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Lipid analysis by ion mobility spectrometry combined with mass spectrometry: A brief update with a perspective on applications in the clinical laboratory

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ABSTRACT

Ion mobility spectrometry (IMS) is an analytical technique where ions are separated in the gas phase based on their mobility through a buffer gas in the presence of an electric field. An ion passing through an IMS device has a characteristic collisional cross section (CCS) value that depends on the buffer gas used. IMS can be coupled with mass spectrometry (MS), which characterizes an ion based on a mass-to-charge ratio (m/z), to increase analytical specificity and provide further physicochemical information. In particular, IMS-MS is of ever-increasing interest for the analysis of lipids, which can be problematic to accurately identify and quantify in bodily fluids by liquid chromatography (LC) with MS alone due to the presence of isomers, isobars, and structurally similar analogs. IMS provides an additional layer of separation when combined with front-end LC approaches, thereby, enhancing peak capacity and analytical specificity. CCS (and also ion mobility drift time) can be plotted against m/z ion intensity and/or LC retention time in order to generate in-depth molecular profiles of a sample. Utilization of IMS-MS for routine clinical laboratory testing remains relatively unexplored, but areas do exist for potential implementation. A brief update is provided here on lipid analysis using IMS-MS with a perspective on some applications in the clinical laboratory.

Background on ion mobility spectrometry-mass spectrometry

Ion mobility spectrometry (IMS) and mass spectrometry (MS) are analytical techniques that measure different physicochemical properties of ions. IMS separates and identifies gas phase ions based on their mobility through a buffer gas in the presence of an electric field, whereas MS sorts and identifies ions in a mass analyzer based on a mass-to-charge ratio (m/z). A limitation of both IMS and MS, is that they cannot readily separate and identify enantiomers. Currently, the main commercial application of IMS is for trace explosives and chemical warfare agent screening, which is routinely performed in airport security checks, as well in military operations due to its high sensitivity and fast analysis time [1,2].

A physicochemical property measured by IMS is an ion's rotationally-averaged collisional cross section (CCS), which is a characteristic value dependent on the specific buffer gases (such as nitrogen or helium) used in an IMS device. The CCS parameter represents the area (in units of square Ångströms, $Å^2$) where collisions between the ion of interest and buffer gas can occur; it is both a function of the mass, shape, and charge of the molecule as well as being directly related to the specific buffer gas used. CCS in an IMS device is calculated via the Mason-Schamp equation [3], which utilizes the mobility (K) parameter. The K

Abbreviations: CCS, collisional cross section; CV, compensation voltage; CVD, cardiovascular disease; DG, diacylglycerol; DMS, differential mobility spectrometry; DTIMS, drift tube ion mobility spectrometry; EV, elution voltage; FAIMS, field asymmetric waveform ion mobility spectrometry; FIA, flow injection analysis; FTICR, fourier-transform ion cyclotron resonance; HDL, high-density-lipoprotein; HRMS, high-resolution mass spectrometry; IMS, ion mobility spectrometry; IMS-MS, ion mobility spectrometry-mass spectrometry; LC, liquid chromatography; LDL, low-density-lipoprotein; LPC, lysophosphatidylcholine; MALDI, matrix-assisted laser desorption/ionization; MS, mass spectrometry; m/z, mass-to-charge ratio; NBS, newborn screening; PC, glycerophosphocholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; RF, radio frequency; TG, triglyceride; TIMS, trapped ion mobility spectrometry; TOF, time-of-flight; TWIMS, traveling wave ion mobility spectrometry; SLIM, structures for loss less ion manipulations; SM, sphingomyelin; SV, separation voltage; VLDL, very-low-density lipoprotein.

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parameter of a given ion correlates with its movement through a buffer gas at a velocity (v_d) under the influence of an electric field (E) by the equation $K = v_d/E$ [3–5].

The concept of coupling gas chromatography (GC) or liquid chromatography (LC) with both IMS and MS (IMS-MS) was initially investigated several decades ago [6,7]. IMS-MS analyses occur on the millisecond time scale and are well suited for pairing with initial GC or LC chromatographic separations, which have analysis times of minutes and peak widths on the order of seconds (Fig. 1).

In combination with GC or LC, IMS has the potential to enhance specificity via improving the chemical separation of isomers, isobars, structurally similar analogs, and other sample interferences that may be indistinguishable by MS alone. Additionally, the CCS value associated with IMS is a property of an ion that can provide complementary physicochemical information (size and shape) to the MS measurement of mass-to-charge ratio (m/z); m/z ratios can be used to determine a molecule's exact molecular weight, isotopic distributions, elemental composition, as well as information about chemical bond connections via fragmentation patterns. CCS values may be incorporated into both targeted and non-targeted MS analyses in order to help remove both false negative and false positive compound identifications. Currently, there are several different commercially available types of IMS devices that are coupled to MS. These include drift tube ion mobility spectrometry (DTIMS), traveling wave ion mobility spectrometry (TWIMS), structures for lossless ion manipulations (SLIM), field asymmetric waveform ion mobility spectrometry (FAIMS), and trapped ion mobility spectrometry (TIMS) [4,5,8,9] (Fig. 2).

DTIMS measures how long it takes for a given ion to travel through a stationary buffer gas within a uniform electric field drift tube and provides a direct calculation of CCS via measurement of the drift time which is connected to the mobility (K). Smaller ions collide less frequently with the buffer gas and, therefore, travel faster than larger ions through the device [4,8,10]. TWIMS does not utilize a uniform electric field, instead it uses a sequence of symmetric potential traveling waves that electrostatically draw ions through the stationary drift gas. Ions are separated by mobility based on differences in drag interaction with the buffer gas as they are pulled through the device's drift region by the traveling waves. Traveling waves in the TWIMS device are created by transient direct current pulses between planar ring electrodes in conjunction with an ion confinement radio frequency (RF) voltage that produces radially confined potential wells. TWIMS detects ions based on their drift time, but cannot readily measure CCS directly as the electric fields applied are complex and not easily related to the mobility (K); the CCS of unknown ions can be calculated by calibrating to ions with known CCS values [4,8,11]. SLIM is a new commercial IMS technique that also utilizes traveling waves to move ions through an extended pathlength in order to increase resolving power [9]. The SLIM device consists of a long pathlength in between two parallel surfaces where ion motion is confined in the path using parallel RF electrodes bordered by direct current guard electrodes. The RF electrodes are arranged perpendicular to the direction of ion motion on the device surfaces and the direct current guard electrodes run parallel to the direction of ion motion [9]. With modifications, the resolving power of a SLIM device can be further increased by having ions do multiples passes of the same pathlength, but a limiting factor is that faster ions can "lap" slower ions leading to potential co-arrival at the detector [12]. A newer version of the SLIM device overcomes this by utilizing multiple stacked pathways where ions are transported from level to level in order to increase the pathlength without ions lapping one another [13].

FAIMS, also called differential mobility spectrometry (DMS), uses an asymmetric radio frequency waveform (separation voltage, SV) applied perpendicular to the direction of ion movement between two parallel electrodes and works like an ion filter (ion discrimination with FAIMS being somewhat comparable to a quadrupole analyzer). After being swept into the device by a carrier gas, ions oscillate up and down between the two parallel electrodes as the SV is varied from low to high fields; ions are filtered based on differences in their mobility towards one of the electrodes in the presence of the carrier gas. A compensation voltage (CV) is applied in order to allow a specific ion to pass through the parallel electrodes of the device without being eliminated by contact with an electrode. The optimal CV for a specific ion is dependent on the selected SV in the device. CV is not comparable to CCS and drift time, parameters that are not determined in a FAIMS device. FAIMS devices can be used for the targeted analysis of ions of interest with optimal CVs selected or in a non-targeted manner where the CV is step-wise scanned across a specified voltage range at selected SVs [4,8,14].

Unlike drift tube-based ion mobility approaches (DTIMS and TWIMS), where an electric field causes ions to be in motion and pulled through a stationary gas, TIMS uses a drift gas to push ions into and out of a stationary cell where they are trapped by an electric field. The ions are scanned out of the TIMS device in the presence of the moving drift gas at specific elution voltages (EVs) as the electric field is decreased. Ions with larger CCS values move out of the TIMS device faster and the associated EV is used to characterize the ions. Calculation of CCS

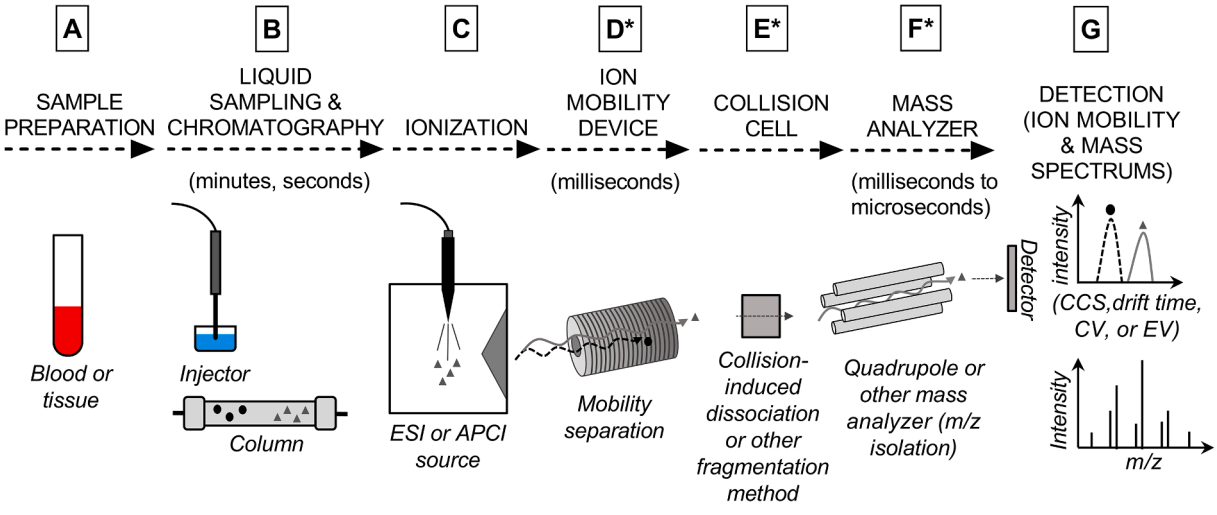

Fig. 1. IMS-MS, from sample preparation to ion analysis. (A) Biological sample clean up and preparation, (B) liquid sampling with subsequent chromatography or FIA, (C) ionization of sample (e.g., electrospray ionization or atmospheric chemical ionization being standard for LC), (D*) ion mobility device, (E*) collision cell, (F*) mass analyzer, (G) ion detection and generation of ion mobility & mass spectrums. (*Order can vary depending on the instrument arrangement, and multiple mass analyzers and collision cells are sometimes utilized.)

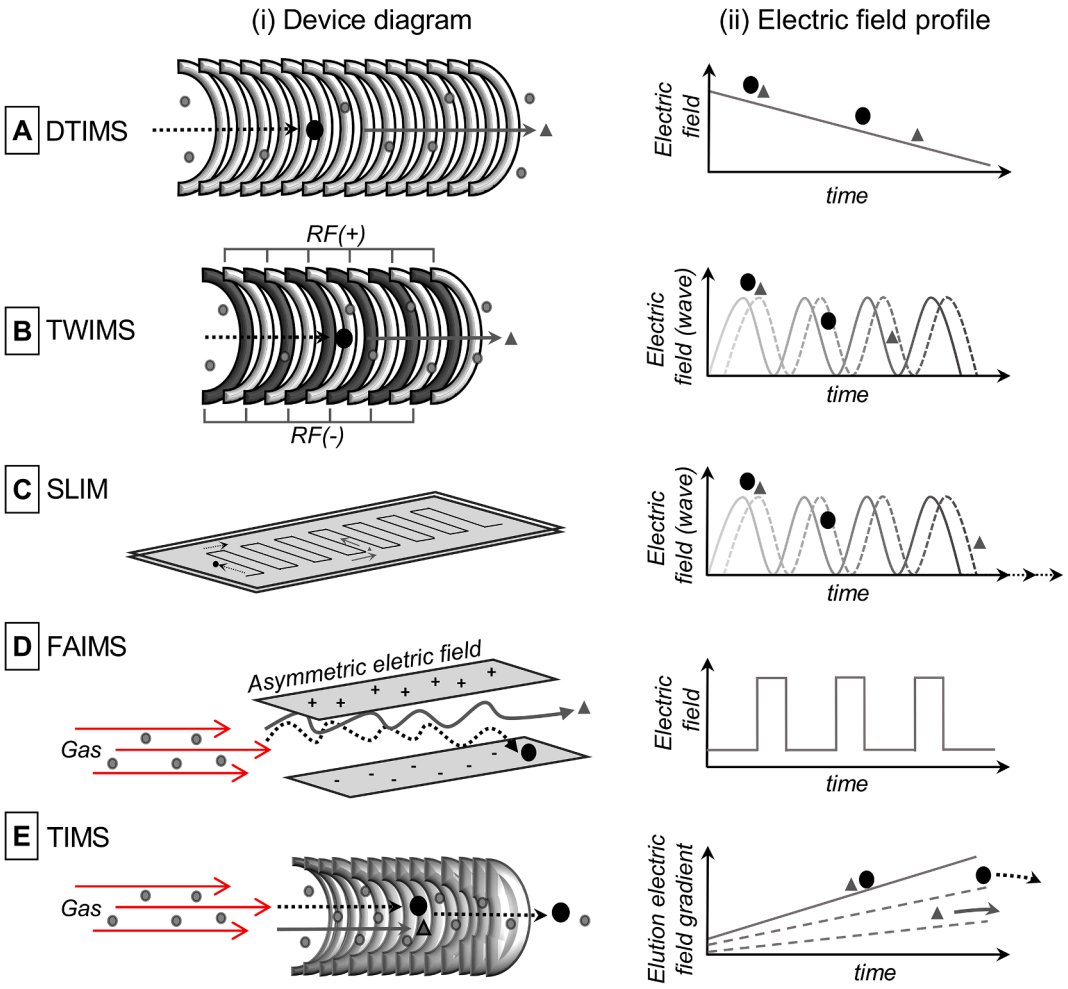

Fig. 2. IMS devices (i) Diagrams and associated (ii) electric field profiles for (A) DTIMS, (B) TWIMS, (C) SLIM, (D) FAIMS, and (E) TIMS.

directly can be done by TIMS, but requires the measurement of key parameters, such as the gas velocity and pressure inside the cell; normally the determination of CCS values by TIMS are done using calibration to ions with known CCS values [4,5,15].

Coupling IMS with MS is dependent on both effective transfer of ions into the devices, as well as compatibility of the IMS and MS analyzer scanning rates. DTIMS, TWIMS, and TIMS devices operate on the millisecond time scale and are most often paired with time-of-flight (TOF) mass analyzers as they operate on the microsecond time scale and multiple MS scans can, therefore, be acquired during an IMS scan [4]. Alternatively, FAIMS is a continuous ion selection device and is compatible with most mass analyzers due to its relatively slow scan rate and does not require low pressures like other IMS devices. Orbitrap and fourier-transform ion cyclotron resonance (FTICR) analyzers have higher mass resolution capabilities than TOF analyzers, but have generally slower scan rates and are not as easily (but have been) paired with other IMS devices besides FAIMS [4,16].

Lipids and the analytical benefit of using IMS-MS

By simple definition, lipids are a group of organic compounds that are for the most part insoluble in water (hydrophobic). The International Lipid Classification and Nomenclature Committee (ILCNC) has classified lipids into eight categories: fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids, and polyketides [17]. Lipids have vital biological roles as they are the main constituent of cell membranes, function as energy storehouses, and are transporters and signaling molecules both intra- and extracellularly [18]. Inherited errors of metabolism (caused by genetic mutations) [19,20] can lead to deficiencies in *de novo* synthesis, catabolism, or transport of lipids within the body. Abnormal lipid homeostasis can result in a broad range of health complications including central and peripheral nervous system problems, skin disorders, growth abnormalities, inflammation, diabetes, and cardiovascular disease [21]. Of note, genetic as well as a complex combination of lifestyle and environmental factors can cause atherogenic dyslipidemia associated with metabolic syndrome and increased lifetime risk of atherosclerotic cardiovascular disease [22,23].

MS plays an integral role in elucidating and quantifying lipid species for both basic science and clinical research. Many lipid species are structurally and chemically similar, requiring, at minimum, separation by chromatographic means for MS characterization and quantitation. IMS-MS offers a way to enhance the separation of LC or GC co-eluting lipids, providing CCS and IMS device drift times for individual lipids, possibly shortening analytical run times, and serving as an analytical tool for when an interference is suspected in a sample. Plotting CCS (also drift time, CV, or EV) vs. m/z (and also vs. LC retention time) can be used to generate 2D and 3D data spaces, and thereby further characterize lipid species [24]. In general, different classes and subclasses of lipids follow linear trend lines when the IMS parameter, such as CCS, is plotted against m/z [25,26]. CCS values may also be potentially utilized for standardized database searching as they are not instrument dependent if the analyses are performed under the same experimental conditions [10,27–29]. Several recent reviews have been published on the application of IMS for lipid analysis [25,30–37]. The following section highlights several recent utilizations of IMS for lipid applications.

Application of IMS-MS to the analysis of plasma and tissue lipids

Fatty acyls, glycerolipids, glycerophospholipids, sphingolipids

A large amount of the biological diversity in lipids comes from the existence of positional isomers as a result of variations in fatty acyl chain locations (*sn*-backbone isomers) on glycerol and the presence of fatty acyl chain double bonds in either *cis* or *trans* geometries. IMS provides a way to enhance the separation of these isomers within lipid subclasses. Dit Fouque et al. utilized LC-TIMS-high-resolution mass spectrometry (HRMS) to investigate the separation of several glycerophosphocholine (PC) and diacylglycerol (DG) lipids with varying acyl chain locations, double bond positions, and double bond geometries found in human plasma [38]. LC was found to be sufficient for separation of PC and DG isomers differing in acyl chain double bond locations or geometries. Application of TIMS was useful for the separation of DG isomers with different acyl chain positions but the same double bond geometries, which could not be separated by LC alone. IMS has also been increasingly used in imaging MS for resolution of isomers. Matrix-assisted laser desorption/ionization (MALDI) TIMS-MS was recently demonstrated to be able to separate several glycerolipid isomers including phosphatidylglycerols (PGs) and PCs [39]. In the study, TIMS was able separate isomers indistinguishable by MS alone and demonstrate different spatial distributions in mouse tissues. Application of tissue MS imaging for clinical use is in the very early stages, but integration of IMS will help to reduce ambiguity arising from isomeric species, as well as other isobaric interferences.

Sphingolipid subclasses (having a common sphingoid base backbone) have also been investigated using IMS-MS. Interestingly, as resolution using IMS can be limited by overall path length, a recent application of a long pathlength prototype SLIM device (utilizing traveling waves) demonstrated robust resolution of ganglioside isomers from mouse brain tissue [40]. Another study investigated potential ceramide biomarkers of Farber disease in plasma and dried blood spot samples from patients, carriers, and a control group using TWIMS [41]. Farber disease is caused by genetic deficiency in the lysosomal enzyme acid ceramidase and currently lacks robust biomarkers. Ceramide C26:0, and particularly one of two isoforms (the isoforms having different CCS values), was a specific and sensitive disease marker [41]. Recently, the plasma elevation of several ceramides have also been found to be associated with major cardiovascular events in patients with and without coronary artery disease [42]. Investigations using IMS-MS on plasma and perhaps plasma subfractions (discussed later) may yield further ceramide cardiovascular biomarkers for use in the clinical setting.

Acylcarnitines also contain a fatty acyl group that can have isobars present in circulation. Flow injection analysis (FIA) using HRMS for newborn screening (NBS), instead of standard approaches by low resolution triple quadrupole MS, has been demonstrated to be a viable means of separating nominal isobaric acylcarnitines, such as malonylcarnitine and 3-hydroxybutyrylcarnitine [43]. Application of IMS to HRMS may provide a future means of separating isomers and removing unknown isobaric interferences in the context of first-tier NBS [44]. Overall, the combination of IMS with MS is useful for the separation and determination of specific lipid isomers arising from relatively small structural differences in the fatty acyl chains.

Steroids

IMS-MS has been used for the analysis of steroids, which are initially derived from cholesterol in the body and primarily act as signaling molecules (hormones) through steroid receptors. Cholesterol and other steroids are also integral components of cell membranes. In general, steroids have the same carbon-fused ring structure containing three cyclohexane rings and one *cyclo*-pentane ring; secosteroids, such as cholecalciferol (Vitamin D_3), have a broken core ring structure. Based on their functionality, steroid hormones can be classified as corticosteroids, sex steroids, and neurosteroids. Corticosteroids are involved in glucose metabolism and immunity (glucocorticoids), and regulation of water and salt in the body (mineralocorticoids). Sex steroids (progestogens, androgens, and estrogens) are involved in reproductive function and secondary sex characteristics. Neurosteroids are active in the brain, acting as inhibitors and excitors of neurotransmission, and also pheromones [45]. The relatively low biological concentration and high number of different, but structurally similar, steroids present in circulation makes them, in general, analytically challenging. A recent review by Rister et al. in 2020 highlighted that the application of IMS-MS for steroid analysis was able to improve signal-to-noise ratios, leading to lower detection limits [46].

FAIMS has been utilized in a panel assay developed for routine clinical measurement of corticosterone, 11-deoxycortisol, 11-deoxycorticosterone, 17-hydroxyprogesterone, and progesterone in human plasma and serum for investigation of congenital adrenal hyperplasia (CAH) [47]. Benefits of using FAIMS were improved separation of the isomers 11-deoxycortisol and corticosterone, relative to LC separation alone, and reduced background noise, which was particularly useful at low analyte concentrations. However, the use of FAIMS did lead to an approximately 5-fold reduction in the signal intensity of all analytes, which was compensated for by an optimized extraction protocol [47]. Application of TWIMS without LC separation was reported to partially separate several steroid isomer pairs (β-estradiol & α-estradiol, androsterone & *trans*-androsterone, and testosterone & epitestosterone) only after derivatization with *p*-toluenesulfonyl isocyanate; the non-derivatized forms not being separable by ion mobility [48]. DTIMS has been demonstrated to be able to separate underivatized 25-hydroxyvitamin D_3 from the interfering epimer 3-epi-25-hydroxyvitamin D_3 in serum without the need for increased LC separation time [49]; a potentially useful application in the clinical laboratory for removing a possible cause of overestimating total 25-hydroxyvitamin D_3 concentration without increasing sample-to-sample analysis time.

DTIMS has also been used for investigating the separation of underivatized endogenous steroid isomers, without LC separation, ionized in monomeric and dimeric form as cation adducts with various metals, including transition metals and alkaline earth metals [50]. Some steroid isomers in monomeric form that were minimally separated were found to be optimally baseline separable as either sodiated dimers or transition metal dimer adducts with selection of a certain IMS drift gas. CCS values for steroid isomers were determined in several different drift gases [50]. Interestingly, an interlaboratory comparison of TWIMS CCS values for a large panel of steroids using N_2 as the drift gas was recently conducted [29] and is a step towards generation of standardized CCS databases. Generation of CCS databases is also of interest in anti-doping analysis to identify isomeric and isobaric compounds not easily separable by LC alone; various steroid and glucocorticoids are among banned substances. Recently, CCS values were determined for a panel of 192 doping agents using LC-TWIMS-HRMS with N_2 as the drift gas [51]. A system of external proficiency samples for CCS evaluation under standardized analytical settings would be beneficial for implementation of IMS-related strategies in the clinical setting.

Application of IMS and IMS-MS to lipoprotein analysis

Lipoprotein particle analysis

IMS has also been utilized in the investigation of lipoproteins, which are a diverse group of particles that transport cholesterol, cholesterol esters, triglycerides (TGs), phospholipid species, and other fats to tissues throughout the body. Increased levels of low-density-lipoprotein (LDL) and decreased levels of high-density-lipoprotein (HDL) are well established risk factors for cardiovascular disease (CVD). The concentration of various particle sizes found within lipoprotein classes is information not captured by routine clinical estimation of total LDL-cholesterol using

the Friedewald equation, or by other direct measurements. In particular, elevations in small dense LDL particles are associated with increased CVD risk [52].

Musunuru et al. utilized IMS to evaluate LDL and HDL particle size profiles and associated concentrations from the plasma of healthy subjects as a prospective predictor of CVD risk [53]. IMS analysis of lipoprotein subfractions was also utilized as part of the JUPITER trial where LDL and HDL particle size and concentration profiles were investigated for CVD risk between patients either on high-intensity statin treatment or placebo [54]. More recently, Vaisar et al. used IMS for the determination of HDL particle size and concentration associated with protection from vascular complications in type 1 diabetes [55]. IMS analysis of the plasma lipoprotein particle size and concentration profile for evaluation of CVD risk is currently offered commercially as a clinical test [56].

Lipid composition of lipoprotein subfractions

IMS alone does not provide direct information about the lipid composition of various lipoprotein particle sizes circulating in the body. Lipidomic investigation of isolated lipoproteins is a fairly new but increasing area of investigation for the identification of novel biomarkers for CVD risk (recently reviewed by Ding et al. [57]). In order to investigate the lipid composition of specific plasma lipoprotein subfractions they must first be isolated, typically by density ultracentrifugation [58], and then extracted. Analysis is most often by LC-MS for either targeted or non-targeted approaches [59,60]. Application of IMS-MS specifically to lipid analysis of isolated LDL and HDL subfractions is limited as of yet, but would improve selectivity where LC alone cannot separate isomers and other interfering species. One example is a study by Ferchaud-Roucher et al. [61], where LC-HRMS with TWIMS was utilized to investigate the lipid composition of isolated plasma subfractions of very-low-density lipoprotein (VLDL), LDL, and HDL to evaluate differences between hypertriglyceridemic patients on niacin treatment vs placebo. Niacin being a drug used for the reduction of circulating TGs and LDL-cholesterol, and increasing HDL-cholesterol. Differences between niacin treatment and placebo for several lysophosphatidylcholine (LPC), phosphatidylethanolamine (PE), sphingomyelin (SM), and TG species were observed for VLDL, LDL, and HDL isolates. The application of TWIMS was indicated to be specifically useful in the study to separate the LC co-eluting TG(50:3) and TG(52:4) species, which were then proposed to be the structural forms TG(16:0/16:1/18:2) and TG(16:0/18:2/18:2), respectively, by HRMS. The positional connectivity of the fatty acid chains was not determined [61]. An area of future clinical investigations of CVD risk might be the correlation of lipoprotein particle size and concentration by IMS against lipidomic profiling of the same lipoprotein subfractions by LC-IMS-MS. Perhaps there may be a role for IMS-MS in automated testing of specific lipoprotein subfraction lipid biomarkers for CVD risk.

Conclusion and future perspective

IMS is useful in the investigation of lipid species for separation of isomers, separation of overlapping signals, lowering background interferences, and determination of CCS values for analyte characterization and database searching. It is a technique where gas phase ions are separated via their mobility (based on CCS) through a buffer gas in the presence of an electric field and provides an additional analytical layer complementary to MS where ions are identified in a mass analyzer based on their m/z. IMS and MS are not completely orthogonal techniques because the mass of an ion also increases as the size of an ion increases. Currently, the utilization of IMS-MS in a clinical diagnostic setting is limited, but this may change as high-resolution MS systems that now often come with IMS functionality become more commonplace in clinical laboratories. Future consideration and development of standardized guidelines for applications of IMS with MS in clinical diagnostic testing and clinical trials will be needed for a broader acceptance of this technique in a regulated environment. A guidance document has been previously published describing processes to standardize the reporting of IMS-MS experimental data [5] and is a step towards harmonization of IMS-MS analyses.

In the future, the implementation of IMS along with, or as a substitute for, traditional LC or GC separation techniques coupled with MS has the potential to increase analytical specificity and reduce sample-to-sample analysis time in the clinical laboratory. Improvements in the overall resolving power of next generation IMS systems (such as SLIM) or other separation techniques are still needed in order to consider future scenarios where IMS might actually replace LC or GC separations in the clinical laboratory. Incorporation of IMS approaches may possibly simplify procedures and speed-up sample-to-sample analysis times, but must still maintain accurate identification and quantitation. This is of particular interest for lipid-related analyses where many endogenous isomers and structural analogues exist and relatively long LC or GC run times are often needed for accurate quantitation. Additionally, new high-speed sampling techniques, such as acoustic droplet ejection in combination with an open-port interface to the electrospray ionization source [62] may also facilitate faster sample-to-sample analysis times, as well as reduce carryover issues associated with traditional needle-based autosampler approaches. One can begin to envision high-speed liquid sampling in combination with IMS-MS approaches that might lead to analysis speeds similar to that of a plate reader for certain applications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could affect the work reported in this paper.

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