Predictors of hormonal and metabolic disorders of arterial hypertension and type 2 diabetes mellitus comorbidity

Oleksandr Bilovol

Department of Clinical Pharmacology, Kharkiv National Medical University, 61000 Kharkiv, Ukraine.

Correspondence to: Prof. Oleksandr Bilovol, Department of Clinical Pharmacology, Kharkiv National Medical University, 2A Malaya Avenue, 61000 Kharkiv, Ukraine. E-mail: Bilovol.Oleksandr@rada.gov.ua

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ABSTRACT

Aim: These experiments studied adipokine and interleukin imbalances during the development and progression of metabolic disorders in patients with arterial hypertension (AH) and type 2 diabetes mellitus (T2DM). Methods: Ninety-five patients with stage II second degree AH (53 males and 42 females, mean age 54.7 ± 5.4 years) were observed. The cohort was separated into: group 1 (n = 48) patients with AH and group 2 (n = 47) patients with both AH and T2DM. Serum protein levels of omentin, adiponectin, tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), resistin, interleukin (IL)-1β, IL-4, and IL-6 were measured. Lipid and carbohydrate metabolism rates were assessed. Results: Peak homeostatic model assessment for insulin resistance (HOMA-IR) index values, as well as circulating insulin and CRP levels, were observed in group 2. Reduced adiponectin levels negatively correlated with HOMA-IR indices (r = -0.52, P < 0.05), triglycerides (r = -0.52, P < 0.05), glucose levels (r = -0.44, P < 0.05), body mass indices (r = -0.44, P < 0.05), and HbA1c levels (r = -0.57, P < 0.01). Group 2 patients demonstrated low omentin levels and high resistin and TNF-α levels. Negative correlations between IL-6 and both omentin and adiponectin (r = -0.46, P < 0.01; r = -0.42, P < 0.01, respectively) were observed. Conclusion: A novel pathogenic link was demonstrated between metabolic disorders, adipokines, and pro-inflammatory IL-6 levels as negative regulators of comorbid AH and T2DM.

INTRODUCTION

Arterial hypertension (AH) is an important public health challenge in both economically developing and developed countries.[1] The reported prevalence of AH has varied globally; the lowest prevalences was found in rural India (3.4% in men and 6.8% in women) and the highest was observed in Poland (68.9% in men and 72.5% in women).[2] Sur et al.[3] in 2010 reported that more than 3 million people in Romania are hypertensive. In 2009, one-fifth of the adult Danish population was hypertensive.[4] Hypertension affects nearly 75 million adults in the USA and is a major risk factor for myocardial infarction, ischemic stroke, chronic kidney disease, and vascular disease. According to an analysis of American data from the Nationwide Emergency Department...
Isolated AH is currently rare. More commonly, physicians encounter clinical situations in which cases of AH are associated with endocrinopathies. The turn of the 21st century was marked by significant prevalence of type 2 diabetes mellitus (T2DM). Increases in incidence worldwide led to discussions about the global diabetes epidemic. The World Health Organization reported in 2016 that the number of people with diabetes mellitus rose from 108 million in 1980 to 422 million in 2014. Among adults over 18 years of age, diabetes mellitus rates rose from 4.7% in 1980 to 8.5% in 2014.\[7\] Given that diabetes mellitus disables patients at very early ages and leads to high mortality rates, the fight against diabetes has been elevated to a top priority for national health care systems across the world.

According to epidemiological studies, in patients with a combination of hypertension and T2DM the risk of fatal coronary heart disease increases 3 to 5 times, stroke increases 3 to 4 times, complete loss of vision increases 10 to 20 times, uremia increases 20 to 25 times, and gangrene of lower extremities becomes 20 times more likely.\[8\]

One explanation for the frequent observation of comorbid type 2 diabetes in hypertensive patients is that the prevalence of overweight and obesity in the population has increased.\[9\] Prospective studies have shown a strong relationship between obesity and type 2 diabetes. Almost 90% of patients with T2DM are obese. Similarly, the risk of hypertension is 50% higher in obese patients compared to those in normal weight ranges.

In the last few years, inflammatory mechanisms have been shown to regulate initiation, maintenance, and development of cardiovascular disease. Associations between cardiovascular diseases and obesity are mediated, in part, by secretory regulation of adipose tissue. Adipose tissue secretes bioactive peptides (adipokines), which have local and distal influences on organ systems through autocrine, paracrine, and endocrine functions. Increased production of adipokines in obese patients impacts multiple bodily functions, many of which are linked with cardiovascular diseases, such as: insulin sensitivity, immunity, angiogenesis, hemostasis, lipid metabolism, and blood pressure. Adipocytes, like T-lymphocytes and macrophages, produce cytokines and are involved in complement activation-stimulating inflammatory signaling cascades.\[8,9\] Cytokine imbalance is a well-established mechanism contributing increased risk of vascular complications. Therefore, elucidating the interaction between adipokines, interleukins, and metabolic disorders in patients with AH and T2DM is relevant.

The present study was undertaken to investigate the effects of adipokine and interleukin imbalances on the development and progression of metabolic disorders in patients managing hypertension with comorbid type 2 diabetes.

**METHODS**

**Patients**

Ninety-five patients with stage II second degree arterial hypertension (53 males and 42 females) were assessed. The mean age of the cohort was 54.7 ± 5.4 years. The patients were sub-divided into 2 groups. Group 1 (n = 48) consisted of hypertensive patients without T2DM. Group 2 (n = 47) was a comorbid population with both AH and T2DM. The control group consisted of 20 age- and gender-matched healthy subjects. AH diagnoses were conducted according to guidelines for the management of arterial hypertension from the European Society of Cardiology (ESC) and the European Society of Hypertension (2013), as well as Ukrainian Cardiology Association recommendations (2013).\[10\]

Criteria supporting diagnosis of abdominal obesity were established based on recommendations by the World Health Organization (1997). Anthropometric measurements were used to calculate body mass
index (BMI). The severity of obesity was determined following guidance from the International Diabetes Federation (2015). Diagnoses of type 2 diabetes were made following general recommendations of the European Association for the Study of Diabetes (2013) and the ESC (2013). Inclusion criteria: fasting blood glucose ≤ 8.5 mmol/L, postprandial hyperglycemia ≤ 11 mmol/L, and HbA1c level ≤ 9%. Exclusion criteria: pregnancy or lactation; self-reporting with insulin-dependent diabetes, previous acute myocardial infarction or ischemic stroke; cardiovascular damage ≥ II by New York Heart Association criteria; liver disease indicated by transaminase values more than 3 times greater than normal; chronic kidney disease with serum creatinine > 2 mg/dL; ongoing dialysis; human immunodeficiency virus positive disease; history of chronic alcohol abuse in the last 2 years; or history of cancer, stroke, or organ transplantation.

RESULTS
Analyses of trophologic parameters revealed specific patterns in both groups. Patients with isolated AH (group 1) exhibited BMI measurements ranging from 18.5 to 24.9 kg/m² (4 patients). The majority of patients with isolated AH and comorbid AH with T2DM (group 2; 65.1% and 54.6%, respectively) had BMI measurements ranging from 30 to 34.9 kg/m². Third-degree obesity (BMI > 40.0 kg/m²) was observed in 2 patients with isolated hypertension and in 6 patients with comorbid AH and T2DM.

Serum lipid spectra were altered with significantly higher frequency in patients with concomitant AH and T2DM rather than AH alone (62.6% and 44.2%, respectively; P < 0.05). Serum TG levels [Table 1] were 1.4-fold (P = 0.0002) higher in group 2 patients (AH plus T2DM) than in group 1 patients (AH alone), and 1.5-fold higher than in the controls (P = 0.0020). HDL-C levels in group 2 patients were significantly reduced compared to controls (53.2% and 21.0%, respectively; P = 0.0020). Group 2 patients with BMI measurements of 30 to 34.9 kg/m² had significantly lower levels of HDL-C compared to control patients (P < 0.05). Progression of lipid disorders in patients with comorbid AH and T2DM directly depended on BMI. Maximum TC and TG levels were observed in patients with BMI measurements of 35 to 40 kg/m² (P = 0.242, P = 0.062, respectively), while HDL cholesterol serum concentrations were the lowest in these patients (P = 0.042).

Next, insulin resistance (IR) indices were analyzed in the cohort. Patients in group 2 exhibited significantly higher HOMA-IR index values, as well as insulin and C-peptide measurements, when compared to group 1 and the controls (P < 0.0001, P = 0.0003, P = 0.0004, respectively) [Table 2]. These data indicated that hyperinsulinemic IR progression was associated with T2DM incidence. HOMA-IR indices in patients with AH alone were 2-fold higher than in controls (P = 0.00001). In patients with both AH and T2DM, HOMA-IR indices were 2.2-fold higher than in controls (P = 0.00001).

Regression analyses of these data identified statistically significant relationships between HOMA-IR levels and: glucose levels (r = 0.42, P = 0.06), C-peptide levels (r = 0.64, P = 0.0001), BMI (r = 0.54, P = 0.0054) and cholesterol levels (r = 0.64, P = 0.056). These results supported the hypothesis that the development and progression of IR correlated with hyperinsulinemia and dyslipidemia. These data also suggest that IR was associated with inflammation and the development of
vascular wall atherosclerotic lesions in patients facing both AH and T2DM.\textsuperscript{[12,13]}

Next, glucose tolerance was tested. Impaired glucose tolerance (IGT) was observed in 9.6% of patients with hypertension only. In contrast, 96.5% of patients with both AH and T2DM were glucose intolerant. Also, HbA1c was significantly increased in group 2 patients compared to controls ($P < 0.05$). These data affirmed that excess body weight had negative impacts carbohydrate metabolism [Table 3]. Furthermore, fasting serum glucose (FG) levels were significantly elevated in group 1 patients (6.2%) compared to controls ($P = 0.034$). This may result from abdominal obesity given that: (1) excess body weight is causally associated with IR development; and (2) we observed the highest FG levels in patients with both AH and T2DM.

Serum adiponectin levels were evaluated. Adiponectin levels were reduced in patients with both isolated AH and comorbid AH/T2DM when compared to controls [Table 4]. Hypoadiponectinemia was most apparent in group 2 patients ($P < 0.05$). Adiponectin levels negatively correlated with HOMA-IR indices ($r = -0.52, P < 0.05$), TG levels ($r = -0.52, P < 0.05$), glucose levels ($r = -0.44, P < 0.05$), BMI ($r = -0.44, P < 0.05$) and HbA1c ($r = -0.57, P < 0.01$). These data supported that adiponectin regulated carbohydrate and lipid metabolisms and was deregulated in cases of IR. Currently, IR is considered a major risk factor contributing to etiology of T2DM, hypertension, dyslipidemia, atherosclerotic vascular disease, and, potentially, coronary heart disease and stroke.\textsuperscript{[13-18]} IR can also predict development of T2DM in individuals who are normoglycemic. Therefore, it is important to identify IR in the pre-diabetic or early disease stages when therapeutic interventions are most likely to succeed.

Further analyses identified a correlation between adiponectin levels and BMI. In patients with AH and T2DM, those with a BMI ranging from 25.0 to 29.9 kg/m\textsuperscript{2} had an average adiponectin level of 12.2 ± 3.6 ng/mL. When group 2 patients had BMIs ranging from 35.0 to 39.5 kg/m\textsuperscript{2}, average adiponectin level dropped to 7.4 ± 2.2 ng/mL ($P < 0.05$). These results suggest that adiponectin levels could be used to identify the development of vascular atherosclerotic lesions in patients with comorbid AH and T2DM [Table 4].

Next, omentin serum levels were evaluated. Patients with both AH and T2DM had 1.5-fold lower serum omentin than control patients ($P = 0.044$), as well as significantly lower omentin than AH patients ($P = 0.052$). There were negative correlative relationships between omentin levels and: systolic blood pressure levels ($r = -0.61, P < 0.05$), diastolic blood pressure levels ($r = -0.68, P < 0.001$), BMI ($r = -0.36, P < 0.05$), TG levels ($r = -0.44, P < 0.001$), CRP ($r = -0.38, P < 0.001$), and TNF-\textalpha{} ($r = -0.44, P < 0.001$). Also, omentin levels positively correlated with HDL-C ($r =

\begin{table}
\centering
\caption{Characteristic of patient’s lipid metabolism (mean ± SD)}
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Index} & \textbf{1. Control group ($n = 20$)} & \textbf{2. AH ($n = 48$)} & \textbf{3. AH + T2DM ($n = 47$)} & \textbf{$P$ value} \\
\hline
Total cholesterol, mmol/L & 4.90 ± 0.64 & 5.80 ± 1.30 & 6.10 ± 1.70 & $P_{1-2} = 0.0470$ \\
Cholesterol of high-density lipoprotein, mmol/L & 1.20 ± 0.06 & 1.00 ± 0.05 & 0.700 ± 0.045 & $P_{1-2} = 0.5400$ \\
Triglycerides, mmol/L & 1.80 ± 0.07 & 1.90 ± 0.09 & 2.70 ± 0.16 & $P_{1-2} = 0.7300$ \\
Cholesterol of low-density lipoprotein, mmol/L & 3.20 ± 0.54 & 3.68 ± 0.60 & 4.04 ± 0.97 & $P_{1-2} = 0.2300$ \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\caption{Characteristic of insulin resistance indexes in observed patients (mean ± SD)}
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Index} & \textbf{1. Control group ($n = 20$)} & \textbf{2. AH ($n = 48$)} & \textbf{3. AH + T2DM ($n = 47$)} & \textbf{$P$ value} \\
\hline
HOMA-IR & 1.64 ± 0.56 & 4.47 ± 0.60 & 5.44 ± 0.72 & $P_{1-2} = 0.00001$ \\
Insulin, μU/mL & 5.58 ± 1.30 & 11.10 ± 2.70 & 13.70 ± 2.60 & $P_{1-2} = 0.0003$ \\
C-reactive protein, ng/mL & 0.490 ± 0.025 & 0.960 ± 0.053 & 1.300 ± 0.075 & $P_{1-2} = 0.0004$ \\
\hline
\end{tabular}
\end{table}

AH: arterial hypertension; T2DM: type 2 diabetes mellitus
Table 3: Characteristic of carbohydrate metabolism indexes in observed patients (mean ± SD)

<table>
<thead>
<tr>
<th>Index</th>
<th>1. Control group (n = 20)</th>
<th>2. AH (n = 48)</th>
<th>3. AH + T2DM (n = 47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasing glucose, mmol/L</td>
<td>4.27 ± 0.94</td>
<td>6.02 ± 1.05</td>
<td>7.76 ± 1.92</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.50 ± 0.85</td>
<td>6.30 ± 1.23</td>
<td>8.70 ± 1.52</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Oral glucose tolerance test, mmol/L</td>
<td>5.16 ± 1.06</td>
<td>10.42 ± 1.89</td>
<td>13.90 ± 2.26</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

AH: arterial hypertension; T2DM: type 2 diabetes mellitus

Table 4: Levels of adipose tissue hormones and inflammatory markers in the studied patients (mean ± SD)

<table>
<thead>
<tr>
<th>Index</th>
<th>1. Control group (n = 20)</th>
<th>2. AH (n = 48)</th>
<th>3. AH + T2DM (n = 47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omentin, ng/mL</td>
<td>397.60 ± 5.30</td>
<td>319.52 ± 11.92</td>
<td>264.52 ± 3.76</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Adiponectin, ng/mL</td>
<td>13.60 ± 2.10</td>
<td>11.40 ± 2.70</td>
<td>7.30 ± 1.83</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Resistin, ng/mL</td>
<td>10.20 ± 2.58</td>
<td>10.30 ± 2.80</td>
<td>23.40 ± 3.80</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>5.24 ± 1.03</td>
<td>12.24 ± 1.60</td>
<td>27.36 ± 1.74</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>IL-1β, pg/mL</td>
<td>36.8 ± 5.6</td>
<td>86.2 ± 6.3</td>
<td>93.1 ± 9.5</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>19.1 ± 1.2</td>
<td>33.5 ± 3.7</td>
<td>36.4 ± 4.3</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>IL-4, pg/mL</td>
<td>42.9 ± 2.4</td>
<td>69.1 ± 3.4</td>
<td>79.4 ± 2.1</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

AH: arterial hypertension; T2DM: type 2 diabetes mellitus; TNF-α: tumor necrosis factor-alfa; IL: interleukin

0.46, P < 0.001) and adiponectin (r = 0.44, P < 0.05). Additionally, negative correlations were observed between omentin and glucose levels (r = -0.34, P < 0.05), as well as HOMA-IR indices (r = -0.46, P < 0.001). These data suggested that omentin levels were involved in progression of metabolic disorders as well as atherosclerosis development in patients with comorbid hypertension and T2DM. Data gathered here support the hypothesis that abnormal omentin production may contribute to the pathogenesis of obesity-related complications, including T2DM and cardiovascular diseases such as AH. [16-18]

The resistin cytokine is attracting considerable research interest, given that it may link obesity and diabetes. Resistin regulates inflammatory cascade activities, endothelial cell activations and proliferation of vascular smooth muscle cells. The cytokine is of interest as a potential link between metabolic and cardiovascular diseases. Resistin plasma levels were measured here.

Results revealed expression dynamics similar to those observed with insulin and glucose levels. Thus, patients with AH and T2DM experienced significantly higher resistin levels than patients with AH alone or than control patients (P = 0.049, P = 0.043, respectively). However, resistin levels between AH patients and controls were not significantly different (P > 0.05). In AH/T2DM comorbid patients, circulating blood resistin increased significantly, which correlated with fasting insulin, fasting glucose and lipid (TC and TG) concentrations. These data suggested that increased adiposity contributed to the etiology of changes in resistin levels. Previous data have provided ambiguous results when characterizing the role of resistin secretion in the pathogenesis of insulin resistance and T2DM. [18-20] The presence of high serum resistin in these comorbid AH and T2DM patients suggested that it was an additional regulator of IR.

Next, the groups were tested for TNF-α serum levels. Both group 1 and group 2 patients experienced significant increases in serum TNF-α levels when compared with controls (P < 0.05). At their highest, TNF-α levels were 4.1-fold increased in AH/T2DM patients (P = 0.0001) [Table 4]. Increased TNF-α levels...
correlated with increased concentrations of TG and glucose ($r = 0.415$, $P = 0.001$; $r = 0.042$, $P = 0.014$, respectively).

Finally, both AH and AH/T2DM patients experienced significant increases in IL-1β levels when compared to controls. The most pronounced differences were observed in patients with both AH and T2DM ($P = 0.008$). These results have been associated with presumptive stimulation of acute-phase protein synthesis, leading to increased disease complications, and ultimately decreased patient life span. In this study, features of hormonal and metabolic disorders in patients with arterial hypertension and type 2 diabetes were investigated. The most significant signals identified were regulators of lipid and carbohydrate metabolisms, insulin resistance, and systemic inflammation development.

The data presented here indicated that all known manifestations of metabolic abnormalities dramatically increase with BMI in the cohort. The results suggested that in hypertensive patients with diabetes mellitus adipose tissue signaling was dysfunctional. Additionally, carbohydrate metabolism signaling alterations demonstrated that metabolic and hormonal signals were disrupted when hypertensive patients also had comorbid T2DM. The data suggested close pathogenetic links between onset of metabolic disorders and expressions of adipokines (omentin, adiponectin, and resistin). Pro-inflammatory IL-6 secretion was also altered, which was a negative regulator of comorbid arterial hypertension and T2DM.

Mounting evidence supports that adipokines are essential to etiology of cardiometabolic disorders. Despite these findings, research directions continue to focus on obesity as the essential therapeutic target for reducing the risk of metabolic syndrome, T2DM, and associated cardiovascular complications. Given the widespread incidence of comorbid hypertension in diabetic patients, identifying new markers responsible for increased blood pressure during insulin resistance is a paramount research concern.

**DISCUSSION**

Presence of comorbid hypertension and type 2 diabetes is often associated with underlying metabolic disorders and central obesity. The combined sequelae lead to increased incidence of disease complications, and ultimately decreased patient life span. In this study, features of hormonal and metabolic disorders in patients with arterial hypertension and type 2 diabetes were investigated. The most significant signals identified were regulators of lipid and carbohydrate metabolisms, insulin resistance, and systemic inflammation development.

The data presented here indicated that all known manifestations of metabolic abnormalities dramatically increase with BMI in the cohort. The results suggested that in hypertensive patients with diabetes mellitus adipose tissue signaling was dysfunctional. Additionally, carbohydrate metabolism signaling alterations demonstrated that metabolic and hormonal signals were disrupted when hypertensive patients also had comorbid T2DM. The data suggested close pathogenetic links between onset of metabolic disorders and expressions of adipokines (omentin, adiponectin, and resistin). Pro-inflammatory IL-6 secretion was also altered, which was a negative regulator of comorbid arterial hypertension and T2DM.

**REFERENCES**


