

SUPPLEMENTARY DATA

Description of euglycemic hyperinsulinemic clamp procedure.

Briefly, insulin (Humulin; Eli Lilly, Indianapolis, IN) was given as a primed continuous infusion targeted to produce plasma insulin levels of $\sim 80 \mu\text{U/ml}$. Thereafter, the insulin infusion rate was fixed at $40 \text{ mU}\cdot\text{m}^2\cdot\text{min}^{-1}$. The blood glucose level was maintained constantly, at about 4.9 mmol/l for the next 120 min, by infusing 20% glucose at varying rates according to blood glucose measurements performed at 5-min intervals (mean coefficient of variation of blood glucose was $<4\%$). The glucose disposal during the clamp was expressed as the amount of glucose infused per kilogram body weight per minute during the last 60 min of the clamp examination. The insulin and blood glucose levels during the steady state of clamp among insulin resistance tertile groups were as follows. High Insulin Resistance Tertile (IRT) glucose levels were $5.3\pm 0.24 \text{ mmol/l}$, medium IRT glucose levels were $5.1\pm 0.2 \text{ mmol/l}$ and low IRT glucose levels were $5.1\pm 0.3 \text{ mmol/l}$ ($p=\text{ns}$, ANOVA). High IRT insulin levels during the steady state of clamp were $719\pm 37 \text{ pmol/l}$, medium IRT insulin levels were $732\pm 32 \text{ pmol/l}$ and low IRT glucose levels were $722\pm 29 \text{ pmol/l}$ ($p=\text{ns}$, ANOVA).

Supplementary Table 1. Clinical characteristics of affected parent of the study subjects

	parents of Low IR FDR	parents of Medium IR FDR	parents of High IR FDR
number	13	14	14
Age (years)	71.6 ± 8.7	66.0 ± 7.1	72.8 ± 10.0
Died (%)	20.0%	12.5%	40.0%
Duration of DM2 (years)	25.0 ± 12.2	12.33 ± 8.0	16.8 ± 8.3
Therapy (oral agent/Insulin)	7/6	10/4	8/6
Macroangiopathy	8	6	7
Microangiopathy	3	1	2

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Supplementary Table 2. Demographic and biochemical data of study subjects stratified for IRS2 expression

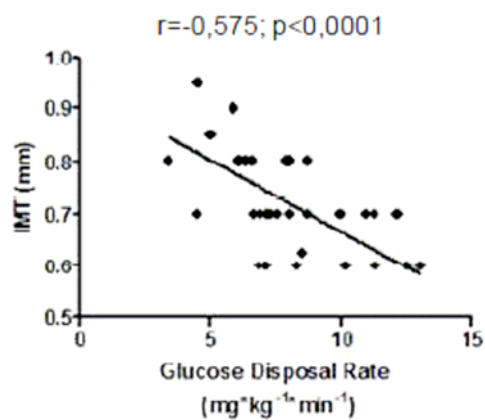
	Low IRS2	Medium IRS2	High IRS2	p
Subjects (n)	14	13	14	
Sex (Men/Women)	4/10	5/8	4/14	
Age (years)	41.6±9.7	32.4±7.6	35.5±11.4	ns
BMI (kg/m²)	25.8±3.6	25.0±3.6	23.1±3.7	ns
Waist (cm)	83.6±13.4	82.7±12.0	79.1±11.4	ns
Hypertension (Yes/no)	2/12	2/11	2/12	ns
NGT/IGT	11/3	10/3	10/4	
SBP (mmHg)	117.2±13.5	117.5±14.1	121.1±17.6	ns
DBP(mmHg)	77.8±7.9	77.9±8.1	80.0±10.3	ns
Total Cholesterol (mmol/l)	4.82±1.12	5.00±1.37	5.00±0.67	ns
HDL Cholesterol (mmol/l)	1.39±0.27	1.5±0.49	1.73±0.40	0.05
LDL Cholesterol (mmol/l)	2.93±1.15	3.35±1.27	3.00±0.87	ns
Triglycerides (mmol/l)	1.30±0.97	1.21±0.74	0.92±0.49	ns
HbA1c (%)	5.46±0.27	5.30±0.15	5.15±0.17	0,05
Fasting plasma glucose (mmol/l)	5.2±0.2	4.9±0.4	4.8±0.4	0,01
Fasting plasma insulin (pmol/l)	58±30	65±41	59±35	ns
HOMA IR index	2.20±1.16	2.40±1.68	1.73±0.86	ns
Glucose disposal index (mg*kg⁻¹*min⁻¹)	7.68±2.52	7.30±2.38	9.39±2.05	0,05
C reactive protein (mg/dl)	8.84±14.04	2.46±3.05	1.21±1.03	ns
IMT (mm)	0.74±0.08	0.70±0.08	0.63±0.06	0,03
FFA (mM/l)	0.42±0.23	0.54±0.24	0.47±0.10	ns
sVCAM-1 (ng/ml)	480.69±427.65	63.44±97.16	138.50±142.19	0,001
sICAM-1 (ng/ml)	180.51±70.81	162.90±41.07	148.84±18.93	ns
sTNF R1 (ng/ml)	1.39±0.41	1.18±0.20	1.22±0.12	ns
sIL6 R (ng/ml)	32.60±7.62	26.33±9.32	19.53±5.86	0,005
sCXCL16 (ng/ml)	4.34±1.13	3.91±0.64	4.03±0.70	ns

Data are percentage or means ± SD. *P* value is reported for significant differences among groups tested with Univariate Analysis of Variance (ANOVA) with Bonferroni's post hoc test

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Supplementary Figure 1. Correlation between Insulin resistance and Intimal Medial Thickness in FDRs included in the study (A). Subjects in the highest insulin resistant tertile show increased Intimal Medial Thickness ($p < 0.001$) (B)

A



B

