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Original Article / Оригинални рад

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Serum Resistin and Adiponectin Relationships with Glucometabolic Control in Patients with Type 2 Diabetes Mellitus

Однос серумског резистина и адипонектина и глукометаболичка контрола код болесника са дијабетесом мелитусом типа 2

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SUMMARY

Introduction/Objective Adiponectin and resistin are important adipokines that play important role in the regulation of blood sugar, beta-oxidation in muscle and insulin resistance.
The aim of this study was to assess and compare the relationships of resistin and adiponectin concentrations with glucometabolic control in patients with Type 2 diabetes mellitus (T2DM).
Methods: A total of 191 subjects were studied. Final selection included 107 patients with type 2 DM (67 males, 40 females) and 84 healthy control subjects (45 males, 39 females). Fasting venous blood samples were analyzed for glucose (FBG), glycosylated hemoglobin (HbA1c), insulin, lipids (total cholesterol–TC, triglycerides–TG), adiponectin and resistin levels. Body composition was evaluated in all subjects: Body Mass Index (BMI) and Waist hip ratio (WHR).
Results: BMI, WHR, FBG, HbA1c, Insulin resistance (IR), TC and TG were significantly higher in individuals having diabetes compared to healthy volunteers. Serum resistin levels were significantly higher (p=0.0259) and serum adiponectin levels were significantly lower (p=0.0001) in type 2 diabetes patients, than in control subjects. Adiponectin levels were significantly lower (p=0.0411) in diabetes patients with poor glycemic control, compared to those with good glycemic control, while the difference was nonsignificant for resistin (p=0.8899). Serum adiponectin levels were discordant with HbA1c (r=-0.274, p=0.004). Linear by linear association showed significant trend of better glycemic control at increasing quartiles of adiponectin levels (p=0.042), while the trend was not significant for resistin levels (p=0.904). Multiple regression analysis revealed FBG, insulin, HOMAIR and HbA1c as significant predictors of adiponectin.
Conclusions: Type 2 DM patients have significantly higher resistin and lower adiponectin levels, when compared to healthy controls. Adiponectin levels were significantly lower in patients with poor glycemic control.
Key Words: Adiponectin, Resistin, dyslipidemia, diabetes mellitus type 2

САЖЕТАК

Увод/Циљ Адипонектин и резистин су адипокини који играју важну улогу у регулисању шећера у крви, бета-оксидацији у мишићима и инсулинској резистенције.
Циљ ове студије је био да процени и упореди односе концентрација резистина и адипонектина са глукометаболичком контролом код болесника са шећерном болести типа 2 (ШБТ2).
Методе Испитивано је укупно 191 испитаника. Коначна селекција обухватила је 107 болесника са ШБТ2 (67 мушкараца и 40 жена) и 84 здравих, контролних особа (45 мушкараца и 39 жена). Анализирани су узорци венске крви за: глукозу (ВГ), гликозиловани хемоглобин (ХбА1ц), инсулин, липиде (укупни холестерол–УХ, триглицериди–ТГ), адипонектин и резистина. Грађа тела оцењена је код свих и то Индекс телесне масе (ИТМ) и однос струк-кукови (ОСК).
Резултати: ИТМ, ОСК, ВГ, ХбА1ц, инсулинска резистенција (ИР), УХ и ТГ били су значајно већи код особа с дијабетесом у поређењу са здравим добровољцима. Ниво резистена у серумау био је значајно виши (p=0.0259), а ниво серумског адипонектина значајно нижи (p=0.0001) код ШБТВ, него код контролних субјеката. Нивои адипонектина су знатно нижи (p=0.0411) код болесника са лишом контролом гликемије, у поређењу са онима са добром гликемијском контролом, док је разлика нивоа резистина била безначајна (p=0.8899). Нивои адипонектина у серуму нису у корелацији са ХбА1ц (p=-0.274, p=0.004). Линеарна корелација показала је значајан тренд боље контроле гликемије код повећања нивоа адипонектина (p=0,042), док тренд није био значајан за нивое резистина (p=0,904). Мултипле регресиона анализа открила је ФБГ, инсулин, ИР и ХбА1ц као значајне предикторе адипонектина.
Закључак: Болесници са ШБТ2 имају знатно повишен резистен и снижен адипонектин у поређењу са здравим особама. Нивои адипонектина су знатно нижи код болесника са слабом контролом гликемије.
Кључне речи: адипонектин, резистин, дислипидемија, шећерна болест тип 2

INTRODUCTION

It is well known that obesity, increases the risk of developing type 2 diabetes mellitus [1]. Adipose tissue is a complex endocrine organ with potential implications on insulin resistance, obesity and diabetes. Many researches have resulted in identification of a large group of adipocyte specific proteins, such as adiponectin, acylation stimulating protein, resistin, leptin which are involved in the

regulation of glucose & lipid metabolism and insulin resistance in obesity and diabetes [2,3] [1, 2]. Therefore, high visceral fat and insulin resistance, have been reported to be independently associated with prediabetes and T2DM [4]. Adipose tissue dysfunction is characterized by ectopic fat deposition in the abdominal viscera and liver, inflammatory and adipokine dysregulation, and insulin resistance which may be an important mediator of diabetes development than total fat mass per se [5, 6].

Adipocyte specific proteins, such as adiponectin, acylation stimulating protein, resistin and leptin [7], have recently been identified. Resistin and adiponectin are important adipokines that regulate insulin sensitivity. Adiponectin,–synthesized in the adipose tissue, appears to play an important role in inflammatory mechanisms, glycemic and lipid control, which cluster together to markedly increase the atherosclerotic risk in diabetes subjects. Plasma adiponectin concentrations are reported to be decreased in patients with obesity [8], T2DM [9], insulin resistance syndromes [10], dyslipidemia [11] and coronary artery disease (CAD) [12]. Resistin is secreted by adipocytes and leads to insulin resistance in vivo and in vitro and is considered to be an important link between obesity and diabetes [13].

Lower levels of adiponectin in obese subjects are associated with higher levels of resistin and are considered to contribute to insulin resistance and accelerated atherogenesis [14]. Plasma adiponectin levels correlate negatively with adiposity and serum adiponectin levels and WHR are independent predictors of hsCRP levels in normoglycemic subjects [15,16,17] Since, both adiponectin and resistin have important biological activity on glucose and lipid metabolism. However, the comparison of these adipokines on glucometabolic control need further investigations. Therefore, the aim of this study was to assess and compare the relationships of resistin and adiponectin concentrations with glucometabolic control in patients with T2DM.

METHODS

This case control study was carried out in the Department of Physiology and Medicine, College of Medicine & King Khalid University Hospital, King Saud University, Riyadh. The study was approved by institutional review board (IRB) of College of Medicine. A total of 191 subjects were selected for the study. Final analysis included 107 patients with T2DM having 67 males & 40 females. Control group included 84 healthy subjects (45 males & 39 females) matched for age, gender & weight, recruited from the staff members and patients companions. All patients were diagnosed cases of type 2 DM based on American Diabetes Association (ADA) criteria and were in stable metabolic condition with at least one year of duration of T2DM [18]. Patients with acute diabetes states, acute or chronic renal problems, thyroid diseases, acute & chronic infections, stroke, taking oral contraceptives or steroids were excluded. Clinical and Demographic data from all participants was recorded on a predesigned proforma which included weight, height, BMI, Waist hip ratio (WHR) measurements and exercise habits. Patients were divided into good and poor glycemic control group based on a cutoff HbA1c value of 7.5% [18]. After 10–12 hours of overnight fasting, venous blood

samples were analyzed for total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), basal insulin, adiponectin and resistin levels. Human insulin, adiponectin and resistin immunoassays were carried out by quantitative standard sandwich ELISA technique using monoclonal antibody specific for resistin with kits supplied by R&D Systems, (Abingdon, United Kingdom). Insulin resistance was calculated by Homeostasis model assessment of Insulin resistance (HOMA-IR) using the formula HOMA-IR = (FPI (mU/L) x FPG (mmol/L))/22.5 [19].

Bioelectrical impendence analysis was used to measure body composition with InBody3.0, (Biospace, Korea) body analyzer according to manufacturer's instructions. All assessments were made in early morning fasting state, light clothing and after emptying of urinary bladder. The machine calculated the amount of each tissue with the difference in electrical impedance [20].

The data was analyzed by computer software program Statistical Package for Social Sciences (SPSS Version 19, Chicago, IL). Descriptive characteristics of the study patients were calculated as mean ± SD (Standard Deviation). The tests applied for statistical analysis was Student's t test for normally distributed data and Mann-Whitney U test for skewed data. We applied and used linear by linear association p-value for significant difference at different quartiles of adiponectin and resistin levels in diabetes patients. Spearman's correlations and multiple regression analysis were done to see the predictors of adiponectin and resistin levels. A p value of <0.05 was taken as statistically significant.

Table 1: Comparison of descriptive characteristics and biochemical profile between control and patients with T2DM (Mean ± SD).

	Control n=84	DM n=107	*p*
M/F	45/39	67/40	
Age (years)	50.16±12.58	52.20±11.07	0.2735
Height (cm)	166.80±8.52	165.71±13.93	0. 2641
Weight (kg)	77.66±14.78	84.23±20.60	0.0515
WHR	0.94±0.12	1.11±0.09	0.0001
BMI (kg/m2)	28.13±4.80	29.72±5.27	0.0227
FBG (mmol/dl)	5.06±0.99	8.88±3.29	0.0001
HbA1c (%)	5.01±0.56	7.67±1.53	0.0001
Insulin (uIU/ml)	22.69±6.12	24.81±9.19	0.0708
HOMA-IR	5.20±2.46	9.73±5.08	0.0001
TC mmol/L	4.25±0.96	4.48±1.12	0.0515
TG mmol/L	1.41±1.19	2.04±1.44	0.0463
LDL mmol/L	2.68±0.86	2.62±0.91	0.1264
HDL mmol/L	1.17±0.23	1.04±0.31	0.1020
TC mmol/L	4.25±0.96	4.48±1.12	0.0515
Exercise n (%)			
No	45 (42.66)	52 (54.34)	0.4949
Yes	39 (41.34)	55 (52.66)	

BMI–body mass index, WHR–waist hip ratio, FBG–fasting blood glucose, HbA1c–glycosylated hemoglobin, TC–total cholesterol, TG–triglycerides , LDL–low density lipoprotein, HDL–high density lipoprotein.

RESULTS

This study reveals relationships between adiponectin and resistin concentrations with glycemic and lipid control in patients with T2DM. Table 1 shows comparison of descriptive characteristics and biochemical profile between control and diabetes patients. BMI, WHR, FBG, HbA1c, HOMA-IR, TC and TG were significantly higher in individuals having diabetes compared to healthy volunteers. Exercise prevalence in each group was also compared and it was non-significant (Table1). T2DM patients were divided into good and poor glycemic control group based on a cutoff HbA1c

value of 7.5%. Table 2 expresses Comparison of descriptive characteristics and biochemical profile between good and poor glycemic control in T2DM patients. BMI (p=0.0257), HOMA-IR (p=0.0002) and TG (p=0.0006) were significantly in poor glycemic control group than in the good glycemic control.

Table 2: Comparison of descriptive characteristics and biochemical profile between good and poor glycemic control in T2DM patients (Mean ± SD).

	HbA1c<7.5 n=50	HbA1c≥7.5 n=57	p
M/F	28/22	30/27	
Age (years)	53.90±10.51	51.32±11.15	0.2283
Height (cm)	167.63±6.01	164.48±17.53	0.2474
Weight (kg)	79.94±15.10	84.78±17.17	0.1342
WHR	0.99 ±0.07	1.01±0.09	0.1613
BMI (kg/m^2)	28.46±4.97	30.77±5.26	0.0257
FBG (mmol/dl)	7.10±1.64	10.20±3.61	0.0001
HbA1c (%)	6.58±0.44	9.66±2.58	0.0001
Insulin (uIU/ml)	23.91±7.51	25.24±10.68	0.4705
HOMA-IR	7.66±3.47	11.19±5.49	0.0002
TC mmol/L	4.19±0.84	4.58±1.26	0.1279
TG mmol/L	1.47±0.69	2.36±1.30	0.0006
LDL mmol/L	2.54±0.85	2.75±0.93	0.3307
HDL mmol/L	1.00±0.24	1.08±0.49	0.3783

BMI–body mass index; WHR–waist hip ratio; FBG–fasting blood glucose; HbA1c–glycosylated hemoglobin; TC–total cholesterol, TG–triglycerides , LDL–low density lipoprotein, HDL–high density lipoprotein.

Box plot represents serum adiponectin & resistin a levels in control, all subjects with diabetes, and in those with good and poor glycemic control (Figure 1, 2). Serum resistin levels were significantly higher (p=0.0259) (Figure 1) and serum adiponectin levels significantly lower (p=0.0001) (Figure 2) in type 2 diabetes patients, than healthy subjects. We observed that serum adiponectin levels were significantly lower (p=0.0411) in diabetes patients with poor glycemic control, compared to those with good glycemic control, but the difference was

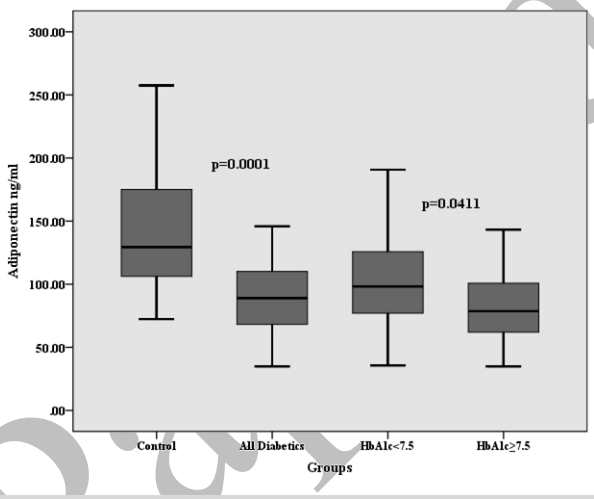

Figure 1: Comparison of adiponectin levels between control, all patients with Type 2 Diabetes Mellitus and those with good (HbA1c<7.5) and poor Glycemic (HbA1c≥7.5) control.

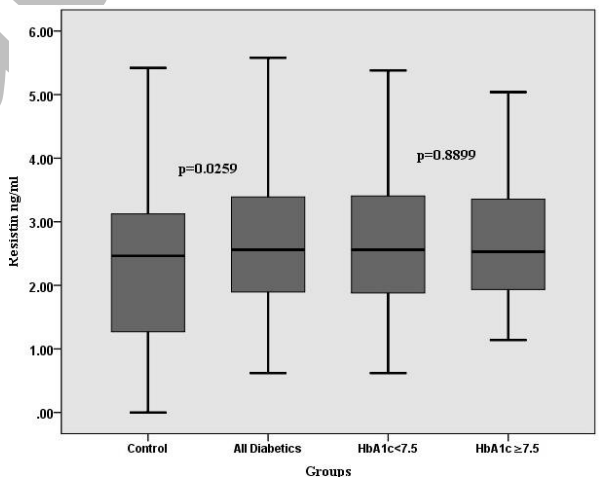

Figure 2: Comparison of resistin levels between control, all patients with Type 2 Diabetes Mellitus and those with good (HbA1c<7.5) and poor Glycemic control (HbA1c≥7.5).

nonsignificant for resistin (p=0.8899). Scatter plot in figure 3 shows the relationship of adiponectin (a) and resistin (b) with glycemic control. Serum adiponectin levels were discordant with HbA1c (r= -0.274, p=0.004). No relationship of HbA1c was observed with resistin levels (r=0.017, p=0.866). Linear by linear association of HbA1c% at different quartiles of adiponectin and resistin levels in diabetes patients was also determined. There was a significant trend of better glycemic control at

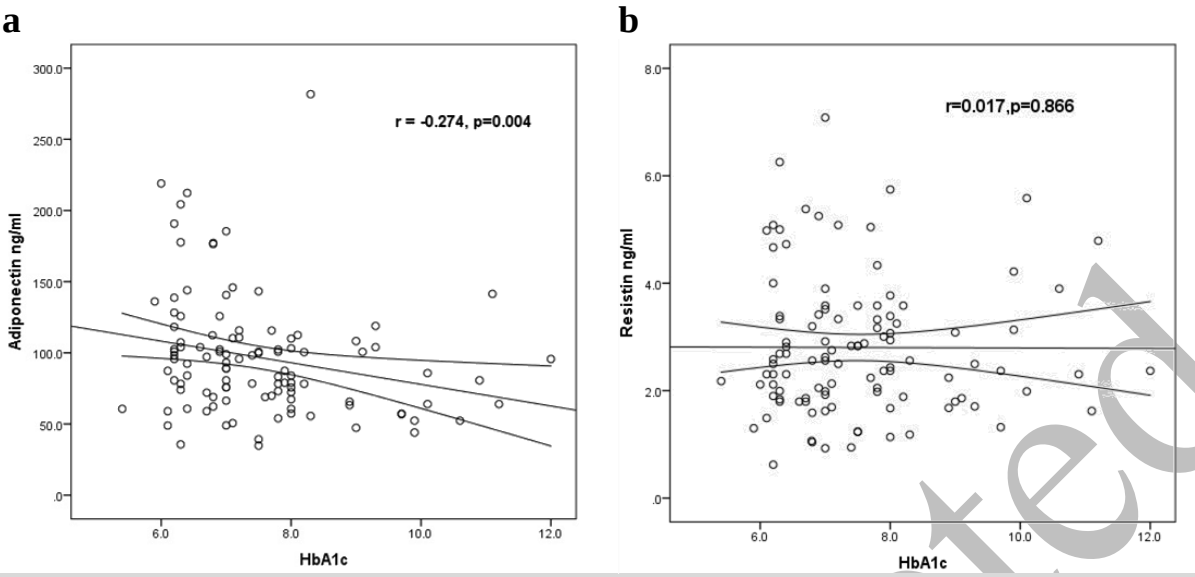

Figure 3: Scatter plot showing the association of circulating levels of Adiponectin (a) & Resistin (b) with Glycosylated hemoglobin (HbA1c).

increasing levels of adiponectin levels (p=0.042), while the trend was not significant for resistin levels (p=0.904) which was depicted by linear by linear association of HbA1c% at different quartiles of adiponectin and resistin levels in diabetes patients as shown in figure 4.

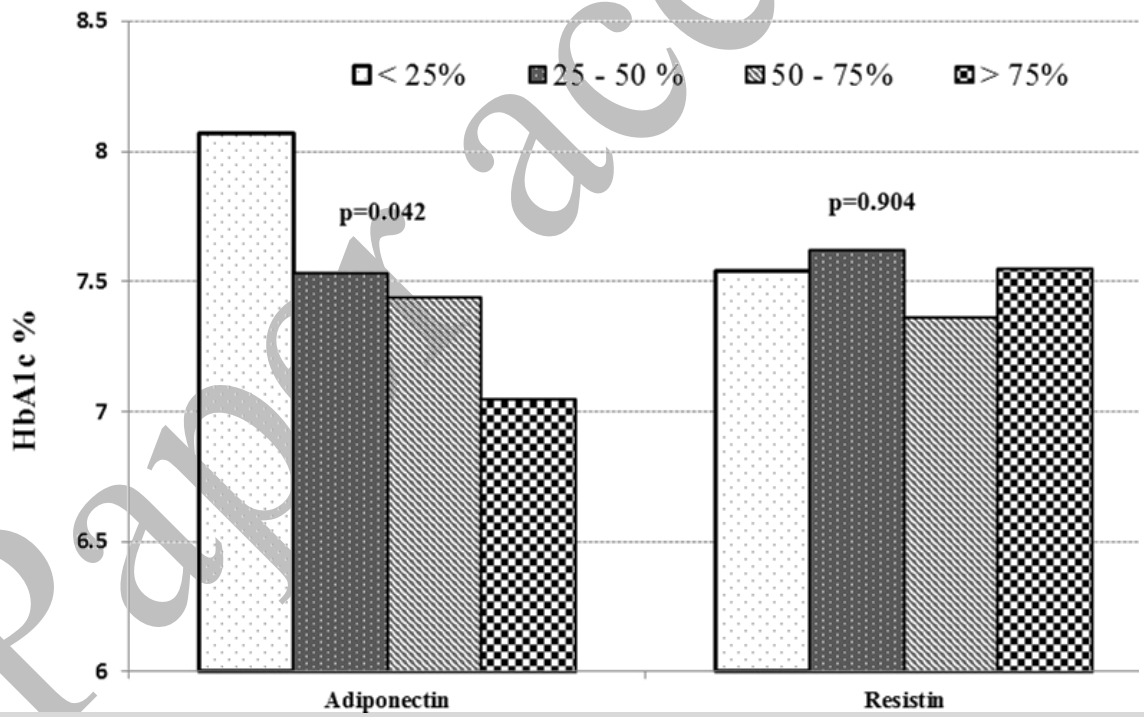

Figure 4: Linear by linear association of HbA1c% at different quartiles of adiponectin and resistin levels in diabetes patients. There is a significant trend of better glycemic control at increasing levels of adiponectin levels (p=0.042) while the trend was not significant for resistin levels (p=0.904).

Multiple regression analysis was performed keeping adiponectin and resistin as dependent variables to determine their predictive factors (Table 3). The significant predictors of adiponectin levels were FBS, insulin, HOMAIR and HbA1c. For resistin none of the variable was significant.

Table 3: Multiple regression analysis for prediction of adiponectin and resistin levels in T2DM patients.

	Adiponectin ng/ml Standardized Beta Coefficients	*p*	Resistin ng/ml Standardized Beta Coefficients	*p*
FBS (mmol/L)	1.498	.015	.481	.507
Insulin (uIU/ml)	1.524	.018	.518	.493
HOMA-IR	-2.317	.016	-.855	.450
HbA1c (%)	-.237	.014	.284	.182
TG (mmol/L)	-.150	.315	-.201	.268
TC (mmol/L)	-.260	.122	.153	.448
HDL (mmol/L)	.074	.618	-.089	.620
LDL (mmol/L)	.133	.472	-.401	.079
Duration (years)	.268	.063	-.186	.283

BMI–body mass index; WHR–waist hip ratio; FBG–fasting blood glucose; HbA1c–glycosylated hemoglobin; TC–total cholesterol, TG–triglycerides , LDL–low density lipoprotein, HDL–high density lipoprotein.

Table 4: Use of medications for diabetes and comorbidities in patients with T2DM.

Medicines for Diabetes	n (%)
• Biguanides	14 (13.1)
• Sulphonylureas	25 (23.4)
• Glinides	11 (10.3)
• Alpha-glucosidase inhibitors	21 (11.2)
• Thiazolidinedione	23 (21.5)
Lipid lowering medicines	25 (23.4)

Table 4 expresses the proportion of patients using of medications for diabetes and comorbidities in patients with T2DM.

DISCUSSION

The present study aimed to assess and compare the relationships of resistin and adiponectin concentrations with glycemic and lipid control in patients with type 2 DM. We observed that Type 2 DM patients have significantly higher resistin and lower adiponectin levels. The effect of glycemic control on resistin levels was not significant. However adiponectin was significantly lower in patients with poor glycemic control, compared to those with good glycemic control. Similar to a report by Schulze et al. [21] our study supports the hypothesis that increased adiponectin levels might be associated with better lipid and glycemic control with reduced inflammation in patients with T2DM. Measures that could increase adiponectin levels might be valuable targets for decreasing the higher CAD risk in diabetes.

In another similar study adiponectin was found to be significantly decreased in type 2 diabetes patients as compared to normal control subjects. Adiponectin levels were negatively associated with hs-CRP, LDL-C, HbA1c, TG, and total cholesterol (TC) and positively with HDL-C. HbA1c had a negative correlation with serum adiponectin. This shows that adiponectin may play an important role in the pathogenesis of diabetes, and may emerge as an independent predictor of the development of type 2 diabetes [22]. Nayak et al showed that Adiponectin decreases with increasing adiposity and insulin resistance regardless of diabetes status. Among non-obese subjects, adiponectin correlated negatively with TG, IL-6, HOMA-IR and positively correlated with HDL. Diabetes status, tumor necrosis factor-α (TNF-α) and BMI were identified as independent predictors of adiponectin. Glucose and adiponectin were useful indicators of type 2 diabetes. Moreover, Insulin mediated glucose turnover was significantly affected by adiponectin and TNF-α [23]. Adiponectin negatively correlated with BMI after adjusting for age, sex and diabetes status [24]. In an interesting study Lau et al. proposed a novel adiponectin-resistin (AR) index by taking into account both adiponectin and resistin levels to provide a better indicator of the metabolic homeostasis and metabolic disorders. A novel

insulin resistance (IRAR) index was derived to provide an improved diagnostic biomarker of insulin sensitivity [25].

Adipocytokines that have been implicated in the pathogenesis of metabolic syndrome, include TNF-α, interleukin-6 (IL-6), angiotensinogen, leptin, plasminogen activator inhibitor-1 (PAI-1) and resistin [26]. The present study supports the evidence that resistin plays an important role in the pathogenesis of obesity and insulin resistance. We reported previously that higher resistin levels in T2DM have a significant positive correlation with body fat mass [27]. However, in the present study although T2DM patients had higher resistin levels, but the effect of glycemic control on resistin levels was not significant. In a study on Chinese T2DM patients 16 weeks of liraglutide administration led to increased adiponectin and decreased resistin levels compared to glimepiride-treated subjects, while inducing similar glycemic changes [28]. Adiponectin, leptin, and resistin levels are affected by use of anti diabetes drugs among which glimepiride shows more effect on adiponectin and resistin levels, while leptin gets affected more by metformin. It shows that the adipokine levels are not affected by diabetes only, suggesting that their alterations in T2DM may be due to obesity. Therefore, there might be important links between adiposity and insulin resistance [29]. The limitation of the present work is its cross sectional design and small sample size. We recommend that further, prospective studies at large scale are required to further explore the true homeostatic roles of adiponectin and resistin in patients with T2DM. Since they are related to glucose and lipid metabolism it would be worth studying them as an integrate approach in relation to different pharmacological interventions and physical fitness programs. They may prove to be useful integrated biomarkers to predict metabolic dysregulation and cardiovascular risk in T2DM .

CONCLUSION

Type 2 DM patients have significantly higher resistin and lower adiponectin levels, when compared to healthy controls. Adiponectin levels were significantly lower in patients with poor glycemic control. However, the effect of glycemic control on resistin levels was not significant.

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