Clinical Research in Diabetes

*Diabetes, Insulin And The Brain*

Diabetologists 2016

Dallas

Pnina Vardi
Combined Clinical And Basic Research Studies

Haifa
Diabetes clinic

Tel Aviv University
Basic research
The Central Unit For Childhood Endocrinology and Diabetes

Haifa & Galilee

Advantageous setting to study diabetes in multiple ethnic population of children and adults
Diabetes = 387 million people were estimated in 2014 to be living with diabetes, estimated to rise to 592 million within the next twenty years.

Prediabetes = 316 million with impaired glucose tolerance are at high risk for diabetes, projecting that over 1 billion people will be living with or at high risk of diabetes in 2035
Standards of Medical Care in Diabetes — 2016
Fasting Plasma Glucose & 2 hr OGTT

Fasting plasma glucose (FPG) *
≥126 mg/dL (7.0 mmol/L)

OR

2-h plasma glucose ≥200 mg/dL *
(11.1 mmol/L) during an OGTT

* In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.
Prediabetes*

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

* For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.

Do We Need A Different Strategy

*Diabetes* does not seem to slow down and it is Supplemented by *prediabetes* threat, despite huge pharma investment and medical progress

- What is really wrong ?
- Are we intervening too late ?
- How can we make a change ?
- Shouldn’t we define a different primarily target for therapy other than BG level ?
Where To Search: Performing A Local Re-search

Clinical observation
Published information
Clinical and Laboratory data
High frequency of pre-diabetes, undiagnosed diabetes and metabolic syndrome among overweight Arabs in Israel.

Published Information

_Diabetes Prevalence In Israel (2010)_

The prevalence of diabetes increased in Israel

From

20/1000 in 1995

↓

63/1000 in 2007
High prevalence of T2DM in the Middle East has been observed in areas undergoing rapid economic development and in developed countries.

High rate of undiagnosed diabetes was observed in some Arab populations.

In Israel, higher prevalence rate of T2DM among Arab women (13.5%) compared with Jewish (4.9%) and among Arab men (9.4%) compared with Jewish (5.7%).
Higher Prevalence Of T2DM In Arab Population

Why?

Genetic background?
Higher consanguinity rates?
Lower socioeconomic status in villages?
Clinical observation

Family History Of T2DM In Childhood Diabetes Clinic

From relatively rare to rising family history of T2DM in I and II degree relatives of children with T1DM
Table 2—Characteristics of subjects by family history of type 2 diabetes and sex

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>P value</td>
<td>Present</td>
<td>Absent</td>
<td>P value</td>
</tr>
<tr>
<td>n</td>
<td>48</td>
<td>285</td>
<td></td>
<td>64</td>
<td>261</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.5 ± 1.0</td>
<td>33.0 ± 0.5</td>
<td>0.047</td>
<td>36.3 ± 1.0</td>
<td>32.7 ± 0.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>26.8 ± 1.1</td>
<td>25.2 ± 0.4</td>
<td>0.187</td>
<td>27.9 ± 1.0</td>
<td>24.1 ± 0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>131.6 ± 5.2</td>
<td>122.3 ± 2.2</td>
<td>0.114</td>
<td>128.1 ± 5.5</td>
<td>112.3 ± 2.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Ever smoker (%)</td>
<td>28 (58.3)</td>
<td>106 (37.9)</td>
<td>0.008</td>
<td>26 (40.6)</td>
<td>90 (34.9)</td>
<td>0.393</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>113.6 ± 1.1</td>
<td>95.9 ± 1.0</td>
<td>0.070</td>
<td>94.1 ± 1.1</td>
<td>81.7 ± 1.0</td>
<td>0.092</td>
</tr>
<tr>
<td>Beck depression index</td>
<td>7.2 ± 1.2</td>
<td>6.0 ± 0.4</td>
<td>0.258</td>
<td>9.8 ± 1.0</td>
<td>8.5 ± 0.5</td>
<td>0.248</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>15 (31.2)</td>
<td>83 (29.1)</td>
<td>0.766</td>
<td>20 (31.2)</td>
<td>51 (19.5)</td>
<td>0.042</td>
</tr>
<tr>
<td>Overt nephropathy</td>
<td>17 (38.6)</td>
<td>77 (29.0)</td>
<td>0.196</td>
<td>20 (33.9)</td>
<td>53 (21.7)</td>
<td>0.050</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>326.1 ± 16.1</td>
<td>333.6 ± 6.8</td>
<td>0.676</td>
<td>354.4 ± 13.6</td>
<td>330.8 ± 6.4</td>
<td>0.107</td>
</tr>
<tr>
<td>Insulin dose (U · kg⁻¹ · day⁻¹)</td>
<td>0.75 ± 0.04</td>
<td>0.74 ± 0.01</td>
<td>0.752</td>
<td>0.67 ± 0.03</td>
<td>0.68 ± 0.01</td>
<td>0.778</td>
</tr>
<tr>
<td>HbA₁ (%)</td>
<td>10.9 ± 0.3</td>
<td>10.8 ± 0.1</td>
<td>0.764</td>
<td>10.6 ± 0.2</td>
<td>10.7 ± 0.1</td>
<td>0.846</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>85.2 ± 1.0</td>
<td>83.4 ± 0.5</td>
<td>0.190</td>
<td>78.0 ± 1.1</td>
<td>76.0 ± 0.5</td>
<td>0.090</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.6 ± 1.2</td>
<td>18.2 ± 0.5</td>
<td>0.629</td>
<td>17.4 ± 1.1</td>
<td>17.5 ± 0.5</td>
<td>0.914</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>11 (22.9)</td>
<td>50 (17.5)</td>
<td>0.375</td>
<td>19 (29.7)</td>
<td>39 (14.9)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data are n (%) or means ± SE.
Men with T1DM have 17% family history of T2DM

Women with T1DM have 24.5% family history of T2DM

A family history of T2DM increases significantly the risk to develop *nephropathy*, *HTN* and *CAD*
Diagnosis Of Children In The Diabetes Clinic

<table>
<thead>
<tr>
<th></th>
<th>T1DM</th>
<th>T2DM</th>
<th>IFG/IGT Non insulin deficient</th>
<th>Overweight Metabolic syndrome</th>
<th>Overweight only</th>
</tr>
</thead>
<tbody>
<tr>
<td>T=51</td>
<td>23</td>
<td>4</td>
<td>4</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

T1DM: Type 1 Diabetes Mellitus
T2DM: Type 2 Diabetes Mellitus
IFG/IGT: Impaired Fasting Glucose/Impaired Glucose Tolerance
Metabolic syndrome is defined by the presence of at least three of the following five conditions: increased waist circumference, high blood pressure, high triglycerides, low HDL cholesterol, and high fasting glucose.

T: Total number of patients
Family Ethnicity Of Children In The Diabetes Clinic (n=51 families)

• Arab=14 (27.5%)
• Non-Ashkenazi Jews=12
• Ashkenazi Jews=22
• Mix=3
Adults Relation To Individual Diabetic Child

- 80 = parents
- 5 = Sibs
- 6 = Related to II° relatives
- 2 = Spouse/family friend
Rate Of Consanguinity

Arabs = 26%

Non-Ashkenazi Jews = 0%

Ashkenazi Jews = 0%
## Disease Classification Of Children In Diabetes Clinic

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Number (T=51)</th>
<th>F/M</th>
<th>Age (yrs)</th>
<th>DM1/DM2 IFG/IGT (prediabetes)</th>
<th>Metabolic synd (MS)</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arabs</td>
<td>14</td>
<td>5/9</td>
<td>6-17</td>
<td>DM1 (6)</td>
<td>DM2/pred. (3)</td>
<td>OB (2)</td>
</tr>
<tr>
<td>Non-Ashkenazi Jews</td>
<td>12</td>
<td>7/4</td>
<td>9-14</td>
<td>DM1 (2)</td>
<td>DM2/pred. (3)</td>
<td>Met. (5)</td>
</tr>
<tr>
<td>Ashkenazi Jews</td>
<td>22</td>
<td>12/9</td>
<td>3-29</td>
<td>DM1 (14)</td>
<td>DM2/pred. (2)</td>
<td>Met. (2)</td>
</tr>
<tr>
<td>Mixed Ash/non-Ash</td>
<td>3</td>
<td>1/2</td>
<td>11-16</td>
<td>DM1 (2)</td>
<td>OB (1)</td>
<td></td>
</tr>
</tbody>
</table>
# Medical History Of Adult 1° Family Relatives

<table>
<thead>
<tr>
<th>Subjects</th>
<th>IFG/IGT</th>
<th>T2DM</th>
<th>Hypoglycemia</th>
<th>Metabolic Syndrome</th>
<th>Early familial CVD Morbidity mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N-79)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arabs (27)</td>
<td>5 (19%)</td>
<td>6 (22%)</td>
<td>-</td>
<td>8 (30%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Non-Ashkenazi Jews (20)</td>
<td>1 (5%)</td>
<td>8 (40%)</td>
<td>-</td>
<td>17 (85%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Ashkenazi Jews (32)</td>
<td>6 (19%)</td>
<td>9 (28%)</td>
<td>2</td>
<td>17 (53%)</td>
<td>13 (41%)</td>
</tr>
<tr>
<td></td>
<td>BG (mg/dl)</td>
<td>Insulin fasting (pmol/l)</td>
<td>Insulin AUC (U x hr)</td>
<td>C-pep fasting (pmol/l)</td>
<td>C-pep AUC (U x hr)</td>
</tr>
<tr>
<td>------------------</td>
<td>------------</td>
<td>--------------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Obese</strong></td>
<td>84±8</td>
<td>125±78</td>
<td>1290 ±545</td>
<td>1200 ±445</td>
<td>5734 ±1493</td>
</tr>
<tr>
<td><strong>IGT &amp; DM</strong></td>
<td>90±14</td>
<td>184 ±129</td>
<td>1793 ±863</td>
<td>1643 ±482</td>
<td>6831 ±2165</td>
</tr>
<tr>
<td><strong>ESMTS</strong></td>
<td>145 ±22</td>
<td>217±132</td>
<td>ND</td>
<td>1429 ± 568</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>84 ± 9</td>
<td>84 ± 22</td>
<td>734 ± 88</td>
<td>617 ±249</td>
<td>ND</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Do We Need A Different Strategy

• What is really wrong?

• Is it high BG level or high insulin secretion or both?

• Can we stop it? Reverse it? Normalize it?

• How can we increase the success rate of diabetes treatment
<table>
<thead>
<tr>
<th>Patient</th>
<th>FBG Mg%</th>
<th>Fasting Insulin (pmol)</th>
<th>Normalization?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>110</td>
<td>180</td>
<td>yes</td>
</tr>
<tr>
<td>Patient 2</td>
<td>110</td>
<td>30</td>
<td>no</td>
</tr>
</tbody>
</table>
Insulin

Not an innocent bystander

Loss of islet bursts, and insulin pulsatility

Loss of proinsulin cleavage to insulin

Loss of regulated insulin secretion
Proinsulin levels predict the development of NIDDM in Japanese-American men.

Proinsulin is an independent predictor of coronary heart disease: Report from a 27-year follow-up study.


Fasting insulin is a stronger cardiovascular risk factor in women than in men.
The Metabolic Syndrome And Its Components

- Hyperinsulinemia
- Coronary heart disease
- Dyslipidemia
- Central/abdominal obesity
- Type 2 diabetes
- Hypertension
- Microalbuminuria

25% disease frequency.
Alzheimer Disease, Type 3 Diabetes

Insulin Action in Brain Regulates Systemic Metabolism and Brain Function. *C. Ronald Kahn, Diabetes 2014*

*(non relevant BG level)*
The present invention discloses a treatment for syndrome-X, and resulting complications, that include hyperlipidemia, hypertension, central obesity, hyperinsulinemia and impaired glucose intolerance. **Diabetic complications include excess proinsulin levels.**
Insulin acts on brain receptors to modulate peripheral metabolism, including regulation of appetite, reproductive function, body temperature, white fat mass, hepatic glucose output, and response to hypoglycemia.

Insulin signaling also modulates neurotransmitter channel activity, brain cholesterol synthesis, and mitochondrial function.

Disruption of insulin action in the brain leads to impairment of neuronal function and synaptogenesis.

…insulin signaling modulates phosphorylation of tau protein, an early component in the development of Alzheimer disease.

Thus, alterations in insulin action in the brain can contribute to metabolic syndrome, and the development of mood disorders and neurodegenerative diseases.
**Anti-diabetic and neuroprotective effects of pancreatic islet transplantation into the central nervous system.**
Diabetes Metab Res Rev. 2016

**Intracranial pancreatic islet transplantation increases islet hormone expression in the rat brain and attenuates behavioral dysfunctions induced by MK-801 (dizocilpine).**
Horm Behav. 2015

**Comment on Gray et al. Insulin regulates brain function, but how does it get there? Diabetes 2014;63:3992-3997.**
Diabetes. 2015
The Epidemics Of Obesity & Diabetes

The current explanation

Sedentary life style

Higher food consumption

Lower energy expenditure

Is it all?
Westernization – Clinical Observation

• Disruption of enlarged family structure

• Appearance of small “isolated” family units

• Loss of daily communication with enlarged family and neighbors

• Replacement of communication by virtual reality (TV, Internet)

• Growing *loneliness* and *depression* compensated by food consumption

• Exposure to aggressive marketing of junk food

• Loss of children ability to dream desire and improvise

*Induces chronic stress, over eating, overweight, over secretion of insulin, which lead to DM and CVD*
The 21th Century
“The Virtual life”

Under expression of Body signals
• Sleepiness
• Hunger
• Desire & curiosity

The Era Of Brain Dominance Over Body Signals
fMRI were used to explore changes in brain activity after body mass reduction.

Obese patients present distinct functional activity patterns compared with lean subjects.

On massive loss of body mass, after bariatric surgery, increases in the CSF concentrations of interleukin (IL)-10 and IL-6 are accompanied by changes in fMRI patterns, particularly in the hypothalamus.

CONCLUSIONS Massive reduction of body mass promotes a partial reversal of hypothalamic dysfunction and increases anti-inflammatory activity in the CSF.
<table>
<thead>
<tr>
<th>Table 1: Blood metabolic and inflammatory parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean: 6 females, 2 males</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>WC (cm)</td>
</tr>
<tr>
<td>HC (cm)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
</tr>
<tr>
<td>HOMA-IR</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
</tr>
<tr>
<td>ESR (mm/1 h)</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
</tr>
<tr>
<td>IL-1β (pg/mL)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HC, hip circumference; HOMA-IR, homeostasis model assessment of insulin resistance; WC, waist circumference. *P < 0.05 vs. lean. §P < 0.05 vs. obese before surgery.
FIG. 3. Functional connectivity maps.

Brain Involvement In Overweight
Background: association reported between chronic stress and indices of poor health, including risk factors for cardiovascular disease and poorer immune function.

Hypothesis: stress impacts health by modulating the rate of cellular aging.

Results: provide evidence that perceived stress and chronicity of stress is significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length, which are known determinants of cell senescence and longevity.

Conclusions: Women with the highest levels of perceived stress have telomeres shorter on average by the equivalent of at least one decade of additional aging compared to low stress women.
Accelerated telomere shortening in response to life stress *PNAS 2004*

Western life style

↓

Chronic stress

↓

Overweight, hyperinsulinemia

↓

Brain dysfunction, Accelerated cellular aging (Diabetes, CVD)
4. Prevention or Delay of Type 2 Diabetes
Testing should begin at age 45 for all patients, particularly those who are overweight or obese. B

Consider testing for prediabetes in asymptomatic adults of any age w/ BMI $\geq 25 \text{ kg/m}^2$ or $\geq 23 \text{ kg/m}^2$ (in Asian Americans) who have 1 or more add’l risk factors for diabetes. B

If tests are normal, repeat at a minimum of 3-year intervals. C

Recommendations: Prediabetes

Predictor of T2DM and MTS

Adolescents

BMI > 38

Females

Family history of T2DM

Fasting hyperinsulinemia

Insulin resistance (HOMA) > 4.6
Methods

- Family involvement in individual diabetic management
- Education & Information
- Evaluate the change in nuclear and enlarged family lifestyle
- Cultural consideration
Treatment Concept

• Higher compliance is achieved with better understanding of the disease

• Patients should be involved in their treatment and follow end-points

• Adults are also concerned about their own health and appearance
Different Treatment Attitude In Families With Diabetic Individuals

- Empower the diabetic child in directing family life style
- Deviate the treatment focus from the child to the whole family
- Offer different disease interpretation such as Aging instead of Diabetes
Overweight is bad

Over secretion of insulin leads to atherosclerosis (death, CVA)

Hyperglycemia and hyperinsulinemia accelerate aging processes
Our Concept

**ADA and WHO criteria for normal BG are not good enough to prevent T2DM development**

**We focus on**

- Weight reduction
- Reduce FBG $\leq$ 80mg%
- Reduce fasting insulin $\leq$ 80pmol/l
A Healthy Community

• Reduce food consumption
• Eliminate in-house junk food
• Keep early supper and early bed time
• Exit house and encourage extra-house encounters
Cultural Consideration In Traditional Societies

Do not recommend Western diet

Establish common TV club

Establish women club

Encourage out-door children activity
Be Your Doctor

Encourage family/community leadership to take responsibility for healthy life style
Aim

To propagate an individual diabetic management toward the enlarged family, focusing on subjects at high risk to develop Diabetes, Metabolic syndrome and Complications (initiated January 2010)

“The Tsunami project”
The Central Unit For Family Diabetes, The Galilee
Thank You For Listening