The Latest Developments in Using Proteomic Biomarkers from Urine and Serum for Non-Invasive Disease Diagnosis and Prognosis

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ABSTRACT: Due to diagnostic improvements, medical diagnostics is demanding non-invasive or minimally invasive methods. Non-invasively obtained body fluids (eg., Urine, serum) can replace cerebral fluid, amniotic fluid, synovial fluid, bronchoalveolar lavage fluid, and others for diagnostic reasons. Many illnesses are induced by perturbations of cellular signaling pathways and associated pathway networks as a result of genetic abnormalities. These disturbances are represented by a shift in the protein composition of the fluids surrounding the tissues and organs that is, tissue interstitial fluid (TIF). These variant proteins may serve as diagnostic "signatures" for a variety of disorders. This review provides a concise summary of urine and serum biomarkers that may be used for the diagnosis and prognosis of a variety of disorders, including cancer, brain diseases, kidney diseases, and other system diseases. The studies reviewed in this article suggest that serum and urine biomarkers of various illnesses may be therapeutically useful for future diagnostics. Correct illness management is crucial for disease prognosis, hence non-invasive serum and urine biomarkers have been extensively studied for diagnosis, subclassification, monitoring disease activity, and predicting treatment results and consequences.

KEYWORDS: Biomarker, proteomics, cancer, brain diseases, kidney diseases, serum, urine

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Introduction

According to the National Cancer Institute's definition, a biomarker is "any biological material in body fluids or tissues that is suggestive of a normal or aberrant process or of a condition or illness." Biomarkers may be found in blood, urine, saliva, and other bodily fluids.[1] The detection of illness, differential diagnosis, disease severity, monitoring, screening, predicting therapy response, and individually tailored therapeutic medication regimens are some of the many distinct phases of disease in which biomarkers may be used. Biological markers can be nucleic acid-based (eg, DNA, RNA), protein-based (eg, enzymes, antibodies), sugar-based, or lipid-based (Figure 1).[2]

Diagnostics, susceptibility, screening, prognosis, monitoring, and safety all rely heavily on the use of biological markers. Biomarkers should be non-invasive, disease specific, sensitive, reasonably priced, generalizable, biologically plausible, and minimally invasive. As new therapies hit the market on a routine basis, effective and reliable biomarkers can be used to determine precision medicine for an individual. Biological biomarkers are indeed a valuable tool in determining patient's condition. These biomarkers have the potential to properly evaluate therapeutic outcomes or prognosis about disease.[3,4]

Novel biomarkers are urgently required to enhance disease diagnosis. Proteomics methods hold considerable potential for the identification of novel biomarkers that could serve as the foundation of physiological and pathophysiological processes.[5] To remedy the unacceptable level of invasiveness, insufficient accuracy, and discomfort associated with the current tests and procedures, sensitive and specific biomarkers based on non-invasive sampling are required.[6]

Because of the potential for repeated sampling, unlimited volumes, and ease of access, serum and urine are useful biological fluids that serve as model non-invasive samples for the exploration of diagnostic markers. Urine and serum collection is usually inexpensive and doesn't have any adverse consequences.[7]

A potential downside of proteomics research is the high level of noise in proteomics assays caused by the patient's genetic background, environmental factors and control subjects. This impedes the successful identification of disease-related biological markers.[8]

Proteomics in Biomarker Exploration

Proteomics is the study of the whole protein profile of a living organism or a part of it, such as a cell, tissue, or bodily fluid (such as serum, urine, cerebrospinal fluid, or plasma.[9]

Proteomics represents one of the most promising approaches for identifying proteins as biological markers. Understanding what a proteome is essential to comprehending proteomics. According to the American Medical Association (AMA) and the National Cancer Institute's Office of Cancer Clinical Proteomics Research, the term proteome was derived from 2 words: protein and genome, so prote—was derived from protein and—ome from genome. As a matter of fact, proteomes are proteins that are expressed by numerous genomes as well as many other cells.

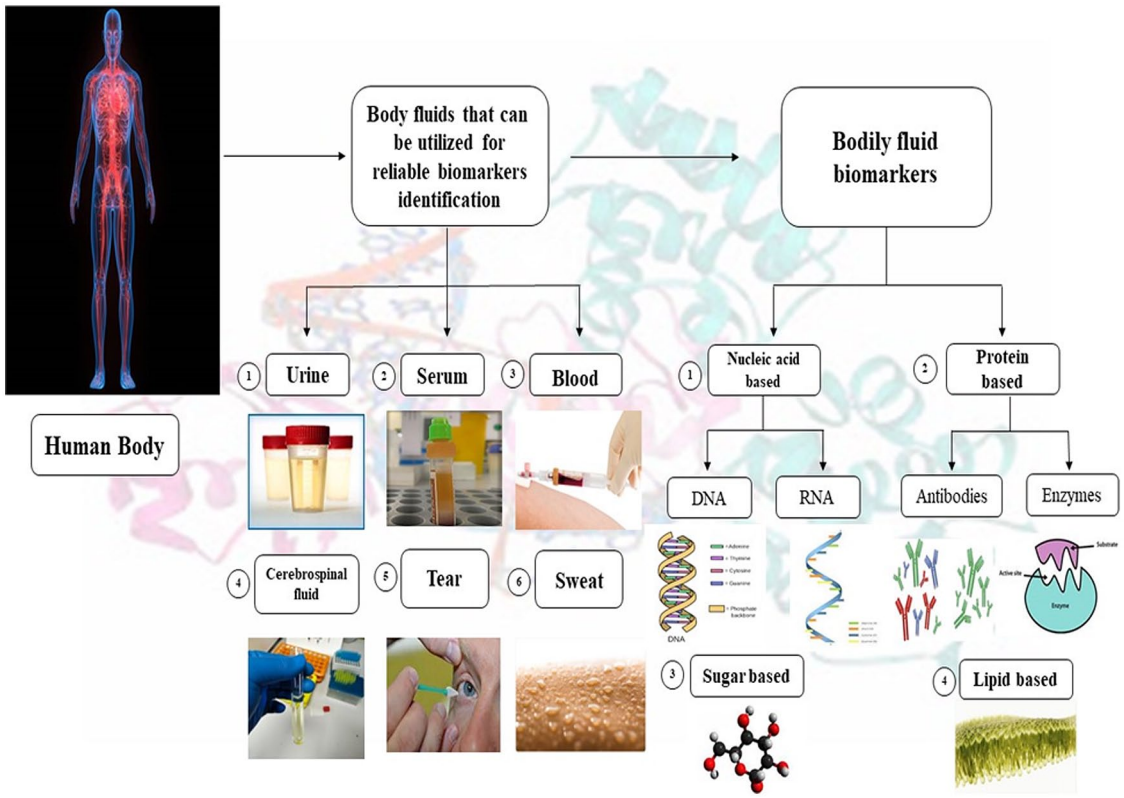

Figure 1. Body fluids that are used in the process of biomarker exploration, as well as the many types of biomarkers that may be obtained from these body fluids.

Nucleic acid, hormones, different receptors, and enzymes can all be reliable biomarkers. Proteins, among all of these different kinds of biomarkers, can be very sensitive to being detected in a very minuscule quantity of a sample to diagnose a specific type of disease in its initial stages.

Proteomics includes the following main steps in order to identify reliable biomarkers for disease diagnosis: sample collection, protein separation, protein identification, and protein verification (Table 1).[10]

Urinary and Serum Biomarkers for Disease Diagnosis and Prognosis

There is a growing demand in the field of medical diagnostics for procedures that are either non-invasive or minimally invasive, due to the breakthroughs that have been made in diagnostic techniques. For diagnostic purposes, other bodily fluids, such as cerebrospinal fluid, amniotic fluid, synovial fluid, bronchoalveolar lavage fluid etc., may be replaced by continuously produced and continuously available body fluids that may be collected through non-invasive means. These fluids include things like urine, serum, tears, saliva, and sweat, among other things.[24]

When compared to the use of tissue, the accessibility, lack of risk associated with tissue sampling through biopsies, low cost, availability of monitoring based on multiple sampling, and potential for the development of large-scale, valuable prognostic and diagnostic tests have all contributed to the increased interest in biological fluids as potential sources for biomarkers. It is essential to distinguish between the use of biological fluids and tissues for biomarker analysis. Tissue analysis carries with it a variety of possible issues, including difficulties in acquiring samples, standardization in light of varied cell types, and the presence of distinct proteolytic enzymes. Due to the little data currently available on these issues, certain obstacles may remain undiscovered.[25]

Proteomics is the interdisciplinary study of proteins and their expression patterns, relationships, and pathways in whole organisms, organs, and tissues. In particular, urine and serum proteomics are hastening the identification and development of novel biomarkers.[26] An in-depth investigation of the human urine and serum proteome has the potential to advance our knowledge of pathophysiology and provide the groundwork for the identification of possible disease biomarkers.[27,28]

The use of reliable biomarkers is becoming increasingly important for the development of patient care as a whole. Recent developments have led to the identification of a number of distinct biomarkers in serum or urine. These biomarkers may be used to evaluate a predisposition toward a disease, identify biological anomalies, and have the potential to evaluate whether or not a therapy intervention was successful.[29]

Urine and serum are straightforward to amass in large quantities from the same individual for follow-up studies in a noninvasive manner.[8,30] Urine and serum are rich sources of protein; in fact, urine contains over 3000 different protein species that

Table 1. Summary of steps and methods in order to identify reliable biomarkers.

SERIAL NUMBER	STEPS	METHOD	REFERENCE
1.	Sample collection	i. **Urine:** A healthy person's clean midstream urine was obtained, and the sample was taken during the second urination or random urination of the day, as first morning urine may have protein contamination from overgrown bacteria as well as bladder epithelial cells. The samples were collected in sterile Falcon sample containers. After separating the sample into aliquots, the urine was centrifuged for 10 min at 2500g at 4°C to clear the debris. ii. **Serum:** Blood was drawn from the target and allowed to clot for 40 to 50 min at room temperature. The sample was then centrifuged for 10 min at 3000rpm to separate the serum, and aliquots were prepared. The aliquots of serum were stored at –20°C and then –80°C until they were employed in the study.	German et al,[11] Lee et al,[12] Altuntas et al[13]
2.	Protein separation	i. 2-dimensional gel electrophoresis (2-DE) ii. Laser capture microdissection (LCM) iii. 2-dimensional difference gel electrophoresis (2D-DIGE)	Chassaigne et al[14] Lawrie et al[15] Pasquali et al[16]
3.	Protein identification	i. Matrix Assisted Laser desorption Ionization—Time of Flight Mass Spectrometry (MALDI-TOF/MS) ii. Liquid Chromatography Mass Spectrometry (LC-MS/MS) iii. Two-dimensional gel electrophoresis-mass spectrometry (2-DE/MS) iv. Surface Enhanced Laser Desorption/ Ionization Time of Flight Mass Spectrometry (SELDI-TOF/MS)	Greco et al[17] Chen et al[18] Rabilloud et al[19] Gemoll et al[20]
4.	Protein verification	i. Enzyme Linked Immunosorbent Assay (ELISA) ii. Multiple Reaction Monitoring—Mass Spectrometry (MRM-MS) iii. Western blot	Brody et al[21] Mani et al[22] Handler et al[23]

may be identified. But it was formerly thought that urine included extremely little proteins; however, many recent investigations have indicated that healthy humans had 0 to 0.8 g/l of protein in their urine.[31] And this abundance of proteins seen in urine and serum may be utilized as potential diagnostic and monitoring biomarkers for a wide variety of systemic diseases.

Because urine and serum contain a high concentration of proteins, using these as a diagnostic tool is not only a simple and cost-effective option, but it also has the potential to revolutionize the diagnostics and prognosis of illness. As a result, urinary and serum proteomics have emerged as some of the most promising areas of study in the field of clinical proteomics. These urine and serum proteins with varied expression levels are used to keep an eye out for illness.[32] As a result, urinary and serum proteomics have emerged as some of the most promising areas of study in the field of clinical proteomics.

Urine and serum are readily available biofluids, as these may be acquired in large sample sizes, and repeated sampling poses minimal difficulty, holds a biochemical record of an individual's health, and may permit monitoring of both the course of the illness and the therapeutic effects.[33]

However, biomarker discovery has been hampered by 3 primary obstacles: Candidate biomarkers are either (a) present in very small amounts in urine and serum, (b) obscured by abundant resident proteins, or (c) quickly destroyed by endogenous or exogenous proteinases.[34] As the "mirror of the body," urine and serum are the ideal medium for health and disease monitoring.[35]

Clinical evaluations of patients usually include tests of urine and serum proteins.[36] The proteomic study of urine and serum, however, is complicated by the large variety of protein concentrations that characterize the composition.

Urine and serum proteins can be used to determine the prognosis of a number of diseases, such as Endometrial cancer, Breast cancer, Prostate cancer, Lung cancer, Pancreatic cancer, Parkinson's disease, Multiple sclerosis, Diabetic Nephropathy, Obstructive nephropathy, Rheumatoid arthritis (RA), Acute appendicitis, Inflammatory Bowel Disease etc.[5]

Cancer

Endometrial cancer. Endometrial cancer (EC) is the kind of cancer that is detected in women's genital tracts, and its prevalence is rising among women who have passed menopause. It is also the sixth most prevalent type of cancer in women worldwide.[37,38] The most characteristic symptom of endometrial cancer is bleeding after menopause. It is commonly acknowledged that the 2 most significant risk factors for the development of endometrioid endometrial cancer are being overweight and having an endometrium that has been subjected to unopposed estrogen stimulation.[39]

Because of the continuity in anatomy between the upper and lower genital systems, a sample of uterine associated proteins and malignant cells may be obtained without invasive procedures.[40]

According to the study conducted by Njoku et al., the diagnostic model that exhibited the most remarkable performance was comprised of a panel consisting of ten markers: SPRR1B, CRNN, CALML3, TXN, FABP5, C1RL, MMP9, ECM1, S100A7, and CF1. This model exhibited impressive predictive

capabilities for endometrial cancer, with an area under the curve (AUC) of 0.92. The sensitivity, or the ability to correctly identify individuals with endometrial cancer, was 83.7%, while the specificity, or the ability to accurately identify individuals without endometrial cancer, was 83.9%. These results indicate the potential of this 10-marker panel as a valuable tool for diagnosing endometrial cancer with high accuracy.[41] Mu et al. using several proteomics approaches (ie, Two-dimensional gel electrophoresis, LC-MS/MS and o-glycan binding lectin), discovered that Zinc alpha-2 glycoprotein, Alpha1-acid glycoprotein and CD59 glycoprotein or MAC inhibitory protein (MAC-IP) varied substantially between control and endometrial cancer patients.[42] Bostanci et al. have suggested Neopterin as a potential urinary biomarker using HPLC.[43] Kacirova et al. have suggested proteins like cadherin-1 (CDH1), vitronectin (VTN) and basement membrane specific-heparan sulfate proteoglycan core protein (HSPG2) that were found to be downregulated in the control group.[44]

Cocco et al. utilizing flow cytometry, real-time polymerase chain reaction (PCR), and immunohistochemistry (IHC) compared normal endometrial tissues with endometrioid cancer tissues and expressed the levels of gene expression for serum amyloid A (SAA) to be considerably elevated in endometrial cancer.[45] Uyar et al. used mass spectrometry (MS)-based proteomics to identify serum proteins and identified over expression of FAM83D in the serum of patients with early-stage low-grade endometrial cancer.[46] Behrouzi et al. depicted serum human epididymis protein 4 (HE4) as upregulated in patients with endometrial cancer.[47]

Breast cancer. Cancer of the breast occurs when cells in the breast proliferate uncontrollably. Breast cancer is a diverse illness with molecular hallmarks such as HER2 activation (encoded by ERBB2), activation of hormone receptors (estrogen receptor and progesterone receptor), and/or BRCA mutations.[48] Breast cancers often begin as ductal hyperproliferation, and after being continuously stimulated by a variety of carcinogenic stimuli, they may progress to become benign tumors or even metastatic carcinomas.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Matrix metalloproteinase (MMP-9) is a potent biomarker detected in the urine of breast cancer patients when measured by gelatin zymography, according to research by Fernandez et al.[49] Matrix metalloproteinase (MMP-9) and ADAM 12 is a potent urinary biomarker for breast cancer when measured by Zymography and immunoblotting (using ADAM 12 antibody), according to research by Pories et al.[50]

Research conducted by Rui et al. utilizing 2D-PAGE combined with MALDI-TOF-MS has revealed HSP27 (up-regulated) and 14-3-3 sigma (down-regulated) as reliable serum-based biomarkers for breast cancer.[51] Huang et al. found Proapolipoprotein A-I, Transferrin, and Hemoglobin, which were upregulated, and Apolipoprotein A-I, Apolipoprotein C-III, and Haptoglobin a2, which were downregulated, as valid serum biomarkers for breast cancer using the 2D-DIGE approach.[52]

Prostate cancer. Prostate cancer is the second most common malignancy in males and the fifth biggest cause of death globally.[53] When cells in the prostate gland start growing out of control, this is the first step toward developing prostate cancer. In men, the prostate gland is located immediately behind the bladder (the urethra). The prostate's primary role is to produce the fluid that nourishes and transports sperm (seminal fluid).

For urine-based biomarkers, Kim et al. identified Stratifin (SFN), Membrane metalloendopeptidase (MME), Parkinson protein 7 (PARK7), and Tissue inhibitor of metalloproteinase 1 (TIMP1) as reliable biomarkers for prostate cancer using LC-MS/MS, Western blot, and SRM-MS-based relative quantification.[54] Li et al. used LC-MS/MS to determine that Osteopontin (SPP1), Prothrombin (F2), Pyridinoline, and deoxypyridinoline as valid biomarkers for prostate cancer.[55] Jedinak et al. used Quantitative iTRAQ, LC-MS/MS, immunoblot on urine samples and depicted Beta-2-M (B2-M), PGA3, and MUC3 as reliable biomarkers for prostate cancer.[56] Davalieva et al. conducted study using 2D-DIGE-MS and immunoturbidimetry to determine that transferrin (TF), alpha-1-microglobulin (AMPB), and haptoglobin (HP) were potential urinary biomarkers for prostate cancer.[57]

Serum-based biomarkers for prostate cancer were identified by Li et al. and Wang et al., which identified fucosylated PSA (Fuc-PSA) and soluble TEK receptor tyrosine kinase (Tie-2) as having the capacity to predict AG PCa (aggressive prostate cancer).[58,59] Human kallikrein 2 (KLK2), a potential prostate cancer serum marker, has been hypothesized to play a crucial role in cancer progression and metastasis.[60]

Lung cancer. Lung cancer refers to malignancies that begin in the lungs, often in the airways (bronchi or bronchioles) or tiny air sacs (alveoli). Lung cancer is the leading cause of cancer-related death in males across the world. In women, however, it is the third leading cause of cancer diagnosis and the second leading cause of cancer related mortality.[61] In the past, the main differentiation between lung cancer subtypes was between small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC).[62]

Zhang et al. analyzed human urine samples from healthy persons and lung cancer patients using proteomic techniques and proposed a panel of 5 urinary biomarkers (FTL: Ferritin light chain; MAPK1IP1L: Mitogen-Activated Protein Kinase 1 Interacting Protein 1 Like; FGB: Fibrinogen Beta Chain; RAB33B: RAB33B, Member RAS Oncogene Family; RAB15: RAB15, Member RAS Oncogene Family) that discriminated lung cancer patients from control groups.[63] Nolen et al. identified a 3-biomarker panel consisting of IGFBP-1, sIL-1Ra, CEACAM-1 that differentiate lung carcinoma patients from healthy individuals.[64]

Research carried out by Huang et al. suggested a serum based reliable biomarker for non-small cell lung carcinoma (NSCLC); Dihydrodiol dehydrogenase (DDH) by using 2D electrophoresis and mass spectrometry.[52] This research demonstrated that DDH is secreted by the adenocarcinoma cell line, A549.

The study conducted by Liu et al. identified ITGAM and CLU as serum exosomal protein markers specific to lung adenocarcinoma.[65] Jiang et al. conducted a study in which they assessed the serum levels of Thrombospondin-2 (THBS2) in patients diagnosed with early-stage non-small cell lung cancer (NSCLC). The researchers employed an ELISA kit to measure THBS2 levels and compared them to those of a control group consisting of healthy individuals. The findings from this study demonstrated a notable and statistically significant elevation in the mean THBS2 level among NSCLC patients when compared to the healthy control subjects.[66]

Pancreatic cancer. Evidence suggests that pancreatic cancer is caused by the accumulation of gene mutations.[67] There are 4 primary pancreatic cancer driver genes: KRAS, CDKN2A, TP53, and SMAD4. Mutations in KRAS and CDKN2A are early events in the development of pancreatic tumor's.[68] The malignancy develops from premalignant lesions in the ductal epithelium into a completely invasive carcinoma. Pancreatic intraepithelial neoplasia is the best characterized histologic precursor to pancreatic cancer.[69]

Blyuss et al. have suggested 3 urine biomarkers; (LYVE1, REG1B and TFF1) in pancreatic cancer patients and healthy controls and proposed PancRISK as a urine biomarker-based risk score 9.[70] Research carried out by Yu et al. using serum samples identified upregulated levels of apolipoprotein E and R-1-antichymotrypsin Inter-R-trypsin inhibitor as valid biomarkers for pancreatic cancer.[71] These biomarkers were identified using the 2D-DIGE, MALDI/TOF/TOF-MS, and Western blot methodologies. Using 2D-PAGE Bloomston et al. identified fibrinogen- γ as a reliable biomarker for pancreatic cancer.[72]

Using 2D-PAGE and μLCMS/MS, Zhao et al. determined that Sialylated plasma protease C1 inhibitor was down-regulated in cancer serum and that N83 glycosylation of R1-antitrypsin was down-regulated.[73] In a study carried out by Xing et al., it was demonstrated that PROZ and TNFRSF6B serve as novel serum biomarkers for the detection of early-stage pancreatic cancer. These biomarkers were found to be effective in distinguishing pancreatic cancer from pancreatic benign tumors as well as from healthy individuals. The study suggests that PROZ and TNFRSF6B hold promise as valuable indicators for the early detection and differentiation of pancreatic cancer.[74]

Brain diseases

Cerebrospinal fluid (CSF) analysis is the gold standard for diagnosing brain illnesses, but it is invasive and uncomfortable due to the necessity of performing lumbar punctures on patients. Therefore, there is a quest for new biological biomarkers that are not only less invasive and more readily available, but also more sensitive and specific. There is relatively little interest in using urine protein as a biomarker of brain illnesses since the brain and urine are not anatomically connected to one another in any significant way. However, the changes that are taking place in the brain are mirrored in the urine in some way.[5] Although, serum has been used earlier as a source for clinical studies as it causes patients minimum distress, which in turn, encourages more frequent testing and closer patient follow-up.

Alzheimer's disease. Amyloid plaques, which form when amyloid β-proteins accumulate outside of cells, and neurofibrillary tangles, which form when tau proteins clump together inside of cells, are the hallmarks of AD, a chronic degenerative illness.[75] Prior to the occurrence of irreparable brain injury or mental deterioration, early detection may be crucial.[5] More than 40 genetic risk loci related to Alzheimer's disease have previously been found. Of these, the APOE alleles have the strongest relationship with the illness. Hereditary factors are responsible for 60% to 80% of the Alzheimer's disease risk.[76]

Watanabe et al. investigated the crude urine levels of apolipoprotein D (ApoD), insulin-like growth factor-binding protein 3 (Igfbp3), and creatinine-adjusted ApoD that were all substantially higher in the Alzheimer's disease patients as compared to the control group determined using Enzyme-linked immunosorbent assays (ELISAs).[77]

German et al. discovered that there are 4 serum-based biomarkers with the following monoisotopic masses: 1690.93, 1777.95, 1864.98, and 2021.09.[11] The spectra for these 4 biomarkers were obtained with a MALDI-TOF-MS. Amyloid beta isoform (Aβ), total tau protein (t-tau) and YKL-40 were measured in serum using ELISA kits and detected as biomarkers for dementia progression.[78]

Parkinson's disease. Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder, after Alzheimer's disease, and one of the major contributors to Parkinson's disease (PD) is the loss and degeneration of dopaminergic neurons in the substantia nigra region of the basal ganglia, along with the appearance of lewy bodies.[79] There is currently no reliable early biomarker for the diagnosis of PD, and its pathogenic mechanism is still unclear.

Li et al. using the urine proteome of transgenic mice, reflected the early clinical diagnosis of PD by following proteins: Formin-2, Splicing factor 3A subunit 1, and Isopentenyl-diphosphate Deltaisomerase 1 by employing quantitative LC-MS/MS.[80] In another study, due to the contradictory findings regarding the overall change in total α-syn levels between individuals with Parkinson's disease (PD) and control subjects, researchers have directed their attention toward investigating

specific forms of α-syn as potential biomarkers. These specific forms include oligomeric α-syn, phosphorylated α-syn and nitrated α-syn. These specific forms of α-syn are considered more relevant biomarkers due to their potential association with the pathology of PD.

The findings from a study conducted by Foulds et al. indicated that phosphorylated α-syn (pS129 α-syn) levels were found to be higher in individuals with Parkinson's disease (PD) compared to healthy controls. However, no significant differences were observed in the levels of total α-syn (t-α-syn) or oligomeric α-syn (o-α-syn) between the PD patients and healthy controls.

Nonetheless, these findings suggest that measuring levels of total α-syn alone may not be sufficient to differentiate PD patients from healthy controls. Instead, a combination of biomarkers targeting specific forms of α-syn may hold greater potential.[81]

Xu et al. described that protein glycosylation plays an important role in the progression of PD.[82] Using glycoproteomics methods with high-resolution mass spectrometry and analyzed 5 Parkinson's disease-associated proteins and revealed site-specific N-glycosylation changes in serum as potential biomarkers for Parkinson's disease.

Multiple sclerosis. In multiple sclerosis, the immune system of the body attacks myelin, which is a lipid-rich plasma membrane that forms an insulating coating around axons or nerve fibers in the brain and spinal cord. Multiple sclerosis is an autoimmune disease. The voltage-gated sodium channels in unmyelinated nodes are the source of the action potential, which then passively moves through the myelinated nerve segment. But because of the demyelination, the disease may cause impairments with speech and vision in addition to weakness and paralysis.[83]

In an intriguing study conducted by Singh et al., an analysis of urine samples from pregnant women revealed significant changes in 2 proteins, namely trefoil factor 3 and lysosomal associated membrane protein 2. These protein alterations not only allowed discrimination between the third trimester of pregnancy and the postpartum period but also enabled differentiation between multiple sclerosis (MS) patients and the control group. The findings of this study highlight the potential of these proteins as valuable biomarkers for monitoring pregnancy progression and potentially diagnosing or monitoring MS.[84]

Keane et al. analyzed serum samples from patients with multiple sclerosis and determined the sensitivity and specificity of inflammasome proteins as potential biomarkers for this disease.[85] The study reported caspase-1, apoptosis-associated speck-like protein containing a caspase recruitment domain, and interleukin (IL) as elevated in the serum of patients as compared to controls. Bittner et al. detected serum-based neurofilament light chain (sNfL) as a protein biomarker for prognosis in patients with multiple sclerosis.[86]

Severe traumatic brain injury (TBI). A traumatic brain injury occurs when the brain receives an external force, such as a blow to the head or body. A traumatic brain injury may also be caused by an item penetrating the skull or brain tissue. Estimates vary from 108 to 332 incidents of traumatic brain injury per 100 000 people per year across countries.[87] Those who survive a severe traumatic brain injury have a reduced life expectancy and a mortality rate that is three and a half times higher than that of the general population.[88] There has been a recent uptick in the research and development of biomarkers for brain injury, which might supplement the more costly and less sensitive neuroimaging techniques now in use.[89]

Olczak et al. identified the role of MAPT protein as a biomarker in cases of traumatic brain injury in urine samples using an ELISA test. MAPT concentrations in urine were found to be elevated in the study.[90] According to findings from a study that was conducted by Rodríguez-Rodríguez et al., it was discovered that S100 β was elevated.[91,92]

Kidney diseases

Diabetic nephropathy. Proteinuria, that is more than 0.5 g/24-hour period has traditionally been used as a diagnostic criterion for diabetic nephropathy. A high quantity of glucose in the blood may cause harm to the kidney's delicate blood capillaries and intricate filtering system. This may also be caused by having high blood pressure. This may result in their leaking, making them less effective overall. When this occurs, abnormally high levels of protein in the blood might be eliminated from the body via the urinary tract. This is often one of the first symptoms of renal disease.[93] Patients with diabetes who are just commencing renal replacement treatment are more likely to develop diabetes,[94] which is associated with a higher risk of cardiovascular mortality.[95]

Sharma et al. and Pejcic et al. found that α1-antitrypsin is elevated in the urine of individuals with diabetic nephropathy by utilizing 2D-DIGE and ELISA.[30,96] UbA52 (Ubiquitin ribosomal fusion protein) was identified as a valid biomarker by Pejcic et al. using SELDI.[30] Dihazi et al. discovered that the processed form of ubiquitin was selectively absent in the urine of patient subjects by using the SELDI technique.[97]

Biomarkers for detecting Diabetic nephropathy (DN) in its earliest stages may include serum neutrophil gelatinase-associated lipocalin (NGAL) and β-trace protein (βTP), which are tubular and glomerular biomarkers, respectively (Motawi et al 2018).[98]

Obstructive nephropathy. The kidney disease that is caused by an obstruction in the flow of urine or tubular fluid is called obstructive nephropathy. A condition known as hydronephrosis refers to a dilation of the urinary tract. Reduced renal blood flow and glomerular filtration rate may result from urinary tract obstruction.[99]

Modified expression of collagen 9 and a fragment of the type V preprocollagen a2 chain was identified as possible urinary biomarkers by Decramer et al. using CE-MS/MS.[100] Decramer et al. revealed that proSAAS (proprotein convertase subtilisin/kexin type 1 inhibitor) was not well expressed in patients by employing a nanoflow system coupled to an LTQ_Orbitrap hybrid mass spectrometer.[101] Jianguo et al. depicted that the increased levels of serum procollagen III (PIIINP) are related to obstructive nephropathy. The research utilized an enzyme-linked immunosorbent assay (ELISA) kit to quantify PIIINP.[102]

Chronic kidney disease (CKD). The gradual loss of renal function, persistent inflammation, oxidative stress, vascular remodeling, and scarring of the glomeruli and tubulointerstitial spaces are the hallmarks of chronic kidney disease (CKD). The most common cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is diabetic nephropathy (DN).[103] With the rising expense of monitoring and follow-up necessary in the treatment of patients with chronic kidney disease (CKD), biomarkers are increasingly being studied for their efficacy in identifying people most at risk of renal function decrease in order to rationalize and focus therapy.[104]

Increased risk of developing chronic kidney disease was shown to be strongly correlated with higher baseline values of urine albumin, renal injury molecule-1, and monocyte chemoattractant protein-1.[105] Pontillo et al. using capillary electrophoresis coupled with high-resolution mass spectrometry (CE-MS) using urine samples suggested CKD 273 for CKD. Recently, the FDA recommended more research using CKD273 as a diagnostic and risk prediction tool in CKD.[106]

Curhan et al. found Cystatin-C as a reliable serum biomarker for chronic kidney disease (CKD) using ELISA.[107] Using LC-MS, Radabaugh et al. found 3-nitrotyrosine peptides in urine and serum as diagnostic biomarkers for chronic kidney disease (CKD).[108] Bolignano et al. found Neutrophil gelatinase-associated lipocalin (NGAL) as a reliable biomarker for chronic kidney disease (CKD) using ELISA for both the biological fluids.[109]

Renal fibrosis. Renal fibrosis is the end stage of chronic kidney disease (CKD), renal fibrosis is characterized by the advanced breakdown of normal kidney tissue architecture brought on by the excessive and persistent deposition of extracellular matrix (ECM), myofibroblasts, and infiltrating inflammatory cells.[110]

A kidney biopsy is the sole clinical technique available to detect fibrosis. However, since this method is intrusive and entails some hazards, it is rarely used on a regular basis. Identifying fibrosis biomarkers is critical to understanding renal fibrosis.[111,112]

Wan et al. found that the Human epididymis protein 4 (HE4) can be used as a reliable biomarker for renal fibrosis by employing the ARCHITECT HE4 test.[113] Using an ELISA kit (Abcam, Cambridge, UK), Zhong et al. identified WNT1-inducible signaling pathway protein-1 (WISP-1) as a reliable biomarker for renal fibrosis.[114] Mansour et al. evaluated urine biomarkers and depicted the role of Transforming growth factor β (TGF-β), Monocyte chemoattractant protein-1 (MCP-1), and Matrix metalloproteinase-2 (MMP-2) in worsening renal function in patients.[115] Ou et al. investigated the role of urinary Gal-3 and showed that patients with higher levels of urinary Gal-3 had the highest proteinuria levels, which associated allied with severe renal fibrosis.[116]

Diagnostic and prognostic biomarker for other diseases

Rheumatoid arthritis. Rheumatoid arthritis (RA) is a progressive, chronic inflammatory disease affecting cartilage and bone that is a leading cause of disability.[117] RA is a prevalent autoimmune illness that has been linked to progressive disability, early mortality, and high socioeconomic consequences. Inflammation of the synovium, which is a membrane that lines the joint, is a defining feature of rheumatoid arthritis. An aggressive tissue front known as the pannus is responsible for the invasion and destruction of adjacent articular structures. Synovium is often an acellular structure with a delicate intimal lining. CD4+ T lymphocytes, B cells, and macrophages invade the synovium and can form lymphoid aggregates with germinal centers in rheumatoid arthritis.[118] Autoantibody production (rheumatoid factor and anti-citrullinated protein antibody [ACPA]), synovial inflammation and hyperplasia ("swelling"), cartilage and bone destruction ("deformity"), and systemic features like cardiovascular, pulmonary, psychological, and skeletal disorders are all hallmarks of rheumatoid arthritis.[119]

A study that was conducted by Kang et al. using ELISA (Enzyme Linked Immunosorbent Assay) revealed that gelsolin (GSN), orosomucoid 1 (ORM-1), orosomucoid 2 (ORM-2) and soluble CD14 (sCD14) had the potential to serve as a possible urinary biomarker for rheumatoid arthritis.[120] A study conducted by Nell et al. using ELISA (Enzyme Linked Immunosorbent Assay) depicted that ACPA-antibody (Anti-Cyclic citrullinated peptide) had the potential to serve as a possible biomarker for rheumatoid arthritis.[121]

S100A8, S100A9, and S100A12 were upregulated in patient serum using MRM-MS, LC-MS, and ELISA as shown by Liao et al.[122] Hu et al. identified serum markers of RA using MS-based proteomics and obtained 24 important markers in normal and RA patient samples. The study suggested ORM1 in serum as a differentially expressed protein that was found to be correlated with disease activity.[123]

Acute appendicitis. Acute appendicitis is one of the most prevalent abdominal illnesses on a global scale having a 7-8% lifetime risk according to estimates.[124] When the appendix, a finger-shaped pouch that extends from the colon on the lower right side of your abdomen, becomes inflamed, a condition

known as appendicitis, occurs. Appendicitis affects individuals between 10 and 30 years old.[125]

Using LC-MS/MS, Zheng et al. and Yin et al. evealed that LYVE1 (lymphatic vascular endothelial hyaluronan receptor 1) and AHCYL1 (adenosyl homocysteinase-like 1) are possible urinary biomarkers for acute appendicitis.[126,127]

According to the study conducted by Zhao et al., the expression of LYVE1 was found to be lower in the group diagnosed with Acute Appendicitis (AA) compared to the Control Acute Abdomen (CON) group. As the appendix is also an immune organ, this lower expression of LYVE1 in AA suggests that inflammation may be more easily triggered in this condition. On the other hand, the study observed an upregulation of AHCYL1 in the CON group, indicating its potential role in this particular group of acute abdominal conditions. Additionally, another protein called APOC1 (apolipoprotein C1) was found to be upregulated specifically in the AA group. This upregulation of APOC1 could potentially indicate the presence of a bacterial infection in Acute Appendicitis, distinguishing it from other conditions within the CON group, such as cholecystitis and pancreatitis.[128,129]

A study conducted using LC-MS/MS by Berbee et al. found that APOC1 (apolipoprotein C1) is upregulated in acute appendicitis.[129] Allister et al. studied serum concentrations of C-reactive protein (CRP) and granulocyte colony-stimulating factor (GCSF) and detected a substantial difference between patients with acute appendicitis and healthy controls.[130]

Inflammatory bowel disease. A chronic inflammatory disorder of the gastrointestinal system is known as inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis.[4] IBD is a condition that lasts throughout one's lifetime and is characterized by symptoms that come and go, as well as repeated flare-ups. The number of people diagnosed with inflammatory bowel disease (IBD) is gradually growing and has emerged as a significant problem for the public's health in both developed nations as well as newly industrialized nations.[131]

Meuwis et al. have identified platelet aggregation factor 4, Haptoglobin a2, Fibrinopeptide A and Myeloid-related protein 8 as a reliable biomarkers for inflammatory bowel disease (IBD) using a Surface-enhanced laser desorption/ionization-time of flight-mass spectrometer (SELDI-TOF-MS).[132]

Gunawan et al. identified chemerin protein in urine samples and investigated its relationship with inflammatory bowel disease using immunoblot and enzyme-linked immunosorbent assays (ELISA). The concentration in the urine was approximately 6000 times lower than that in the serum. Urinary chemerin was not related to its serum levels, did not correlate with serum C-reactive protein levels, and negatively correlated with serum creatinine. According to the findings of this investigation, urine chemerin may be a useful non-invasive biomarker for IBD surveillance.[133]

Limitations

There are some limitations to this study. This review article has omitted an in-depth discussion regarding the methodologies employed in the exploration of biomarkers for various diseases. Additionally, it focused predominantly on commonly encountered diseases, providing only the names of the potential biomarkers without elaborating on the intricate mechanisms underlying disease pathogenesis.

Conclusion

Over the course of the past several years, proteomics has proven itself to be a highly promising method for the investigation of proteins. Various proteomics techniques, such as 2-dimensional difference gel electrophoresis (2D-DIGE), Matrix Assisted Laser desorption Ionization—Time of Flight Mass Spectrometry (MALDI-TOF/MS), Liquid Chromatography Mass Spectrometry (LC-MS/MS), etc., will be performed on patient serum and urine in order to identify potential biomarkers for the detection of the illness at an early stage or for the decision-making process regarding therapy.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Author Contribution(s)

Anurag Shama: Conceptualization; Writing—original draft; Writing—review&editing. **Thomson Soni:** Conceptualization; Writing—review & editing. **Ishwerpreet Kaur Jawanda:** Conceptualization; Writing—review & editing. **Garima Upadhyay:** Conceptualization; Writing—review & editing. **Anshika Sharma:** Conceptualization; Writing—review & editing. **Vijay Prabha:** Conceptualization; Formal analysis; Project administration; Supervision; Validation; Writing—review & editing.

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Availability of Data and Materials

Not applicable.

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