Influence of hepatic and peripheral insulin resistance on glucose tolerance in non-diabetic subjects: the RISC study

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INTRODUCTION

Fasting hyperglycaemia is prevented as long as hepatic autoregulation maintains endogenous glucose production (EGP) within the normal range. On the other hand, postprandial glycaemia starts to increase long before hepatic autoregulation is lost, mainly because of insulin resistance both at the level of the muscle and liver (through impaired suppression of EGP). The contribution of hepatic insulin resistance (HIR) to fasting and/or postprandial glucose concentrations is still uncertain.

AIM OF THE STUDY

To evaluate EGP and HIR in a large group of non-diabetic subjects and their relation to peripheral insulin resistance and ß-cell function.

METHODS

The RISC is an ongoing prospective study to evaluate the possible relationship between insulin resistance and cardiovascular risk in a low-risk Caucasian population. Between June 2002 and July 2004, the RISC study recruited >1,500 non-diabetic subjects (aged 30-60 years) without hypertension or dyslipidaemia. Each subject underwent measurement of body composition, liver enzymes, lipid profile, peripheral insulin sensitivity (by the euglycaemic hyperinsulinaemic clamp), ß-cell function (by modelling of C-peptide) and glucose tolerance (from the OGTT). In a subgroup of subjects (n=398), 6,6-^{2}H-glucose was used to determine EGP and glucose disposal (Rd) during fasting and clamp. HIR was calculated as the product of fasting EGP and fasting plasma insulin concentration.

Figure 1. The RISC Study (Relationship between Insulin Sensitivity and Cardiovascular disease) was carried out in 19 European recruiting centres in 14 countries. (*ref. 1*)

RESULTS

We measured glucose tolerance (by OGTT) and insulin sensitivity (by combining the clamp with tracer glucose infusion) in 1,306 subjects. Subjects were divided in quartiles of fasting and 2-hour plasma glucose concentrations (Tables 1 and 2). Peripheral insulin sensitivity, M/I, varied widely (16-967 $\mu mol \cdot min^{-1} \cdot kg_{ffm}^{-1}$) as did fasting glucose production EGP (6-43 $\mu mol \cdot min^{-1} \cdot kg_{ffm}^{-1}$) and hepatic insulin resistance (HIR) (87-3045 $\mu mol \cdot min^{-1} \cdot kg_{ffm}^{-1} \cdot pM$)

FASTING PLASMA GLUCOSE (FPG)

Across quartiles of FPG, there was a graded increase in age, BMI, waist circumference and hepatic insulin resistance (HIR=EGPxIns). On the other hand, peripheral insulin sensitivity (M/I) and ß-cell function (glucose sensitivity) concomitantly declined.

Table 1. Clinical characteristics according to FPG quartiles

	FPG-Q1 N=316	FPG-Q2 N=348	FPG-Q3 N=313	FPG-Q4 N=329
AGE	41±1	43±1*	45±1*	47±1*
BMI	24.3±0.2	24.9± 0.2*	25.6± 0.2*	27.2± 0.2*
WAIST	81±1	84±1*	88±1*	93±1*
Fasting EGP	16.8±0.5	16.4±0.5	15.1±0.4	16.4±0.4
Clamp EGP	3.9±0.5	4.1±0.6	3.5±0.5	4.7±0.4
Hepatic insulin resistance	307 [212-536]	370 [280-473]	411* [277-572]	481* [378-755]
M/I	136 [100-182]	138 [98-186]	126 [93-184]	115* [79-156]
Glucose sensitivity	145±6	138±5	132±5*	111±4*
Rate sensitivity	1068±80	1122±74	1160±74	856±50*
Potentiation	2.0±0.1	2.0±0.1	2.1±0.1	2.0±0.1
Adiponectin	9.7±0.2	8.6±0.2*	8.0±0.2*	7.3±0.2*

* p<0.05 vs Q1

OGTT PLASMA GLUCOSE (2h-PG)

Across quartiles of 2h-PG, there was a graded increase in age, BMI, waist circumference and hepatic insulin resistance (HIR=EGPxIns). On the other hand, peripheral insulin sensitivity (M/I) and beta cell function (glucose sensitivity) concomitantly declined.

Table 2. Clinical characteristics according to 2h-PG quartiles

	2h-PG-Q1 N=313	2h-PG-Q2 N=365	2h-PG-Q3 N=318	2h-PG-Q4 N=310
AGE	42±1	44±1*	44±1*	46±1*
BMI	24.4±0.2	25.0±0.2*	25.7±0.2*	26.9±0.2*
WAIST	84±1	85±1	87±1*	90±1*
Fasting EGP	16.4±0.5	16.1±0.4	16.9±0.5	15.4±0.5
Clamp EGP	4.4±0.6	3.9±0.5	4.0±0.5	3.8±0.6
Hepatic insulin resistance	306 [215-481]	375 [233-532]	432* [311-582]	461* [290-720]
M/I	152 [115-207]	137* [106-186]	123* [87-165]	100* [70-145]
Glucose sensitivity	154±5	150±6	126±4*	94±3*
Rate sensitivity	1294±104	1008±60*	1019±60*	890±45*
Potentiation	2.9±0.1	2.1±0.1*	1.6±0.1*	1.5±0.1*
Adiponectin	9.0±0.2	8.6±0.2	8.4±0.2*	7.5±0.2*

* p<0.05 vs Q1

Relationship between OGTT glucose and insulin concentrations and sensitivity

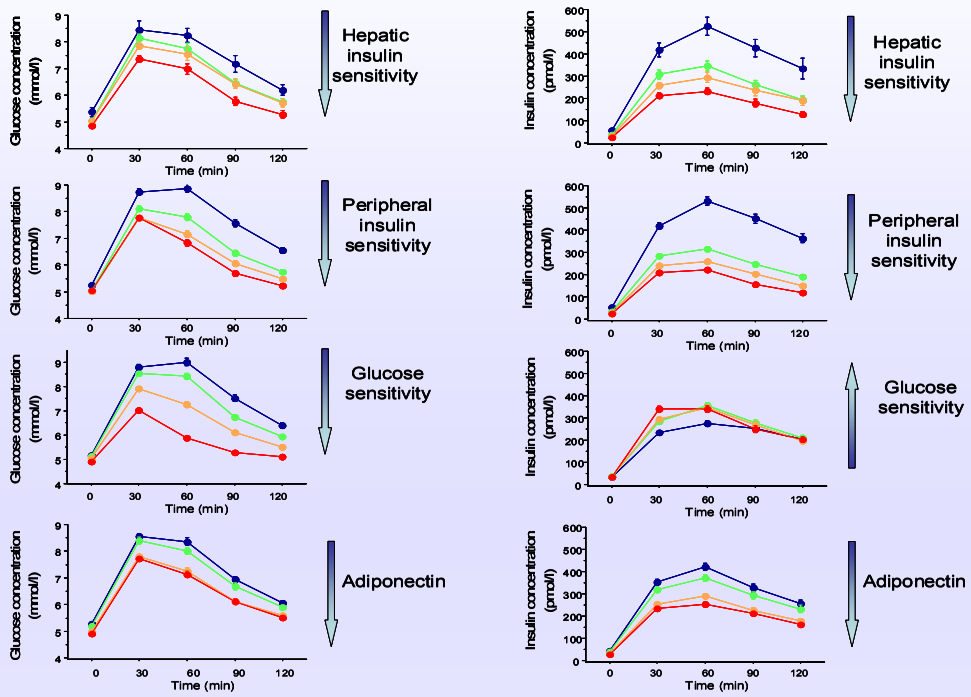

Figure 2. Changes in glucose and insulin concentrations during OGTT across quartiles of hepatic and peripheral insulin sensitivity, quartiles of glucose sensitivity and adiponectin. While glucose concentrations tended to be higher as hepatic and peripheral insulin sensitivity and glucose sensitivity decreased, insulin concentrations varied widely across quartiles of hepatic and peripheral insulin sensitivity, and were similar across quartiles of glucose sensitivity.

CORRELATIONS

We explored the main determinants of fasting and 2-hour glucose levels using multivariate models adjusted for sex, age, BMI and centre with HIR, M/I and glucose sensitivity as dependent variables. Fasting glucose independently correlated with hepatic insulin sensitivity (partial r=-0.26, p<0.0001), M/I (partial r=-0.12, p=0.01) but not with glucose sensitivity.

On the other hand, 2-hour glucose was best predicted by peripheral insulin sensitivity (M/I, partial r=-0.23 p<0.0001) and glucose sensitivity (partial r=-0.21 p<0.0001), while correlation with hepatic insulin sensitivity was not significant.

Adiponectin, when included in the above model, was independently correlated with both fasting (partial r=-0.14 p=0.007) and 2-hour glucose levels (partial r=-0.13 p<0.009) while the associations with insulin sensitivity indexes were maintained. Thus, adiponectin can be considered a biochemical marker of elevated glucose concentrations both fasting and postprandially.

CONCLUSIONS

- In non-diabetic subjects, higher fasting plasma glucose are best predicted by the presence of hepatic insulin resistance, while reduced peripheral insulin sensitivity and ß-cell function play a minor role.
- Glucose intolerance (2h-PG) is best predicted by reduced peripheral insulin sensitivity and ß-cell function while hepatic insulin resistance does not seem to play a major role.
- Adiponectin is an independent marker of elevated glucose concentrations both fasting and postprandially.

References

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