

Abstract: Influence of Family History of Type 2 Diabetes on Insulin Resistance in Type 1 Diabetic Patients
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Objective: Insulin resistance can contribute to hyperglycemic excursions and has been shown to be associated with clinical endpoints in type 2 diabetes. The role of insulin resistance in type 1 diabetes is not fully understood. Especially it is not clear if there is a link between family history of type 2 diabetes and insulin resistance in type 1 diabetes. The objective of this study was to quantify insulin resistance in type 1 diabetic patients with and without family history of type 2 diabetes mellitus by means of an euglycemic hyperinsulinemic glucose clamp. **Methods:** Family history of type 2 diabetes was defined by parents or grandparents with or without type-2-diabetes. 24 Type 1 diabetic patients had a positive family history of type 2 diabetes (age 37.5 ± 11.9 yrs., diabetes duration 17.5 ± 1.8 yrs., HbA1c 7.6 ± 2.1%, BMI 23.3 ± 2.6 m²/kg, female 54%) Except from gender the 24 type 1 diabetic patients without a family history of type-2-diabetes (age 41.1 ± 10.1 yrs., disease duration 16.9 ± 10.3 yrs., HbA1c 7.3 ± 1.1%, BMI 23.8 ± 2.0 m²/kg, female 25%) did not differ significantly with respect to the referred sample characteristics. Insulin resistance was quantified by glucose disposal rate related to total and lean body mass from minute 120 to minute 150 after initiation of the glucose clamp. Blood samples were drawn to determine plasma levels of insulin, cortisol and epinephrine. **Results:** Total glucose disposal (8.0 ± 2.2 vs. 10.6 ± 2.5 mg/kg/min, P<.01) as well as glucose disposal of lean body mass (10.0 ± 2.6 vs. 13.3 ± 2.9 mg/kg/min, P<.01) were significant lower in patients with family history of type 2 diabetes compared to type 1 diabetes without a positive family history. There were no significant differences in plasma levels of insulin (P=.84), cortisol (P=.86) or epinephrine (P=.38) between the two groups. **Conclusion:** Type 1 diabetic patients with and without a family history of type 2 diabetes had a comparable BMI, age, disease duration and glycemic control, but differed significantly with respect to total glucose disposal rate and glucose disposal of lean body mass. This suggests an increased insulin resistance in type 1 diabetic patients with a presumed type 2 diabetes predisposition. The prognostic and therapeutic impact of these findings should be clarified in further prospective studies and obese type 1 diabetic patients.

Objective: Insulin resistance is a potential etiological factor for the development of type 2 diabetes. Offsprings of type 2 diabetic patients have a greater risk for this disease, thus a strong heredity of insulin resistance can be assumed. Insulin resistance in type 2 diabetes is associated with a poorer glycemic control and a poorer prognosis.

Type 1 diabetes is caused by an autoimmune process leading to β-cell destruction. Since the etiology of type 1 and type 2 diabetes are independent from each other, patients with a type 1 diabetes could have an additional insulin resistance, if they are an offspring of type 2 diabetes patients. Insulin resistance in type 1 diabetes is known as a complicating factor of an euglycemic orientated insulin therapy and a risk factor for the development of micro- and macrovascular late complications.

The objective of this study was to quantify insulin resistance in type 1 diabetic patients with and without a family history of type 2 diabetes mellitus by means of an euglycemic hyperinsulinemic glucose clamp.

Methods: Eligible to this clamp study were type 1 diabetic patients without late complications. Family history of type 2 diabetes was defined by parents or grandparents with or without type-2-diabetes. 48 type 1 diabetic patients participated in this study; half of them had a positive family history of type 2 diabetes whereas the other half did not (see table 1). Except from gender, patients with and without a family history of type-2-diabetes did not differ significantly with respect to demographic or biomedical characteristics.

After an overnight fast the hyperinsulinemic glucose clamp started. Therefore an antecubital venous catheter for infusion of insulin and glucose was inserted. Another antecubital catheter was inserted in the non-dominant hand for continuous blood glucose measurement. This hand was placed in a heating box for arterialization of venous blood. Blood samples were drawn every 5 minutes and immediately analyzed, using a HemoCue®-Photometer (Mallinkrodt, Bad Hoenef, Germany). A constant infusion of insulin (1,5 mU kg⁻¹ min⁻¹) was used to induce hyperinsulinemia. According to the blood glucose readings glucose infusion of 20% Dextrose was adapted using the formula of DeFronzo et al to maintain euglycemia at 100 mg/dl. Lean body mass was measured by a bioelectric impedance analyzer.

Insulin resistance was quantified by glucose disposal rate related to total and lean body mass from minute 120 to minute 150 after initiation of the glucose clamp (test phase). Before this measurement period blood glucose was calibrated from minute 0 to minute 120 in a pretest phase. Blood samples were drawn to determine plasma levels of insulin, cortisol, norepinephrine and epinephrine.

Results: Euglycemia could be stabilized during the whole glucose clamp, there were no substantial differences between the two patients groups (see table 2). The glucose infusion rate is depicted in figure 1. The distribution of glucose disposal related to total and lean body mass are depicted in figures 2 and 3. Type 1 diabetic patients with a family history of type 2 diabetes can clearly be distinguished from the patient group without a positive type 2 diabetes history. Sex adjusted glucose disposal rates in the pretest and test phase are significantly lower in patients with a family history of type 2 diabetes (figure 4). There were no significant differences in plasma levels of insulin (P=.84), cortisol (P=.86) (figures 5 and 6) between the two groups. Norepinephrine (P=.22) and epinephrine levels (P=.38) were also comparable in both groups.

Conclusion: Type 1 diabetic patients with and without a family history of type 2 diabetes had a comparable BMI, age, disease duration and glycemic control, but differed significantly with respect to total glucose disposal rate and glucose disposal of lean body mass. This suggests an increased insulin resistance in type 1 diabetic patients with a presumed type 2 diabetes predisposition.

For safety reasons type 1 diabetic patients with signs of severe late complications were excluded from this clamp study. Thus differences in late complications, which is the most relevant prognostic factor, between patients with and without a family history could not be observed. The prognostic and therapeutic impact of elevated insulin resistance in type 1 diabetes should be clarified in further prospective studies and obese type 1 diabetic patients.

table 1: sample characteristics

variable	without type 2 history	with type 2 history	P
age (yrs.)	41,1 ± 10,1	37,5 ± 11,9	.27
disease duration (yrs.)	16,9 ± 10,3	17,5 ± 11,8	.84
% female	25	54,2	.04
A1c (%)	7,3 ± 1,1	7,6 ± 2,1	.61
BMI (kg/m ²)	23,8 ± 2,0	23,3 ± 2,6	.40

table 2: blood glucose characteristics during glucose clamp

variable	without type 2 history	with type2 history	P
bloodglucose (mg/dl) 0-120 min.	96,7 8,1	97,3 ± 2,5	.83
variation coefficient (%) 0-120 min.	17,1 ± 11,2	15,5 ,5	.51
bloodglucose (mg/dl) 120-150 min.	98,5 ± 3,1	99,0 ± 2,5	.43
variation coefficient (%) 120-150 min.	6,2 ± 3,4	5,9 ± 2,2	.63

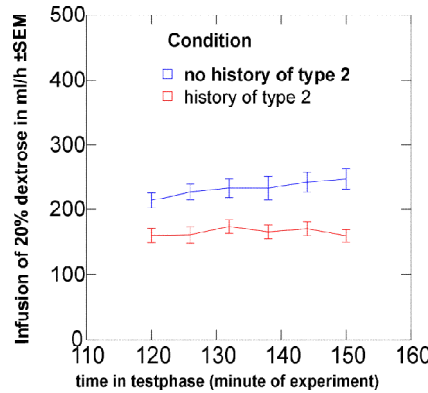


figure 1: Glucose infusion (20% dextrose) during test-period (minute 120-150).

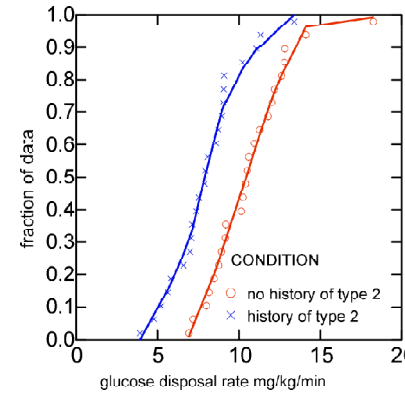


figure 2: distribution of glucose disposal rate in total body mass

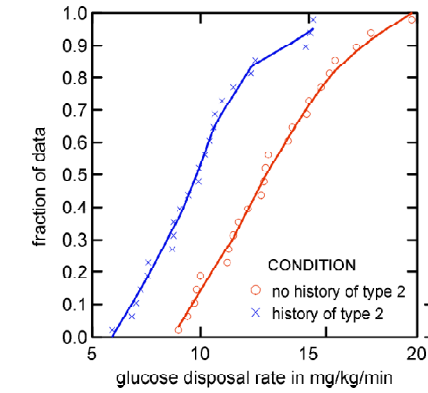


figure 3: distribution of glucose disposal rate in lean body mass

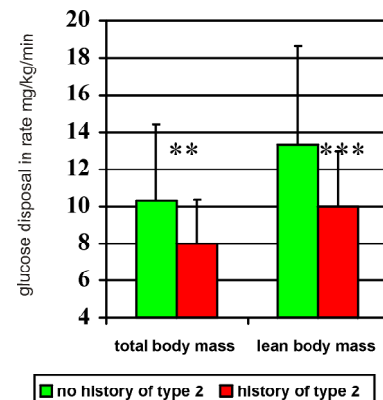


figure 4: glucose disposal rate in test (* P<.05, ** P>.01; *** P<.001)

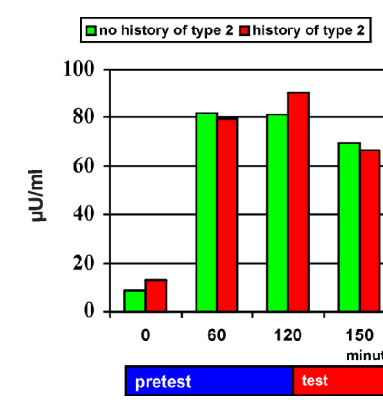


figure 5: Insulin concentration during clamp (P = .82)

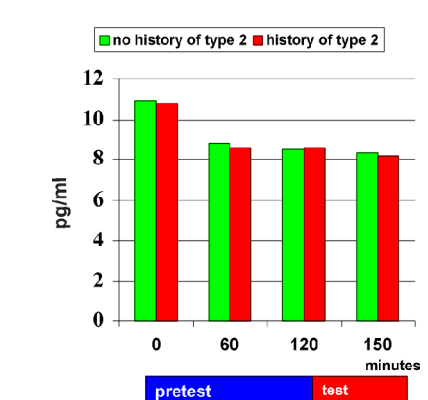


figure 6: Cortisol during clamp (P = .99)