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Research Article

Resistin as Marker of Metabolic and Cardiovascular Abnormalities in OSA Patients

Radostina Vlaeva Cherneva[1]*, Ognian Borisov Georgiev[1], Daniela Stoichkova Petrova[1], Emil Ivanov Manov[2] and Julia Ivanova Petrova[3]

[1]*Department of Internal Medicine, Division of Pulmonary Medicine, Medical University, Sofia, Bulgaria*

[2]*Department of Internal Medicine, Division ofCardiology, Medical University, Sofia, Bulgaria*

[3]*Department of Neurology, Medical University, Sofia, Bulgaria*

***Corresponding author**

Radostina Vlaeva Cherneva, Department of Internal Medicine, Division of Pulmonary Medicine, Medical University, Sofia, Georgi Sofiiski 1str, Sofia, 1431, Pierce O'Macchoni 7str, ap.3, Bulgaria, Tel: 3598885129402; Email: cherneva_radost@yahoo.com

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- Resistin marker
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Abstract

Background: Resistin is a novel adipokine that has been reported as an independent predictor for hypertension and a marker for insulinresistance in the general population. Its rolein patients with obstructive sleep apnea, has not been investigated yet.

Aim: To explore the role of resistinas a marker of insulin resistanceand nighttime blood pressure abnormalities in obstructive sleep apnea patients.

Materials and methods: A total of 77hypertensive patients with newly diagnosed obstructive sleep apnea have been investigated.Patients were divided into three groups in regards to their glucose tolerance and the association between resistin and markers of insulin resistancewas analysed. In non-diabetic OSA patients ABPM was additionally performed. The relation between resistin and nocturnal hypertension was analysed.

Results: Resistin plasma levels were higher in patients with diabetes (6,12 ±5,93ng/ml), compared to those withIGT (3,85±2,81ng/ml, p-0,021) and NGM (3.97±2.98,p***-0,038). Resistin did not differ between patients with IGT andNGM (p-0,843). In OSA patients with BMI>40 resistin plasma levels did not correlate to the clinical parameters, associated with adiposity.They were higher in subjects with nocturnal hypertension in comparison to those with normal blood pressure - (7.81±4.43 vs. 4.90±2.92 ng/mL).

Conclusions: Resistsin plasma levels in OSA patients with BMI>40 may be used in amultipanel of markers to discern patients with diabetes from those with IGT. Hyperresistinemia could contribute to thepathogenesis of nocturnal hypertension in non-diabetic obstructive sleep apnea patients.

BACKGROUND

Resistinis a polypeptide,that was originally describedas providing a link between obesity and insulin resistance [1]. In contrast to rodents, in humans the putative involvementof resistin in obesity and insulin resistance, is largely debated [2,3]. Human resistin is expressed not only by adipose tissue peripheral monocytes/macrophages, but also by peripheral one [4,5]. Recent studies have shown the causative associationbetween resistin and systemic inflammation [6], especiallyin endothelium [7]. It is already known that resistin increasesproportionally to the inflammatory mediatorlevels and is assumed as a predictor for the severity of coronary atherosclerosis [8]. Resistin up regulates endothelin-1, vascular cell adhesion molecule and intracellular adhesion molecule expressionon human endothelial cells. This helps the 'rolling'' and attachment of leukocytes, causing vascular injury [9,10]. Several cross sectional studies have reported that resistin is an independent predictor of both systolic (SBP) and diastolic BP (DBP) in patientswith diabetes, even after adjustment for body mass index (BMI) [11]. Moreover resistin plasma levels are higher in "healthy" individuals with prehypertension compared to healthyindividuals with normotension [12]. Similar are the findings when subjects with masked hypertension and normotensives have been investigated [13].

In OSA hypertensives the role of resistin has not been

studied, neither from the view point of an adipokine responsible for insulin resistance and adiposity, nor from the view point of an inflammatory marker. Insulin resistance and adipose tissue dysfunction are major triggers for arterial hypertension in OSA. In the general populationresistin is an adipokine that has been associated to each of them. Thus its investigation may be of importance.

We designed our study in order to explore: 1) whether resistin could predict nocturnal hypertension in OSA patients; 2) whether its plasma levels are more closely associated with markers of obesity (BMI, waist circumference) and/or insulin resistance (IRI, HOMA-I, HbA1C)

PATIENTS AND METHODS

Our study included 77 patients treated for hypertension that had newly diagnosed obstructive sleep apnea. The study was conducted between January /December 2011 at the Clinic of Internal Medicine, Division of Pulmonology, University Hospital "Alexandrovska". It was approved by the local Ethics Committee. Each participant was adequately informed about the aim of the present studybefore he/she accepted to be enrolled. All participants signed an informed consent.

Subjects with heart failure, coronary arterydisease, previous cerebrovascular insult, atrial fibrillation,congenital heart disease, valvular heartdisease, neoplastic disease,cirrhosis of the liver, kidney failure, respiratory failure, renovascularand renoparenchymal diseaseor endocrine disorders (Cushing's, Conn'ssyndrome, and pheochromocytoma) were excludedfrom the study. Patients who reported that their sleep was severely disturbed when wearing the ambulatory blood pressure monitoring (ABPM) were also excluded.

Exclusion criteria included also: 1) age > 80 years; 2) current prescription of anti-inflammatory drugs, statins, steroids; 3) the presence of any of the following medicalconditions: chronic kidney diseases, chronic respiratoryfailure, primary heart diseases, endocrine disorders orneoplasm.

The anthropometric measures (height, weight)and laboratory analyses (level of fasting glucose,total cholesterol, low and high-density lipoprotein cholesterol, triglycerides) were taken from all the subjects included in the study. Impaired glucose tolerance was established by an oral glucose tolerance test according to the established criteria [14]. Dyslipidemia was defined by a total cholesterol level >240 mg/dl or taking lipid-lowering agents. Body mass index (BMI) was calculated as weight (kg)/height (m)2.

LABORATORY ASSAYS

Clinical blood tests

Routine blood examinations included: peripheral blood cell counts; hormones - TSH, FT3, FT4, morning and night cortisol; basic biochemistry - fasting plasma glucose, fasting serum insulin, creatinine, liver enzymes, fasting serum triglyceride, low density, very low density and high-density-lipoprotein cholesterol. Insulin resistance was calculated using the HOMA index: plasma glucose (mmol/l) x serum insulin(mU/l)/22,5 [15].

An oral glucose tolerant test was performed to definethe patients with impairments in glucose metabolism.The test was performed as described by WHO [15] –subjects were fasting for at least 10 hours. After thesampling of fasting glucose they were loaded with 75g glucose. Blood glucose and IRI were measured within2 hours. Impaired fasting glucose was defined as fastingglucose – 6,1-7mmol/l; impaired glucose tolerance – asblood glucose in the range 7,8-11,1mmol/l two hoursafter the glucose burden; diabetes – fasting blood glucose >7mmol/l at least twice or random blood glucose>11,1mmol/l. All laboratory tests were performed inthe Central Clinical Laboratory, University Hospital

Resistin plasma level measurements

Blood samples were centrifuged immediately after collection and isolated plasma was stored in vials at –80 ° C until assayed. Resistin was determined by an ELISA kit following the producer's protocol (RayBio_ Human Resistin, Cat#:ELH-Resistin-001) The intra- and interassay coefficients of variation in this assay kit ranged from 10 to 12%. Plasma resistin levels were measured in ng/ml.

Respiratory measurements

Full polysomnography was performed in all the patients (Compumedics, E-series, Australia). Continuous recordings were taken with electrode positions C3/A2-C4/A1-Cz/01 of the international 10–20 Electrode Placement System. Eye movements, chin electromyogram and ECG modified V2 lead. Sleep was scored manually according to standard criteria [16]. Airflow was measured using nasal pressure associated with the sum of buccal and nasal thermistor signals. Respiratory efforts were monitored with abdominal and thoracic bands. Arterial oxygen saturation (SaO2) was measured using a pulse oximeter (Medair, Hudiskvall, Sweden). An apnoea was defined as a complete cessation of airflow for > 10s, and a hypopnoea as a > 50% reduction in the nasal pressure signal or a 30–50% decrease, associated with either oxygen desaturation of > 3% or an arousal both lasting for > 10 s [17]. Apnoeas were classified as obstructive, central or mixed according to the presence or absence of respiratory efforts. The classification of hypopnoeas as obstructive or central was based upon the shape of the inspiratory part of the nasal pressure curve. In our study, diagnosis of OSA was retained if AHI >15 h-1.

24-h Ambulatory BP Monitoring (ABPM)

Non-invasive 24-h ABPM was performed on the non-dominantarm using BOSO TM2420/TM 2480 Profilemanager (Bosh&Sohns,Germany). The device wasprogrammed to obtain BP readings at 20-minintervals during the day (07.00–22.00 hours) andat 30-min intervals during the night (22.00–07.00 hours). The ABPM was always performed during aworking day. The recording wasthen analysed to obtain 24-h daytime and nighttimeaverage SBP, DBP, mean arterial pressure and heartrates. When the readings exceeded at least 80% ofthe total readings programmed for the testing period,the recording was considered as valid and satisfactory [18]. The nocturnal dipping was defined as a reduction in average SBP and DBP at night, which was >10% and <20%, respectively, compared with average daytime values; non-dippers had a nocturnal reduction

<10%. Nocturnal hypertension was defined as SBP>120mmHg and/or DBP>70mmHg [18].

Statistical analysis

Statistical analysis was performed using SPSS (version14.0; SPSS) A p<0,05 was considered of statistical significance.Data were presented as mean ± standard deviation (SD) or the number of subjects and their percentages. Groups were compared using the Independent-Samples t-test or the Mann-Whitney U test. Kolmogorov-Smirnov was used to find if normaldistribution existed. Comparison between the threegroups wasmade using one way analysis of variance (ANOVA) Categorical variables were compared using the χ2 or the Fisher exact test. The relationships between dependent variables were evaluated with bivariate correlation analysis. (Pearson or Spearman's rank, whichever is appropriate).

RESULTS

Resistin as a marker of nocturnal hypertension

A total of 86 subjects were recruited in the study and 77 of them met the inclusion and exclusion criteria. The role of resistin as a marker of nocturnal hypertension was investigated only in non-diabetic OSA patients – 54 patients. According to the ABPM profiles they were divided into 25 with normal nocturnal BP values and 29 with nocturnal hypertension. The characteristics of the subjectsare presented in Table 1. There were no significantdifferences between the groups regarding age, gender or smoking status. BMI, waist and neck circumference however differed substantially Table 1.The hypnogram was nearly similar in the two groups. Patients were predominantly with severe apnea (approximately 60% in both groups). Important discrepancies, however could be detected when analysis of parameters, characterising sleep disturbances, is performed. The arousal index and AHI were higher in patients with nocturnal hypertension, but not of statistical value. Significant discrepancies are observed regarding the duration of sleep at SaO2<90% – Table 2.

Glucometabolic parameters varied substantially. Insulin resistance presented by HOMA-Iand immmunoreactive insulin were significantly higher in patients with nocturnal hypertension – Table 3. The same is established when HbA1c levels are analysed.

Table 4 presents the correlation analysis between resistin and the analysed parameters.. No associations could be observed between resistin plasma levels and the investigated parameters.

Resistin as a marker of insulin resistance

The role of resistin as a marker of insulin resistance was studied in all the patients. Accordingto their glucose metabolism they were divided into three groups– patients with alreadyknown diabetes – 23; patients with impaired glucose tolerance– 27; patients with normal glucose metabolism –27. Anthropometric, glucometabolic, sleep study andbiological characteristics of the three groups are presented in Table 5. No large discrepancies existed in regards to anthropometric and sleep study characteristicsThe lipid profilesdid not differ also. The analysis of the indicators related to the glucosemetabolism

Table 1: General characteristic of non-diabetic OSA patients with nocturnal hypertension.

	Nocturnal normotensive (25)	Nocturnal hypertensive (29)
General		
Age, y	48.21±7.93	49.81±9.98 p-0.171
M:F	24:1	27:2
Anthropometrics		
BMI, kg/m^2	32.69±8.77	37.81±5.91 p-0.008
Waist circumference, cm	113.5±17.01	128±19.12 p-0.01
Neck circumference, cm	44.41±2.38	47.30±3.11 p-0.028
Haemodynamic characteristics		
Daytime BP profiles		
Average Systolic BP, mmHg	140.53±12.11	127.81±13.19
Average Diastolic BP,mmHg	77.9±7.62	78.61±8.99
Nighttime BP profiles		
Average Systolic BP, mmHg	115.63±12.14	127.73±15.79
Average Diastolic BP,mmHg	67.26±7.41	76.43±10.09
Office BP profiles		
Average Systolic BP, mmHg	128.53±8.14	131.32±6.87
Average Diastolic BP,mmHg	83.12±7.21	85.31±7.14
Cardivascular risk factors		
BMI>30kg/m^2, %	84	87
Current smoking,%	80	84
Dyslipidaemia, %	21	27
Biomarkers		
Resistin, ng/ml	4.90±2.92	7.81±8.43 p-0.42

Table 2: Sleep study characteristics in non-diabetic OSA patients with nocturnal hypertension.

Sleep study characteristics	Nocturnal normotensive (25)	Nocturnal hypertensive (29)
Mild-moderate OSA	8/25 (32%)	9/29(31%)
Severe OSA	17/25(68%)	20/29(69%)
AHI, e/h	34.65±24.04	57.76±26.24 p-0.028
Time spent at $SatO_2$<90%,%	25.43±8.72	61.74±26.28 p-0.000
Arousal Index, e/h	35.76±20.58	45.75±25.22 p-0.341

showed a statistically significant differencein the plasma levels of the immunoreactive insulin. In comparison to those withdiabetes patients with IGT had higher levels (31,06±28,05 vs.18,92±16,57; p –0.006).HOMA-index did not differ much between the groups.The glycated haemoglobin however was statistically higherin patients with IGT in comparison to those with normalone (6,41±1,06*vs.*5.42±0.38, p***-0.027). The same trendcould be found when diabetics and patients withnormal

Table 3: Glucometabolic parameters of non-diabetic OSA patients with nocturnal hypertension.

	Nocturnal normotensive (25)	Nocturnal hypertensive (29)
Glucometabolic parameters		
IRI, mU/l	12.77±4.00	19.74±10.15 p-0.012
HbA1C	5.58±0.35	6.08±0.82 p-0.067
HOMA-I	2.72±0.93	4.97±2.72 p-0.002

Table 4: Correlation analyses of resistin and markers of adiposity, insulin resistance and respiratory disturbances in non-diabetic OSA patients.

	Correlation Coefficient	p-value
BMI, kg/m^2	0.41	0.83
Waist circumference, cm	0.76	0.17
Neck circumference, cm	0.27	0.24
IRI, mU/l	0.13	0.20
Glucose, mmol/l	0.23	0.45
HbA1C	0.14	0.33
HOMA-I	0.21	0.15
AHI, e/h	0.21	0.98
Average Desat Index, %	0.12	0.67
Sleep Duration, min	0.01	0.98
Time spent at $SatO_2$<90%,%	0.11	0.45
Arousal Index, e/h	0.02	0.83

Table 5: General characteristic of the studied OSA patients.

	Diabetic (23)	Impaired Glucose Metabolism (27)	Normal Glucose metabolism (27)
Age, y	56.95±10.38	49.76±9.04	48.31±8.12 p-0.751
M:F	17/6	23/4	25/2
Anthropometrics			
BMI, kg/m^2	42.86±7.29 40.	36±9.37	39.91±7.9 p-0.945
Waist circumference, cm	133.2±20.84	130.12±15.96	134.48±13.84 p-0.349
Sleep study characteristics			
Mild-moderate OSA	2/23(9%)	11/27(40%)	4/27 (15%)
Severe OSA	21/23 (91%)	16/27 (60%)	23/27 (85%)
AHI, e/h	58.79±34.25	53.00±35.33	60.73±28.41 p-0.731
Time spent at $SatO_2$<90%,%	70.85±25.99	56.03±33.44	50.14±29.3 p-0.324
Glucometabolic parameters			
IRI, mU/l	18.92±16.57 p*-0.006	31.06±28.05 p**-0.349	21.94±16.14 p***-0.192
HbA1C	6.69±1.11 p*-0.253	6.41±1.06 p**-0.027	5.42±0.38 p***-0.000
HOMA-I	4.86±4.46	7.48±7.66	5.31±3.12 p***-0.184
Biomarkers			
Resistin, ng/ml	6.12±5.93 p*-0.021	3.85±2.81 p**-0.843	3.97±2.98 p***-0.038

p- Kruskall –Wallis comparison between three groups; p*- Mann -Whithney comparison diabetics vs IGT; p**- Mann -Whithney comparison IGT vs NGM; p***- Mann -Whithney comparison diabetics vs NGM.

Table 6: Correlation analyses of resistin and markers of adiposity, insulin resistance and respiratory disturbances.

	Correlation Coefficient	p-value
Age	0.64	0.62
BMI, kg/m^2	0.87	0.902
Waist circumference, cm	0.83	0.376
IRI, mU/l	0.54	0.583
Glucose, mmol/l	0.18	0.762
HbA1C	0.74	0.849
HOMA-I	0.93	0.694
AHI, e/h	0.78	0.619
Sleep Duration, min	0.41	0.988
Time spent at $SatO_2$<90%,%	0.65	0.284

glucose metabolism were compared (6,69±1,11 vs5.42±0.38, p***-0.000). Resistin plasma levels were significantlyhigher in patients with diabetes - 6.12±5.93 incomparison to those with normal glucose metabolism -3.97±2.98, p***-0.042. Similar are the results when diabeticsand patients with impaired glucose metabolism are compared– p –0.021. The significant difference stays evenafter adjustment for age, BMI and HOMA-I.

The analysis of the relationship between resistin plasmalevels and anthropometric, clinical, biologicaland sleep apnea parametersisshown in Table 6. Resistin plasma levels did not correlateto any of the clinical parameters.

DISCUSSION

Adipose tissue is now assumed as an endocrine organ whose dysfunction is responsible for much of the cardiovascular and metabolic disorders in the general population [6]. Its major role in OSA is attributed to the fact that intermittent hypoxia (oxidative stress), accompanying the apneas/hypopneas, aggravates local hypoxia that otherwise exists in the adipose tissue of overweight patients [19]. This leads to an imbalanced secretion of adipokines whose plasma levels are associated with BP control and metabolic derangements [2,7,13].

Resistin is a 12-kDa polypeptide that was initially linkedto insulin resistance in animal models. Early reportssuggested that resistin is associated with obesity and insulinresistance in rodents. In humans, however, data is rather controversial. A number of studies have examined resistin plasma levels or resistin adipose tissue expression, and have found variable associations with insulin resistance [20,21].The Framingham offspringcohort study found a significant relationship between insulinresistance and resistin. This relationship however wasweaker than the relationship with adiponectin,and was lost after adjustment for BMI [22].

According to our results there is not a significantdifference between resistin plasma levels in patients with impaired and normal glucose tolerance.The two groups were comparable regarding the age,BMI, waist circumference and the severity of OSA. Theduration of sleep, the average desaturation index and thetime spent under SpO2 <90% did not differ muchbetween groups.The analysis of resistin plasma levels showed correlation neither to the anthropometric(age, BMI, waist circumference,

smoking status), nor tothe sleep study or glucometabolic characteristics. Assuming this data it seems that resistinalone is not a trigger of insulin resistance in obese OSApatients, but more likely plays a secondary role in thecomplex adipokine signaling, accompanying adipose tissuedysfunction.Neither in patients with normal,nor in those with IGT and diabetes,any association between IRI, HOMA-I and resistin was found. This is in controversy towhat is reported in the general populationof obese patients (BMI-33) without diabetes [23]. It is assumable that extremeOSA per se attenuates resistin secretion.

In human adipose tissue, resistin is secreted mainly by infiltrating macrophages [4,8] and is responsible of systemic inflammation [6], especiallyin the vascular endothelium [7]. These observations are confirmed in OSA patientsby Yamamoto and Lee. Yamamatoet al., [24] shows that resistin plasma levels increase withthe severity of OSA. This correlates best with AHI andis associated to increased inflammation and higher concentrations of IL-6. Similar are the findings ofLee et al. [2]. They also demonstrate that resistinplasma levels increase with the severity of OSA and that thistrend correlates best to AHI. Both studies are, however, performed in Asian population whichdeters the application of their findings in Caucasians. Inpediatric OSA where much of the confoundingfactors are abolished the increase in plasma resistin levelswith the severity of AHI is very persuasive [25]. In our study we demonstrate a trend for an increase ofresistin with the severity of OSA, not reachingstatistical significance. A reason for this can be that ourpatients were extremely obese – the average BMI >40.

Data is even more complicated when analyzing the association between resistin and the pathogenesis of hypertension. At experimental levels resistin upregulates IL-6 andTNF-α, probably *via* theNF-κB pathway [7]; stimulates the proliferation of human vascularsmoothmusclecells [26], induces inflammation within thevascular wall and may be the reason for vascular injury remodeling and hypertension.

Human studies of the association between resistin and hypertensionare rather limited and controversial.Resistin is reported as an independent marker for the occurrence of hypertension in non-diabetic women with a 14-year - follow-up [27]. Similar is the data in non-diabetic patients with prehypertension [12]. These findings suggest that resistin might beassociated with hypertension in the general population without diabetesand that increased resistin levels may exist before the occurrenceof clinical hypertension. According to our studyin OSA hypertensives resistin plasma levels are higher in patients with nocturnal hypertension. They do not correlate to any of the markers, indicative of obesity – BMI or waist circumference. This corroborates the data of a recent report from Stepien et al, [28]. Who demonstrated no association between resistin plasma levels in patients with moderate (BMI-32) or severe obesity (BMI-38). In OSA patients Yamamoto et al, [24] also did not find an association between BMI and resistin, even in a population within the lower range of adiposity (BMI-27). The lack of correspondence between resistin plasma levels and visceral obesity in non-diabetic OSA patients makes us assume that adipose tissue is not the single source of resistin and its plasma levels cannot serve as an adjunct surrogate marker for obesity. Based on our findings patients with nocturnal hypertension, though normoglycaemic have insulin resistance (HOMA-I >2,5). All the biochemical markers, presenting an insulin resistant state are significantly higher in this patient group. None of them, however correlates to resistin plasma levels. This makes us speculate that insulin resistance is not a result of hyperresistiemia. It seems that both phenomena are independent of each other and may contribute to hypertension by different pathophysiological mechanisms and pathways.

In conclusion in non-diabetic OSA patients with average BMI>30-35and nocturnal hypertension resistin plasma levels are higher. They do not correlate to the clinical markers of obesity and insulin resistance andmay be used in amultipanel of clinical markers to discern patients with diabetes from those with IGT. In OSA patientswith BMI >40 resistin could discern patients with diabetes from those with NGMand is independent of insulin resistance and severity of OSA.

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