Relative Hypoleptinemia in Poorly Controlled Patients with Type 1 Diabetes

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Key words
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Abstract

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Introduction

Insulin sensitivity is strictly related to body fat mass. Several studies in type 2 diabetes (T2DM) demonstrated that insulin regulates leptin (Lep) per se, regardless of adiposity [1,2]. On the contrary, plasma adiponectin (Apn), another molecule specifically secreted from adipocytes, is negatively correlated with insulin resistance and body mass index (BMI) [3,4]. Unlike the HOMA-IR, an index of insulin resistance, the adiponectin/leptin ratio (A/L ratio) is not influenced by fasting glucose plasma levels and could be considered a sensitive and reliable marker of insulin resistance in T2DM. Type 1 diabetes mellitus (T1DM) is an organ-specific autoimmune disease resulting from the T-cell mediated destruction of pancreatic β-cells, though glycemic control is also related to reduction in insulin sensitivity. Although it is well known that adipocytokines, principally Lep, may influence T-cell function [5,6], their role in insulin sensitivity has not been sufficiently investigated in Type 1 diabetes.

Material and Methods

The aim of this prospective study was to evaluate whether insulin sensitivity could influence glycemic control in patients with T1DM after 5 years from the onset. The patients were classified, in accordance to ADA criteria, as T1DM because of acute onset of symptoms, DKA and positive pancreatic β-cell auto-antibodies (anti-GAD and/or anti-IA2). We studied 25 consecutive (20 males, 5 females) non-obese (BMI 23.66±3.49 Kg/m^2; range 19–29.5) T1DM subjects, aged 22±9.21 years. We excluded patients with obesity (class I–III) in order to eliminate those who had clear insulin resistance associated to T1DM. All subjects followed a balanced nutritional scheme and kept a diary to quantify compliance to the diet program (number of days of free food intake). After three months we assessed insulin resistance by evaluating clinical signs and symptoms (acanthosis nigricans, waist circumference, BMI, blood pressure), biochemical parameters (HbA1c, lipids, uricemia), adipocytokine levels (Apn, Lep and A/L ratio) and endothelial dysfunction markers (microalbuminuria and PCR). Residual β-cell function was determined by measuring urinary (UCP) and serum C-peptide levels evaluation before and after a glucagon test (0′ and 6′). The Institutional ethics committee approved the study and all participants signed informed consent. Data are presented as mean±SD. The Mann–Whitney U test was used to compare groups. A linear logistic regression model was applied to determine the relationship between dependent (HbA1c) and independent variables (IR, Waist, BMI, CPU, 0′ and 6′ C-peptide, Adp, Lep, A/L ratio, number of days of non-regular diet).

Results

Patients were divided in two groups based on BMI: BMI <26 kg/m^2 (18/25, Group A) and BMI >26 kg/m^2 (7/25, Group B). Lep values were significantly higher (9.4±6.4 ng/ml vs. 3.3±2.9 ng/ml; p=0.005) and A/L ratio significantly lower (2.4±1 vs. 18.6±25.9; p<0,001) in group B. No significant differences were found for other parameters examined, suggesting that glycemic control and

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Table 1 Clinical and metabolic parameters in Type 1 diabetic patients with <26 Kg/m^2 (Group A) and >26 Kg/m^2 (Group B) BMI

	Group A BMI <26 Kg/m^2 n=18		**Group B BMI >26 Kg/m^2 n=7**		
	Media	**Dev. St.**	**Media**	**Dev. St.**	**P†**
Diagnosis of T1DM (years)	21.22	8.9	24.71	10.22	0.389
BMI (kg/m^2)	22.05	2.64	27.78	1.25	–
Waist Circumference (cm)	81.42	8.36	95.42	6.21	<0.001*
Systolic blood pressure	113.06	7.88	120	13.22	0.297
Diastolic blood pressure	72.50	9.43	75.71	9.32	0.38
Leptin (ng/ml)	3.36	2.97	9.40	6.42	0.005*
Adiponectin (ng/ml)	24.32	10.24	17.70	4.25	0.097
Adiponectin/leptin ratio	18.64	25.96	2.4	1.07	<0.001*
Total cholesterol (mg/dl)	165.16	35.88	170.42	17.75	0.574
HDL cholesterol (mg/dl)	47.03	12.3	45.54	11.52	0.976
Triglycerides (mg/dl)	86.27	35.50	95.28	37.45	0.657
LDL cholesterol (mg/dl)	100.83	34.83	105.97	20.97	0.458
HbA1c (%)	7.33	1.19	7.44	1.50	0.790
Insulin Requirement (U/Kg/BW)	0.50	0.33	0.52	0.15	0.357
CPU (μg/24 h)	26.05	23.33	30.65	17.83	0.458
Basal C-peptide (nmol/l)	0.61	1.08	0.53	0.58	0.976
6′ C-peptide (nmol/l)	0.66	0.4	0.78	0.80	0.976
Delta C-peptide (0′–6′)	0.13	3.13	0.77	1.8	0.244
Serum creatinine (mg/dl)	0.84	0.23	0.96	0.10	0.178
Microalbuminuria (mg/l)	10.14	13.74	38.34	65.73	0.745
C-Reactive Protein (mg/l)	0.89	1.03	1.44	1.39	0.178
	n	%	***n***	%	***p*††**
Sex					
Males	14	77.8	1	14.3	0.656
Females	4	22.2	6	85.7	
DM family history	10	55.5	6	85.7	0.355
Obesity family history	8	44	5	71	0.378
Acanthosis nigricans	1	5	1	14	0.490

†Mann–Whitney Test; ††χ^2 Test; *Significant values when $p<0.05$

residual β-cell function did not differ in normal weight patients (group A) and overweight patients (group B) (**Table 1**). Using a multiple linear logistic regression model to evaluate which of the independent variables could influence HbA1c, we found that high HbA1c values correlated with increased BMI (β=0.73; p=0.034), IR (β=0.74; p=0.001), number of days of non-regular diet (β=0.40; p=0.015) and reduced Lep levels (β=−0.71; p=0.004). A/L ratio was significantly lower in group B (overweight), as Apn levels (related to insulin resistance) did not differ in the two groups, and only Lep values (obviously higher in group B) markedly influenced A/L ratio. Thus it is not possible to assert that these patients are less insulin sensible only on the basis of A/L ratio.

Conclusions

In conclusion, we have found an association between poor compliance to diet and elevated HbA1c with relative hypoleptinemia in nonobese patients with T1DM, similar to patients affected by the metabolic syndrome [7]. Hypoleptinemia could accelerate lipogenesis and reduce FFA oxidation in muscle and liver, thus decreasing insulin sensitivity in these tissues. From our study, we hypothesize that the transient lipotoxicity is able to influence glycemic control and HbA1c values in Type 1 diabetes.

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