THE ROLE OF TOXICITY IN THE EPIDEMIC OF OBESITY AND METABOLIC DISORDERS

Paul Mannion
OBESITY AND DIABETES EPIDEMIC IN AUSTRALIA

Australia’s Health 2012 in brief. Australian Institute of Health and Welfare

ARE ALL CALORIES REALLY CREATED EQUAL?

1000 CALORIES
YOU WOULDN’T EAT 22 PACKS OF SUGAR*. WHY ARE YOU DRINKING THEM?

Extra calories in sugar-loaded drinks may lead to obesity, diabetes, heart disease and some cancers. CHOOSEHEALTHLA.com
IS IT LACK OF EXERCISE, OR IS IT THE FOOD?

4 miles a day for one week
**Background:** This study investigates whether the incidence of new-onset diabetes mellitus (DM) is associated with statin use among postmenopausal women participating in the Women's Health Initiative (WHI).

**Methods:** The WHI recruited 161,808 postmenopausal women aged 50 to 79 years at 40 clinical centers across the United States from 1993 to 1998 with one of 10,242 incident cases of self-reported DM over 1,004,466 person-years of follow-up. Statin use at baseline was associated with an increased risk of DM (hazard ratio [HR], 1.71; 95% CI, 1.61-1.83). This association remained after adjusting for other potential confounders (multivariate-adjusted HR, 1.48; 95% CI, 1.38-1.59) and was observed for all types of statin medications. Subset analyses evaluating the association of self-reported DM with long-term statin use were also conducted.
STATINS INCREASE RISK OF DIABETES BY 47% OVER THREE YEARS

<table>
<thead>
<tr>
<th>Description</th>
<th>Statin Use Only at Baseline</th>
<th>Statin Use Only at 3-y Follow-up</th>
<th>Statin Use at Baseline and 3-y Follow-up</th>
<th>Never Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, No.</td>
<td>1531</td>
<td>9571</td>
<td>7076</td>
<td>107,397</td>
</tr>
<tr>
<td>Incident DM cases, No.</td>
<td>98</td>
<td>644</td>
<td>442</td>
<td>4,294</td>
</tr>
<tr>
<td>Cumulative incidence rate, %</td>
<td>6.40</td>
<td>6.73</td>
<td>6.25</td>
<td>4.00</td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)a</td>
<td>1.75 (1.43-2.14)</td>
<td>1.81 (1.67-1.97)</td>
<td>1.82 (1.65-2.00)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and race/ethnicityb</td>
<td>1.65 (1.35-2.01)</td>
<td>1.79 (1.65-1.95)</td>
<td>1.81 (1.64-2.00)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Multivariatec</td>
<td>1.49 (1.19-1.86)</td>
<td>1.65 (1.51-1.81)</td>
<td>1.56 (1.41-1.74)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Propensity scored</td>
<td>1.49 (1.20-1.85)</td>
<td>1.63 (1.49-1.78)</td>
<td>1.43 (1.28-1.58)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Multivariate, including propensity scoree</td>
<td>1.44 (1.15-1.80)</td>
<td>1.60 (1.47-1.75)</td>
<td>1.47 (1.32-1.64)</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

BUT WAIT, THERE’S MORE

Although lifestyle changes have contributed to the increase in the prevalence of chronic diseases in developing countries, obesity, T2DM, and other diseases associated with insulin resistance are increasing in developed countries where there have been no recent changes in diet or physical activity.

“About once in every generation we start using a different kind of pesticide...one reason is because of resistance, the other is that negative effects on human health and the environment start to emerge.”
Jones Beach
1948
"DDT is good for me-e-e-e!"
It’s no longer a mystery. We know what’s killing the bees.

They’re being poisoned by neonicotinoid insecticides.

Tell the EPA to Ban Neonicotinoid Pesticides Before They Devastate the U.S. Bee Population.

facebook.com/organicconsumers www.organicconsumers.org
CHEMICAL DISASTERS REVEAL STARTLING FINDINGS

Diabetes and Agent Orange

Agent Orange Linked to Risk of Parkinson’s, Heart Disease

Fish and crabs from these waters contain chemicals and may be harmful to eat, especially for women and children.

Learn more! Call NYS Department of Health 1-800-456-1156

Warning!
TOXIC NURSES FOUND TO HAVE 3x HIGHER RISK OF T2DM

A ‘COCKTAIL’ OF POPs CAN TRIPLE THE PREVALENCE OF PREDIABETES

Cumulative effect of all five POPs (POLL5)

Fig. 1 The prevalence of prediabetes increases with increased circulating levels of POPs. Black circles, PCBs (15 congeners); black squares, \( p,p' \)-DDE; white squares, \( p,p' \)-DDT; black diamonds, HCB; white diamonds, \( \beta \)-HCH; white circles, POLL5.

WHAT ARE POPs?

• Persistent organic pollutants (POPs) are characterised by their ability to persist in the environment, their low water and high lipid solubility and their bio-magnification in the food chain
• POPs include – Organochlorines, DDT, PCBs, dioxins, dibenzo-p-furans (PCDFs), polybrominated biphenyls (PBB), hexachlorobenzene (HCB)
• POPs can travel great distances and can end up in countries other than those in which they were produced

AROUND 95% OF POPs INTAKE IS THROUGH DIETARY INTAKE OF ANIMAL FATS


METABOLIC DISORDERS LINKED TO EDCs?

TOXIN EXPOSURE AFFECTS HYPOTHALAMIC REGULATION OF ENERGY

# MITOCHONDRIAL TOXINS

## Table 1. Possible mitochondrial toxins and their targets and phenotypes

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Category</th>
<th>Target</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral agents</td>
<td>Medicine</td>
<td>mtDNA density&lt;sup&gt;78&lt;/sup&gt;</td>
<td>Insulin resistance, metabolic syndrome&lt;sup&gt;79&lt;/sup&gt;</td>
</tr>
<tr>
<td>Atrazine</td>
<td>POP (herbicide)</td>
<td>Respiratory complexes I and III&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Insulin resistance, obesity&lt;sup&gt;68&lt;/sup&gt;, gestational diabetes&lt;sup&gt;80&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bisphenol-A</td>
<td>POP</td>
<td>Adiponectin,&lt;sup&gt;81&lt;/sup&gt; TNFα, IL6,&lt;sup&gt;82&lt;/sup&gt;</td>
<td>Metabolic syndrome, obesity&lt;sup&gt;82&lt;/sup&gt;, cardiovascular disease, diabetes&lt;sup&gt;84&lt;/sup&gt;</td>
</tr>
<tr>
<td>2,3,7,8-Tetrachloro-dibenzo-p-dioxin (TCDD)</td>
<td>POP</td>
<td>Gene encoding insulin receptor substrate-1&lt;sup&gt;85&lt;/sup&gt;</td>
<td>Diabetes, atherosclerosis, hypertension&lt;sup&gt;86&lt;/sup&gt;</td>
</tr>
<tr>
<td>Organochlorine</td>
<td>POP</td>
<td>Basal metabolic rate, oxidative capacity&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Obesity&lt;sup&gt;67&lt;/sup&gt;</td>
</tr>
<tr>
<td>3-Nitropropionic acid (3-NPA)</td>
<td>POP</td>
<td>Succinate dehydrogenase&lt;sup&gt;87&lt;/sup&gt;</td>
<td>Neurodegenerative disorders&lt;sup&gt;87&lt;/sup&gt;</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Heavy metal</td>
<td>Insulin signal transduction, adipocyte differentiation, insulin sensitivity&lt;sup&gt;88,89&lt;/sup&gt;</td>
<td>Type 2 diabetes&lt;sup&gt;64&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

POP, persistent organic pollutant; IL6, interleukin 6.

INSULIN RESISTANCE LINKED TO MITOCHONDRIAL DYSFUNCTION

IS METABOLIC SYNDROME AN ADAPTIVE RESPONSE TO MITOCHONDRIAL DAMAGE?

The development of obesity, hyperglycaemia, and hypertension might be viewed as compensatory responses to the decreased mitochondrial unit of the body: maintaining core temperature by decreasing heat loss and increasing heat production, increasing the availability of fuels, and stimulating energy metabolism as a whole through activation of the sympathetic nervous system.

DIOXIN ASSOCIATED WITH MITOCHONDRIAL DAMAGE AND DIABETES

TCDD = Tetrachlorodibenzodioxin
Charcoal stripped human serum
NFG - normal fasting glucose
IFG - impaired fasting glucose
DM – diabetes mellitus

Both TCDD and patient sera decreased the ATP turnover rate and mitochondrial total respiratory capacity. *P < 0.05, **P < 0.01 vs. control, n = 4.

POPs AFFECT GENE EXPRESSION & LEAD TO INSULIN RESISTANCE

POPs DRIVE FATTY LIVER AND VAT

HF – high fat diet
HFR – High fat diet containing refined fish oil (Atlantic salmon)
HFC – high fat diet containing crude fish oil (Atlantic salmon)

POPs CAN MAKE FAT ‘SICK’

POPs HIDE AWAY IN FAT TISSUE AND CAN SLOWLY LEAK OUT

THE FAT LOSS PARADOX

It has been suggested that weight loss induces a significant increase in plasma organochlorine levels in humans. This rise in plasma organochlorine concentration has also been associated with a decrease in T3 concentration, resting metabolic rate and skeletal muscle capacity for fat oxidation.

FAT LOSS PATIENTS NEED SUPPORT TO PREVENT POPs DAMAGE

When fatty acids are released from adipose tissue, POPs are released simultaneously. This can damage mitochondria in endocrinologically active tissues such as the liver and muscle. Thus, POPs may decrease mitochondrial oxidative capacity in various organs.

GGT LEVELS RISE IN RESPONSE TO TCDD LEVELS

GLUTATHIONE ESSENTIAL FOR DETOXIFICATION OF XENOBIOTICS

EVEN LOW EXPOSURE DEPLETES GLUTATHIONE

• Even at low doses POPs induce responses like phase I, phase II, and phase III xenobiotic metabolism pathways.

• In particular, phase II glutathione (GSH) conjugation can lead to chronic consumption and depletion of intracellular GSH.

• Intracellular GSH depletion can cause mitochondrial dysfunction which is closely related to inflammation and ectopic fat accumulation and type 2 diabetes.

Lee DH, Porta M, Jacobs DR Jr, Vandenberg LN. Chlorinated Persistent Organic Pollutants, Obesity, and Type 2 Diabetes. Endocr Rev. 2014 Jan 31
N-ACETYLCYSTEINE REPLENISHES LOW GSH IN SUBJECTS WITH OXIDATIVE STRESS

PCB DAMAGE REDUCED BY RESVERATROL

• Results from this study indicate that resveratrol reduces PCB induced oxidative stress in adipose tissue while simultaneously enhancing Nrf2 signaling.
• This may have contributed to protection from PCB-induced impairment of glucose and insulin tolerance.
• Supplementation with resveratrol may be a potential therapy for populations with known PCB exposures to lower the risk of developing diabetes.

LIPID REPLACEMENT IMPROVES MITOCHONDRIAL FUNCTION

OBESE MICROBIOME GOOD AT HARVESTING ENERGY

• Studies have confirmed that the obese gut microbiome has an increased capacity to harvest energy from the diet influencing body weight, and to interfere with metabolic changes.

• Most recently, the transfer of intestinal microbiota from human lean donors has been shown to increase insulin sensitivity also in men with metabolic syndrome.

GENIPOSIDE INHIBITS TNF-α AND IL-6 RELEASE INDUCED BY LPS (A) OR LIPID A (B)

MINIMISING TOXIC EXPOSURE

- Minimise consumption of large fish & shellfish
  - Reduce consumption of farmed fish
- Reduce consumption of fatty meat – remove as much fat and skin as possible
- Reduce consumption of full fat dairy products
- Wash or peel fruit and vegetables before eating
- Eat organic meat, dairy, fruit and vegetables when possible
- Drink purified or filtered water, avoid plastic bottles
- Use non-toxic cleaning agents
- Use non-toxic building materials, paints and carpets
- Use natural cosmetics, shampoos, nail polish & fragrances
- Use BPA free drink bottles and containers
- Wash clothing before wearing it
- Don’t overheat empty non-stick cookware (or don’t use it!)
- Allow fresh air into the home and vacuum regularly, leave shoes outside.
ENDOCRINE DISRUPTORS

- **Household product ingredient:** Chemicals found in items such as appliances, vehicles, building materials, electronics, crafts, textiles, furniture, and household cleaning products.

- **Personal care product/cosmetic ingredient:** Chemicals found in products such as cosmetics, shampoos, lotions, soaps, deodorants, fragrances, and shaving products.

- **Food additive:** Antioxidants, dyes, compounds used in food processing and as components in food packaging.

- **Flame retardant:** Chemicals used to prevent fires.

- **Plastic/Rubber:** Components, reactants, or additives used in the manufacturing of rubbers or plastics.

- **Pesticide ingredient:** Insecticides/acaricides (miticides), herbicides, fungicides, rodenticides, and other biocides, including chemicals described as 'inert'.

- **Antimicrobial:** Chemicals that prevent the growth of and/or destroy microorganisms.

EXERCISE AND SAUNA HELPS CLEAR FAT-SOLUBLE TOXINS

A program known as the Hubbard Purification Rundown consisted of:

- Physical exercise for 20-30 minutes
- Sauna, 140-180°F, done in 30 minute sessions for a total of 2.5-5 hours daily
- Increasing doses of niacin each day and a multivitamin
- Water and electrolyte (NaCl, K) replacement
- Oil, 1-8 Tbsp daily
- Balanced meals and adequate sleep

Ten electrical workers who did 3 weeks of this protocol were studied. They experienced a 7.8% drop in adipose pesticide levels and a 4.7% drop in PCB levels. In the 3 months after treatment ended, the pesticides continued to be cleared from the workers’ bodies. At the 3-month follow-up, the mean total drop in pesticides from pre-treatment levels for the treatment group was 21.2% (2.3% for PCBs).

CALORIE RESTRICTION STIMULATES AUTOPHAGY

LONG-TERM EFFECTS OF A PALEOLITHIC-TYPE DIET IN OBESE POSTMENOPAUSAL WOMEN: A 2-YEAR RANDOMISED TRIAL

Dr David Perlmutter, 2014.