Effect of Glycemic Control on Adipokines in Diabetic Patients with Pulmonary Hypertension

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Abstract

Background: Recent studies suggested a role of diabetes in regulating the outcome of pulmonary hypertension. Several cytokines are dysregulated in pulmonary hypertension, and were considered accurate predictors of the prognosis.

Aim of Study: To evaluate the effects of glycemic control on hemodynamics, metabolic and adipokines (leptin, apelin and adiponectin) levels in patients with pulmonary hypertension and diabetes.

Subjects and Methods: Thirty-five pulmonary hypertension patients with diabetes assigned into two groups according to glycosylated hemoglobin (HbA1c) level; tightly controlled group (Group I) (n=20) and conventionally controlled group (Group II) (n=15). Demographic characteristics, hemodynamic assessment, metabolic and serum adipokines levels were assessed.

Results: Both groups showed insignificant difference in age, BMI and left ventricular ejection fraction; while mean pulmonary arterial pressure, HbA1c, fasting blood glucose, insulin, HOMA-IR, Cholesterol, triglycerides, Interleukin-6, leptin and apelin were significantly decreased in group I. IL-6, leptin and apelin have significant positive correlation with glucose, insulin, HOMA-IR, Cholesterol, TG and MPAP in both groups.

Conclusion: Good glycemic control has an impact on hemodynamics, metabolic, inflammatory and adipokine pattern in diabetic patients with pulmonary hypertension, which may affect the progression of the disease.

Key Words: Diabetes – Leptin – Apelin – Adiponectin – IL6 – Pulmonary hypertension.

Introduction

DIABETES is the main fourth cause of death from non-communicable diseases [1]. It results in systemic macro- and microvascular dysfunction, and multiple mechanisms explain the well-defined, coincident endothelial dysfunction [2].

Pulmonary arterial hypertension (PAH) was previously considered an isolated disease of pulmonary circulation; now, it is linked to insulin resistance and metabolic dysfunction [3] with many factors contributing to its occurrence and progression [4].

Endothelial cells from pulmonary arteries in pulmonary hypertension secrete leptin and their regulatory T-cells have increased leptin receptor [4]. In addition, vascular inflammation is associated with development of pulmonary hypertension. Moreover, adiponectin suppresses vascular inflammation [6] and adiponectin deficiency affect the development of pulmonary hypertension with a role linked to vascular inflammation and pulmonary artery remodeling [6,7].

Apelin is expressed in the lungs, especially in pulmonary vasculature [8] while IL-6 is produced by several cells [9].

Moreover, intensive diabetes control could decrease microvascular complications of diabetes [10,11].

Although, previous studies showed that diabetic patients have an increased risk for developing PH independent of other risk factors; yet, fewer reports if any, reported the effect of glycemic control on metabolic, adipokine and hemodynamic pattern in diabetic patients with pulmonary hypertension.

Patients and Methods

The study included 35 subjects. The study was conducted in Echocardiographic Unit (Zagazig University Hospital) Cardiology Department, Medical Biochemistry and Molecular Biology Department and Medical Physiology Department, Faculty of Medicine, Zagazig University between August
2015 and September 2016. All patients gave adequate informed consent. They were classified into two groups:

**Group I (with HbA1c < 6%):** Included 20 male patients, considered as tightly glycemic controlled.

**Group II (with HbA1c ≥ 6%):** Included 15 patients (10 male, 5 females) considered as conventionally glycemic uncontrolled [11].

All patients were subjected to detailed history taking, examination, standard ECG and conventional Echocardiography: A complete M-mode, two-dimensional and pulsed Doppler echocardiography was performed in each patient. The left ventricular ejection fraction (EF) was calculated using the biplane modified Simpson’s method in the four and two chamber apical views. The RV systolic function was measured by the fractional area change (RVFAC in the apical 4-chamber view.

Where the normal values for RVFAC according to the American society of echocardiography guide lines for chamber quantification ranges from 35-63. Tricuspid annular plane systolic excursion (TAPSE) as a parameter for RV long axis function was assessed with M-Mode cursor positioned at the free wall angle of the tricuspid valve annulus (J. Am. Soc. Echocardiography (2010).

Patients with PH proved by echocardiography then calculating mean pulmonary artery pressure.

**Biochemical measurements:** Venous blood samples were collected from all cases and centrifuged at 3,000 r.p.m. for 10 minutes, serum samples were stored at −70°C until analyzed for: Fasting glucose, insulin, cholesterol, triglycerides, HDL, IL-6, Leptin, adiponectin and Apelin. HOMA IR was calculated by the equation:

\[
\text{HOMA-IR} = \frac{\text{FBG (mg/dL)} \times \text{HbA1c} \%}{22.5} - 3.86
\]

**Statistical analysis:** Quantitative variables were presented as mean (standard deviation; qualitative variables as numbers and percentages. Quantitative variables were tested by Student t-test. Relationships were assessed using Pearson correlation coefficient; p-value <0.05 was considered significant. Analysis of the results was performed using the Statistical Package for the Social Sciences (SPSS), version 19.0 (SPSS Inc., Chicago, IL, United States).

**Results**

Demographic and metabolic data of the studied groups showed insignificant difference in age and BMI. Group II had significantly higher FBG, insulin, HOMA-IR, cholesterol, triglycerides and HbA1c % than group I (Table 1).

Adipokine levels were significantly different between the studied groups (Table 2); Group II showed significantly higher IL-6, Leptin and Apelin associated with lower Adiponectin compared to group I.

Hemodynamic data from the studied groups revealed no significant difference between groups in LVEF%; while TAPSE, RVFAC, RVS were significantly lower in group II whose MPAP were higher than group I (Table 3).

Apart from significant negative correlation with HDL, significantly positive correlation between serum IL-6 and FBG, HOMA-IR, cholesterol, triglycerides and HbA1c % was reported. Also, Leptin and apelin had the same correlation; in addition to significant positive correlation with insulin and HbA1c %. Adiponectin showed significant negative correlation to all metabolic and serum parameters except HDL (Table 4).

Serum adipokines (IL-6, Leptin, and Apelin) were positively correlated to MPAP in the studied groups; while adiponectin showed negative correlation (Fig. 1).

**Table (1): Shows comparison of demographic and metabolic data of the studied groups.**

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.8±4.4</td>
<td>52.3±1.8</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (100%)</td>
<td>10 (66.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0%)</td>
<td>5 (33.3%)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>22.6±1.3</td>
<td>21.9±1.7</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>109.5±16.3</td>
<td>194±50.1*</td>
</tr>
<tr>
<td>Insulin (µg/L)</td>
<td>6.6±0.6</td>
<td>10.5±1.9*</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>218.7±10.6</td>
<td>296.8±13.9*</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>88.6±13.8</td>
<td>111.1±6.8*</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>35.7±8.3</td>
<td>32.2±4.4</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>5.2±0.5</td>
<td>7.7±1.0*</td>
</tr>
</tbody>
</table>

**BMI:** Body mass index.

**HOMA-IR:** Homeostatic Model Assessment of Insulin Resistance.

**HDL:** High density lipoproteins.

**HbA1c:** Glycated hemoglobin.

*p<0.001 using student t-test.

**Table (2): Shows comparison of adipokine pattern of the studied groups.**

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg/ml)</td>
<td>126.3±15.5</td>
<td>166.6±39.8*</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>9.6±3.1</td>
<td>14.2±1.4*</td>
</tr>
<tr>
<td>Adiponectin (ng/ml)</td>
<td>5.9±1.9</td>
<td>2.98±0.9*</td>
</tr>
<tr>
<td>Apelin (µg/L)</td>
<td>11.7±2.2</td>
<td>18.7±1.2*</td>
</tr>
</tbody>
</table>

*p<0.001 using student t-test.
Table (3): Shows Comparison of hemodynamic data of the studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=20)</th>
<th>Group II (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF %</td>
<td>53.3±2.9</td>
<td>52.7±2.1</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>17.9±0.7</td>
<td>15.9±0.6*</td>
</tr>
<tr>
<td>RVFAC %</td>
<td>3.8±0.7</td>
<td>36.4±0.6*</td>
</tr>
<tr>
<td>RVS (cm/s)</td>
<td>10.5±0.3</td>
<td>9.9±0.2*</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>29.5±4.3</td>
<td>59.7±5.4*</td>
</tr>
</tbody>
</table>

LVEF : Left ventricular ejection fraction.
TAPSE : Tricuspid annular plane systolic excursion.
RVFAC : Right ventricular fractional area change.
RVS : Right ventricular systolic wave.
MPAP : Mean pulmonary arterial pressure.
*<p>0.05 using student t-test.

Table (4): Shows Pearson correlations between serum IL-6, leptin adiponectin and Apelin in the studied groups and metabolic parameters.

<table>
<thead>
<tr>
<th></th>
<th>IL-6</th>
<th>Leptin</th>
<th>Adiponectin</th>
<th>Apelin</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG</td>
<td>0.660***</td>
<td>0.457**</td>
<td>-0.385*</td>
<td>0.731***</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.295NS</td>
<td>0.627***</td>
<td>-0.508**</td>
<td>0.781***</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.555***</td>
<td>0.667***</td>
<td>-0.551**</td>
<td>0.905***</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.623***</td>
<td>0.794***</td>
<td>-0.606***</td>
<td>0.883***</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.395*</td>
<td>0.825***</td>
<td>-0.486**</td>
<td>0.587***</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.182NS</td>
<td>-0.799***</td>
<td>0.656***</td>
<td>-0.374*</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>0.466**</td>
<td>0.535***</td>
<td>-0.475**</td>
<td>0.873***</td>
</tr>
</tbody>
</table>

*p<0.05. **p<0.01. ***p<0.001 and NS p>0.05 using student t-test.

**Discussion**

The results of the present study showed that metabolic parameters namely FBG, insulin, HOMA-IR, cholesterol and triglycerides, were significantly higher in conventionally controlled than tightly controlled diabetics; dyslipidemia was found to be more severe with increased levels of HbA1c %, [13]. Annadurai et al., [14] reported higher FBG, cholesterol and triglycerides in diabetic group who have higher HbA1c % and suggested useful roles of HbA1c % not only indicating long-term glycemic control but also, the onset of complications at clinical and molecular levels.

Arterial remodeling, vascular smooth muscle cells proliferation and migration and altered activity could result from hyperglycemia [15]; also, ad-
advanced glycation end products (AGEs) block nitric oxide (NO) activity in the endothelium [16].

Moreover, insulin resistance and dysregulated glucose metabolism act as disease modifier of pulmonary hypertension owing to enhancement of inflammatory processes, deregulation of the NO pathway and endothelial damage [17]. In animal models of insulin resistance, the animals developed pulmonary hypertension suggesting the promoting role of insulin resistance in pulmonary vascular disease [3].

The result of the present study showed significantly higher IL-6 levels in conventionally than tightly controlled PH patients. Jayashree et al. [18] found that serum IL-6 levels were significantly increased in diabetic patients compared to control; over-production of IL-6 was largely restored after proper glycemic control [19]. Insulin resistance itself has an inflammatory action; levels of IL-6 have been shown to increase with diabetes [20].

Moreover, studies reported that IL-6 is implicated in the pathogenesis of PH; serum levels of IL-6 are elevated in patients with PH [21] and higher levels of IL-6 are associated with poor prognosis of those patients [22]. In line with the results in this study, pulmonary hypertension patients who had higher levels of IL-6 had significantly worse right ventricular function (FAC, TAPSE) [21].

This study showed that, serum leptin and apelin levels were significantly higher in conventionally controlled than tightly controlled diabetic PH patients. Improved glycemic control decreases plasma leptin levels, was also demonstrated [23]. Pulmonary hypertension patients had increased serum leptin levels compared to controls, with much of leptin secretion originating from pulmonary endothelial cells [5]. Abnormal over activation of leptin/leptin receptor axis in pulmonary vascular wall, contributes to susceptibility and progression of pulmonary hypertension [24] as leptin contributes to systemic vascular remodeling acting as a proliferative and migratory factor for vascular SMCs, and as a potent immunomodulator for vascular wall inflammatory cell infiltration [25].

Apelin levels were found to be increased in diabetic subjects compared with the controls and plasma apelin levels correlated positively with HOMA-IR, BMI, TC, LDL-C, FBG and plasma insulin [26].

A positive correlation between plasma apelin concentrations and HbA1c was described [27].

Although previous studies demonstrated decreased serum apelin levels in pulmonary hypertension patients [28] and the benefits of augmented apelin signaling in ameliorating symptoms of pulmonary hypertension in rodent models [29], yet in this study, patients exhibit insulin resistance which accompanies increased plasma apelin levels [30]. High apelin levels observed in insulin-resistance, could suggest a compensatory mechanism to reduce insulin resistance and to improve impaired secretion [31] and the link between dysfunctional pulmonary endothelial cells and apelin-APJ axis in these cells may be implicated in the pathogenesis of PH [32].

Regarding adiponectin, an adipokine with known insulin-sensitizing, anti-inflammatory, and antiproliferative properties, this study revealed significant decrease in adiponectin levels in conventionally than tightly controlled PH patients.

Poorly controlled diabetic patients showed significant deregulation of adiponectin and this was reversed by improved glycemic control [33]. An inverse correlation between adiponectin and insulin resistance was also demonstrated [34]. Moreover, adiponectin levels were shown to be inversely proportionate to the degree of pulmonary hypertension [35].

In line with the current study, adiponectin is associated positively with HDL-C and negatively with HbAlc [36].

The results of the current study revealed significantly worse hemodynamic parameters (TAPSE, RVFAC, RVSW and MPAP) in conventionally controlled (Higher HbA1c) than those of tightly controlled (lower HbA1c) PH patients. A relationship was confirmed between HbA1c and hemodynamic parameters in pulmonary hypertension patients [37]. Also, at the time a patient is diagnosed with PH, HbA1c was an independent predictor of survival [38]. The right ventricle is adversely impacted by diabetes in patients with Pulmonary hypertension, hyperglycemia and insulin resistance [39].

Collectively, the present study illustrates the favorable impact of good glycemic control on metabolic, hormonal and hemodynamic patterns in pulmonary hypertensive diabetic patients which suggests a role in the outcome of the disease. Limitations of this study are that it is performed on small number of patients in one centre and, it was cross-sectional approach without long follow-up period.
References


Effect of glycemic control on adipokines in diabetic patients.


