Diabetes Update 2011
for the OC Diabetes Group

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Diabetes Update 2011 - Agenda

- Diabetes Update: Highlights from ADA 2010 and EASD 2010
  - HbA1c Targets
  - Diabetes Complications
    - Cardiovascular Risk
    - Nephropathy, Neuropathy
    - Sleep apnea
    - Cancer, Depression
    - Hypoglycemia
  - Potential New Therapies
  - Diagnostic Criteria for Diabetes
- New Insights in Nutrition
- Environmental Health Hazards
  - Endocrine disrupting chemicals
  - Air Pollution and "Electromagnetic Pollution"

HbA1c – No More "One Size Fits All" Targets

Figure 1. Balancing the Risks and Benefits of Tight Glucose Control

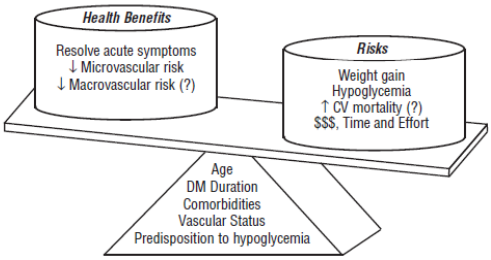


Figure 2. Proposed Individualized Glycemic Targets Based on Patient Comorbidities

Considerations
1. High risk for hypoglycemic event(s)
2. Likely low benefit from HbA1c reduction (e.g., age, comorbid conditions, advanced disease)
3. Glycemia difficult to control despite efforts
4. Increased 'vascular age' (e.g., known cardiovascular disease)

Number of Considerations	Target HbA1c
If 0 →	<6.5-7%
If 1 →	<7.5%
If 2+ →	7.5-8.0%

Glucose Control and Cardiovascular Risk

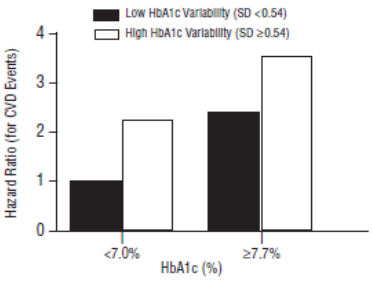
- The "Legacy Effect" – concept of metabolic memory
- CV benefit from intensive glucose control may take 15-20 years to become statistically manifest
  - EDIC (Epidemiology of Diabetes Interventions and Complications) -despite HbA1c levels that essentially converged during the post-randomized study follow-up period, a nearly 50% reduction in the composite CV event endpoint was realized in the intensive therapy cohort in the original DCCT
  - In the UKPDS follow-up, tighter control with sulfonylureas and insulin was eventually associated with a 15% relative risk reduction in myocardial infarction despite similar HbA1c trends between the initially randomized groups.
- RACED substudy from the VADT - selected participants underwent coronary artery calcium (CAC) scoring by electron beam computed tomography (EBCT) at baseline. Those with baseline CAC scores of >400 Agatston units had worse outcomes with tighter glucose control, whereas the opposite was true in those with scores <100.

Asymptomatic Diabetics at Risk for Subclinical Cardiovascular Disease

- 20 Type 1 diabetics, 27 Type 2 diabetics without a history of CVD were evaluated for the presence of cardiomyopathy, hypoperfusion, and cardiac autonomic neuropathy
- Treadmill testing was negative in all patients
- Echocardiography showed diastolic dysfunction in 10% and 11% of patients with Type 1 and Type 2 diabetes, respectively
- Hypoperfusion by nuclear imaging was found in 35% of the Type 1 and 60% of Type 2 diabetic cohorts
- Cardiac autonomic dysfunction (based on heart rate variability, spectral analysis, and a battery of tests developed originally by Ewing) was diagnosed in 60% of Type 1 and 77% Type 2 patients

HbA1c Variability and Cardiovascular Risk

Figure 2. Risk of CVD Events by Mean and SD of HbA1c



- 689 Japanese Type 2 diabetic patients had an average of 26 ± 14 HbA1c values during a mean follow-up of 3.3 years. 61 patients met the primary endpoint, which included all incident CVD events (i.e. stroke, myocardial infarction, or angina requiring revascularization)
- 5-yr cumulative CVD incidence was 4.9, 8.7, 17.1, and 26.2% in the 1st to 4th quartiles of SD (measurement of variability; $p<0.001$)
- As expected, cumulative CVD incidence was higher in patients with higher mean HbA1c
- HbA1c SD and mean HbA1c were significantly correlated ($r=0.54$, $p<0.001$).

Glucose Variability & Autonomic Dysfunction

- After adjustment for age, SDG (measurement of glucose variability) was negatively correlated with baroreflex effectiveness index and indices of heart rate variability (with greater variability indicating a more functional autonomic system)
- After adjustment for 48-hour mean glucose, the correlation with the baroreflex index remained statistically significant (r=-0.572, p=0.008).
- HbA1c, in contrast, was not correlated with any of the autonomic measures.
- Thus, glucose variability, as assessed by CGM, was associated with autonomic dysfunction, whereas HbA1c was not
- These data give support to the notion that it is the variability in blood glucose that has a greater impact on end organs than does mean blood glucose.

Renal Protection

- In the follow up to the DCCT, past intensive glucose control continued to benefit renal outcomes, even after 20 years.
- Development of serum creatinine levels >2 mg/dl was reduced by more than 60% and the need for dialysis or transplantation by more than 70%.

Table 4. Preventing/Delaying Renal Disease in Diabetes

- Glycemic control
- Blood pressure reduction
- Renin-angiotensin-aldosterone axis inhibition
- Avoid acute kidney injury
  - Avoid/minimize use of NSAIDs
  - Avoid/minimize use of radiocontrast dyes
  - Prevent or treat promptly any urinary tract infections

Diabetic Neuropathy

Type of Neuropathy	*Symptoms*
Distal somatosensory polyneuropathy	■ Pain or loss of sensation in toes, feet, legs, hands, and arms ("stocking-glove" sensory loss)
Acute mononeuropathies	■ Cranial: most commonly affecting III, IV, and VI (diabetic opthalmoplegia), or facial nerve (Bell's palsy) ■ Lumbar polyradiculopathy (most commonly affects L2-L4 roots): pain in the thighs, hips, or buttocks, weakness in the legs ■ Thoracic polyradiculopathy (less common, affects T4-T12 roots): severe abdominal pain, often with band-like pattern ■ Peripheral: most commonly affecting the median or peroneal nerves ■ Mononeuropathy multiplex: multiple mononeuropathies in the same patient
Autonomic neuropathy	■ CV: postural hypotension, postprandial hypotension, fixed tachycardia, silent MI, sudden cardiac death ■ GI: esophageal motility disorders, gastroparesis, constipation, diarrhea, incontinence ■ GU: bladder dysfunction, incontinence, sexual dysfunction ■ Distal anhidrosis, gustatory sweating ■ Abnormal pupillary responses

Sleep Apnea = Risk Factor for Diabetic Neuropathy

- In a study of 190 diabetic patients (45% Caucasian/55% South Asian, 58% men, mean age 57±12 yrs, mean BMI 33.5, mean HbA1c 8.2%±1.6), OSA (obstructive sleep apnea) was shown to be a significant predictor of diabetic neuropathy after adjustment for blood pressure, HbA1c, cholesterol, triglycerides, duration of diabetes, smoking, alcohol, gender, renal function, BMI, age, and use of antihyperglycemic, antihypertensive, antiplatelet, and lipid-lowering agents (OR 2.3, 95% CI 1.14-4.6; p=0.02).
- prevalence of diabetic neuropathy was significantly higher in those with OSA(58.3%) than in those without (29.9%).
- Moreover, the AHI (apnea-hypopnea index) significantly correlated with the neuropathy score.

Sleep Apnea Associated with Severe Metabolic Derangements

- 22 of 30 (73%) consecutive obese patients with Type 2 diabetes were determined to have OSA based on an AHI ≥10/hour observed during polysomnography
- Patients with OSA had higher HbA1c levels (9.7% vs. 8.9%; p=0.03), BMI (33.8 vs. 29.4; p=NS), triglycerides, insulin resistance scores, C-reactive protein, and lower HDL-c, as compared to controls
- HbA1c correlated best with AHI ($r = 0.39$, $p<0.001$)
- these data raise the concern that OSA and diabetes may have additive, or perhaps even synergistic, effects on risk of cardiovascular events.

Diabetes and Cancer

- cancer is a close contender to cardiovascular disease as the leading cause of death in Type 2 diabetes (29% vs. 31% in a population study by the US Centers for Disease Control[CDC]), and may soon overtake it
- People with Type 2 diabetes have an increased risk of certain cancers, predominantly those of the endometrium (OR 2.10), liver (OR 2.50), breast(OR 1.20), and pancreas (OR 1.82)
- People with Type 2 diabetes have a higher mortality rate from cancer as compared to the general population; many factors such as obesity, hyperinsulinemia, hyperglycemia, or delayed screening may contribute to this increased mortality rate
- Metformin use has been associated with reduction in colon cancer and breast cancer

Diabetes and Depression

- Inflammation may mediate the relationship between diabetes and depression
- Elevated levels of interleukin-6 (IL-6), TNF-α (TNF), and C-reactive protein (CRP) are common to both Type 2 diabetes and depression.
- 3,014 adults, aged 70-79 yrs, who participated in the Health ABC Study
- IL-6 was significantly higher ($p<0.05$) among DM2 patients with depression (4.4 versus 2.7 for diabetes only, 2.6 for depression only, and 2.3 for healthy controls).
- CRP was significantly higher in DM2 and depression (5.3) compared to depression only (2.9, $p<0.05$) or healthy controls (2.8, $p<0.05$), and approached statistical significance for diabetes only (3.6, $p=0.07$).
- After adjustments for potential confounding factors, the interaction between DM2 and depressed mood with levels of IL-6 and CRP was significant.

Hypoglycemia

- 16-year follow-up study on cognitive function in Type 1 diabetics exposed to severe hypoglycemia before the age of 10 years
  - 27 DM1 children matched with controls of the same sex, age, and social background were followed into adulthood. 9 had been exposed to severe hypoglycemia and 18 had not
  - Diabetics with early severe hypoglycemia had reduced cognitive ability, with an overall score of -1.0 SD (95% CI -0.5 to -1.5), whereas diabetics without severe hypoglycemia were similar to controls (-0.1 SD, 95% CI -0.4 to 0.2).
  - Specifically, they scored lower in problem solving (-2.2 SD), verbal function (-1.5 SD), and psychomotor efficiency (-1.3 SD).
  - cognition scores were lowest in those exposed to hypoglycemia before 6 yrs of age (overall -1.3 SD).

Hypoglycemia (cont'd)

- Retrospective analysis of 860,845 DM2 patients within a large healthcare claims database
  - Using a multiple logistic regression model with adjustment for confounding variables, they found that people with hypoglycemic events had a 79% greater risk of CV sequelae (OR 1.79, 95% CI 1.69-1.89) than people without hypoglycemia.
  - Only two variables, age (OR 13.25 for age 65+) and prior CV disease (OR 2.87) held a greater risk for acute CV events than hypoglycemia

Continuous Glucose Monitoring

Table 2. Impact of CGM vs. SMBG on HbA1c and Glucose Excursions

Outcome	*All CGM vs. SMBG*	*'Real Time' CGM vs. SMBG*	*'Retrospective' CGM vs. SMBG*
HbA1c (relative % Δ from baseline):			
4-8 wks	-4.7*	-4.7*	N/A
12-16 wks	-8.4*	-9.3*	-4.6*
24-26 wks	-2.7*	-2.7*	N/A
Duration BG (min/day)			
≤55 mg/dl	-4.3*	-9.3*	-9.3*
≤80 mg/dl	-11.3*	-10.4*	-10.4‡
71-180 mg/dl	59.5*	69.8*	69.8‡
≥240 mg/dl	-49.3*	-49.3*	N/A
Hypoglycemic events/day (BG <70 mg/dl)	0.1*	0.0	0.3†

BG = blood glucose, CGM = continuous glucose monitoring, SMBG = self-monitoring of capillary blood glucose.
*p<0.0001; †p<0.001; ‡p=NS

Table 1. Pharmacological Therapies for Type 2 Diabetes

Class	*Examples*	*Mechanism*	*Action*
Sulfonylureas	Glyburide Glipizide Glimepiride	Closes K_{ATP} channels	↑ Pancreatic insulin secretion
Glinides	Repaglinide Nateglinide	Closes K_{ATP} channels	↑ Pancreatic insulin secretion
Biguanides	Metformin	Activates AMP-kinase in the liver	↓ Hepatic glucose production
Thiazolidinediones	Rosiglitazone Pioglitazone	Activates PPAR-γ, mainly in adipocytes	↑ Peripheral insulin sensitivity
α-Glucosidase inhibitors	Acarbose Miglitol	Blocks small intestinal alpha-glucosidase	↓ Intestinal carbohydrate absorption
GLP-1 agonists	Exenatide Liraglutide	Activates GLP-1 receptors	↑ Pancreatic insulin secretion; ↓ pancreatic glucagon secretion; delays gastric emptying; ↑ satiety
Amylinomimetics	Pramlintide	Activates amylin receptors	↓ Pancreatic glucagon secretion; delays gastric emptying; ↑ satiety
DPP-4 inhibitors	Sitagliptin Saxagliptin	Inhibits dipeptidyl peptidase-4, ↑ endogenous incretin levels	↑ Pancreatic insulin secretion; ↓ pancreatic glucagon secretion
Bile acid sequestrants	Colesevelam	Binds bile acid cholesterol	unknown
D2 agonists	Bromocriptine	Activates dopaminergic receptors	Alters hypothalamic control of insulin sensitivity
Insulin	NPH, Regular, Glargine, Detemir, Lispro, Aspart, Glulisine	Activates insulin receptors	↑ Glucose disposal; ↓ hepatic glucose production; ↓ proteolysis, lipolysis, ketogenesis

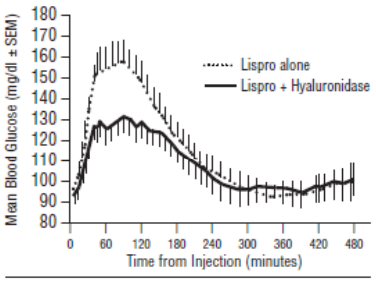
Potential New Therapies for Type 2 Diabetes

- **Sodium-glucose cotransporter (SGLT)-2 inhibitors** block glucose reuptake in the proximal nephron leading to glycosuria, particularly in the postprandial period
  - While modest efficacy and weight loss have been shown in early clinical trials, concern has been raised about potential for increasing urinary tract and genital infections
- **SPPARMs:** PPAR-γ activation improves insulin resistance, hyperglycemia, endothelial function, and markers of inflammation. But it is also associated with unwanted side effects such as weight gain, fluid retention, and increased risks of heart failure and bone fractures. SPPARMs are selective modulators of the PPAR-γ receptor developed to separate insulin-sensitizing actions from the less desirable effects.
  - Early evidence from clinical studies suggests favorable metabolic effects and potentially fewer adverse effects with the SPPARM INT131
- **PTP-1B Antisense Inhibitors:** Protein tyrosine phosphatase 1B (PTP-1B) is a negative regulator of insulin action. Reduction of PTP-1B activity enhances insulin sensitivity.
  - weekly injections of ISIS 113715 showed favorable effects on glycemia and dyslipidemia, increase in adiponectin and modest weight loss
- **GPR-119 Agonists:** GRP-119 is a G-protein coupled receptor that regulates glucose by enhancing glucosesensitive insulin secretion while simultaneously stimulating incretin hormone release from the intestines. Suppressive effects on food intake and GI motility have also been described.

More Physiologic Rapid-Acting Insulins

- Hyaluronidase (an enzyme that increases tissue permeability, accelerating insulin absorption) was used in combination with the rapid-acting insulin analogue, lispro, to determine if postprandial glycemic variability can be improved in Type 1 (n=22) and Type 2 (n=23) diabetic patients
- Two hrs before a standardized liquid meal, patients were titrated to a target glucose of 110 ± 20 mg/dl with iv glucose +/- insulin. Immediately pre-meal, lispro was injected with or without hyaluronidase; plasma insulin and glucose were then measured for 8 hrs.
- Co-injection with hyaluronidase reduced hyperglycemic excursions in both groups with equal (Type 1) or less (Type 2) risk of hypoglycemia.
- A greater percentage of patients met the ADA postprandial glucose goal of <180 mg/dl with hyaluronidase/lispro combination vs. lispro alone (Type 1: 91% vs. 55%; Type 2: 71% vs. 48%)

Figure 5. Type 1 Diabetes Meal Study with Lispro + Human Hyaluronidase



New Insulin Formulations

VIAject – ultra rapidly absorbed form of human regular insulin

- VJ7 (VIAject 100IU/mL, pH7) exhibited a significantly faster absorption than lispro (Tmax, 23 vs. 60 minutes; difference, -30 minutes [p<0.05]) and faster onset of action measured by time to early half-maximal glucose infusion rate (GIR): 25 vs. 44 minutes (difference, -18 minutes [p<0.05])

Degludec – ultra long-acting insulin

- Upon subQ injection, degludec forms soluble multi-hexameric structures, resulting in a protracted pharmacological profile, allowing once daily or even 3 times a week injections

"Smart Insulins" which combine insulin with a built-in glucose sensor are in development, with Phase 1 studies imminent

Alternate Insulin Delivery

- Nasulin – intranasal ultra-rapid insulin
  - In healthy volunteers, Tmax was significantly shorter with Nasulin (18.7±2.73minutes) than for lispro 10 IU (43.1±3.46 minutes) (p<0.001)
  - smaller counter-regulatory glucagon response afterwards
  - Less frequent symptomatic hypoglycemia
- Sublingual administration of insulin
  - Viatab technology
- Buccal Insulin
  - Ora-lyn Rapidmist – liquid formulation of Regular Human Insulin with spray propellant
- Oral Insulin
  - IN-105 (Biocon) is a human insulin molecule conjugated on position B29 with polyethylene glycol to reduce degradation
- Inhaled Insulin
  - Technosphere

Exenatide Before Islet Transplant?

- GLP-1 receptor agonist, exenatide, has been shown to improve insulin secretion in response to glucose in addition to protecting beta cells from apoptosis and promoting beta-cell regeneration in animals.
- Exenatide pretreatment of non-human primates before islet transplantation has been associated with long-term normoglycemia and robust insulin secretory responses for up to 2 years after transplantation
- Beta-cell function of pancreatectomized cynomolgous monkeys that underwent islet transplantation improved post-transplant in the animals that were pretreated with exenatide (53.3% vs. 94.9%), while a marked decrease was noted in untreated animals (20.2% vs. 1.89%), as well as in animals treated only post-transplant (28.8% vs. 13.8%). IV glucose tolerance tests showed normal glucose and insulin curves in the pre-treated group only

Gut Microflora and Metabolism

- Vrieze *et al. from the Netherlands and* Finland conducted a double-blind study in which 18 male subjects with newly diagnosed and untreated metabolic syndrome (BMI ≥30, FPG >100 mg/dl, triglycerides >142 mg/dl) underwent bowel lavage through a duodenal tube followed by randomization to either allogenic fecal transplantation (from lean males, n=9) or autologous fecal transplantation (reinfusion of own collected feces, n=9)
- At 12 weeks after the procedure, fasting triglycerides (as measured by TG/ApoB ratio) were significantly reduced (1.43 ± 0.21 to 1.11 ± 0.18, $p<0.01$) among the subjects who received allogenic donor feces (from lean subjects), but not after autologous feces infusion.
- Improvement was seen in both peripheral insulin sensitivity as measured by clamp (from 26.2 to 45.3 µmol/kg.min, $p=0.02$) and hepatic insulin sensitivity (suppression of endogenous glucose production; from 51.5% to 61.6 %, $p=0.08$) at 6 weeks in the allogenic group, but not in the autologous group.
- These results suggest a potential role of gut flora in the disturbances of glucose and lipid metabolism in obesity

Diagnostic Criteria for Diabetes

Table 1. 2010 ADA Criteria for Diagnosis of Diabetes and Pre-Diabetes

	Prediabetes	*Diabetes*
Fasting plasma glucose (mg/dl)	100-125	≥126
2-hour plasma glucose (mg/dl)	140-199	≥200
HbA1c (%)	5.7-6.4	≥6.5

- **Problems with HbA1c**
  - not a sensitive test and estimations of prevalent diabetes based on it may not be correct;
  - assay is variable
  - ethnic/age differences exist in its relationship to glucose;
  - many conditions interfere in the performance of the assay (hemoglobinopathies, anemia, renal failure)
- ARIC study
  - 11,092 participants without cardiovascular disease or diabetes at baseline
  - 15 years of follow-up
  - HbA1c 5.7-6.4% was associated with increased risk for subsequent diagnosed diabetes(HR 3.0), coronary artery disease (HR 1.6), ischemic stroke (HR 1.6), and all-cause mortality (HR 1.4).

Diagnostic Criteria for Diabetes

- Catalonia , Spain - 1,144 non-diabetic subjects (ages 45-75 years) screened annually. (65% women, mean age 61.4 years, BMI 29.9)
- Individuals were categorized as normoglycemic (64.8% using 2-hr PG, 68.7% using FPG, 83.4% using HbA1c), prediabetic (26.6% using 2-hr PG, 28.5% using FPG, 15.3% using HbA1c), and diabetic(8.6% using 2-hr PG, 2.8% using FPG, 1.3% using HbA1c)
- Among individuals diagnosed with diabetes either by 2-hr PG or HbA1c, only 12.9% were identified by both criteria, underscoring the large proportion of discordant cases.
- Australia: over 50,000 individuals screened for diabetes risk between years 2006-2008
- Using OGTT, 9.6% identified as diabetic, 16.9% as IGT, and 8.2% as IFG
- HbA1c identified fewer subjects with diabetes (6.5%) and classified an additional 17% as high risk for diabetes, using HbA1c 6.0-6.4%
- Among those classified as diabetic by glucose criteria, majority (60.7%) had HbA1c below 6.5%.
- the concordance between glucose and HbA1c criteria was poor

Diagnostic Criteria for Diabetes

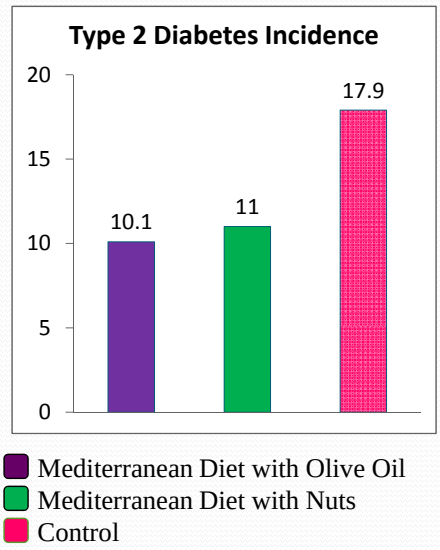
- France: 1,157 individuals at risk for diabetes underwent an OGTT, and HbA1c was also obtained.
- Fewer patients met the criteria for diabetes based upon OGTT (n=76) than HbA1c (n=113). A similar number of individuals met criteria for prediabetes (n=307 and 299, respectively).
- the concordance between the tests was poor—a third of individuals with HbA1c ≥6.5% had a normal OGTT result.
- Further analysis showed that individuals with both an abnormal OGTT and increased HbA1c (≥5.7%) were at the highest diabetes and cardiovascular risk.
- Korea: 35,624 individuals screened for FPG and HbA1c
- Roughly similar proportions were identified as diabetic (3.2% by FPG and 2.9% by HbA1c), but the tests classified different individuals with the disease.
- among those meeting either criteria, 31.6% were diagnosed by FPG only, 23.5% were diagnosed by HbA1c only, and 44.9% by both tests.
- Those identified only by HbA1c were older, had lower hemoglobin concentration, lower blood pressure, lower fasting insulin, and lower HOMA-IR compared to those identified only by FPG.
- the metabolic derangements in the groups diagnosed by FPG and by HbA1c may be quite different.

PREDIMED Study – Mediterranean Diet Decreases Risk of Type 2 Diabetes

- Substudy **PREDIMED-Reus** was conducted in the only one of the Spanish centers of the overall trial to require a yearly oral glucose tolerance test in nondiabetic individuals.
  - 418 nondiabetic subjects aged 55 to 80 years were randomized to the low-fat diet (control group), or one of two Mediterranean diets supplemented with either free virgin olive oil (1 L/week) or nuts (30 g/day). Diets were without limits, and no advice on physical activity was given.
- The principal components defining a traditional Mediterranean diet, which were recommended in the present study, are:
  - Abundant use of olive oil for cooking and dressing.
  - Increased consumption of fruit, vegetables, legumes, and fish.
  - Reduction in total meat consumption, recommending white meat instead of red or processed meat.
  - Preparation of homemade sauce with tomato, garlic, onion, and spices with olive oil to dress vegetables, pasta, rice, and other dishes.
  - Avoidance of butter, cream, fast-food, sweets, pastries, and sugar-sweetened beverages.
  - In alcohol drinkers, moderate consumption of red wine.

PREDIMED Results

- After median follow-up of 4 years:
- 52% reduction in Diabetes incidence without weight loss
- Multivariable-adjusted hazard ratios were 0.49 and 0.48 in the Mediterranean-diet groups supplemented with olive oil and nuts respectively, compared with the control group.



EDC – Endocrine Disrupting Chemicals

- An endocrine-disrupting substance is a compound, either natural or synthetic, which through environmental exposures alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment.
- Issues key to understanding the mechanisms of action and consequences of exposure include age at exposure, latency from exposure, the mixture of chemicals, dose-response dynamics, and long-term latent effects.
- Because of the shared properties of the chemicals and the similarities of the receptors and enzymes involved in the synthesis, release, and degradation of hormones, no endocrine system is immune to endocrine disrupting chemicals.
- Effects of endocrine disrupting chemicals may be transmitted to further generations through germline epigenetic modifications or from continued exposure of offspring to the environmental insult.
- The evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis.
- The Precautionary Principle is key to enhancing endocrine and reproductive health, and should be used to inform decisions about exposure to, and risk from, potential endocrine disruptors.

EDCs and Glucose Metabolism

- epidemiological studies have linked high dioxin levels with increased risk for diabetes or altered glucose metabolism
- BPA at environmentally relevant doses inhibits the release of adiponectin, an adipocyte-specific hormone that increases insulin sensitivity
- Low doses of BPA were shown to impair the molecular signaling that leads to secretion of glucagon by suppressing intracellular calcium ion oscillations in cells in response to low blood glucose levels
- BPA exposure, particularly in development, increases the risk of mammary cancer, obesity, diabetes, and reproductive and neuroendocrine disorders.
- a cross-sectional analysis in over 1400 adults in the US showed a significant correlation between BPA concentrations in urine with cardiovascular disease and abnormal concentrations of liver enzymes

EDCs and Obesity

- An overview of the toxicology literature suggests that exposure to many other environmental chemicals, including pesticides, can cause weight gain
  - eg. organochlorines such as DDT, endrin, lindane, and hexachlorobenzene; organophosphates; carbamates; polychlorinated biphenyls; polybrominated biphenyls which are used as fire retardants; other plastic components such as phthalates; perfluoroctanoic acid (PFOA); heavy metals such as cadmium, lead, and arsenic; and solvents.
- The weight gain associated with these chemicals tends to occur at low levels of exposure, not at high doses in which most toxicity studies have been conducted.

EDCs and Cardiometabolic Disease

- Recent data clearly suggest that a heterogeneous group of exogenous advanced glycation end-products (AGEs) have a negative impact on cardiometabolic tissues.
- Tobacco use and food cooked at high temperatures, precooked meals, and some beverages contain large amounts of AGEs that are absorbed from the human gastrointestinal tract.
- AGEs cause tissue injury through intracellular generation of free radicals and triggering oxidative stress, through the interaction of AGEs with a multiligand cell surface receptor called RAGE
- a single oral administration of an AGE-rich beverage acutely (within 90 min) resulted in temporarily impaired endothelial function assessed by flow-mediated arterial vasodilation, increased serum C-reactive protein, and plasminogen activator inhibitor-1 levels in both diabetic and healthy subjects

EDC - Bisphenol A (BPA)

- BPA is a component of polycarbonate plastics and epoxy resins that is receiving much attention due to its high production volume (>800 million kilograms annually in the U.S. alone) and its widespread human exposure.
- It is used in the manufacture of numerous products and has been shown to leach from the linings of food cans, polycarbonate baby bottles and other beverage containers and dental sealants and composites
- studies have shown measurable BPA levels in human urine, serum, breast milk, and maternal and fetal plasma, amniotic fluid, and placental tissues
- Low environmentally-relevant doses of BPA have been reported to inhibit adiponectin synthesis and to stimulate the release of inflammatory adipokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) from human adipose tissue, suggesting BPA is involved in obesity and metabolic syndrome
- Elevated BPA levels found in women with PCOS (polycystic ovarian syndrome)
- BPA now classified as toxic substance by Canadian Government (1st country to do so)

Radiofrequency Exposures

- The SAR (specific absorption rate) exposure limit was developed in 1982 in an attempt to establish a safety limit that was set to be lower than levels of radiofrequency (RF) exposures known to induce heat changes in tissues.
- More than a decade later, there are numerous papers showing that a range of biological effects can occur to cells at levels of RF emissions below the SAR exposure limit.
- The current exposure limits that are used by the FCC to set standards were developed in 1997 and were based on the 90th percentile of a military recruit—a 200-pound 6-foot tall man with an 11-pound head—using a phone for 6 minutes. This standard is obviously neither applicable to children and women nor to current use patterns where average call length is considerably longer.

"Dirty Electricity"

- High frequency voltage transients found on electrical wiring both inside and outside of buildings are caused by an interruption of electrical current flow. The electrical utility industry has referred to these transients as ''dirty power.''
- Dirty power generated by electrical equipment in a building is distributed throughout the building on the electric wiring. Dirty power generated outside the building enters the building on electric wiring and through ground rods and conductive plumbing.
- EMF (Electromagnetic field) and dirty electricity has been associated with increased risk of cancer, cardiovascular disease, diabetes, immune dysfunction and neuropsychological adverse effects.
- The bioinitiative report released in 2007 documents bioeffects, adverse health effects and public health conclusions about impacts of non-ionizing radiation (electromagnetic fields including extremely-low frequency ELF-EMF and radiofrequency/microwave or RF-EMF fields)

Air Pollution and Diabetes

- Ruhr Valley Study (Germany)
  - 1775 diabetes-free women aged 54-55 in 1990 followed for 16yrs compared to control group in non-industrialized towns nearby
  - the risk of diabetes increased by 15-42% as result of exposure to particulate matter and traffic-related air pollution
  - living within 100 meters of a road that carried 10,000+ cars per day more than doubled the risk of diabetes
- US analysis of pollution patterns and diabetes prevalence (EPA data from 2004 and 2005 compared to county-level diabetes prevalence data from CDC)
  - a 1% rise in diabetes with each increase of 10mcg/m^3 particulate matter air pollution
  - The increase in diabetes rates associated with air pollution persisted even after adjusting for covariates including obesity rates, population density, ethnicity, income, education and health insurance
  - Even for counties within guidelines for EPA exposure limits, those with highest exposure had a greater than 20% increase in diabetes prevalence even after controlling for diabetes risk factors

Basics for Optimal Health

- Rather than just using pharmacology (and even before vitamin and herbal supplementation), need to first address the basic needs of the human mind-body:
  - Nutrition
  - Exercise
  - Sleep (Quality and Quantity)
  - Stress reduction; promoting inner peace and happiness
  - Healthy Environment

Resource - Type 1 Diabetes Toolkit

- Resource available from JDRF (Juvenile Diabetes Research Foundation) – Adult Type 1 Diabetes Toolkit
- To receive a copy of the Adult Type 1 Toolkit, please contact:
  - Michelle Popoff (Outreach Manager, JDRF)
  - 949-885-5025 or 714-381-2944
  - mpopoff@jdrf.org

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