Original Article

Serum resistin a biomarker of type II diabetes development

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Abstract

Background: *Resistin and ghrelin are hormones that have roles in the glucose and lipid homeostasis and weight regulation. Human studies regarding resistin and ghrelin in diabetic patients are scarce, especially in the cases of normotensive and non-obese patients. This study was designed to illuminate some of the missing points.*

Methods: *Eighty diabetic patients and eighty healthy individuals participated in this study; according to the inclusion criteria [age, gender, body mass index (BMI), blood pressure (BP) and diabetes type]. Fasting and postprandial glucose, hemoglobin A1c (HbA1c), insulin, acylated-ghrelin and resistin were evaluated for all the participants while HOMA and QUICKI were calculated.*

Results: *Fasting and postprandial glucose, HbA1c, insulin and calculated HOMA increased, while QVICKI decreased among the diabetic patients ($p<0.001$). All patients also had reduced acylated-ghrelin that was more predominant among type I cases ($p<0.001$), while resistin was significantly reduced among the female patients ($p<0.001$). Furthermore, a significant negative correlation between circulating insulin and resistin of older healthy subjects [female ($R=-0.72$, $p<0.001$) and male ($R=-0.59$, $p<0.01$)] was detected which was absent for the patient groups.*

Conclusion: *None of the diabetes indicators correlated with the circulating ghrelin or resistin that may indicate reductions in the results of protective phenomena due to excess glucose, increase insulin, or high circulating lipids usually observed among the diabetic patients. On the other hand, a strong negative correlation between the insulin and resistin among the older (38-55 years) healthy individuals that indicate the rise of resistin can be a sign of initiation of type II diabetes.*

Key words: *Diabetes (type I and II), Acylated-ghrelin, Resistin, Insulin, HOMA, QUICKI.*

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Adipose tissue is no longer regarded as a passive depot of energy excess or storage in the form of triglycerides. This tissue actively secretes proteins such as leptin, adiponectin and resistin, with various autocrine/paracrine functions, such as glucose and lipid homeostasis and body weight regulation (1). Resistin is a member of a class of cysteine-rich proteins that collectively termed resistin-like molecules which has been implicated in the pathogenesis of obesity-mediated insulin resistance and type II diabetes mellitus, at least in rodent models (2). Earlier studies showed resistin is up-regulated in rodent models of obesity and insulin resistance and down-regulated by an insulin-sensitizer (rosiglitazone) while immune-neutralization of resistin reduced hyperglycemia and improved insulin sensitivity (3). These observations not only brought resistin to much scientific attention, but characterized it as a potential etiological link between obesity and diabetes with a clear functional role as a pathogenic factor contributing to insulin resistance. While most of the human studies investigated scenery of resistin in type II diabetic patients or its role in obesity, the data regarding plasma resistin in human is scarce especially in the cases of type I diabetic patients or non-obese individuals (4-7).

Ghrelin is another hormone which is mainly secreted by endocrine cells of gastrointestinal tract and regulates feeding behavior by increasing food intake and modulating expression levels of orexigenic peptides in the hypothalamus (8,9). Plasma ghrelin is also reduced in obese subjects compared to lean ones and weight recovery normalizes ghrelin values (9). The relationship between plasma ghrelin and adiposity markers is controversial too, since most studies analyzing this issue have been carried out in obese individuals or only type II diabetic patients (10-15). Moreover, only a few studies considered ghrelin and resistin at the same time in diabetic patients and reached different conclusions depending to their experimental design (10, 16-20). As mentioned above, the data regarding plasma resistin and ghrelin in human are scarce especially in the cases of non-obese diabetic individuals. This study was designed to elucidate the missing points of the previous studies and look into the influence of age, gender, body mass index (BMI), blood pressure (BP), types of diabetes (type-I and type-II) and their correlations with routine indicators of diabetes [fasting blood glucose (FBS), postprandial glucose (PPS) and hemoglobin A1c (HbA1c)] or circulating resistin and acylated-ghrelin (active form of ghrelin).

Methods

The Research Approval and Ethics Committee of Kerman University of Medical Sciences approved the protocol for this study. Eighty patients (equal number of type I and II diabetes patients, 20 male and 20 female in each group) who were attending a diabetic clinic in a regular basic were selected by the clinic's physician. These patients were on anti-diabetic drugs only [either on insulin for the type I patients or Glibenclamide (Glyburide) or/and Metformin for the type II patients]. They were also not suffering from any diabetes complications and other diseases for the last six months. The criteria for the patient selection included normal daily activity, normal BP (both systolic and diastolic) and BMI less than 25 kg/m^2.

A questionnaire including their personal information and a space to fill up for the measurement of blood pressure, height and weight of the participants was completed by the same physician the same day of sample collection. A fasting blood samples were collected to evaluate the circulating level of fasting glucose (FBS), HbA1c, acylated-ghrelin, resistin and insulin. To evaluate postprandial glucose, other blood samples were collected 2 hours after giving breakfast to the patients. Eighty healthy individuals without any medical illness for the last six months served as the two control groups. The physical examination of all the participants was carried out by the same physician and their BP pressure, height and weight were recorded. The criteria for the control group selection also included a normal BP and daily activity, a BMI of less than 25 kg/m^2, and lack of any illness for the last six months. The fasting and postprandial sample collection of the control groups was also identical to the patients' protocol.

Five ml of fasting blood samples were collected from all the participants. Part of that (2 ml) was added to EDTA tube. Half of this sample was centrifuged and the plasma was used for the determination of acylated ghrelin (according to protocol provided by the manufacturer of Kit), while the whole blood was used to measure HbA1c. The fasting sera separated from the clotted blood samples were also used for evaluation of FBS, resistin and insulin, while sera separated from the second samples was used for the evaluation of PPS. The serum glucose was determined using an endpoint glucose oxidase method with an automated chemistry analyzer (RA-1000 Technicon, USA).

HbA1c was determined using an automated analyzer base on chromatography method (Drew DS5, UK). For the evaluation of acylated ghrelin and resistin ELISA kits manufactured by BioVendor Laboratory Medicine Industry (Czech Republic) were used and serum insulin was evaluated using Elisa kit bought from IBL (Germany). All the steps in the Elisa methods were taken according to the manufacture of the kits. The final readings were taken by Stat-Fax (Awareness, USA) plate reader. BMI [weight (kg)/square of height (m)], homeostasis model assessment (HOMA) [HOMA=Insulin (mU/L) x glucose (mM)/22.5] and quantitative insulin sensitivity check (QUICK) [QUICKI= 1/(log Insulin (mU/L) +log FBS (mg/dl)] were calculated to determine their correlation with the different evaluated parameters. The data were analyzed using SPSS (Version 16.0) PC program. After checking the normal distribution of data, the independent sample T-test was used to compare the two groups. For multiple assessment of circulating acylated-ghrelin or resistin of four groups, the one-way ANOVA (post Hoc Tukey's model) was used. The determination of correlations was carried out using Pearson's two-tailed bivariate model. P values less than 0.05 was considered as a significant difference.

Results

The evaluated parameters and calculated data for all the participants are shown in table 1 and 2, which is divided according to the type of diabetes and gender of participants. The analysis of data for the different groups showed no significant differences between the ages, BMI, BP or activities (daily activity was classified as low=1, normal=2 and high=3) of the patients and their corresponding control groups except one group, though we tried to match the groups. The statistical analysis of data showed the juvenile female control who had significantly lower BMI and were younger which in return may be a drawback in this study.

As it was expected, there were significant increases in the levels of FBS, PPS and HbA1c of the diabetic patients when compared with the appropriate control groups which confirmed the precise selection of diabetic patients and the appropriate healthy control groups. The circulating insulin level of all the four groups of patient was also significantly ($p<0.05$) higher than their corresponding control group.

Several methods for evaluating insulin resistance have been developed; HOMA and QUICKI are two calculated indicators that depend to the levels of FBS and insulin (21). Our data showed all four groups of patients who had significantly ($p<0.001$) higher calculated HOMA and lower QUICKI when compared with the corresponding healthy individuals. The correlation analysis also showed that HOMA and insulin had a 99% correlation among the control groups. This correlation reduces to 91-93% for the male patients (both type I and II) and 73% for the type I or 86% for the type II female patients. The negative correlation between insulin and QUICKI was also 93-96% for the control groups, while it was reduced to 68- 72% for type I (both gender) and 84-86% for type II patients.

The plasma levels of fasting acylated-ghrelin of four groups of patients were lower than the equivalent control participants (figure 1). This reduction was more predominant ($p<0.001$) among type I diabetic patients compared to the type II ($p<0.03$). Furthermore, while the circulating level of patients' ghrelin did not show any dependency to the age or gender, there was a noticeable negative correlation between ghrelin and age of healthy participants. Statistically, the negative correlation between the age and fasting level of circulating ghrelin was detected among the healthy female ($R=-0.29$, $p<0.05$), that was not significant for the male participants ($R=-0.14$, $p=0.39$). The correlation analysis of data also showed the reduction of circulating ghrelin with the age that was significant ($p<0.05$) for the female in the control groups while was not significant for the healthy male. In the end while all the female patients had significantly lower circulating resistin than their respective control groups, fasting resistin of male patients (both types) did not differ much from the corresponding values obtained for their respective control groups. This reduction among the female patients was also dependent to the age and type of diabetes; in such a way that this reduction was more predominant ($p<0.01$) among the type II cases compared to the type I patients ($p<0.05$).

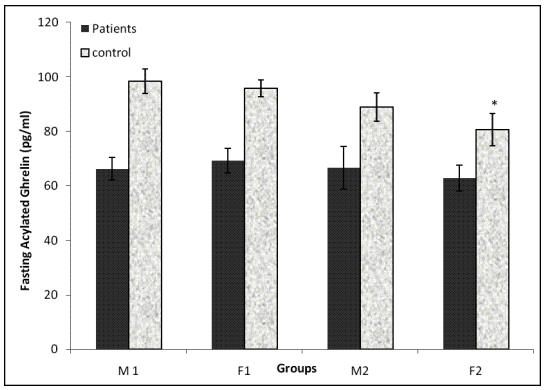

Figure 1: Plasma levels of fasting acylated-ghrelin of four groups of test and corresponding age and gender matched control healthy participants. * p<0.05

The correlation analysis of data showed there was a significant negative correlation between the insulin and circulating resistin of older (38-55 years) healthy subjects [female ($R=-0.72$, $p<0.001$) and male ($R=-0.59$, $p<0.01$)] (figure 2), which was absent for all the patient groups or healthy juvenile subjects.

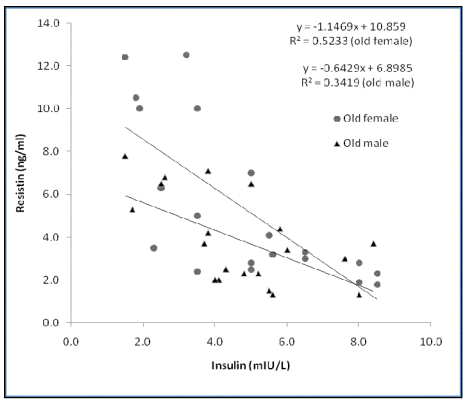

Figure 2: Negative correlation between fasting insulin and circulating resistin of elderly healthy control participants.

Table 1: Different parameters evaluated or calculated for the type I diabetic subjects and appropriated control groups. Number of cases in each group, n=20. The values in the bracket are standard deviation.

Groups / variables	Male patients (type 1) Mean±SD	Male control Mean±SD	P value	Female patients (type1) Mean±SD	Female control Mean±SD	P value
Age (years)	28.29 ±6.22	25.70±2.60	0.124	29.25±5.21	23.55±3.27	0.001
BMI (Kg/m^2)	23.68 ±3.41	23.38±2.31	0.750	25.91±4.37	21.93±2.49	0.001
Systolic (mm Hg)	114.44 ±11.5	115.50±5.10	0.723	105.0±12.25	104.5±8.41	0.880
Diastolic (mm Hg)	71.67 ±7.07	71.00±9.12	0.802	70.47±8.05	73.75±8.87	0.223
Activity (score)	2.0 ±0.34	1.95±0.22	0.603	1.86±0.36	2.00±0.32	0.189
FBS (mg/dl)	210.11±69.25	82.20±4.82	<0.001	189.33±62.56	77.10±6.21	<0.001
PPS (mg/dl)	280.61±62.21	95.90±6.34	<0.001	266.14±67.64	92.84±7.39	<0.001
HbA1C (%)	11.61±3.76	4.89±0.44	<0.001	9.96±2.43	4.80±0.97	<0.001
Insulin (mIU/ml)	9.68±6.33	5.53±2.26	0.011	10.38±4.76	5.79±2.32	0.001
HOMA	4.59±3.08	1.12±0.46	<0.001	4.60±2.37	1.11±0.48	<0.001
QUICKI	0.31±0.03	0.39±0.03	<0.001	0.31±0.02	0.39±0.04	<0.001
Resistin (ng/ml)	3.13±1.67	3.33±1.68	0.719	3.00±1.10	4.04±1.69	0.024
Ghrelin (pg/ml)	66.28±17.64	98.48±20.07	<0.001	69.29±20.25	95.75±13.65	<0.001

Table 2: Different parameters evaluated or calculated for the type II diabetic subjects and appropriated control groups. Number of cases in each group, n=20. The values in the bracket are standard deviation.

Groups / Variables	Male patients (type 2) Mean±SD	Male control Mean±SD	P value	Female patients (type2) Mean±SD	Female control Mean±SD	P value
Age (years)	43.12±5.95	45.30±4.41	0.222	45.15±3.34	44.20±5.06	0.446
BMI (Kg/m^2)	25.30±3.64	24.08±2.64	0.244	25.76±3.34	25.42±4.09	0.757
Systolic (mm Hg)	115.29±8.74	122.00±6.96	0.314	118.89±11.87	120.50±6.86	0.590
Diastolic (mm Hg)	74.71±6.24	79.50±8.26	0.580	75.56±7.51	78.00±6.96	0.261
Activity (score)	1.94±0.43	2.00±0.00	0.542	1.96±0.34	2.00±0.00	0.627
FBS (mg/dl)	200.29±49.80	86.40±5.85	<0.001	188.48±59.54	88.25±7.09	<0.001
PPS (mg/dl)	267.88±42.54	102.50±7.99	<0.001	271.93±45.90	101.25±8.14	<0.001
HbA1C (%)	11.22±2.96	5.16±0.56	<0.001	10.30±2.22	5.23±0.67	<0.001
Insulin (mIU/ml)	7.30±2.78	4.70±1.92	0.003	8.83±4.34	4.79±2.32	<0.001
HOMA	3.51±1.76	1.01±0.43	<0.001	4.02±2.40	1.03±0.50	<0.001
QUICKI	0.32±0.03	0.39±0.04	<0.001	0.32±0.02	0.39±0.04	<0.001
Resistin (ng/ml)	3.51±1.77	3.88±2.11	0.566	3.17±1.66	5.37±3.68	0.008
Ghrelin (pg/ml)	70.20±27.69	88.90±23.09	0.031	67.24±17.73	83.64±21.32	0.006

Discussion

HOMA and QUICKI are two calculated indicators of insulin resistance, which depend to the levels of FBS and circulating insulin (21). Though our data showed a 99% correlation between circulating insulin and HOMA or 93-96% between fasting insulin and QUICKI among healthy subjects, neither HOMA nor QUICKI showed such correlation among the diabetic patients. Furthermore, we showed age and gender of the patients of the two other affecting factors that could influence the correlation between insulin and HOMA [male patients 91-93% (both type I and II) and female patients 73% (type I) to 86% (type II)]. On the other hand, the calculated correlations for the QUICKI were also lower among the patients (68-72% for the type I and 84-86% for the type II) without any significant effect on gender or age. To compare with the previously reported data, our findings also showed increase in the values of HOMA and reduction in the value of QUICKI which were indicators of insulin resistance among the diabetic patients (22,23), but according to our data, since age and gender of patients effected these calculations, these factors should be considered when using HOMA and QUICKI for the assessment of insulin resistance. Furthermore, Katsuki et al. (24) believes that HOMA and QUICKI are not good indicators of poorly controlled type II old diabetic patients. Since the present study, all the participants patients had nearly controlled diabetes as indicated by the values of their PPS or HbA1c, we may also add another point to the importance of HOMA and QUICKI that besides the appropriate control diabetes, gender and age are also affecting factors which should be considered when HOMA is used for the evaluation of patients' insulin resistance.

The development of type II diabetes and insulin resistance is mostly associated with obesity, but even among obese subjects, insulin sensitivity varies widely. Moreover, most of the type I diabetic patients are not obese and control of their diabetes depends on the use and amount of external insulin that could affect their circulating insulin too. While previous studies had agreement for the correlation between obesity (5,25,26) or BP (4,27) and circulating resistin among type II diabetic patients, there are arguments regarding gender, age or daily activities of diabetic patients (1,2,6,28-30), especially in the cases of type I patients. For clarifications of vague points regarding resistin and ghrelin, in this study we selected none-obese normotensive (systolic as well as diastolic) diabetic patients who had normal daily activity. Our data (table 1 and 2) showed circulating fasting resistin of male diabetic patients (both types) who did not differ from their respective controls, while the female had significantly reduced resistin. These finding clearly indicate diabetes' marker (FBS, PPS, HbA1c, HOMA and QUICKI) and BP could not influence the production and circulating level of resistin, even among diabetic patients with normal BMI. Furthermore, reduced resistin detected among the female patients could indicate production of resistin is sex dependent and the reduction is more noticeable among the old people. We think higher production of resistin among the healthy female can not be the results of increase in the body's adipose tissue especially visceral adipose tissue that determine the synthesis and release of resistin as a protective inflammatory marker (31,32) to control the production of insulin or/and glucose transporter-4 (GULT-4) on the surface of different cells including subcutaneous adipose tissue, to reduce the amount of fat deposition in the body. This hypothesis may be confirmed by an apparent but none significant increase of resistin with age among our healthy participants (table 1 and 2) that may be the results of increased visceral adipose tissue usually developed among the older people. In addition, a detection of a negative and significant correlation between the circulating resistin and fasting insulin (figure 2) among the older healthy subject could be another supporting point to confirm our hypothesis and point out the known fact that the amount of adipose tissue is an important influencing factor for the development of type II diabetic among the older people. On the other hand, lower circulating level of resistin detected among the diabetic patients could be the result of insulin therapy (type I patients) and the use of drugs such as Glibenclamide (promoter of insulin production) or Metformin (increases the number of GULT-4) that could suppress the production of resistin, through a feedback mechanism(s) (3, 33-35).

Ghrelin which was initially identified as an endogenous ligand for the growth hormone secretagogue receptor and was predominantly produced by the stomach, is now known produced by many tissues such as pituitary, hypothalamus, duodenum, jejunum, ileum, colon, lung, heart, pancreas, kidney, ovary and testis (36) that act as paracrine hormone, locally. In addition to stimulation of GH release, systemic ghrelin stimulates appetite and food intake (through neuro-peptide Y), enhancing fat mass deposition and weight gain (9). Besides these main actions, acylated-ghrelin regulates gastric motility and acid secretion in the digestive system,

exerts cardiovascular and anti-inflammatory effects, modulates cell proliferation and influences endocrine and exocrine pancreatic secretion, as well as glucose and lipid metabolism (9,36).

Similar with the previous studies we also detected a decrease in the circulating acylated-ghrelin among our diabetic patients (both types) (10-12,37), but without any significant correlation with age, BMI, BP, or diabetic indicators (FBS, PPS, HbA1c, insulin, QUICKI and HOMA) as detected before (13,14,37,38). These findings suggest reduction of systemic ghrelin among the diabetic patients may not be the main predictor of diabetes, but its production may be somehow controlled by insulin like growth factor-1 (IGF-1) as suggested before (13) or the high level of either circulating glucose or insulin (14,38). The reduction of circulating ghrelin among diabetic patients may also be the results of a protective system to reduce the appetite, thereby, decreasing snack intake and daily energy intake, promoting weight loss and prolong the inter-meal interval as suggested before (39). Finally, we detected an age dependent reduction of systemic acylated-ghrelin among the healthy people that were significantly lower among the female, which could explain the reduction in the appetite of older people in the results of this protection phenomenon, though our data could not demonstrate any significant correlation between age and fasting ghrelin (besides a significant decrease with the age detected among the healthy female) to support our hypothesis. In conclusion, none of the diabetes indicators (FBS, PPS, HbA1c, QUICKI, HOMA and insulin) correlated with the circulating levels of fasting acylated-ghrelin or resistin of diabetic patients (both types), but our data suggest their reductions could be the results of protective phenomena due to excess glucose, increase insulin, or high circulating lipids usually observed among diabetic patients. In the end, the strange negative correlation between the fasting insulin and circulating resistin detected among the older (38-55 years) healthy individuals indicated increased circulating resistin that could be a biomarker for the development of type II diabetes.

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