May hepatic steatosis be associated with gynecomastia and epicardial fat? A retrospective study of 599 male patients

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Abstract

Objective

There is no study in the literature investigating the association of hepatic steatosis with both gynecomastia and epicardial fat thickness together. We aimed to determine the correlations between hepatic steatosis through liver density, gynecomastia and epicardial fat thickness in patients undergoing CT scans due to suspected COVID-19 symptoms.

Methods

A total of 599 male patients who underwent chest CT scans due to a presumed diagnosis of COVID-19 in our radiology clinic were included in the study. Patients’ age, diameters of the subareolar glandular tissues of the right and left breasts, the right retroareolar fatty tissue, liver and spleen density, epicardial fat thickness and biochemical parameters were recorded and analyzed. The laboratory analyses were performed according to the standard methods.

Results

The mean age of the patients was 47.21±15.00 years. The left subareolar tissue thickness and the right retroareolar fatty tissue thickness that are used to indicate the presence of gynecomastia were found to be significantly correlated with liver density in negative direction (r=−.137, p<0.001; r=−.172, p<0.001; respectively). Epicardial fat thickness was statistically significantly correlated with right subareolar tissue thickness (r=.085, p=0.037), left subareolar tissue thickness (r=.101, p=0.014) and right retroareolar fatty tissue thickness (r=.148, p<0.001).

Conclusion

The results of this study showed that gynecomastia was significantly correlated with both age and hepatic steatosis. Epicardial fat thickness was also associated with liver steatosis. We demonstrated the significant correlations between epicardial fat thickness and gynecomastia for the first time. Nevertheless, our results need to be confirmed by further comprehensive studies.

Introduction

Hepatic steatosis, also known as fatty liver disease, refers to the accumulation of triglycerides within cytoplasmic vesicles of hepatocytes. Hepatic steatosis is associated with liver damage ranging from simple steatosis to liver fibrosis, cirrhosis and hepatocellular carcinoma (1). Numerous risk factors of developing hepatic steatosis have been identified, including diabetes mellitus, insulin resistance, obesity, dyslipidemia, hypertension and alcohol overuse (2). The prevalence of hepatic steatosis has been
reported between 3%-39% due to variable and subjective diagnostic criteria (3, 4). Several imaging modalities such as ultrasound, CT and MRI can show changes in hepatic steatosis in a non-invasive manner. CT can provide more objective measurement of liver density, thus hepatic steatosis (5). Non-contrast CT scan can detect hepatic steatosis with a sensitivity of 82% and specificity of 100% (6).

Gynecomastia is the benign proliferation of breast glandular tissue in men. It is the most common male breast abnormality and is thought to develop due to a hormonal imbalance through multiple mechanisms (7). Gynecomastia can be physically disturbing, causing psychological distress and may have negative effects on body image and self-confidence. Glandular tissue of ≥2 cm in the subareolar area is generally accepted as gynecomastia (8). The prevalence of gynecomastia has been reported between 32-65% depending on the diagnostic method, age and lifestyle (9). However, the actual incidence of gynecomastia in the general population is not clear, because most of these patients are asymptomatic and breast screening is not routinely performed in men. The widespread use of CT for other indications results in gynecomastia to be reported commonly as an incidental finding on thoracic CT (10). Some studies have reported that hepatic liver disease is among the risk factors of developing gynecomastia (11). Patients with hepatic steatosis often have high estrogen and low testosterone levels that clinically manifest as testicular atrophy, palmar erythema and gynecomastia (12). However, the exact mechanism through which hepatic steatosis can contribute to the development of gynecomastia has yet to be clarified.

On the other hand, the severity of hepatic steatosis has been associated with epicardial fat thickness, which is a marker of visceral fat (13). Hepatic steatosis may coexist and interplay with epicardial fat. Quantification of epicardial fat thickness can be easily obtained with multislice CT. Measurement of the epicardial fat thickness on CT is performed using regions of interest (ROIs) on short axis views (14). To our best knowledge, there is no study in the literature investigating the association of hepatic steatosis with both gynecomastia and epicardial fat thickness. In this study, we aimed to determine the correlations between hepatic steatosis through liver density, gynecomastia and epicardial fat thickness in patients undergoing CT scans due to suspected COVID-19 symptoms.

**Material And Methods**

Before the beginning, this retrospective study was approved by the local ethical committee of our hospital (2/2021.K-49). The study was conducted in accordance with the ethical principles of 1964 Declaration of Helsinki and its later amendments.

A total of 599 male patients who underwent chest CT scans due to a presumed diagnosis of COVID-19 in our radiology clinic between 2018 and 2021 were included in the study. Female patients, those with established heart disease, hepatic failure, renal failure, active infection, malignancy, chronic systemic inflammatory disease and patients with missing data were excluded from the study. Patients’ age, diameters of the subareolar glandular tissues of the right and left breasts, diameter of the right retroareolar fatty tissue, liver density, spleen density, epicardial fat thickness and biochemical parameters
including fasting blood glucose, the levels of cholesterol, triglycerides, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) were recorded and analyzed.

Blood samples were collected from the patients after a 12-h fasting for laboratory analysis of fasting blood glucose, cholesterol, triglycerides and liver enzymes. The laboratory analyses were performed according to the standard methods.

**Ct Examinations**

All images were taken using a 160-slices 320-row area detector CT device (Aquilion Prime ONE 320, Toshiba Medical Systems). CT protocols were performed at 120 kV, 100-200 mA and reconstructed at a slice thickness of 1 mm. The diagnosis of gynecomastia was established as a glandular tissue diameter (long axis of the area showing increased density) ≥ 2 cm at the nipple level in the axial plane or a glandular tissue diameter between 1-2 cm accompanied by vertical growth consistent with gynecomastia. The measurements of axial diameters were made separately for both breasts (Figure 1). Hepatic steatosis was defined as a liver density at least 10 Hounsfield Units (HU) smaller than the spleen density or a liver density < 40 HU as measured on CT images (Figure 2). Epicardial fat thickness was measured from the visceral epicardium to the outside of the myocardium, and perpendicular to the surface of the heart on the axial section in millimeters (Figure 3).

**Statistical Analysis**

All statistical analyses were performed with SPSS 25.0 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) software. Continuous variables were expressed as mean±standard deviation, while categorical variables were given as frequency (n) and percentage (%). Normal distribution of the data was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Statistical correlations between hepatic steatosis, gynecomastia, epicardial fat and laboratory parameters were examined with Pearson's correlation analysis (r).

**Results**

A total of 599 male patients with a diagnosis of gynecomastia were included in the study. The mean age of the patients was 47.21±15.00 years. Age distribution of the gynecomastia patients is shown in Figure 1.

When parameters of epicardial fat were examined; the mean diameter of right subareolar granular tissue was measured as 12.27±5.95 mm, the mean diameter of left subareolar granular tissue as 14.70±7.07 mm and the mean diameter of right retroareolar fatty tissue as 18.29±9.55 mm.
The mean liver density of the patients was measured as 51.03±10.85 HU and the mean spleen density as 48.12±8.06 HU. The mean epicardial fat thickness was measured as 5.91±3.88 mm. Laboratory findings of the biochemical parameters are shown in Table 1.

| Biochemical parameter      | Mean  | ± SD   |
|---------------------------|-------|-------|
| Cholesterol               | 122.13| 33.59 |
| Triglycerides             | 130.27| 80.78 |
| Fasting Blood Glucose     | 113.85| 40.78 |
| AST                       | 37.37 | 268.74|
| ALT                       | 50.45 | 310.62|
| ALP                       | 88.51 | 147.88|
| GGT                       | 66.30 | 112.73|

AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyltransferase; SD: standard deviation

The correlations between gynecomastia, hepatic steatosis, epidural fat thickness and biochemical parameters were evaluated with Pearson's correlation analysis. Accordingly, age was found to be positively correlated with the left subareolar glandular tissue diameter (r=.113, p=0.05), and right retroareolar fatty tissue diameter (r=.116, p=0.04), and epicardial fat thickness (r=.189, p<0.001) and negatively correlated with spleen density (r=-.125**, p=0.002). Statistically significant strong correlations were found between right subareolar tissue thickness, left subareolar tissue thickness, right retroareolar fatty tissue thickness, liver density, spleen density and epicardial fat thickness (Table 2).
Table 2
Correlations between the study parameters

|                                | Right subareolar tissue thickness | Left subareolar tissue thickness | Right retroareolar fatty tissue thickness | Liver density | Spleen density | Epicardial fat thickness |
|--------------------------------|----------------------------------|---------------------------------|------------------------------------------|---------------|----------------|--------------------------|
| Right subareolar tissue thickness | r 1                              | .524**                          | .304**                                   | 0.004         | -0.032         | .085*                    |
|                                | p <0.001                          | <0.001                          | 0.929                                    | 0.441         | 0.037          |                          |
| Left subareolar tissue thickness | r .524**                          | 1                               | -0.43                                    | -.137**       | -0.009         | .101*                    |
|                                | p <0.001                          | 0.299                           | 0.001                                    | 0.827         | 0.014          |                          |
| Right retroareolar fatty tissue thickness | r .304**                          | -0.43                           | 1                                        | -.172**       | -.064          | .148**                   |
|                                | p <0.001                          | 0.299                           | <0.001                                   | .116          | <0.001         |                          |
| Liver density                  | r 0.004                           | -.137**                         | -.172**                                  | 1             | .278**         | .178**                   |
|                                | p 0.929                           | 0.001                           | <0.001                                   | <0.001        | <0.001         |                          |
| Spleen density                 | r -0.032                          | -0.009                          | -.064                                    | .278**        | 1              | -.003                    |
|                                | p 0.441                           | 0.827                           | .116                                     | <0.001        | 0.947          |                          |
| Epicardial fat thickness       | r .085*                           | .101*                           | .148**                                   | .178**        | -.003          | 1                        |
|                                | p 0.037                           | 0.014                           | <0.001                                   | <0.001        | .947           |                          |

On the other hand, liver density showed a strong positive correlation with cholesterol (r=.262, p<0.00) and a strong negative correlation with triglycerides (r=-.122, p=0.004), while spleen density was strongly correlated with cholesterol (r=.194, p<0.001), AST (r=.235, p<0.001) and ALT (r=.232, p<0.001) in positive direction. No statistically significant correlation was observed between the other study parameters.

**Discussion**

Currently ongoing COVID-19 pandemic, has led to an increase in the number of CT scans performed due to a presumed diagnosis of pneumonia worldwide (8). This has caused various diseases and/or medical conditions to be noticed incidentally in CT examinations (15, 16, 17). On the other hand, this situation could be seen as an opportunity to retrospectively examine the relationships between various parameters through these CT scans with more objective measurements. In the present study, we investigated the correlations between hepatic steatosis as determined on CT images of male patients who underwent chest imaging due to suspected COVID-19, gynecomastia and epicardial fat thickness.
In the present study, the mean age of patients with gynecomastia was found as 47.21 years. Kim et al. reported the mean age as 56.99 years in 650 male patients with gynecomastia (9). Aslan et al. reported the most common age group with gynecomastia as 30-39 years (8). This range was 36-55 years in our study, although age ranges were different between the two studies general ranges were similar. Similar to our study, Aslan et al. examined CT images of male patients who were admitted during the coronavirus disease-2019 (COVID-19) pandemic to determine the prevalence of gynecomastia. The authors found significant correlations between age, right breast glandular tissue diameter ($r=.235, p<0.001$) and left breast glandular tissue diameter ($r=.219, p<0.001$) (8). In the present study, age was found to be positively correlated with the left subareolar glandular tissue diameter ($r=.113, p=0.05$), and right retroareolar fatty tissue diameter ($r=.116, p=0.04$) (Figure 2). These findings suggest a relationship between age and gynecomastia, possibly due to decreased testosterone levels with ageing.

Studies investigating the relationship between liver disease and gynecomastia have reported conflicting results. Hepatic steatosis has been associated with low testosterone and high estrogen levels, diminished libido and gynecomastia, which is the most common benign condition characterized by enlargement of the male breast (18). Furthermore, there are studies reporting that testosterone administration to cyrrhotic patients has decreased the prevalence of gynecomastia (19). However, others could not find such a relationship and proposed that breast tissue sensitivity to a raised ratio of estrogen/testosterone is highly variable (11). In the present study, the left subareolar tissue thickness and the right retroareolar fatty tissue thickness that are used to indicate the presence of gynecomastia were found to be significantly correlated with liver density in negative direction ($r=-.137, p<0.001; r=-.172, p<0.001$; respectively) suggesting a relationship between hepatic steatosis and gynecomastia. Nevertheless, there is no sufficient data in the literature to draw a definitive conclusion on this issue and mechanisms of such a potential correlation are yet to be clarified.

Epicardial fat accounts for 20% of heart weight and constitutes 80% of the heart's surface. Although it is a relatively neglected component of the heart, it has been proposed as a marker of cardiovascular risk (20, 21). On the other hand, previous studies have reported the relationship of epicardial fat thickness with various diseases and medical conditions. Shemirani et al. reported a correlation between epicardial fat thickness and the severity of coronary artery disease (22). Metwally et al. observed elevated epicardial fat thickness in pediatric patients with congenital adrenal hyperplasia (23). According to Petta et al., in patients with non-alcoholic fatty liver disease (NAFLD), a higher epicardial fat thickness is associated with the severity of the disease (13). Iacobellis et al. reported that epicardial fat thickness is a good indicator of hepatic steatosis in obese patients (24). Results of our study indicated a strong correlation between epicardial fat thickness and liver density, which is used to determine the presence of hepatic steatosis ($r=.178, p<0.01$).

Although epicardial fat thickness is known to be closely associated with fat deposition, no study could be found to investigate its correlation with fat proliferation in men's breasts, namely gynecomastia. In the present study, epicardial fat thickness was statistically significantly correlated with right subareolar tissue thickness ($r=.085, p=0.037$), left subareolar tissue thickness ($r=.101, p=0.014$) and right retroareolar fatty
tissue thickness \( r = .148, p<0.001 \). However, the mechanisms underlying these correlations are yet to be clarified.

**Study Limitations**

Major limitations of this study include its retrospective design and being performed in a single center. In addition, the same correlations could be investigated between obese and non-obese patients as epicardial fat thickness is closely associated with obesity. Finally, our results on the correlation between epicardial fat thickness and gynecomastia could not be compared due to the lack of similar studies. On the other hand, the number of our patients is relatively large and we examined the associations between hepatic steatosis, gynecomastia and epicardial fat thickness together, as the first time in the literature.

**Conclusion**

The results of this study showed that gynecomastia was significantly correlated with both age and hepatic steatosis. However, currently there is no clear data especially on the relationship between hepatic steatosis and gynecomastia. In addition, epicardial fat thickness was also associated with liver steatosis. On the other hand, we demonstrated the significant correlations between epicardial fat thickness and gynecomastia for the first time. Nevertheless, our results need to be confirmed by further comprehensive multi-center studies with a larger series of patients.

**Declarations**

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**Conflict of Interest:** Authors reported no conflict of interest to disclose.

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**Data Availability:** Data used in this study are included in the manuscript.

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Figures

Figure 1

Measurements of gynecomastia parameters on CT sections: right subareolar glandular tissue diameter (left), left subareolar glandular tissue diameter (middle) and right retroareolar glandular tissue diameter (right).
Figure 2

Measurements of hepatic steatosis parameters on CT images in Hounsfield Units (HU): liver density (left), spleen density (right).

Figure 3

Measurement of epicardial fat thickness from the visceral epicardium to the outside of the myocardium.
Figure 4

Distribution of the patients by age groups.

Figure 5

Correlations between age and glandular tissues of the left and right breasts