

Serum resistin concentrations are associated with HbA1c in obese non-diabetics, but not in obese diabetics: a cross-sectional human study

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Abstract

OBJECTIVE: Glycosylated hemoglobin (HbA1c) and resistin may be influenced by diabetes, but their associations remain unclear. We hypothesized that serum resistin might be parallel to Hb1c.

DESIGN AND SETTING: We measured serum resistin in 134 obese non-diabetic (73 women and 61 men), and 65 obese diabetic (33 women and 32 men) humans, and examined their relationships with HbA1c. The presence of diabetes was the only differentiating factor between the groups.

RESULTS: Resistin, non-diabetic vs. diabetic, median and interquartile range, respectively: resistin (ng/mL) 26.08, 16.09 and 22.14, 14.54, $p > 0.5$. To investigate the influence of HbA1c on resistin, both groups were divided into tertiles based on HbA1c. In diabetics, resistin was similar in high, intermediate, and low HbA1c subgroups, $p > 0.05$, and resistin was not influenced by HbA1c: $r = -0.1785$; $p = 0.15$. In non-diabetics, resistin differed between HbA1c tertiles, $p < 0.001$, and was influenced by HbA1c, $r = -0.3599$; $p = 0.0003$.

CONCLUSIONS: Resistin concentrations are similar in diabetic and non-diabetic humans with the same range of obesity. However, resistin is associated with HbA1c only in non-diabetic obese individuals which may point to the fact that resistin is a marker of glycaemic balance in obesity but not in diabetes.

INTRODUCTION

Facing an epidemic of type 2 diabetes, clinicians seek valuable markers that could serve as a tool in the management of this disorder. Glycosylated haemoglobin (HbA1c) and resistin may both be influenced by diabetes and insulin treatment, and thus their measurements may help manage diabetic patients. Nonetheless, whereas HbA1c is

the cornerstone of a modern approach to diabetes, the role of resistin in diabetes arouses controversy (Fargnoli *et al.* 2010; Gharibeh *et al.* 2010; Tuttolomondo *et al.* 2010).

Resistin (FIZZ3/ADSF) belongs to endocrine substances, or adipocytokines, secreted by adipose tissue that also include adiponectin, leptin, IL-6,

TNF α (Spiegelman & Flier 1996; Friedman & Halaas 1998; Prins 2002; Steppan & Lazar 2002). Resistin belongs to the family of cysteine-rich resistin-like molecules (RELM) (Steppan & Brown *et al.* 2001), together with RELM- α and RELM- β . Serum concentrations of resistin are increased in obese mice and influence insulin action (Steppan & Bailey *et al.* 2001), however, although resistin might link obesity with insulin resistance and diabetes in mice models, numerous studies in rodent models have called this interesting idea into question (Juan *et al.* 2001; Le Lay *et al.* 2001; Way *et al.* 2001). In humans, the role of resistin is even more controversial. In contrast to mice, human resistin is barely detectable in adipose tissue (Nagaev & Smith 2001; Savage *et al.* 2001), and no correlation was found between resistin expression of isolated adipocytes and obesity or type 2 diabetes (Nagaev & Smith 2001; Savage *et al.* 2001; Janke *et al.* 2002). Furthermore, serum resistin levels were found to be related to body mass index (BMI) in human subjects by some authors (Azuma *et al.* 2003; Degawa-Yamauchi *et al.* 2003; Fujinami *et al.* 2004), whereas others did not demonstrate this association (Heilbronn *et al.* 2004; McTernan *et al.* 2003; Youn *et al.* 2004).

Elevated concentrations of circulating resistin have been associated with type 2 diabetes, obesity and insulin resistance by some (Gharibeh *et al.* 2010; Tuttolomondo *et al.* 2010), but not by other authors (Fargnoli *et al.* 2010; Yuan *et al.* 2010) whereas data regarding resistin and the markers of glycaemic control in diabetes are more limited and conflicting (Mojiminiyi *et al.* 2007; Fargnoli *et al.* 2010; Bajnok *et al.* 2008). Therefore, we have put forward a hypothesis that serum resistin might be parallel to Hb1c, as they both reflect the metabolic status. To prove this hypothesis, we aimed to measure resistin concentrations in non-diabetic and diabetic humans with a similar range of trunkal obesity, and to examine whether they were related to the levels of HbA1c. Under the condition, the presence of diabetes was the only differentiating factor between two groups of frankly obese humans

MATERIALS AND METHODS

The study group consisted of 134 obese non-diabetic subjects (73 women and 61 men), and 65 obese and diabetic subjects (33 women and 32 men), recruited by local advertising. Both groups were sex- and age-matched. Their age was 51 ± 6.9 , and 52 ± 6.7 years, respectively. Obesity was defined according to the WHO criterion (BMI, >30 kg/m²). In all non-diabetics, diabetes was excluded by means of the standard oral glucose tolerance test: 75 grams of glucose was administered orally and the plasma glucose concentration was measured in 2 hours. In the diabetes group, all subjects presented with type 2 diabetes mellitus. Diabetes was defined according to the WHO criterion (fasting glucose of 126 mg/dL, or 6.99 mmol/L, on two various

days). All subjects were treated with oral sulfonylureas. All subjects were otherwise healthy according to history, clinical examination, and routine laboratory findings. In particular, none of the studied subjects had evidence of acute or chronic inflammatory disease, had a history of alcohol overconsumption, was completely sedentary, or involved in athletics. All subjects were examined in the morning (at 08:00) after an overnight fast. For women, the examination was made in the middle of the menstruation cycle according to self report. All women had no history of menstrual disturbances or infertility and showed no clinical features of hyperandrogenism or PCOS. Height and weight were measured, and the percentage of body fat was determined with a bioimpedance technique (Bodystat 1500, by BODYSTAT Isle of Man Ltd., U.K.). Repeated bioimpedance tests were performed at the same time after an overnight fast (08:00 A.M.). Exercise, and alcohol or caffeine consumption was banned 24 hrs prior to the bioimpedance test. Premenstrual women and women during menstruation were excluded, as well as patients using diuretics. A venous blood sample was obtained for the measurement of plasma levels of glucose (expressed as mmol/litre, mmol/l) at the hospital's routine chemistry laboratory. Serum levels of resistin were measured using an ELISA method (R&D Systems, Inc., Minneapolis, MN) and were expressed as nanograms per milliliter. Resistin was measured according to the manufacturer's recommended protocol, with a sensitivity of 0.026 ng/mL. An intra-assay and inter-assay coefficients of variation were 5.25% and 6.47%, respectively. The values are given as the median and interquartile range. Mann-Whitney test, Kruskal-Wallis test, Dunn test (for post hoc analysis), and Spearman correlation analysis were used for statistical examinations. Standard computer software (STATISTICA 6.0 by Statsoft, Inc.) was applied to the statistical analyses. *p*-values of less than 0.05 were considered statistically significant.

The study was approved by the ethics committee of the Poznań University of Medical Sciences. All subjects gave informed consent to participate.

RESULTS

The clinical data of the diabetic and non-diabetic subjects are shown in Table 1. Both study groups were of similar age, and their body mass indices and percent body fat did not differ. However, as expected, diabetic subjects showed higher levels of HbA1c and plasma glucose. Resistin concentrations did not differ between diabetic and non-diabetic subjects, *p*=0.6977.

To investigate the influence of HbA1c on serum concentrations of resistin, both study groups were divided into tertiles according to their HbA1c levels. In diabetics, as seen in Table 2, except HbA1c, all parameters did not differ between the tertile subgroups. The plasma concentrations of resistin did not differ significantly between the high (H), intermediate (I), and

Tab. 1. Clinical characteristics of non-diabetic and diabetic subjects examined. Data are shown as median and inter-quartile range, and presented separately for women, separately for men, and for both genders together.

	Non-diabetics			Diabetics			p-value		
	Women	Men	Both genders	Women	Men	Both genders	Women	Men	Both genders
Number of subjects	73	61	134	33	32	65	73 vs. 33	61 vs. 32	134 vs. 65
BMI (kg/m ²)	37.30; 10.40	33.10; 9.10	35.35; 10.30	36.30; 7.40	34.05; 9.25	36.20; 8.40	0.583	0.739	0.906
Waist (cm)	110.5; 21.50	112.0; 24.0	111.0; 20.0	111.0; 13.0	116.0; 17.5	115.0; 14.0	0.213	0.177	0.074
Hip (cm)	123.5; 21.50	110.0; 22.0	117.0; 22	120.0; 20.0	115.5; 16.5	117.0; 20.0	0.590	0.396	0.958
Glucose (mmol/L)	5.4; 1.10	5.60; 0.80	5.50; 0.90	7.73; 3.07	6.70; 1.20	6.75; 2.13	<0.05	0.054	<0.01
HbA1c	5.9; 0.90	5.9; 0.80	5.90; 0.90	7.45; 2.25	7.25; 1.25	7.40; 1.40	<0.0001	<0.0001	<0.0001
Resistin (ng/mL)	26.88; 15.25	25.47; 16.86	26.08; 16.09	20.75; 15.69	27.43; 12.14	22.37; 14.54	0.208	0.486	0.736

low (L) HbA1c levels subgroups (in Kruskal-Wallis test: $p=0.8854$; Dunn test: H vs. I, $p=1.000$; H vs. L, $p=1.000$; I vs. L, $p=1.000$, respectively). Moreover, the serum concentration of resistin was not influenced by HbA1c levels: in Spearman's correlation coefficient analysis, the serum resistin levels were not correlated with HbA1c levels ($r = -0.1785$; $p=0.1549$).

The results in non-diabetic subjects are shown in Table 3. Unlike in diabetics, resistin was influenced by HbA1c levels because it differed between the high (H), intermediate (I), and low (L) HbA1c levels subgroups (in Kruskal-Wallis test: $p=0.0003$; Dunn test: H vs. I, $p=0.2539$; H vs. L, $p=0.0002$; I vs. L, $p=0.040$, respectively), and it correlated with HbA1c levels ($r = -0.3599$; $p=0.0003$).

In order to evaluate the influence of sex on resistin levels, and gender relation to HbA1c, we estimated all correlations for diabetic females and males separately, in an identical manner. Results were similar to those in the whole cohort. However, due to relatively low numbers of participants we decided not to present the data as reliable conclusions could not have been drawn on their basis.

DISCUSSION

Findings from animal model studies suggested that resistin could be an important factor in the development of the metabolic syndrome, type 2 diabetes and its main complication, i.e., coronary heart disease (Steppan and Bailey *et al.* 2001; Burnett *et al.* 2005; Reilly *et al.* 2005; Ohmori *et al.* 2005; Pang & Le 2006; Muse *et al.* 2007). In spite of this, the link between resistin and obesity in humans is less clear, and conflicting results were reported. Most of the human studies failed to show this link (Nagaev *et al.* 2001; Savage *et al.* 2001; Patel *et al.* 2003), and only a few studies demonstrated that resistin serum concentrations were elevated in obese patients

Table 2. Diabetic subjects divided into tertiles based on their HbA1c levels.

	high	intermediate	low	p-value
Number of subjects	21	22	22	
BMI (kg/m ²)	36.80, 7.60	35.10, 9.00	35.35, 10.60	0.854
Body fat (%)	48.80, 7.50	41.90, 14.70	42.45, 9.80	0.135
HbA1c	9.00, 1.40	7.40, 0.50	6.50, 0.90	<0.0001
Resistin (ng/mL)	21.05, 17.14	24.89, 14.01	25.17, 11.74	0.885

Data are shown as median and inter-quartile range. Abbreviations used are as follows: BMI, Body Mass Index, HbA1c, glycosylated hemoglobin.

Table 3. Non-diabetic subjects divided into tertiles based on their HbA1c levels.

	high	intermediate	low	p-value
Number of subjects	44	45	45	
BMI (kg/m ²)	39.75, 7.30	33.50, 10.20	36.60, 12.40	<0.05
Body fat (%)	50.0, 7.55	38.25, 17.85	43.30, 12.00	<0.01
HbA1c	6.45, 0.30	5.90, 0.25	5.20, 0.60	<0.0001
Resistin (ng/mL)	18.92, 14.24	25.10, 16.10	30.39, 6.17	<0.001

Data are shown as median and inter-quartile range. Abbreviations used are as follows: BMI, Body Mass Index, HbA1c, glycosylated hemoglobin.

and could be related to obesity (McTernan *et al.* 2002; McTernan *et al.* 2002, Owecki *et al.* 2010), or, as we previously reported, associated with plasma lipids (Owecki *et al.* 2010a).

Even less is known about the relationships between resistin and HbA1c, which prompted us to investigate this problem: to date, and to our knowledge, very few papers covering this topic have been published, and their results were conflicting. As mentioned above, HbA1c is an established tool for the evaluation of management of diabetes mellitus. Presumably, an association between HbA1c and resistin might implicate an involvement of resistin in the pathogenesis of diabetes, as it seemed logical to us that the serum resistin might be parallel to HbA1c.

Unexpectedly however, what we demonstrated in this study was that not in diabetic but only in non-diabetic obese subjects, HbA1c positively correlated with resistin. This is partially in contrast to what found Fargnoli *et al.* (2010), who in a recent study examined 1065 healthy women, Nurses' Health Study participants and showed that resistin was positively associated with the inflammatory markers but not with any biomarkers of endothelial function, glycemia, insulinemia, or markers of insulin secretion, also including HbA1c. Here, we do not find an association between resistin and HbA1c in diabetic patients but we demonstrate a strong correlation in non-diabetics. The explanation of this result may be difficult, but we suggest that in diabetes, numerous factors influence resistin levels, and therefore, changes of HbA1c and resistin are not parallel. In contrast, in obese individuals, less concomitant factors are present and thus, HbA1c reflecting glycemia might also reflect resistin levels.

Consequently, the explanation of the lack of an association between resistin and HbA1c in diabetic patients in spite of its presence in similarly obese non-diabetics might also be difficult. Particularly, one should consider here that the sources of resistin differ between rodents and humans. The adipocyte is presumably the sole source of resistin in mice, whereas in humans the majority of resistin is secreted by macrophages and monocytes, and only little is produced by adipocytes. Presumably, a due to inflammatory processes in diabetes, larger amounts of resistin might be secreted by macrophages and monocytes, which would certainly influence the inter-relations between resistin and HbA1c. This hypothesis necessitates further research.

In addition, we would like to comment on the approach we used in this study. Here we investigated two groups of obese patients, in whom the presence of type 2 diabetes was the only differentiating factor. However, we decided to examine only diabetic subjects with a correct, or nearly correct fasting plasma glucose achieved on medication. One may argue about this limitation, which is in contrast to many other studies. This approach diminished our sample but gave us the opportunity to rule out the influence of imbalanced

diabetes on the secretion of resistin. In other words, we analyzed a strictly limited group of obese diabetic and euglycemic individuals, with the diabetic subgroup well balanced on medication. Also, because gender may be a confounding factor, we studied both men and women, and evaluated them separately. Including only women and only men into the analyses yielded comparable results as including all individuals.

Based on our results, we show here that resistin levels are correlated with the serum HbA1c levels only in non-diabetic obese humans, whereas this association is absent in similarly obese diabetic individuals. Presumably, the overlapping multi-factorial influence of diabetes is the cause of the disappearance of this association in diabetes. The findings from our study may be another piece of information to the discussion about the role of resistin in human metabolism, obesity and type 2 diabetes mellitus.

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