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ORIGINAL ARTICLE

# Evaluation of Copeptin as a Novel Marker for Predicting the Prognosis of Fatty Liver Disease and its Complications in Obesity

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**Abstract**

*Objectives*: **Copeptin is an independent, persistent plasma marker for vasopressin (VP) linked to all aspects of the metabolic syndrome and overweight. The study aimed to evaluate copeptin levels as a surrogate marker for predicting liver disorders in obese patients.**

*Methods*: **Cross sectional study include 20 obese males with mean of age (42.50 ± 3.17) years and 20 obese females with mean of ages (44.55 ± 2.82) years, the plasma copeptin level was measured and related with fatty liver disease according to a validated liver enzyme, lipid profile, BMI and abdominal ultrasound.**

*Results*: **Highly significant increase liver enzyme, lipid profile and BMI in both males and females obese fatty liver patients, significant elevated Copeptin concentration in both gender (13.84 ± .27), (13.88 ± .40) and highly significant positive correlated with ferritin, BMI and TC, (r = .651, .496, .491 and .457), while showed Copeptin significant negative correlated with HDL (−.508, −.490).**

*Conclusions*: **Obese individuals with the fatty liver disease showed associated with highly increased plasma copeptin, also this marker considers a useful tool for the diagnostic pathway to risk factors of metabolic disease such as diabetes mellitus although this hypothesis needs further studies to be confirmed.**

*Keywords:* Copeptin, Obese and fatty liver

## Introduction

The pituitary gland secreted hormone called Vasopressin (VP) in response to low blood pressure, decrease level of plasma volume and increased plasma osmolality. Copeptin: is produced from cleavage "C-terminal portion" of VP precursor, which has a strong correlation with plasma VP concentrations, Copeptin is therefore currently thought of as the circulating surrogate VP biomarker (Barchetta et al., 2019). Beside its function in triggering reactive vasoconstriction, preventing diuresis, and thus regulating blood volume (Roussel et al., 2014). Major impacts of VP include regulated lipid and glucose metabolism by stimulating the hepatocytes gluconeogenesis, glycogenolysis and fat production, also modulating secretion of glucagon and insulin from Langerhans' islets in pancreatic organ (Sofia Enhörning et al., 2010). Elevated levels of copeptin can associated with increased risk factors of cardiovascular diseases, T2D, hypertension, high triglycerides, dysfunctional glucose regulation and accumulation of visceral fat deposition (Taveau et al., 2015). In recent years, fatty liver disease has received a lot of attention, because it is the most prevalent chronic liver disease in the world, estimated to affect up to 25% of the general population and 80 percent of obese people. (Bedogni et al., 2007). Copeptin stimulates the formation of triglycerides, which has a direct impact on fat metabolism in hepatic cells. Clinical research on humans demonstrates an association between elevated copeptin levels and hepatic cirrhosis, possibly indicating a role for copeptin as a prognostic marker

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of liver illness. (Tawfik et al., 2018). Therefore, the goals of this study are to examine the relationship between plasma copeptin levels and the existence of fatty liver as well as to examine clinical correlations of elevated copeptin levels with other parameters.

## Material and methods

### *Study design*

For this cross-sectional study, 40 patients were included. with obese include 20 males with range of age (20–65 years) and mean of ages (42.50 ± 3.17), 20 females with range of ages (22–65 years) and mean of ages (44.55 ± 2.82) and 20 health individuals used as control 10 males with range of age (20–61years) and mean of ages (44.90 ± 4.87), 10 females with range of age (20–65 years)) and mean of ages (40.70 ± 4.66) who attended to Hematology Unit, in the laboratory of AL-Hussein hospital for the period from November 2021 to January 2022. All participants met the following inclusion criteria for this study: no history of alcohol drinking, negative hepatitis B or C virus testing, no cirrhosis, absence causes lead to liver diseases such as (Wilson's disease, hemochromatosis, autoimmune hepatitis), or treated with any drugs that cause liver steatosis, while exclusion criteria for this study: smoker person, diabetes mellitus disease, People with kidney disease and when BMI ≥30 kg/m2. Identification of hepatic steatosis during abdominal ultrasound evaluation using a Toshiba (Aplio XV) scanner (Japan). The body mass index (BMI, kg/m2) was determined by measuring the weight and height while they were wearing light clothing and without shoes.

### *Laboratory tests*

For all participants in the study withdraw 5 ml of venous blood in the morning after 12 h fasting for routine analyses and metabolic characterization. Spectrophotometer used for liver function test includes aspartate aminotransferase (AST, IU/L), alanine aminotransferase (ALT, IU/L), alkaline phosphatase (ALP, IU/L), Total protein (TP), Albumin (ALB), Total Bilirubin (TB, mg/dL). Lipid profile test include: Total cholesterol (TC mg/dL), high-density lipoprotein cholesterol (HDL, mg/dL), Low-density lipoprotein cholesterol (LDL, mg/dL), triglycerides (TG mg/dL) and ferritin measurement (ng\ml). Tubes containing ethylenediaminetetraacetic acid (EDTA) were used for Plasma samples copeptin (pmol/L) evaluation, this plasma was frozen immediately and stored at (−80 °C) after separation, 50 μL plasma samples were used to assess serum copeptin utilizing an immunoassay in a chemiluminescence coated tube format ProAVP kit Germany by Enzyme-linked immunosorbent assay (ELISA) (Morgenthaler et al., 2006).

### *Statistical analysis*

All the data have been performed using software SPSS version 24. Values are shown as (mean ± SD) compared between patients and control used T-test at level (($P \leq .05$ and $P \leq .01$), Pearson correlations between serum copeptin concentration with different laboratory data used at level ($P \leq .05$ and $P \leq .01$).

## Results

Table (1), (2) showed high significant differences for all liver function tests in male and females obese patients (ALT, AST, ALP, TP, ALB and TB) (3.55, 2.15, 11.59, .34, .12 and .32) (51.67, 46.61, 166.69, 6.38, 1.75 and 4.88) respectively as compared to control. In table (3), (4) found high significant differences for all lipid profile test in male and females obese patients (HDL, LDL, TC, TG) (38.60, 160.01, 321.80,

*Table 1. Compared biochemical parameters of liver function test (LFT) in both control and obesity patients males with presence of fatty liver disease (FLD).*

| sex | Parameters | Groups | N | Mean | S. E | t − test | p.v |
|---|---|---|---|---|---|---|---|
| Male | ALT u\l | control | 10 | 34.75 | 1.83 | −4.702 | .000 |
| | | patients | 20 | 59.28 | 3.55 | | |
| | AST u\l | control | 10 | 31.52 | .91 | −4.856 | .000 |
| | | patients | 20 | 46.71 | 2.15 | | |
| | ALP u\l | control | 10 | 65.13 | 2.11 | −5.356 | .000 |
| | | patients | 20 | 154.07 | 11.59 | | |
| | Total protein (TP) gm\dl | control | 10 | 7.25 | .10 | 2.260 | .032 |
| | | patients | 20 | 6.14 | .34 | | |
| | Albumin (ALB) gm\dl | control | 10 | 4.24 | .15 | 13.033 | .000 |
| | | patients | 20 | 1.58 | .12 | | |
| | Total Bilirin (TB) gm\dl | control | 10 | .65 | .03 | −9.063 | .000 |
| | | patients | 20 | 4.84 | .32 | | |

ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatases.

*Table 2. Compared biochemical parameters of liver function test (LFT) in both control and obesity patients females with presence of fatty liver disease (FLD).*

| sex | Parameters | Groups | N | Mean | S. E | t - test | p.v |
|---|---|---|---|---|---|---|---|
| Females | ALT u\l | control | 10 | 33.33 | 1.78 | −4.947 | .000 |
| | | patients | 20 | 51.67 | 2.45 | | |
| | AST u\l | control | 10 | 30.76 | 1.27 | −6.530 | .000 |
| | | patients | 20 | 46.61 | 1.58 | | |
| | ALP u\l | control | 10 | 79.67 | 1.52 | −5.127 | .000 |
| | | patients | 20 | 166.69 | 11.87 | | |
| | Total protein (TP) gm\dl | control | 10 | 7.21 | .06 | 1.785 | .085 |
| | | patients | 20 | 6.38 | .32 | | |
| | Albumin(ALB) gm\dl | control | 10 | 4.30 | .21 | 10.777 | .000 |
| | | patients | 20 | 1.75 | .13 | | |
| | Total Bilirin (TB) gm\dl | control | 10 | .63 | .03 | −19.370 | .000 |
| | | patients | 20 | 4.88 | .15 | | |

ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatases.

*Table 3. Compared biochemical parameters of lipid profile test (LPT) in both control and obesity patients males with presence of fatty liver disease (FLD).*

| Sex | Parameters | Groups | N | Mean | S. E | t - test | p.v |
|---|---|---|---|---|---|---|---|
| Males | HDL mg\dl | control | 10 | 59.35 | 1.44 | 12.129 | .000 |
| | | patients | 20 | 38.60 | .97 | | |
| | LDL mg\dl | control | 10 | 97.37 | 2.33 | −9.981 | .000 |
| | | patients | 20 | 160.01 | 4.25 | | |
| | TC mg\dl | control | 10 | 167.40 | 4.98 | −8.969 | .000 |
| | | patients | 20 | 321.80 | 11.82 | | |
| | TG mg\dl | control | 10 | 72.60 | 2.40 | −11.695 | .000 |
| | | patients | 20 | 160.50 | 5.14 | | |

HDL: High density lipoprotein; LDL: Low density lipoprotein: TC: Total cholesterol: TG: Triglyceride.

*Table 4. Compared biochemical parameters of lipid profile test (LPT) in both control and obesity patients females with presence of fatty liver disease (FLD).*

| sex | Parameters | Groups | N | Mean | S. E | t - test | p.v |
|---|---|---|---|---|---|---|---|
| Females | HDL mg\dl | control | 10 | 58.87 | 1.44 | 13.520 | .000 |
| | | patients | 20 | 37.10 | .89 | | |
| | LDL mg\dl | control | 10 | 114.90 | 11.17 | −4.090 | .000 |
| | | patients | 20 | 154.85 | 4.15 | | |
| | TC mg\dl | control | 10 | 163.80 | 5.56 | −10.087 | .000 |
| | | patients | 20 | 321.30 | 10.60 | | |
| | TG mg\dl | control | 10 | 77.50 | 1.92 | −9.930 | .000 |
| | | patients | 20 | 152.30 | 5.20 | | |

HDL: High density lipoprotein; LDL: Low density lipoprotein: TC: Total cholesterol: TG: Triglyceride.

160.50) (37.10, 154.85, 321.30, 152.30) respectively as compared to control. Result of table (5) found high significant increase of Ferritin in males and females patient (3159.15 ± 333.55) (2940.65 ± 325.78) comparison to control (251.90 ± 8.68) (112.40 ± 10.03) Consecutively. Also, a highly significant increase of copeptin in males and females patient (13.84 ± .27) (13.88 ± .40) compared to control (3.21 ± .27) (3.21 ± .31) respectively table (6). The result in table (7) demonstrated highly positive correlation

*Table 5. Level of serum ferritin in both male and female's obesity patients with presence of fatty liver disease comparison to control.*

| sex | Parameters | Groups | N | Mean | S. E | t - test | p.v |
|---|---|---|---|---|---|---|---|
| Males | Ferritin gm\dl | control | 10 | 251.90 | 8.68 | −6.108 | .000 |
| | | patients | 20 | 3159.15 | 333.55 | | |
| Females | | control | 10 | 112.40 | 10.03 | −6.084 | .000 |
| | | patients | 20 | 2940.65 | 325.78 | | |

*Table 6. Level of serum Copeptin in both male and female's obesity patients with presence of fatty liver disease comparison to control.*

| sex | Parameters | Groups | n | Mean | S. E | t - test | p.v |
|---|---|---|---|---|---|---|---|
| Males | Copeptin pmol/L | control | 10 | 3.21 | .27 | −24.539 | .000 |
| | | patients | 20 | 13.84 | .27 | | |
| Females | | control | 10 | 3.21 | .31 | −17.605 | .000 |
| | | patients | 20 | 13.88 | .40 | | |

*Table 7. Study correlation of copeptin with BMI and Ferritin in males and females obesity patients with presence of fatty liver disease.*

| sex | Parameters | BMI | Ferritin |
|---|---|---|---|
| males | Copeptin pmol/L | .001 | .651** |
| **females** | | .496** | −.328 |

between copeptin and ferritin in males (r = .651) and with BMI in females (r = .496). In table (8) found highly positive correlation between copeptin and ALT (r = .543) in males. Copeptin showed highly negative correlation with HDL in males and females (r = −.508, r = −.490), and highly positive correlation with TC in males and females (r = .491, r = .457) table (9). Ferritin revealed high positive correlation with ALT, AST, ALP and **TB** in male (r = .446, .444, .830, .668) and females (r = .678, .528, .684, .734) respectively, while Ferritin revealed high negative correlation with ALB in males and females (r = −.711, −.579) table (10). In table (11) ferritin showed negative correlation with HDL in males and females (r = −.668, −.692), while showed positive correlation with LDL, TC, TG in males (r = .628, .687, .620) and females (r = .416, .778, .704) (see Table 12).

## Discussion

In the present study there were high increase in AST, ALT, ALP enzyme in fatty liver patients and this corresponded with (McPherson et al., 2010) explain presence this elevated of liver enzyme evidence for fibrosis in fatty liver. In our study significant increase found in total cholesterol, triglycerides and that in agreement with (El Nakeeb et al., 2017) they investigation strong correlation between obese fatty liver patients and hypercholesterolemia. In our result found high increase of copeptin in serum and high association with liver enzyme and lipid profile, also we showed association of copeptin with obesity and many studies

*Table 9. Study correlation of copeptin with Lipid Profile Test (LPT) in males and females obesity patients with presence of fatty liver disease.*

| sex | Parameters | Copeptin | HDL | LDL | TC |
|---|---|---|---|---|---|
| males | HDL mg\dl | −.508** | | | |
| | LDL mg\dl | −.306 | −.620** | | |
| | TC mg\dl | .491* | −.096 | .086 | |
| | TG mg\dl | .102 | −.436 | −.029 | .199 |
| Females | HDL mg\dl | −.490* | | | |
| | LDL mg\dl | .043 | −.26 | | |
| | TC mg\dl | .457* | −.347 | .157 | |
| | TG mg\dl | .130 | −.281 | −.079 | −.077 |

HDL: High density lipoprotein; LDL: Low density lipoprotein: TC: Total cholesterol: TG: Triglyceride.

demonstrated the function of copeptin in lipid and glucose metabolize that observed elevated copeptin level associated with increased risk of metabolic and cardiovascular diseases (Taveau et al., 2015). Highly association found between copeptin and BMI of obese individual and this agree with (Barchetta et al., 2019) showed value of copeptin increased with fatty liver obese individuals. In a different study, serum copeptin was employed as a predictive biomarker for either acute or chronic liver failure (ACLF) and the mortality in patients because it plays a role in the pathogenesis and development of disease, indicators of hemodynamic systemic disturbance, such as the hepatic venous pressure gradient "HVPG", that associated with organ failure. According to the recent study High levels of serum copeptin have been associated with hemodynamics disorder, such as decreased cardiac output and portal hypertension (>12 mmHg) (Kerbert et al., 2015), numerous additional factors, including hyperosmolarity, physiological and psychological stress, and drugs, may also have an impact on copeptin levels i.e beta blockers, vasopressors and diuretics. Until now, a few researches have looked into the prognostic copeptin in the context of liver disease, and these studies demonstrated increase the severity of liver

*Table 8. Correlation of copeptin with liver function test (LFT) in males and females obesity patients with presence of fatty liver disease.*

| Sex | Parameters | Copeptin | ALT | AST | ALP | Total protein (TP) | Albumin (ALB) |
|---|---|---|---|---|---|---|---|
| Males | ALT u\l | .543** | | | | | |
| | AST u\l | −.014 | .227 | | | | |
| | ALP u\l | .280 | −.174 | −.096 | | | |
| | Total protein (TP) | −.101 | .005 | −.047 | .449* | | |
| | Albumin(ALB) gm\dl | .066 | .401 | .111 | .116 | .194 | |
| | Total Bilirin(TB) gm\dl | .247 | −.098 | .368 | .138 | −.022 | −.326 |
| Females | ALT u\l | .030 | | | | | |
| | AST u\l | −.145 | .268 | | | | |
| | ALP u\l | −.249 | .168 | −.073 | | | |
| | Total protein (TP) | −.235 | −.071 | −.050 | .672** | | |
| | Albumin(ALB) gm\dl | −.194 | .069 | .022 | .389 | .488* | |
| | Total Bilirin(TB) gm\dl | .242 | .070 | −.365 | .188 | .236 | .009 |

*Table 10. Correlation of Ferritin with Liver Function Test (LFT) in males and females obesity patients with presence of fatty liver disease.*

| sex | Parameters | Ferritin | ALT | AST | ALP | Total protein (TP) | Albumin (ALB) |
|---|---|---|---|---|---|---|---|
| Males | ALT u\l | .446* | | | | | |
| | AST u\l | .444* | .583** | | | | |
| | ALP u\l | .830** | .389* | .439* | | | |
| | Total protein (TP) | −.129 | −.258 | −.305 | .004 | | |
| | Albumin(ALB) gm\dl | −.711** | −.548** | −.619** | −.638** | .421* | |
| | Total Bilirin(TB) gm\dl | .668** | .537** | .717** | .663** | −.348 | −.854** |
| Females | ALT u\l | .678** | | | | | |
| | AST u\l | .528** | .666** | | | | |
| | ALP u\l | .684** | .561** | .513** | | | |
| | Total protein (TP) | −.056 | −.272 | −.276 | .232 | | |
| | Albumin(ALB) gm\dl | −.579** | −.597** | −.685** | −.528** | .451* | |
| | Total Bilirin(TB) gm\dl | .734** | .671** | .694** | .707** | −.251 | −.865** |

*Table 11. Correlation of Ferritin with Lipid Profile Test (LPT) in males and females obesity patients with presence of fatty liver disease.*

| sex | Parameters | Ferritin | HDL | LDL | TC |
|---|---|---|---|---|---|
| males | HDL mg\dl | −.668** | | | |
| | LDL mg\dl | .628** | −.712** | | |
| | TC mg\dl | .687** | −.809** | .777** | |
| | TG mg\dl | .620** | −.896** | .801** | .824** |
| Females | HDL mg\dl | −.692** | | | |
| | LDL mg\dl | .416* | −.500** | | |
| | TC mg\dl | .778** | −.886** | .552** | |
| | TG mg\dl | .704** | −.856** | .514** | .768** |

HDL: High density lipoprotein; LDL: Low density lipoprotein: TC: Total cholesterol: TG: Triglyceride.

*Table 12. The effect of age and BMI in both male and female's obesity patients with presence of fatty liver disease comparison to control.*

| sex | parameters | sample | N | Mean | S. E | t- test | p.v |
|---|---|---|---|---|---|---|---|
| male | Age | Control | 10 | 44.90 | 4.87 | .425 | .674 |
| | | patients | 20 | 42.50 | 3.17 | | |
| | BMI ≥30 | Control | 10 | 23.94 | .52 | −9.103 | .000 |
| | | patients | 20 | 36.14 | .90 | | |
| female | Age | Control | 10 | 40.70 | 4.66 | −.746 | .462 |
| | | patients | 20 | 44.55 | 2.82 | | |
| | BMI ≥30 | Control | 10 | 23.99 | .37 | −13.761 | .000 |
| | | patients | 20 | 39.88 | .79 | | |

disease is correlated with serum copeptin levels that called Child-Pugh class (Kerbert et al., 2016). Additionally, circulating copeptin concentration was found to predict short- and long-term transplant death in individuals with various stages of cirrhosis., as well as a prospective study demonstrated plasma copeptin's capacity to anticipate the emergence of cirrhosis related complications and death within three months of hospitalization (Katan et al., 2008). In our study high correlation between copeptin level and BMI that may related to insulin resistant in obese people (Tenderenda-Banasiuk et al.) This result in agreement with (Tuli et al., 2021) found strong association between increase copeptin levels and obesity, also relationship cardiovascular risk factor (Sofia Enhörning et al., 2011) revealed in his study positive correlation between elevated plasma copeptin concentration and metabolic syndrome in obese children (Refardt et al., 2019). Our result correspond to (Sofia Enhörning & Malan, 2019) they revealed strong correlation between high copeptin and non-alcoholic fatty liver disease (NAFLD). That similar to (S. Enhörning et al., 2013) demonstrated biopsy-proven from obese patients with non-alcohol fatty liver disease (NAFLD) most higher in copeptin level than both non-obese individuals or obese patients without NAFLD. When fatty liver is known to be metabolic syndrome, associations between copeptin and impaired glucose tolerance and measures of obesity that mean increased copeptin is regarded as a risk factor for the onset of diabetes and the metabolic syndrome. (Sofia Enhörning et al., 2011). Our research found ferritin level high increase in obese fatty liver disease compared to intact non obese individuals this increase may be related to disturbed glucose, lipid, and iron metabolism that similar to what found by (Mohammed et al., 2020) hyperferritinemia, and advanced fibrosis have been linked to obesity, insulin resistance (IR), and cardiovascular disease, all of which are disorders inherently related to NAFLD. Other study suggested that strong correlation between increased serum ferritin concentration and the metabolic syndrome including fatty liver (Nelson et al., 2011). Also found significant correlation between ferritin and BMI, ALT, AST and ALP the same result found by (El Nakeeb et al., 2017).

## Conclusion

Our study demonstrates that elevated copeptin levels in obese individuals high associated with liver enzyme, lipide profile, and ferritin accumulation which means increased copeptin concentration associated with fatty liver disorder and other

metabolic diseases such as diabetes mellitus, we need more studies to confirm that.

## Funding

No finding.

## Authors contributions

All authors contributed to collecting the data drafted the results, drafted the manuscript and all authors revised the manuscript.

## Ethics

We confirm that all the Figures and Tables in the manuscript is ours. Authors sign on ethical consideration's approval-Ethical Clearance: The local ethical committee approved the project in AL-Hussein Teaching Hospital.

## Conflicts of interest

There are no conflicts to report.

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