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SHORT COMMUNICATION

Correlation of the leptin:adiponectin ratio with measures of insulin resistance in non-diabetic individuals

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Abstract
Aims/hypothesis Obesity is the dominant cause of insulin resistance. In adult humans it is characterised by a combination of adipocyte hypertrophy and, to a lesser extent, adipocyte hyperplasia. As hypertrophic adipocytes secrete more leptin and less adiponectin, the plasma leptin:adiponectin ratio (LAR) has been proposed as a potentially useful measure of insulin resistance and vascular risk. We sought to assess the usefulness of the LAR as a measure of insulin resistance in non-diabetic white adults.

Methods Leptin and adiponectin levels were measured in 2,097 non-diabetic individuals from the Ely and European Group for the Study of Insulin Resistance (EGIR) Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) study cohorts. LAR was compared with fasting insulin and HOMA-derived insulin sensitivity (HOMA-S) in all individuals and with the insulin sensitivity index (*M*/*I*) from hyperinsulinaemic–euglycaemic clamp studies in 1,226 EGIR RISC participants.
Results The LAR was highly correlated with HOMA-S in men ($r=-0.58$, $p=4.5\times10^{-33}$ and $r=-0.65$, $p=1.1\times10^{-66}$

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within the Ely and EGIR RISC study cohorts, respectively) and in women (r=−0.51, p=2.8×10^{-36} and r=−0.61, p=2.5×10^{-73}). The LAR was also strongly correlated with the clamp *M/I* value (r=−0.52, p=4.5×10^{-38} and r=−0.47, p=6.6×10^{-40} in men and women, respectively), similar to correlations between HOMA-S and the *M/I* value.

Conclusions/interpretation The leptin:adiponectin ratio is a useful measure of insulin resistance in non-diabetic white adults. These data highlight the central role of adipocyte dysfunction in the pathogenesis of insulin resistance. Given that variations between fasting and postprandial leptin and adiponectin levels tend to be small, the leptin to adiponectin ratio might also have potential value in assessing insulin sensitivity in the non-fasted state.

Keywords Adipocytokine · Adiponectin · Insulin resistance · Leptin

Abbreviations

EGIR	European Group for the Study of Insulin Resistance
HOMA-S	HOMA-derived insulin sensitivity
LAR	Leptin:adiponectin ratio
RISC	Relationship between Insulin Sensitivity and Cardiovascular Risk

Introduction

Obesity-induced insulin resistance is a major aetiological factor in the pathogenesis of type 2 diabetes mellitus. We hypothesised that the ratio of plasma leptin to adiponectin (LAR) might be a useful measure of insulin sensitivity, given: (1) the central role of excess adipose tissue in insulin resistance; (2) the now well-recognised capacity of adipose tissue to produce hormones (adipocytokines) involved in the regulation of energy balance and insulin action; and (3) the fact that the two best characterised adipocytokines (leptin and adiponectin) respond in a reciprocal manner to increasing adiposity [1]. The ratio has previously been shown to correlate with carotid intimal medial thickness [2] and to predict the presence of the metabolic syndrome [3]. However, its correlation with insulin sensitivity has not previously been established.

Methods

Leptin and adiponectin were measured in stored fasting serum samples of 2,097 individuals from two large epidemiological cohorts, using previously described assays [4, 5]. All individuals had HOMA-derived insulin sensitivity (HOMA-S) estimated using an online calculator (www.dtu.ox.ac.uk/homa) [6]. In addition, 1,226 individuals in the European Group for the Study of Insulin Resistance (EGIR) Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) study had insulin sensitivity measured using the hyperinsulinaemic–euglycaemic clamp technique. Insulin sensitivity was expressed as the ratio of the mean glucose infusion rate (*M*, adjusted for fat-free mass) to the mean plasma insulin (*I*) over the final 40 min of the clamp (*M/I*).

Medical Research Council Ely Cohort The study design, methods and measurements for this predominantly Europid-population-based cohort study in Ely, Cambridgeshire, UK have been described previously [7]. Briefly, individuals were recruited between 1990 and 1992, using a sampling frame of all non-diabetic adults living in Cambridgeshire. Participants attended the testing site after an overnight fast, and had blood samples drawn once. Written informed consent was obtained. Approval for the study was obtained from the Cambridge Local Research Ethics Committee.

EGIR RISC study cohort This prospective, observational cohort study involved participants from 19 centres across Europe, as described previously [8]. Healthy men and women aged between 30 and 60 years were included. Exclusion criteria were hypertension, dyslipidaemia, prevalent diabetes, pregnancy, treatment for obesity, known cardiovascular or chronic lung disease, weight change of 5 kg in the preceding 6 months, cancer within the previous 5 years or renal failure. However, unlike the Ely cohort, individuals with incident diabetes diagnosed at the time of their study visit were included in the current analysis. Local ethics committee approval was obtained by each recruiting centre, and all participants provided written informed consent. During the hyperinsulinaemic–euglycaemic clamp, exogenous insulin was administered as a primed-continuous intravenous infusion at a rate of 240 pmol min^{-1} m^{-2} simultaneously with a variable 20% (wt/vol.) glucose infusion. This was adjusted every 5 to 10 min to maintain plasma glucose levels within 0.8 mmol/l of the target glucose level (4.5–5.5 mmol/l). The *M/I* value for insulin sensitivity was calculated from the integral of the glucose infusion rate during the final 40 min of glucose infusion, divided by the steady-state insulin concentration.

Descriptive statistics are presented as means with 95% confidence intervals. Non-normally distributed data were log transformed prior to analysis, using the natural log (*e*). In order to compare the LAR with other standard indices of insulin resistance (fasting insulin and HOMA-S), linear regression models were used to separately derive standardised beta coefficients (β±standard error) between log LAR, log HOMA-S and log fasting insulin (as predictors) and log *M/I* (as outcome). Correlations between these measures were calculated using Pearson's correlation. Analyses were stratified by study cohort and by sex,

Table 1 Baseline characteristics of participants in the Ely and EGIR RISC studies

Baseline characteristics	Ely study		EGIR RISC study	
	Men	Women	Men	Women
n	356	515	534	692
Age (years)	54.3 (53.4–55.1)	53.3 (52.6–53.9)	43.2 (42.5–43.9)	44.4 (43.8–45.1)
BMI (kg m^{-2})	25.9 (25.6–26.2)	25.6 (25.2–26.0)	26.4 (26.1–26.6)	24.8 (24.4–25.1)
Fasting insulin (pmol/l)[a]	39.0 (36.9–41.2)	38.2 (36.5–40.0)	32.9 (31.4–34.4)	29.2 (28.1–30.4)
Fasting triacylglycerols (mmol/l)[a]	1.35 (1.28–1.42)	1.11 (1.06–1.16)	1.12 (1.08–1.17)	0.85 (0.82–0.88)
Fasting glucose (mmol/l)	5.82 (5.77–5.87)	5.60 (5.56–5.65)	5.22 (5.17–5.26)	4.94 (4.90–4.99)
HOMA-S[a]	131.9 (124.7–139.4)	135.9 (129.7–142.4)	160.5 (153.5–167.8)	183.1 (176.1–190.5)
Leptin (ng/ml)[a]	3.69 (3.35–4.07)	13.84 (12.88–14.86)	4.01 (3.64–4.40)	14.62 (13.75–15.54)
Adiponectin (μg/ml)[a]	5.23 (4.99–5.47)	8.22 (7.90–8.55)	6.07 (5.88–6.26)	9.24 (8.97–9.50)
LAR[a] (ng/μg)[a]	0.71 (0.63–0.79)	1.68 (1.54–1.84)	0.66 (0.60–0.73)	1.58 (1.47–1.70)
Clamp *M/I* (μmol min^{-1} kg FFM^{-1} $nmol^{-1}$)[a]			110.8 (106.4–115.4)	140.6 (135.9–145.4)

Values are arithmetic mean (95% CI)

[a] Geometric mean

FFM, fat-free mass

because there were significant interactions for the LAR with sex and with study cohort.

Results

Participant characteristics are outlined in Table 1. Overall, 12.7% of study participants were obese (Electronic supplementary material [ESM] Table 1). Leptin, adiponectin and the LAR were higher in women than in men. There were strong and statistically significant correlations between LAR and fasting insulin and HOMA-S in both sexes and both cohorts, as summarised in Table 2. When analysed separately, correlations with fasting adiponectin and leptin levels were consistently less good than those achieved with the LAR (data not shown). In linear regression modelling, the overall association between log LAR and log *M/I* was similar to the association between log 1/HOMA-S and log *M/I* (β=−0.49±0.025 and −0.48±0.025, respectively; p=0.68), and was also similar to the association between log fasting insulin and log *M/I* (β=−0.49±0.025; p=0.86). In subgroup analyses of lean, overweight and obese male and female participants separately, the strengths of the associations between LAR and other measures of insulin sensitivity retained statistical significance and remained similar (ESM Table 2).

Table 2 Correlations between measures of insulin resistance in participants from the Ely and EGIR RISC studies

	Men		Women	
	r (95% CI)	*p* value	*r* (95% CI)	*p* value
Ely study				
Correlations with log LAR				
Log fasting insulin	0.57 (0.50, 0.64)	1.9×10^{-32}	0.51 (0.45, 0.57)	7.5×10^{-36}
Log HOMA-S	−0.58 (−0.64, −0.50)	4.5×10^{-33}	−0.51 (−0.58, −0.45)	2.8×10^{-36}
EGIR RISC study				
Correlations with log LAR				
Log fasting insulin	0.66 (0.60–0.70)	4.5×10^{-67}	0.62 (0.57, 0.66)	1.5×10^{-73}
Log HOMA-S	−0.65 (−0.70, −0.60)	1.1×10^{-66}	−0.61 (−0.66, −0.57)	2.5×10^{-73}
Correlations with log *M/I*				
Log fasting insulin	−0.52 (−0.58, −0.46)	1.4×10^{-38}	−0.46 (−0.52, −0.40)	1.8×10^{-37}
Log HOMA-S	0.51 (0.45–0.57)	2.5×10^{-37}	0.45 (0.39, 0.51)	5.9×10^{-36}
Log LAR	−0.52 (−0.58,−0.45)	4.5×10^{-38}	−0.47 (−0.53, −0.41)	6.6×10^{-40}

Discussion

Leptin and adiponectin differ from almost all other adipocytokines in being secreted exclusively by adipocytes. Although details of all the factors regulating their synthesis, secretion and clearance remain incomplete, plasma leptin levels increase proportionally with fat mass, whereas adiponectin levels decrease with weight gain. Accumulating data suggest that the capacity of adipose tissue to accommodate ongoing energy excess is finite [9], and that 'overloaded' adipocytes ultimately undergo necrosis or apoptosis, precipitating an inflammatory response which may contribute to the development of insulin resistance [10]. Given the central role of obesity in the pathogenesis of insulin resistance, we hypothesised that the ratio of plasma leptin and adiponectin levels would reflect compromised adipose tissue function and provide a useful index of insulin action. Our analysis of this ratio in two large, population-based samples strongly supports this hypothesis. Furthermore, our analyses confirm that the LAR is at least as strongly associated with the gold standard measure of insulin resistance (clamp *M/I* value) as currently used methods such as fasting insulin or HOMA-S. Given the size of the populations studied, and the statistical significance of the associations, these findings are robust.

Further studies are required in younger people and in those with diabetes to determine the validity of the LAR as a measure of insulin resistance in these groups. However, emerging data in young people suggest that leptin and adiponectin are good markers of insulin resistance [11]. Use of the LAR as a marker of insulin resistance in diabetic individuals requires further clarification, as previous observations involved skewed data from relatively small numbers of patients [12], though it has been shown to reflect atherosclerotic change in diabetic individuals [2]. Also, rare exceptions exist where insulin resistance is associated with high adiponectin concentrations and where the ratio would clearly not be valid [13]. Additionally our data pertain to two predominantly white populations, in whom adiponectin levels tend to be higher than in other ethnic groups [14] and so further validation studies are required in these groups. Last, the relative expense of leptin and adiponectin assays compared with cheaper glucose and insulin assays might limit their utility.

Notwithstanding these limitations, this study affirms the central role of excess adiposity in modulating insulin action, and offers a potentially useful tool for quantifying insulin resistance on a large scale. Moreover, given that circadian and postprandial variations in leptin and adiponectin levels are modest [15], the LAR has potential additional value as a measure of insulin resistance because, in contrast to conventional indices of insulin action, it may be a valid measure of insulin resistance even when measured in the non-fasted state. Leptin and adiponectin are also very stable in plasma or serum whereas insulin is not (data not shown). Clearly this is an area that requires further investigation, as our analysis included only participants who had samples taken while fasting. However, removing the need for fasting samples would significantly increase the efficiency and feasibility of insulin resistance measurements in large population-based studies.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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