What's New in Diabetes for 2022-23?

Family Medicine Foundation of West Virginia Winter Meeting

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Objectives

- Review the benefits of routine use of continuous glucose monitoring (CGM) for primary care physicians
- Present recent ADA/ACE recommendations to use CGM in hospital setting
- Introduce "smart" insulin pens & a new "insulin patch"
- Review Tirzepatide (Mounjaro®) a "dual GIP/GLP-1 receptor agonist" & Finerenone (Kerendia®); a non-steroidal aldosterone antagonist which were FDA approved this year
- Describe addition of serum Cystatin-C to monitoring/predicting CKD in diabetic patients
- Present status of current attempts to prevent both T2DM & T1DM

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Use of Continuous Glucose Monitors (CGM) in Primary Care

Routine assessment of patient CGM data has been used by endocrinologists managing patients with T1DM for over 15 years; but it's use is now being encouraged for primary care providers to use in any individual with diabetes & an A1C >8%

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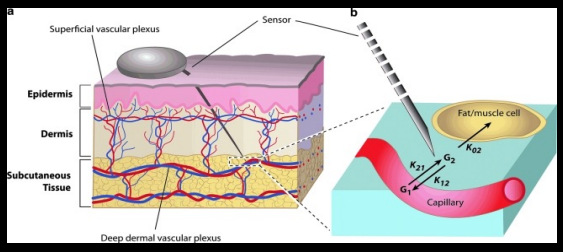
CGM's Measure Glucose Levels in Fluid (Interstitial) Beneath the Skin



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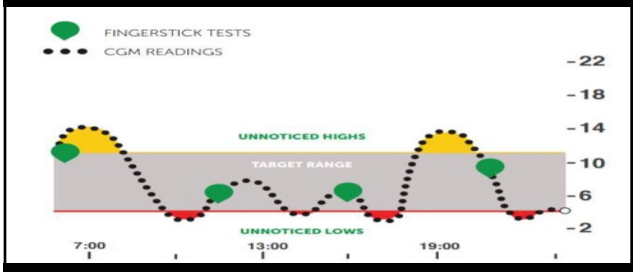
CGM vs Fingerstick Glucose Levels: 270 glucose values/day vs 1-4 fingerstick values/day



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Use of "Flash CGM" in Primary Care

- Patient wears a Abbott Libre CGM® patch on arm (does not need to do anything else except protect it) & returns to office in 2 weeks for data download (takes 2-3 min)
- Glucose data can reviewed & interpreted by health care provider at their convenience
- Provider looks for recurrent abnormal glucose excursions
- Data can then be reviewed with patient by a physician, NP, PA or patient educator & changes can be made in the treatment plan to correct major issues

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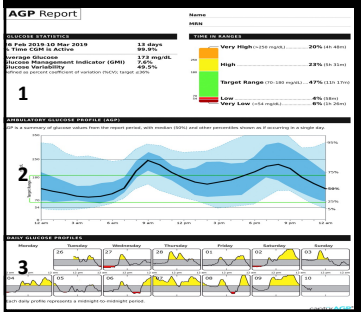
Components of a CGM AGP Report



3 Major Components of a AGP Report:

(1) Glucose Statistics; including Time in Range (TIR), estimated A1C (GMI), & Glycemic Variability (GV)

(2) Summarized CGM Glucose Profile modal day

(3) Daily Glucose Profiles of days monitored

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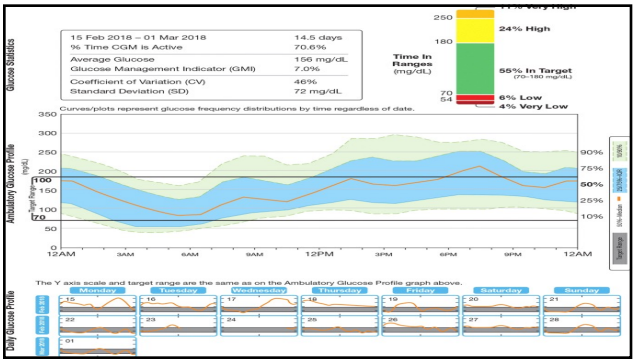

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Priorities of CGM Review

Identify asymptomatic hypoglycemia & eliminate it

(50% of hyperglycemia will be rebound from hypoglycemia)

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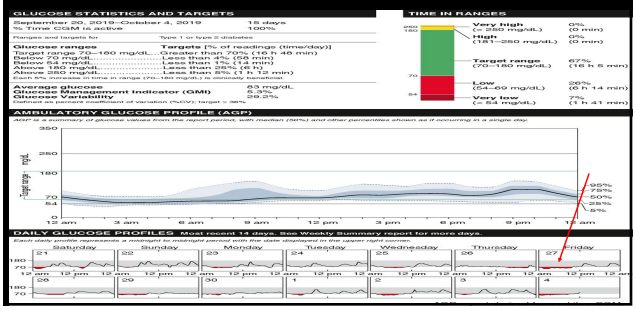
Detection of Asymptomatic Hypoglycemia



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Reviewing the Ambulatory Glucose Profile With Patients

- Can be done by physician, physician extenders, or educator
- Great opportunity to demonstrate to patients directly their daily glucose patterns & reasons for making changes in life-style or medications
- Ability to repeat CGM at later time to demonstrate improvements or reinforce reasons for previous recommendations

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Reasons for Lack of PCP Adoption of CGM

- Lack of opportunities for Libre CGM® training of physicians & their clinical staff on the proper use of the CGM systems in their clinics
- Lack of understanding of the simple process for initiating a patient point-of- care CGM study, return for data download & interpretation, or how to bill for the procedure
- Lack of opportunities for PCP training in the interpretation of the CGM data; "Ambulatory Glucose Profile (AGP)" generated by the Libre software following download
- Clinician discomfort with titration of new medications; especially insulin-based therapy

Johnson, M. et. Al. Diabetes Technology & Therapeutics 2019 Vol. 21, No. S2

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Adding CGM Protocols For Your Clinic; AAFP Website

https://www.aafp.org/pubs/fpm/blogs/inpractice/entry/cgm_guide.html

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Adding CGM Protocols For Your Clinic

- Choose a device; Abbott Freestyle® is simplest & least expensive system
- Get administration & staff buy-in; initial cost is usually <$1,000 for most practices (designate a "staff champion" to lead the practice)
- Map out the clinical protocol for placing a CGM patch in clinic & education about the device & food diary(10 minutes), scheduling 2 weeks return for patient CGM data download (3 minutes), data review & interpretation by provided (5 minutes), & then patient follow up for review of data & then initiation of treatment plan changes (can be same day)
- Establish a billing/reimbursement process & projected amount of use/cost/income

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Use of CGM in Hospital Setting?

- CGM use in the hospital setting has been adopted in most major hospital systems since the Covid-19 epidemic & increased risk in severe hyperglycemia in persons with diabetes given glucocorticoids
- CGM in the hospital decreases the frequency & staff requirements for fingerstick point of care capillary blood glucose testing & use of personal protective equipment (PPG)
- For patients it decreases the frequency of significant hyperglycemic & hypoglycemic episodes, as well as length of stay in hospital

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CGM in Hospital Setting Recommendations in 2022

- There are 2 CGM systems that are calibrated in the factory & do not require additional hospital calibration; Abbott FreeStyle Libre series (FreeStyle Libre 14 day & FreeStyle Libre 2) & the Dexcom G6
- Patients on insulin pumps using CGM should be allowed to continue using their devices as long at they or responsible family member are capable of it
- Patients in DKA or experiencing unstable glucose control in ICU's are ideal candidates to reduce at bedside work load
- CGM technology is not consistently reliable in the operating room (OR); attributed to electrocautery interference
- Criteria for appropriate patient selection must be established in each hospital; however interfacing with EMR's remains a problem

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Conclusions About CGM in Primary Care

- Flash CGM & rtCGM use improves glucose control, reduces A1c between -0.5% & -1.0% in patients with A1C's >8%; which translates into major decreases in risk for long-term complications, decreased costs & improved quality & length of life
- Flash CGM will identify patients with asymptomatic hypoglycemia which reduces CV morbidity & mortality
- Flash CGM can be used in any primary care setting with minimal training & interpretation of the 14 day report & is reimbursed

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Smart Insulin Pens

A reusable injector pen with insulin cartridges linked by Bluetooth to intuitive smartphone applications that can help people with diabetes better manage meal bolus insulin injections by calculating their bolus insulin doses with a "bolus wizard"

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"Smart Insulin Pen" Functions

- "Smart pens" communicate by Bluetooth to smart phone apps & are capable of calculating bolus insulin dose based on current blood sugar level, carbohydrate content of meal, & active insulin on board (similar to an insulin pump)
- Settings are prescribed by health care provider & indicated for patients on meal-time bolus insulin & uses rapid-acting insulin cartridges
- Keeps track of the time & amount of each insulin dose, has meal reminders to help prevent skipped or missed doses of insulin, & reduces frequency of hypoglycemia
- Notifies patient if insulin has expired or exceeded its temperature range to prevent using ineffective insulins
- Tracks diabetes data which can be downloaded at time of appointment or sent to health care team whenever needed

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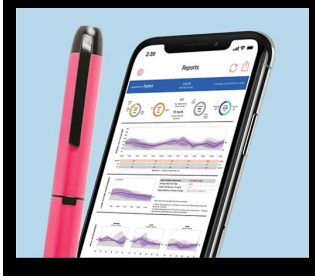
Smart Insulin Pens Available in US



- InPen® was the first FDA-cleared smart pen system & developed by Medtronic
- NovoPen® 6 & NovoPen Echo® Plus developed by Bigfoot Biomedical & Novo Nordisk & links with several CGM & database applications such as Diasend® (GlookoAB,) FreeStyle LibreLink® (Abbott), & mySugr® GmbH

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Can be dosed in 0.5 U increments

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CeQur™ Simplicity "Insulin Patch"

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CeQur Simplicity™ Insulin Patch

3 day single use "patch" which is filled with 200 U of short-acting insulin for meal-time or correction bolus & dosed in 2 U increments

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CeQur Simplicity™ Insulin Patch

- Compared to insulin pens in a clinical trial of patients using basal/bolus insulin & CGM the patch seemed to increase patient compliance & was preferred by a small majority of patients
- Covered by most insurance plans with average $50/mo co-pay

Bergenstal, R. et.al. Comparing Patch vs Pen Bolus Insulin Delivery in Type 2 Diabetes Using Continuous Glucose Monitoring Metrics and Profiles. J Diab. Sci. & Tech. Vol 16, 1167-1173 Sept. 2022

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New Diabetes Medications for 2022

- Tirzepatide (Mounjaro®) a "dual GIP/GLP-1 receptor agonist" presented @ last years meeting was FDA approved in May 2022
- Finerenone (Kerendia®) a "non-steroidal aldosterone receptor antagonist" FDA approved in 2021 & released this year

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Tripeptide (Mounjaro®)

A once-weekly dual glucose-dependent insulinotropic polypeptide (GIP) & glucagon-like peptide-1 (GLP-1) receptor agonist I discussed last year

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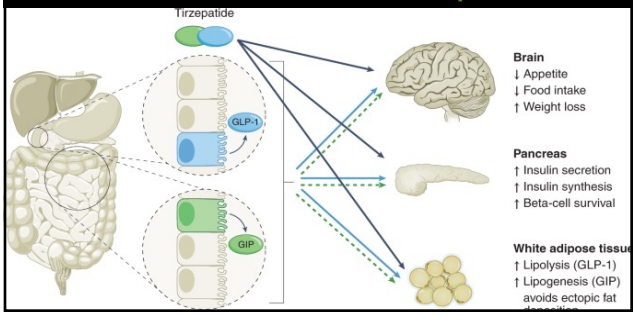
Mechanisms of Action of Tirzepatide



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Clinical Effects of Tirzepatide

		GLP-1	GIP
Pancreas	Beta cells	↑Insulin synthesis ↑Insulin secretion ↑Cell proliferation ↑Glucose sensing	↑Insulin synthesis ↑Insulin secretion ↑Cell proliferation ↑Glucose sensing
	Alpha cells	↓Glucagon secretion	↑Glucagon secretion
Brain		↑Satiety ↓Appetite	
Gastrointestinal		↓GI motility ↓Gastric emptying	
Adipose tissues			↑Lipolysis ↑Fatty acid synthesis ?Anti-lipogenic effect

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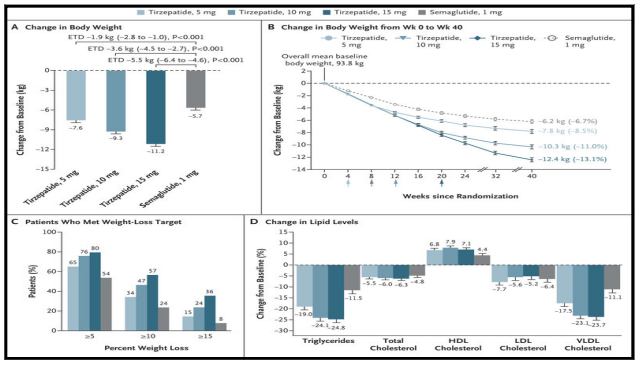

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Clinical Effects of Tirzepatide

- Reduction in A1c by 1.6% compared to placebo
- Reduced A1c by 0.5% more than semaglutide
- Lowers body weight by 22.5% at the highest dose of 15 mg/wk
- At highest dose, 63% of participants achieved a ***weight loss of over 20%*** of their body weight

Frias, J. et. Al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes August 5, 2021 N Engl J Med 2021; 385:503-515

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General Consensus for Tirzepatide

Most Potent Diabetes Medication Class Developed so Far……..

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Finerenone (Kerendia®)

FDA approved *nonsteroidal* Aldosterone receptor antagonist indicated for hypertension, renal & heart protection in patients with diabetes

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Finerenone (Kerendia®)

- FDA approved to reduce the risk of kidney function decline, kidney failure, cardiovascular death, non-fatal heart attacks, & hospitalization from heart failure in adults with chronic kidney disease (CKD) associated with T2DM
- Major adverse event as expected was mild hyperkalemia

Bakris, G. et. Al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. NEJM 2020; 383:2219-2229

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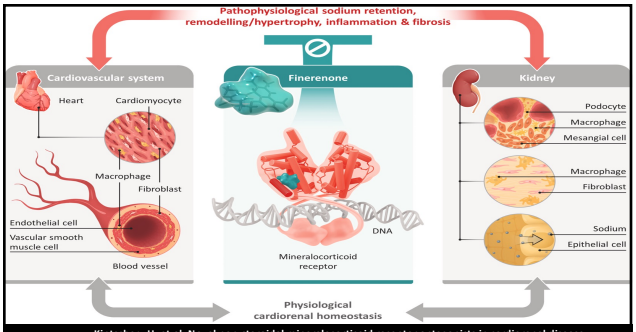

Kintscher, U. et.al. Novel non-steroidal mineralocorticoid receptor antagonists in cardiorenal disease. British Journal of Pharmacology Volume 179, Issue13, pp 3220-3254, Jul 2022

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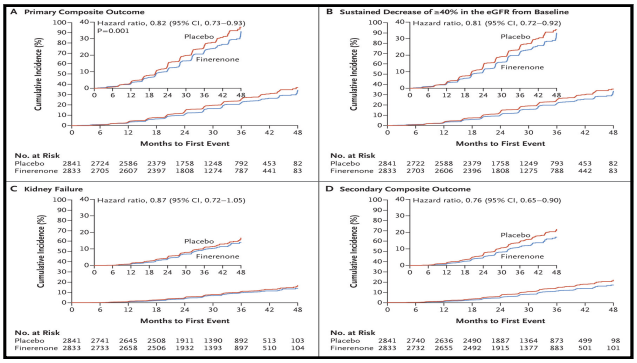

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Outcome	Finerenone (N=2833) no. of patients with event (%)	Placebo (N=2841) no. of patients with event (%)	Finerenone (N=2833) per 100 patient-yr	Placebo (N=2841) per 100 patient-yr	Hazard Ratio (95% CI)	P Value
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m²	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—

0.50 1.00 2.00
Finerenone Better Placebo Better

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SGLT2 Inhibitors vs Finerenone: One or The Other or Both?

- SGLT-2 inhibitors are much more potent than Finerenone in both renal & cardioprotection ……*plus they are potent diabetes medications*
- However, finerenone does add renal/cardioprotection when added for blood pressure control
- Head to head studies with finerenone vs ACE or ARB inhibitors have not been done

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CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) Equation (eGFR)

Was developed in an effort to create a more precise formula to estimate glomerular filtrate rate (GFR) from serum creatinine & reduce the underestimation of GFR decline with aging (lower BMI's) & racial bias of the previous calculation

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eGFR Calculator of National Kidney Foundation

- Normal GFR varies according to age, sex, body size, & declines with age. The National Kidney Foundation recommends using the CKD-EPI Creatinine Equation (2021) to estimate GFR.
- https://www.kidney.org/professionals/kdoqi/gfr_calculator
- Serum Cystatin C levels are recommended as well

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Cystatin C as Estimate of GFR

- Cystatin C is a low-molecular-weight (LMW; 13-kD) basic protein that is produced at a constant rate by all nucleated cells. It is freely filtered by the glomerulus & reabsorbed by the proximal tubule cells so that little is normally excreted in the urine
- Cystatin C is not affected by muscle mass like creatinine & is now used as a biomarker of renal disease eliminating bias of race, age, & most chronic diseases
- Normal Cystatin C levels are very low (~0.62 – 1.15 mg/L) but increases with decline in GFR in acute or chronic kidney disease
- *Cystatin C levels increase with use of glucocorticoids & certain inflammatory disease associated with high hsCRP levels so its use in these situations are not helpful*

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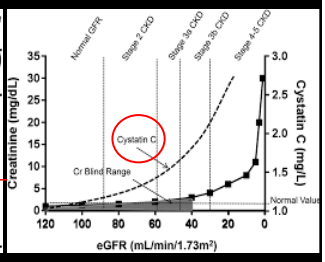
eGFR & Cystatin C-Based GFR Equations

Table-2: An equivalence guideline of S.CysC with GFR by CCL.

Cystatin C (mg/L)	GFR (CCL) ml/min/1.73m²
0.5 - 0.6	135 - 145
0.6 - 0.7	125 - 135
0.7 - 0.8	110 - 125
0.8 - 0.9	100 - 110
0.9 - 1.0	88 - 100
1.0 - 1.1	75 - 88
1.1 - 1.2	65 - 75



Kar, S. et. Al Cystatin C Is a More Reliable Biomarker for Determining eGFR to Support Drug Development Studies. The Journal of Clinical Pharmacology 2018, 00(0) 1–9 C 2018, T

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Conclusions About eGFR including Cystatin C

- **Improves detection of early renal dysfunction (both acute & chronic kidney injury) allowing for earlier intervention to preserve renal function**
- **Cystatin C rises before microalbumin**
- **Screening should be done annually in all patients with T2DM > 40 yrs.. of age**
- **Screening in children/adolescents with T1DM has not been advocated ….yet**

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The Good News With Diabetes

Over the past twenty-five years, research has shown that good control of diabetes, treatment of high blood pressure, high cholesterol can greatly reduce the complications of both T1DM & T2DMs by more than 30 percent.

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Prevention of T2DM

Overwhelming evidence that T2DM can be prevented with life-style intervention & multiple medications…..however the prevalence continued to rise exponentially until 2008

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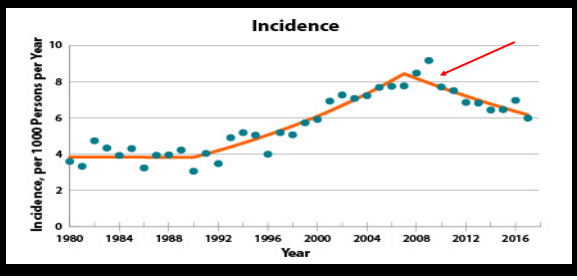
Prevalence of T2DM in US



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Why The Sudden Decrease in Prevalence of T2DM in US?

Unfortunately the decrease in new cases of diagnosed T2DM has been in non-Hispanic white adults most likely from increased public information, screening, & diabetes prevention programs in this population

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Prevalence of T2DM in West Virginia; 15.2%

Highest prevalence in country & has not decreased since 2010 but has increased from 11%!

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Prevention of T2DM

- **T2DM can be prevented with life-style changes; weight loss (5-7% of TBW), increased daily physical exercise, eating a healthier diet (less simple carbs/saturated fats), substituting water as principle source of fluids (rather than artificial sweeteners which increase weight gain & risk for DM) & finally not smoking (increases risk 30-40%)**
- **There are multiple organized diabetes prevention program's National Diabetes Prevention Program (NDDP) including WV which utilize the protocols; YMCA's, county health departments, major hospitals & universities have programs**
- ***But they are not being advocated by State health care agencies adequately enough or by primary care providers to their patients***

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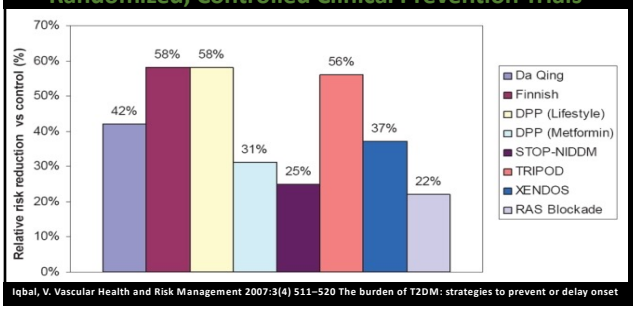
Relative Risk Reduction (%) of New-Onset T2DM in Randomized, Controlled Clinical Prevention Trials



Iqbal, V. Vascular Health and Risk Management 2007:3(4) 511–520 The burden of T2DM: strategies to prevent or delay onset

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Life-Style Changes Are More Effective Than Most Medications to Prevent T2DM

Except…..

GLP-1 agonists

Dual GIP/GLP-1 agonists?

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Medications Which Prevent T2DM

- Metformin
- TZD's (Pioglitazone)
- α-glucosidase inhibitors
- Orlistat
- ACE/ARB inhibitors
- GLP-1 agonists
- Dual GIP/GLP-1 agonists?

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Relative Effectiveness of These Medications at Reducing Risk for T2DM

- TZD's; pioglitazone (TRIPOD) & rosiglitazone (DREAM) trials are *3X more effective than metformin* at reducing conversion of IGT into overt T2DM (72 & 62%) respectively compared to metformin (32%)
- α-Glucosidase inhibitors; acarbose (STOP-NIDDM) & decrease conversion of IGT to T2DM by 36%
- Ramipril also slightly effective at reducing risk of T2DM
- GLP1 agonist; liraglutide was recently shown to risk for T2DM *3X compared* to usual therapy, & improve CV risk factors

Lancet Volume 389, No. 10077, p1399–1409, 8 April 2017

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In West Virginia we have go to do better!!

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Prevention of T1DM

T1DM is an autoimmune disease in which the β-cells are gradually destroyed by a T-cell immune infiltration of the islets. Studies are ongoing to preserve β-cell function to prevent diabetes or β-cell/ islet cell transplantation once hyperglycemia is established

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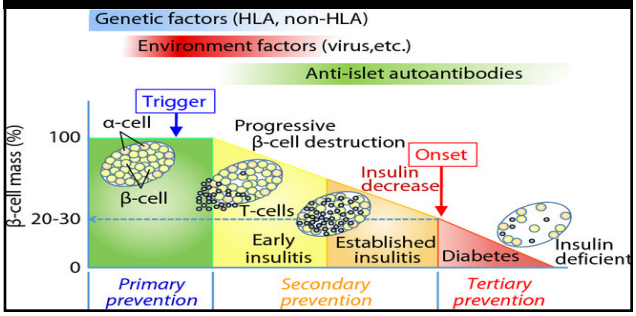
Natural History & Pathogenesis of T1DM



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Strategies at Primary Prevention of T1DM

- Identify those at genetic risk for T1DM; *but…….90% of new-onset T1DM have no family history*
- Early screening for autoantibodies to insulin (IAA), GAD65 (GAD antibody [GADA]), ZnT8 (ZnT8A), & tyrosine phosphatase (ICA512A or IA2A) in family members with T1DM *(15-fold increased risk)*
- Relatives with "high titers" of multiple islet autoantibodies (IAA's) have a 75% risk of developing T1DM within 5 years
- Intervention prior to total destruction of β-cells with some form of immunological approach has been studied for the past 30 years

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Strategies at Primary Prevention of T1DM

- The T1DM Trial was the first attempt to prevent progression to diabetes in ICA+ relatives by administering either oral or SQ insulin prior to onset of DM; these studies failed
- Use of various vaccine agents such as; GAD, GAD-alum, Coxsackie B3, & BCG in various studies have failed so far
- A trial of different infant formulas (hydrolyzed & non-hydrolyzed) at birth in children born to T1DM parents is in clinical trial

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Strategies at Primary Prevention of T1DM

- Screening for autoantibodies to insulin (IAA), GAD65 (GAD antibody [GADA]), ZnT8 (ZnT8A), & tyrosine phosphatase (ICA512A or IA2A) in family members with T1DM *(15-fold increased risk)*
- Relatives with "high titers" of multiple islet autoantibodies (IAA) have a 75% risk of developing T1DM within 5 years
- IAA+ patients are currently have been enrolled in several primary prevention trials using either CTLA4-Ig (Abatacept), an anti-CD3 antibody (Teplizumab) while a study using siplizumab (anti-CD2 monoclonal antibody) begins this month

Harold, K. et.al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes
N Engl J Med 2019; 381:603-613

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Strategies at Secondary Prevention of T1DM (New or Recent-Onset T1DM)

- In patients with new-onset T1DM with IAA+ & residual c-peptide multiple medications are also in clinical trials to preserve endogenous insulin secretion
- Teplizumab in clinical trials is most successful so far & has shown to delay a diagnosis of T1DM for up 5 years

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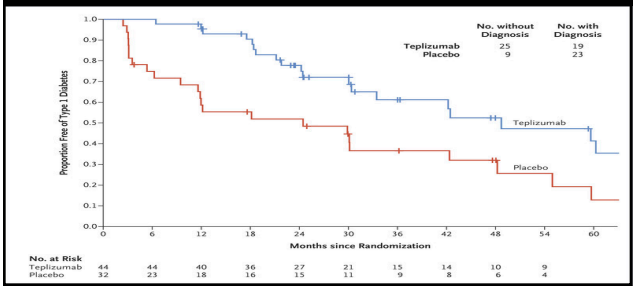
Teplizumab in Relatives at Risk for T1DM

Harald, K. et.al. N Engl J Med 2019; 381:603-613, Aug 2019



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Vaccines for Secondary Prevention of T1D

- bacillus Calmette-Guérin (BCG) the old TB vaccine has been studied for over 10 yrs. by a group @ Harvard
- 3 yrs. after two BCG injections the treatment corrects the "over-methylation" of the Treg gene Foxp3, a characteristic of the autoimmune form of diabetes
- They hope that administration of the vaccine earlier in life would prevent β-cell destruction & new onset T1DM

Faustman DL, Wang L, Okubo Y, Burger D, Ban L, Man G, Zheng H, Schoenfeld D, Pompei R, Avruch J, Nathan DM. Proof-of-concept, randomized, controlled clinical trial of Bacillus-Calmette-Guerin for treatment of long-term type 1 diabetes. PLoS One. 2012;7(8):e41756. doi: 10.1371/journal.pone.0041756. Epub 2012 Aug 8.

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Strategies at β-Cell Replacement for Treatment of T1DM

- Transplantation of cadaver or living donor isolated islet cells into the portal vein was partially successful in 1999 using the "Edmonton Protocol." However, patients have to be maintained on immune suppression to prevent rejection & long-term survival of islets is now 6 yrs. @ the University of Alberta
- Encapsulation of islet cells for transplant removes the requirement of immunotherapy & also raises the possibility of xenotransplants from animals
- Induction of stem cells into functional β-cells for transplant has been the "Holy Grail" for many years as it eliminates need for immunosuppression & offers a limited supply of functional β-cells for transplant

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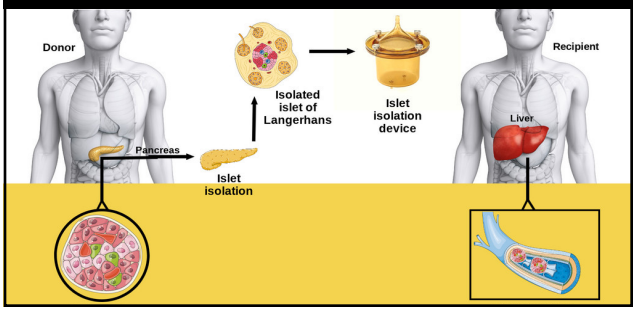
Edmonton Protocol for Islet Cells Transplantation



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Pluripotent Human Stem Cells Have Successfully Been Differentiated into Functional Islet Cells In Vitro, & Transplanted into T1DM Patients

Encapsulated stem-cell derived islet cells have been implanted subcutaneously or infused intravenously by two different groups & shown to produce insulin/C-peptide & functionally respond to a meal challenge

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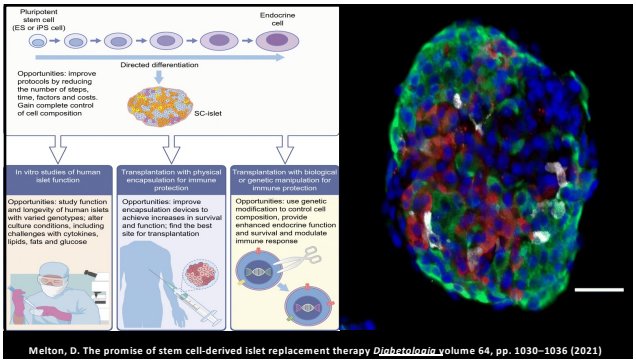

Melton, D. The promise of stem cell-derived islet replacement therapy *Diabetologia* volume 64, pp. 1030–1036 (2021)

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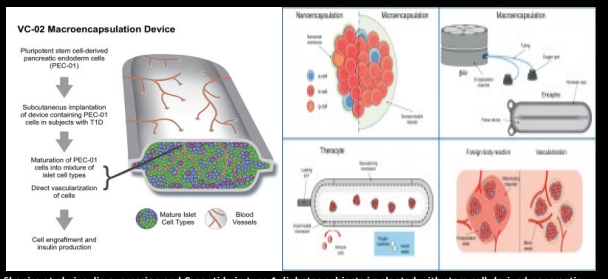
Encapsulation of Islet Cells for Transplantation



Shapiro et al., insulin expression and C-peptide in type 1 diabetes subjects implanted with stem cell-derived pancreatic endoderm cells in an encapsulationdevice2021, Cell Reports Medicine 2, 100466 December 21, 2021 ª 2021

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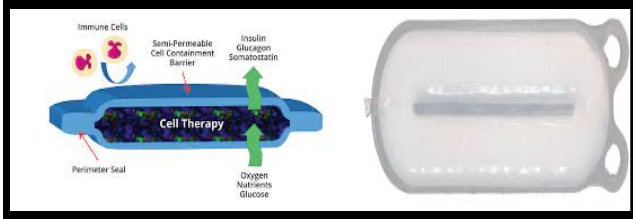
ViaCyte's Encaptra Cell Delivery System



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Encapsulated of Islet Cells for Transplantation

- Engraftment & insulin expression were observed in 63% of VC-02 units explanted from subjects at 3-12 months post-implant. Six of 17 subjects (35.3%) demonstrated positive C-peptide as early as 6 months post-implant. Shapiro, A. et. al. Cell Rep Med. 2021 Dec 2;2(12):100466.
- In a related study, the group reported another set of patients had increased fasting C-peptide levels, increased glucose-responsive C-peptide levels, developed mixed meal-stimulated C-peptide secretion. Explanted grafts contained cells with a mature β cell phenotype that were immunoreactive for insulin, islet amyloid polypeptide, & MAFA. Ramzy, A. et. Al. Cell Stem Cell. 2021 Dec 2;28(12):2047-2061.e5.
- Vertex Pharmaceuticals is currently conducting a Phase I clinical trial infusing human derived stem cells (VX-880) intravenously into 17 patients

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Conclusions

- "Flash" CGM is a very effective adjunct to self-glucose monitoring in primary care for individuals with all forms of diabetes & it's use improves A1C levels & reduces risk for long-term complications
- "Smart" insulin pens & "insulin patches" are now available for patients requiring bolus insulin injections
- eGFR/Cystatin C improve early detection of diabetic nephropathy reducing age, weight-based, & racial bias which under estimates this risk
- T2DM has been proven preventable for nearly 20 yrs.. & there are multiple nationally established programs available while efforts to delay or prevent the onset of T1DM, as well as β-cell replacement are progressing rapidly

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