INNSPUB

International Journal of Biosciences | IJB |
ISSN: 2220-6655 (Print), 2222-5234 (Online)
http://www.innspub.net
Vol. 15, No. 4, p. 312-317, 2019

RESEARCH PAPER OPEN ACCESS

Serum resistin levels in patients with type 2 diabetes mellitus and its relationship with glycosylated hemoglobin

Maheen Saad[1], Fatima Ehsan[2], Kirn-e-Muneera[1], Muhammad Adnan Saeed[3*], Sobia Ali[4], Hafsa Aziz[3]

[1]*Departmeny of Biochemistry, Fazaia Medical College, Islamabad, Pakistan*

[2]*Departmeny of Physiology, IIMC, Riphah International University, Islamabad, Pakistan*

[3]*NORI, Islamabad, Pakistan*

[4]*Departmeny of Biochemistry, Khyber Medical College, Peshawar, Pakistan*

Key words: Resistin levels, Fasting blood glucose and HbA1c, Type 2 diabetes mellitus.

http://dx.doi.org/10.12692/ijb/15.4.312-317 Article published on October 27, 2019

Abstract

To compare serum resistin levels in type 2 diabetic patients (T2DM) and normal controls and to assess the relationship between serum resistin level and glycosylated hemoglobin (HbA1c) in type 2 diabetic patients. The study comprised of two groups i.e. Group A and Group B. Group A consisted of 100 diabetic patients and group B consisted of 100 healthy individuals (control). Blood samples were taken and analyzed for serum resistin, fasting blood glucose (FBG) and glycosylated hemoglobin. SPSS version 19 was used to analyze the data obtained. The values were stated as mean±SD. Assessment of relationship between resistin and HbA1c was done through Pearson's correlation co-efficient. Type 2 diabetic patients showed significantly higher level of resistin as compared to the normal control (30.4±8.50 vs. 18.9±2.31, p = <0.05).The diabetic group manifested significantly higher values of HbA1c (8.5±1.73 vs. 4.0±0.76) and FBG (158.5±28.30 vs. 84.9±20.01). Serum resistin levels showed a strong positive association (p < 0.001) with glycosylated hemoglobin (r .816) in the diabetic group through Pearson's correlation co-efficient r. Type 2 DM patients have significantly higher resistin levels than healthy individuals which is positively correlated with fasting blood sugar and HbA1csupporting the evidence that resistin plays an important role in the pathogenesis of insulin resistance which could indirectly contribute to the development of type 2 DM.

* **Corresponding Author:** Muhammad Adnan Saeed ✉ dasnmc@gmail.com

Introduction

Diabetes has emerged as a global epidemic. According to world health organization report, Type 2 diabetes mellitus is responsible for about 85 to 95% of total diabetic population and the prevalence of diabetes in Pakistani population is 9.8% (WHO report 2016). International Diabetes Federation (Cho *et al*, 2018) has ranked Pakistan at 7th position with respect to the prevalence of diabetes mellitus. It is estimated that 451 million people are living with diabetes till 2017 globally and this figure may rise to 693 million by year 2045.

Glycated hemoglobin (HbA1c) is a widely accepted marker of long-term glucose control, reflecting average glucose over the previous 2–3 months, and one of the diagnostic criteria for diabetes (Bonora *et al.*, 2011). In 2010, the American Diabetes Association (ADA) recommended that HbAlc of 6.5 % or higher be used for the diagnosis of diabetes mellitus. However, Pajunen *et al.* (2011), in their Finnish Diabetes prevention study 2011, said that HbA1c has a relatively poor affinity with diabetes diagnosed by fasting plasma glucose (FPG) and/or 2-hour plasma glucose (2hPG) levels. This may indicate that HbA1c levels are in part ascertained by factors not shared by glucose levels.

Human resistin is a 12.5 kDa polypeptide hormone, secreted by adipocyte which lead to resistant in vivo and in vitro and considered to have relationship with diabetes and obesity (Steppan and Lazar, 2004). The normal level of resistin in human being is 7-22 ng/dl (Jamaluddin *et al.* 2012). This discovery revolutionized the investigations all around the globe. Way *et al* showed increased levels of resistin are being linked with insulin resistance in animal models.However, structure and biology of resistin gene differ substantially between species, and its association with insulin sensitivity in humans, remain controversial (Barnes and Miner, 2011).Evidence fails to show connection between resistin's role in rodents and humans due to significant differences among the two species with respect to resistin's gene and protein structure and tissue-specific distribution as mentioned (Huang and Yang, 2016). However it is commonly believed that resisten play role in insulin signaling pathway by inhibiting insulin receptor.

Plasma resistin levels have been observed to be higher in diabetic individuals than in apparently healthy individuals (Zaidi and Shirwany, 2015). However, the primary source of resistin in rodents is adipocytes, whereas the major source in humans has been shown to be macrophages suggesting that it may play a critical role in the pathogenesis of diabetes and its complications atherosclerosis and cardiovascular disease (CVD) along with other inflammatory conditions (Jamaluddin *et al.* 2012). The debate is still ongoing regarding the exact role it plays in insulin sensitivity and the development of type 2 diabetes mellitus (DM2).

It has been reported by He *et al.*(2015) that plasma resistin levels have a positive correlation with fasting blood glucose and glycated hemoglobin in rodents, as well as humans (Gokhale *et al.* 2014). However, some studies failed to detect any significant change in plasma resistin levels with DM or glycated hemoglobin (Uslu *et al.* 2012). In addition, according to Burnett *et al.*these differences in resistin expression among different populations could be due to genetic or environmental factors.

Taken altogether, these findings indicate that the role of resistin in the pathogenesis of diabetes is still to be further elucidated. The work done on resistin in our country is negligible and needs to be further studied in our population. Thus, the present study was planned to see the relationship between serum resistin, fasting blood glucose and glycated hemoglobin in our community.

Methodology

Study design

This was an analytical and cross sectional study. It was conducted at Ayub Medical College from May 2017 to April 2018. The protocol was approved by the ethical review committee of the hospital and informed written consent was taken from all the participants

with proper explanation of objectives of the study. Patients who fulfilled the study criteria were enrolled in two groups.

Patient selection

The study included two groups i.e. group A and group B. Group A: Type-II diabetic patients (patients were selected according to reported criteria of American diabetes association) attending Ayub Medical Complex (AMC) and District Headquarter (DHQ) Hospital, Abbottabad were selected randomly from endocrinology and medical OPDs and wards.

Group B: Normal subjects were randomly selected from workers of hospital or patients visiting other departments of hospital who has no history/diagnosis of diabetes. Each group have both males and females, having age 40 years and above.

Protocol of study

After proper selection of the patients (Group A) and Controls (Group B) as per inclusion criteria, Blood sugar Fasting, HbA1c and Serum resistin levels tests were carried out in each patient.

Blood collection

Collection of blood samples was carried out under aseptic conditions in morning after overnight fasting. A total of 5ml of venous blood was drawn from the patients and control, 2ml of blood was transferred to EDTA tube for the analysis of HbA1C, while serum was obtained from the rest of 3ml of blood by centrifugation. Measurement of blood glucose was carried out on fresh samples while rest of the sample was stored at -20°C.Samples was later used for estimation of serum resistin levels using commercially available ELIZA kits from Biovendor Germany. ELISA (Enzyme Linked Immunosorbant Assay). Al the samples were tested in duplicate and mean serum resisten level was measured by using commercially available kit according to the instruction of manufacture. HbAIc was measured on Cobas 6000. Urea, creatinine, cholesterol, triglyceride were also tested.

Statistical analysis

Data obtained was analyzed using SPSS version 19. The values were stated as mean±SD (Standard Deviation). Comparison of different parameters was done through student's-t test. p value less than 0.05 was considered as significant. The association of resistin with fasting blood glucose and HbA1c was established with Pearson's correlation co-efficient r.

Results

The study participants underwent a clinical assessment after obtaining an informed written consent. A detailed medical history with the help of questionnaire and a clinical examination including body mass index (BMI) was calculated as weight divided by square of height (kg/m2), waist circumference and blood pressure were recorded.

Table 1. Biochemical parameters of group A (Diabetic) and group B (Control group).

Parameters	Group A	Group B	P.Value
FBS (mg/dL)	158.5±28.30	84.9±20.01	<0.05
HBA1C%	8.5±1.73	4.0±0.76	<0.05
Resistin (ng/mL)	30.4±8.50	18.9±2.31	<0.05

A total of 200 diabetic and non-diabetic subjects were recruited from May 2017 to April 2018.Diabetic subject group included male 47% and female 53%. Non diabetic subject group include male 44% and female 56%. The mean age of the patients in diabetic subject group61.7±11.26 and in non-diabetic subjects group60.1±12.06. Significant difference in fasting blood glucose level was observed between diabetic and nondiabetic group. FBG concentration was significantly higher in diabetic subject 158.5 ±28.30 than non-diabetic 84.9 ±20.01. Similarly resistin level in patient group with diabetic is 30.4±8.50 higher than subjects in normal group18.9±2.31, $p = 0.04$. Data shows significant difference in resistin

level between diabetic and normal group (Table 1).

Patients in diabetic group were divided in to four groups according to age (<40, 41-50, >50-60,>70 years) to find the effect of age on serum resistin level. Tendency of serum resistin level with age in diabetic group compared with healthy control group No significant difference was observed. However in diabetic group as the age of diabetic subject increases serum resistin also increases (Table 2).

Table 2. Resistin level according to different age groups of the study population.

Age Group (Years)	Group A	Group B	p.value
40-50	29.2±10.15	18.1±2.55	<0.05
51-60	31.3±7.16	19.4±1.81	<0.05
61-70	29.9±8.58	18.7±2.29	<0.05
> 70	30.7±9.29	19.5±2.45	<0.05

Table 3 shows the association of resistin with Age, Fasting blood sugar (FBS), HBA1Cin Group A and group B. The association was established with Pearson's correlation co-efficient. Resistin levels show a strong positive association ($p < 0.001$) with glycosylated hemoglobin levels (r .816) in the diabetic group. Serum resistin in group A showed positive correlation with all three parameter but significant correlation observed in HBA1C. In group B serum resistin level showed negative correlation FBS (fasting blood sugar) and HBA1C.

Table 3. Correlation of resistin with different parameters in group A and group B.

Parameters	Group A (Patients)		Group B (Controls)	
	R	P	R	P
Age	.068	.499	.183	.068
FBS	.156	.122	-.056	.582
HBA1C	.816	<0.01**	-.035	.727

** Correlation is significant at the 0.01 level.

Discussion

In the present study, the relationship between diabetes mellitus and resistin has been discussed widely in recent past years. Circulating levels of serum resistin were measured and found significantly higher in diabetics as compared to controls. The results of Azab *et al.* (2016) also agree with our results as they revealed that serum resistin levels were significantly higher in diabetic patients compared to control subjects. A recent study by Shiv Narayan lahariya *et al.*(2015), has also confirmed that resistin levels with T2DM are significantly higher than those of healthy subjects. In that study a total of 150 periodontitis patients with diabetes mellitus and 150 periodontitis patients without diabetes mellitus were selected for the study. Serum resistin also showed a significant positive association with HbA1c in accordance with our study.

The results of our study apparently suggest resistin levels to be directly related to susceptibility of TDM 2. A similar study was conducted in Jordanian population in which resistin levels were raised in type 2 diabetics with high FBG and glycated hemoglobin. However the resistin levels significantly increased with increased age in their study which showed no significant association in our study. Furthermore, plasma resistin concentrations were higher in type 2 diabetic obese patients than in non-diabetic obese subjects (P<0.01), whereas in our case plasma resistin levels were raised in diabetic group with and without obesity (Gharibeh *et al.* 2010). However it is certain

that resistin does play a role in the pathogenesis of insulin resistance which may contribute to the development of type 2 diabetes.

A study conducted in Japan on 397 T2DM subjects also revealed a positive association between resistin and glycated hemoglobin. According to this studyduration of T2DM, and HbA1c were significantly associated with serum resistin levels. One year duration of T2DM and 1% of HbA1c increase serum resistin levels by 0.19 and 0.54 ng/ml, respectively (Horikawa *et al. 2000*). Hence serum resistin levels increased with longer duration of diabetes type 2 as well as higher HbA1c.

The role of resistin in insulin resistance and TDM2 is further clarified by recent preliminary test done on rhesus monkey in China. It was conducted for correlation analysis of clinical parameters and serum resistin levels in rhesus monkey models of T2DM (Gokhale *et al.*2014). These results suggested that resistin was significantly increased in T2DM monkeys (P <0.01), and that resistin had a positive correlation with fasting plasma glucose (FPG), fasting insulin (FPI) and glycated hemoglobin (HbA1c) again supporting our findings. However a negative correlation with islet β-cell function (HOMA-β) was also predicted.

Our finding have certain limitation, as larger study samples provide more reliable result than those obtained from our relatively small sample. Conclusively, it could be stated that the work on resistin is still in the beginning and further extensive studies at molecular level are needed to elucidate the exact role of this hormone in insulin resistance or diabetes mellitus and their metabolic consequences. Future studies with larger study populations and diversity are required to generalize the effects of biochemical markers for T2DM.

Ethical approval

The protocol was approved by the ethical review committee of the hospital and informed written consent was taken from all the participants with proper explanation of objectives of the study.

Conflict of interest

The authors declare no conflict of interest.

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