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

International Diabetes Federation
2014

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

American Diabetes Association®

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.

American Diabetes Association

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

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.**

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

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 then BG level ?

Where To Search:
Performing A Local Re-search

Clinical observation

Published information

Clinical and Laboratory data

Clinical observation

Ethnicity And Diabetes In Israel

High frequency of pre-diabetes, undiagnosed diabetes and metabolic syndrome among overweight Arabs in Israel.

Increased prevalence of microvascular complications in type 2 diabetes patients with the metabolic syndrome. *Abdul-Ghani MA…..Vardi P, et al., 2006*

Published Information

Diabetes Prevalence In Israel (2010)

The prevalence of diabetes increased in Israel

From

20/1000 in *1995*

↓

63/1000 in *2007*

Published information

Arab Ethnicity Is A Very High Risk Factor For T2DM

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

Published information

History *of type 2 and CAD in type 1 diabetes, Diabetes Care 1998*

Table 2—*Characteristics of subjects by family history of type 2 diabetes and sex*

	Men			Women		
	Present	Absent	*P* value	Present	Absent	*P* value
n	48	285		64	261	
Age (years)	35.5 ± 1.0	33.0 ± 0.5	0.047	36.3 ± 1.0	32.7 ± 0.5	0.003
Duration of diabetes (years)	26.8 ± 1.1	25.2 ± 0.4	0.187	27.9 ± 1.0	24.1 ± 0.5	0.001
LDL cholesterol (mg/dl)	131.6 ± 5.2	122.3 ± 2.2	0.114	128.1 ± 5.5	112.3 ± 2.4	0.005
Ever smoker (%)	28 (58.3)	106 (37.9)	0.008	26 (40.6)	90 (34.9)	0.393
Triglycerides (mg/dl)	113.6 ± 1.1	95.9 ± 1.0	0.070	94.1 ± 1.1	81.7 ± 1.0	0.092
Beck depression index	7.2 ± 1.2	6.0 ± 0.4	0.258	9.8 ± 1.0	8.5 ± 0.5	0.248
Hypertension (%)	15 (31.2)	83 (29.1)	0.766	20 (31.2)	51 (19.5)	0.042
Overt nephropathy	17 (38.6)	77 (29.0)	0.196	20 (33.9)	53 (21.7)	0.050
Fibrinogen (mg/dl)	326.1 ± 16.1	333.6 ± 6.8	0.676	354.4 ± 13.6	330.8 ± 6.4	0.107
Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)	0.75 ± 0.04	0.74 ± 0.01	0.752	0.67 ± 0.03	0.68 ± 0.01	0.778
HbA_1 (%)	10.9 ± 0.3	10.8 ± 0.1	0.764	10.6 ± 0.2	10.7 ± 0.1	0.846
Waist (cm)	85.2 ± 1.0	83.4 ± 0.5	0.190	78.0 ± 1.1	76.0 ± 0.5	0.090
BMI (kg/m^2)	17.6 ± 1.2	18.2 ± 0.5	0.629	17.4 ± 1.1	17.5 ± 0.5	0.914
CAD (%)	11 (22.9)	50 (17.5)	0.375	19 (29.7)	39 (14.9)	0.006

Data are *n* (%) or means ± SE.

History *Of Type 2 And CAD In Type 1 Diabetes*

Diabetes Care 1998

SUMMARY

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

	T1DM	T2DM	IFG/IGT Non insulin deficient	Overweight Metabolic syndrome	Overweight only
T=51	23	4	4	10	10

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

Ethnicity	Number (T=51)	F/M	Age (yrs)	DM1/DM2 IFG/IGT (prediabetes) Metabolic synd (MS) Obesity
Arabs	14	5/9	6-17	DM1 (6) DM2/pred. (3) MS. (3) OB (2)
Non -Ashkenazi Jews	12	7/4	9-14	DM1 (2) DM2/pred. (3) Met. (5) OB (2)
Ashkenazi Jews	22	12/9	3-29	DM1 (14) DM2/pred. (2) Met. (2) OB (5)
Mixed Ash/non-Ash	3	1/2	11-16	DM1 (2) OB (1)

Medical History Of Adult I° Family Relatives

Subjects (N-79)	IFG/IGT	T2DM	Hypoglycemia	Metabolic Syndrome	Early familial CVD Morbidity mortality
Arabs (27)	5 (19%)	6(22%)	-	8 (30%)	4 (15%)
Non-Ashkenazi Jews (20)	1(5%)	8 (40%)	-	17 (85%)	9 (45%)
Ashkenazi Jews (32)	6 (19%)	9 (28%)	2	17 (53%)	13 (41%)

Blood Glucose And Insulin Response In Obese Adolescents

Vardi et al., Metabolic Syndrome: Clinical Research & Reviews 2007

			Mean		
	BG fasting (mg/dl)	Insulin fasting (pmol/l)	Iinsulin AUC U x hr	C-pep fasting (pmol/l)	C-pep AUC (U x hr)
Obese	84±8	125±78	1290 ±545	1200 ±445	5734 ±1493
IGT & DM	90±14	184 ±129	1793 ± 863	1643 ± 482	6831 ±2165
ESMTS	145 ±22	217±132	ND	1429 ± 568	ND
Normal	84 ± 9	84 ± 22	734 ± 88	617 ±249	ND
P	*<0.0001*	*0.0001*	*<0.0001*	*<0.0001*	*0.06*

Do We Need A Different Strategy

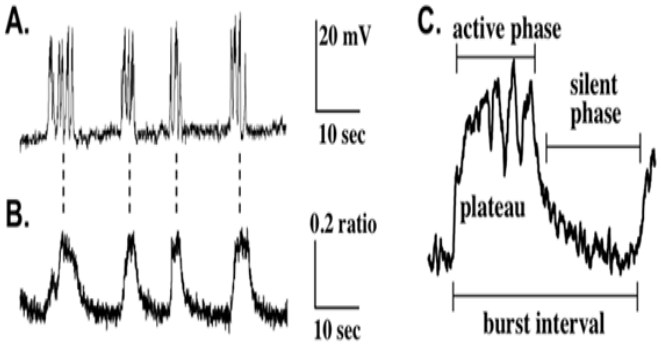
- What is really wrong ?
- Is it high BG level or high insulin secretion or both ?
- Can we stop it ? Reverse it ? Normalize it ?
- How can we increase the success rate of diabetes treatment

Laboratory Data And Islet Pathogenesis

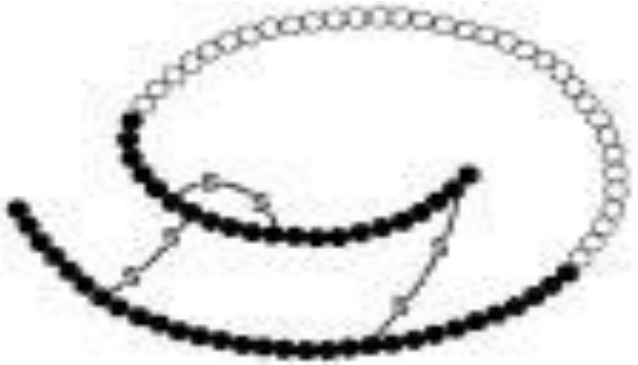
	FBG Mg%	Fasting Insulin (pmol)	Normalization ?
Patient 1	110	180	yes
Patient 2	110	30	no

Insulin

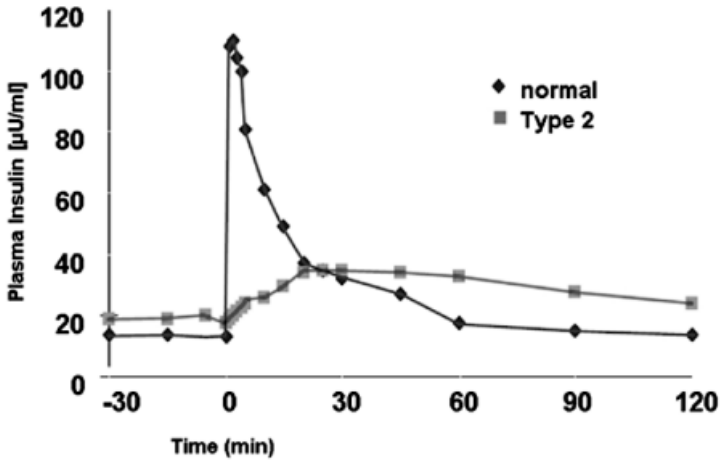
Not an innocent bystander



Loss of islet bursts, and insulin pulsatility



Loss of proinsulin cleavage to insulin



Loss of regulated insulin secretion

Proinsulin insulin *and CVD*

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.

Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study.

Fasting insulin is a stronger cardiovascular risk factor in women than in men.

The Metabolic Syndrome And Its Components



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)

Targeting Insulin And Proinsulin In Diabetes Treatment

United States Patent **6,197,765**

Use of **diazoxide** for the treatment of metabolic syndrome and diabetes complications

Abstract
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.**

Vardi , et al. **March 6, 2001**

Insulin action in brain regulates systemic metabolism and brain function. Kahn CR, Diabetes. 2014.

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.

Insulin Delivery Into The Brain

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

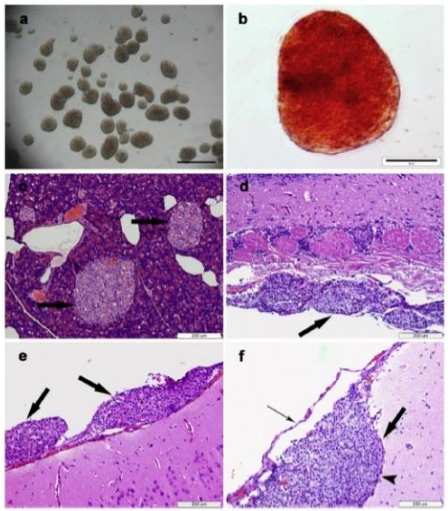


Fig. 2. Morphology and histology of endogenous and grafted islets. (a) Representative images of unstained freshly isolated islets, (b) and islet stained with DTZ, (c) H&E staining: endogenous islets in the pancreas, (d) islets grafted onto the olfactory bulb, (e, f) frontal cortex. Bold arrows (islets), thin arrow (arachnoid mater), arrowhead (pia mater). Bars: 400 μm (a), 50 μm (b), 200 μm (c–f).

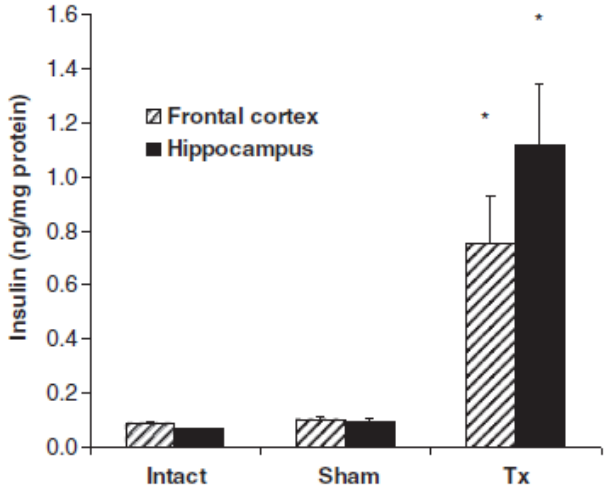


Fig. 5. Brain insulin content in the frontal cortex and the hippocampus. Brain insulin levels (ng/mg protein of tissue) in the frontal cortex and the hippocampus of intact, sham-operated and islet transplanted rats. *P < 0.001 compared to intact and sham-operated rats. Data are shown as means ± SE. N = 8–9 animals per group.

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

Partial Reversibility of Hypothalamic Dysfunction and Changes in Brain Activity After Body Mass Reduction in Obese Subjects
Diabetes 2011

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 1
Blood metabolic and inflammatory parameters

	Lean	Obese before surgery	Obese after surgery
	6 females, 2 males	11 females, 2 males	
Age (years)	29.5 ± 4	34.0 ± 10	
BMI (kg/m^2)	20.9 ± 2.4	39.1 ± 1.9*	28.1 ± 2.8*§
WC (cm)	72.2 ± 9.2	110.3 ± 9.9*	89.7 ± 8.7*§
HC (cm)	91.3 ± 7.3	127.0 ± 5.2*	105.0 ± 7.5*§
Glucose (mg/dL)	80.6 ± 3.1	84.3 ± 6.1	77.9 ± 7.3
HbA_{1c} (%)	4.8 ± 0.2	5.2 ± 0.3	5.1 ± 0.3
Insulin (pmol/L)	25.0 ± 10.3	68.7 ± 38.1*	21.5 ± 10.4§
HOMA-IR	0.7 ± 0.3	2.1 ± 1.2*	0.6 ± 0.2§
Cholesterol (mg/dL)	189 ± 28	153 ± 24	141 ± 16
HDL (mg/dL)	74.5 ± 25.7	36.9 ± 5.8*	52.6 ± 9.1*§
LDL (mg/dL)	99.5 ± 22.4	97.6 ± 26.4	73.6 ± 16.1
Triglycerides (mg/dL)	75.5 ± 38.9	94.1 ± 27.1	76.6 ± 19.9
CRP (mg/dL)	0.13 ± 0.02	0.91 ± 0.70*	0.17 ± 0.02§
ESR (mm/1 h)	14 ± 12	26 ± 16*	16 ± 9§
Adiponectin (μg/mL)	6.9 ± 1.7	2.7 ± 1.8*	7.8 ± 1.6§
Leptin (ng/mL)	21.4 ± 6.2	36.8 ± 12.0*	17.0 ± 13.9§
TNF-α (pg/mL)	5.8 ± 5.5	25.6 ± 10.3*	12.4 ± 9.8§
IL-1β (pg/mL)	2.0 ± 1.8	42.9 ± 26.7*	13.6 ± 4.3*§
IL-6 (pg/mL)	4.1 ± 4.2	26.3 ± 10.2*	8.5 ± 6.4§
IL-10 (pg/mL)	14.0 ± 10.1	15.6 ± 16.5	15.8 ± 5.5

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.

Brain Involvement In Overweight

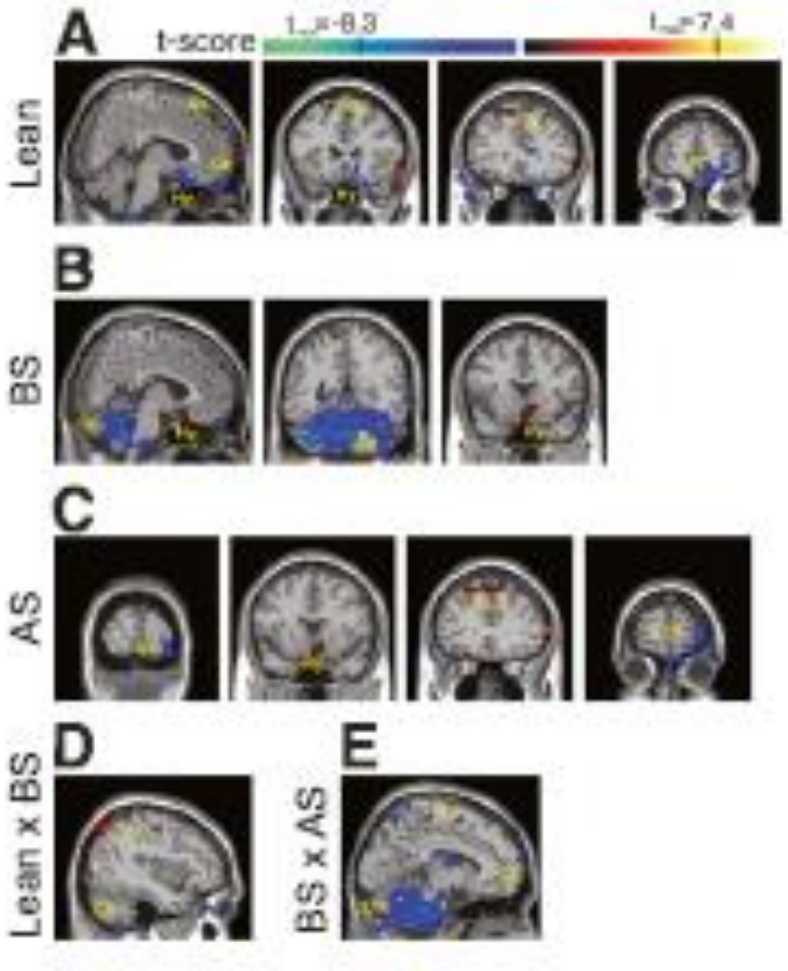


FIG. 3. Functional connectivity maps.

Accelerated Telomere Shortening In Response To Life Stress *PNAS 2004*

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

Recommendations: Prediabetes

- **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 ≥25 kg/m2 or ≥23 kg/m2 (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**

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S13-S22

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 life style
- Cultural consideration

Treatment Concept

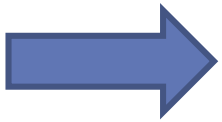
- Higher compliance is achieved with better understanding of the disease

- 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*

Information II

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 ≤80mg%

Reduce fasting insulin ≤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

