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REVIEW ON BIOCHEMICAL ANALYSIS OF BODY FLUIDS

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ABSTRACT
Human body consists of many different types of fluids. These fluids have their own importance in maintaining body functions. Body fluids are the liquids excreted and secreted from the human body. The body fluids may contain biomarkers that are not found in blood or are at different concentration than in blood. Therefore estimation of body fluids plays an important role in the diagnosis of diseases. Some body fluids are present in healthy individuals and some are found in the disease conditions. For example, amniotic fluid is only found in pregnancy and pleural fluid is only seen in noticeable quantities in diseases. The importance obtained through using less common body fluids helps us in understanding of the disease processes. In this review paper we have focussed on the biochemical tests done on CSF, pleural, peritoneal, pericardial, synovial, amniotic fluids, tears, sweat, saliva and semen.

KEYWORDS: Body fluids, CSF, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid, amniotic fluid, tears, sweat, saliva, semen.

INTRODUCTION

Human body fluids are important sources for clinical markers. As for disease diagnosis and prognosis, advantages of body fluid testing include low invasiveness, low cost, rapid sample collection and processing. The tests in body fluids reflect the change of physiological states and cellular networks of the diseased tissue/organ. The analysis of human body fluid has become one of the most promising approaches to discover biomarkers or reveal pathophysiological mechanisms for human diseases. Human body fluid analysis is inherently challenging due to their unique characteristics such as protein complexity and wide dynamic range of protein abundances. With the remarkable advances in the methods for sample preparation, proteomics technology and quantitation, it is now possible to analyse body fluids with higher sensitivity. In the biochemistry laboratory, most routine samples that are collected for laboratory testing are blood and urine samples. Fluids such as cerebrospinal fluid, synovial fluid, peritoneal fluid and ascitic fluid are not common as compare to blood and urine samples. This is due to these fluids requiring complicated procedures to aspirate from the body. This review paper is focussed on the possible biochemical tests in body fluids.

(1) CSF

Cerebrospinal fluid (CSF) is a clear, colourless body fluid found in brain and spine produced in choroid plexuses of ventricles of the brain. CSF usually contains a small amount of protein and glucose, may also have few white blood cells. Any condition that disrupts the normal pressure or flow of CSF or the protective ability of blood brain barrier can result in abnormal results of CSF testing. CSF analysis usually involves the tests namely, colour, clarity, pressure during collection, protein and glucose CSF analysis is used to diagnose a wide variety of diseases and conditions affecting brain and spinal cord. i.e., infectious diseases such as meningitis and encephalitis haemorrhage in the brain or skull, autoimmune disorders and tumors located within the central nervous system (CNS) or that spread to CNS (metastatic cancer).

The parameters namely proinflammatory cytokines, interleukin 1β (IL1β), tumour necrosis factor α (TNFα) of the anti-inflammatory cytokine TGFβ of tau protein, a marker for neurodegeneration and of β amyloid (Aβ) can be assayed in CSF using ELISA method. The results of a study demonstrated that the increased production of the proinflammatory cytokine, TNFα and decreased production of anti-inflammatory cytokine TGFβ in patients with Mild Cognitive Impairment at risk to develop Alzheimer's disease (AD), suggesting a propensity towards inflammation in this patient group and indicating that CNS inflammation is an early hallmark in the pathogenesis of AD.[1]

Measurement of biochemical marker in CSF, such as total tau protein and β-amyloid peptide42 (Aβ42), shows robust alterations that highly correlate with the clinical diagnosis of AD but generally lack sufficient diagnostic accuracy. The diagnostic usefulness of the CSF ratio of phospho-tau to Aβ42 is superior to either measure alone and can be recommended as an aid to evaluating individuals suspected of having dementia.[2]

The results of a study suggest that the CSF concentrations of tau and phosphotau are increased in about two thirds of patients with probable AD and in half of those with possible AD but are normal in Frontotemporal dementia (FTD), subcortical arteriosclerotic encephalopathy (SAE) and Parkinson's disease (PD) compared with normal aging. Values in the normal range do not exclude AD.[3] A study was done to investigate the CSF levels of tau and the light neurofilament protein (NFL) in patients with FTD and other common dementia disorders as well as normal control subjects. No significant differences were found in CSF NFL or CSF tau when comparing patients who did and did not possess the APOE-ε4 allele within each diagnostic group. The results suggest a differential involvement of these cytoskeleton proteins in FTD and EAD, with NFL primarily involved in the pathophysiology of FTD and tau in that of EAD. The increase in CSF NFL found in LAD might reflect the white-matter degeneration found in a proportion of LAD cases.[4] Increased CSF-tau and decreased CSF-Aβ42 levels in probable and possible AD these biomarkers may have a role in the clinical workup of patients with cognitive impairment, especially to differentiate early AD from normal aging and psychiatric disorders.[5]

The discovery of mutations in the SNCA gene encoding α-synuclein in familial Parkinsonism and the accumulation of α-synuclein in the PD brain suggested a critical role for this protein in PD etiology. The levels of CSF α-synuclein oligomers were higher in patients with PD compared to patients with PSP or AD or control subjects. The results of this study demonstrated that the levels of α-synuclein oligomers in CSF and the oligomers/total-α-synuclein ratio can be useful biomarkers for diagnosis and early detection of PD.[6]

(2) Plural fluid

Pleural fluid is the fluid found between the layers of pleura, membranes that line thoracic cavity and surround lungs. The space containing fluid is known as pleural cavity or pleural space. Pleural fluid analysis is used to diagnose the cause of accumulation of fluid in chest cavity (pleural effusion). There are two types of fluid that may be produced, namely, transudate or exudate. Transudate: An imbalance between the pressure within blood vessels and the amount of protein in blood can result in accumulation of fluid. Transudates are most frequently caused by congestive heart failure or cirrhosis. If the fluid is determined to be a transudate, then usually no more tests on the fluid are necessary. Exudate: Injury or inflammation of the pleurae may cause abnormal collection of fluid. If the fluid is an exudate, then additional testing is often ordered. Exudates are associated with a variety of conditions and diseases, namely infectious diseases, bleeding, inflammatory conditions, malignancies etc. Additional testing on exudate fluid may include PF glucose, lactate, amylase, triglyceride and tumor markers.

Adenosine Deaminase (ADA) levels significantly lowers in the transudate effusions than in post-CABG, malignant and other exudative effusions. ADA levels in nontuberculous lymphocytic effusions seldom exceeded the diagnostic cut-off for TB. Effusion ADA levels cannot be predicted from total or differential leukocyte counts. Post-CABG pleural fluids had ADA levels similar to other nontuberculous lymphocytic effusions. ADA is stable in effusion fluids, and its measurement is reproducible.[7] Pleural effusion is not pathognomic and distinguishing between transudates and exudates often presents a diagnostic dilemma. The inclusion of pleural fluid NT-pro Brain Natriuretic Peptide (NT-pro BNP) measurement in the routine diagnostic panel would enhance discrimination among the different causes of pleural effusions.[8]

Virtually all patients with a newly discovered pleural effusion should undergo thoracentesis to aid in diagnosis and management. The routine peritoneal fluid evaluation usually includes the following: cell count and differential; tests for protein, LDH, glucose, ADA, cytology and, if infection is a concern, pH and bacterial and mycobacterial cultures. Natriuretic peptide assays significantly improve the accuracy of a diagnosis of cardiac pleural effusion, whereas pleural fluid mesothelin levels greater than 20 nmol/L are highly suggestive of mesothelioma.[9]

A study was conducted to determine the validity of pleural fluid C-reactive protein (CRP) concentrations and/or pleural fluid to serum CRP ratio for differentiating tuberculous pleuritis (TBP) from malignant pleural fluid (MPE) in patients presenting with lymphocytic exudative pleural effusions. Pleural fluid and serum CRP levels were significantly higher in the TBP group than in the MPE group. The ratio of pleural fluid to serum CRP was significantly higher in the TBP group than in the MPE group. A correlation between serum and pleural fluid CRP levels was observed in TBP patients but not in MPE patients. In patients presenting with lymphocytic exudative pleural effusion, a simple marker of raised pleural fluid CRP level may be helpful in discriminating between TBP and MPE.[10]

(3) Peritoneal fluid

Peritoneal fluid is a liquid made in the abdominal cavity which lubricates the surface of tissue that lines the abdominal wall and pelvic cavity. It covers most of the organs in the abdomen. An increased volume of peritoneal fluid is called ascites. The analysis is used to

diagnose the cause of peritoneal fluid accumulation (ascites) and/or inflammation of the peritoneum (peritonitis). Ninety percent of ascitic fluids are transudates and are caused by either congestive heart failure or cirrhosis. Exudates can be caused by a variety of conditions and diseases and usually require further testing to aid in the diagnosis.

Peritoneal Fluid NT-pro-BNP is a very useful biomarker with high diagnostic accuracy for distinguishing pleural effusions of cardiac origin.[11] Peritoneal fluid NT-proBNP levels were correlated with serum NT-proBNP levels. It may be useful in the diagnosis of pleural effusion resulting from heart failure. The test may be especially useful in heart failure patients with exudates who have been treated with diuretics.[12]

A significant correlation was observed between serum and Peritoneal Fluid protein levels in transudates and exudates, but the correlation between serum and pleural fluid LDH (FLDH) levels was insignificant. FLDH is the most accurate marker for the diagnostic separation of transudates and exudates and Serum to Pleural Fluid ratio of LDH (LDHR) has no role in this process. Combining total protein with FLDH appears to improve the diagnostic accuracy slightly.[13] High pleural LDH and low pleural ADA (PADA) levels are suggestive of pleural effusion due to bronchogenic carcinoma, whereas high levels of PADA alone can be indicative of tuberculous pleural effusion and high levels of both markers can show complicated parapneumonic effusions or empyema.[14] Pleural TNF-α may contribute to the identification of patients with no purulent Complicated Parapneumonic Effusions with at least the same diagnostic accuracy, if not better, than the use of pH, glucose or LDH.[15]

Activation of both the complement and kinin systems seems possible in both blood and peritoneal fluid at the low alpha 2-M concentrations found in severe attacks of acute pancreatitis.[16] During endometriosis the presence of peritoneal disease and not of ovarian endometriotic cysts, influences leptin concentrations in PF. The leptin may play a role in the development of peritoneal endometriosis, and that different biochemical phenomena might be involved in the pathogenesis of the ovarian form of the disease.[17] The ascitic fluid cholesterol determination offers an excellent, cost-effective discrimination of ascites due to cirrhosis vs. ascites caused by malignancies.[18] ADA levels are used for diagnosing tuberculosis in several locations and ADA determination is a fast and discriminating test for diagnosing peritoneal tuberculosis (PTB).[19] A study in a selected group of prevalent PD patients assessed after more than 6 months of PD therapy shows that, (1) inflammation was an independent predictor for mortality; (2) reduced TFR was associated with impaired nutritional status, decreased small solute clearance and inflammation; and (3) peritoneal transport status was not significantly associated with nutritional status and was not associated with subsequent patient survival. The results suggest that more attention should be given to inflammation and inadequate fluid removal as predictors of mortality in PD patients.[20]

(4) Pericardial Fluid

Pericardial fluid is the serous fluid secreted by the serous layer of the pericardium into the pericardial cavity. The pericardium consists of two layers, an outer fibrous layer and the inner serous layer. Pericardial fluid analysis is used to help diagnose the cause of inflammation of the pericardium called pericarditis and/or fluid accumulation around the heart (pericardial effusion). Transudates are most often caused by congestive heart failure or cirrhosis. If the fluid is determined to be a transudate, then usually no more tests on the fluid are necessary. Exudates can be caused by a variety of conditions and diseases. The blood glucose, protein or albumin may be ordered to compare concentrations with those in the pericardial fluid.

Although malignancy remains the most common cause in developed countries, tuberculosis disease should be considered in patients from areas where tuberculosis is endemic. Percutaneous pericardiocentesis remains an effective measure for the immediate relief of symptoms in patients with cardiac tamponade, although its diagnostic yield in tuberculous pericarditis is relatively low.[21] Measurement of pericardial CA 72-4 levels offered a high diagnostic accuracy for malignancy, particularly in bloody pericardial effusions. None of the biochemical parameters tested was useful for the discrimination of malignant from benign effusions. However, measurement of pericardial CA 72-4 levels in bloody pericardial effusions yielded a high diagnostic accuracy and thus offers the potential as a diagnostic tool to distinguish between malignant and benign effusions.[22]

(5) Synovial fluid

Synovial fluid is found in the cavities of synovial joints. It reduces friction between the articular cartilages of synovial joints during movement. It is used to diagnose the cause of joint inflammation, pain, swelling and fluid accumulation. The biochemical tests with synovial fluid include glucose, protein and uric acid. Synovial Fluid leptin concentrations were closely related to the radiographic severity of Osteoarthritis (OA), suggesting that synovial fluid leptin levels could be used as an effective marker for quantitative detection of OA.[23] Synovial fluid is a dynamic reservoir for proteins originating from serum, synovial tissue and cartilage. The composition of the Synovial fluid proteome may reflect the pathophysiological conditions affecting the circulatory system and cartilage. 2D-PAGE can be used under standard conditions to screen Synovial fluid samples and identify a small subset of proteins, which are potential markers associated with OA.[24]

(6) Amniotic fluid

Amniotic fluid is present in the amniotic sac. It is generated from maternal plasma and passes through the foetal membranes by osmotic and hydrostatic forces. When foetal kidneys begin to function in about week 16, foetal urine also contributes to the fluid. During pregnancy, amniotic fluid provides a cushion that protects the baby from injury and allows room for growth, movement and development. It keeps the umbilical cord from being compressed between baby and the uterine wall. The amount of amniotic fluid reflects the baby's urine output, which is an important measure of a baby's well-being.[25]

Multivariate regression analysis that controlled for maternal height, prepregnancy weight, smoking behavior, infant gender, gestational age, parity, as well as amniocentesis week showed that higher AF IGF BP1 was associated with lower birth weight. Regression analyses revealed that Amniotic fluid IGF BP3 was positively associated with birth weight within large for gestational age (LGA) and macrosomia subpopulations. These results show that 2nd trimester AF IGF BP1, BP3, and IGF II may emerge as early indicators of fetal growth.[26]

An earlier study evaluated a set of oxidative stress biomarkers in the amniotic fluid of women carrying Down syndrome (DS) fetuses that could prove in vivo the early occurrence of oxidative damage in DS. This study showed an increased level of oxidative stress, as indexed by increased protein oxidation, lipid peroxidation and reduction of GSH and Trx levels and induction of the HSP response. By a redox proteomics approach, we identified selective proteins which showed increased oxidation in DS fetuses compared with healthy controls. The identified proteins are involved in iron homeostasis (ceruloplasmin and transferrin), lipid metabolism (zinc-α2-glycoprotein, retinol-binding protein 4 and apolipoprotein A1) and inflammation (complement C9, α-1B-glycoprotein, collagen α-1V chain) with critical relevance in the clinical outcome of DS. Our results indicate that oxidative damage is an early event in the DS pathogenesis and might contribute to the development of deleterious DS phenotypes, including abnormal development and AD-like neuropathology.[27]

The oxidative stress occurs early in pregnancy and supports the idea of testing amniotic fluid whether prenatal antioxidant therapy may prevent or delay the onset of oxidative stress diseases in the DS population.[28] The amniotic fluid can be a reliable and practical source of cells for the engineering of select fetal tissue constructs.[29] Proteomic analysis of amniotic fluid cells may lead to the discovery of novel markers for embryonic abnormalities. A two-dimensional database for proteins of normal human amniotic fluid cells was constructed. The amniotic fluid cell extract was analyzed by two-dimensional gel electrophoresis and the proteins were identified by matrix-assisted laser desorption ionisation-time of flight-mass spectrometry. The database comprises 432 different gene products, which are in the majority enzymes, structural proteins, heat shock proteins, and proteins related to signal transduction. The obtained data showed that the amniotic fluid population maybe either heterogeneous, originating from different fetal compartments and embryo tissues or is still pluripotent. Many proteins which are known to belong to certain cell types were found in the amnion cell fluid. This indicates that some types of fetal cells are already differentiated at the time of amniocentesis (about the 16th week of gestation). Moreover, the finding of proteins highly expressed in embryonic stem cells suggests that amniotic fluid could be used as a cell pool for transplantation therapy.[30]

(7) Tears

Tears act as both a delivery and an excretory route for nutrients and metabolic products of the corneal epithelium and anterior stroma, since it has been shown that the diffusional route from the limbus into the avascular cornea is inadequate. Tearing, lacrimation or lachrimation is the secretion of tears, which often serves to clean and lubricate the eyes in response to an irritation of the eyes.[31] Tears formed through crying are associated with strong internal emotions such as sorrow, elation, love, awe or pleasure. The lacrimal glands secrete lacrimal fluid, which flows through the main excretory ducts into the space between the eyeball and lids. When the eyes blink, the lacrimal fluid is spread across the surface of the eye. In tears of climatic droplet keratopathy (CDK) patients, increased levels of N-glycosylated proteins including haptoglobin, polymeric immunoglobulin receptor, immunoglobulin J chain, as well as a decrease in the N-glycosylation level of one N-glycosylated protein, lacritin were observed. However, the overall levels of these five proteins showed no appreciable changes between control and CDK samples. The findings could be clinically significant in terms of disease etiology and biomarkers.[32] The human tear fluid film consists of a superficial lipid layer, an aqueous middle layer and a hydrated mucin layer located next to the corneal epithelium. The superficial lipid layer protects the eye from drying and is composed of polar and neutral lipids provided by the meibomian glands. Excess accumulation of lipids in the tear film may lead to drying of the corneal epithelium.[33]

Components of tear fluid contribute to biochemical defence system of the eye. To reveal whether the immune mediator and lipopolysaccharide binding galectin-3 is present in tears, tear samples were collected from eyes in healthy and pathological states. Investigation of expression of galectin-3 and galectin-3 reactive glycoligands in normal human conjunctival and corneal epithelia was also initiated as a step to understand the role of galectin-3 in ocular surface pathology. Galectin-3 was found only in tears from patients with ocular surface disorders. It was expressed

in normal corneal and conjunctival epithelia but not in lacrimal glands. Inflammatory leucocytes and goblet cells found in galectin-3 containing tear fluid also expressed galectin-3. Galectin-3 binding sites were detected on the surface of conjunctival and corneal epithelial cells co-localising with desmoglein. This study revealed expression of galectin-3 in tear fluid obtained from patients with eye diseases. The role of this endogenous lectin (produced by inflammatory as well as epithelial cells) in antimicrobial action and inflammation modulation could be expected.[34]

(8) Sweat

Sweat is one of the less employed biofluids for discovery of markers in spite of its increased application in medicine for detection of drugs or for diagnosis of cystic fibrosis (CF). Available data on sweat as a biological material for the diagnosis of various disorders point out several discrepancies with respect to wide variations in sample collections, methods used for analysis, uniformity in standardizations and validation of results. National audits done in the past have pointed out several lacunae with respect to variations in the performance of sweat tests. Some recent advances in sweat analysis have established its usefulness to detect drugs of abuse as well as alcohol consumption by measuring its level in sweat. Measurement techniques such as HPLC and Mass Spectroscopy have established sweat testing as very clinically useful laboratory diagnostic tools for various diseases. Screening of neonates for various disorders using sweat is also an emerging laboratory diagnostic field as it uses non-invasive technique. Sweat is also a convenient sample to screen for illicit drugs usage replacing blood and urine as testing material. Sweat is now being used to test lipids, electrolytes and for testing rare metals like mercury, lead, arsenic & cadmium as they accumulate in sweat during perspiration and is now found to be a route for elimination. Protein disorders and hormone deficiency such as cortisol could also be tested more reliably using sweat than other biological materials.[35]

(9) Saliva

Saliva and sweat are modified by CF. In both cases the chloride and sodium ion concentrations for healthy subjects and CF patients differ, this representing a possible alternative tool for CF diagnosis. Thus, saliva as a tool for CF diagnosis can be considered a new challenge and a population study including patients in all age classes needs to be performed, in different countries over the world, to extend the database to include a broad spectrum of information in order to identify normal ion concentration ranges for CF patients according to age, genotype and environment.[36]

(10) Semen

Detection and identification of semen stains, encountered at a crime scene, are very important aspects of forensic science today. This study targets the development of a non-destructive, confirmatory method for body fluid identification based on Raman spectroscopy coupled with advanced statistical analysis. Dry traces of semen obtained from multiple donors were probed using a confocal Raman microscope with a 785-nm excitation wavelength under controlled laboratory conditions. Results demonstrated the capability of Raman spectroscopy to identify an unknown substance to be semen with high confidence.[37]

CONCLUSION

The body fluids may contain biomarkers that are not found in blood or are at different concentration than in blood. Therefore estimation of body fluids plays an important role in the diagnosis of diseases. They are the important sources for clinical markers. Body fluid testing is useful for disease diagnosis and prognosis. Besides, altered protein expression profiles in body fluids reflect the change of cellular networks on the diseased tissue/organ. As the body fluid analysis is used for early detection, monitoring and mechanism of disease progression and drug efficacy, this review will be useful for the laboratory professionals.

REFERENCE

1. E Tarkowski, N Andreasen, A Tarkowski and K Blennow. Intrathecal inflammation precedes development of Alzheimer's disease. J Neurol Neurosurg Psychiatry, 2003; 74: 1200-1205.
2. Alessia Maddalena, Andreas Papassotiropoulos, Britta Muller-Tillmanns, Hans H Jung, Thomas Hegi, Roger M Nitsch and Christoph Hock. Biochemical Diagnosis of Alzheimer Disease by Measuring the Cerebrospinal Fluid Ratio of Phosphorylated tau Protein to β-Amyloid Peptide. Arch Neurol, 2003; 60(9): 1202-1206.
3. M Sjogren, P Davidsson, M Tullberg, L Minthon, A Wallin, C Wikkelso, A-K Granerus, H Vanderstichele, E Vanmechelen and K Blennow. Both total and phosphorylated tau are increased in Alzheimer's disease. J Neurol Neurosurg Psychiatry, 2001; 70: 624-630.
4. M Sjogren, L Rosengren, L Minthon, P Davidsson, K. Blennow and A Wallin. Cytoskeleton proteins in CSF distinguish frontotemporal dementia from AD. Neurology, 2000; 54(10): 1960-4.
5. Niels Andreasen, Lennart Minthon, Pia Davidsson, Eugeen Vanmechelen, Hugo Vanderstichele, Bengt Winblad and Kaj Blennow. Evaluation of CSF-tau and CSF-Aβ42 as Diagnostic Markers for Alzheimer Disease in Clinical Practice. Arch Neurol, 2001; 58(3): 373-379.
6. T Tokuda, MM Qureshi, MT Ardah, S Varghese, SAS Shehab, T Kasai, N Ishigami, A Tamaoka, M Nakagawa and OMA E Agnaf. Detection of elevated levels of α-synuclein oligomers in CSF from patients with Parkinson disease. Neurology, 2010; 75(20): 1766-72.
7. YC Gary Lee, Jeffrey T Rogers, R Michael Rodriguez, Kent D Miller and Richard W. Light. Adenosine Deaminase Levels in Nontuberculous

Lymphocytic Pleural Effusions. Chest, 2001; 120(2): 356-361.
8. Janos Tomcsanyi, Erzsebet Nagy, Miklos Somloi, Judit Moldvay, Attila Bezzegh, Bela Bozsik and Janos Strausz. NT-brain natriuretic peptide levels in pleural fluid distinguish between pleural transudates and exudates. European journal of heart failure, 2004; 6(6): 753–756.
9. Jose M Porcel. Pearls and myths in pleural fluid analysis. Respirology, 2011; 16(1): 44–52.
10. Nitipatana Chierakul, Apichart Kanitsap, Angkana Chaiprasert and Ronnachai Viriyataveekul. A simple C-reactive protein measurement for the differentiation between tuberculous and malignant pleural effusion. Respirology, 2004; 9(1): 66–69.
11. Surinder Janda and John Swiston. Diagnostic accuracy of pleural fluid NT-pro-BNP for pleural effusions of cardiac origin: a systematic review and meta-analysis. BMC Pulmonary Medicine, 2010; 10: 58.
12. Chang Hoon Han, Jung Eun Choi and Jae Ho Chung. Clinical Utility of Pleural Fluid NT-pro Brain Natriuretic Peptide (NT-proBNP) in Patients with Pleural Effusions. Internal Medicine, 2008; 47(19): 1669-1674.
13. J Joseph, P Badrinath, GS Basran and SA Sahn. Is the pleural fluid transudate or exudate? A revisit of the diagnostic criteria. Thorax, 2001; 56: 867-870.
14. Dilek Ernam , Figen Atalay, H. Canan Hasanoglu and Ozgul Kaplan. Role of biochemical tests in the diagnosis of exudative pleural effusions. Clinical Biochemistry. 2005; 38(1): 19–23.
15. Jose Manuel Porcel, Manuel Vives and Aureli Esquerda. Tumor Necrosis Factor-α in Pleural Fluid: A Marker of Complicated Parapneumonic Effusions. Chest, 2004; 125(1): 160-164.
16. Lasson A and Ohlsson K. Protease inhibitors in acute human pancreatitis. Correlation between biochemical changes and clinical course. Scandinavian Journal of Gastroenterology, 1984; 19(6): 779-786.
17. G De Placido, C Alviggi, C Carravetta, ML Pisaturo1, V Sanna, M Wilding, GM Lord and G Matarese. The peritoneal fluid concentration of leptin is increased in women with peritoneal but not ovarian endometriosis. Hum Reprod, 2001; 16(6): 1251-1254.
18. Dieter Jungst, Alexander L Gerbes, Robert Martin and Gustav Paumgartner. Value of ascitic lipids in the differentiation between cirrhotic and malignant ascites. Hepatology, 1986; 6(2): 239–243.
19. Riquelme Arnoldo, Calvo Mario, Salech Felipe, Valderrama Sebastian, Pattillo Alejandro, Arellano Marco, Arrese Marco, Soza Alejandro, Viviani Paola and Letelier Luz Maria. Value of Adenosine Deaminase (ADA) in Ascitic Fluid for the Diagnosis of Tuberculous Peritonitis: A Meta-analysis. Journal of Clinical Gastroenterology, 2006; 40(8): 705-710.
20. SH Chung, O Heimburger, P Stenvinkel, T Wang and B Lindholm. Influence of peritoneal transport rate, inflammation, and fluid removal on nutritional status and clinical outcome in prevalent peritoneal dialysis patients. Perit Dial Int., 2003; 23(2): 174-183.
21. Christopher R Gibbs, Robert DS Watson, Shyam P Singh and Gregory YH Lip. Management of pericardial effusion by drainage: a survey of 10 years' experience in a city centre general hospital serving a multiracial population. Postgrad Med J., 2000; 76: 809-813.
22. Konstantinos Karatolios, Sabine Pankuweit and Bernhard Maisch. Diagnostic value of biochemical biomarkers in malignant and non-malignant pericardial effusion. Heart Failure Reviews, 2013; 18(3): 337-344.
23. Jung Hoei Ku, Choon Key Lee, Bo Sun Joo, Byeong Min An, Seung Hyun Choi and Tae Hyun Wang Hyung Lae Cho. Correlation of synovial fluid leptin concentrations with the severity of osteoarthritis. Clinical Rheumatology, 2009; 28(12): 1431-1435.
24. Hiroshi Yamagiwa, Gobinda Sarkar, M. Cristine Charlesworth, Daniel J. McCormick and Mark E. Bolander. Two-dimensional gel electrophoresis of synovial fluid: method for detecting candidate protein markers for osteoarthritis. Journal of Orthopaedic Science, 2003; 8(4): 482–490.
25. Larsen and William J. Human embryology (3.ed.). Philadelphia, Pa: Churchill Livingstone, 2001; 490.
26. Daniel K. Tisi, Xu-Jing Liu, Linda J Wykes, Cameron D Skinner and Kristine G Koski. Insulin-Like Growth Factor II and Binding Proteins 1 and 3 from Second Trimester Human Amniotic Fluid Are Associated with Infant Birth Weight J Nutr, 2005; 135(7): 1667-1672.
27. Marzia Perluigi, Fabio di Domenico, Ada Fiorini, Annalisa Cocciolo, Alessandra Giorgi, Cesira Foppoli, D. Allan Butterfield, Maurizio Giorlandino, Claudio Giorlandino, M. Eugenia Schinina and Raffaella Coccia. Oxidative stress occurs early in Down syndrome pregnancy: A redox proteomics analysis of amniotic fluid. Proteomics clinical applications, 2011; 5(3-4): 167–178.
28. S Perrone, M Longini, CV Bellieni, G Centini, A Kenanidis, L De Marco, F Petraglia and G Buonocore. Early oxidative stress in amniotic fluid of pregnancies with Down syndrome. Clinical Biochemistry, 2007; 40(3–4): 177–180.
29. Amir Kaviani, Tjorvi E. Perry, Alexander Dzakovic, Russell W. Jennings, Moritz M. Ziegler and Dario O Fauza. The amniotic fluid as a source of cells for fetal tissue engineering. Journal of Pediatric Surgery. 2001; 36(11): 1662–1665.
30. George Tsangaris, Rachel Weitzdorfer, Daniela Pollak, Gert Lubec and Michael Fountoulakis. The amniotic fluid cell proteome. Electrophoresis. 2005; 26(6): 1168–1173.
31. Farandos NM, Yetisen AK, Monteiro MJ, Lowe CR and Yun SH. Contact lens sensors in ocular diagnostics. Adv Healthc Mater. 2015; 4(6): 792-810.

32. Lei Zhou, Roger W Beuerman, Ai Ping Chew, Siew Kwan Koh, Thamara A. Cafaro, Enrique A. Urrets-Zavalia, Julio A. Urrets-Zavalia, Sam FY Li and Horacio M Serra. J. Quantitative Analysis of N-Linked Glycoproteins in Tear Fluid of Climatic Droplet Keratopathy by Glycopeptide Capture and iTRAQ. Proteome Res., 2009; 8(4): 1992–2003.
33. Matti Jauhiainen, Niko L Setla, Christian Ehnholm, Jari Metso, Timo M. T Tervo, Ove Eriksson and Juha M. Holopainen. Phospholipid Transfer Protein Is Present in Human Tear Fluid. Biochemistry, 2005; 44(22): 8111–8116.
34. Enkela Hrdlickova-Cela, Jan Plzak, Karel Smetana, Jr, Zora Melkova, Herbert Kaltner, Martin Filipec, Fu-Tong Liu and Hans-Joachim Gabius. Detection of galectin-3 in tear fluid at disease states and immunohistochemical and lectin histochemical analysis in human corneal and conjunctival epithelium. Br J Ophthalmol, 2001; 85: 1336-1340.
35. Rajeswari S, Dhananjayan R and Swaminathan S. Recent advances in the diagnostic usefulness of sweat as biological sample, 2015; 2(4): 1119-1136.
36. Aline Cristina Gonçalves, Fernando Augusto de Lima Marson, Regina Maria de Holanda Mendonça, Jose Dirceu Ribeiro, Antonio Fernando Ribeiro, Ilma Aparecida Paschoal and Carlos Emilio Levy. Saliva as a potential tool for cystic fibrosis diagnosis. Diagnostic Pathology, 2013; 8: 46.
37. Vitali Sikirzhytski, Kelly Virkler and Igor K. Discriminant Analysis of Raman Spectra for Body Fluid Identification for Forensic Purposes. Lednev Sensors, 2010; 10(4): 2869-2884.