03 (1.28, 3.21)

Ssentongo P et al: PLoS ONE 15(8): e0238215; 2020

Risk Factors for COVID-19 Hospitalization and Severe Disease in Children

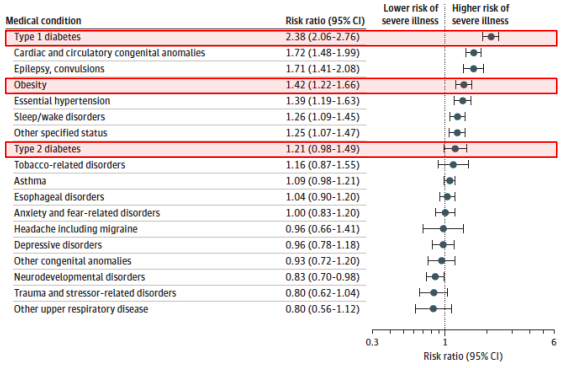
Hospitalization



Medical condition	Risk ratio (95% CI)
Type 1 diabetes	4.60 (3.91-5.42)
Obesity	3.07 (2.66-3.54)
Cardiac and circulatory congenital anomalies	2.12 (1.83-2.45)
Epilepsy, convulsions	1.97 (1.62-2.39)
Other specified status	1.96 (1.63-2.37)
Trauma and stressor-related disorders	1.82 (1.51-2.18)
Neurodevelopmental disorders	1.64 (1.47-1.83)
Type 2 diabetes	1.59 (1.30-1.95)
Depressive disorders	1.58 (1.34-1.87)
Essential hypertension	1.51 (1.29-1.78)
Anxiety and fear-related disorders	1.47 (1.27-1.70)
Asthma	1.23 (1.13-1.34)
Tobacco-related disorders	1.15 (0.96-1.38)
Other congenital anomalies	1.15 (0.93-1.41)
Esophageal disorders	1.14 (0.98-1.34)
Other upper respiratory disease	1.14 (0.89-1.45)
Sleep/wake disorders	1.09 (0.93-1.28)
Headache including migraine	1.06 (0.81-1.39)

43,465 COVID-19 patients; ≤18 years

Severe Illness When Hospitalized



Medical condition	Risk ratio (95% CI)
Type 1 diabetes	2.38 (2.06-2.76)
Cardiac and circulatory congenital anomalies	1.72 (1.48-1.99)
Epilepsy, convulsions	1.71 (1.41-2.08)
Obesity	1.42 (1.22-1.66)
Essential hypertension	1.39 (1.19-1.63)
Sleep/wake disorders	1.26 (1.09-1.45)
Other specified status	1.25 (1.07-1.47)
Type 2 diabetes	1.21 (0.98-1.49)
Tobacco-related disorders	1.16 (0.87-1.55)
Asthma	1.09 (0.98-1.21)
Esophageal disorders	1.04 (0.90-1.20)
Anxiety and fear-related disorders	1.00 (0.83-1.20)
Headache including migraine	0.96 (0.66-1.41)
Depressive disorders	0.96 (0.78-1.18)
Other congenital anomalies	0.93 (0.72-1.20)
Neurodevelopmental disorders	0.83 (0.70-0.98)
Trauma and stressor-related disorders	0.80 (0.62-1.04)
Other upper respiratory disease	0.80 (0.56-1.12)

Kompaniyets L et al: JAMA Netw Open 2021;4(6):e2111182. doi:10.1001/jamanetworkopen.2021.11182

Summary

1. The risk of mortality from COVID-19 in people with type 1 and type 2 diabetes is increased in those who are older, with poor glycemic control or CKD.
2. Other comorbid conditions occurring with diabetes also increase the risk of mortality.
3. Type 1 diabetes, type 2 diabetes and obesity are risk factors for hospitalization of youth with COVID-19.

Outline

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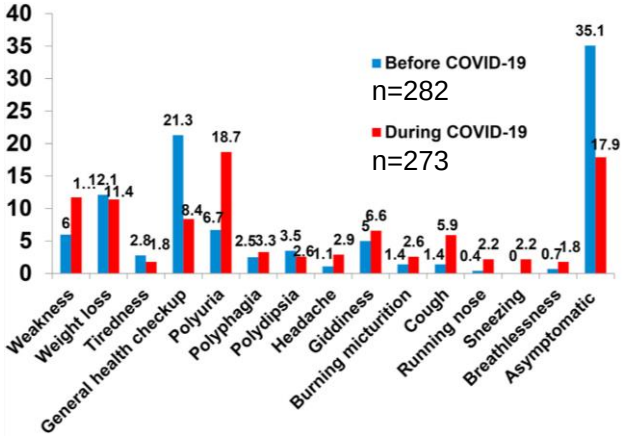
5. Post-Acute Sequalae of COVID-19 (Long COVID)

Features of New Onset Diabetes with SARS-CoV-2 Infection and Before COVID-19



Ghosh A et al: Diabetes Metab Syndr 15:215-220; 2021

Hyperglycemic Presentation of People with Severe or Moderate COVID-19

1. Diabetic ketoacidosis
2. New onset hyperglycemia at admission
3. New onset hyperglycemia during hospitalization
4. Aggravation of known type 1 and 2 diabetes

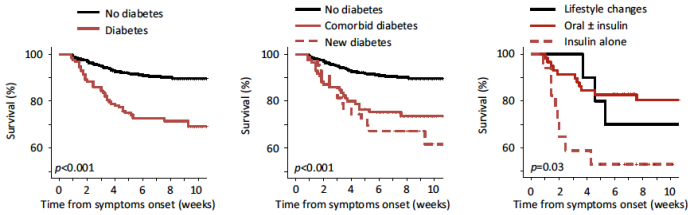
Features in Patients With DKA With and Without COVID-19 (Glytec Database)

In patients with COVID-19:

- Older, more men and greater percent with diabetes complications, including CVD and heart failure
- Obese vs. overweight, with similar proportion with diabetes (>90%)
- HbA1c (>11.2%) not different, blood glucose lower (523 vs. 588 mg/dL)
- Required more insulin (5.0 vs. 3.6 U/h) and DKA treated for longer (34 vs. 23 hours)
- Three-fold greater AKI (30% vs. 10%) and six-fold greater in-hospital mortality (30% vs. 5%)

Pasquel FJ et al: JAMA Netw Open 4(3):e211091; 2021

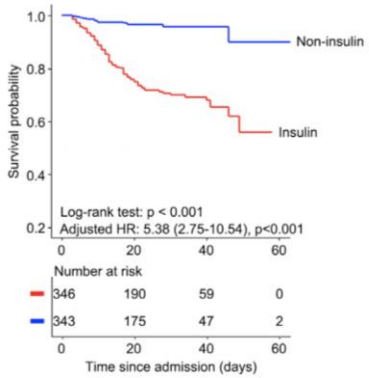
Survival After COVID-19 Pneumonia by Diabetes Status and Glycemia



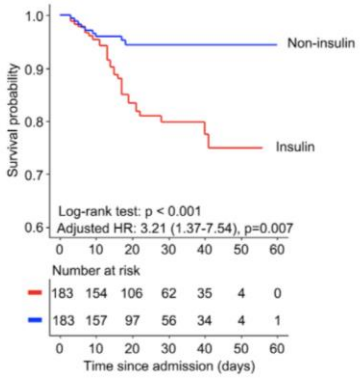
Lampasona V et al: Diabetologia 63:2548-2558; 2020

Clinical Outcomes of COVID-19 Patients Based on Insulin vs. Non-insulin Use

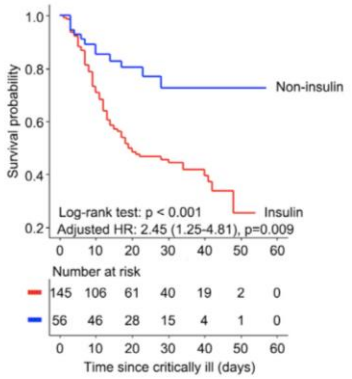
All Patients with Type 2 Diabetes



Propensity Score Matched Patients with Type 2 Diabetes



Critically Ill Patients with Type 2 Diabetes



Yu B et al: Cell Metab 33:65-77; 2021

Survival of COVID-19 Patients Based on Insulin vs. Oral Agent Use

Insulin vs.	# PSM Pts.	Mortality Insulin	Mortality Oral Agent	Adjusted HR (CI)	p value
Metformin	92	22.8%	2.2%	22.67 (2.92-175.72)	<0.001
α-glucosidase inhibitor	81	23.5%	2.5%	38.12 (3.61-402.48)	<0.001
Sulfonylureas	52	13.5%	0%	--	--
DPP-4 Inhibitors	16	6.2%	0%	--	--

PSM = propensity score matching

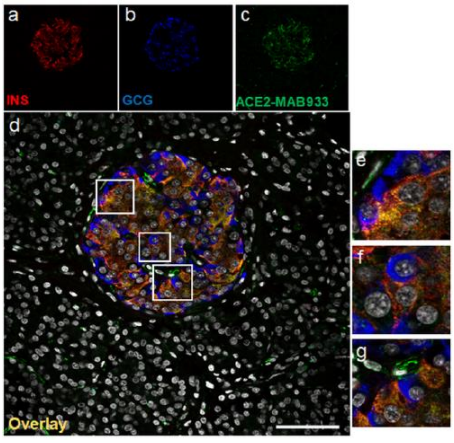
Yu B et al: Cell Metab 33:65-77; 2021

Medications for COVID-19 Treatment and Effects on Glycemia

1. Glucocorticoids – worsen glycemia by inducing insulin resistance, decreasing insulin and increasing glucagon secretion
2. Tocilizumab – improves glycemia by blocking IL-6
3. Remdesivir – no clear data

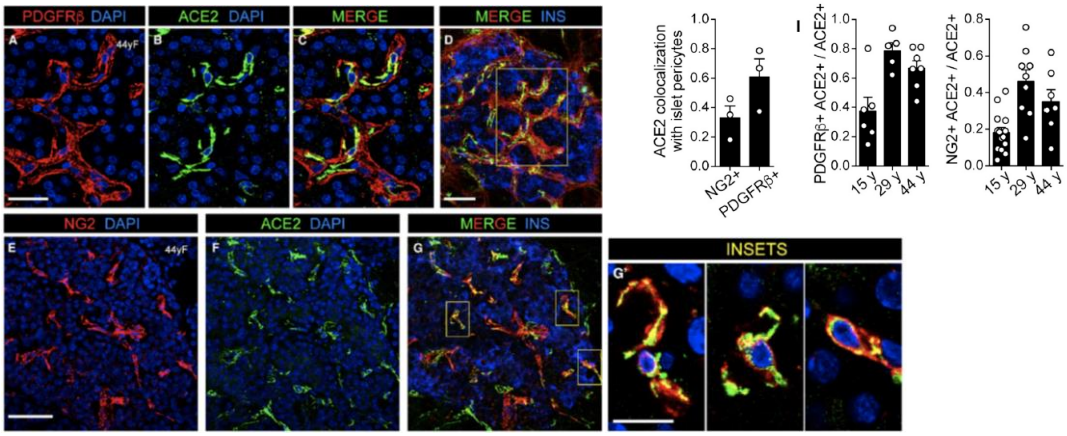
Pathophysiology of the Islet With SARS-CoV-2 and in COVID-19

ACE2 is Detected in Islet β Cells and Endothelial Cells in Adult Human Pancreas



Fignani D et al: Front Endocrinol - https://doi.org/10.3389/fendo.2020.596898

ACE2 Protein is Detected in Islet Pericytes in Adult Human Pancreas



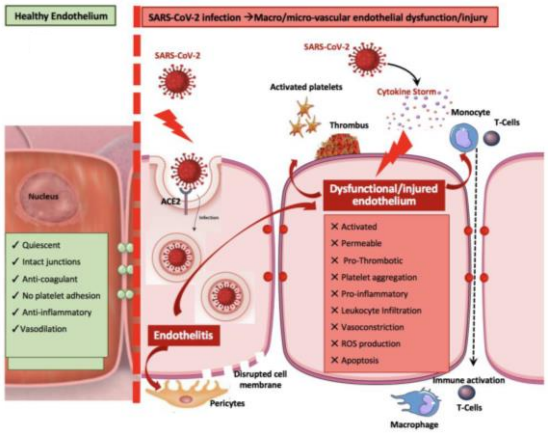
Coate KC et al: Cell Metab 32:1028-1040; 2020

Summary of Key Findings of ACE2 Expression in the Pancreas

Observations	Methodologies/Cells Analyzed	Comments	References
"Yes" ACE2 Expression	Immunostaining with anti-ACE2 antibody on a pancreatic tissue section	Tissue from a single donor; antibody clone was not identified	Yang JK et al: Acta Diabetol 47:193-199; 2010
	Immunofluorescence of isolated primary islets and iPSC derived organoids	Isolated islets or iPSC organoids may have different expression pattern	Yang L et al: Cell Stem Cell 27:125-136; 2020
	Immunostaining of control pancreatic tissue sections	Observed preferential expression of short/non virus binding ACE2 isoform	Fignani D et al: Front Endocrinol - https://doi.org/10.3389/fendo.2020.596898
	Immunofluorescence of isolated islets and pancreatic tissue sections from control subjects and immunostaining of pancreatic tissue sections from COVID-19 autopsies	Infection of human islet cells *in vitro* does not prove infection *in vivo*	Muller JA et al: Nat Metab 3:149-165; 2021
	Immunofluorescence of pancreatic tissue sections from control subjects and immunostaining of pancreatic tissue sections from COVID-19 autopsies	Infection of human islet cells *in vitro* does not prove infection *in vivo*	Wu CT et al: Cell Metab 33:1565-1576; 2021
"No" or Limited ACE2 Expression	Control pancreatic tissue sections	RNA expression supports protein expression pattern	Hikmet F et al: Mol Syst Biol 16:e9610; 2020
	Control pancreatic tissue sections	RNA expression supports protein expression pattern	Coate KC et al: Cell Metab 32:1028-1040; 2020
	Control and COVD-19 pancreatic tissue sections	mRNA expression supports protein expression pattern	Kusmartseva I et al: Cell Metab 32:1041-1051; 2020

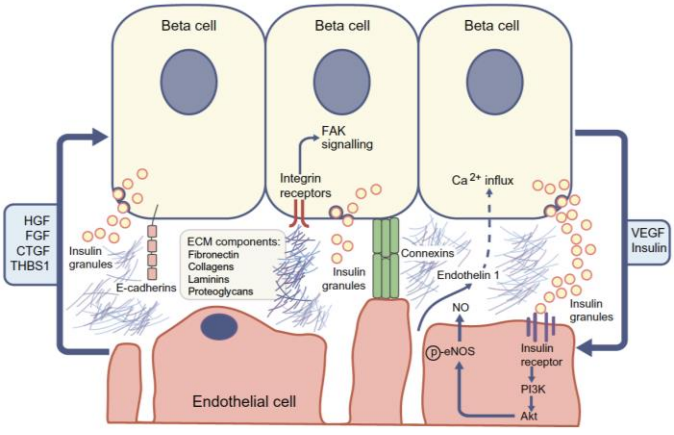
1. Most human islet cells do not possess the molecular machinery for permissive SARS-CoV-2 infection.
2. A small subset of β cells may possess the SARS-CoV-2-associated receptors ACE-2, TMPRSS2, NRP1 and TFRC.
3. While in vitro data suggests it is possible to infect β cells, autopsy evidence supporting SARS-CoV-2 infection of β cells is inconclusive; proximal inflammation is possible.

Dysregulation of Endothelial Cell Function by SARS-CoV-2



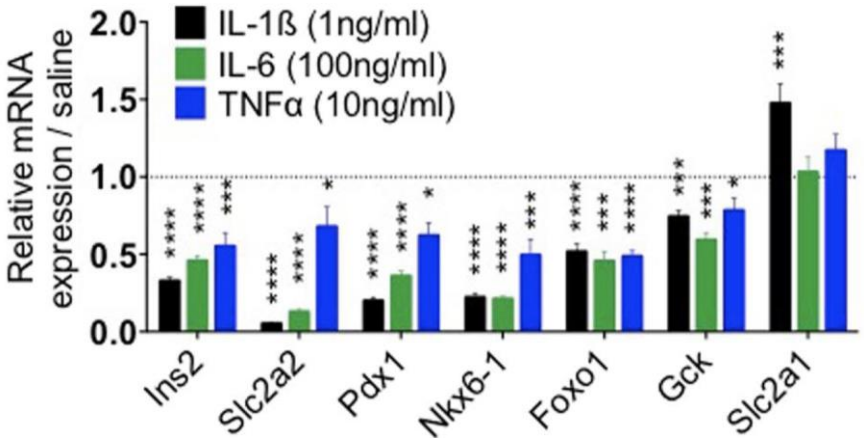
Evans PC et al: Cardiovasc Res 116:2177-2184; 2020

Main Factors Regulating the Islet-Endothelial Cell Axis



Hogan MF and Hull RL: Diabetologia 60:952-959; 2017

Dedifferentiaton of Mouse β Cells Induced by IL-1β, IL-6 and TNFα



Nordmann TM et al: Sci Rep 7:6285; 2017. doi: 10.1038/s41598-017-06731-w

Summary

1. The presentation of diabetes during the pandemic may differ somewhat from what we are used to.
2. People on insulin have poorer outcomes, perhaps in keeping with them having more severe diabetes.
3. SARS-CoV-2 may gain entry into the β cell, but not many cells can be shown to contain viral protein. Other islet cell types such as endothelial cells and pericytes may be affected.

Outline

1. Considerations in the need to find answers to a new disease entity
2. Epidemiology of the disease
3. Hyperglycemia in COVID-19 – a “new” vs. “old” disease entity?
4. Response to medications in patients with diabetes – real or unreal?
5. Post-Acute Sequalae of COVID-19 (Long COVID)

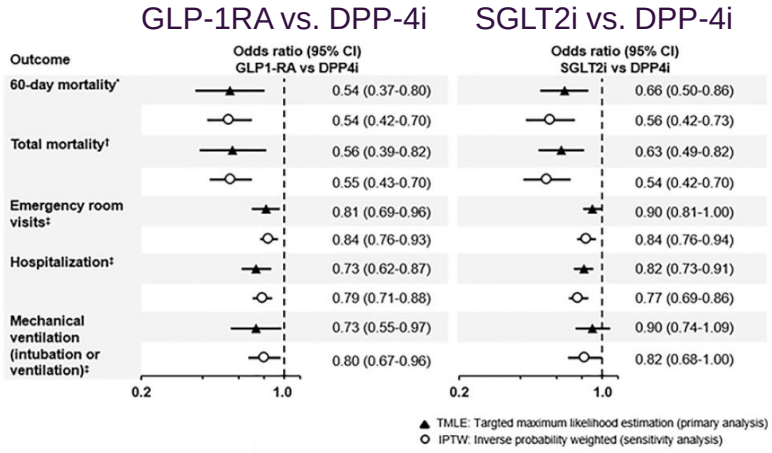
Effect of Metformin on Mortality and Secondary Outcomes in COVID-19

	Time-varying Cox Model Exposure Before PSM		Hazard in All Groups After PSM	
Metformin vs. Non-metformin	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Mortality	0.87 (0.36, 2.12)	0.757	1.65 (0.71, 3.86)	0.247
ARDS	0.66 (0.46, 0.96)	0.028	0.85 (0.61, 1.17)	0.317
DIC	0.44 (0.05, 4.00)	0.467	1.68 (0.26, 10.9)	0.586
Heart failure	0.61 (0.43, 0.87)	0.006	0.59 (0.41, 0.83)	0.003
Acute kidney injury	0.71 (0.18, 2.79)	0.627	0.65 (0.19, 2.24)	0.491
Acute heart injury	1.14 (0.73, 1.79)	0.559	1.02 (0.62, 1.66)	0.947

PSM: propensity score-matching

Cheng X et al: Nat Med 32:537-547; 2020

GLP-1RA and SGLT2i Reduce COVID-19 Adverse Outcomes Compared to DPP-4i

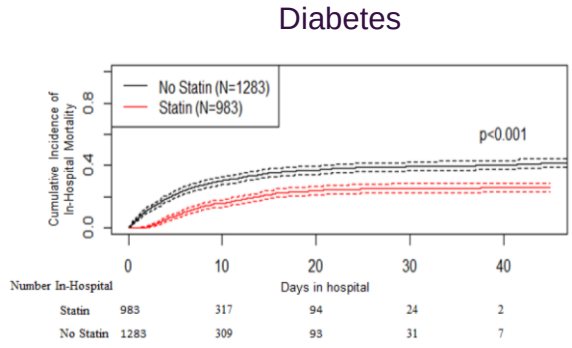


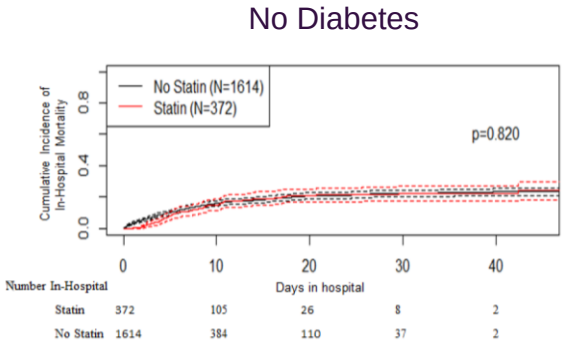
January 2018-February 2021

- 12,446 individuals
- Mortality within 60 days of positive SARS-Cov-2 test
- ER visit, hospitalization and mechanical ventilation within 14 days of positive SARS-Cov-2 test
- Total mortality during observation period

Kahkoska AR et al: Diabetes Care 2021 Jun 16;dc210065. doi: 10.2337/dc21-0065

Differential Survival from COVID-19 in Hospitalized Statin Users with Diabetes





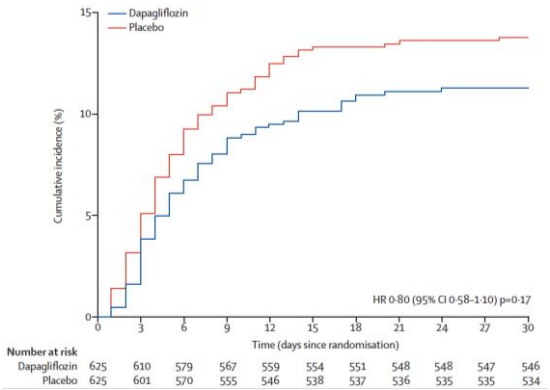
Saeed O et al: JAHA - https://www.ahajournals.org/doi/pdf/10.1161/JAHA.120.018475

Glucose-Lowering Agents in Clinical Trials in Patients with COVID-19

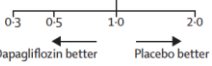
- Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19)
- Semaglutide to Reduce Myocardial Injury in Patients with COVID-19 (SEMPATICO)

https://clinicaltrials.gov/ct2/show/NCT04350593?term=dapagliflozin&cond=covid&draw=2&rank=1
https://clinicaltrials.gov/ct2/show/NCT04615871

DARE-19 Primary Outcome: Prevention of Organ Dysfunction and Death



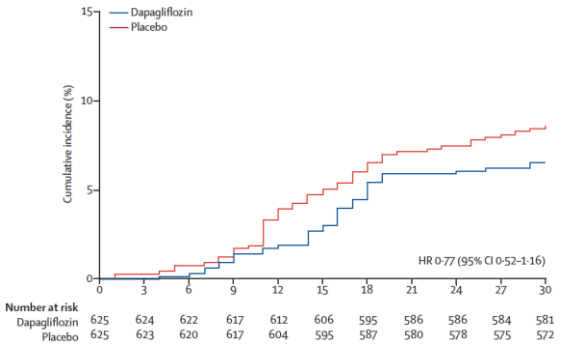
	Dapagliflozin n/N	Placebo n/N	HR (95% CI)
Primary composite outcome	70/625	86/625	0·80 (0·58–1·10)
New or worsening organ dysfunction	64/625	80/625	0·80 (0·57–1·11)
Respiratory decompensation	58/625	70/625	0·85 (0·60–1·20)
Cardiac decompensation	47/625	58/625	0·81 (0·55–1·19)
Kidney decompensation	24/625	35/625	0·65 (0·38–1·10)
Death from any cause	41/625	54/625	0·77 (0·52–1·16)



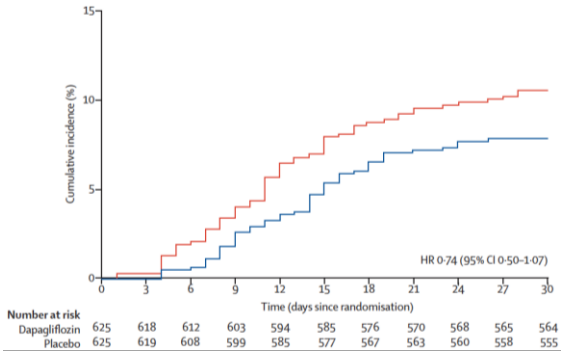
Kosiborod MN et al: Lancet Diabetes Endocrinol 2021 Jul 21;S2213-8587(21)00180-7. doi: 10.1016/S2213-8587(21)00180-7

DARE-19 Key Secondary Outcomes: All Cause Mortality and Acute Kidney Injury

All Cause Mortality



Acute Kidney Injury



Kosiborod MN et al: Lancet Diabetes Endocrinol 2021 Jul 21;S2213-8587(21)00180-7. doi: 10.1016/S2213-8587(21)00180-7

Summary

1. Randomized clinical trials comparing glucose-lowering agents have not been reported.
2. Data suggest that the glucose-lowering medications metformin, GLP-1 receptor agonists and SGLT2 inhibitors may be beneficial.
3. The SGLT2 inhibitor dapagliflozin does not reduce mortality in people with severe COVID-19 and diabetes.

Outline

1. Considerations in the need to find answers to a new disease entity
2. Epidemiology of the disease
3. Hyperglycemia in COVID-19 – a “new” vs. “old” disease entity?
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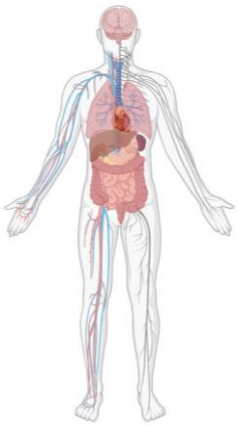
Parallel in Pathology of Long COVID-19 and Chronic Diabetes

Long COVID-19

Microvascular endothelitis

Inflammation Autoimmunity

Metabolism



Diabetes

Microvascular endothelitis

Inflammation Autoimmunity

Metabolism

Adapted from Feldman EL: Diabetes 69:2549-2565; 2020

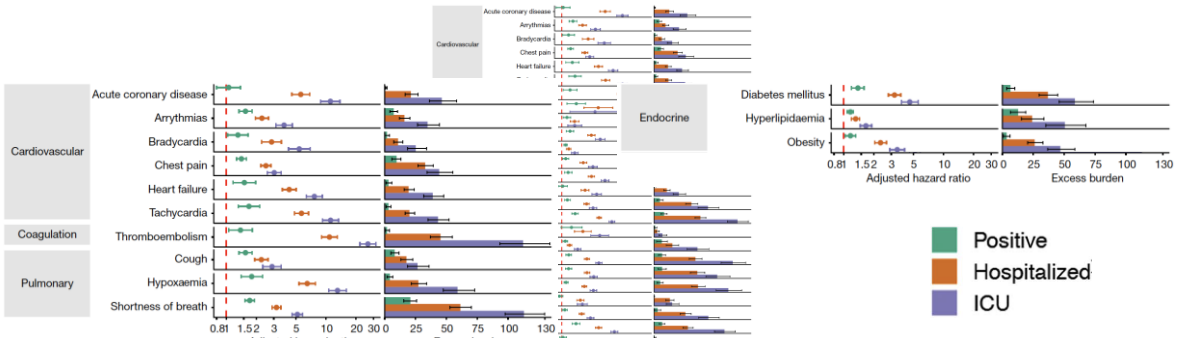
Diabetes as a Consequence of COVID-19 in Hospitalized Chinese Patients

"58 patients without self reported history of diabetes were newly diagnosed with the condition at follow-up."

Total subjects followed: 2,469-736 = 1,733
Rate: 58/1,733 = 3.35%

Huang C et al: Lancet 397:220-232; 2021

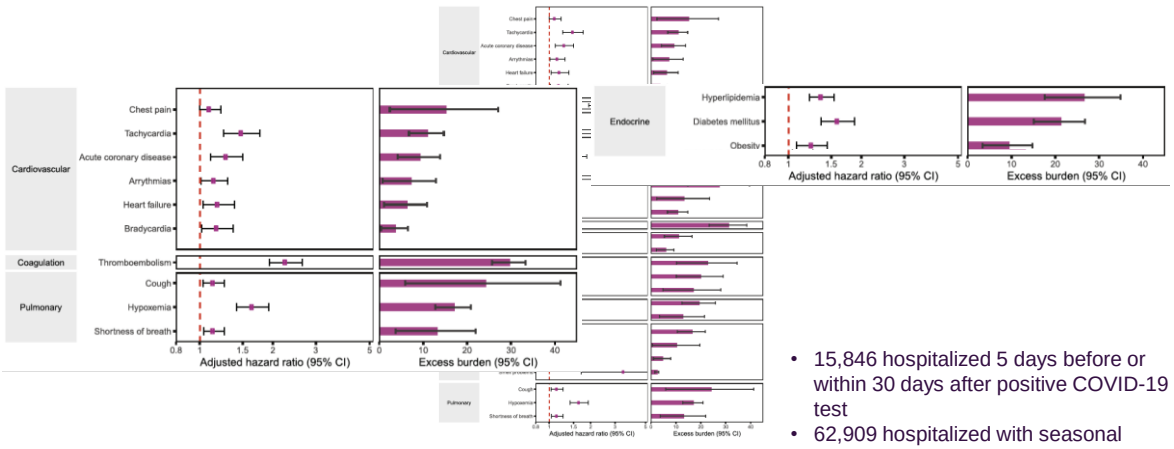
Incident Diagnoses and Excess Burden of Post-Acute Sequalae of COVID-19 in U.S. Veterans



- 74,435 COVID-19 survivors beyond 30 days of infection
- 4,990,835 without COVID-19 (all VHA users)

Al-Aly Z et al: Nature 594:259-264; 2021

Incident Diagnoses and Excess Burden of Post-Acute Sequalae of COVID-19 in U.S. Veterans



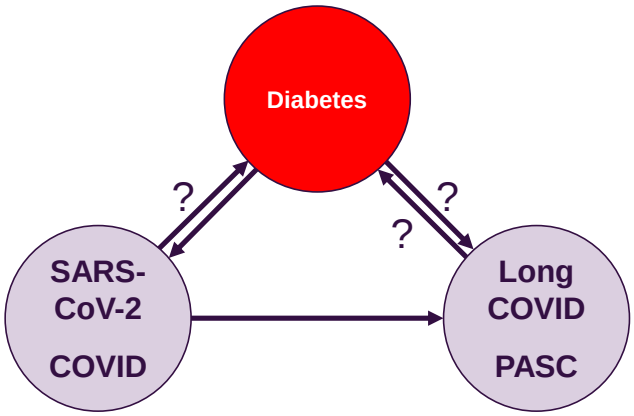
- 15,846 hospitalized 5 days before or within 30 days after positive COVID-19 test
- 62,909 hospitalized with seasonal influenza without COVID-19

Al-Aly Z et al: Nature 594:259-264; 2021

Summary

1. Post acute sequelae of COVID-19 (PASC) is a consequence of SARS-CoV-2 infection that affects many organ systems.
2. Retrospective studies suggest new onset diabetes may be a feature of COVID-19 at the time of acute illness or as part of PASC.
3. Whether COVID-19 impacts diabetes complications in those with pre-existing diabetes is unknown.

Knowledge Gaps



Acknowledgements

Numerous fellows, faculty and colleagues who have helped formulate my thoughts over the years.

Department of Veterans Affairs
NIH/NIDDK
American Diabetes Association

Diabetes Care Summit

OU Health | Harold Hamm Diabetes Center

ADCES Association of Diabetes Care & Education Specialists

Breakout Session I:

Diabetes-Related Complications and Comorbidities in Youth

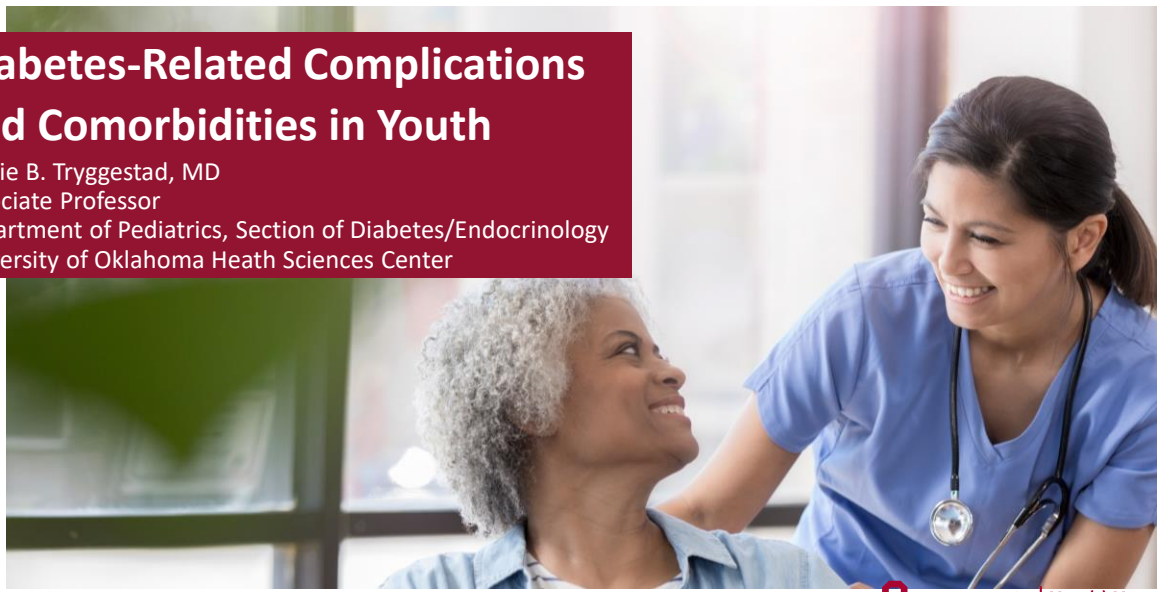
Diabetes Care Summit

OU Health | Harold Hamm Diabetes Center

ADCES Association of Diabetes Care & Education Specialists

Diabetes-Related Complications and Comorbidities in Youth

Jeanie B. Tryggestad, MD
Associate Professor
Department of Pediatrics, Section of Diabetes/Endocrinology
University of Oklahoma Heath Sciences Center



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Disclosure

- I have no personal or financial disclosures

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Objectives

- To review Diabetes-related micro- and macrovascular complications in type 2 diabetes
- To discuss the prevalence of diabetes complications in youth onset type 2 diabetes
- To examine the most recent evidence regarding the prevalence of microvascular complications in youth

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Complications and Comorbidities of Type 2 Diabetes

- Macrovascular Complications
  - Coronary Artery disease
  - Peripheral Artery Disease
  - Cerebrovascular Disease
  - Cardiomyopathy
- Microvascular Complications
  - Nephropathy
  - Retinopathy
  - Neuropathy

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Macrovascular Disease

- Leading cause of morbidity and mortality in diabetes
- Cardiovascular disease is the leading cause of death in patients with diabetes
- 2/3 of deaths in people with T2DM is related to cardiovascular disease
- Risk factors
  - Hypertension
  - Dyslipidemia
  - Arterial stiffness

ADA Standards of Care - 2021

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Microvascular Disease

- Nephropathy
  - Occurs in 20-40% of patients with Diabetes
  - May be present in persons with T2DM at diagnosis
  - Is the leading cause of End Stage Renal Disease (ESRD) in US
  - Increases cardiovascular risk
- Retinopathy
  - The leading cause of blindness in 20-74 year old
  - Strongly associated with diabetes duration and glycemic control
- Neuropathy
  - Heterogenous group including peripheral, autonomic, and GI neuropathies
  - Glycemic control is key to stopping progression

ADA Standards of Care - 2021

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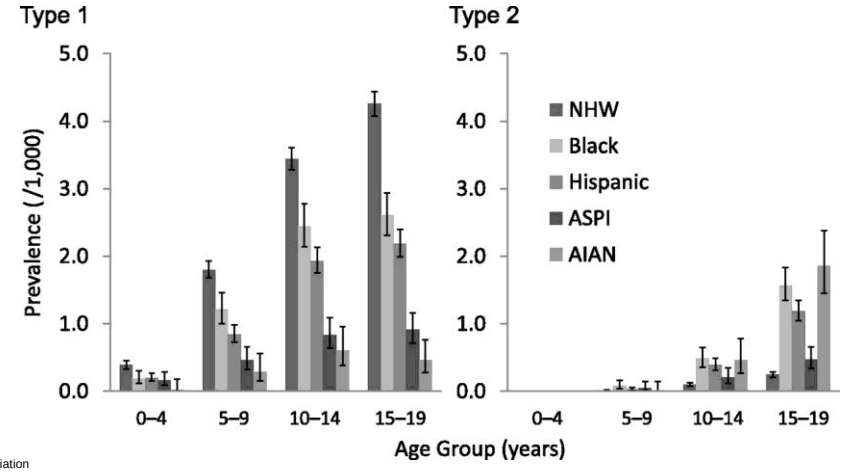
Youth Onset T2DM



American Diabetes Association.

David J. Pettitt et al. Dia Care 2014;37:402-408

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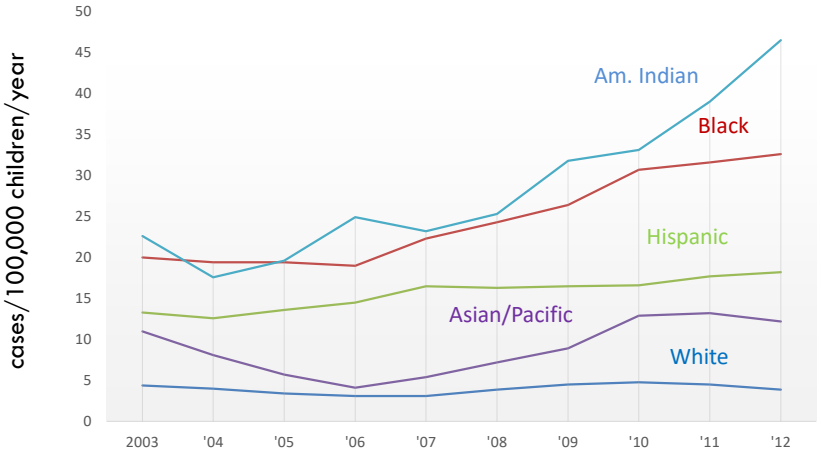
Youth Onset T2DM



Mayer-Davis, *JAMA* 376:1419, 2017

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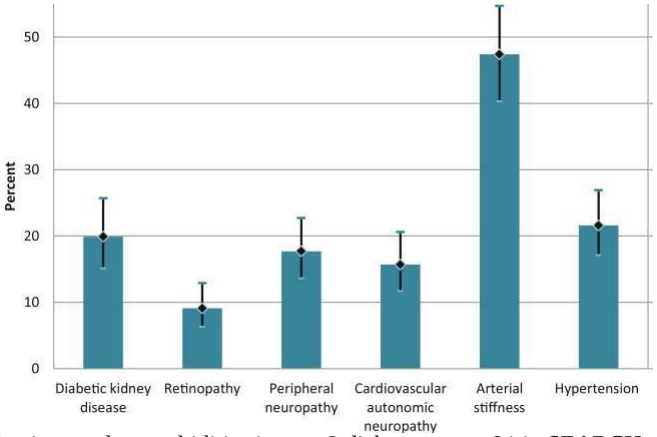
Complications and Comorbidities In Youth Onset T2DM - SEARCH



Estimated prevalence of complications and comorbidities in type 2 diabetes at age 21 in SEARCH

Jensen ET, Dabelea D. Type 2 Diabetes in Youth: New Lessons from the SEARCH Study. *Curr Diab Rep*. 2018;18(6):36. Published 2018 May 8. doi:10.1007/s11892-018-0997-1

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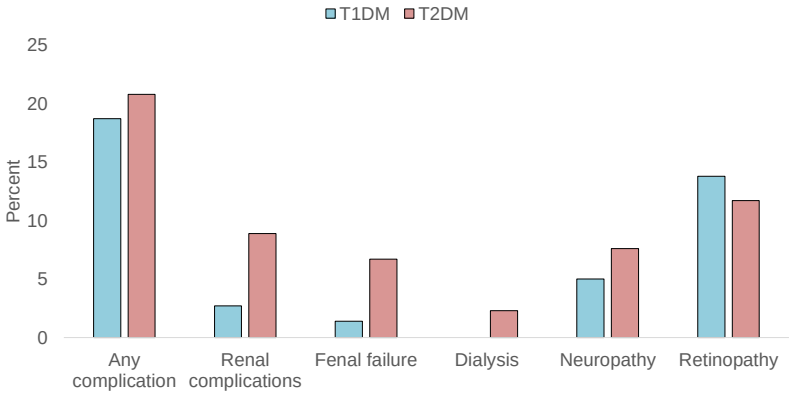
Complications and Comorbidities In Youth Onset T2DM - Canada



Estimated prevalence of complications and comorbidities in type 2 diabetes at age 18 in Canada

Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA. Earlier onset of complications in youth with type 2 diabetes. Diabetes Care. 2014 Feb;37(2):436-43. doi: 10.2337/dc13-0954. Epub 2013 Oct 15. PMID: 24130346.

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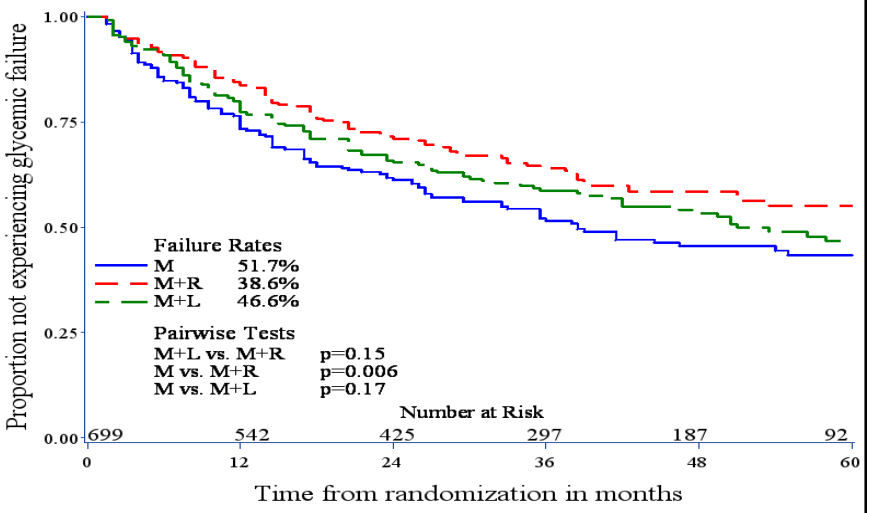
TODAY Study



The NEW ENGLAND JOURNAL of MEDICINE

TODAY Study Group. N Engl J Med 2012;366:2247-2256

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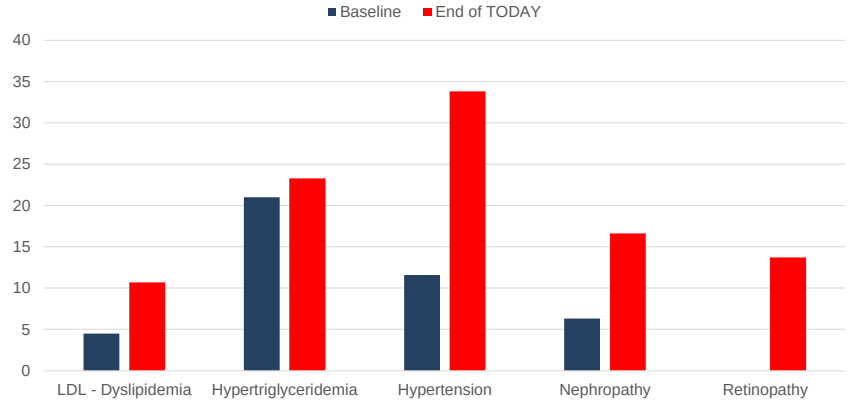
Complications and Comorbidities In Youth Onset T2DM - TODAY



Percentage of TODAY study participants experiencing complications and comorbidities at baseline and end of study.

Tryggestad JB, Willi SM. Complications and comorbidities of T2DM in adolescents: findings from the TODAY clinical trial. *J Diabetes Complications*. 2015;29(2):307-312. doi:10.1016/j.jdiacomp.2014.10.009

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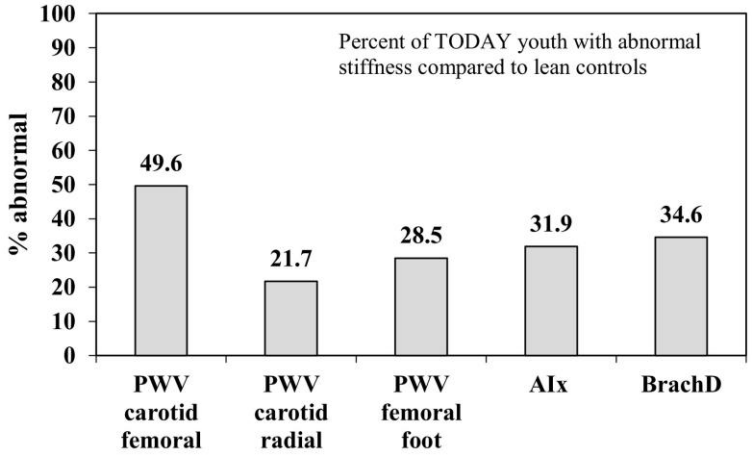
Complications and Comorbidities In Youth Onset T2DM – TODAY Cardiovascular



Shah AS, El Ghormli L, Gidding SS, Bacha F, Nadeau KJ, Levitt Katz LE, Tryggestad JB, Leibel N, Hale DE, Urbina EM. Prevalence of arterial stiffness in adolescents with type 2 diabetes in the TODAY cohort: Relationships to glycemic control and other risk factors. J Diabetes Complications. 2018 Aug;32(8):740-745. doi: 10.1016/j.jdiacomp.2018.05.013. Epub 2018 May 25. PMID: 29936086; PMCID: PMC6444355.

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Complications and Comorbidities In Youth Onset T2DM – TODAY Cardiovascular

Variable	TODAY, *n* = 397	Obese control subjects, *n* = 133	*P* value	
			Unadjusted	Adjusted
SDNN (ms)*	58.1 ± 29.6	67.1 ± 25.4	<0.0001	<0.0001
RMSSD (ms)*	53.2 ± 36.7	67.9 ± 35.2	<0.0001	<0.0001
PNN50 (%)*	26.3 ± 23.7	39.7 ± 23.0	<0.0001	<0.0001
LF Power (n.u.)†	47.3 ± 20.0	39.5 ± 19.7	0.0001	<0.0001
HF Power (n.u.)*	52.7 ± 20.0	60.5 ± 19.7	0.0001	<0.0001
LF:HF ratio†	1.4 ± 1.7	1.0 ± 1.1	<0.0001	<0.0001

HRV indices in TODAY participants versus obese control subjects

•Unadjusted means ± SD are shown in the table. Total power for TODAY participants was 2,576 ± 2,919. *P* value from general linear model comparing mean of the obese control subjects to the TODAY participants. SDNN, RMSSD, and LF:HF ratio were log transformed prior to testing because of skewed distribution. A nonparametric rank-based test was used to compare the PNN50 values. Unadjusted and adjusted *P* values for age, sex, race-ethnicity, smoking, and BMI are given for the cardiac autonomic function measures. n.u., normalized units.

•* Lower = worse.

•† Higher = worse.

Shah AS, El Ghormli L, Vajravelu ME, et al. Heart Rate Variability and Cardiac Autonomic Dysfunction: Prevalence, Risk Factors, and Relationship to Arterial Stiffness in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study. *Diabetes Care*. 2019;42(11):2143-2150. doi:10.2337/dc19-0093

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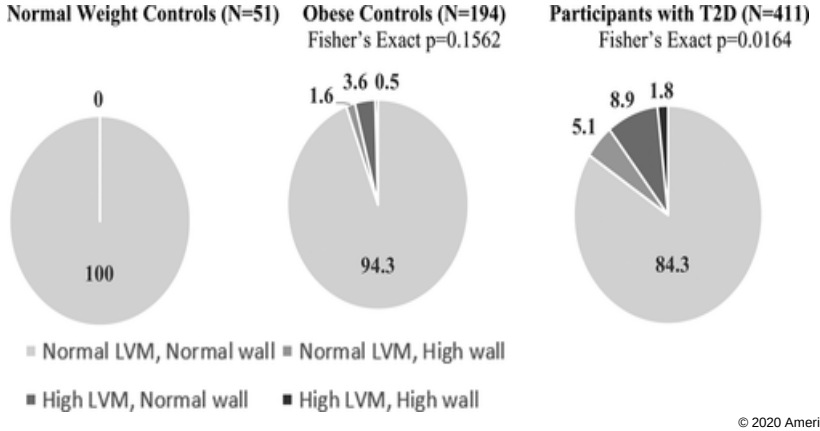
Complications and Comorbidities In Youth Onset T2DM – TODAY Cardiovascular



TODAY Study Group. Longitudinal Changes in Cardiac Structure and Function From Adolescence to Young Adulthood in Participants With Type 2 Diabetes Mellitus: The TODAY Follow-Up Study. Circ Heart Fail. 2020 Jun;13(6):e006685. doi: 10.1161/CIRCHEARTFAILURE.119.006685. Epub 2020 Jun 5. PMID: 32498621

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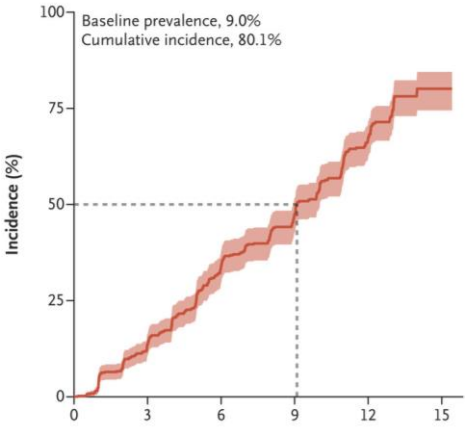
Complications and Comorbidities In Youth Onset T2DM – TODAY2

Baseline Prevalence and Cumulative Incidence of any Microvascular Disease



TODAY Study Group, Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, Tesfaldet B, Tryggestad J, White NH, Zeitler P. Long-Term Complications in Youth-Onset Type 2 Diabetes. N Engl J Med. 2021 Jul 29;385(5):416-426. doi: 10.1056/NEJMoa2100165. PMID: 34320286.

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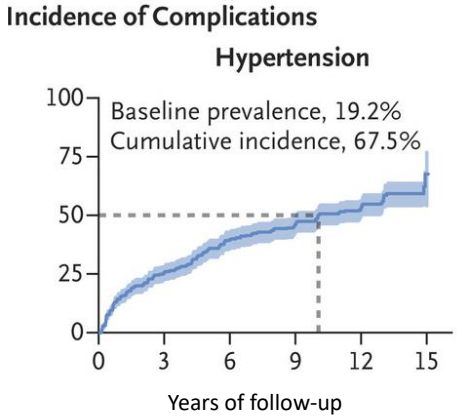
Complications and Comorbidities In Youth Onset T2DM – TODAY2



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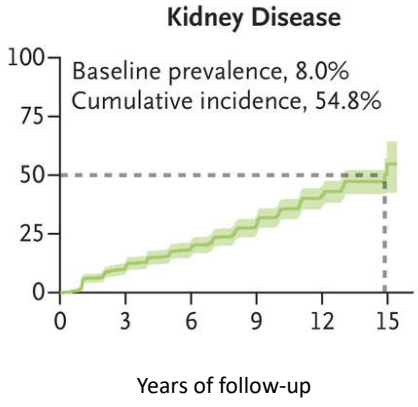

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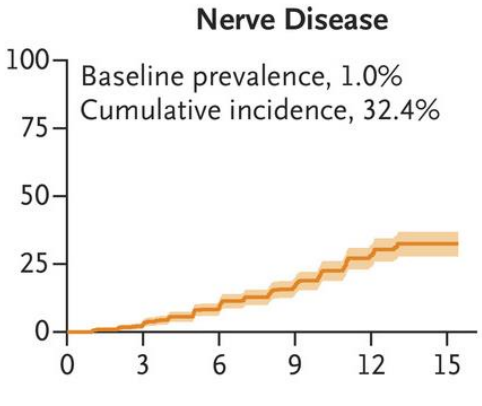

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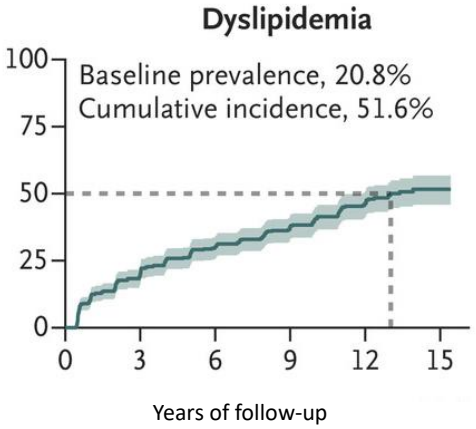

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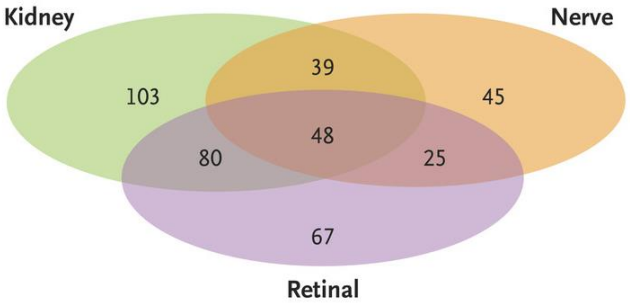
Complications and Comorbidities In Youth Onset T2DM – TODAY2

C Number of Patients with Each Microvascular Complication



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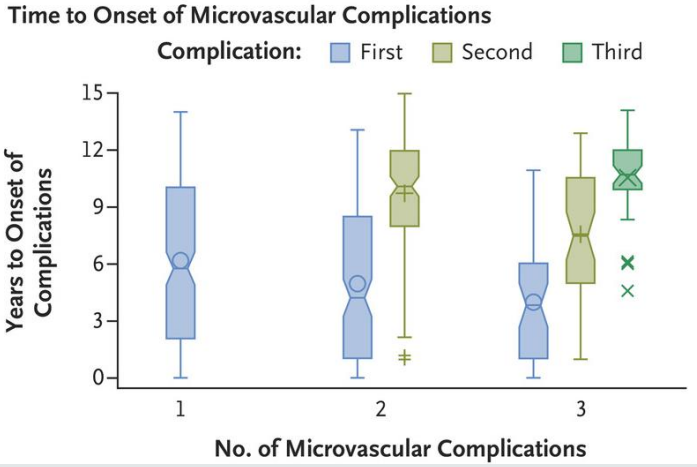

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Complications and Comorbidities In Youth Onset T2DM – TODAY2

Table 3. Unadjusted and Minimally Adjusted Models for the Risk of Accumulation of Microvascular Complications.*

Risk Factors	Number of Complications				Odds Ratio (95% CI)
	0	1	2	3	
Female vs. male — %	34.8	31.2	34.7	54.2	0.84 (0.63–1.13)
Race and ethnic group, vs. Non-Hispanic White — %†					
Non-Hispanic Black	27.4	39.1	32.6	39.6	1.80 (1.20–2.68)
Hispanic	38.9	38.6	43.8	39.6	1.57 (1.06–2.33)
Other	9.3	5.1	8.3	6.3	NA
Non-Hispanic White	24.4	17.2	15.3	14.6	—
Treatment, vs. metformin — %‡					
Metformin plus rosiglitazone	35.9	32.6	31.3	31.3	0.97 (0.69–1.36)
Metformin plus lifestyle intervention	33.0	37.2	29.9	25.0	1.31 (0.93–1.84)
Metformin	31.1	30.2	38.9	43.8	—
Age at baseline, per each increase of 1 yr of age	14.0±2.0	14.0±2.0	13.8±2.1	14.7±1.9	1.02 (0.95–1.09)
Duration of type 2 diabetes at baseline, per each increase of 1 mo of duration	7.4±5.6	7.8±5.8	8.4±6.4	7.8±5.4	1.02 (0.99–1.04)
Unadjusted models					
Glycated hemoglobin level, per each increase of 1% or 11 mmol/mol	7.0±1.7	8.2±1.9	9.6±1.7	10.4±1.3	1.78 (1.64–1.93)
Mean BMI, per each increase of 5	35.5±6.9	36.9±8.3	35.6±7.4	39.4±8.9	1.09 (1.00–1.20)
Mean log insulin sensitivity, per each increase of 1 SD§	0.054±0.030	0.046±0.026	0.043±0.026	0.038±0.017	0.65 (0.56–0.74)
Hypertension — %	40.7	61.9	72.2	83.3	3.09 (2.31–4.15)
Dyslipidemia — %	40.4	54.0	70.8	66.7	2.43 (1.83–3.22)
Adjusted models¶					
Glycated hemoglobin level, per each increase of 1% or 11 mmol/mol					1.80 (1.65–1.95)
BMI, per each increase of 5					1.09 (0.99–1.19)
Natural log insulin sensitivity, per each increase of 1 SD§					0.64 (0.56–0.74)
Hypertension					3.18 (2.35–4.30)
Dyslipidemia					2.77 (2.05–3.72)

* Plus–minus values are means ±SD. NA denotes not applicable.
† The odds ratio for the "other" category was not calculated because of heterogeneity within the group. The odds ratio for non-Hispanic Black versus Hispanic was −0.13 (95% CI, −0.45 to 0.19).
‡ The odds ratio for metformin plus lifestyle intervention versus metformin plus rosiglitazone was 0.74 (95% CI, 0.53 to 1.04).
§ Insulin sensitivity was defined as 1÷fasting insulin.
¶ The models were adjusted for the following preselected covariates: sex, race and ethnic group, baseline age, and baseline duration of type 2 diabetes.

TODAY Study Group, Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, Tesfaldet B, Tryggestad J, White NH, Zeitler P. Long-Term Complications in Youth-Onset Type 2 Diabetes. N Engl J Med. 2021 Jul 29;385(5):416-426. doi: 10.1056/NEJMoa2100165. PMID: 34320286.

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Conclusions

- T2DM is increasing rapidly in youth.
- Among youth who have onset of type 2 diabetes in youth, the risk of complications, including microvascular complications, increased steadily over time and affected most participants by the time of young adulthood.
- Complications are more common among participants of minority race and ethnic group and among those with hyperglycemia, hypertension, and dyslipidemia.
- Youth onset T2DM must be treated aggressively.

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Recommendations

- Glycemic Control
  - Start metformin at onset
  - If A1c is above 8.5% insulin therapy with a long acting analogue is needed
  - Consider GLP-1 analogues to optimize glucose control
- Screening/Treatment
  - Screen for dyslipidemia, hypertension, nephropathy and retinopathy at diagnosis and annually thereafter
  - Start antihypertensive if BP>95% for height or over 135mmHg systolic
  - Start ACEI for urine albumin/Cr ratio >30mg/g

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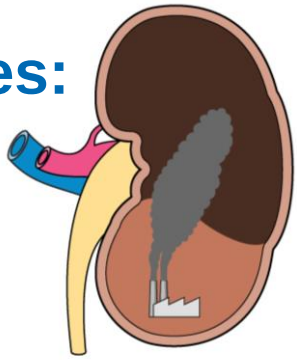
Contact Information

Mailing Address	1200 Children's Ave, Suite 4D Oklahoma City, OK 73104
Email Address	Jeanie-Tryggestad@ouhsc.edu
Phone Number	(405) 271-6764

SEPTEMBER 10TH, 2021

Diabetic kidney disease in young persons with diabetes: a metabolic disorder



PETTER BJORNSTAD, M.D.
ASSISTANT PROFESSOR OF PEDIATRICS AND MEDICINE
BOETTCHER INVESTIGATOR

Children's Hospital Colorado
Here, it's different.

Affiliated with
Department of Pediatrics
SCHOOL OF MEDICINE
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Presenter Disclosure

- AstraZeneca: Consultancy, Advisory Board, Grant support
- Bayer: Consultancy, Advisory Board, Data Monitoring Committee Member
- Boehringer Ingelheim: Consultancy, Advisory Board
- Bristol-Meyer Squibb: Consultancy
- Eli Lilly: Consultancy
- Horizon Pharma: Advisory Board and Grant Support
- Merck: Grant Support
- Novo Nordisk: Advisory Board, Consultancy and Grant Support
- Sanofi: Consultancy
- XORTX Scientific: Advisory Board

Overview

1. The high burden of DKD in youth-onset T2D
2. Risk factors and mechanisms of DKD in youth-onset T2D
3. Current and novel therapies to mitigate DKD in youth-onset T2D
4. Future directions and need for an integrated biological approach
5. Summary

Children's Hospital Colorado
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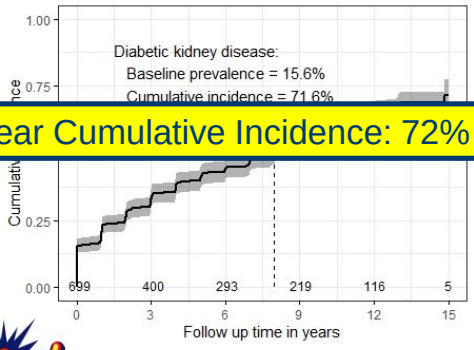
SCHOOL OF MEDICINE
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

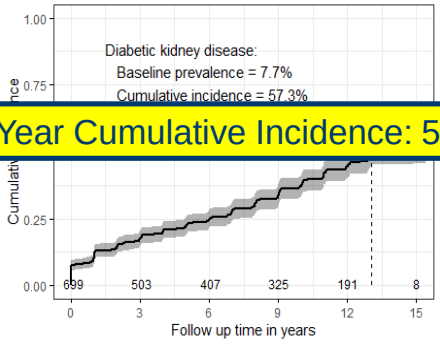
1. High Burden of DKD in Y-T2D

UACR ≥ 30 mg/g and/or eGFR ≥ 135 ml/min/1.73m²



15-Year Cumulative Incidence: 72%

UACR ≥ 30 mg/g

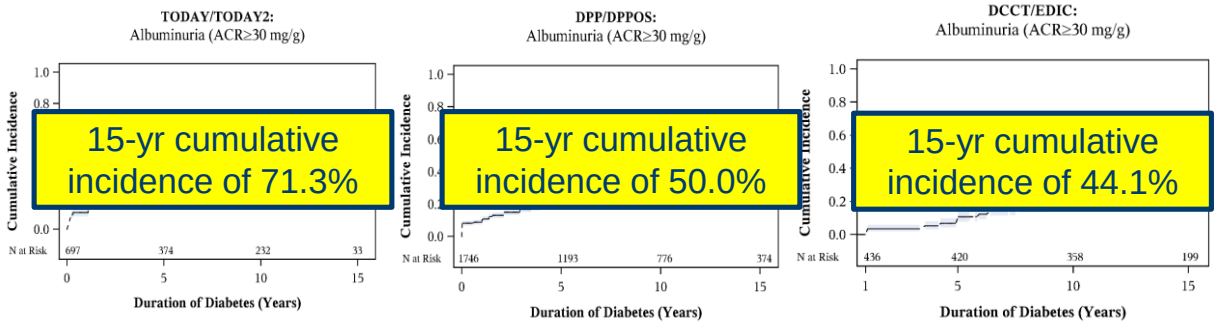


15-Year Cumulative Incidence: 57%

TODAY

TODAY Study Group. NEJM 2021

1. Burden of DKD in Y-T2D vs. A-T2D, T1D



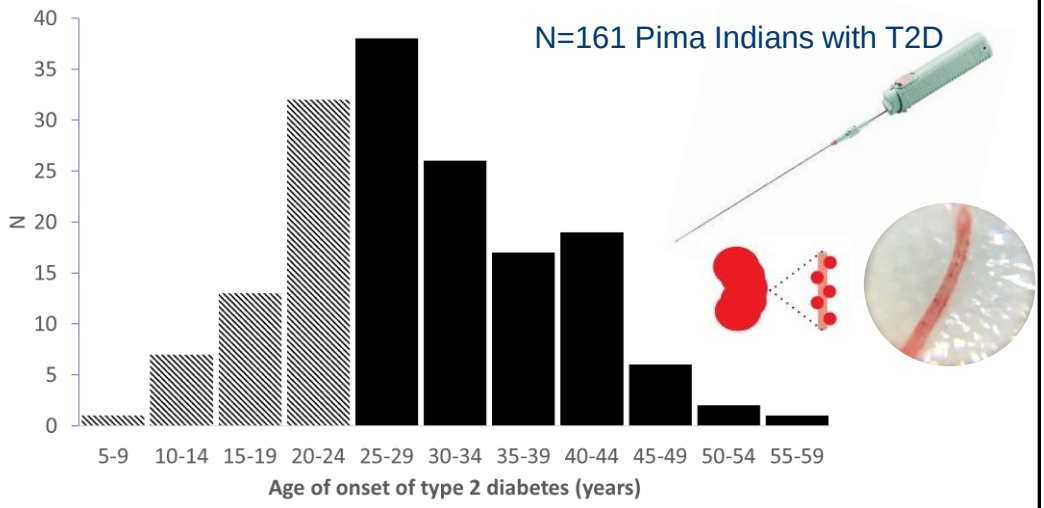
15-yr cumulative incidence of 71.3%

15-yr cumulative incidence of 50.0%

15-yr cumulative incidence of 44.1%

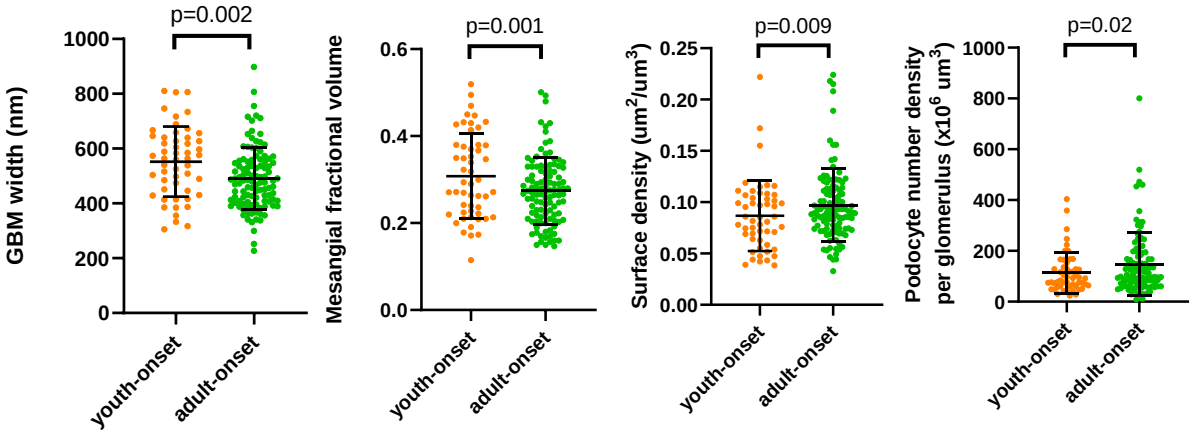
TODAY2, DPP/DPPOS and DCCT/EDIC groups

1. DKD in Y-T2D vs. A-T2D



Looker, Pyle. Saulnier, Najafian, Mauer, Nelson and Bjornstad. ADA 2021

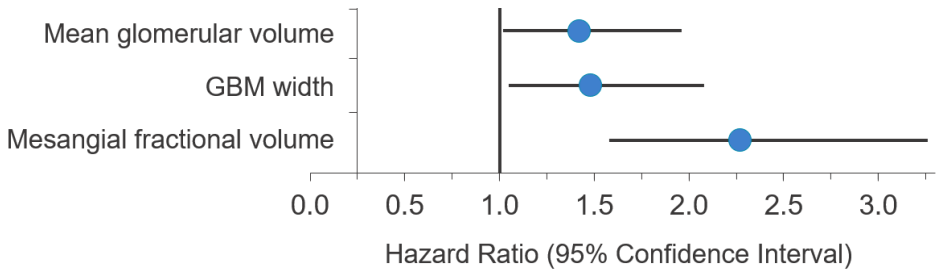
1. Structural parameters in Y-T2D vs. A-T2D



Looker, Pyle. Saulnier, Najafian, Mauer, Nelson and Bjornstad. ADA 2021

1. Associations of structural lesions and DKD progression in Pima Indians with T2D

Hazard Ratio and 95% CI for ≥40% Loss of GFR per 1 SD Increment of Each Morphometric Variable



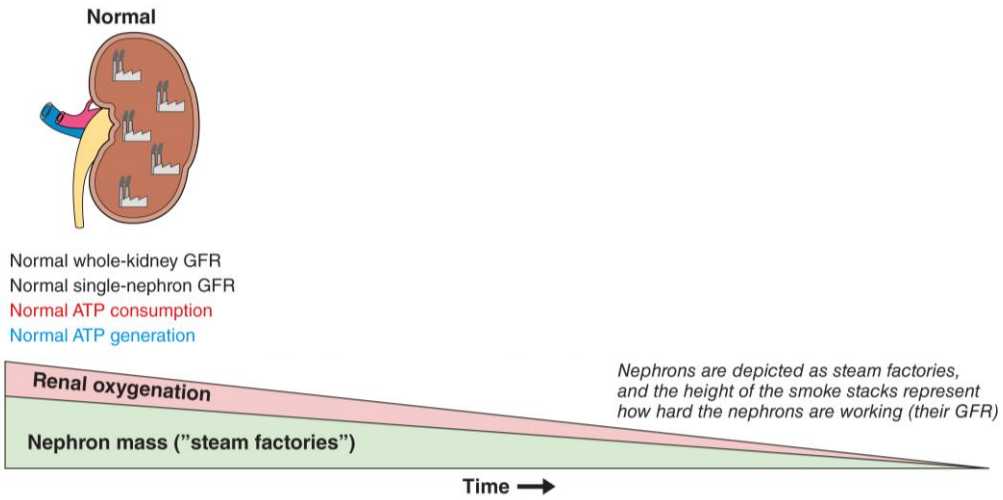
Fufaa GD, *Clin J Am Soc Nephrol*, 2016

2. Risk factors of DKD in Y-T2D

Characteristics (reference group or unit change)*	UACR ≥30 mg/g			UACR ≥300 mg/g		
	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Loss of glycemic control during TODAY (yes vs. no)	2.30	1.75, 3.03	<.0001	4.75	2.59, 8.71	<.0001
Hypertension (yes vs. no)	1.82	1.39, 2.40	<.0001	4.36	2.29, 8.28	<.0001
Hyperfiltration (yes vs. no)	1.63	1.21, 2.18	0.001	1.84	1.08, 3.12	0.02
Log insulin sensitivity (per SD)	0.73	0.64, 0.82	<.0001	0.75	0.60, 0.92	0.007
Log C-peptide ODI (per SD)	0.66	0.60, 0.74	<.0001	0.65	0.53, 0.80	<.0001

TODAY group. Diabetes Care 2021

STAGES OF DIABETIC KIDNEY DISEASE

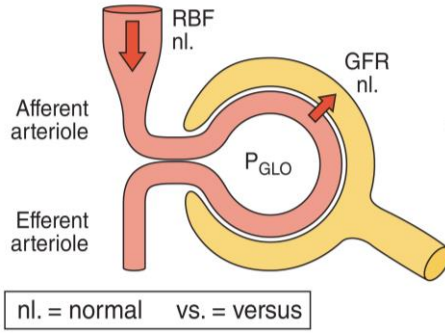


ATP = energy currency

HEALTHY KIDNEYS

Energy delivery Energy demand

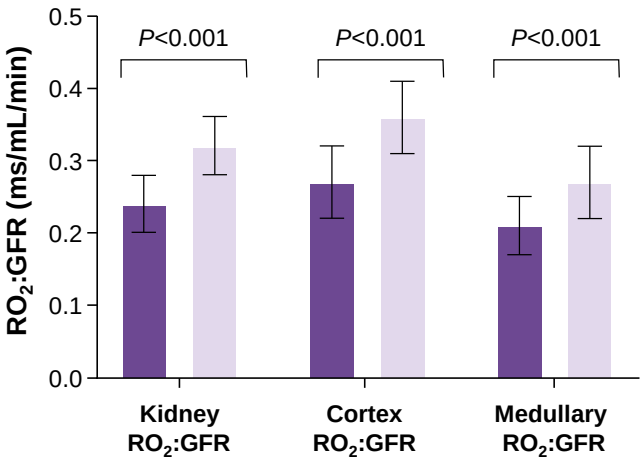
ATP generation ≈ ATP consumption



nl. = normal vs. = versus

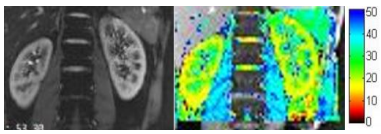
ATP = energy currency

2. Kidney hypoxia early in the course of diabetes



Type 1 diabetes (n=50)

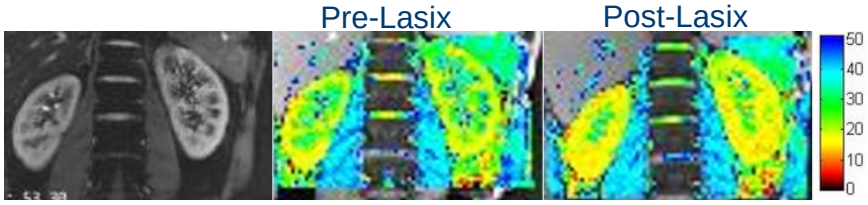
Controls (n=20)

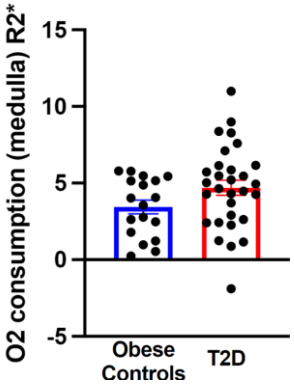


JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES. CASPER

Vinovskis and Bjornstad et al. Diabetes 2020

2. Renal oxygen consumption in Y-T2D

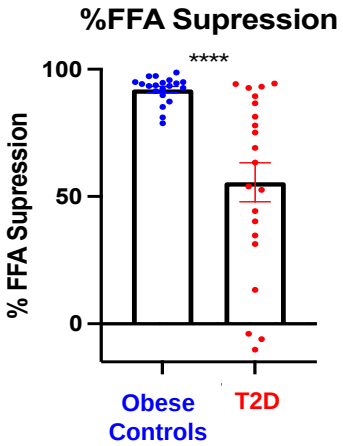


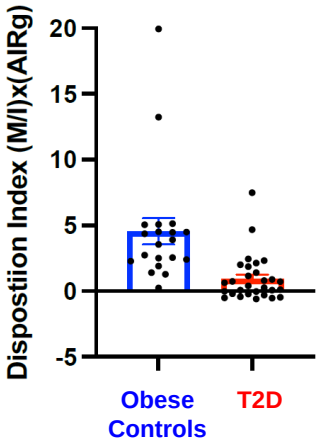


Preliminary morphometric analyses of the kidney biopsies in Y-T2D (17±2 years of age) indicate inverse relationships among GBM width (**r:-0.63, *p*=0.02**), mesangial expansion (**r:-0.64, *p*=0.02**) and kidney oxygenation normalized by GFR.

Unpublished data

2. FFA suppression and DI in Y-T2D





Unpublished data

2. FFA suppression relates to DKD markers

FFA suppression (%)

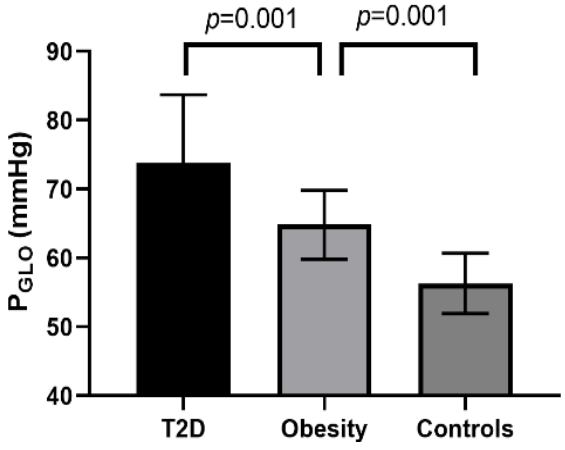
	r	*p*-value
Albuminuria (U		
Intraglomerua		*05*
Renal vascula		*005*
Furosemide-s		*05*

FFA is an inefficient substrate for kidney cells; fewer ATP synthesized per O_2 consumed compared with other common substrates (glucose, citrate, glutamate)

Similar relationships with DI

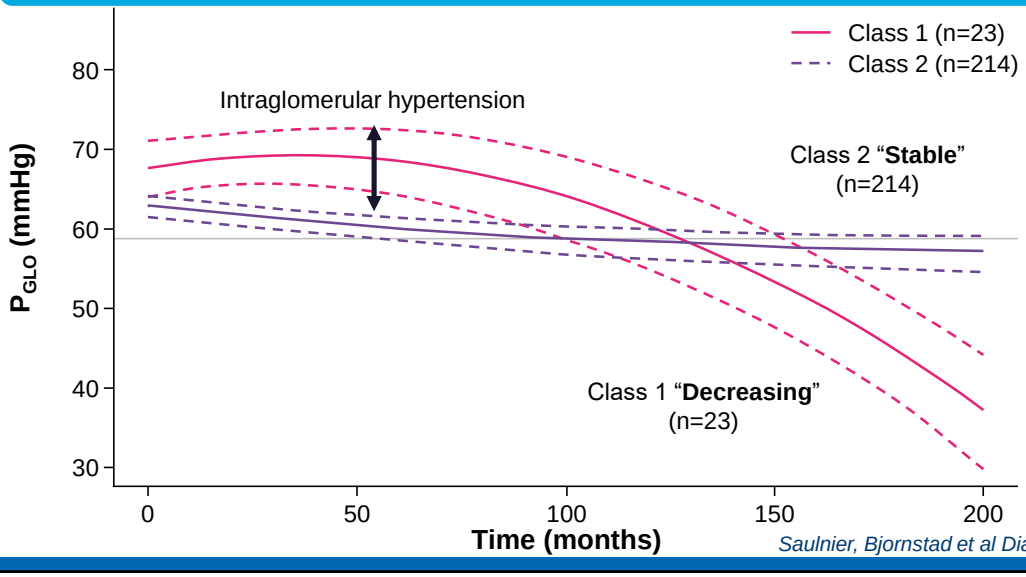
Unpublished data

2. Intraglomerular hypertension in Y-T2D



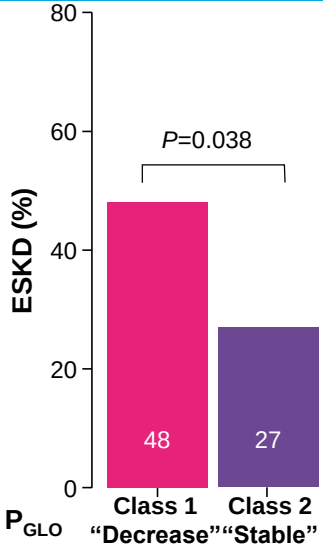
Unpublished data

2. Intraglomerular hypertension in early T2D



Saulnier, Bjornstad et al Diabetes 2021

2. Elevated P_{GLO} and ESKD risk in T2D

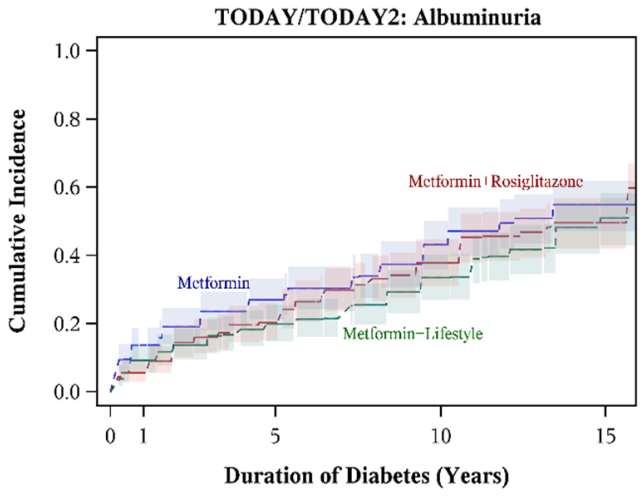


HR: 2.53
(95% CI: 1.24, 5.14)
***P*=0.01**

adjusted for baseline age, sex, diabetes duration, HbA_{1c}, RAASi and GFR

Saulnier, Bjornstad et al Diabetes 2021

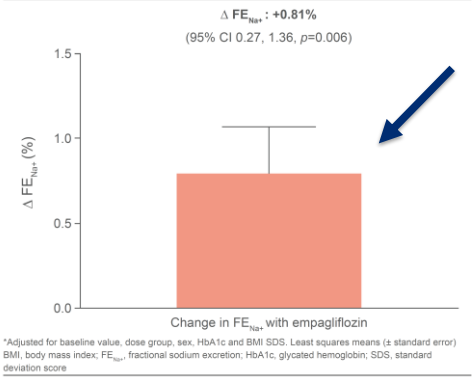
3. Interventions to mitigate DKD in Y-T2D



TODAY2 group

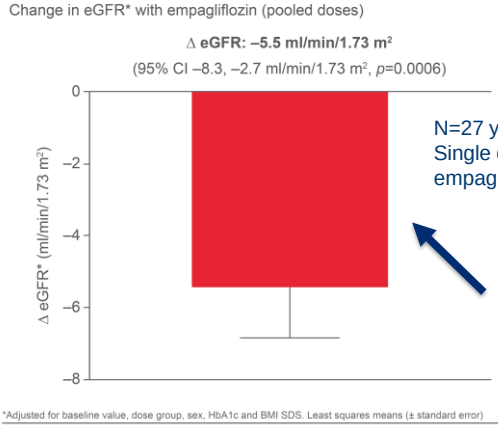
3. SGLT2 inhibitors in Y-T2D

Figure 1. Adjusted* changes from baseline FE_{Na+} after a single dose of empagliflozin (n=27)



*Adjusted for baseline value, dose group, sex, HbA1c and BMI SDS. Least squares means (± standard error)
BMI, body mass index; FE_{Na+}, fractional sodium excretion; HbA1c, glycated hemoglobin; SDS, standard deviation score

Figure 2. Adjusted changes from baseline eGFR after single dose administration of empagliflozin (n=27)

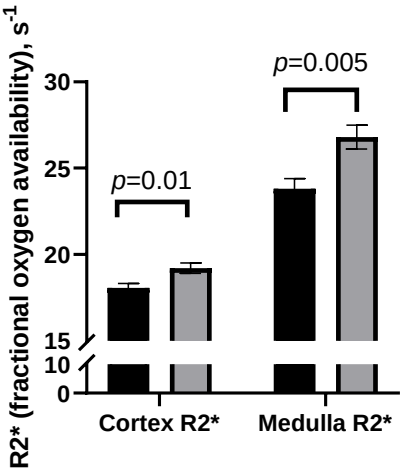


N=27 youth with T2D
Single dose of empagliflozin

*Adjusted for baseline value, dose group, sex, HbA1c and BMI SDS. Least squares means (± standard error)

Bjornstad et al. Diabetes Care 2018

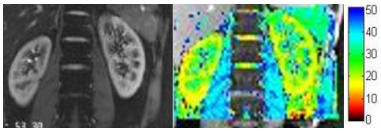
3. SGLT2 inhibitors in Y-T2D



SGLT2 inhibitors

No SGLT2 inhibitors

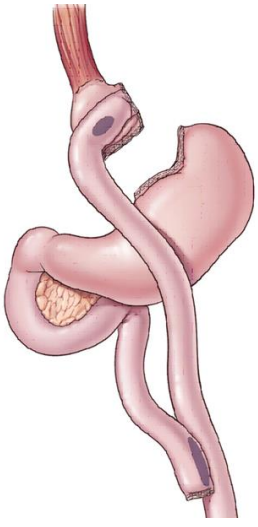
N=25
Youth-onset T2D



Adjusted for sex, GFR and BMI

Bjornstad et al. *Unpublished*

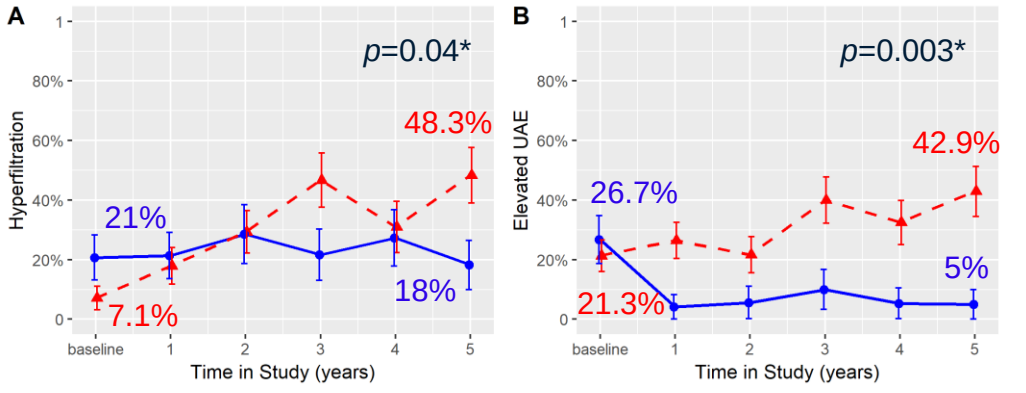
3. Bariatric Surgery and DKD in Y-T2D



3. Effects of MBS on DKD in Y-T2D

- **MBS** = metabolic bariatric surgery
- Secondary analysis of data from **TODAY** and **Teen-LABS**.
- **TODAY** participants were randomized to metformin alone or in combination with rosiglitazone or intensive lifestyle intervention, with insulin therapy given for glycemic progression.
- **Teen-LABS** participants underwent MBS.
- **TODAY** participants (n=63) frequency matched to 30 **Teen-LABS** participants with T2D using: baseline age (13-18 years); race/ethnicity, sex and baseline BMI (>35kg/m^2)

3. Effects of MBS on DKD in Y-T2D

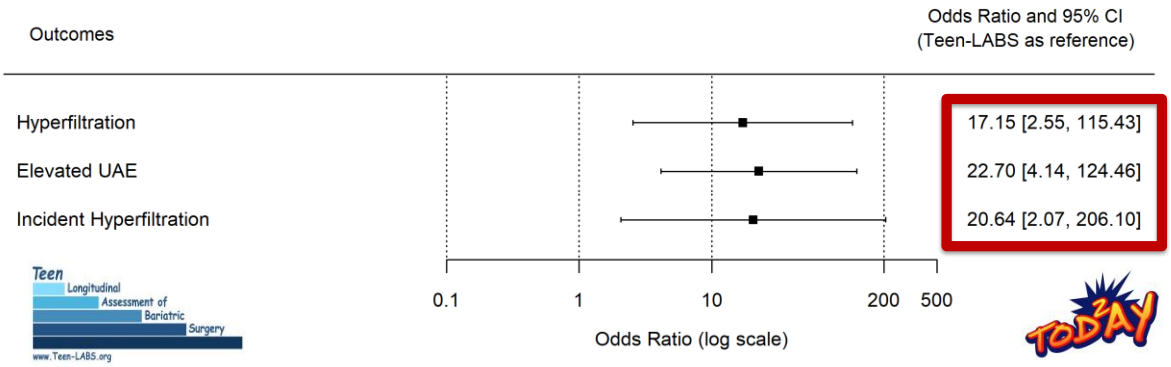


*Adjusted for baseline age, sex, HbA1c, insulin sensitivity, BMI and antihypertensive use

Teen-LABS TODAY

Bjornstad et al. Diabetes Care 2019

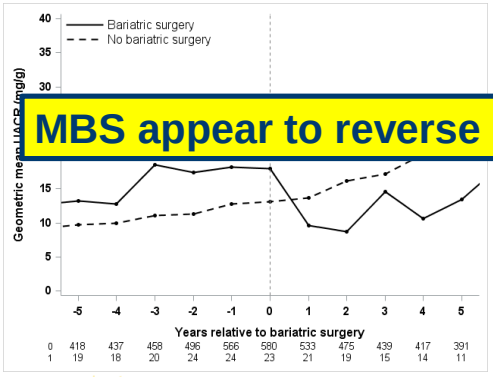
3. Effects of MBS on DKD in Y-T2D

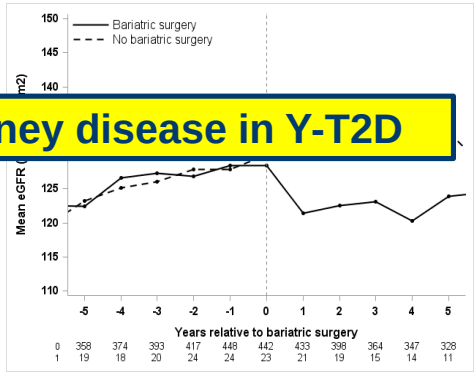


Bjornstad et al. Diabetes Care 2019

3. Effects of MBS on DKD in Y-T2D

- Secondary analysis of data from TODAY2 (observational)



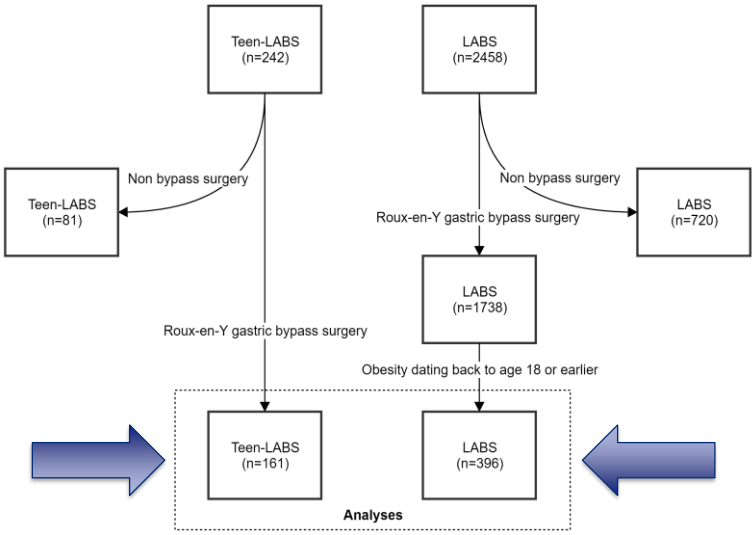


MBS appear to reverse kidney disease in Y-T2D

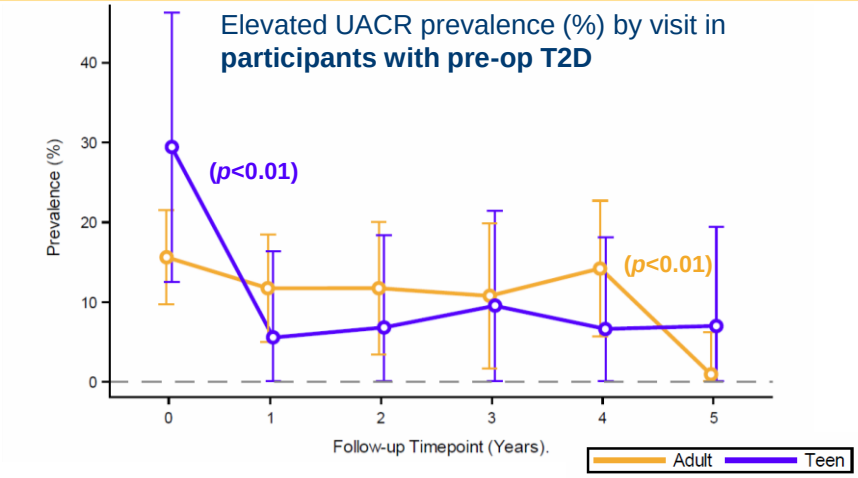
TODAY2

TODAY Study Group

3. Impact of age at MBS on DKD reversal

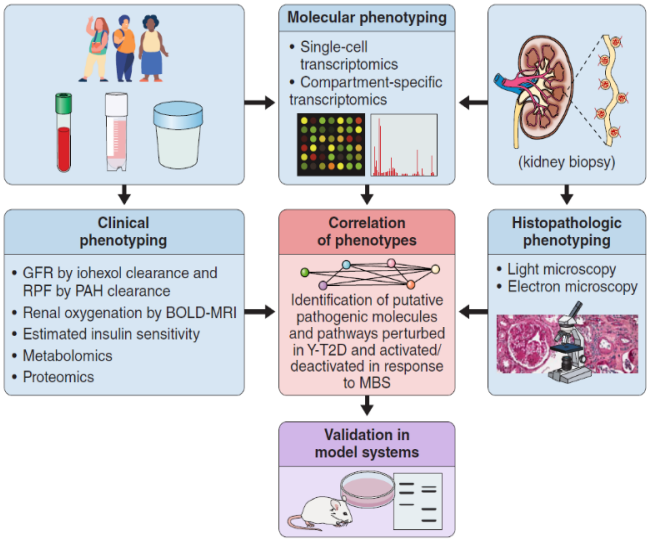


3. Impact of age at MBS on DKD reversal



Bjornstad et al. Kidney International 2020

4. Integrative Biological Approach



5. Summary

- Burden of DKD is high in Y-T2D.
- Insulin resistance and relative kidney hypoxia are important risk factors of DKD in Y-T2D.
- SGLT2i and MBS may reverse early evidence of DKD in Y-T2D.
- Younger age at MBS predicts earlier attenuation of DKD.
- Metabolic and molecular mechanisms of nephroprotection mediated by MBS remain poorly understood.
- To uncover novel targetable molecular pathways for the development of non-surgical therapeutic targets, we need to apply an integrative biological approach.

Collaborators

University of Colorado:
- Kristen J Nadeau
- Phil Zeitler
- Tom Inge
- Laura Pyle
- Judy Regensteiner
- Michal Schafer
- Michel Chonchol
- Jane Reusch
- Carlos Roncal
- Richard J Johnson
- Paul Wadwa
- Arleta Rewers
- Marian J Rewers
- Janet Snell-Bergeon
- Lorna Browne
- Alex Barker

CCHMC:
- Eddie Nehus
- Mark Mitsnefes

NIDDK:
- Robert G. Nelson

Stanford University:
- David M. Maahs

University of Chicago:
- Pottumarthi Prasad

CDC:
- Meda Pavkov

Johns Hopkins:
- Chirag Parikh

University of Washington:
- Ian de Boer

University of Michigan:
- Matthias Kretzler
- Jeff Hodgin

UCSD:
- Joachim Ix

University of Toronto:
- David Z. Cherney
- Farid Mahmud
- Bruce A. Perkins
- Julie Lovshin
- Yuliya Lytvyn
- Daniel Scarr
- Erik Lovblom
- Etienne Sochett

VU University Medical Center:
- Daniel van Raalte
- Lennart Tonneijck
- Erik van Bommel

UMCG:
- Hiddo Lambers Heerspink

Steno Diabetes :
- Peter Rossing
- Frederik Persson

University of Poitiers
- Pierre J. Saulnier

Children's Hospital Colorado
Here, it's different.

Affiliated with
Department of Pediatrics
SCHOOL OF MEDICINE
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Center for Women's Health Research

https://www.bjornstadlab.org

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  - U2C DK114886 (Subaward #2: Bjornstad and Waikar)
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Diabetic Retinopathy: Lessons from Adolescents

Rose A. Gubitosi-Klug, MD, PhD
Department of Pediatrics
Rainbow Babies and Children's Hospital
Case Western Reserve University School of Medicine

University Hospitals Rainbow Babies & Children's Hospital

Case Western Reserve University

Presenter Disclosure

Nothing to disclose.

Cases to learn from…

1. Pathogenesis of Diabetic Retinopathy
2. Registry of youth with diabetes
3. DCCT/EDIC Adolescents
4. Youth-onset T2D and retinopathy progression

Rising rates of retinopathy

In America…

- 3.7 million individuals age 40 and older are blind or visually impaired (2010)
  - Diabetic retinopathy is the leading cause of blindness among working age adults
- 7.7 million individuals age 18 or older with diabetic retinopathy
  - Progressive disorder
  - Costs of medical expenses and lost productivity is soaring…$500 million annually

Diabetic Retinopathy: Stages

Goal:
target early stages

Therapies

****** Significant vision impairment**

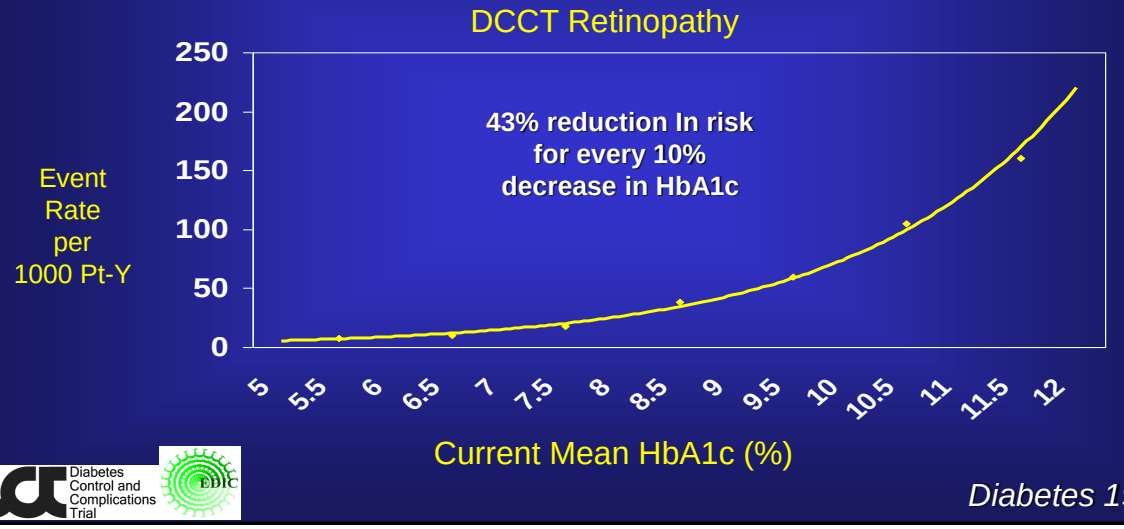
Disease Progression

Early (non-proliferative, background)
Capillary degeneration, nonperfusion
Microaneurysms
Exudates
Macular edema (both stages)

Late (proliferative)
Retinal ischemia
Neovascularization
Vitreous hemorrhage
Retinal detachment

Davis *et al. International Textbook Diabetic Retinopathy* (1997)

Relationship between Glycemia and Complications



Diabetes Control and Complications Trial

EDIC

Diabetes 1995

Even more children at risk

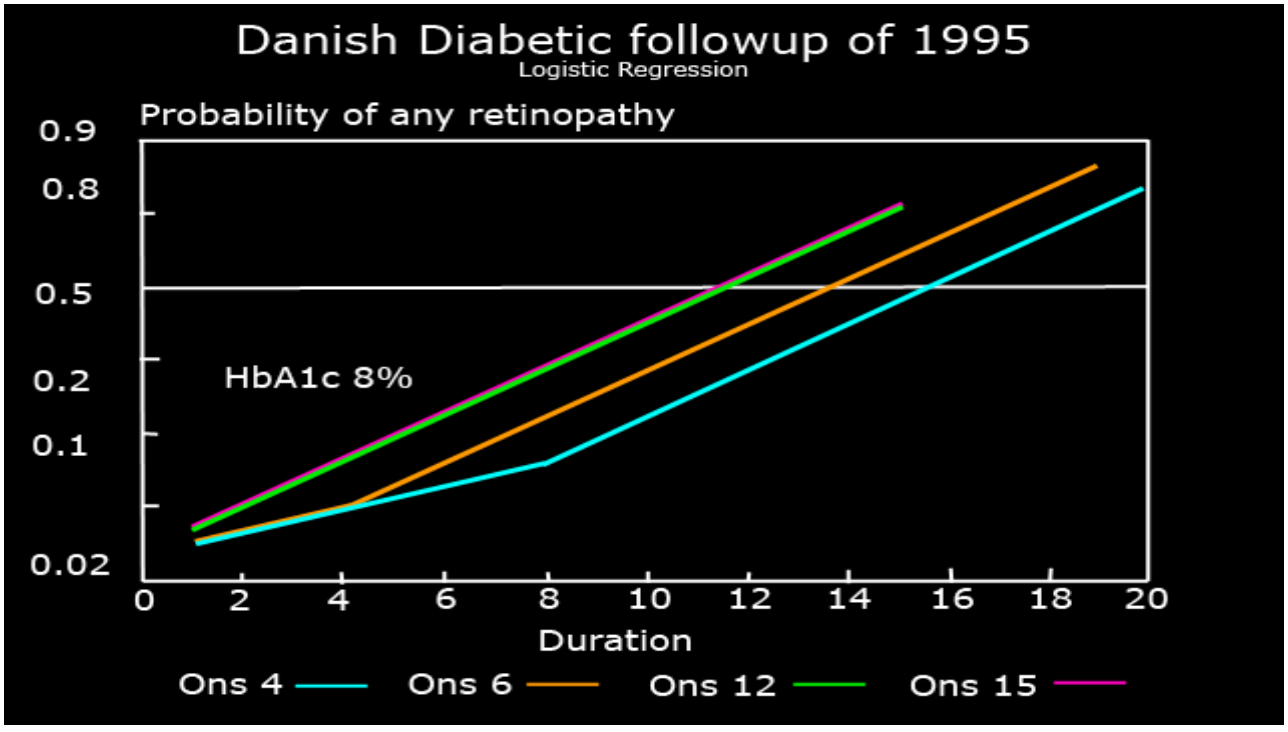
- Obesity epidemic with rising rates of T2DM in children
  - Treatment Options for Type 2 Diabetes in Youth (TODAY)
  - Difficult to manage with 40-50% treatment failure rates within one year

    (TODAY Study Group, NEJM 2012)

Even more children at risk

- Youth with T2D develop complications at a faster rate than T1D
  - Within four years of diagnosis…
    - 30% with hypertension
    - 45% with hyperlipdemia
    - 17% microalbuminuria
    - 14% with retinopathy
  - Major complications, including blindness, reported by 10 years post-diagnosis

Diabetes Care 2014; 37, 436-43



DCCT/EDIC Adolescents: Cases of PDR and CSME increase from 18 to 21 years of age

		PDR		CSME	
	Follow-up*	Cases	Rate# (95% UCL)	Cases	Rate# (95% UCL)
Age < 18 (n=195)	456.9	0	0 (6.6)	1	2.2 (10.4)
Age < 19 (n=222)	642.6	0	0 (4.7)	2	3.1 (9.8)
Age < 20 (n=244)	846.4	0	0 (3.5)	3	3.5 (9.2)
Age < 21 (n=290)	1056.4	3	2.8 (7.3)	7	6.6 (12.4)

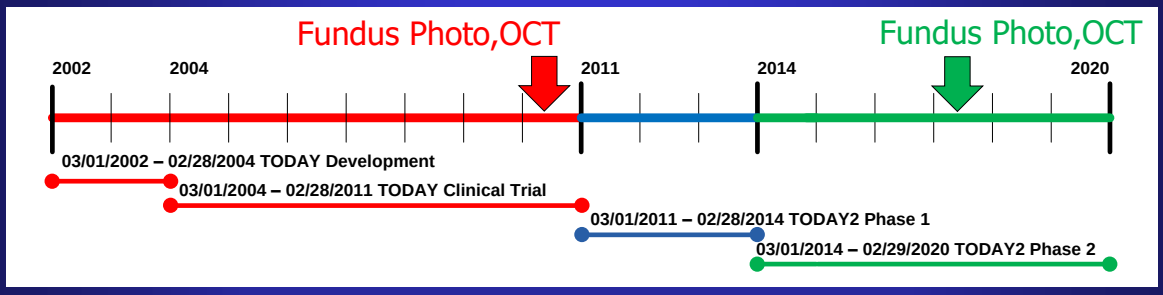
*Total follow-up (years); # Rate per 1,000 individuals at risk for one year; UCL=upper confidence limit.

Diabetes Control and Complications Trial

EDIC

Gubitosi-Klug, et. al., Pediatric Diabetes 2019;20(6): 743-9

TODAY Through TODAY2



TODAY and T2P1

- All Visits: Height, Weight, BP, HbA1c, Diabetes Care/ Management, Medical History
- Annually: Neuropathy Measures, Lipids, Kidney Function Labs

T2P2

- Annually: Height, Weight, BP, HbA1c, Neuropathy Measures, Lipids, Kidney Function Labs
- Biannually: Medical History

TODAY – TODAY2 Cohort Characteristics

		TODAY (n=699)	T2P1 (n=572)	T2P2 (n=517)
Age in years (mean, SD)		14.0 (2.0)	18.3 (2.5)	21.2 (2.5)
Female		64.7%	64.7%	65.0%
Race/Ethnicity	Hispanic	39.8%	39.7%	38.1%
	Non-Hispanic Black	32.5%	32.9%	34.0%
	Non-Hispanic White	20.5%	20.5%	20.3%
	Other	7.3%	7.0%	7.5%
Years since diagnosis of T2D (mean, SD)		0.6 (0.5)	4.5 (1.5)	7.5 (1.5)
Years since randomization in TODAY (mean, SD)		--	3.9 (1.3)	6.9 (1.3)
BMI in kg/m^2 (mean, SD)		34.9 (7.6)	36.5 (8.2)	36.3 (8.4)
HbA1c in % (mean, SD)		6.0 (0.7)	8.4 (2.9)	9.3 (3.0)

Fundus Photography Results

	TODAY	TODAY2
Mean T2D duration (years)	4.92	11.93
Diabetic retinopathy stages		
No definitive diabetic retinopathy	317 (86%)	187 (51%)
Very mild NPDR	53 (14%)	82 (22%)
Mild NPDR	0 (0%)	60 (16%)
Moderate NPDR	0 (0%)	14 (4%)
Moderately severe NPDR	0 (0%)	3 (1%)
Severe NPDR	0 (0%)	5 (1%)
Early or stable, treated PDR	0 (0%)	10 (3%)
High risk PDR	0 (0%)	4 (1%)
≥ 3 step progression on ETDRS scale	--	65 (18%)
Macular edema	0 (0%)	13 (4%)

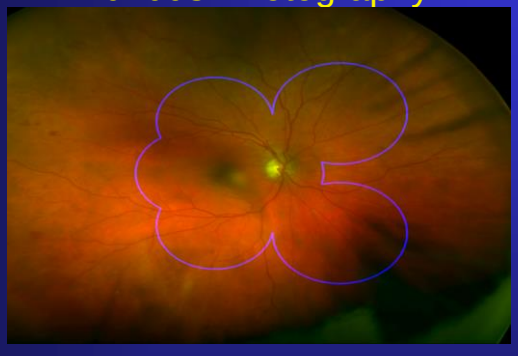
Risk Factors Associated with ≥3 Step Diabetic Retinopathy Progression

Risk Factors	HR [95% CI]
Age at baseline (per year)	0.97 [0.5, 1.88]
Sex (female vs. male)	0.59 [0.34, 1.02]
Race/Ethnicity (Ref: Non-Hispanic White)	
Hispanic	1.48 [0.65, 3.35]
Non-Hispanic Black	1.82 [0.8, 4.13]
Ever smoker	1.02 [0.6, 1.75]
T2D duration at TODAY2 Fundus exam	2.1 [0.85, 5.2]
Loss of glycemic control (HbA1c ≥ 8%)	**19.23 [4.62, 80.07]**
Mean HbA1c (per 1% increase)	**2.23 [1.81, 2.75]**
Mean BMI (per 5 kg/m^2 increase)	0.84 [0.7, 1.02]
Mean C-Pep total AUC (per 100 ng/ml·min increase)	**0.8 [0.73, 0.89]**
Mean Glucose total AUC (per 1000 mg/dL·min increase)	**1.18 [1.12, 1.24]**

Hazard ratios for significant risk factors (P<0.05) highlighted in red

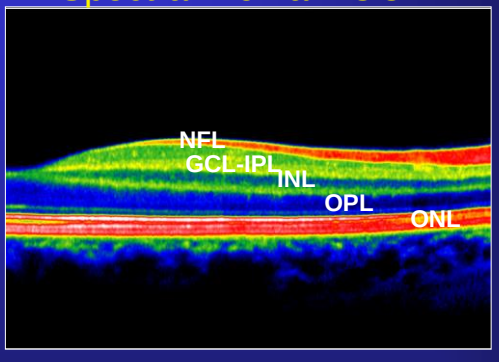
Fundus Photographs and Optical Coherence Tomography

Fundus Photography



Diabetic retinopathy assessment based on 7-standard field Early Treatment Diabetic Retinopathy Study (ETDRS) scale

Spectral-Domain OCT



Retinal thickness measurement based on digital Optical Coherence Tomography (OCT) centerfield and inner subfield of the retina.

TODAY2

Fundus Photographs and OCT Exams

- Fundus and OCT exams were conducted in 2011 and 2018.
- In 2011, OCT was conducted on time-domain at some sites, and on spectral domain at other sites
- Longitudinal analyses focus on patients with repeated exams.
- Retinal Thickness (SD-OCT) will be analyzed cross-sectionally.

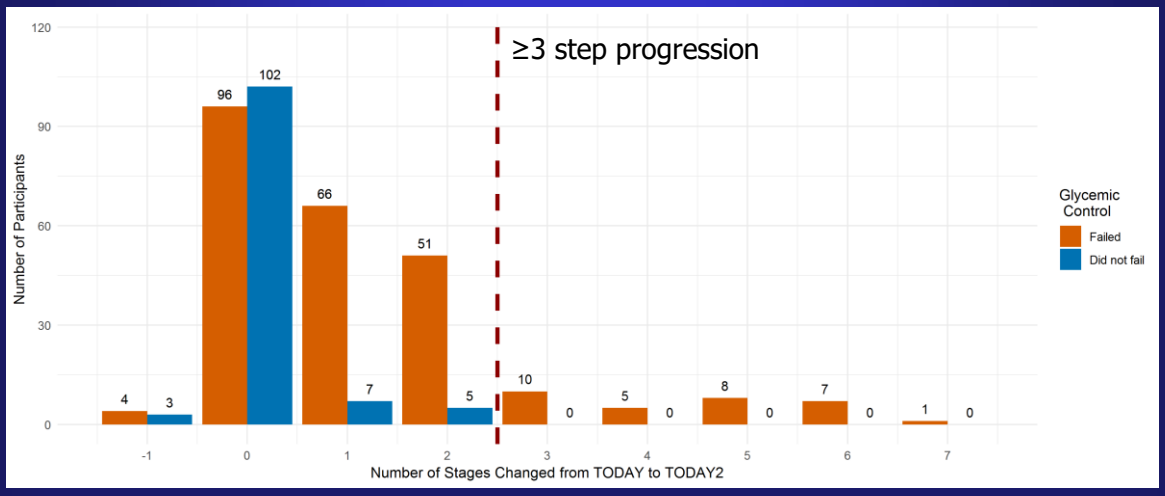
	2011	2018	Longitudinal sample
Fundus	518	419	370
OCT	515	414	367
SD-OCT	216	414	157

TODAY2

Fundus Photography Results

	TODAY	TODAY2
Diabetic retinopathy		
No definitive diabetic retinopathy	317 (86%)	187 (51%)
Very mild NPDR	53 (14%)	82 (22%)
Mild NPDR	0 (0%)	60 (16%)
Moderate NPDR	0 (0%)	14 (4%)
Moderately severe NPDR	0 (0%)	3 (1%)
Severe NPDR	0 (0%)	5 (1%)
Early or stable, treated PDR	0 (0%)	10 (3%)
High risk PDR	0 (0%)	4 (1%)
>= 3 step progression	--	65 (18%)
Macular edema	0 (0%)	13 (4%)

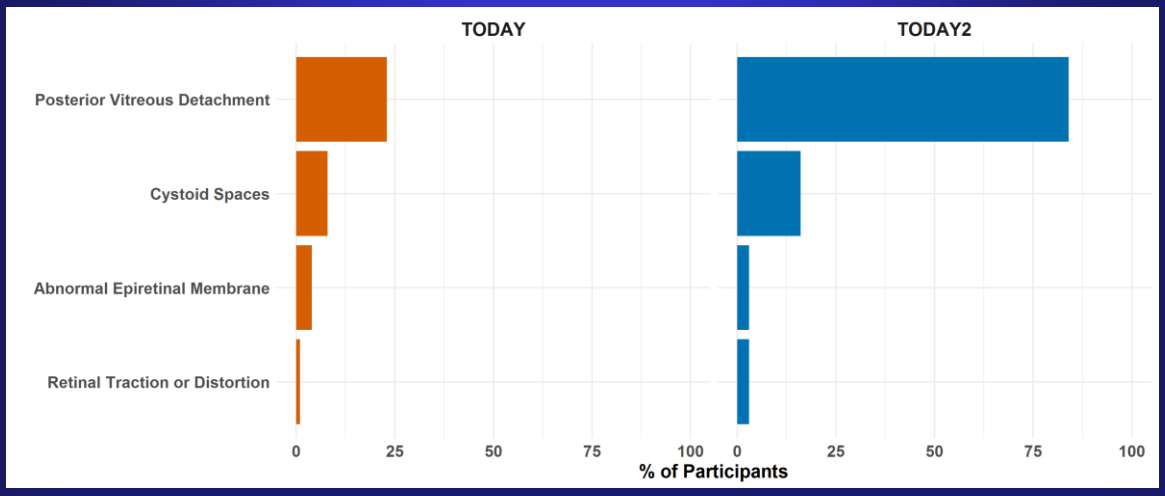
Durable Control and Retinopathy Progression



≥3 Step Diabetic Retinopathy Progression – Risk Factors

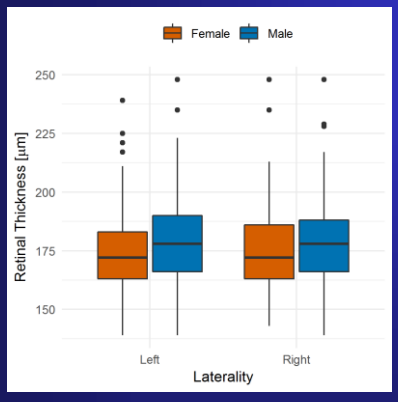
- Highly significant risk factors of ≥ 3 step progression of diabetic retinopathy (DR) are:
  - Higher Mean HbA1c (%) increases risk
  - Lower Mean C-Peptide AUC (ng/dl·min) increases risk
  - Higher Mean Glucose AUC (mg/dl·min) increases risk
- Race, sex, and duration of diabetes were not significant at the 5% level.

Optical Coherence Tomography (OCT) Results



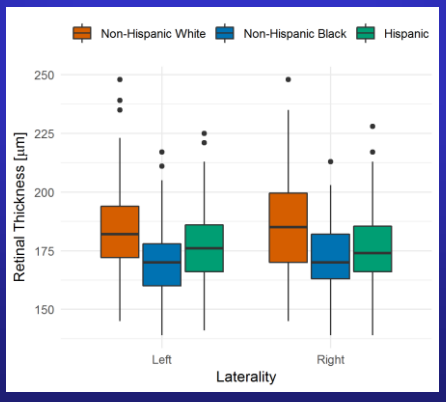
Retinal Thickness During TODAY2

Sex



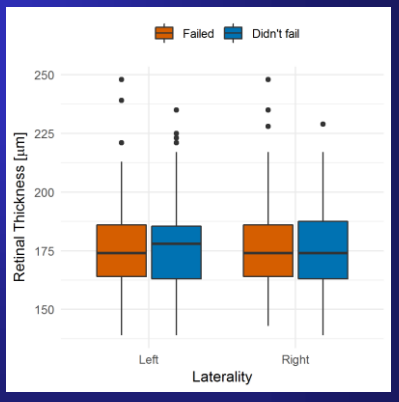
Global p = 0.001 (***)

Race/Ethnicity



Global p < 0.0001 (***)
NHW vs. NHB: p < 0.0001
NHW vs. H: p < 0.0001

Glycemic Control



Global p = 0.62 (NS)

Retinal Thickness (RT) – Risk Factors

- Retinal thickness is significantly influenced by
  - Race/ Ethnicity: NHB and Hispanic had lower RT than NHW.
  - Sex: Females had lower RT
  - Diabetes duration: Participants with longer T2D duration at exam had lower RT
- Mean HbA1c, BMI, Glucose AUC, C-Peptide, and Cholesterol were not significant at the 5% significance level.

Adjudicated Eye Disease Events

	# Patients	% Patients*	Event Rate (per 1000 PYr)
Individual Events			
NPDR	54	21.3	9.08
PDR	14	5.5	2.35
Macular edema	11	4.3	1.85
Vitreous hemorrhage	6	2.4	1.01
Cataracts	4	1.6	0.67
Glaucoma	3	1.2	0.50
All Events	92	36.2	15.47

*based on number of patients with any CAC eye report **N= 254**

Summary

- Loss of glycemic control is a predictor for progression of diabetic retinopathy
  - Advanced diabetic retinopathy requiring treatment is present in 9 % of the TODAY cohort with mean 12 years T2D duration
- Retinal thickness varies by race/ethnicity and by sex

Acknowledgements

Collaboration among investigators, research coordinators, and participants!

Diabetes Care Summit

OU Health | Harold Hamm Diabetes Center

ADCES Association of Diabetes Care & Education Specialists

Breakout Session II:

- *Pharmacology Update*
- *The Role of Mental Health in Diabetes Care*

Diabetes Care Summit

OU Health | Harold Hamm Diabetes Center

ADCES Association of Diabetes Care & Education Specialists

Pharmacology Updates

Katherine O'Neal, PharmD, MBA, BCACP, CDCES, BC-ADM, CLS, AEC, FADCES
Associate Professor OU College of Pharmacy
Katherine-oneal@ouhsc.edu

OU Health | Harold Hamm Diabetes Center

Objectives

1. Describe the 2021 ADA Standards of Care Treatment recommendations
2. Summarize key evidence from trials supporting expanded FDA indications for anti-glycemic agents
3. Compare and contrast GLP1 agonists, SGLT2 inhibitors and insulin

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3

Agenda

1. ADA 2021 Treatment Algorithm
2. GLP-1 Agonists
3. SGLT-2 Inhibitors
4. Insulin Review
5. Other Medications
6. Medication Access

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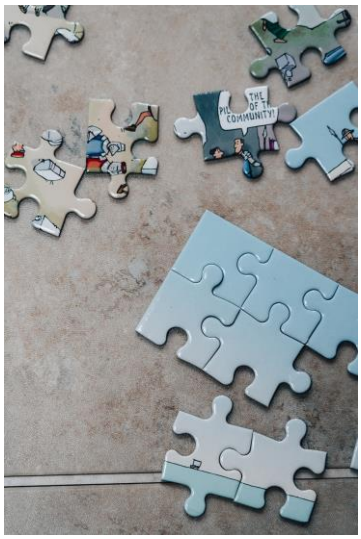
4

Treatment Options

- Biguanide
- Sulfonylureas (SU)
- Metglitinides
- Thiazolidinediones (TZD)
- Alpha-glucosidase inhibitors (AGi)
- Dipeptidyl Peptidase-4 Inhibitors (DPP4)
- Glucagon-like Peptide-1 Agonists (GLP1)
- Sodium Glucose Co-Transporter-2 Inhibitors (SGLT2)
- Amylin Analogue
- Dopamine Agonist
- Bile Acid Sequestrant (BAS)
- “Others”



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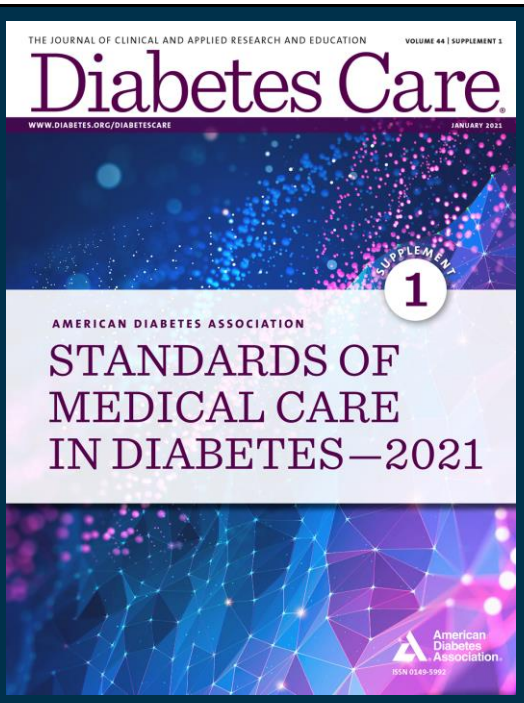
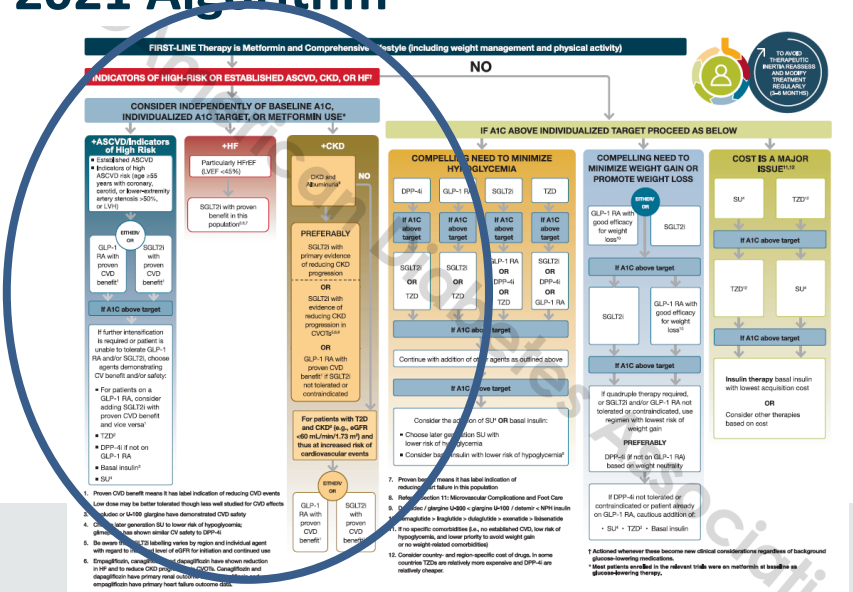
6



ADA 2021 Treatment Algorithm

2021 Algorithm



Diabetes Care 2021;44(1) Figure 9-1

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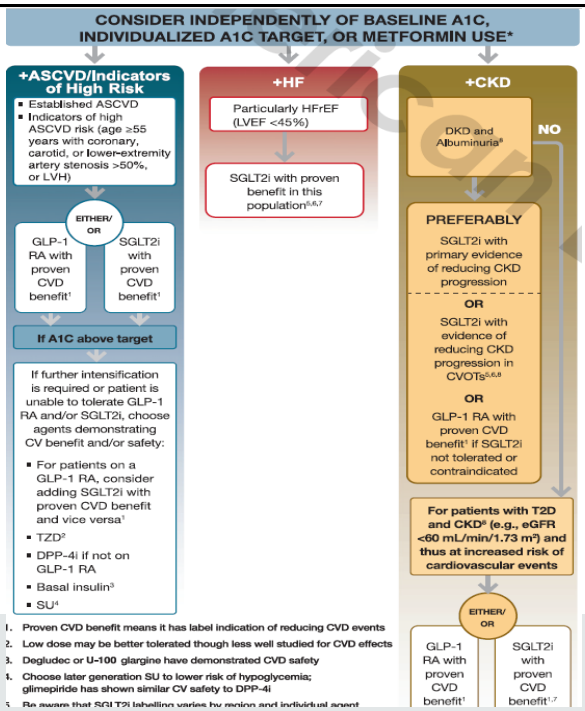
8

Established or high risk of ASCVD, CKD, or HF



ASCVD: Atherosclerotic Cardiovascular Disease; CKD: Chronic Kidney Disease; HF: Heart Failure. . Diabetes Care; 2021;44(1). Figure 9-1

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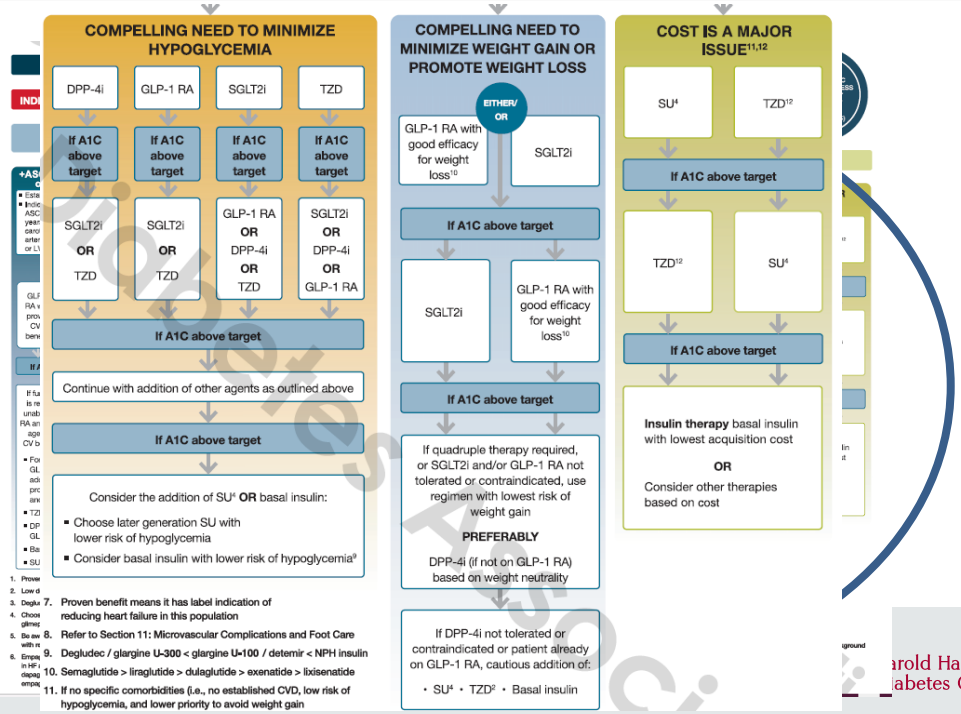
9

No Risks



Diabetes Care; 2021;44(1). Figure 9-1

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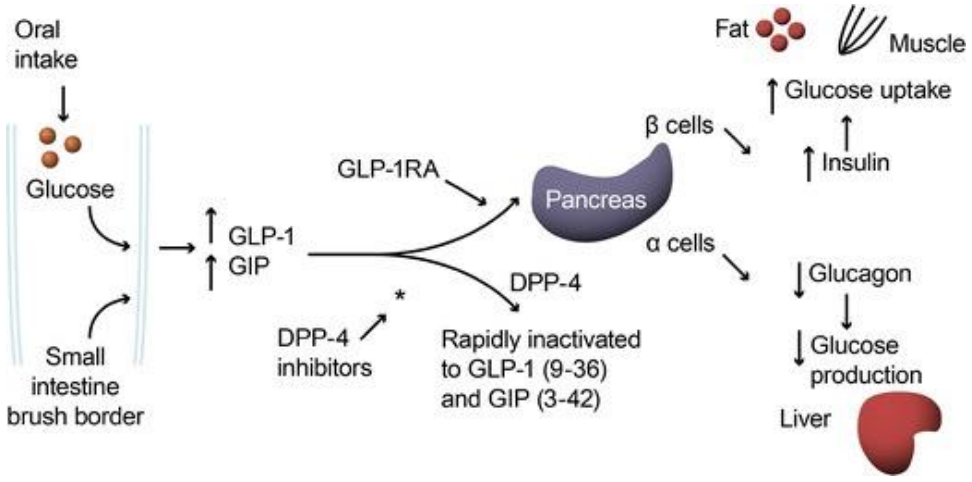
GLP-1 Agonists and SGLT-2 Inhibitors

GLP1 Mechanism of Action



12

GLP1 Class Overview

Drugs	• Exenatide (4/2005) • Liraglutide (1/2010) • Dulaglutide (9/2014) • Lixisenatide (7/2016) • Semaglutide (12/5/2017)
Efficacy	• ~1-2% A1c lowering

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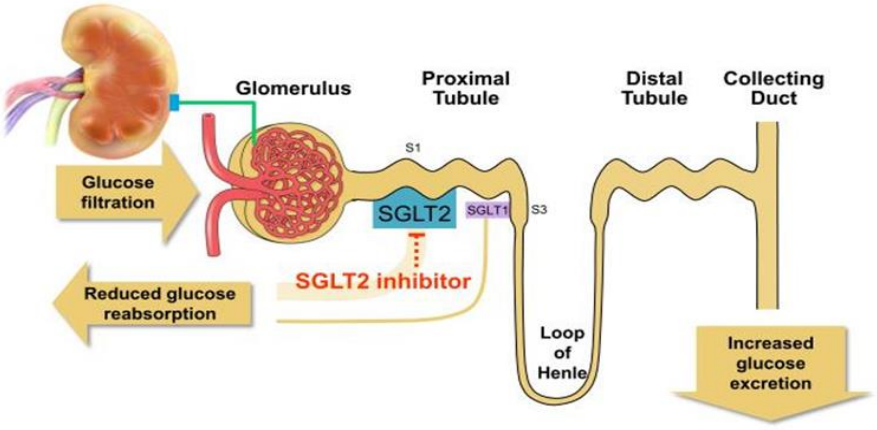
SGLT2 Mechanism of Action



14

SGLT2 Class Overview

Drugs	• Canagliflozin (approved 3/2013) • Dapagliflozin (approved 1/2014) • Empagliflozin (approved 8/2014) • Ertugliflozin (approved 12/20/2017)
Efficacy	• ~0.5-1% A1c lowering

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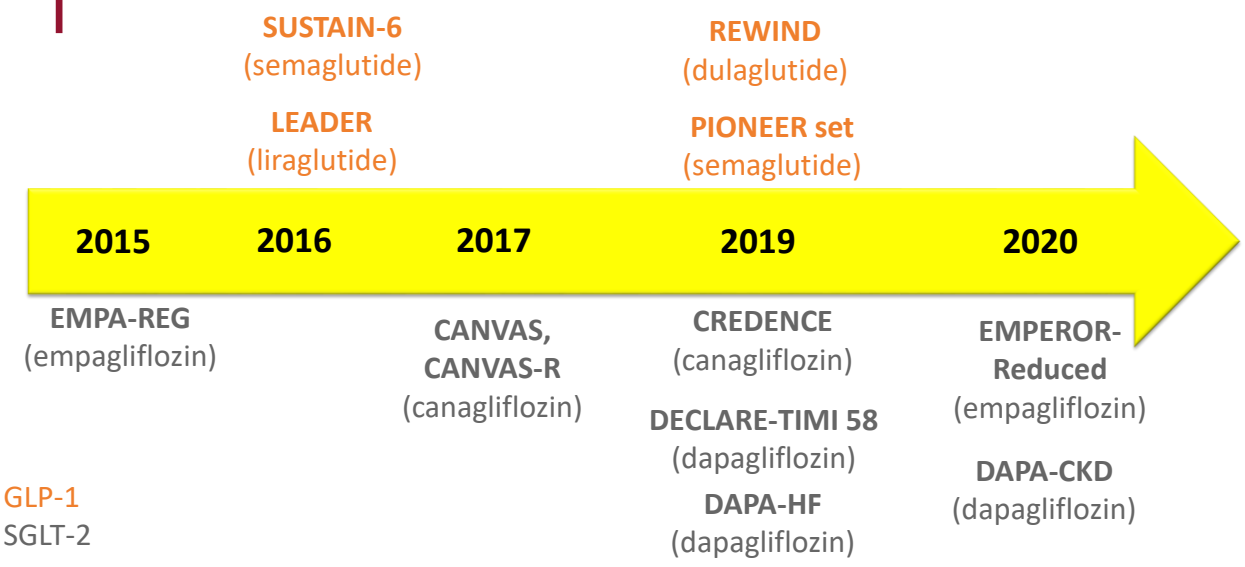
Historic Timeline of Evidence



Chilton RJ. Cardiovascular risk and the implications for clinical practice of cardiovascular outcome trials in type 2 diabetes. Primary Care Diabetes. 2020; 193. Diabetes Care; 2021;44(1)

16

PIONEER-6

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Mansoor Husain, M.D., Andreas L. Birkenfeld, M.D., Morten Donsmark, Ph.D., Kathleen Dungan, M.D., M.P.H., Freddy G. Eliaschewitz, M.D., Denise R. Franco, M.D., Ole K. Jeppesen, M.Sc., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Ofri Mosenzon, M.D., Sue D. Pedersen, M.D., Cees J. Tack, M.D., Mette Thomsen, M.D., D.M.Sc., Tina Vilsbøll, M.D., D.M.Sc., Mark L. Warren, M.D., and Stephen C. Bain, M.D., for the PIONEER 6 Investigators*

PIONEER-6 Design

Drug	• Semaglutide (oral) vs. placebo
Design	• 3,183 patients • 214 sites • 21 countries
Primary Endpoint	• CV death, MI, or stroke
Duration	• 15.9 months
Population	• T2DM • Age ≥ 50 with CVD or CKD or ≥ 60 with CV risk factor
Published	• 2019

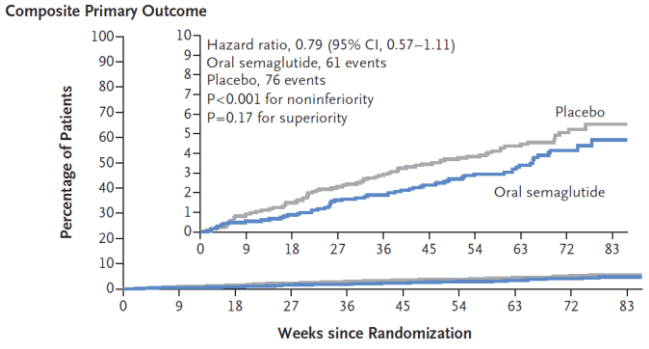
PIONEER-6 Baseline Characteristics

	Placebo (n=1592)	Semaglutide (n=1591)
Mean age	66	66
Mean BMI	32.3	32.3
Diabetes duration	15.1	14.7
Mean A1c	8.2%	8.2%
Systolic Blood Pressure	136	135
Diastolic Blood Pressure	76	76
Established CVD	84.5%	84.9%
CVD Risk Factors	15.5%	15.1%
eGFR ≤59 (mL/min/1.73m^2)	26.5%	27.3%

NEJM. 2019;381:841

PIONEER-6 Primary Endpoint

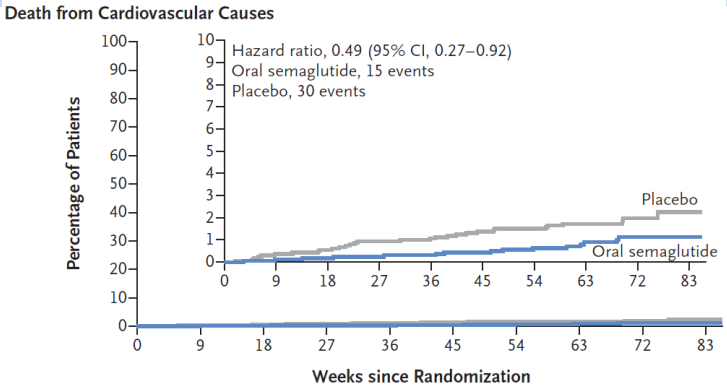
	Placebo (n=1592)	Semaglutide (n=1591)	Hazard Ratio (95% CI)	p-value
CV death, MI, stroke	4.8%	3.8%	0.79 (0.57-1.11)	p<0.001(N)



NEJM. Figure 1A. 2019;381:841

PIONEER-6 Cardiovascular Outcomes

	Placebo (n=1592)	Semaglutide (n=1591)	Hazard Ratio (95% CI)
Death from CV Cause	1.9%	0.9%	0.49 (0.27-0.92)



NEJM. Figure 1D. 2019;381:841

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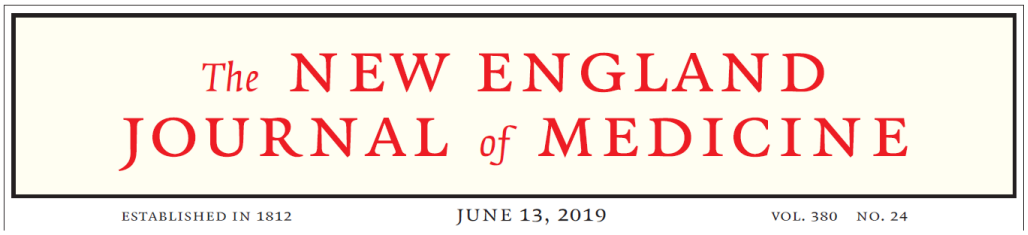
CREDENCE



Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

NEJM. 2019;380:2295

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CREDENCE Design

Drug	• Canagliflozin vs. placebo
Design	• 4,401 patients • 690 sites • 34 countries
Primary Endpoint	• Composite end-stage kidney disease, doubling of serum creatinine, or death from renal or CVD
Duration	• 2.62 years
Population	• T2DM • Age ≥ 30 with A1c 6.5-12% with GFR 30 to <90 and urinary albumin-to-creatinine ratio >300 to 5000
Published	• 2019

NEJM. 2019;380:2295

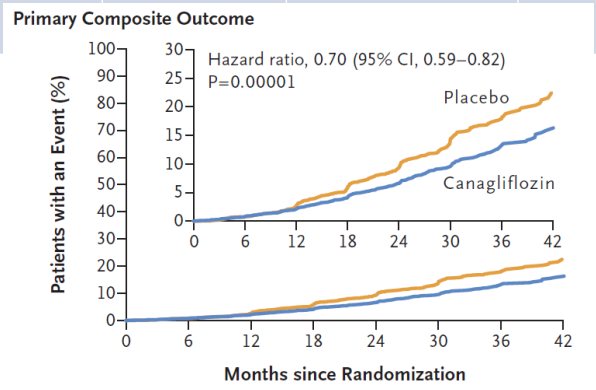
CREDENCE Baseline Characteristics

	Placebo (n=2199)	Canagliflozin (n=2202)
Mean age	63.2	62.9
Mean BMI	31.3	31.4
Diabetes duration	16	15.5
Mean A1c	8.3%	8.3%
Systolic Blood Pressure	140.2	139.8
Diastolic Blood Pressure	78.4	78.2
Established CVD	50.3%	50.5%
eGFR (mL/min/1.73m^2)	56.3	56

NEJM. 2019;380:2295

CREDENCE Primary Endpoint

	Placebo (n=2199)	Canagliflozin (n=2202)	Hazard Ratio (95% CI)	p-value	NNT
End-stage renal disease, doubling of serum creatinine, or death from renal or CVD	340	245	0.70 (0.59-0.82)	p=0.00001	22

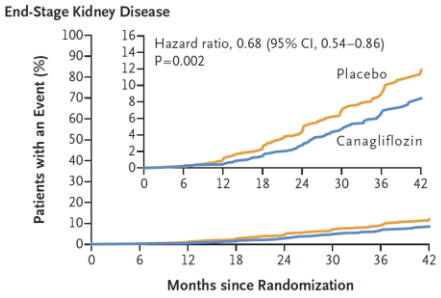


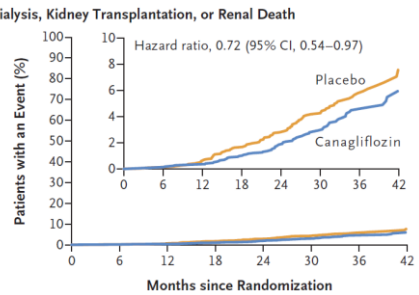
NEJM. Figure 1A. 2019;380:2295

25

CREDENCE Renal Outcomes

	Placebo (n=2199)	Canagliflozin (n=2202)	Hazard Ratio (95% CI)	p-value	NNT
End-Stage Kidney Disease	165	116	0.68 (0.54-0.86)	p=0.002	24
Dialysis, kidney transplant, or renal death	78	105	0.72 (0.54-0.97)		





NEJM. Figure 1C and 1D. 2019;380:2295

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CREDENCE CV Outcomes

	Placebo (n=2199)	Canagliflozin (n=2202)	Hazard Ratio (95% CI)	p-value	NNT
Death from CV Cause	140	110	0.78 (0.61-1.00)	p=0.05	
Composite CV death or hospitalization for HF	179	253	0.69 (0.57-0.83)	p<0.001	
CV death, MI, or stroke	269	217	0.80 (0.67-0.95)	p=0.01	40
Hospitalization for HF	141	89	0.61 (0.47-0.80)	p<0.001	46

NEJM. Figure 1C. 2019;380:2295

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DAPA-HF

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

NEJM. 2019;381:1995

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DAPA-HF Design

Drug	• Dapagliflozin vs. placebo
Design	• 4,744 patients • 410 sites • 20 countries
Primary Endpoint	• Composite of worsening HF or CV death
Duration	• 18.2 months
Population	• Age ≥ 18 with an ejection fraction of 40% or less and NYHA Class II, III or IV symptoms
Published	• 2019

NEJM. 2019;381:1995

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DAPA-HF Baseline Characteristics

	Placebo (n=2371)	Dapagliflozin (n=2373)
Mean age	66.5	66.2
Mean BMI	28.1	28.2
Diabetes	990	993
Previous Hospitalization for HF	47.5%	47.4%
Systolic Blood Pressure	121.6	122
Left Ventricular Ejection Fraction	30.9%	31.2%
NYHA Class II	67.4%	67.7%
NYHA Class III	31.7%	31.5%
NYHA Class IV	1%	0.8%
eGFR <60 (mL/min/1.73m^2)	40.7%	40.6%

NEJM. 2019;381:1995

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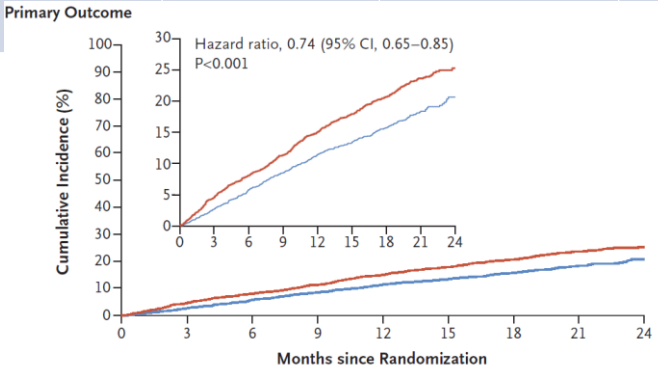
DAPA-HF Primary Endpoint

	Placebo (n=2371)	Dapagliflozin (n=2373)	Hazard Ratio (95% CI)	p-value
Composite of worsening HF or death from CV cause	502	386	0.74 (0.65-085)	p<0.001



NEJM. Figure 2A. 2019;381:1995

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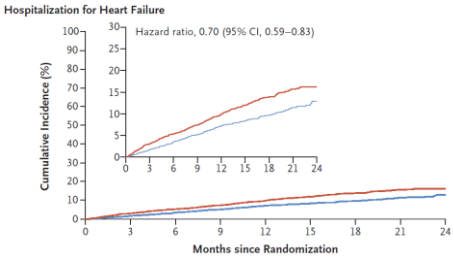
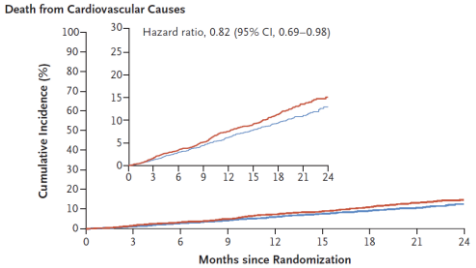
DAPA-HF Other Endpoints

	Placebo (n=2371)	Dapagliflozin (n=2373)	Hazard Ratio (95% CI)	p-value
Hospitalization for HF or death from CV cause	20.9%	16.1%	0.75 (0.65-0.85)	p<0.001
Hospitalization of Heart Failure	13.4%	9.7%	0.70 (0.59-0.83)	
Death from CV Cause	11.5%	9.6%	0.82 (0.69-0.98)	





NEJM. Figure 2B and 2C. 2019;381:1995

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EMPEROR-Reduced


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

EMPEROR-Reduced Design

Drug	• Empagliflozin vs. placebo
Design	• 3,730 patients • 520 sites • 20 countries
Primary Endpoint	• Composite of CV death or hospitalization for HF
Duration	• 16 months
Population	• Age ≥ 18 with HF (NYHA Class II, III, or IV) with a left ventricular ejection fraction of 40% or less
Published	• 2020

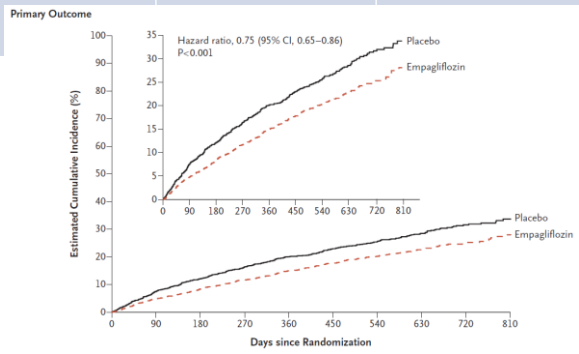
EMPEROR-Reduced Baseline Characteristics

	Placebo (n=1867)	Empagliflozin (n=1863)
Mean age	66.5	67.2
Mean BMI	27.8	28
Diabetes	49.8%	49.8%
Previous Hospitalization for HF	30.7%	31%
Systolic Blood Pressure	121.4	122.6
Left Ventricular Ejection Fraction	27.2%	27.7%
NYHA Class II	75%	75.1%
NYHA Class III	24.4%	24.4%
NYHA Class IV	0.6%	0.5%
eGFR <60 (mL/min/1.73m^2)	48.6%	48%

NEJM. 2020;383:1413

EMPEROR-Reduced Primary Endpoint

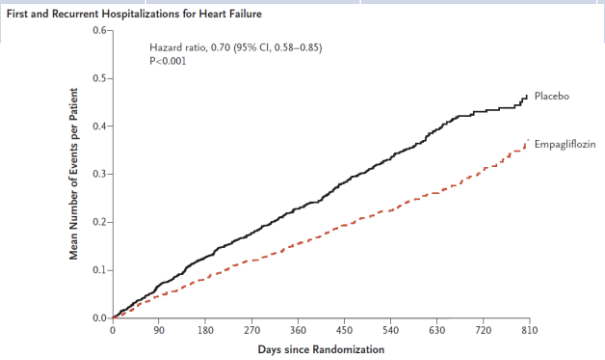
	Placebo (n=1867)	Empagliflozin (n=1863)	Hazard Ratio (95% CI)	p-value
Composite hospitalization for HF or CV death	24.7%	19.4%	0.75 (0.65-0.86)	p<0.001



NEJM. 2020;383:1413

EMPEROR-Reduced Secondary Endpoint

	Placebo (n=1867)	Empagliflozin (n=1863)	Hazard Ratio (95% CI)	p-value
First and Recurrent hospitalization for HF	553	388	0.70 (0.58-0.85)	p<0.001



NEJM. 2020;383:1413

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DAPA-CKD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

NEJM. 2020;383:1436

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DAPA-CKD Design

Drug	• Dapagliflozin vs. placebo
Design	• 4,304 patients • 386 sites • 21 countries
Primary Endpoint	• First occurrence of a decline in 50% in eGFR, onset of end-stage renal disease, or death from renal or CV causes
Duration	• 2.4 years
Population	• Adults with or without type 2 diabetes with eGFR 25-75 and urinary albumin-to-creatinine ratio of 200 - 5000
Published	• 2020

NEJM. 2020;383:1436

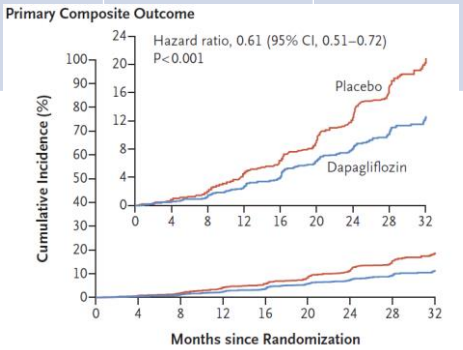
DAPA-CKD Baseline Characteristics

	Placebo (n=2152)	Dapagliflozin (n=2152)
Mean age	61.9	61.8
Mean BMI	29.6	29.4
Diabetes	67.4%	67.6%
HF	10.8%	10.9%
Systolic Blood Pressure	137.4	136.7
Diastolic Blood Pressure	77.5	77.5
eGFR (mL/min/1.73m^2)	43.2	43

NEJM. 2020;383:1436

DAPA-CKD Primary Endpoint

	Placebo (n=2152)	Dapagliflozin (n=2152)	Hazard Ratio (95% CI)	p-value
First occurrence of a decline in 50% in eGFR, onset of end-stage renal disease, or death from renal or CV causes	14.5%	9.2%	0.61 (0.51-0.72)	p<0.001



NEJM. 2020;383:1436

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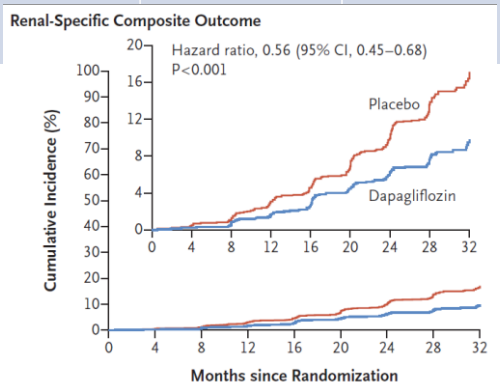
DAPA-CKD Secondary Endpoint

	Placebo (n=2152)	Dapagliflozin (n=2152)	Hazard Ratio (95% CI)	p-value
Composite of decline in eGFR ≥50%, end-stage kidney disease, or death from renal causes	11.3%	6.6%	0.56 (0.45-0.68)	p<0.001



NEJM. 2020;383:1413

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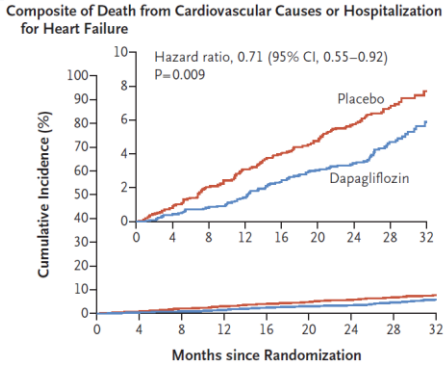
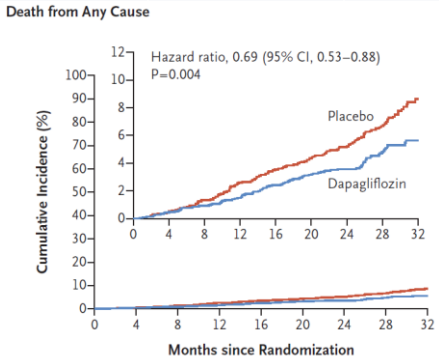
DAPA-CKD CV Outcomes

	Placebo (n=2152)	Dapagliflozin (n=2152)	Hazard Ratio (95% CI)	p-value
Composite of death from CV Cause or hospitalization for HF	6.8%	4.6%	0.71 (0.55-0.92)	p=0.009
Death from any cause	6.8%	4.7%	0.69 (0.53-0.88)	p=0.004





NEJM. 2020;383:1413

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GLP1 Comparison

	Trulicity (dulaglutide)	Byetta/Bydureon (exenatide)	Victoza (liraglutide)	Adlyxin (lixisenatide)	Ozempic/Rybelsus (semaglutide)
Dose	0.75-4.5 mg SubQ once **weekly**	5-10 mcg SubQ **twice daily**; 2 mg SubQ once **weekly**	0.6-1.8 mg SubQ **once daily**	10-20 mcg SubQ **once daily**	0.25-1 mg SubQ **once weekly** 3-14mg PO **Once daily**
Renal/ Hepatic Dosing	None	CrCl <30 NR	None	eGFR <15 NR	None
A/E	Nausea	Nausea	Tachycardia	Antibody development	Increased serum lipase; Nausea (*highest incidence*)
FDA Labeling Additions	Risk reduction of major CV events with established CVD or CV risk factors		Risk reduction of major CV events with established CVD (Saxenda = weight loss)		Risk reduction of major CV events with established CVD (ozempic only) (Wegovy = weight loss)
SoonerCare Tier	Tier 2	Tier 2 (Byetta) PA (Bydureon)	Tier 2	PA	Tier 3 (Ozempic) PA (Rybelsus)

LexiComp; NR: Not Recommended; PA: Prior Authorization; PO: By mouth

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GLP1 Combination Products

	Soliqua (insulin glargine + lixisenatide)	Xultophy (insulin degludec + liraglutide)
Class	Basal insulin + GLP-1	Basal insulin + GLP-1
Starting Dose	Initial:15 units (15 units glargine, 5 mcg lixisenatide) once daily Switch from 30-60 units basal: 30 units (30 units glargine, 10 mcg lixisenatide) Max: 60 units (60 units of glargine, 20 mcg lixisenatide)	Initial: 10 units (10 units of degludec, 0.36 mg liraglutide) once daily Switch: 16 units (16 units of degludec, 0.58 mg liraglutide) Max: 50 units (50 units degludec, 1.8 mg liraglutide)
Price	$61.86 per mL SoonerCare Tier 3 (must demonstrate why Lantus + alternative GLP1 cannot be used)	$91.63 per mL SoonerCare Tier 3 (must demonstrate why Lantus + Victoza cannot be used)

Lexi-Comp

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SGLT2 Comparison

	Invokana (Canagliflozin)	Jardiance (Empagliflozin)	Farxiga (Dapagliflozin)	Steglatro (Ertugliflozin)
Dose	100-300 mg once daily	10-25 mg once daily; HF or CKD 10 mg once daily	5-10 mg once daily DM; 10mg HF; DKD/CKD 10 mg	5-15 mg once daily
Renal/ Hepatic Adjustments	eGFR 30- <60 max dose 100 mg; eGFR <30 UA >300 continue 100 mg; UA ≤300 not recommended; NR in severe hepatic impairment	eGFR <30 NR for new initiation	eGFR <45 NR for DM only; eGFR <25 no new initiation for HF or DKD/CKD	eGFR 30- <60 NR; eGFR <30 C/I; NR in severe hepatic impairment
A/E	Lower limb amputations; ketoacidosis, bone fractures; necrotizing fasciitis; acute renal injury; urinary tract infections, genitourinary fungal infections; electrolyte abnormalities			
FDA Labeling Additions	Risk reduction of CV events in established CVD, risk reduction in end-stage renal disease, doubling of serum creatinine, CV death, and hospitalization for HF with nepropathy and UA >300	Risk reduction of CV events with established CVD; HF*	Risk reduction for hospitalization for HF in established CVD; HF; CKD	
SoonerCare Tier	Tier 3	Tier 2	Tier 2	Tier 3

LexiComp; UA = urinary albumin excretion; NR: Not recommended

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SGLT2 Combination Products

Drug	Strengths Available	SoonerCare Tier
Canagliflozin + Metformin (Invokamet and Invokamet XR)	50/500, 50/1000, 150/500, 150/1000 mg XR: 50/500, 50/1000, 150/500, 150/1000 mg	Tier 3
Dapagliflozin + Metformin (Xigduo XR)	2.5/1000, 5/500, 5/1000, 10/500, 10/1000 mg	Tier 2
Empagliflozin + Linigliptin (Glyxambi)	10/5, 25/5 mg	Tier 2
Empagliflozin + Metformin (Synjardy and Synjardy XR)	5/500, 5/1000, 12.5/500, 12.5/1000 mg XR: 5/1000, 10/1000, 12.5/1000, 25/1000 mg	Tier 2
Dapagliflozin + Saxagliptin (Qtern)	5/5, 10/5 mg	Tier 3
Ertugliflozin + Metformin (Segluromet)	2.5/500, 2.5/1000, 7.5/500, 7.5/1000 mg	Tier 3
Ertugliflozin + Sitagliptin (Steglujan)	5/100, 15/100 mg	Tier 3
Empagliflozin + Linagliptin + Metformin (Trijardy XR)	10/5/1000, 25/5/1000, 5/2.5/1000, 12.5/2.5/1000 mg	PA

LexiComp

FDA Labeling Updates

Sodium-glucose Cotransporter-2 Inhibitors (SGLT-2)

- Jardiance (empagliflozin): CVD, HF*
- Invokana (canagliflozin): CVD, CKD, HF/CKD
- Farxiga (dapagliflozin): CVD, HF, CKD

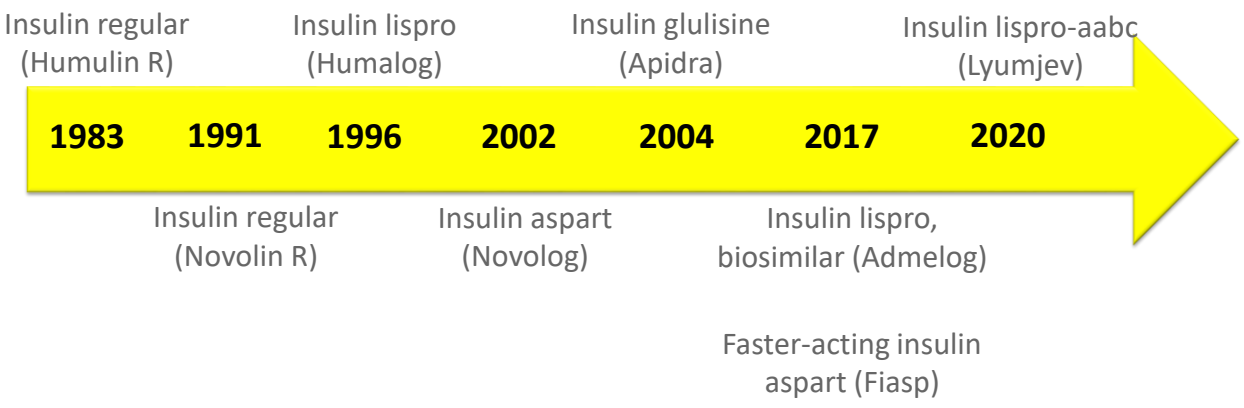
Glucagon-like Peptide 1 Agonists (GLP-1)

- Victoza (liraglutide): CVD
- Trulicity (dulaglutide): CVD
- Ozempic (semaglutide): CVD

CVD: Cardiovascular disease; HF: Heart failure; HF*: off-label indication; CKD: chronic kidney disease, Diabetes Care; 2021;44(1); FDA Package Labeling

Insulin

Historic Timeline of Rapid Acting Insulin



Wong EY, Kroon L. Ultra-rapid-acting insulins: how fast is really needed? Clinical Diabetes. Epub ahead of print. https://doi.org/10.2337/cd20-0119, Figure 1

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New Rapid Acting

Drug(s)	• Lyumjev (insulin lispro-aabc)
Dose	• Administer at the start of a meal or within 20 minutes after starting
Mechanism	• Contains treprostinil, a prostacyclin analogue, that enhances the absorption through increased local vasodilation and citrate, which speeds up absorption by enhancing vascular permeability
Product Formulations and Cost	• 100 unit/mL vial (~$300) • 100 unit/mL and 200 unit/mL KwikPens (~$126-252/pen)
Pharmacokinetics	• Onset: ~15-32 minutes • Peak Effect: ~2 to 2.9 hours • Duration: ~4.6-7.3 hours
FDA Approval	• June 2020

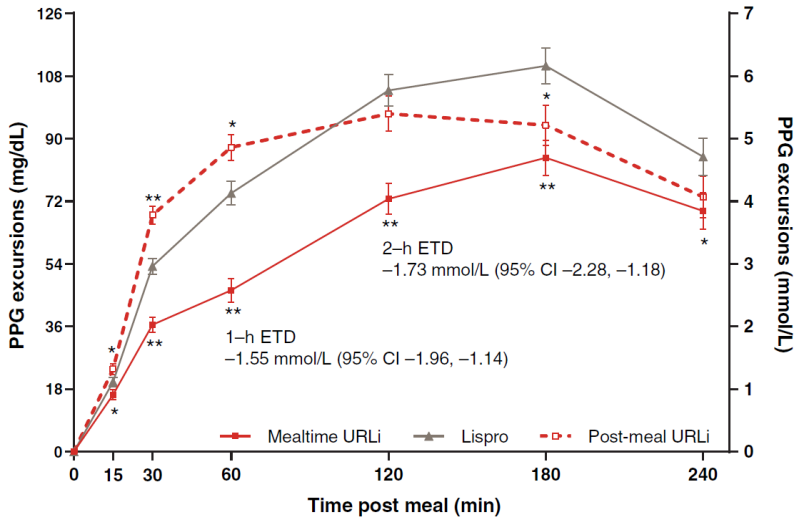
FDA Package Labeling

PRONTO-T1D

Participants	• Adults with type 1 diabetes using insulin for ≥1 year and A1c 7-9.5%, BMI ≤ 35 kg/m2 treated with rapid-acting insulin for ≥90 days and basal insulin for ≥30 days
Study Design	• 26-week trial (with 8-week lead in to optimize basal insulin glargine or degludec) • Participants randomized in a 4:4:3 to one of three groups 1) double-blind mealtime ultra rapid lispro (URLi) (n=451), 2) lispro (n=442), or 3) open-label post meal URLi (n=329)
Primary Endpoint	• Change in A1c
Outcomes	• URLI was noninferior to lispro in mealtime and post meal • Mealtime URLi was superior to lispro in reducing 1 and 2-hour post prandial excursions starting at 15 minutes ($p<0.001$)

Klaff L, et al. Diabetes Obes Metab. 2020;22:1799

PRONTO-T1D



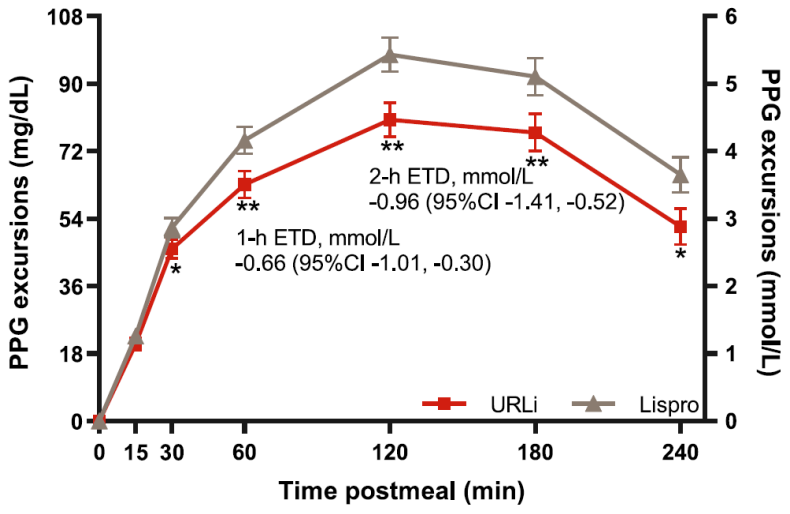
Klaff L, et al. Figure 2. Diabetes Obes Metab. 2020;22:1799

PRONTO-T2D

Participants	• Adults with type 2 diabetes using insulin for ≥1 year and A1c 7-10% treated with basal insulin in combination with one or more prandial insulin injections for ≥90 days and treated with up to 3 oral agents with stable dosing for ≥90 days
Study Design	• 26-week trial (with 8-week lead in to optimize basal insulin glargine or degludec) • Participants randomized in 1:1 to one of two groups 1) double-blind ultra rapid lispro (URLi) (n=336) or 2) lispro (n=337)
Primary Endpoint	• Change in A1c
Outcomes	• URLI was noninferior to lispro • Mealtime URLi was superior to lispro for 1 and 2-hour post prandial control starting at 30 minutes (p<0.001)

Blevins T, et al. Diabetes Care. 2020;43:2991

PRONTO-T2D



Blevins T, et al. Figure 2. Diabetes Care. 2020;43:2991

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Biosimilar Insulin

Insulin glargine-yfgn
- Brand name Semglee
- FDA Approved June 2020

PK
- No pronounced peak effect
- Duration of action ~24 hours
- Time to peak ~12 hours

Biosimilar
- FDA approved July 28, 2021
- First biosimilar interchangeable insulin
- Reference product insulin glargine (Lantus)

Cost
- ~$110/vial
- ~$33/pen

www.fda.gov

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Other Medication Updates

Statin Recommendations

Primary Prevention

- Age 40-75 without ASCVD moderate intensity
- Age 20-39 with ASCVD risk factors, consider statin
- High risk with multiple ASCVD risk factors or aged 50-70, use high intensity
- 10-year ASCVD risk 20% or higher, high intensity and consider ezetimibe to help reduce LDL by ≥50%

Secondary Prevention

- All ages and ASCVD high intensity
- Very high risk, if LDL ≥70 mg/dL on maximally tolerate statin, consider adding ezetimibe or PCSK9 inhibitor
- Age >75 and already on statin and tolerating, can continue

ASCVD:

- Acute coronary syndrome
- History of MI
- Stable or unstable angina
- Stroke
- Transient ischemic attack
- Peripheral artery disease

ASCVD High Risk:

- History of multiple major ASCVD events or
- 1 major ASCVD event and multiple high-risk conditions

Diabetes Specific ASCVD Risk Factors:

- Long duration of diabetes (≥10 years for type 2 and ≥20 years for type 1)
- Albuminuria ≥30 mcg
- eGFR <60
- Retinopathy
- Neuropathy
- ABI <0.9

ASCVD: atherosclerotic cardiovascular disease, Diabetes Care; 2021;44(1), 2018 AHA/ACC Guideline on the Management of Blood Cholesterol

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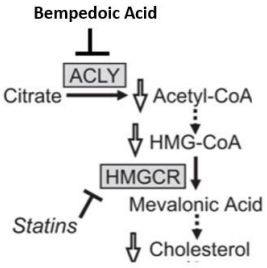
New Cholesterol Option

Drug(s)	• Nexletol (bempedoic acid)
Class and Mechanism	• Adenosine triphosphate-citrate lyase (ACL) inhibitor
Indication	• Treatment of established atherosclerotic cardiovascular disease as an adjunct to diet and maximally tolerated statin therapy in adult patients who require additional LDL lowering • Treatment of heterozygous familial hypercholesterolemia
Formulation	• 180mg once daily or combination with ezetimibe 180mg/10mg
FDA Approval	• February 2020



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FDA Package Labeling

Nexletol (bempedoic acid) Considerations

Adverse Effects	• Gout, hyperuricemia, afib, abdominal pain, increased liver enzymes, increased serum creatine kinase
Monitor	• Lipid levels, signs/symptoms of hyperuricemia
Caution	• Tendon rupture within weeks to months of treatment initiation; avoid concomitant use with simvastatin >20mg and pravastatin >40mg
Price	• $13.99/tablet • https://www.nexletolhcp.com/access $10 copay card

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FDA Package Labeling; Lexi-Comp

Nexletol (bempedoic acid) Clinical Trials

Evidence for Approval	2 randomized, double-blind, placebo-controlled, multicenter 52-week studies enrolling 2330 participants in study 1 and 770 participants in study 2 (CLEAR Wisdom).
Outcomes	In Study 1, the mean baseline LDL was 103mg/dL and the primary endpoint was statistically significant for the percent change from baseline to week 12 in LDL, -18% or 19.2mg/dL, p<0.001. In Study 2, the mean baseline LDL was 120.4mg/dL, and the primary endpoint was statistically significant for the percent change from baseline to week 12 in LDL, -17%, p<0.001. With the exception of gout, the adverse effects were not significantly different compared to placebo.
Place in Therapy	Provides a non-statin alternative for LDL lowering for patients that cannot tolerate statins due to muscle pain. An ongoing trial (CLEAR CV Outcomes) is assessing the impact on event risk reduction

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Nexletol FDA package insert. Ray K. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med. 2019;380:1022. Goldberg AC. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease. JAMA. 2019;322:1780.

Glucagon Formulations

Drug	• Gvoke for the treatment of severe hypoglycemia in patients ≥2 years of age
Dose	• Prefilled syringe/auto-injector 0.5mg/0.1mL for pediatric patients <45kg and 1mg/0.2mL for adult patients
Price	• $336/device (auto-injector or prefilled syringe)

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FDA Package Labeling

On the Horizon

Tirzepatide: Dual GIP/GLP-1 Agonist

SURPASS-1

- 478 adults with type 2 diabetes and average diabetes duration of 4.7 years with average A1c 7.94%, randomized to 5, 10, or 15mg vs placebo for 40 weeks
- Average A1c improvements ranged from 1.69-1.75%, 31-52% of participants achieved A1c < 5.7%
- Average weight loss ranged from 6.3-7.8kg, 13-27% of participants achieved a 15% weight loss

SURPASS-2

- 1,879 adults with type 2 diabetes uncontrolled on metformin with average A1c 8.28% randomized to 5, 10, or 15mg vs semaglutide 1mg for 40 weeks
- Average A1c improvements ranged from 2.01-2.3% and was noninferior and superior to semaglutide, 29-51% of participants achieved A1c <5.7%
- Average weight loss ranged from 1.9-5.5kg, 40% of participants achieved a 15% weight loss

SURPASS-3

- 1,444 participants with type 2 diabetes uncontrolled with metformin ± SGLT2 with average A1c 8.17%, average duration of 8.4 years randomized to 5, 10, or 15mg or basal insulin (degludec) for 52 weeks
- Average A1c improvements ranged from 1.93-2.37%, 82-93% of participants achieved A1c <7%
- Weight loss ranged from 7.5-12.9kg

SURPASS-5

- 475 adults with type 2 diabetes uncontrolled with basal insulin (glargine) ± metformin randomized to 5, 10, or 15mg or placebo average A1c 8.31%, average duration 13.3 years for 40 weeks
- Average A1c improvements ranged from 2.2-2.9%, 93-97% participants achieved A1c <7%
- Average weight loss ranged from 6.2-10.9kg

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SURPASS Data www.healio.com; Rosenstock J, et al. SURPASS-1 Lancet 2021; Frias JP, et al. SURPASS-2 N Engl J Med 2021

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Medication Access

SoonerCare Traditional Coverage

- Claims for preferred testing supplies and CGMs will not count against monthly script limit
- CGMs require a prior authorization
- One glucometer kit per year (Freestyle, One Touch, Precision)
- One bottle of control solution per year
- 200 insulin syringes/month
- 200 lancets/month
- 100 ketone strips/month
- 200 pen needles/month

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https://oklahoma.gov/ohca/individuals/mysoonercare/soonercare-benefits/prescriptions-drugs.html

SoonerCare CGM Eligibility

- Finger stick blood sugars ≥ 4/day
- On insulin pump or multiple daily insulin injections ≥ 3/day
- Insulin treatment requires frequent adjustment based on glucose results
- Hypoglycemic episode within previous 6 months of two or more level 2 (<54 mg/dL) or one level 3 (severe)
- Health care visit with treating provider within 6 months of start

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https://oklahoma.gov/ohca/individuals/mysoonercare/soonercare-benefits/prescriptions-drugs.html

SoonerCare Prior Authorization Clues

Anti-Diabetic Medications Tier-2 Approval Criteria:

- A trial of 1 Tier-1 medication (must include a trial of metformin titrated up to maximum dose), or a patient-specific, clinically significant reason why a Tier-1 medication is not appropriate.
- For initiation with dual or triple therapy, additional Tier-2 medications may be approved based on current American Association of Clinical Endocrinologists (AACE) or American Diabetes Association (ADA) guidelines.
- A clinical exception will apply for medications with a unique FDA approved indication not covered by all Tier-1 medications. Tier structure rules for unique FDA approved indications will apply.

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SoonerCare Coverage

DIABETIC MEDICATIONS

TIER 1	TIER 2	TIER 3	SPECIAL PA
BIAGUANIDES • METFORMIN (GLUCOPHAGE®) • METFORMIN SR (GLUCOPHAGE XR®) • METFORMIN-GLYBURIDE (GLUCOVANCE®) • METFORMIN-GLIPIZIDE (METAGLIP®) SULFONYLUREAS • CHLORPROPAMIDE • GLIMEPIRIDE (AMARYL®) • GLYBURIDE (DIABETA®) • GLYBURIDE MICRONIZED (MICRONASE®) • GLIPIZIDE (GLUCOTROL®) • GLIPIZIDE SR (GLUCOTROL XL®) • TOLBUTAMIDE ALPHA-GLUCOSIDASE INHIBITORS • ACARBOSE (PRECOSE®) GLINIDES • REPAGLINIDE (PRANDIN®) THIAZOLIDINEDIONES • PIOGLITAZONE (ACTOS®)	DDP-4 INHIBITORS • LINAGLIPTIN (TRADJENTA®) • LINAGLIPTIN-METFORMIN (JENTADUETOTM) • SITAGLIPTIN (JANUVIA®) • SITAGLIPTIN-METFORMIN (JANUMET®) • SITAGLIPTIN-METFORMIN ER (JANUMET XR®) SGLT2 INHIBITOR • DAPAGLIFLOZIN (FARXIGA®) • DAPAGLIFLOZIN-METFORMIN (XIGDUO™ XR) • EMPAGLIFLOZIN (JARDIANCE® • EMPAGLIFLOZIN/METFORMIN (SYNJARDY®) • EMPAGLIFLOZIN/METFORMIN ER (SYNJARDY® XR) GLINIDES • NATEGLINIDE (STARLIX®) • REPAGLINIDE-METFORMIN (PRANDIMET®) GLP-1 AGONISTS • DULAGLUTIDE	DDP-4 INHIBITORS • ALOGLIPTIN-METFORMIN (KAZANO®) • ALOGLIPTIN (NESINA®) • ALOGLIPTIN-PIOGLITAZONE (OSENI®) • SAXAGLIPTIN (ONGLYZA®) • SAXAGLIPTIN-METFORMIN (KOMBIGLYZE®, KOMBIGLYZE®XR) THIAZOLIDINEDIONES • ROSIGLITAZONE (AVANDIA®) • PIOGLITAZONE-METFORMIN (ACTOPLUS MET®, ACTOPLUS MET XR®) • PIOGLITAZONE-GLIMEPIRIDE (DUETACT®) • ROSIGLITAZONE-METFORMIN (AVANDAMET®) • ROSIGLITAZONE-GLIMEPIRIDE (AVANDARYL®) ALPHA-GLUCOSIDASE INHIBITORS • MIGLITOL (GLYSET®) SGLT2 INHIBITOR	BIAGUANIDES • METFORMIN SOLUTION (RIOMET®) • METFORMIN LONG ACTING (FORTAMET®, GLUMETZA®) • METFORMIN ER SUSPENSION (RIOMET ER™) AMYLINOMIMETIC • PRAMLINTIDE (SYMLIN®) DDP-4 INHIBITORS • LINAGLIPTIN-METFORMIN (JENTADUETO® XR)* SGLT2 INHIBITOR • CANAGLIFLOZIN/METFORMIN (INVOKAMETTM XR) GLP-1 AGONISTS • EXENATIDE ER (BYDUREON® BCISE™) • LIXISENATIDE (ADLYXIN®) • SEMAGLUTIDE (RYBELSUS®) SGLT-2/DPP-4 INHIBITOR/BIGUANIDES

https://oklahoma.gov/ohca.html

• MIGLITOL (GLYSET®)
SGLT2 INHIBITOR
• CANAGLIFLOZIN (INVOKANA®)
• CANAGLIFLOZIN/METFORMIN (INVOKAMETTM)
• ERTUGLIGLOZIN (STEGLATRO™)
• ERTUGLIFLOZIN/METFORMIN (SEGLUROMET™)
DOPAMINE AGONIST
• BROMOCRIPTINE (CYCLOSET®)
SGLT-2/DPP-4 INHIBITOR
• DAPAGLIFLOZIN/SAXAGLIPTIN (QTERN®)
• ERTUGLIFLOZIN/SITAGLIPTIN (STEGLUJAN™)
GLP-1 AGONISTS
• SEMAGLUTIDE (OZEMPIC®)
GLP-1 AGONISTS/INSULIN
• INSULIN DEGLUDEC/LIRAGLUTIDE (XULTOPHY® 100/3.6)
• INSULIN GLARGINE/LIXISENATIDE (SOLIQUA™ 100/33)
SGLT-2/DPP-4 INHIBITOR/BIGUANIDES
• DAPAGLIFLOZIN/SAXAGLIPTIN/METFORMIN ER (QTERNMET® XR)
• EMPAGLIFLOZIN/LINAGLIPTIN/METFORMIN ER (TRIJARDY™ XR)

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SoonerCare Insulin Prior Authorizations

Basaglar® (Insulin Glargine) Approval Criteria:

- An FDA approved diagnosis of diabetes mellitus; AND
- A patient-specific, clinically significant reason why the member cannot use Lantus® (insulin glargine) or Levemir® (insulin detemir).

Fiasp® (Insulin Aspart) Approval Criteria:

- An FDA approved diagnosis of diabetes mellitus; AND
- A patient-specific, clinically significant reason why the member cannot use NovoLog® (insulin aspart) must be provided.

Humulin® R U-500 Vials (Insulin Human 500 Units/mL) Approval Criteria:

- An FDA approved diagnosis of diabetes mellitus; AND
- A patient-specific, clinically significant reason why the member cannot use the Humulin® R U-500 KwikPen® (insulin human 500units/mL), which is available without prior authorization, must be provided.

Humalog® KwikPen® U-200 (Insulin Lispro 200 Units/mL) and Lyumjev™ (Insulin Lispro-aabc 200 Units/mL) Approval Criteria:

- An FDA approved diagnosis of diabetes mellitus; and
- Authorization of the 200 units/mL strength requires a patient-specific, clinically significant reason why the member cannot use the 100 units/mL strength (the brand formulation of Humalog® U-100 is preferred).

Toujeo® (Insulin Glargine) Approval Criteria:

- An FDA approved diagnosis of diabetes mellitus; AND
- A patient-specific, clinically significant reason why member cannot use Lantus® (insulin glargine), and member must be using a minimum of 100 units of Lantus® (insulin glargine) per day.

Tresiba® (Insulin Degludec) Approval Criteria:

- An FDA approved diagnosis of diabetes mellitus; AND
- A patient-specific, clinically significant reason why the member cannot use Lantus® (insulin glargine) or Levemir® (insulin detemir).

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WalMart $4 Program

Diabetes

	$4 30 Day Qty	$10 90 Day Qty
GLIMEPIRIDE 1MG, 2MG, 4MG	30	90
GLIPIZIDE 5MG, 10MG	60	180
METFORMIN 500MG, 850MG, 1000MG	60	180
METFORMIN ER 500MG TAB	120	360
METFORMIN ER 750MG TAB	60	180
	$9 30 Day Qty	**$24** 90 Day Qty
GLIPIZIDE ER 2.5MG, 5MG, 10MG	30	90
GLYBURIDE/METFORMIN 2.5/500MG, 5/500MG	60	180
	$15 30 Day Qty	**$38** 90 Day Qty
PIOGLITAZONE 15MG, 30MG, 45MG	30	90

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OU Campus Pharmacies

USE/GENERIC NAME (BRAND)	STRENGTH	#100	#200	#300	#400
ANTI-DIABETIC					
Glipizide (Glucotrol)	5mg	$10.00	$18.24	$26.92	$34.00
Glipizide (Glucotrol)	10mg	$10.00	$19.00	$27.00	$34.00
Metformin (Glucophage)	500mg	$10.00	$10.00	$14.54	$19.08
Metformin (Glucophage)	850mg	$10.00	$17.82	$26.29	$34.00
Metformin (Glucophage)	1000mg	$10.00	$17.06	$25.14	$33.22
Metformin ER (Glucophage XR)	500mg	$10.00	$19.00	$27.00	$34.00

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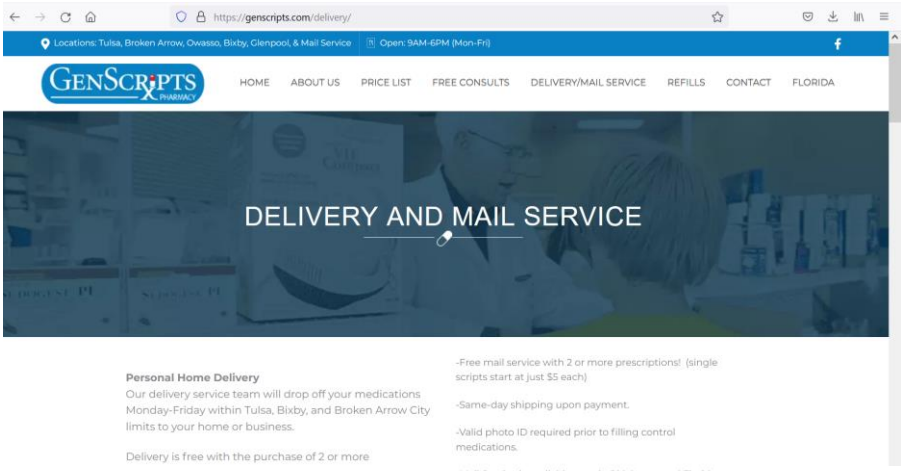
GenScripts Pharmacy



Example Pricing

- Glipizide 5mg: Qty 100 = $10.00; Qty 200 = $19.00; Qty 300 = $27.00; Qty 400 = $34.00

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Prescription Assistance Programs

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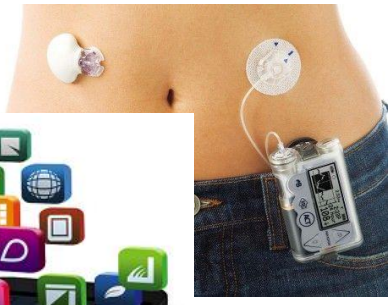
In Summary……



- Armamentarium is growing
- Patient-centered

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Pharmacology Updates

Katherine O'Neal, PharmD, MBA, BCACP, CDCES, BC-ADM, CLS, AEC, FADCES
Associate Professor OU College of Pharmacy
Katherine-oneal@ouhsc.edu

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Diabetes Care Summit

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ADCES Association of Diabetes Care & Education Specialists

The Role of Mental Health in Diabetes Care

Kathryn Jeter, PhD
Department of Pediatrics

OU Health | Harold Hamm Diabetes Center

Outline

- Common Psychological Disorders & Impact on Diabetes Care
- Distinguishing Diabetes Distress and Depression in Clinical Practice
- Mental Health Screening and Treatment Recommendations

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Common Psychological Concerns Among People with Diabetes

- **Depression**
- **Anxiety**
- **Diabetes Distress**

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51.5 million

Estimated number of U.S. adults aged 18 or older affected by any mental health disorder in 2019.

Prevalence of Depression & Diabetes

- **Increased risk of depression for youth & adults with T1D & T2D**
  Depressive symptoms affect 1 in 4 adults with diabetes.
  Rates of clinical depression nearly 2-3x higher than general population.

- **Greater risk for depression among specific groups:**
  Women, those with longer diabetes duration, higher BMI, diabetes-related complications, and lower levels of education.

- **Depression appears more persistent in people with diabetes.**
  Depressive episodes are longer in duration, higher chance of recurrence; prognosis is worse than when each disease occurs separately.

Anderson, Freedland, Clouse, & Lustman, 2001; Kreider, 2017; Hermanns et al., 2013; Peyrot and Rubin, 1999; Ludman et al., 2004; Egede et al., 2005.

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Depression Impacts Diabetes Self-Care

Table 1—*Meta-analysis results aggregated by type of self-care*

	n	*z* (*P*)	Weighted *r*	95% CI	Heterogeneity *Q* (df) and I^2	Fail-safe *n* (*r* = 0.05)
Overall analysis	47	9.81 (<0.001)	0.21	0.17–0.25	217.66 (46); $P < 0.001$; $I^2 = 78.87$	149
Appointment keeping	4	21.58 (<0.001)	0.31	0.29–0.34	1.79 (3); $P = 0.617$; $I^2 = 0.00$	22
Composite measures	18	9.66 (<0.001)	0.29	0.23–0.34	38.60 (17); $P = 0.002$; $I^2 = 55.96$	88
Diet	18	7.60 (<0.001)	0.18	0.13–0.22	33.67 (17); $P = 0.009$; $I^2 = 49.51$	37
Medication	18	5.15 (<0.001)	0.14	0.09–0.20	49.73 (16); $P < 0.001$; $I^2 = 65.82$	24
Exercise	13	7.89 (<0.001)	0.14	0.10–0.17	14.43 (12); $P = 0.274$; $I^2 = 16.86$	22
Glucose monitoring	15	3.50 (<0.001)	0.10	0.04–0.16	31.00 (14); $P = 0.006$; $I^2 = 54.82$	4
Foot care	2	0.88 (0.380)	0.07	−0.08 to 0.21	4.27 (1); $P = 0.039$; $I^2 = 76.59$	NA

Gonzalez et al., 2008.

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Impact of Depression & Diabetes

- **Increased risk of complications**
- **Increased risk of hospitalizations**
- **Increased risk of morbidity and mortality**
- **Higher medical expenditures**

Ciechanowski et al., 2000; Gary et al., 2000; Hanninen et al., 1999; de Groot, Anderson, Freedland, Clouse, & Lustman, 2001.

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Prevalence of Anxiety

- Adults with diabetes have a 20% increased prevalence of anxiety disorders compared to those without diabetes.
- Prevalence of anxiety is similar among T1D & T2D. Only PTSD significantly predicted later development of T2D.
- Risk for anxiety disorders is highest among women, younger individuals, those with longer diabetes duration, and those with additional medical conditions

Grigsby et al., 2002.

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Impact of Anxiety

- Worry about complications, frustration with imperfection, and fear of others' reactions may lead to avoidance of diabetes self-care behaviors.
- Fear of hypoglycemia may lead to intentional underdosing.
- Fear of needles/injections/blood can impact engagement in diabetes self-care behaviors.
- Fear of invasive self-care behaviors may impede site rotation and/or use of a new location for self-care tasks.

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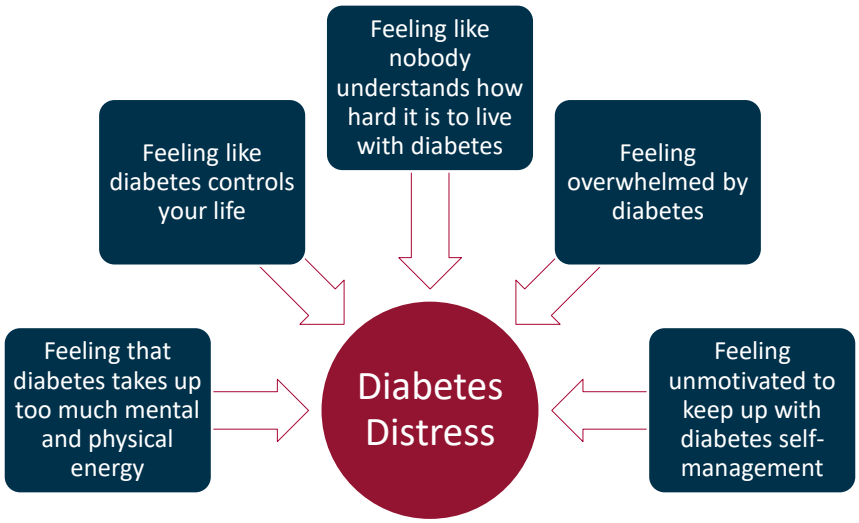
Diabetes Distress

refers specifically to the negative emotional experience resulting from the challenges of living with the demands and burden of diabetes.

Diabetes Distress



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Prevalence of Diabetes Distress

- Prevalence of diabetes distress ranges between 18-45% in T1D & T2D
- Almost 50% of people with diabetes experience diabetes distress over an 18-month period
- Approximately 1/3rd of adolescents with Type 1 diabetes
- Well-documented among partners of those with diabetes and parents of youth with diabetes

Perrin et al., 2017; Polonsky, Fisher, Hessler, & Johnson, 2016; Markowitz et al., 2012; Skinner, Joensen, & Parkin, 2020; Weissberg-Benchell & Antisdel-Lomaglio, 2011.

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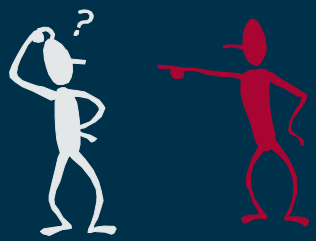
What causes diabetes distress?



Potential Causes of Diabetes Distress

- Acceptance of diabetes / Desire to be "normal"
- Self-judgment about diabetes care
- Feeling powerless
- Frustration with diabetes demands
- Competing demands / chaotic Schedules
- Self-consciousness
- Navigating insurance/ healthcare system
- Lack of knowledge about diabetes in community
- Difficulty communicating with medical team
- Difficulty getting supplies, medications, etc
- Excessive worry about long-term complications
- Poor confidence in ability to manage diabetes

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Potential Causes of Diabetes Distress

- Managing diabetes is 24/7/365.
- Feeling restricted with food choices
- Thoughts and feelings about blood sugars
- Loneliness, feeling "different"
- Negative interactions with family, friends, and medical team
- Cost of diabetes medications
- Lack of transportation
- Daily checks and insulin
- Carb counting
- Stigma
- Judgement from others
- Feelings of worry, shame, and self-judgement
- Family communication
- Intolerance of uncertainty
- Family conflict

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Major Depressive Disorder

What are the diagnostic criteria for MDD?

Major Depressive Disorder

- Depressed mood (includes irritable mood in youth)
- Loss of interest/pleasure
- Excessive sleepiness or insomnia
- Feelings of worthlessness or excessive guilt nearly every day
- Fatigue or loss of energy
- Psychomotor changes severe enough to be observable by others
- Diminished ability to think, concentrate, or make decisions
- Recurrent thoughts of death or suicide
- Significant unexplained weight loss, weight gain, or change in appetite (e.g., 5% of body weight within a month)

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Major Depressive Disorder

≥5 symptoms during the same two week period.
Symptoms must represent a change from previous functioning
Symptoms must be present most of the day, nearly every day.

Depressed mood and/or anhedonia must be present.
May be subjective or observed by others (e.g., appears tearful)
In youth, may present as irritable mood
Markedly diminished interest/pleasure in all or almost all activities

Exclude symptoms clearly attributable to another psychological or medical condition.

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Overlap between Major Depressive Disorder and Diabetes Distress

- Depressed mood (includes irritable mood in youth)
- Loss of interest/pleasure
- Excessive sleepiness or insomnia
- Feelings of worthlessness or excessive guilt nearly every day
- Fatigue or loss of energy
- Psychomotor changes severe enough to be observable by others
- Diminished ability to think, concentrate, or make decisions
- Recurrent thoughts of death or suicide
- Significant unexplained weight loss, weight gain, or change in appetite (e.g., 5% of body weight within a month)

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Estimated Prevalence Distribution

Distressed	20-30%	5-15%	Distressed & Depressed
Minimal Levels of Distress/Depression	50-70%	5-10%	Depressed

Skinner, Joensen, & Parkin, 2020. Kreider, 2017.

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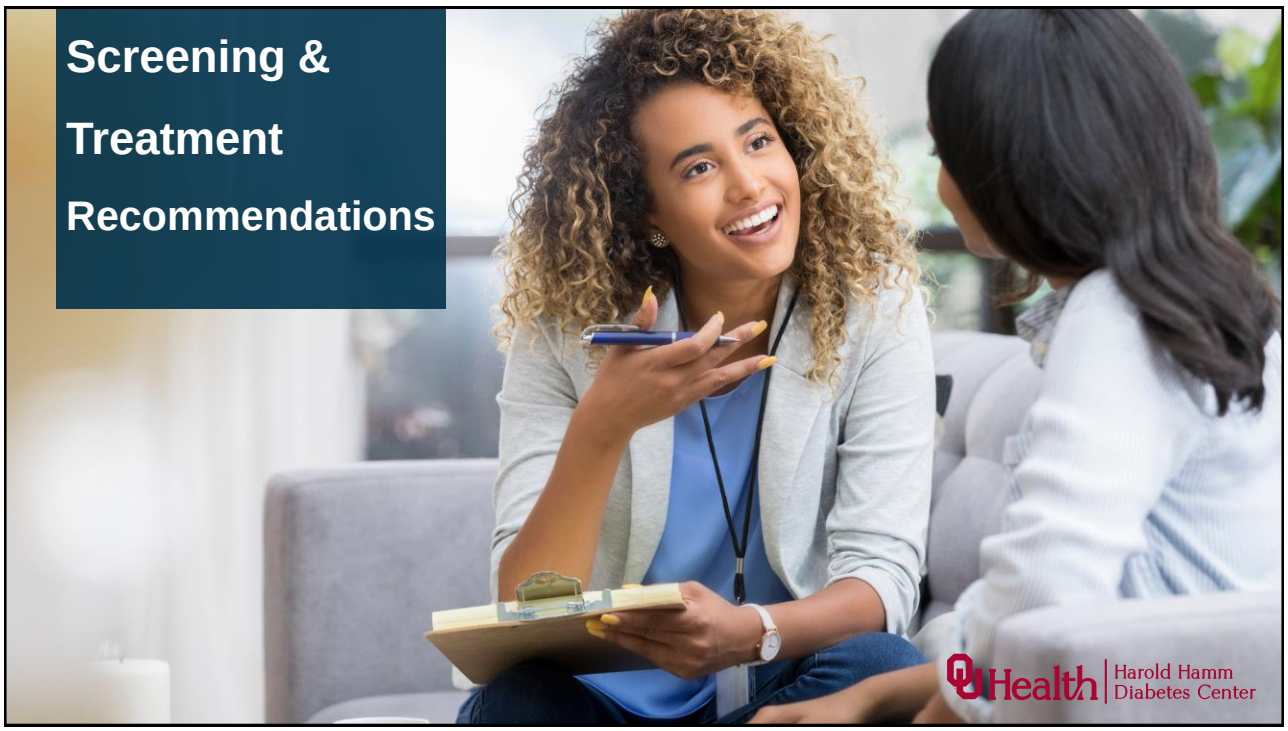
Screening & Treatment Recommendations



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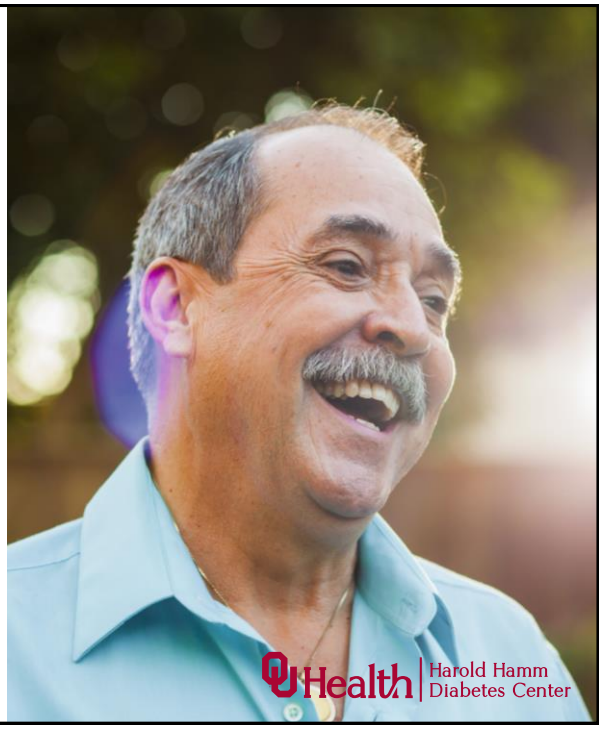
Screening Recommendations

Consider screening:

- Diabetes distress
- Depression
- Anxiety
- Disordered eating
- Cognitive capabilities

At the following time points:

- Initial visit
- Periodic intervals (e.g., annually)
- When there is a change in disease, treatment, or life circumstance



Screening Diabetes Distress

Measure	Description	Validated Population (s):
Problem Areas in Diabetes (PAID)	20-item measure of diabetes-specific distress (emotional distress, diabetes-specific burden)	Adults with T1D & T2D
Diabetes Distress Scale (DDS)	17-item measure of diabetes-specific distress in 4 domains: emotional burden, diabetes interpersonal distress, physician-related distress, and regimen-related distress	Adults with T1D & T2D
PAID – Peds Version	20-item measure of diabetes burden	Youth (ages 8–17 years) with T1D
PAID – Teen Version	26-item questionnaire measuring perceived burden of diabetes	Adolescents (ages 11–19 years) with diabetes
PAID – Parent Revised Version	18-item questionnaire assessing perceived parental burden of diabetes	Parents of children and adolescents (ages 8–18 years) with T1D

Young-Hyman, D., & Peyrot, M. (2012). *Psychosocial care for people with diabetes*. American Diabetes Association.

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Screening Depression

Measure	Description	Validated Population (s):
Patient Health Questionnaire-9	9-item measure of depressive symptoms (corresponding to criteria for major depressive disorder)	Adults and Youth age 12 and older
Beck Depression Inventory–II (BDI-II)	21-item questionnaire evaluating somatic and cognitive symptoms of depression	Adults
Child Depression Inventory-2 (CDI-2)	27-item measure assessing depressive symptoms using child and parent report	Youth (ages 7–17 years)
Geriatric Depression Scale (GDS)	15-item measure was developed to assess depression in older adults	Adults (ages 55–85 years)

Young-Hyman, D., & Peyrot, M. (2012). *Psychosocial care for people with diabetes*. American Diabetes Association.

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Screening Anxiety

Measure	Description	Validated Population (s):
Beck Anxiety Inventory (BAI)	21 items assessing self-reported anxiety	Adults
Hypoglycemia Fear Survey-II (HFS-II)	33 items assessing behavioral and worry dimensions of hypoglycemia in adults	Adults with type 1 diabetes
Children's Hypoglycemia Index (CHI)	27-item measure assessing depressive symptoms using child and parent report	Youth (ages 7–17 years)
Geriatric Depression Scale (GDS)	15-item measure was developed to assess depression in older adults	Adults (ages 55–85 years)

Young-Hyman & Peyrot, 2012. *Psychosocial care for people with diabetes*. American Diabetes Association.

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Treatment Recommendations

Diabetes Distress vs Depression/Anxiety

Addressing Diabetes Distress

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Emotion Focused Support

- **Person-Centered Communication Style**
  - Adopt a non-judgmental approach
  - Express empathy
  - Build partnership
  - Support autonomy

Fisher, Polonsky, & Hessler, 2019.

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Emotion Focused Support

- **Acknowledge and label feelings**
- **Summarize and Reflect**
- **Normalize**
- **Facilitate New Perspective**
- **Develop a Plan (if necessary)**
- **Follow-up**

Fisher, Polonsky, & Hessler, 2019.

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Referral to Mental Health Services

- No improvement in diabetes self-care following tailored education
- Self-identified difficulties making and maintaining behavioral changes
- Presence of mood symptoms or suspected psychological disorders that may impact diabetes care (e.g., mood disorders, serious mental illness, disorders that impact attention/cognitive functioning)
- Presence of symptoms or concern for disordered eating behaviors
- Diabetes-related family conflict
- Declining or impaired ability to perform diabetes self-care tasks

Young-Hyman, D., & Peyrot, M. (2012). *Psychosocial care for people with diabetes*. American Diabetes Association.

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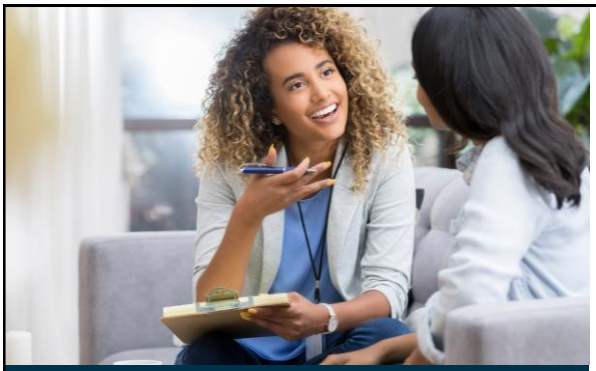

Treatments for Depression and Anxiety

Psychotropic medication

and/or

Evidence Based Psychotherapy

- Cognitive Behavior Therapy (CBT)
- Interpersonal Therapy (IPT)
- Acceptance and Commitment Therapy (ACT)

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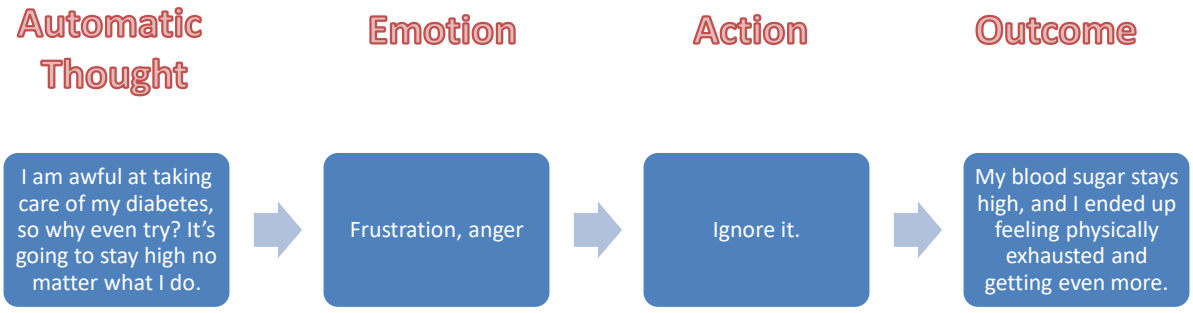
Cognitive Behavior Therapy



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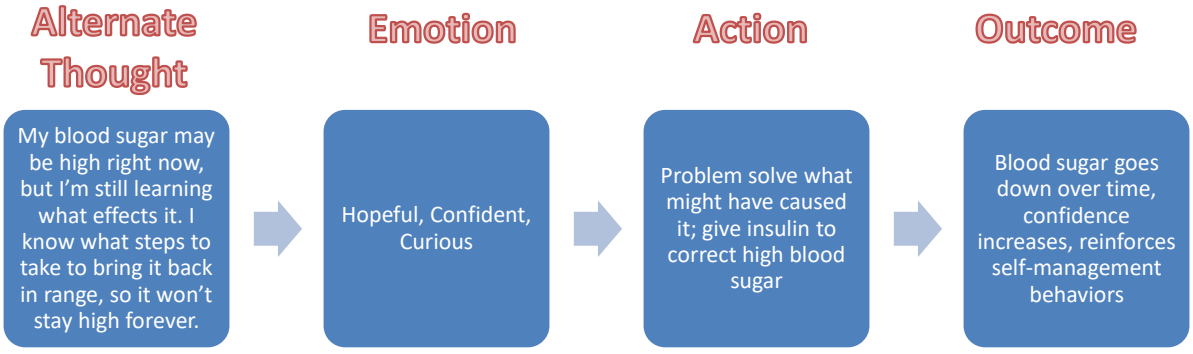
Cognitive Behavior Therapy



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How to Discuss Referrals for Ancillary Services:

- Summarize any concerns mentioned during your visit.
- Collaborate & develop a plan.
  - Ask about what patient thinks might help.
  - Offer additional possibilities
  - Incorporate patient's ideas
- Assess barriers to potential plans/referrals, and strategies to overcome barriers.
- Develop a follow-up plan.

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Contact Information

Mailing Address 1200 Children's Avenue
Oklahoma City, OK 73104

Email Address Kathryn-Jeter@ouhsc.edu

Phone Number (405) 271 4407

Diabetes Care Summit

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ADCES Association of Diabetes Care & Education Specialists

Overview of Nonalcoholic Fatty Liver Disease (NAFLD)
09/10/2021

Sirish K. Palle, MD
Assistant Professor
Department of Pediatrics
Oklahoma University Health Sciences Center

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Case

- 19 year old female referred from primary care due to abnormal ALT
- She is asymptomatic and not entirely sure why she is in the liver clinic
- Past medical history significant for:
  Diabetes with a hemoglobin A1C of 7.2% and states she is diet controlled
  Obesity, BMI 31 kg/m2
- No Family history of Liver disease
- No alcohol consumption
- PE: significant for central adiposity, no stigmata of advanced liver disease or cirrhosis

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Case

- Total Bilirubin 0.9
- Alanine aminotransferase(ALT): 90
- Aspartate aminotransferase (AST): 60
- Alkaline phosphatase: 100
- Viral Hepatitis serologies: Immune to hepatitis A and B, negative for hepatitis C
- Antinuclear antibody (ANA): 1:40
- Ferritin 300, percent saturation: 33%
- Ultrasound shows a liver with increased echogenicity

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Differential Diagnosis

- Viral hepatitis excluded
- ANA positive with a low grade titer – could this be autoimmune hepatitis?
- Ferritin elevated, but normal % saturation- iron overload? Hereditary hemochromatosis?
- Evidence of fat on ultrasound in a non drinker with facets of the metabolic syndrome
- Low grade ANA titers are present in up to 33% of patients with NAFLD. Titers >1:320 are rare
- Mild increases in serum ferritin are not uncommon among patients with insulin resistance and do not reflect iron overload
- This is a good starting point for a clinical diagnosis of NAFLD

Vuppalanchi. Hepatol 2009

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AASLD guidance – recent updates

- Stronger emphasis on assessment for metabolic risk factors in NAFL
- patients with NAFLD have increased morbidity and mortality
- Advanced liver fibrosis is associated with increasing number of metabolic comorbidities
- Early identification and treatment of individual components of the metabolic syndrome are critical in preventing both cardiovascular and liver-related mortality

Ando et al Jan 2021

Abnormal Liver enzymes in a patient with diabetes

- Is Nonalcoholic Fatty Liver Disease (NAFLD) a real disease?
- Assessment of Disease severity
- Currently available interventions
- Future Interventions
- Management Algorithm

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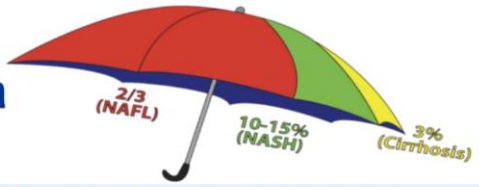
Is NAFLD a real disease?

The NAFLD Umbrella



Phenotypes	
NAFLD (covers spectrum)	Fatty infiltration of the liver >5% by imaging or histology No significant alcohol intake No genetic disease No Medications that cause steatosis
NAFL	Bland steatosis
NASH	Steatosis with inflammation, ± hepatocellular injury (ballooning), ± fibrosis
NAFLD with fibrosis	NAFL or NASH with periportal, portal, sinusoidal or bridging fibrosis
NAFLD with cirrhosis	Cirrhosis in the setting of NAFLD

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017;64:319-334.

NASPGHAN NASPGHAN FOUNDATION ©2017 NASPGHAN FOUNDATION

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Is NAFLD a real disease?

Secondary causes of hepatic steatosis

TABLE 1. Common Causes of Secondary HS

Macrovesicular steatosis
- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- WD
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g., mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids)

Microvesicular steatosis
- Reye's syndrome
- Medications (valproate, antiretroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g., lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman's disease)

Chalasani et al Hepatology 2018

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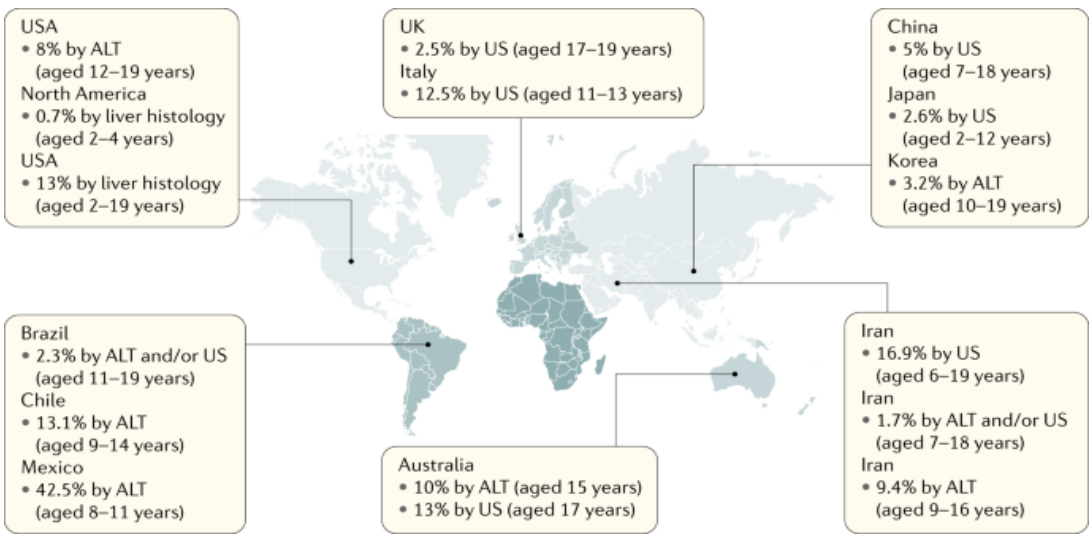
Is NAFLD a real disease?

Mapping the prevalence of paediatric NAFLD



Nobili et al Nature reviews Gastro & Hepta 2019

Is NAFLD a real disease?

NAFLD – Prevalence in Children

- NAFLD is the most common cause of pediatric liver disease
- There are very few studies describing the incidence of NAFLD in children
- Prevalence of NAFLD parallels obesity
- 2.7 fold increase 1980's to current era
- NAFLD prevalence depends on –population screened and screening method used (ALT, imaging, liver biopsy)
- 2-4 yrs 0.7%, 15-19 yrs 17.3%, obese children by ALT elevation- 29-38%
- Ethnicity

  Hispanic 11-22 yrs – 4 fold increased risk

  - Asian children – 10.2%
  - White children – 8.6%
  - Black children – 1.5%

Welsh JA et al Pediatrics 2013
Schwimmer JB et al Pediatrics 2006
Louthan JPGN 2005
Patton JPGN 2006

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Is NAFLD a real disease?

NAFLD-Prevalence in children

Prevalence in higher in certain population

- Overweight/Obese
- Males>Females
- Ethnicity: Hispanics>Asian>Caucasian>Black
- Prediabetes or type 2 diabetes
- Obstructive sleep apnea (OSA)
- Hypothalamic dysfunction/hypopituitarism

Nadeau KJ et al JOGN 2005
Sundara SS et al J Pediatrics 2014
Nobili V et al Am J Resp. Crit Med 2014

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Is NAFLD a real disease?

Is NAFLD a real disease? NAFLD incidence in adults

- Incidence of NAFLD from Asian countries

-Based in ultrasound 19-30 per 1,000 years

-Based on MRI and TE 13.5% (34 per 1,000 person-years)

- Incidence rates of NAFLD in Western countries

-Study from England 29 per 100,000 person-years

-Study from Israel 28 per 1,000 person-years

- Recent meta-analysis pooled regional incidence of NAFLD from Asia to be 52.34 per 1,000 person-years where as from the West ~28 per 1,000 person-years

Chalasani et al Hepatology 2018

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Is NAFLD a real disease?

Is NAFLD a real disease

- NAFLD is common

Prevalence depends on population studied and method used to make

diagnosis

1 in 3 American adults has simple steatosis

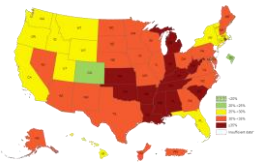
Ultrasound data estimates prevalence ~50%

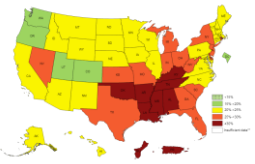
NHANES III estimate range from 8-24%

Prevalence in bariatric surgery patients may be as high as 90%, up to 55% may have NASH and 12% with bridging fibrosis

Global prevalence 24% (meta analysis)

- Incidence of new NAFLD rising in step with increasing rates of obesity, diabetes and physical inactivity





Williams, Gastro 2011
Clark et al AJG 2207
Younossi et al Hepatology 2016
www.cdc.gov

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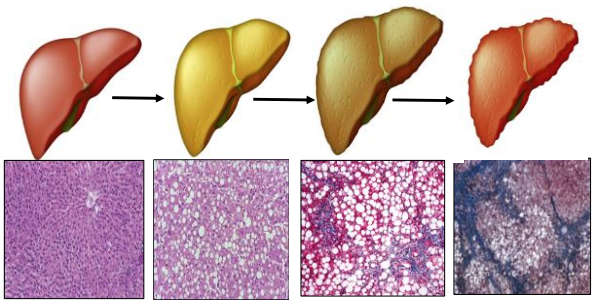
Is NAFLD a real disease?

NAFLD is a progressive disease



5-20%

Who will progress?

- Risk Factors

-Central obesity
-Hypertension
-Dyslipidemia
-**Type 2 Diabetes**
-Metabolic syndrome
-Advancing age
-Polycystic ovary syndrome

- ALT is not a reliable indicator of disease severity

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Is NAFLD a real disease?

Insulin Resistance and Diabetes Mellitus

- **Increased risk of NASH if NAFLD with:**
  - **Insulin resistance (OR: 1.8)**
  - **Diabetes mellitus (OR: 2.6)**
- **Correlation between hepatic fat and prevalence of insulin resistance**
- **Baseline fat content predicts long-term (~2y) insulin sensitivity**

Newton KP et al. *JAMA Pediatr* 2016;170(10):e162199.
Cali AMG et al. *Hepatol* 2009;49(6):1896–1903.
Kim JY et al. *Diab Care* 2013;36:1547–1553.

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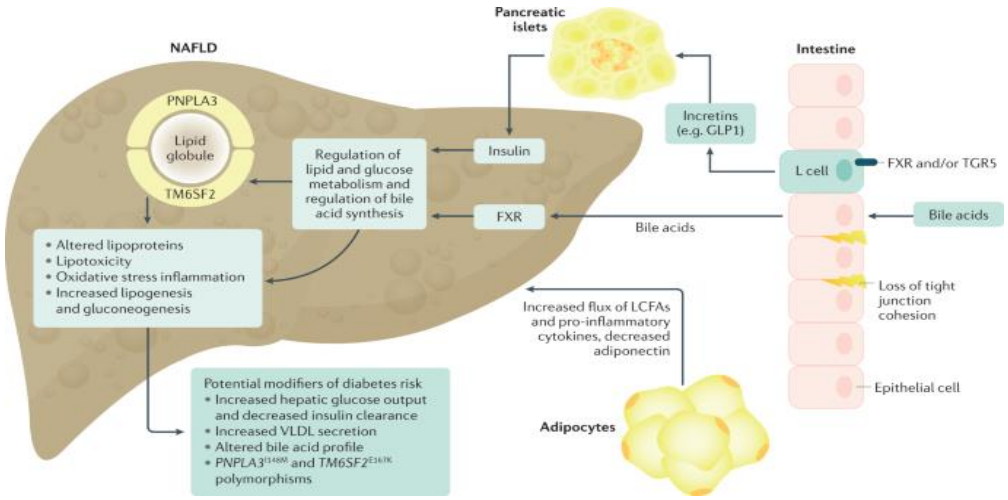
Is NAFLD a real disease?

Potential hepatic mediators of diabetes risk in NAFLD: bile acid metabolism, FXR and TGR5 receptor activity and adipose function



Targher et al Nature reviews Gatro. & Hepat. 2021

Is NAFLD a real disease?

Re-defining non-alcoholic liver disease: What's in a name?

A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement

Mohammed Eslam, Philip N. Newsome, Shiv K. Sarin, Quentin M. Anstee, Giovanni Targher, Manuel Romero-Gomez, Shira Zelber-Sagi, Vincent Wai-Sun Wong, Jean-François Dufour, Jörn M. Schattenberg, Takumi Kawaguchi, Marco Arrese, Luca Valenti, Gamal Shiha, Claudio Tiribelli, Hannele Yki-Järvinen, Jian-Gao Fan, Henning Grønbæk, Yusuf Yilmaz, Helena Cortez-Pinto, Claudia P. Oliveira, Pierre Bedossa, Leon A. Adams, Ming-Hua Zheng, Yasser Fouad, Wah-Kheong Chan, Nahum Mendez-Sanchez, Sang Hoon Ahn, Laurent Castera, Elisabetta Bugianesi, Vlad Ratziu, Jacob George

1.Presence of metabolic dysfunction rather than absence of other conditions
2. Better define and phenotype MAFLD patient population
3.Does not reference alcohol reduce stigmatizing patients

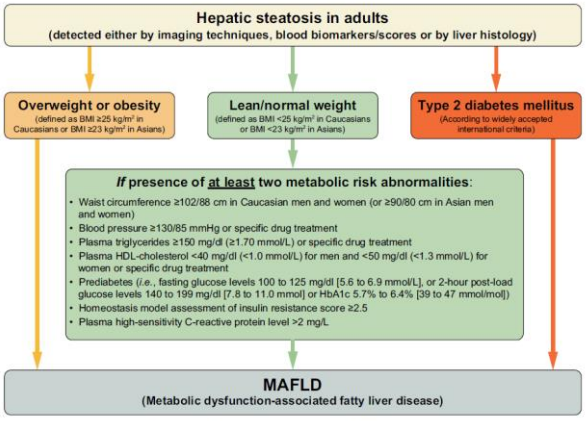
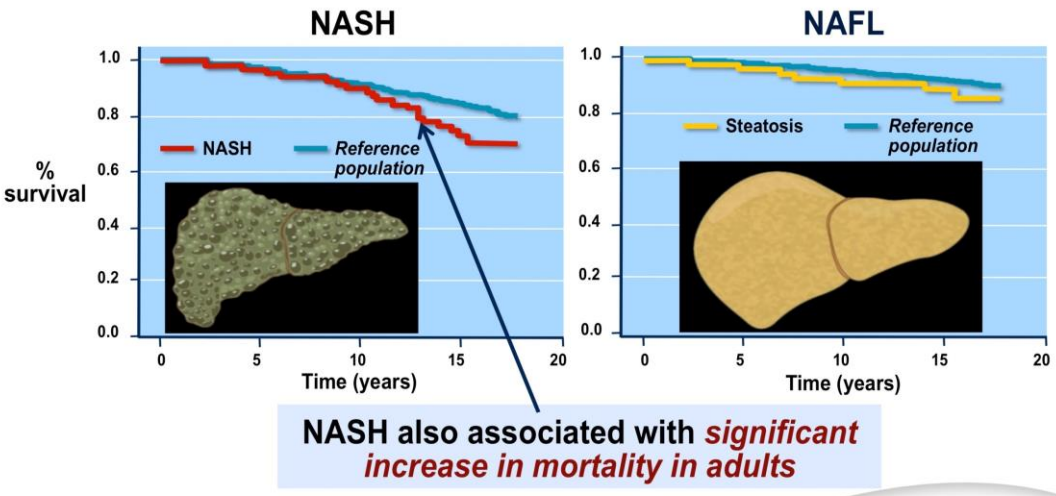


Fig. 1. Flowchart for the proposed "positive" diagnostic criteria for MAFLD.

Is NAFLD a real disease?

Natural History NASH vs. NAFL



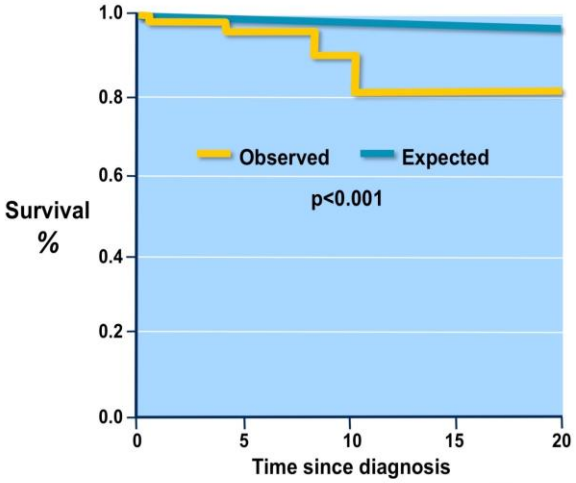
NASH also associated with *significant increase in mortality in adults*

Eksted et al. *Hepatol* 2006;44:865-73.

Is NAFLD a real disease?

Increased Mortality in Pediatric NAFLD

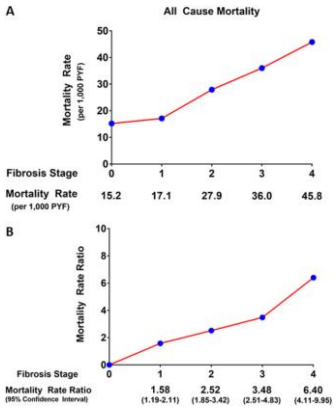
- 66 children
  (mean age 13.9 years)
  - Mean follow up: 6.4 years (Range 0.05-20 years)
  - Total of 409 person years follow up
  - 4 events
    - 2 patients died, 2 liver transplant
    - Observed vs. expected survival - p<0.001



Feldstein AE et al. *Gut* 2009;58(11):1538-44.

Assess disease Severity

Fibrosis progression is associated with increased mortality



Hepatology, Volume: 65, Issue: 5, Pages: 1557-1565, First published: 28 January 2017, DOI: (10.1002/hep.29085)

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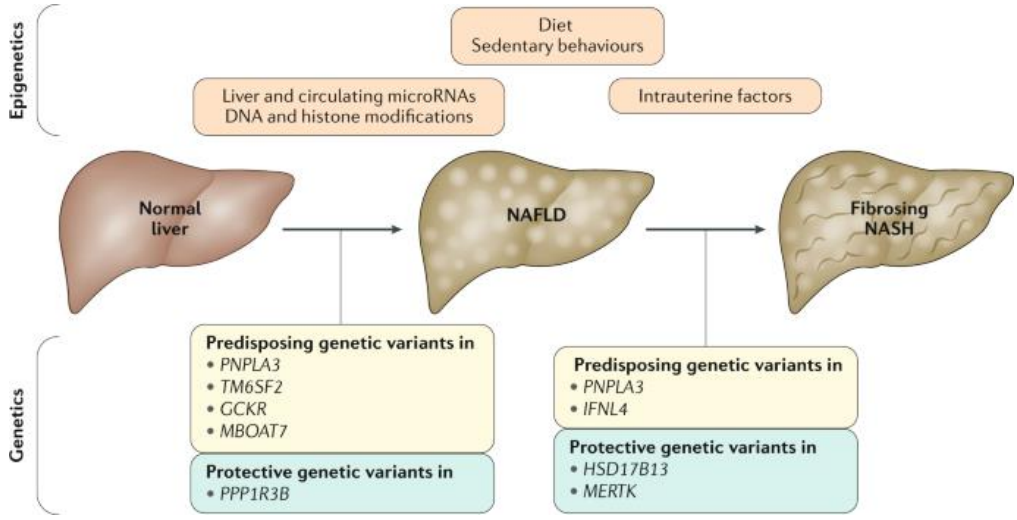
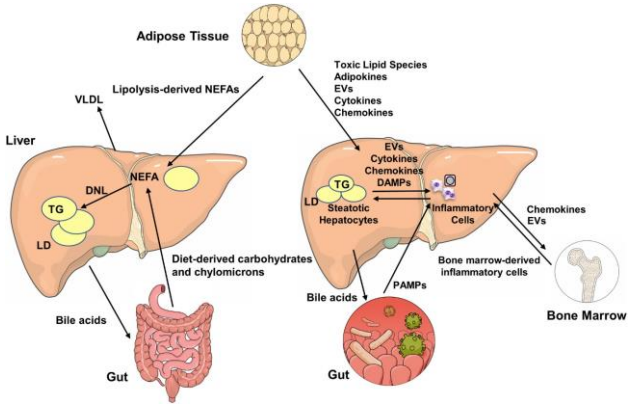
Interaction between inherited and environmental factors in the pathogenesis of NAFL and NASH

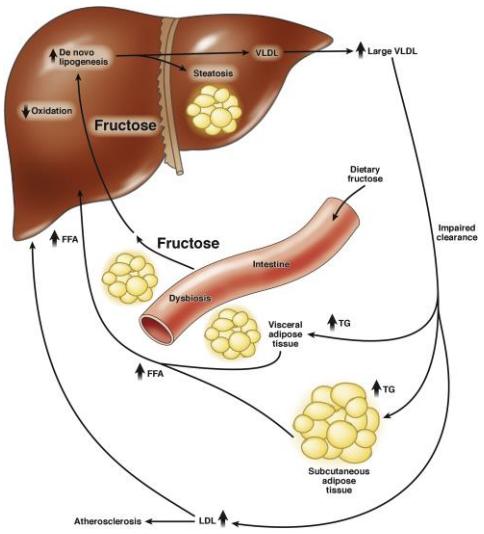


Alkhouri et al Nature Reviews 2021

Pathogenesis of Nonalcoholic Steatohepatitis: An Overview



Hepatology Communications, Volume: 4, Issue: 4, Pages: 478-492, First published: 14 January 2020, DOI: (10.1002/hep4.1479)



Vos & Goran, *Gastroenterology* 2017

NAFLD pathogenesis

- Adipose tissue inflammation
- **De novo Lipogenesis (DNL)**
- **Insulin resistance**
- Lipotoxicity
- **Mitochondrial Dysfunction**
- **Oxidative stress**
- Endoplasmic Stress

Assess disease Severity

NAFLD Screening

Upper Limit for ALT?

- Regional laboratories use local population for norms
  - Do not exclude overweight/obese or other causes of liver disease
  - Median ULN at children's hospitals 53 U/L (range 30-90)
- 95 percentile for ALT in healthy weight, metabolically normal, liver disease free, NHANES adolescent group (12-17 yrs)

ALT 25.8 U/L for BOYS

ALT 22.1 U/L for GIRLS

Schwimmer JB et al. *Gastroenterology* 2010;138:1357-64.
Colantonio DA et al. *Clin Chem* 2012;58:854-68.

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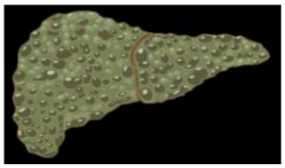
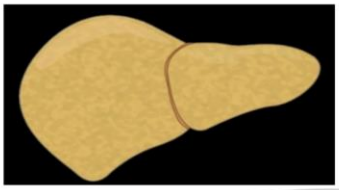
Assess disease Severity

Limitations of ALT

- **Poor correlation with histology**
  - Some studies suggest AST, GGT better correlated with fibrosis
  - ALT changes even with placebo!
- **Fluctuations over time**
- **Cannot always differentiate between**

NASH 

NAFL 

Loomba R et al. *Clin Gastro Hepatol* 2008;6(11):1243-8.

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Assess disease Severity

Non-Invasive assessment of disease

- Several clinical prediction scores for assessing severity of disease
- NFS

1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/l) – 0.66 × albumin (g/dl)

- FIB-4

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

- Both are reasonable to use
- Comparable to AUROC scores
- NFS 0.81, FIB-4 0.82
- Inexpensive
- On hand held devices
- Many others with similar accuracy

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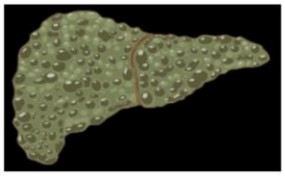
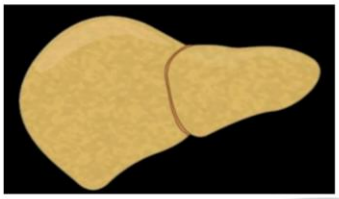
Assess disease Severity

Ultrasound

- **Pros:**
  - Non-invasive
- **Cons**
  - Low sensitivity/specificity particularly lower degrees of steatosis (not recommended for screening in NASPGHAN Guidelines)
  - Cannot differentiate between

NASH 

NAFL 

Awai HI et al. *Clin Gastroenterol Hepatol* 2014;12:765–73.

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Assess disease Severity

Non-Invasive assessment of disease

Vibration Controlled Transient Electrography (Firboscan)

- Liver stiffness measured in kilopascals and correlated with fibrosis stage, F0-F4
- AUROC for F3 or higher disease 0.93 in NAFLD

Controlled Attenuation Parameter (CAP)

- Steatosis measured in dB/m and correlated with steatosis grade, S0-S3
- AUROC score for S1 and greater 0.86

Wong. Hepatol 2010
Karlas, J Hepatol 2017

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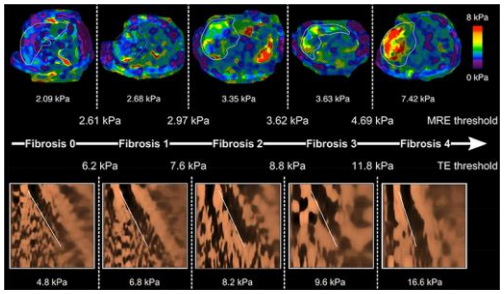
Assess disease Severity

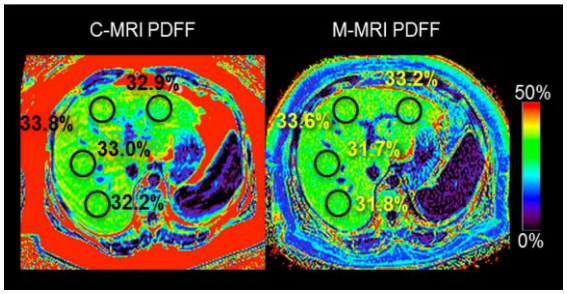
Magnetic Resonance Imaging Technology

MR-Elastography (MRE) for Fibrosis

2D and 3D MRE have AUROC > 0.92
Multiple single center trials show MRE > VCTE



MR-Proton density fat fraction for steatosis (MR-PDFF)



Kim, Radiology 2013
Caussy, Hepatology 2018
Hsu, Clin Gastroenterol Hepatol 2018

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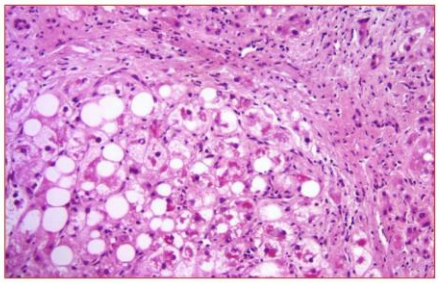
Assess disease Severity

Assessment of Steatosis

- **Liver biopsy**
  - Traditionally used to quantify steatosis
  - Steatosis in >5% of hepatocytes is abnormal
  - NAFLD Activity Score (NAS)
    - Research: steatosis grading 0-3



- **Imaging**
  - Investigative ultrasonography
  - MR-based technologies

} Cost and availability limit their use

Brunt EM et al. *Hum Pathol* 2004;35:1070-1082.
Kleiner DE et al. *Hepatol* 2005;41(6):1313-21.
Mencin AA et al. *Nat Rev Gastroenterol Hepatol* 2015;12:617-628.

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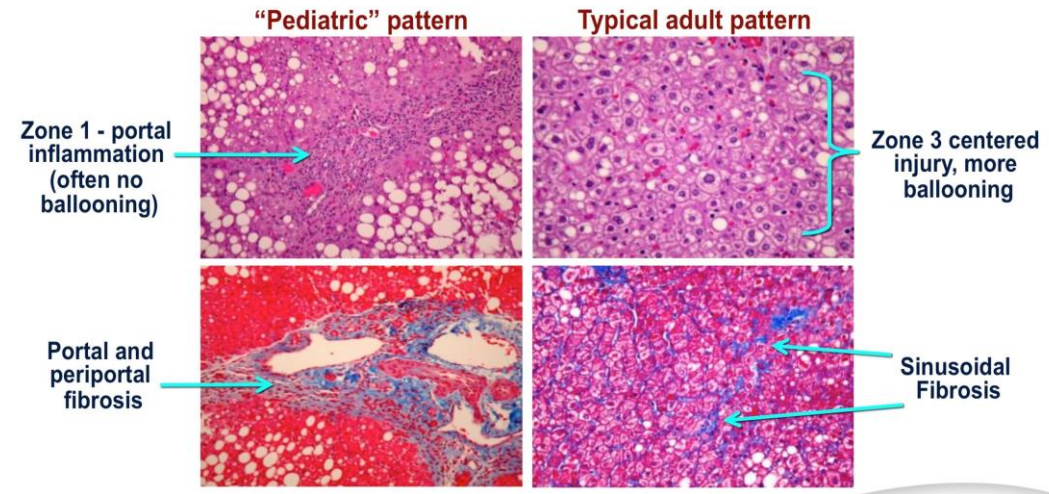
Assess disease Severity

Portal Predominant NASH in Many Pediatric Patients, Rarely in Adults



Schwimmer JB et al. *Hepatol* 2005;42:641-49.
Carter-Kent C et al. *Hepatol* 2009;50:1113-20.

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Assess disease Severity

Benefits and Limitations of Each Diagnostic Approach

Liver Biopsy

- ☑ Differentiates NAFL from NASH
- ☑ Excludes other liver diseases
- ☑ Clinical reference for diagnosis

Liver Biopsy

- ☑ Invasive
- ☑ Samples a small fraction of the liver

Serum Biomarkers

- ☑ Non-invasive
- ☑ Cheap

Serum Biomarkers

- ☑ Often have low sensitivity/specificity
- ☑ Some remain to be validated

Imaging Modalities

- ☑ Non-invasive
- ☑ Imaging of entire liver
- ☑ Can exclude certain conditions
- ☑ Cost varies

Imaging Modalities

- ☑ U/S has low sensitivity/specificity
- ☑ CT exposes to radiation
- ☑ MRI/MRS: diagnostic cutoffs unclear

Vos et al. *J Pediatr Gastroenterol Nutr* 2017;64:319–334.

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Assess disease Severity

Screening

- Screening should be considered between 9 and 11 years for
- Children (BMI ≥ 95TH percentile)
- Children (BMI ≥ 85th and 94th percentile) with additional risk factors like central obesity, insulin resistance, prediabetes or diabetes, dyslipidemia, hypopituitarism, sleep apnea or family history of NAFLD/NASH
- Best test currently is ALT
- Sex specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys)
- Persistently (>3 months) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD
- ALT of >80 U/L warrants increased clinical concern and timely evaluation

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Assess disease Severity

Problem: NAFLD is difficult to confirm

- Confirmation is invasive (biopsy).
- Serum tests (ALT, AST) are not reliable predictors of steatosis/fibrosis.
- Imaging tools have limitations (MRI, ultrasound) or may not be widely available (MRS, Fibroscan).
- Biomarkers for NAFLD in adults may not perform as well in children.
- Biomarkers tested in children often lack biopsy confirmation, appropriate control groups, or longitudinal assessments.

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Purpose

To determine if:

Serum miR-122 and/or -192 are increased in pediatric NAFLD patients compared to normal weight and obese peers.

Abundance of miR-122 and/or -192 in serum are inversely correlated with their content in liver in pediatric NAFLD patients.

Serum miR-122 and/or -192 are better biomarkers of pediatric NAFLD than the current standard biomarker, ALT.

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Participant characteristics

mean ± SD

	Norm Weight	Obese	NAFLD
Girls/Boys	9 F / 16 M	13 F / 11 M	10 F / 15 M
Age (years)	15.7 ± 2.3	16.5 ± 2.6	16.0 ± 2.2
Weight (kg)	55.6 ± 12.1	92.7 ± 24.5	94.6 ± 22.6
BMI (%)	55 ± 25	98 ± 2	98 ± 2

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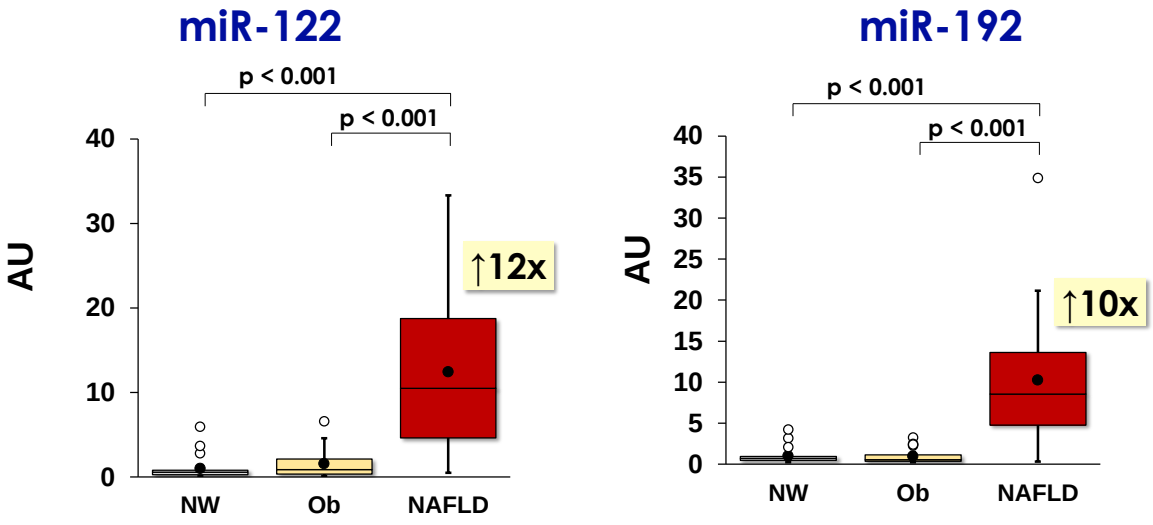
Serum miRNA abundance



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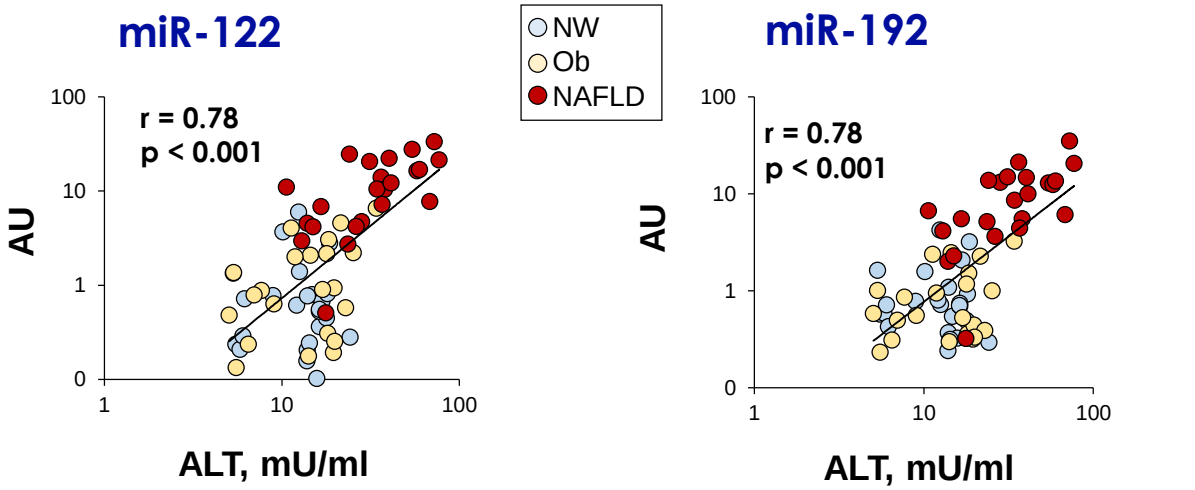
miR-122 and -192 are correlated with ALT



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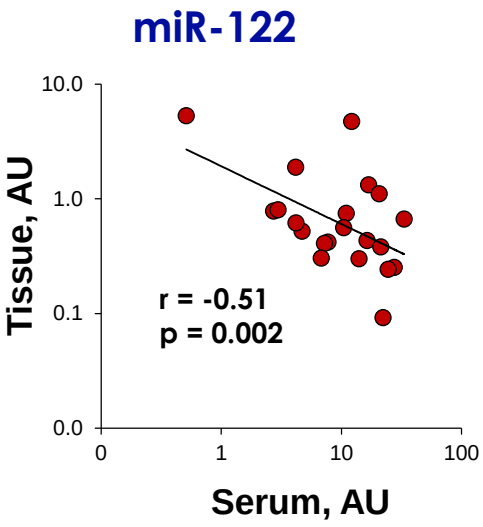
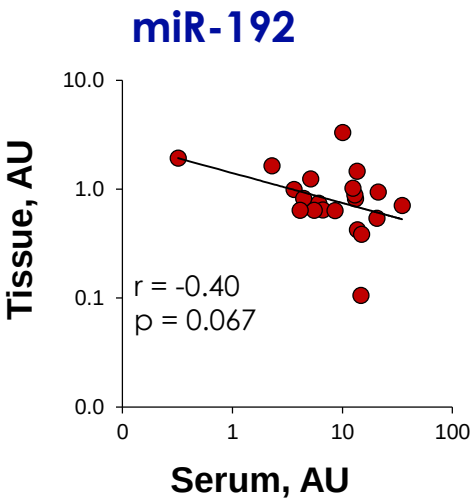
Serum vs. tissue abundance





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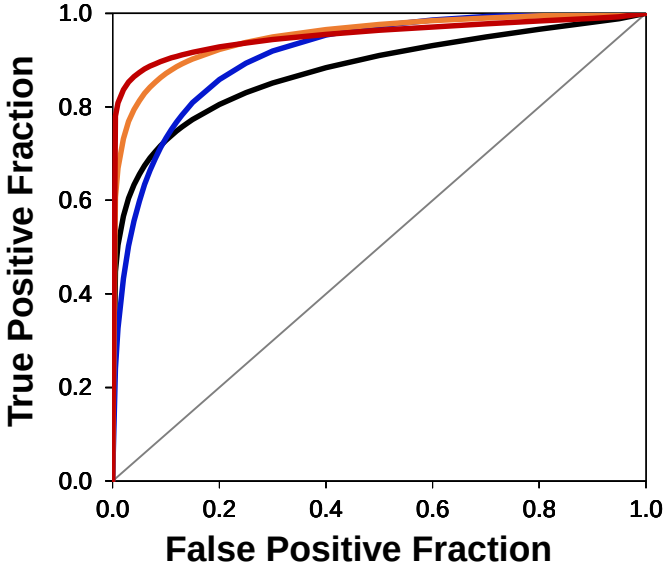
Detecting presence of NAFLD



AUROC	
ALT	0.88
GGT	0.91
miR-122	0.95
miR-192	0.95

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Consider the entire patient

- All cause mortality in the general population
- CVD
- Cancer
- ~12.Liver Disease
- All cause mortality in the patient with NASH
- CVD
- Cancer
- Liver Disease

- We can address these risks in a complimentary manner with currently available medications
- Cardiovascular risks-Statins
- Cancer risk- Statins, metformin, weight loss
- Metabolic syndrome- HTN, dyslipidemia, diabetes
- Obesity
- NASH specific

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NAFLD and CVD risk

Cardiovascular disease is the leading cause of death in adults with NAFLD.

Fatty liver exacerbates dyslipidemia, thrombosis, systemic inflammation, oxidative stress, neuroendocrine system, vascular tone.

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NAFLD and CVD risk

EASL and AASLD recommend screening and treatment of CVD risks

Most work has been performed in adults:

Are increased CVD risks evident in pediatric NAFLD?

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Summary of CVD risk factors

	NAFLD versus control
HDL-C	↓
Triglycerides	↑
Fatty acids	↑
Aerobic fitness	↔
Blood pressure	↑
Pulsewave velocity	↑
Heart rate variability	↓

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Impact of Treatment

- **Treating dyslipidemia in the context of NAFLD:**
  - No data on hepatic impact of dyslipidemia treatment
- **Treating NAFLD – impact on dyslipidemia:**
  - TONIC: NASH resolution associated with improvement in cholesterol, not TG
  - DHA superior to placebo for TG improvement
  - Low fructose diet improved oxidized LDL

Lavine JE et al. *JAMA* 2011;305(16):1659-68.
Nobili V et al. *Nutr Metab Cardiovasc Dis* 2013;23:1066–1070.
Vos MB et al. *Arch Pediatr Adolesc Med* 2009;163(7):666-666.

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Current Interventions

Potential Treatment Options

- **Lifestyle**
- **Dietary supplements**
- **Medications**
- **Surgery**

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017; 64(2):319-334.

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Current Interventions

Lifestyle Interventions

Review

EASL JOURNAL OF HEPATOLOGY

Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: A systematic review

Christian Thoma[1,2,3], Christopher P. Day[1,2], Michael I. Trenell[1,2,3,*]

- 11 diet studies, 2 exercise only studies, 7 combo studies
- In general interventions were brief (1-6 months)
- Many lacked control group, only a few used histology
- Magnitude of body weight change reflected in change in liver fat
- Exercise only interventions may change liver fat while body weight is neutral

- Need significant and sustained weight loss to have an impact
- ≥5% weight loss reverses NASH
- ≥10% weight loss reverses fibrosis

Thoma et al Hpatol 2012
Villar-Gomez, Gastro 2015

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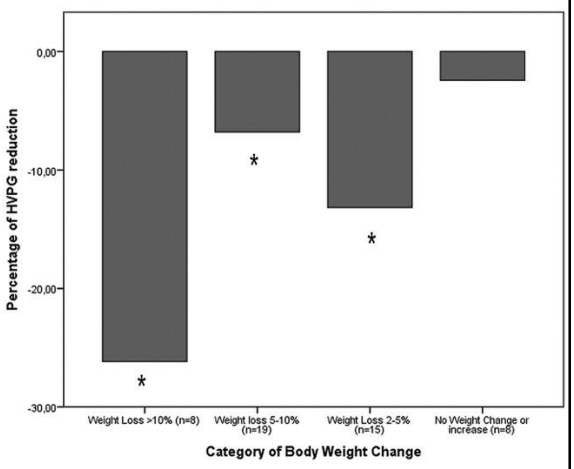
Current Interventions

Life style modification: It's never too late

Effect of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: the SportDiet study

- Weight loss might safely reduce portal pressure in obese cirrhotic patients with portal hyprtension
- Spanish multicenter study of 60 obese patients with cirrhosis sand HVPG>6mmHg who underwent a 16 week lifestyle intervention aimed at reducing body weight
- Lifestyle intervention decreased body weight by -5.0±4.0 kg; (p<0.0001 vs. baseline)
- Associated with a significant decrease in waist circumference and percentage of body fat



Berzigotti et al Hepatology 2017

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Current Interventions

Lifestyle Targets

- Avoid sugar-sweetened beverages
- Healthy, well-balanced diet
- Moderate to vigorous exercise
- Limit screen time to < 2 hours per day

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017; 64(2):319-334.

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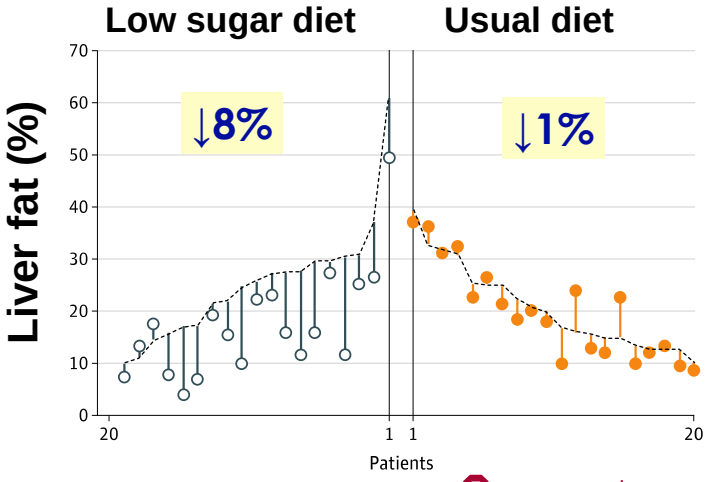
Current Interventions

Effect of a Low Sugar Diet vs Usual Diet on Liver Fat in Adolescent Boys with NAFLD

8-week intervention:
Usual diet vs.
Sugar < 3% energy intake

N = 20 boys/group
Age ~13y
95% Hispanic



Schwimmer, *JAMA* 32: 256, 2019

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Current Interventions

Components of a lifestyle approach to NAFLD

Energy restriction
- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake
- Avoid fructose-containing food and drink

Coffee consumption
- No liver-related limitations

Comprehensive lifestyle approach

Daily alcohol intake
- Strictly below 30 g men and 20 g women

Macronutrient composition
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Physical activity
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

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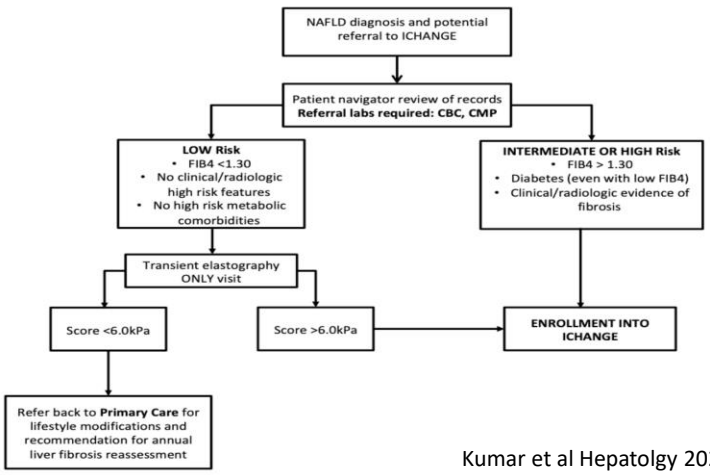
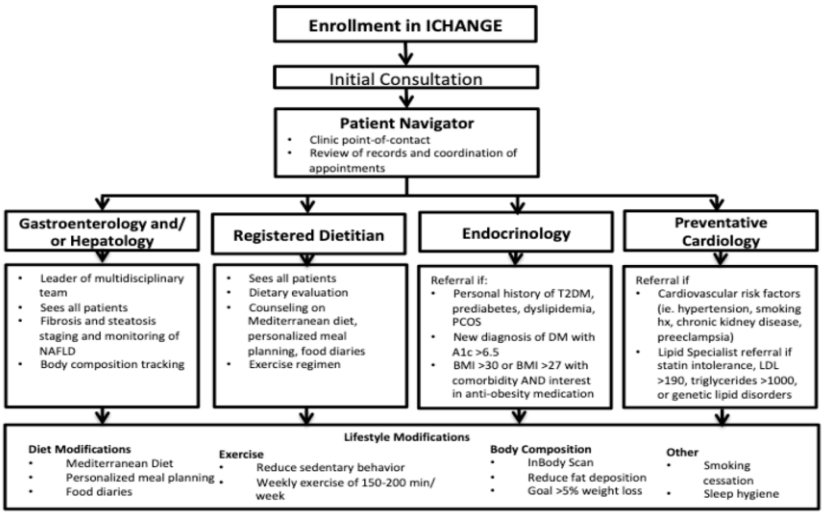
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Multi-Disciplinary Clinic Models: A Paradigm of care management of Nonalcoholic Fatty Liver Disease



Kumar et al Hepatolgy 2021

Multi-Disciplinary Clinic Models: A Paradigm of care management of Nonalcoholic Fatty Liver Disease



Kumar et al Hepatolgy 2021

Current Interventions

Pioglitazone and Vitamin E

247 adults with NASH and without diabetes

-Pioglitazone 30mg/day (80)

-Vitamin E 800 IU/day (84)

-Placebo (83)

96 weeks

- *Outcome: histological improvement (p< 0.025 fro multiple comparisons)

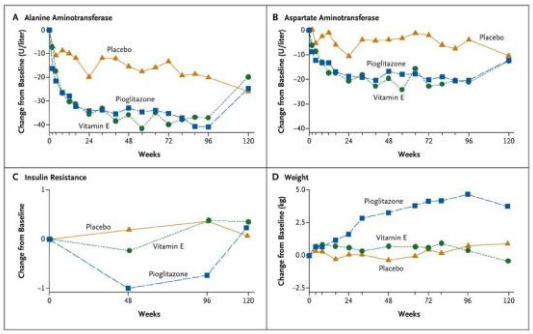
Results – primary outcome

- Vit E superior to placebo for histological improvement of NASH (43% vs. 19%, p=0.001)
- Pioglitazone no different from placebo (34% vs. 19%, p=0.04)

Sanyal et al NEJM 2010

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*



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Current Interventions

Glucagon-like peptide (GLP)analogue

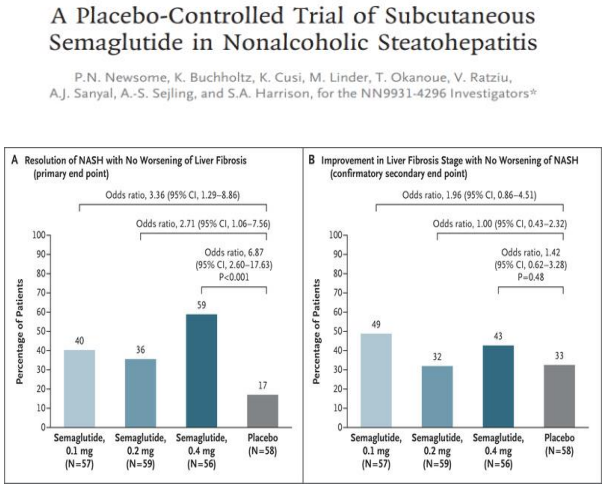
- 320 adults
- 230 (F2/F3 fibrosis)
- Semaglutide

-0.1mg (80 pts)

-0.2 mg (78 pts)

-0.4 mg (82 patients)

- NASH resolution (40 % vs 36% vs 59% vs 17%)
- Improvement in fibrosis – NS



Newsome et al NEJM 2021

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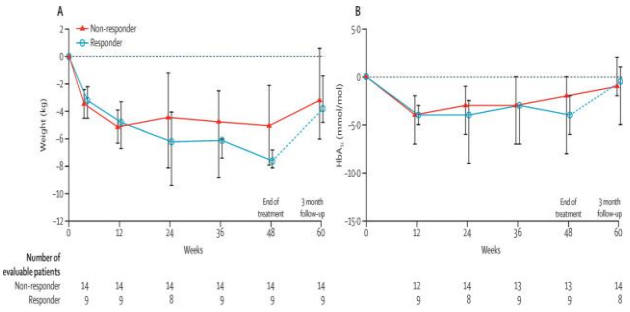
Current Interventions

Liraglutide/LEAN trial

- Glucagon-like peptide 1 reduces liver fat, ALT and insulin resistance in mice models
- Phase 2b DBRCT liraglutide vs placebo x 48 weeks
- Resolution of NASH in 9/23 (39%) vs. 2/22 (9%) placebo p=0.019
- Secondary outcomes showed improvements in weight and ALT
- Liraglutide well tolerated



Armstrong et al LANCET 2016

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Current Interventions

AASLD NAFLD guidance

- Piaglitazone only for patients with biopsy proven NASH
  - Discuss risks and benefits
  - Not recommended for patients without biopsy proven disease
- It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NASH
- Vitamin E may be considered for non diabetic adults with biopsy proven NASH
  - Discuss risks and benefits
  - Not recommended for diabetic NAFLD without biopsy or cirrhosis
- Other medications like UDCA and omega 3 fatty acids should not be used as specific treatment for NAFLD

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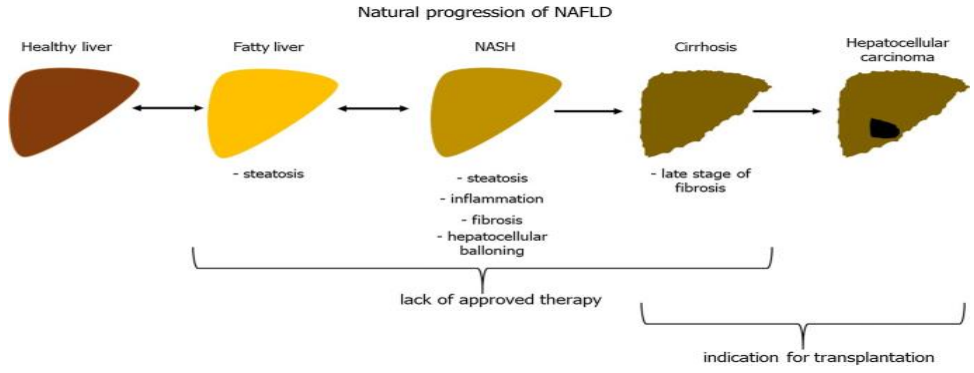
Future Interventions



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Future Interventions

Elafibranor

- Peroxisome proliferator activated (PPAR) α/δ agonist improves multiple factes of the metabolic syndrome
- Anti-inflammatory
- Lacks PPAR ϒ associated with weight gain and edema

PPAR α → Fatty acid oxidation, Triglyceride lowering, HDL increasing, Inflammation

PPAR δ → Lipoprotein metabolism, Glucose homeostasis, Energy metabolism, Inflammation

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Future Interventions

Elafibranor

Gastroenterology 2016;150:1147–1159

CLINICAL—LIVER

Elafibranor, an Agonist of the Peroxisome Proliferator–Activated Receptor–α and –δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening

Vlad Ratziu,[1,2] Stephen A. Harrison,[3] Sven Francque,[4] Pierre Bedossa,[5] Philippe Lehert,[6,7] Lawrence Serfaty,[8] Manuel Romero-Gomez,[9] Jérôme Boursier,[10] Manal Abdelmalek,[11] Steve Caldwell,[12] Joost Drenth,[13] Quentin M. Anstee,[14] Dean Hum,[15] Remy Hanf,[15] Alice Roudot,[15] Sophie Megnien,[15] Bart Staels,[16] and Arun Sanyal,[17] on behalf of the GOLDEN-505 Investigator Study Group

- Elafibranor is a PPAR agonist which improves insulin sensitivity, glucose homeostasis, lipis metabolism and reduces inflammation
- Phase ii clinical trial off patients with NASH
- Elafibranor 80mg n=93
- Elafibranor 120 mg n=91
- Placebo n=90
- Study x 52 weeks, primary outcomes of resolution of NASH without fibrosis worsening

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Future Interventions

Elafibranor

- ITT: no difference between drug and placebo
- In post-hoc analyses of patients with NAFLD activity score 4, elafibranor 120mg resolved NASH in larger proportions of patients than placebo based on the protocol definition (20% vs 11%)
- Patients with NASH resolution after receiving elafibranor 120 mg had reduced liver fibrosis stages compared with those without NASH resolution
- Drug well tolerated
- Secondary end points all showed improvement in elements of the metabolic syndrome
- Modified end points were sufficient to justify phase III trial

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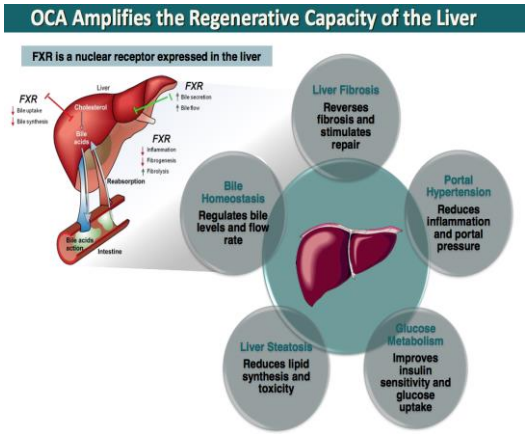
Future Interventions

Obeticholic acid

- FXR agonist will decrease hepatic fat and may improve insulin resistance as well as other facets of the metabolic syndrome
- Significance of LDL unknown



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Future Interventions

Obeticholic acid

- 141:142 obiticholic acid vs. placebo
- 45% improved liver histology compared with 21% in the placebo group (RR 1.9, 95% CI 1.3 to 2.8; p=0.0002)
- 23% of 141 patients in the obeticholic acid developed pruritus compared with 6% of 142 in the placebo group
- OCA patients had increasing TC and LDL with decreasing HDL
- Trial stopped early by DSMB due to clear effect

Neuschwander-Tetri et al, Lancet 2015

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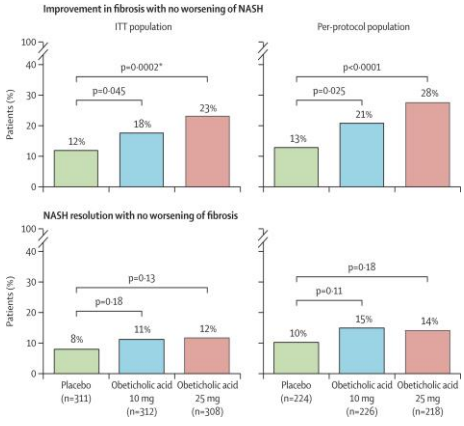
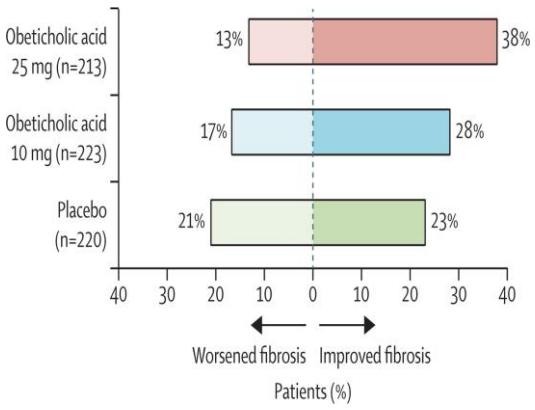
Future Interventions

Obeticholic acid





Younossi et al Lancet 2019

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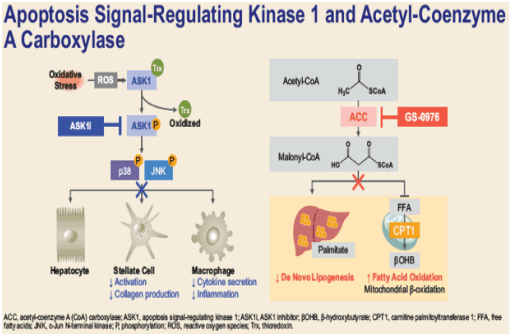
Future Interventions

Selonsertib

- ASK1 inhibitor (apoptosis inhibitor)
- Activated in NASH and correlated with fibrosis stage
- Inhibition improves steatosis, Inflammation and fibrosis in mice



Bates AASLD 2017

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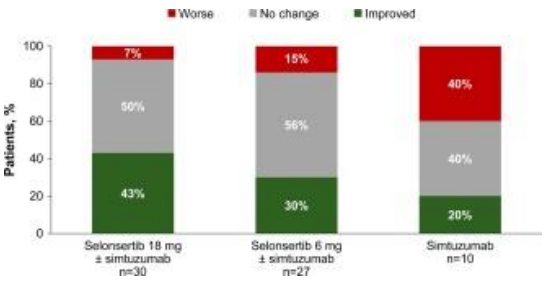
Future Interventions

Selonsertib

- Phase 2 RCT
- Selonsertib +/- simtuzumab for 24 weeks
- No placebo arm
- Primary end point was improved fibrosis
- 43% on SEL 18 mg had improved histology

The ASK1 inhibitor selonsertib in patients with nonalcoholic steatohepatitis: A randomized, phase 2 trial

Rohit Loomba [1], Eric Lawitz [2], Parvez S Mantry [3], Saumya Jayakumar [4], Stephen H Caldwell [5], Hays Arnold [6], Anna Mae Diehl [7], C Stephen Djedjos [8], Ling Han [8], Robert P Myers [8], G Mani Subramanian [8], John G McHutchison [8], Zachary D Goodman [9], Nezam H Afdhal [10], Michael R Charlton [11], GS-US-384-1497 Investigators



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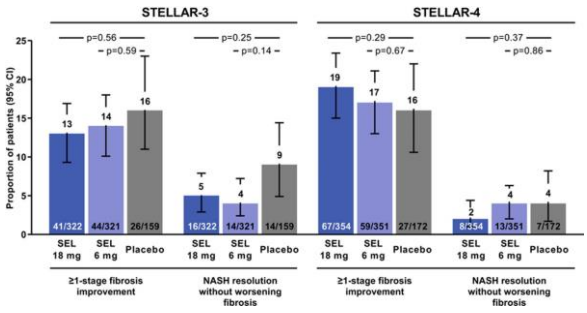
Future Interventions

Selonsertib

- PHASE III STELLAR trials
- Forty-eight weeks of selonsertib monotherapy had no antifibrotic effect in patients with bridging fibrosis or compensated cirrhosis due to NASH.



Future Interventions

Cenicriviroc

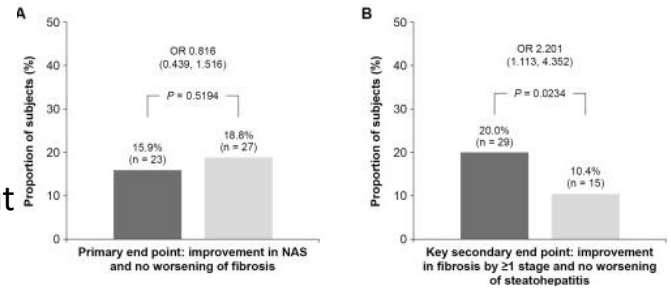
- Dual antagonist of C-C chemokine receptor types 2 and 5 (CCR2/CCR5)
- Antifibrotic effect (blockade of CCR2/5 inhibits stellate cell activation)
- Anti-inflammatory effect (Inhibits Kupffer cells and monocyte/macrophage recruitment)

Friedman et al Hepatology 2018

Future Interventions

Cenicriviroc

- Phase 2 RCT
- 289 NASH patients with and without Diabetes
- Preliminary endpoint of improved histology not met, but appears to have antifirbotic effect
- Antifibrotic effect justified phase 3 clinical trials



Friedman et al Hepatology 2018

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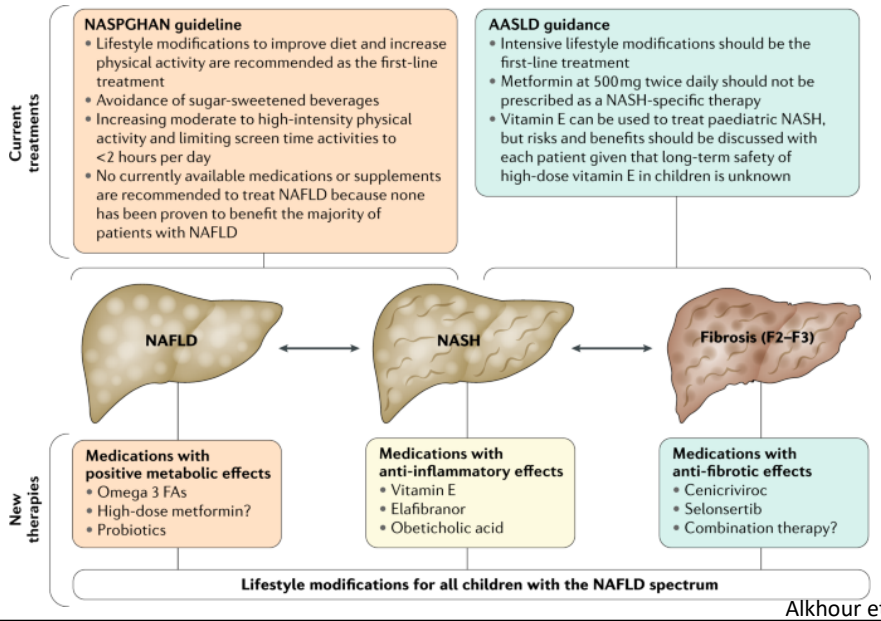
Schematic representation of current pharmacological interventions and new promising therapies



Alkhour et al Nature Reviews 2021

Challenges of treating NASH will continue

- If/when there are successful FDA approved interventions for NASH, questions and challenges will remain
- Are these lifetime drugs?
- Interventions to pause disease while patients fix lifestyle probems
- Cardiovascular risk
- Cancer isk
- Trial efficacy vs. real world effectiveness

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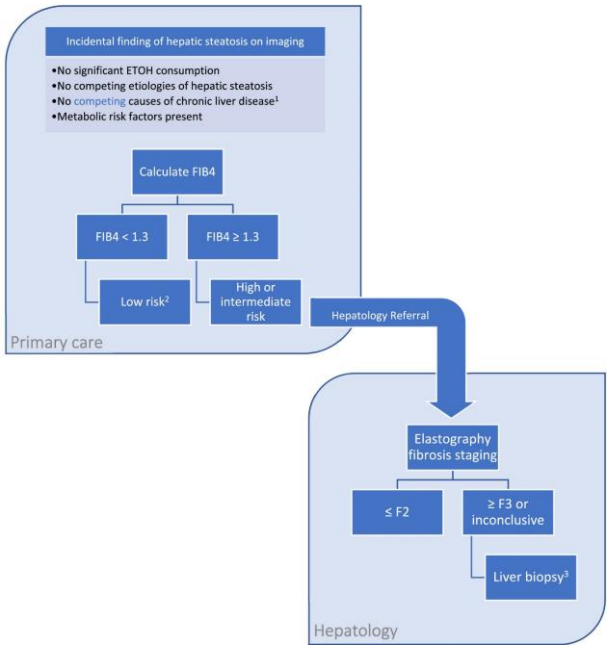
Management algorithm

Nonalcoholic Fatty Liver Disease and Recent Guideline Updates



Clinical Liver Disease, Volume: 17, Issue: 1, Pages: 23-28, First published: 01 February 2021, DOI: (10.1002/cld.1045)

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Case Epilogue

- NAFLD fibrosis score=1.977 presence of significant fibrosis
- Transient elastography 7.5 kPa, interpreted as F2-3 disease
- Liver biopsy shows stage 2 fibrosis, NASH activity score 5
- Minimal success with lifestyle intervention and risk factor control
- Enrolls in a clinical trial

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Key Take-Away Slide

- Know your local lab and what they report as “normal”
- Some labs may not be flagged as “abnormal”, but still may be clinically elevated
- NAFLD is a common progressive disease where disease progression is associated with liver related and all cause mortality
- Address the whole patient by considering cardiovascular, cancer, and liver-specific health risks
- New medications are on the horizon, but duration and timing of use is still unknown

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Unanswered questions and research priorities

- Natural history of NAFLD starting in childhood
- Risk factors in pediatric NAFLD that predict progression to cirrhosis and HCC
- Noninvasive diagnostics
- Longitudinal studies of biomarkers and imaging
- Treatment questions: role of dietary interventions, type and duration of exercise, validation of promising therapeutics and role of weight loss surgeries
- Cost effectiveness and public health questions: Effective prevention strategies, cost effectiveness of screening, diagnosis and follow up

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Future directions

- Improvement in understanding of the disease will lead to improved outcomes
- As pediatricians, prevention is a priority but not yet focus for funding
- Collaborative efforts exist nationally and internationally
  - -NASPGHAN NAFLD scientific advisory board
  - - The Liver Forum
  - - NIH sponsored NASH Clinical Research Network
  - - Industry supported natural history studies

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