
ORIGINAL RESEARCH ARTICLE**Pleural Fluid Glucose – Routine but Vital Biochemical Parameter for
Differential Diagnosis of Effusions**

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Abstract

Biochemical parameters in pleural fluid are usually done to identify the cause of pleural effusion. Differentiating the effusion into either transudative or exudative is a logical first step, with further investigations dictated by the clinical features and these results. Light's criteria and other biochemical parameters help to obtain a result for differentiating the effusion. Not a single laboratory value will draw a conclusion of being the effusion as transudative or exudative, hence combining number of biochemical test will help to obtain a definitive result.

Pleural glucose measurement is routine and age old parameter used to identify cause of pleural effusion. In this review we tried to evaluate the usefulness of pleural glucose in effusion. In country like India, where all routine and specialized biochemical parameters may not be available for identifying the specific cause of effusion, the estimation of pleural glucose may help to draw an initial approach for classifying an effusion.

Key Words:

Pleural effusion, glucose, Light's criteria, Exudate, Transudate

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Introduction:

The pleura comprise two thin layers of a tissue that protects and cushions the lungs. The inner layer (visceral pleura) wraps around the lungs. The outer layer (parietal pleura) lines the inside of the chest wall and diaphragm. A liquid, called pleural fluid, lubricates the pleural cavity so that the two layers of pleural tissue can slide against each other. Pleural fluid is an ultra-filtrate of plasma. Usually there is less than 10 ml of fluid in each pleural cavity.⁽¹⁾ (Approximately 1 ml of fluid). Pleural fluid is filtered from the systemic capillaries in the parietal pleural compartment through pressure gradient into the pleural space.

Pleural fluid is secreted into the pleural space and is greatest at the apex while absorption is maximum towards the diaphragm and mediastinum, where more lymphatic are located. The fluid is drained out predominantly through the stomata of the parietal lymphatic present between the parietal mesothelial cells. These small lymphatic

ultimately drains into the mediastinal lymph nodes. This lymphatic drainage is capable to drain up to several hundred millilitres of additional fluid per day without the development of an effusion.

Normal pleural fluid has the following characteristic:

- Clear ultra-filtrate of plasma that originates from the parietal pleura
- A pH of 7.60 – 7.64
- Glucose content similar to that of plasma
- Protein content of less than 2 % (1-2 g/dL)
- Lactate dehydrogenase (LDH) less than 50 % of plasma
- Fewer than 1000 white blood cells (WBCs) per cubic millimetre

Pleural effusion, also called “water on the lungs”, is an excessive build-up of fluid in the pleural space resulting from excess fluid production and/or decreased absorption.

Fluid production is increased if there is:

- i. Elevation of the hydrostatic pressure gradient (e.g. in congestive cardiac failure, portal hypertension)
- ii. A decreased in colloid osmotic pressure (e.g. in hypoproteinemia)
- iii. Increased permeability of the capillary vessels (e.g. in infection, malignancy, inflammation)

Fluid removal is decreased if there is:

- i. Impaired lymphatic drainage (e.g. in some neoplasm)
- ii. Decreased pressure in the pleural space (e.g. in bronchial obstruction, atelectasis)

Pleural fluid is one of the common body fluid that is submitted for biochemical analysis. Thoracentesis are always performed for new and unexplained pleural effusions when sufficient fluid is present to allow a safe procedure. When pleural fluid is sent for examination, the laboratory is often asked to determine whether it is a transudate or an exudate. Transudate, which is formed from ultrafiltration across a membrane, has low protein content, whereas exudates are formed by active secretion or leakage and has high protein content. The presence of a transudate effusion signifies a non-inflammatory process

caused by a disturbance of hydrostatic or colloid osmotic pressure with no pleural disease involvement. In contrast, an exudate signifies involvement of the pleura by an inflammatory or malignant process causing increased capillary permeability.

The initial diagnostic consideration while dealing with a pleural effusion is to distinguish it into either transudates or exudates. Looking back into the history of biochemical analysis of pleural fluid, glucose was one of the important biochemical parameter to be analysed. To our knowledge, the first documented research article on estimation of sugar in pleural fluid was published in 1929. ⁽²⁾Subsequently numerous authors ^(3 - 11) has determined the diagnostic value of sugar in pleural effusions. Hence, sugar was the first biochemical parameter to be analysed in evaluation of pleural fluid, which was the followed by estimation of protein. ⁽¹²⁾However, these initial parameters fails to clearly distinguish the effusion into transudate and exudate.

Although a number of biochemical tests have been proposed to distinguish transudate from exudate, the criteria proposed by Light *et al* ⁽¹³⁾ have become the standard criteria (Table 1).

Table 1:

Pleural fluid is classified as exudate if any of the following criteria are met:

	Light's Criteria
1.	Pleural fluid to serum protein ratio greater than 0.5
2.	Pleural fluid to serum LDH ratio greater than 0.6
3.	Pleural fluid LDH level greater than two thirds normal serum value

Light's criteria requires measurement of both pleural and serum protein and LDH. However, a meta-analysis of 8 studies with 1448 patients suggest that the following combined pleural fluid measurements may have sensitivity and specificity comparable to the criteria proposed Light's *et al* for identifying exudates.⁽¹⁴⁾

- Pleural fluid LDH value greater than 0.45 of the upper limit of normal serum values
- Pleural fluid cholesterol level greater than 45 mg/dL
- Pleural fluid protein level greater than 2.9 g/dL

The criteria proposed by Light *et al* and these alternative criteria distinguish nearly all exudates from transudates correctly, but they misclassify approximately 20 – 25 % of transudates as exudates, usually in the patients of long – term diuretic therapy for congestive cardiac failure (because of the concentration of protein and LDH within the pleural space due to diuresis).⁽¹⁵⁾ Using the criteria of serum

minus pleural protein concentration level of less than 3.1 g/dL will more correctly identifies exudates in these patients. Although pleural fluid albumin is not typically measured, a gradient of serum albumin to pleural fluid albumin of less than 1.2 g/dL will also identify exudates in these patients.⁽¹⁶⁾

In 2006, Muller T and Haltmayer I⁽¹⁷⁾ found that serum and pleural fluid N-terminal pro-brain natriuretic peptide (NT-proBNP) was increased in pleural fluid of patients with congestive cardiac failure. The value above 4000 ng/L was found to have sensitivity and specificity of 90 and 93% respectively, and hence may help to confirm heart failure as the cause of an otherwise idiopathic chronic effusion.

Pleural Fluid Glucose:

Glucose measurement is commonly requested on pleural fluid samples. Many times the sample is often sent without fluoride oxalate preservative and simultaneous serum glucose is rarely measured. In addition to previously discussed tests, glucose should be

measured during the initial thoracentesis. A glucose concentration greater than 95 mg/dL is nearly always associated with a transudate. Lower concentrations are reported in exudates with infections and in malignancy but the glucose concentration is extremely variable in exudates overlapping many diseases.^(18, 19)

At the initial stages for the diagnostic value of glucose in pleural effusions, these authors⁽²⁻¹¹⁾ have used either Folin – Wu^(20,21) or Hagedorn – Jensen⁽²²⁾ method or the method is not mentioned. These methods are not specific for estimation for glucose and they calculate total reducing sugars and reducing substances present in the given body fluid. Hence they give apparent glucose value rather than true glucose value. With the establishment of other specific methods like glucose oxidase and peroxidase,⁽²³⁾ the results obtained were of true glucose.

Although numerous biochemical parameters are studied for differential diagnosis of exudates, only few are measured for transudates. As stated earlier, pleural glucose concentration in transudate is same as that of blood glucose level; however, uric acid⁽²⁴⁾ concentration is increased in transudates as compared to exudates. The capillary bed of the lungs is comprised of non-specific tissues, which have small pores that admit molecules upto a molecular weight of 1000.⁽²⁵⁾ Thus,

glucose molecule with a molecular weight of 180 should easily pass between the pleural fluid and plasma. If there were no block in the transport of glucose from the blood to the pleural cavity, the pleural fluid glucose concentration should remain at the same level as that in plasma. Hence the pleural glucose level in transudate is same as that of plasma.⁽²⁵⁾

The documented causes of decreased glucose levels in pleural effusions are due to inflammatory disorders like tuberculosis, malignancy, parapneumonic effusion, rheumatoid pleurisy, esophageal rupture and empyema.^(18, 19, 26 - 32) Other rare causes are paragonimiasis, haemothorax, the Churg – Strauss syndrome and occasionally lupus pleuritis.⁽³²⁾

Tuberculous and malignant effusion has pleural glucose level below than 60 mg/dL.⁽³²⁾ There are two reasons suggested for this. These are over-utilization of glucose by pleural fluid and pleural thickening causing transport defect of glucose. There occurs acidosis of pleural fluid in tuberculous and malignant effusion and the cause of this acidosis is the accumulation of lactic acid and dissolved carbon dioxide as the end product of glucose metabolism.⁽³³⁾ Acidic effusions have low glucose and pH and high lactate.^(26, 27, 34) Sources of metabolic end product are

leucocytes, pleural cells, bacterial and malignant cells. ^(26, 33, 35, 36)

Further Sakchai Limthongkulet *al* ⁽³⁷⁾ stated that in tuberculous and malignant effusion, there is overproduction of lactic acid and carbon dioxide due to over-utilization of glucose and oxygen. The decreasing pleural fluid pH and increasing pleural fluid carbon dioxide has a significant linear relationship with decreasing PO₂, increasing protein and decreasing glucose in pleural fluid. These indicated a leakage of serum protein into the pleural cavity and the over-utilization of glucose relative to transport defect of low pleural fluid glucose concentration in the acidotic fluid of tuberculous and malignant effusion. ⁽³⁸⁾ A de Pablo *et al* ⁽³⁹⁾ stated that patient with residual pleural thickening more or equal to 10 in tuberculosis had a significantly low glucose level.

Light RW *et al* ⁽²⁷⁾ stated that patients with complicated parapneumonic effusion have low glucose and pH and high LDH. Patients with pleural fluid glucose 40 mg/dL and pH below 7.0 had complicated parapneumonic effusion and immediate tube thoracotomy should be done. Pleural glucose above 40 mg/dL either had a complicated or uncomplicated parapneumonic effusion. Sahn and Light ⁽⁴⁰⁾ proposed that if the pleural pH is above 7.30, glucose 60 mg/dL and LDH value

below 1000 IU/L, the the parapneumonic effusion is uncomplicated and surgical drainage is not necessary.

A low level of pleural glucose is always seen in empyema with very low level occurs with some frequency. ^(41, 42) The predominant mechanism for this is increased utilization of glucose by the constituent of the pleural fluid, namely, multiplying bacteria and phagocytosing leukocyte. ⁽⁴¹⁾ A relative block to the influx of glucose into the pleural membrane may also play a role. ⁽²⁸⁾

Very low level of pleural glucose i.e. less than 10 mg/dL is almost seen in rheumatoid effusion. ⁽⁴³⁾ This is because the pleural fluid glucose concentration in acidotic pleural fluid correlates with the degree of pleural fluid acidosis rather than the disease state itself. ⁽⁴⁴⁾ While Light RW ⁽⁴⁵⁾ have suggested that accumulation of glucose end product resulting from pleural metabolism probably contributes to the low pH of rheumatoid effusion, it appears that the efflux block to H⁺ by the rheumatoid pleura is a more important factor for the low level of glucose.

Some authors have suggested that pleural glucose level also indicate the outcome of pleurodesis in malignant pleural effusion. ⁽⁴⁶⁾ The pleural level of glucose below 60 mg/dL is associated with pleurodesis failure. ⁽⁴⁷⁾

Conclusion:

A vast range of biochemical tests has been put forward as being useful in the investigation of pleural fluid collections, with the dual aim of differentiating transudates from exudates and knowing the cause of effusion. In country like India, where all biochemical tests required for definitive diagnosis of effusions at a health institute may be not available, routine biochemical test including glucose may give a direction to approach the definitive diagnosis and to initiate a treatment in pleural effusions.

Pleural glucose concentration below 30 mg/dL indicates rheumatoid pleuritis or empyema and between 30 – 60 mg/dL indicates tuberculous, malignant or lupus effusion, or esophageal rupture.

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