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Review Article

Mass spectrometry in clinical laboratory: applications and future prospects

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ABSTRACT

Innovations in laboratory medicine face additional challenges due to the unmet need for extremely precise methods of disease diagnosis. Developments in mass spectrometry-based disease biomarker identification are constantly expanding the field of clinical diagnosis. More mass spectrometry-based in vitro diagnostics are anticipated to move from the bench to the bedside shortly, although several are currently incorporated into standard clinical procedures. The molecular detection by mass spectrometry technique is very effective in diagnosis of the disease and therapeutic monitoring because of its extremely high sensitivity, specificity, and short turnaround time. Mass spectrometry is a potent analytical instrument that may be used to analyse a variety of materials and matrices; its use in clinical laboratory medicine applications is rising. For clinical prognostics and diagnostic purposes, mass spectrometry imaging has been widely utilized to distinguish between healthy and diseased tissues. Modern single-cell studies will benefit from its cutting-edge applications, which will offer comprehensive cellular biochemical data for mechanistic comprehension and, eventually, the development of therapeutic interventions. Within the field of laboratory medicine, the application of mass spectrometry is crucial, especially in terms of diagnostics and therapeutic drug monitoring. This review on the clinical application of mass spectrometry and its future prospects promises an insightful exploration of the evolving landscape of mass spectrometry in clinical settings, delving into its current applications and shedding light on its potential future advancements, for which a comprehensive search in the PubMed, ScienceDirect, and Web of Science databases was conducted.

Keywords: Mass, Spectrometry, Diagnosis, Laboratory, Therapeutic

INTRODUCTION

Medical diagnostic tests must be performed swiftly and precisely to promote clinical decision-making and enhance patient care. Over the past half-century, the development of novel analytical techniques and methodologies has had a significant impact on diagnosis and therapeutic interventions. While immunoassays are used in most in vitro diagnostic procedures to detect the target analyte, several drawbacks to this approach force us to consider more effective alternatives that should have high throughput, high sensitivity, and high specificity. Mass spectrometry (MS) has recently generated a lot of enthusiasm due to its extraordinarily high sensitivity, which can reach the femtomolar range, surpassing traditional chemical/biochemical measures in diagnostic molecular pathology.[1]

MS is a highly sensitive, high-throughput analytical technique pivotal for both qualitative and quantitative analysis of various analytes with clinical significance.[2] This technology extends its analytical capabilities when integrated with gas or liquid chromatographs, broadening its application scope in clinical contexts.[3] Since J. J. Thomson's original development of MS technology more than a century ago, the field has continued to advance with novel ion source designs, improvements in resolution and sensitivity, and miniaturization. Novel diagnostic biomarkers developed through MS-based research have become more and more significant in the assessment of disease risk, screening, prognosis, choice of pharmaceuticals, and monitoring. The enhanced applicability of the MS through swift in situ techniques has been made possible by the recent invention of ambient ionization MS, which allows direct analysis of biological samples with little to no sample preprocessing. This makes it possible to use MS as a point-of-care tool in a clinical context to rapidly detect biomarkers while a patient is present, facilitating an early diagnosis and prompt medical judgment.[4]

MS offers distinct advantages in the clinical laboratory and is swiftly transitioning beyond specialized testing to a wider range of applications. The detection of inborn errors of metabolism, the measurement of steroid hormones, and the validation of immunoassay-positive drug screens has all been significant historical effects of MS. In the recent past, MS has significantly reduced the amount of time needed for microbiological identifications. The analytical specificity of MS serves as a foundation for this transformation, which is being propelled by ongoing advancements in analytical platforms. Different principles underpin the conclusive identification of molecules ranging in size from tens of daltons (small molecules) to hundreds of thousands of daltons (biomolecules).[5]

Over the last two decades, substantial progress has emerged in detecting biomarkers for diagnosing diseases, refining protein measurement techniques, enhancing methodologies crucial for precise therapeutic drug monitoring, and introducing innovative automation and high-throughput technologies. Within this period, clinical chemistry and laboratory medicine has actively embraced the swiftly evolving realm of MS, aiming to showcase the most recent methodologies and their applications, promising significant transformations in clinical testing. This review on the clinical application of mass spectrometry and its prospects promises an insightful exploration of the evolving landscape of MS in clinical settings, delving into its current applications and shedding light on its potential future advancements.

METHODS

This study is based on an extensive literature search conducted on 13 December 2023, utilizing the PubMed and Cochrane databases. The search employed medical topic headings (MeSH) and encompassed a comprehensive range of related terms available in the databases. To ensure inclusivity and thoroughness, a manual search was additionally performed using Google Scholar, leveraging reference lists from previously identified papers as a starting point. The objective was to gather pertinent information from publications discussing Mass Spectrometry, specifically its applications in clinical laboratories such as biomarker discovery, proteomics, metabolomics, and drug monitoring, alongside exploring its potential future applications.

DISCUSSION

During MS analysis, samples undergo ionization, followed by separation based on their mass-to-charge ratio (m/z), before being detected.[6] Beyond the current uses of MS in trace metal analysis and newborn screening, it has also been applied to the quantitation of protein-based biomarkers like thyroglobulin, insulin-like growth factor 1, and monoclonal immunoglobulins for the specific or untargeted detection of novel psychoactive substances, the classification of amyloidosis, and the identification of microorganisms. The versatility of MS platforms in clinical laboratory medicine is demonstrated by their uses in inborn errors of metabolism, endocrinology, and clinical toxicology, among other fields. Nevertheless, there are major challenges and legal issues related to MS adoption because these assays are primarily laboratory-developed diagnostics.[7]

Applications of MS in clinical laboratory

We discuss here the applications of MS in the context of clinical diagnostics and drug monitoring with the current evidence from the literature.

Clinical diagnostics

The realm of laboratory medicine is gradually changing owing to several factors, one of which is the increased sensitivity and specificity of analytical methods. For instance, measurements of testosterone and other sex

steroids have been employed, where MS is the recommended approach. Another clinical example where MS has been demonstrated to provide better assay quality than conventional immunoassays is the determination of thyroglobulin.[5] With its ability to give spatial molecular data from a tissue biopsy for patient diagnosis and prognoses, imaging MS is an emerging technology for clinical applications. Matrix-assisted laser desorption ionization (MALDI) imaging MS is an emerging technology that offers unmatched sensitivity and specificity for mapping molecules within tissues. It can be used in two different ways: either all-inclusive molecular imaging of the biopsy, or histology-directed analysis of specific sections. Almost every tissue sample can yield a series of molecular maps from a full image analysis of a biopsy.[8]

Pathologists may favour the histology-directed mode/approach in clinical practice, in which they direct discrete measures. To generate the molecular signatures of both diseased and normal tissue, a model-building validation set of 50–100 biopsies is typically constructed using verified disease cases and normal tissues. The pathologist next evaluates patient biopsies to check for these signals in every place they have indicated.[8] Clinical diagnosis using histology-directed MALDI imaging IMS of melanocytic lesions in human skin samples embedded in formalin-fixed paraffin is shown in Figure 1. The introduction of a simple, swift, high throughput, affordable, and effective identification method has been made possible by the development of matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) devices, which have completely changed the routine identification of microorganisms in clinical microbiology laboratories. With its adaptation to the limitations of clinical diagnostic laboratories, this technology can either replace or enhance traditional methods of identifying bacterial and fungal strains. Except for the few challenging strains that call for additional attention and method improvement, the resolution of MALDI-TOF MS enables reliable identification at the species level of the majority of Gram-positive and Gram-negative bacterial strains using normal operating procedures. Similarly, regular MALDI-TOF MS identification of yeast isolates is faster and more reliable than conventional approaches.[9]

The identification of proteins as bio-taxonomy markers, with molecular weights ranging from 2 to 20 kDa, is the foundation of MALDI-TOF MS technique. This approach utilizes just a few seconds to complete the testing and analysis, which includes sample preparation and data interpretation. The MALDI-TOF MS approach uses distinctive protein patterns that are obtained from bacteria to identify organisms. These patterns are then compared to the device system's library of spectra database. The library database plays the most crucial role in the MALDI-TOF MS system's ability to successfully identify organisms down to the species level.[10] Recent research has demonstrated that, under certain standardized protocols being developed for these microbes, MALDI-TOF MS may also be able to reliably identify filamentous fungus and dermatophytes. Additionally, MALDI-TOF MS has been effectively applied to subspecies microbiological typing and identification, indicating that this method has the potential to be an effective tool for taxonomical categorization and epidemiological research.[9]

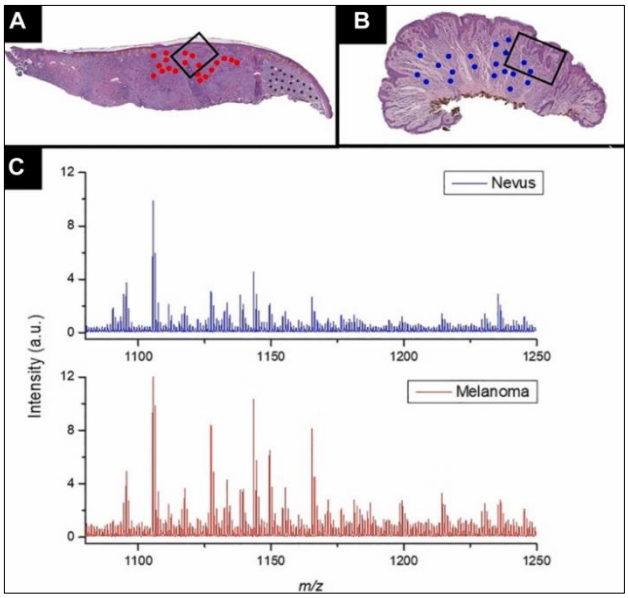

Figure 1: Clinical diagnosis using histology-directed MALDI imaging MS of melanocytic lesions in human skin samples embedded in formalin-fixed paraffin.[8]

Biomarkers are being utilized not just to diagnose and categorize various forms of cancer, but also to differentiate between diseases that share comparable histological traits. Spitz Nevi and Spitzoid malignant melanoma, which primarily affects children, is one instance of this. While Spitz Nevi is a benign skin lesion, chemotherapy and surgery are necessary for Spitzoid malignant melanoma. Based solely on histological criteria, these two diseases are highly difficult to differentiate and can lead to misdiagnoses.[11] Lazova et al compared the protein profiles of Spitz Nevi and Spitzoid malignant melanoma in a study that used MALDI-MS imaging. A total of 12 discriminating peaks were identified, and the top five peptide peaks for differentiating between the two disorders were utilized to construct a classification.[12]

The utilization of MS methods in biomarker discovery stands as a primary focus within proteomics and metabolomics. Studies exploring human metabolites and proteins using contemporary MS technology, specifically metabolomics and proteomics, have continued. Several of these investigations have yielded fascinating insights into human biology.[13] Nevertheless, only a limited number of biomarkers have transitioned into clinical tests. MS serves the dual purpose of identifying proteins and metabolites that exhibit alterations in response to stimuli and quantifying these variations.[14] Despite the ongoing growth in the use of MS for clinical diagnostics, progress has been

made in creating new platforms that may be utilized in the operating room, laboratory, and point-of-care settings. Functional MS-based approaches' sensitivity and selectivity have made it possible to achieve detection limits that are comparable to, or even better than, those of older methods, demonstrating the viability of early detection screening. The drive to use these technologies for point-of-care testing in the field is increasing, with the expectation of real-time results, since sample preparation and separation are no longer the limiting processes in analysis.[15]

Since customized medicine is becoming more and more important, MS has the inherent capacity to enhance clinical decision-making by measuring biomarkers that other approaches might not be able to identify. For instance, existing B-type natriuretic peptide measurements for cardiovascular diseases using immunoassays lack the specificity to identify the whole B-type natriuretic peptide molecule while simultaneously assessing its shortened variants that coexist in the bloodstream. Considering this, recently it has been demonstrated that the distribution of these various truncated forms must be understood using MS, and that a subset of these forms was helpful in risk classification of patients with acute heart failure. Moreover, the development of disease has been linked to the influence of the gut microbiome.[16,17]

Notably, the gut-derived molecule trimethylamine N-oxide has been demonstrated to be an independent prognostic predictor in a variety of cardiovascular disease states since it was first identified using MS-based nontargeted metabolomics. Trimethylamine N-oxide is not routinely determined in clinics, but the required preparations are being made to include it in routine clinical analysis. Additional MS-based research utilizing global 'omics-based methodologies, like proteomics and metabolomics, is probably going to reveal more novel disease-specific biomarkers that exhibit direct or associative mechanistic relationships with the development of diseases and/or future risk of unfavourable events.[18]

Therapeutic drug monitoring (TDM)

In modern times, TDM which measures drug concentrations in biological matrices to inform potential posological modifications is playing an increasingly significant role in the management and enhancement of various treatments, particularly when pharmaceuticals with limited therapeutic indices are used. Alternative matrices for TDM have received a lot of interest lately, either because they are less intrusive, cost less, or provide better information on drug concentrations at the active sites. The improving sensitivity and specificity of TDM tests is primarily due to the growing application of liquid chromatography coupled with mass spectrometry (LC-MS) techniques for the study of minuscule compounds.[19]

Drug dosage is optimized by TDM using drug concentrations, mostly from plasma. Drug dosage optimization may lessen toxicity, enhance therapeutic results, and lower the chance of developing acquired drug resistance. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) requires quite small sample volumes and provides higher sensitivity and selectivity than other analytical techniques. Furthermore, because sufficient separation with short run times may be achieved even with non-selective sample preparation methods, multi-analyte assays are simpler to conduct.[20]

In present times, hyphenated MS is widely used in forensic toxicology, clinical toxicology, and TDM. Numerous MS devices are available in conjunction with various entry systems, such as chromatography, electrophoresis, MALDI, or paper spray, to suit the diverse uses in these domains. In TDM, tandem MS linked to ultra-high-pressure liquid chromatography is currently the standard. High-resolution MS devices appear to be a virtual one-stop shop for applications in TDM as well as human toxicity, particularly in forensic toxicology and clinical toxicology. They offer very high identification power and make the development of qualitative and quantitative procedures quite simple. Therefore, if hardware becomes more affordable and software becomes more user-friendly, high-resolution MS will swiftly become the industry standard.[21]

Since most patients need more than one medicine, TDM has been used in cardiovascular therapy more recently. Because there are more drug-drug interactions in this combinatorial treatment, there is an increased chance of adverse drug reactions. High-performance liquid chromatography (HPLC) and LC-MS/MS assays are therefore widely used in laboratories for the simultaneous detection and monitoring of a wide variety of cardiovascular medication classes. Using 100 µl of serum or plasma, Dias et al. developed and assessed an LC–MS/MS technique for 34 regularly prescribed cardiovascular medications or drug metabolites. This assay monitors 67 drug types, including digoxin, fenofibrate, and niacin, as well as anticoagulants, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium channel blockers, diuretics, statins, and vasodilators.[22,23] The findings of the study by Gao et al demonstrated that electrospray ionization in the positive ion mode combined with a multiple reaction monitoring mode allowed for the achievement of mass detection. For pyrazinamide, isoniazid, ethambutol, streptomycin, and rifampicin, the corresponding lower limit of quantification and dynamic range was 200–4000 ng/ml, 80–2000 ng/ml, 0.2–1000 ng/ml, 2000–0000 ng/ml, and 200–4000 ng/mL. The accuracy and precision, both intra- and inter-day, were less than 15% and within ±15.0%. The technique has been successfully used to simultaneously measure four first-line anti-tuberculosis medications in patient plasma.[24]

Moreover, dosing adjustments intended to maximize antibacterial activity and minimize toxicity may be guided by TDM. For real-time TDM, rapid and precise analytical

techniques are essential. The authors further concluded that clinically effective real-time TDM is best served by a reliable high-throughput multiplex HPLC-MS/MS technology for simultaneous measurement of plasma concentrations of 12 daily administered antibiotics.[25] Additionally, Barco et al reported that excellent accuracy (ranging from 85.3 to 112.7) and reproducibility (ranging from 1.3 to 9.7) were demonstrated by the assay, and none of the drugs tested had matrix effects (<15%). The quantitative lower limits ranged from 0.1 to 2 mg/l. For every drug tested, the recovery rate was higher than 85%. Establishing dependable operational methods was made possible by the evaluation of stability under various circumstances. A wide range of drugs with various chemical properties may be promptly quantified in a small volume of plasma using the LC-MS/MS platform, which has been approved for clinical use. This makes it appropriate for real-time TDM-guided personalized antimicrobial treatment in critically ill patients.[26]

Furthermore, Van der Gugten et al stated that the LC-MS/MS test showed no interference from endogenous antibodies to infliximab and reliably reported concentrations based on drug manufacturer targets; immunoassay approaches did not exhibit these performance features.[27] Results of a study from Cafaro et al. also showed that the LC-MS/MS approach yielded robust, specific, and swift quantification of baricitinib from a small sample of plasma (50 µl) because it was reliable and reproducible without matrix effects and resulted linearly throughout vast concentration ranges (1.024-100 ng/ml). The mean±standard deviation of the baricitinib plasma concentration in the patient samples was 11.25±10.86 ng/ml. Hence, this innovative LC-MS/MS technique can direct treatment optimization for pediatric patients and is appropriate for the therapeutic drug monitoring of baricitinib.[28]

However, selecting the appropriate sample preparation technique, column technology, internal standard, and mass spectrometric settings is crucial for guaranteeing precise drug measurement while preventing interference from drug metabolites and matrix effects. Although LC-MS/MS is a more complex approach than automated immunoassays, it is becoming a more appealing and practical option for TDM in clinical laboratories due to technological advancements, including online solid phase extraction and the creation of pipetting robots.[29]

Future applications

MS has become a fundamental technology in personalized drug therapy, impacting areas from genetic discovery to clinical testing. Its transformative role in specific domains has expedited the development and implementation of personalized drug treatments. The convergence of MS with personalized drug therapy has led to the emergence of MS-based personalized drug therapy. This evolving field includes TDM, pharmacogenomics, pharmaco-microbiomics, pharmacoepigenomics, and immune-peptidomics, all essential for the progression of customized drug therapies. MS exceptional sensitivity and specificity allow for intricate analysis of complex biological samples, aiding in the customization of drug treatments to align with the unique biological markers of individual patients.[30]

The expansion of MS into extracellular vesicle-based diagnostics is notably promising, providing a robust method for detecting low-concentration DNAs, RNAs, and proteins. This enhances the prediction of drug efficacy and adverse drug reactions.[31,32] Additionally, MS's role in organoid and organ-on-a-chip analysis offers unprecedented insights into the development and pathology of organs, including the brain, liver, and tumors. This progress suggests potential replacement or supplementation of traditional research models, such as animal studies.[33] In oncology, MS is vital for advanced cancer diagnostics and therapy monitoring. Its unparalleled precision in identifying biomarkers and tracking molecular changes in tumors is crucial for more personalized and effective cancer treatment strategies.[34]

Challenges

Despite its progress, MS encounters several challenges in clinical applications. A significant limitation is its capability to only identify known genetic mutations and modifications, thereby requiring integration with next-generation sequencing to discover novel variants. The high cost of MS equipment is another barrier, particularly in clinical settings where reducing testing costs is imperative. To overcome this, the development of technologies that can enhance throughput and simultaneously detect various mutations or modifications is needed. Furthermore, the high sensitivity of MS makes it prone to contamination, potentially leading to false positives.[35] This risk underscores the need for a controlled laboratory environment and highly skilled technicians for accurate MS analysis.[30] Additionally, there is an urgent need for advancements in MS process automation, which would reduce the dependence on specialized skills and improve both consistency and efficiency in MS operations. The availability of commercially certified reference materials, calibrators, and quality control materials is also crucial for standardization and accuracy in MS results, yet this area significantly lacks development and requires substantial improvement.[36] Our review delves deeply into the applications of MS in clinical laboratory settings and includes evidence from the literature of recent times. However, due to the diverse and vast applications of MS in clinical settings, all aspects could not be covered, which is the limitation of our study, and we aim to discuss them in future successive research studies.

CONCLUSION

In the era of advanced medicine and technology, MS is increasingly being utilized practically in every aspect of laboratory medicine as its clinical applications continue

rising. Within the field of laboratory medicine, the application of MS is crucial, especially in terms of diagnostics and TDM. In the future, it is anticipated that the integration of MS into more medical specialities will only accelerate due to the development of new applications and technological advancements.

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