A study of plasma copeptin level as a predictor of severity during acute exacerbation of bronchial asthma
Ahmed G. El Gazzara, Khaled M. Belal, Tarek S. Essawy, Neveen M. Abd-Elfattah

Background An exacerbation of asthma is an episode, characterized by a progressive increase in one or more typical asthma symptoms (shortness of breath, wheezing, cough, and chest tightness).

Copeptin is a 39-amino acid glycopeptide that is derived from the C-terminal part of the pro-hormone of arginine vasopressin.

Aim The aim of our study was to evaluate the role of copeptin in asthmatic patients and its relationship to disease severity.

Patients and methods This was a prospective observational study carried out on 45 patients during acute exacerbation of bronchial asthma (15 mild, 15 moderate, and 15 severe cases) and 15 healthy participants.

Results Our study showed no significant difference in age, sex, and BMI between case and control groups. There was a statistically highly significant differences in pulmonary function tests, partial pressure of oxygen in arterial blood, partial pressure of carbon dioxide in arterial blood, and oxygen saturation among mild, moderate, and severe cases, and significant increase in total leukocytic count and hospital stay in severe cases than mild and moderate cases. There was a highly significant increase of plasma copeptin in moderate and severe cases than mild cases and control groups. There were nonsignificant correlations between copeptin and pulmonary function tests in mild cases; a significant negative correlation between copeptin and forced expiratory volume in 1 s (FEV1) actual in moderate cases; significant negative correlations between copeptin, FEV1 actual, FEV1% predicted, forced vital capacity% predicted, and peak expiratory flow% predicted in severe cases; and highly significant negative correlations between copeptin and partial pressure of oxygen in arterial blood and oxygen saturation in all cases ($P<0.001$). Partial pressure of carbon dioxide in arterial blood exhibited a nonsignificant positive correlation with copeptin ($P<0.05$).

Conclusion Copeptin is proven to be a novel biomarker and is increased in patients with asthma as compared with healthy controls.

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Keywords: acute exacerbation, asthma, copeptin

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Introduction
Asthma is defined as a common lung inflammatory disorder of the airways that causes the bronchi to swell; this results in difficulties of breathing, chest tightness, cough, and wheezing. Severe exacerbation of bronchial asthma was defined as a life-threatening condition that should be managed as an emergency, and patients need hospital admission owing to worsening asthma, need for systemic corticosteroids, or morning peak flow decrease more than 25% of baseline in two successive days [1].

Copeptin, a 39-amino acid glycopeptide, is a carboxy-terminal part of the precursor (pro-vasopressin). Vasopressin has an antidiuretic action on kidney so it is termed antidiuretic hormone. It is involved in renal and cardiovascular functions [2].

Xue et al. [3] evaluated the prognosis of copeptin utility in 525 patients who have acute dyspnea owing to asthma. They found that copeptin was a significant independent predictor of prolonged hospital stay and mortality in patients who have acute dyspnea owing to bronchial asthma.

Aim The aim of this study is to measure the level of plasma copeptin during acute exacerbation of bronchial asthma to determine if there is a change in its level that correlates with changes in the ventilatory functions.

Patients and methods
Patients
This was a prospective observational study carried out on 60 patients at Benha University Hospital Chest Department. They were classified into four groups: control group comprised 15 apparently healthy nonsmoker patients, and asthma group comprised 45 patients (15 mild cases, 15 moderate cases, and 15 severe cases), classified according to Global Initiative for Asthma 2016 guidelines [4].
Inclusion criteria
Patients during acute exacerbation of bronchial asthma, admitted to inpatient Chest Department, Benha University Hospital, were included.

Exclusion criteria
In our study, we excluded patients who have renal impairment, patients of chronic obstructive pulmonary disease (COPD), patients of cardiac asthma, and pregnant female.

Methods
All participants were subjected to the following:

(1) Full clinical history: some features strongly support the diagnosis of asthma such as nocturnal attack, periodicity of symptoms, and diurnal and seasonal variations. Symptoms resulting owing to exertion, allergen exposure, and presence of atop in the patient or his/her family also support the diagnosis. Patients were also asked about duration of the disease, previous hospital admission, the therapy needed to control the symptoms, the family history, and history of other allergies such as skin or nasal allergy.

(2) Clinical examination (general and local chest) revealed signs of airway obstruction.

(3) Plain chest radiography lateral and posteroanterior views to exclude any associated radiological abnormality.

(4) Complete blood count for determination of total and differential leukocytic counts.

(5) Pulmonary function tests using JAEFER MS-PFT by Care Fusion (Germany). Was performed after administration of bronchodilators, 6–8 h after stability of patient’s acute asthma exacerbation.

(6) Arterial blood gases analysis using Sensa Core Medical Instrumentation Pvt Ltd (India).

(7) Measurement of copeptin levels: ∼2.5–5 ml of blood samples was taken from patients in test tubes containing EDTA as an anticoagulant. Centrifugation of the samples for 15 min at 1000 g within 30 min of collection was done, and samples were stored in aliquots at −20 to −80°C until the time of measurement. To determine plasma copeptin concentration samples, a new sandwich immuneluminometric assay was used. In brief, the EDTA plasma samples were incubated with antibodies diluted in 10–20 ml of standard assay buffer under agitation (170–300 rpm) for 2 h at room temperature (18–24°C). The polyclonal antibodies used were directed against the amino acid sequence 132–164 of pre–pro-vasopressin. Then the test tubes were washed four times with 1 ml of LUMI test wash solution, and bound chemoluminescence was measured for 1 s per tube with an LB952T Luminometer (Berthold, Wildbad, Germany).

Patients gave written informed consent for their participation. Ethics committee approved the study.

Statistical analysis
The data were analyzed with SPSS software (version 20; SPSS Inc., Chicago, Illinois, USA). The relationship between patients’ characteristics and mortality was tested using a $\chi^2$ test in the univariate analysis. A $P$ value of less than 0.05 was considered to be statistically significant.

Results
A total of 60 patients were classified into four groups: control group comprised 15 apparently healthy nonsmoker patients, and asthma group comprised 45 patients with acute exacerbation of bronchial asthma (15 mild cases, 15 moderate cases, and 15 severe cases).

In the comparison between the cases and control group regarding age of the patient, it is apparent that mean±SD of the age was 44.27±9.92 years in case group and years and 41.67±2.69 years in control group, with nonsignificant difference ($P>0.05$).

Regarding sex, males represented 17.8% of the case group and 23.3% of the control group, and females represented 82.2% of the case group and 86.7% of the control group, with no significant difference between both the groups ($P>0.05$).

Mean±SD of BMI was 30.44±5.6 in cases and 29.63±3.53 in the control group. Student $t$ test showed nonsignificant difference in the BMI ($P>0.05$) (Table 1, Fig. 1).

There was a statistically highly significant increase in pulmonary function tests in mild cases than moderate and severe cases ($P<0.001$) (Table 2).

There were statistically highly significant differences in partial pressure of oxygen in arterial blood ($\text{PaO}_2$) and saturated oxygen ($\text{SaO}_2$) among mild, moderate, and severe cases ($P<0.001$) (Table 3, Fig. 2).

There was a statistically significant increase in total leukocytic count and hospital stay in severe cases than
mild and moderate cases ($P<0.05$) (Table 4, Fig. 3). The means±SD of plasma copeptin are 17.47±5.42, 24.33±6.61, 29.15±9.11, and 6.31±1.46 in mild cases, moderate case, severe cases, and controls. $F$ test shows highly significant increase of plasma copeptin in moderate and severe cases than mild cases and control group ($P<0.001$) (Tables 5).

There was a significant negative correlation between forced expiratory volume in 1 s (FEV1) actual and copeptin in moderate cases ($P<0.05$) (Table 7). There were significant negative correlations between copeptin and FEV1 actual, FEV1% predicted, forced vital capacity% predicted, and peak expiratory flow % predicted in severe cases ($P<0.05$) (Table 8). There were nonsignificant differences in copeptin levels between males and females in all groups ($P>0.05$) (Table 9). There were high significant negative correlations between copeptin and $PaO_2$ and $SaO_2$ in all cases.
P<0.001), but PaCO₂ exhibited a nonsignificant positive correlation with copeptin (Figs 4–7). (P<0.05) (Table 10, Figs 8 and 9).

Copeptin level of 12.5 pg/ml predicts good prognosis and survival among patients with sensitivity of 97.8%, specificity of 100%, positive predictive value (PPV) of 100% and negative predictive value (NPV) of 93.8% with an accuracy of 98.3% and area under the curve (AUC) of 1 (P<0.001) (Table 11).

Copeptin level of 12.5 pg/ml predicts good prognosis and survival among mild patients with sensitivity of 93.3%, specificity of 100%, PPV of 100%, and NPV of 93.8%, with an accuracy of 96.7% and AUC of 1 (P<0.001) (Table 12).

Copeptin level of 16.6 pg/ml predicts good prognosis and survival among moderate patients with sensitivity of 86.7%, specificity of 100%, PPV of 100%, and NPV of 88.2%, with an accuracy of 93.3% and AUC of 1 (P<0.001) (Table 13).

Copeptin level of 18.65 pg/ml predicts good prognosis and survival among severe patients with sensitivity of 86.7%, specificity of 100%, PPV of 100%, and NPV of 88.2%, with an accuracy of 93.3% and AUC of 1 (P<0.001) (Table 14).

Discussion
Arginine vasopressin is a posterior pituitary hormone that is synthesized in the hypotalamic periventricular and suprapotic nuclei and then is stored and released from the posterior pituitary gland as a result of certain stimuli, such as hypoxia, infections, hypotension, acidosis, and hyperosmolarity, and it is claimed to be a sensitive marker in these situations. Short half-life and instability of arginine vasopressin (AVP) caused limitations in its measurement. However, copeptin is more stable in plasma and serum. So it mirrors arginine vasopressin concentrations in individual stress response. Copeptin level has a marked increase when disease severity is increased, and in critically ill patients [5].

To evaluate patient’s need for hospitalization and initiate a specific treatment, we need to know factors that predict a worse outcome in asthma. The use of biomarkers helps to estimate the presence of infections, their severity, and response to treatment. Copeptin can reflect both the inflammatory cytokine responses, which correlate with the severity of asthma, and the individual stress responses, and also the presence of hemodynamic and osmoregulatory disturbances. So, the aim of our study was to evaluate the role of copeptin in asthmatic patients and its relationship to disease severity.

Our study was carried out on 45 patients during acute exacerbation of bronchial asthma (15 mild cases, 15 moderate cases, and 15 severe cases) and 15 healthy participants.
Figure 3

Comparison between the studied groups according to total leukocytic count and hospital stay.

Figure 4

Correlation between copeptin and FEV1 actual among group of cases. FEV1, forced expiratory volume in 1 s.

Figure 5

Correlation between copeptin and FVC% predicted among group of cases. FVC, forced vital capacity.
In the present study, mean±SD of the age was 44.27±9.92 years in case group and 41.67±2.69 years in control group, with nonsignificant difference (P>0.05).

Our results are in agreement with Morgenthaler et al. [6]. Their research assay measured copeptin level in serum and plasma of healthy individuals and patients to evaluate its clinical importance in a variety of...
pathologies in which arginine vasopressin secretion is reportedly disturbed, and they revealed that there was no major difference in median copeptin concentrations after stratification according to age groups.

Regarding sex, males represented 17.8% of case group and 23.3% of control group and females represented 82.2% of patient group and 86.7% of control group, with no significant difference between both groups ($P>0.05$).

This study showed nonsignificant differences in copeptin levels between males and females in all groups ($P>0.05$).

Table 8 Correlation between copeptin and pulmonary function tests in severe disease group

<table>
<thead>
<tr>
<th>Copeptin</th>
<th>Severe cases (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 actual</td>
<td>−0.41 0.06 (NS)</td>
</tr>
<tr>
<td>FEV1% predicted</td>
<td>−0.65 0.009 (S)</td>
</tr>
<tr>
<td>FVC% predicted</td>
<td>−0.65 0.009 (S)</td>
</tr>
<tr>
<td>PEF% predicted</td>
<td>−0.57 0.03 (S)</td>
</tr>
</tbody>
</table>

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; NS, nonsignificant; PEF, peak expiratory flow. Significance considered when $P$ value less than 0.05.

Table 9 Comparison of copeptin level between male and female in all groups

<table>
<thead>
<tr>
<th>Sex (copeptin levels)</th>
<th>Mild cases (15) (mean±SD)</th>
<th>Moderate cases (15) (mean±SD)</th>
<th>Severe cases (15) (mean±SD)</th>
<th>Control group (15) (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>14.46 ±0.90</td>
<td>30.17±1.5</td>
<td>32.27</td>
<td>8.2±0.85</td>
</tr>
<tr>
<td>Female</td>
<td>18.98 ±6.15</td>
<td>22.87±6.6</td>
<td>28.38±8.44</td>
<td>6.02±1.31</td>
</tr>
</tbody>
</table>

$t$ test 1.61 1.85 0.65 2.24

$P$ value 0.133 0.09 0.53 0.083

Significance considered when $P$ value less than 0.05. Highly significant considered when $P$ value less than 0.001.

Our results were contrary to Bhandari et al. [7] who found that copeptin levels were significantly higher in healthy males than females ($P<0.001$).

Pulmonary function tests showed highly statistically significant decrease in moderate and severe cases than mild cases ($P<0.001$).

Ian and Fred [8] explained that airway inflammation occurs in both allergic and nonallergic forms of asthma and is a feature of all grades of asthma severity.

This study showed statistically highly significant differences in $\text{PaO}_2$ and $\text{SaO}_2$ among mild, moderate, and severe cases.

There was a significant increase in plasma copeptin, total leukocytic count, and hospital stay in severe and moderate cases than mild cases.

These results are in agreement with Al Salahy et al. [9], who found that elevated plasma copeptin levels reflect disease severity and predict long hospital and ICU stay.

Muller et al. [10] found that in patients with community acquired pneumonia (CAP), acute

Table 10 Correlation between copeptin and partial pressure of oxygen in arterial blood, partial pressure of carbon dioxide in arterial blood, and oxygen saturation

<table>
<thead>
<tr>
<th>Copeptin</th>
<th>Total cases (45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r$</td>
<td>$P$</td>
</tr>
<tr>
<td>PaO$_2$</td>
<td>−0.62 0.001**</td>
</tr>
<tr>
<td>PaCO$_2$</td>
<td>0.26 0.088</td>
</tr>
<tr>
<td>SaO$_2$</td>
<td>−0.72 0.001**</td>
</tr>
</tbody>
</table>

PaCO$_2$, partial pressure of carbon dioxide in arterial blood; PaO$_2$, partial pressure of oxygen in arterial blood; SaO$_2$, oxygen saturation. Significance considered when $P$ value less than 0.05. Highly significant considered when $P$ value less than 0.001. **Highly significant.

Figure 8

Correlation between copeptin and PaO$_2$. PaO$_2$, partial pressure of oxygen in arterial blood.
Exacerbation of chronic obstructive pulmonary disease (AECOPD), and exacerbation of asthma, copeptin levels were also significantly higher as compared with controls ($P < 0.001$).

Xue et al. [3] evaluated the utility of copeptin as a prognostic marker in 525 patients with acute dyspnea owing to asthma, COPD, pneumonia, bronchitis, and influenza. They concluded that copeptin is a significant independent predictor of increased hospital stay and mortality in patients with acute dyspnea of noncardiac origin.

There were highly significant negative correlations between copeptin and PaO2 and SaO2 in all cases.
levels can be a tool for the risk stratification in patients with bronchial asthma as compared with healthy controls. Copeptin is secreted in blood in an equimolar ratio to AVP and is more reliable to assay. Copeptin has been utilized as a surrogate marker of AVP activity in recent investigations.

Financial support and sponsorship Nil.

Conflicts of interest There are no conflicts of interest.

References
3 Xue Y, Tong J, Clopton P. Elevated copeptin is associated with increased 90 day mortality in patients with acute dyspnea from non-cardiac causes: Secondary results from the BACH study. JACC 2012; 59:E945.