Chapter

Lipidomics as a Tool in the Diagnosis and Clinical Therapy

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Abstract

The lipids are essential compounds of cells, with biochemical and structural properties. Lipids are classified according to their chain length or saturation levels and biogenesis. Lipidomics is a spectroscopic and spectrometric technique, like Mass Spectrometry and Nuclear Magnetic Resonance, as well as bioinformatics to quantify and characterize the lipid profile. Lipidomics enables the fundamental understanding of lipid biology, the identification of drug targets for therapy, and the discovery of lipid biomarkers of disease cohorts. Therefore, lipidomics allows knowing the diagnosis and clinical follow-up in medical therapy towards any disease. In this way, the lipid profile allows us to monitor the administration of a clinical treatment and assertively diagnose human diseases.

Keywords: clinical biomarkers, lipid biomarker, lipidomic methodology, lipidomic profile, personalized medicine

1. Introduction

Lipids are prominent among the four main macromolecules (the others being amino acids, carbohydrates, and nucleic acids) in the diversity of molecular species [1]. They are essential to the biochemical and biophysical properties of all cells [2, 3]. Lipids serve as energy storage sources [4], homeostasis regulators [5], and nutrients; besides, they participate in events of pathophysiological importance [6]. Current estimates place the number of lipids at 100,000–500,000 [6].

Classification of lipids is based on their chain length, backbone, or saturation levels. Chain length classification is self-explanatory, while lipids are categorized into phospholipids, glycolipids, SPH, and sterols based on their backbone or saturated or unsaturated according to their saturation level [3, 7]. Complex

lipids, such as glycolipids and sphingolipids, are combinations of carbohydrates or sphingoid bases and fatty acids [3]. Ceramides are bioactive lipids that participate in biochemical reactions, such as metabolism, apoptosis, and inflammation, that produce cardiovascular diseases when dysregulated [8]. Lipids comprise around one-third of the components of cells and are essential to metabolism and intracellular signaling. Thus, fully understanding their dynamic is fundamental to preventing, diagnosing, and treating a wide range of human diseases [9], such as cancer, where lipid biosynthesis is often increased [10]. However, the diversity and number of lipids as well as their variation between individuals is a current topic under study [6].

Lipidomics is a sub-branch of metabolomics devoted to studying the complete lipid profile within a cell, tissue, or organism through spectroscopic and/or spectrometric methods in combination with bioinformatic analysis [4, 9, 11]. This combined approach provides a comprehensive understanding of the role of the lipid profile –the lipidome– in biological systems [12]. Thus, the stability and reproducibility of the analytical methods are critical for producing reliable output [13]. The degree of understanding of lipid biology available through lipidomics facilitates biomarker discovery and offers therapeutic possibilities [6]. A case in point, it developed a mouse model for the Gulf War Illness through lipidomics, which led to a therapy scheme that effectively modified the lives of roughly 250,000 soldiers affected by the disease. This chapter reports on the importance of lipidomics in diagnosing and clinical follow-up in medical therapy [14, 15].

2. Toward personalized medicine

2.1 Omics sciences: the big data age

Lipid analyses performed on clinical chemical analyzers, such as TAG, HDL-C, and FC, have traditionally been used to analyze and predict the state of health and/or the risk of developing a disease [16]. But with the advent of the post-genomic era, these individual analyses are quickly being replaced by broad "-omics" studies, made possible by a rampant development of precision instrumentation and computational resources [4]. This technology allows analyzing a large number of biological samples in a profitable way for clinical tests [17]. Multi-omics research strategies have proven to be a comprehensive system for the identification of biomarker molecules, which can detect individuals with potential risk of diseases, as well as their nutritional evaluation [18]. Illnesses can be studied in greater detail through lipidomics since they comprehensively evaluate the metabolites and metabolic pathways [19], allowing the simultaneous study of several lipid species in body fluids [20]. This balance between flexibility and detail is the cornerstone of personalized medicine.

The use of omics over classical markers has clear advantages. It has, for instance, yielded more practical and valuable indicators for diabetes, contributing to a broader picture of the disease [21]. Moreover, lipidomics findings are being combined with other omics studies –such as transcriptomics, metabolomics, and proteomics–and advanced imaging to reach a previously unattainable degree of precision phenotyping in progressively numerous cohorts. Undoubtedly, biomarkers and pharmaceutical targets discovered through these combined approaches are rapidly gaining importance in clinical scenarios [22, 23].

2.2 Lipid biomarkers in the clinic

Biomarkers are quantifiable characteristics distinctive of metabolic or pathogenic processes; the latter enables diagnostic, treatment assignment, and response monitoring [18, 24]. Individual lipids and lipid profiles have been appointed as biomarkers of human diseases and are analyzed by means of various chromatography techniques coupled with mass spectrometry, as summarized in **Table 1**.

Pre-analysis	**Instrumentation**	**Analysis/Post-analysis**	**Ref.**
Disease (biological sample)	**(Mass analyzer) system**	**Results/Conclusions**	
44 cystic fibrosis patients (plasma)	(ion-trap) LC-MS	PC and LPC detected species	[25]
DM-2 and NAFLD patients (plasma)	GC-MS *NMR^1H	Liver fat content is strongly associated with Chol synthesis independently of obesity	[26]
6 **preeclampsia patients** (placental)	(Q-trap) LC-MS	Lipids of STBM are implicated in immune response, coagulation, oxidative stress and apoptosis.	[27]
7,500 Atrioventricular septal defect patients (blood)	(Q-Trap) LC-MS GC-MS	Biomarkers will be assessed for association, calibration, discrimination and reclassification	[23]
3 Gaucher disease patients (plasma and urine)	(ion trap) nLC–ESI–MS/MS	20 plasma and 10 urinary lipids were selected as significant species of Gaucher disease	[28]
10 CKD patients (stage 4/5 renal disease) (plasma)	(LTQ) LC-MS/MS	Lipid alterations in CKD disease (plasmenyl ethanolamines, sulfatides, Cer and Chol sulfate)	[29]
8 CVD patients: lipoprotein apheresis treatment (plasma)	LC-MS/MS	Increases of anti-inflammatory lipid mediators derived from AA or EPA and DHA.	[30]
150 coronary disorders Tunisian patients (blood)	GC/MS-SIM	PA and PS as biomarkers of peroxisomal metabolism disorders in atherosclerosis progression.	[31]
30 hypercholesterolemia pregnant women (plasma)	(QTOF) UPLC- MS/MS	PC (16:0/20:4) (18:0/20:4) lipid species in cord blood affected by gestational hyper-cholesterolemia.	[32]
75 anorexia nervosa patients (plasma)	GC/MS	Increased: ω-3 ALA, EPA. Decreased: ω-6 to ω-3, LA, ALA, AA, EPA. Dysregulated PUFA metabolism	[18]
18 advanced rectal cancer patients: CAPOX-treatment (plasma)	MRM-LC-MS/MS	LPE (22:5/0:0), SM (d18:2/18:1), LPC (16:0/0:0), LPC (15:1(9z)/0:0) and PC (40:2) are lower in NRP	[33]
20 myeloid leukemia patients (plasma)	(QTOF)UPLC-ESI-MS. GC-MS	Increase of AA precursors in leukemia patients' plasma. New targets for drug therapy	[5]
30 nascent MetS patients (plasma)	(QTOF) LC-MS/MS	Increases of PC (34:2) in patients with MetS. Novel biomarker in MetS.	[34]

Pre-analysis	**Instrumentation**	**Analysis/Post-analysis**	**Ref.**
Disease (biological sample)	**(Mass analyzer) system**	**Results/Conclusions**	
172 AD patients (plasma)	(LTQ) UHPLC-ESI-MS/MS	TAG (50:1), DAG (18:1) and PE (36:2) present in brain atrophy.	[35]
15 DM-1 and diabetic nephropathy children (urine)	(Triple TOF) UHPLC-MS	Increase of Cer (44;0,2) and HexCer species, suggesting as biomarkers of renal function decline.	[36]
70 endometriosis (plasma/peritoneal)	(QTOF) LC-MS/MS	Biomarkers: LPC 16:0, PE O-20:0, PE O 34:1, PC 36:2, PC 36:4, PC 36:5, PC 38:4, PC 38:6 and SM 34:1.	[37]
Liver/gastric/lung/colorectal/thyroid cancer (plasma-urine)	(ion trap) nUHPLC-ESI-MS/MS	LPE and PS high in thyroid cancer. Validation of cancer-specific lipid markers	[38]
432 DM-1 patients (plasma)	(triple Q)LC-MS/MS	lactosyl-Cer: predicts macroalbuminuria in DM-1	[39]
Multiple sclerosis patients (plasma)	(triple TOF) LC-MS	Cer-induced DNA-methylation of antiproliferative genes.	[40]
67 unipolar/bipolar disorders patients (plasma)	(Q Trap) LC-ESI-MS/MS	Increases: Cer (C16, C18, C20, C22, C24, C24:1, C24:1GluCer, C24 lactosylceramide), DAG, TAG	[41]
20 colorectal cancer patients (colon tissue)	LC-MS/MS	Increases of LPC, LPE, LPI (18:1) and LPI (18:0)	[42]
63 cutaneous leishmaniosis patients: treatment (plasma)	(triple TOF) LC-MS/MS	LTB4, 5-HETE, 5-oxo-HETE, 12-HETE, 11-HETE, PGE2, and 15-HETE. Targets of therapy	[43]
29 SARS-CoV-2 patients (plasma)	UHPLC-MS/MS	Alterations in PAs, sterols, SPHs and LPAs. Increases of Cer-phosphorylethanolamine and PE.	[44]
13 multiple sclerosis patients (post mortem brain tissue)	(Q-Trap) LC-MS/MS	Multiple sclerosis lesions: decrease: dhCer, Cer and SM subspecies. Increase: HexCer, Cer 1-phosphate	[45]
47 mTLE-HS patients (hippocampal sclerosis)	(QTOF) UPLC-ESI- -MS	33 lipids expressed. Decreased: Cer and lactosylceramide levels in mTLE-HS patients.	[46]
40 MetS patient (plasma)	(QTOF)/(Q-orbitrap) UHPLC-MS	PC: 18:1/16:0, o-22:3/22:3, P-18:1/16:1. Choline metabolism is affected. Biomarkers with prediction.	[24]
221 myopia children/adolescents (serum)	UHPLC-MS	275 metabolite presents in 33 pathways	[47]
106 colorectal cancer patient (tumor tissue)	(Q-Trap) HRMS/LC- MS/MS	Presence: LPC (16:1, 18:1, 20:4, 22:6) and SM species. Cer: C24:0–C26:0. GPL, GL and SM	[48]
Mild/moderate/severe asthma patients (bronchoscopy)	(orbitrap)-UPLC-MS	Increase: PC, LPC, bis (monoacylglycerol) phosphate. Decrease: OXPHOS (severe asthma).	[49]
33 lupus erythematosus patients (blood)	(triple Q) LC-MS/MS	Increase: LPL, PS species. Decrease of plasmalogen.	[50]

Pre-analysis	Instrumentation	Analysis/Post-analysis	Ref.
Disease (biological sample)	**(Mass analyzer) system**	**Results/Conclusions**	
826 AD cirrhosis patients (serum)	LC-MS/MS	SM permit distinguish between patients with compensated and decompensated cirrhosis.	[51]
15 Niemann-Pick disease patients (plasma)	LC-MS/MS	Increase: DG, AA and CE.	[52]
COVID-19 asymptomatic patients (serum)	(TOF) UHPLC-TIMS	15 lipids present in asymptomatic COVID-19 patients.	[53]
29 lung adenocarcinoma (tumor tissue)	(Q-orbitrap) LC-MS/MS	Increases of free-cholesterol and CE (18:1 and 20:4)	[54]
37 persons recovered/severe (SARSCoV-2) (plasma donor)	(QTOF) HILIC-LC-MS	Levels of fatty acyls and GPL were lower in recovered patients	[55]
SARS-CoV-2 peripheral leukocytes, colon/jejunum (plasma)	HPCL-MS/MS	Infection involving EPA, AA and gonadal steroids. ω-3 FFA associated with SARS-CoV-2 receptors	[56]
132 metastatic castration-resistant prostate cancer patients ENZA/AA drugs (plasma)	LC-MS	Increased Cer was associated with androgen receptor signaling inhibitors resistance.	[57]
60 CHD/HLP patients: *Salvia milthiorriza* treated (plasma)	(QTOF) UPLC-MS	Presence: PC (18:0/18:4; 18:2/16:0), PE (15:0 /22:1), LPC (0:0/18:0). *S. miltiorrhiza* reduce lipids	[58]
256 arthritis rheumatoid patients (serum)	(Q-orbitrap) UPLC-MS	Biomarkers: PE 16:0-18:2, TG 18:0-18:1-18:2	[13]
Patient: proteinuria, Fabry disease (plasma)	(Orbitrap) HRMS-UHPLC-MS	Galabiosylceramide-related lipid biomarker was higher in the patient's renal tissue biopsy	[12]
126 COVID-19 patients (serum)	(QTOF) UHPLC-MS	Biomarker: LPC 22:6, PC 36:1, bile acids. Lipidomics/machine learning techniques	[59]
206 obstructive sleep apnea patients (plasma)	(QTOF) UHPLC-ESI-MS/MS	GPL and bile acids are present. Adaptive mechanisms in response to obstructive sleep apnea	[60]
20 radiation/atherosclerotic carotid plaques patients	(QTOF) DESI-UPLC-MS	Biomarkers: 6 TG in the radiation-induced carotid plaques and atherosclerotic carotid plaques.	[61]
112 cystic fibrosis patients: drugs ELX/TEZ/IVA (plasma)	LC-MS/MS	Decrease: Cer (C16, C18, C20, C24:1). Up-regulation dhCer C24. ELX/TEZ/IVA	[62]

[*] *Spectroscopy method.*

Table 1.
Methodology, instrumentation, and human diseases diagnosed by lipidomic profiles.

In CKD, TAG, and N–acyl taurines increased, although total lipid and cholesterol levels, usually evaluated in clinical biochemistry, remain unchanged [29]. In patients infected with DNefHIV, lipidomic profiles revealed differences in the abundance of PS and SPH [63]. ACLF patients present with a particular lipid profile, mainly

comprising CEs. These lipids also predict AD treatment outcomes [51]. In adverse pregnancies, the STBM contained the potential biomarkers SM, Chol, PS, PC, and PI [27]. In patients with CVD, the presence of the Cer d18:1/16:0, Cer d18:1/24:1, and Cer d18:1/24:0 were associated with a fatal outcome [8]. In DM-1, lipidomics can predict changes in SPH distribution associated with increased vascular permeability in different organs; this occurs only during the early onset of the disease and plays a critical role in developing complications [39]. In mTLE-HS patients, alterations to the hippocampus lipidome with potential for lipidomics-based therapies were reported. [46]. Lysophosphatidyl ethanolamine and lysophosphatidyl inositol species were associated with a number of cancer types. They are present in the liver (four PI and DAG 16:1_18:0), gastric (PI 34:2, 36:3, and 36:4, and LPA 18:2), lung (LPI 16:0, SM d18:1/20:0 and TAG 50:1 and 54:4), and thyroid cancer (LPI 18:0 and 18:1) [38]. Lipid differences between tumor and normal tissue have been proved to be of diagnostic and therapeutic significance [64]. Meanwhile, the upregulation of SPH downregulation of PI and glycerol phospholipid metabolism are associated with worse survival in patients with adrenocortical carcinoma [65].

In patients with depressive conditions, oxylipin concentration fluctuates between depression states. Dietary ω-6 (LA, AA) and ω-3 (EPA and DHA) fatty acids may underlie inflammatory states in symptomatic major depressive disorder with a seasonal pattern [66]; while brain lipidome changes include decreased PI, PA, and CL contents have been described [67]. Obese children with NAFLD showed increased hepatic epoxyeicosanoids with higher grades of steatosis and unaltered PUFA precursors [68]. In addition, in ACLF, Lipoxin A5 and epoxy keto octadecenoic acid formed a signature associated with coagulation and liver failures [69]. Moreover, in myocardial infarction, lipidomics showed an association between 2-aminoadipic acid and alterations of plasma metabolic signaling of hexoses, amino acids, biogenic amines, acylcarnitines, glycerophospholipids, and SPH showing the diagnostic and prognostic limits in acute and chronic heart failure [70].

Exposure to environmental pollutants can also alter lipid profiles; Cer, SPH, and TAG are potential biomarkers of lipotoxicity [71]. Macrophages reprogram their lipid metabolism in response to environmental cues [2]. Finally, there is an association between ether lipid signature and exceptional human longevity [72]. The diversity of conditions associated with differences in lipid profiles supports the growing importance of lipidomics as a clinical diagnostic tool.

2.2.1 Lipidomics in animal health

The study of lipidomics focuses not only on human health issues but also on animal health topics. Lipidomics helped explain the dynamics of inflammation during a bacterial attack in bovine mastitis [73] and provided a diagnostic biomarker for fatty liver disease in dairy cows [74]. Similarly, lipidomics contributed to understanding cystic fibrosis lung disease in newborn pigs [75] and identifying ganglioside disease markers in cats undergoing gene therapy [76]. Examples like these are poised to increase in the coming years as lipidomics extends its prognostic threshold to humans and animals, both economically relevant and wild.

2.3 Lipidomics in the study of rare diseases

Rare disorders remain a challenge even to modern medicine, and mounting evidence shows the prominent role of lipidomics in this scenario [12]. In patients with

Gaucher disease, the lipid profile allowed the diagnosis during enzyme replacement therapy [28]. Olmsted syndrome caused striking decreases in 15-LOX and dhCer levels [77]. In patients with Fabry disease, the presence of glycosphingolipids, galabiosylceramide, and globotriaosylsphingosine is observed in vascular endothelium, nerves, cardiomyocytes, and renal glomerular podocytes [12]. A dysregulation in lipids involved in both cellular structure and membrane integrity was identified in fragile X syndrome, suggesting that X chromosomal deletion disorders are not limited to alterations in neuronal functions [78]. Barth syndrome showed a significant decrease in linoleic acid (18:2)-enriched molecular species, most notably tetra-18:2 (18:2-18:2-18:2-18:2), which is the major molecular species of cardiolipin in the myocardium [79].

2.3.1 Tay-Sachs Disease: an unwanted inheritance

The Tay-Sachs disease (TD) is a very rare (1:300 000) autosomal-recessive lysosomal storage disease [80]. This disorder is caused by mutations in the HEXA gene, which encodes for the β-hexosaminidase (Hex) enzyme [81]. Hex deficiency or low activity causes fatal inherited disorders [80]. Lysosomal enzyme Hex degrades the GM2 ganglioside; gangliosides are glycolipids present in neuronal cell plasma membranes. There are different Hex isoenzymes. HexA has two subunits (α and β), which are encoded by HEXA and HEXB genes, respectively. Hex B is a homodimer (two β-subunits), and HexS is a homodimer (two α-subunits) (**Figure 1**) [82].

Lyso-GM2 ganglioside concentrations in plasma and the brain of TD patients are elevated in association with loss of alpha-hexosaminidase activity. This molecule is thus a useful diagnostic and monitoring biomarker for this disease [83].

2.4 Lipidomics of COVID-19

The ongoing COVID-19 pandemic caused by SARS-CoV-2 has demonstrated the devastating impact of a critical illness on a global scale [44, 84]. In an equally unprecedented effort, the scientific community joined efforts to understand this disease from every conceivable point of view. Almost expectedly, SARS-CoV-2 infection disrupts the cellular lipid profile. Serum from recovered patients displayed different cytokine and lipidomic compositions than patients with severe disease [55]. The overall lipid metabolism increased the production of short- and medium-chain production of saturated fatty acids, acyl-carnitines, and SPH [44]. Lipidomic signatures, including n-3 long-chain PUFA, hydroxy fatty acids, and female gonadal steroids, were linked to SARS-CoV-2 infection [56]. Moreover, in a study by Castane et al. (2022), O-octanoyl-R-carnitine, LPE, AA, and oxylipins were the most altered parameters in COVID-19 patients compared to healthy volunteers, although the number of cases studied was small [59]. SARS-CoV-2 dysregulates lipid metabolism, especially the enhanced membrane phospholipid synthesis, and alters SPH homeostasis, implicating the specific host immune, inflammatory, and antiviral responses in asymptomatic COVID-19 [53] (Hao et al., 2021). Global response to COVID-19 infection highlighted the importance of cost- and time-effective biomarker detection, which is a requirement that lipidomic and machine learning fulfilled in a timely manner [59].

2.5 Lipidomics of pharmacologic interactions

Despite constant scientific advances, resistance and adverse reactions remain a pressing issue in clinical practice [85]; several groups report lipid profile alterations as

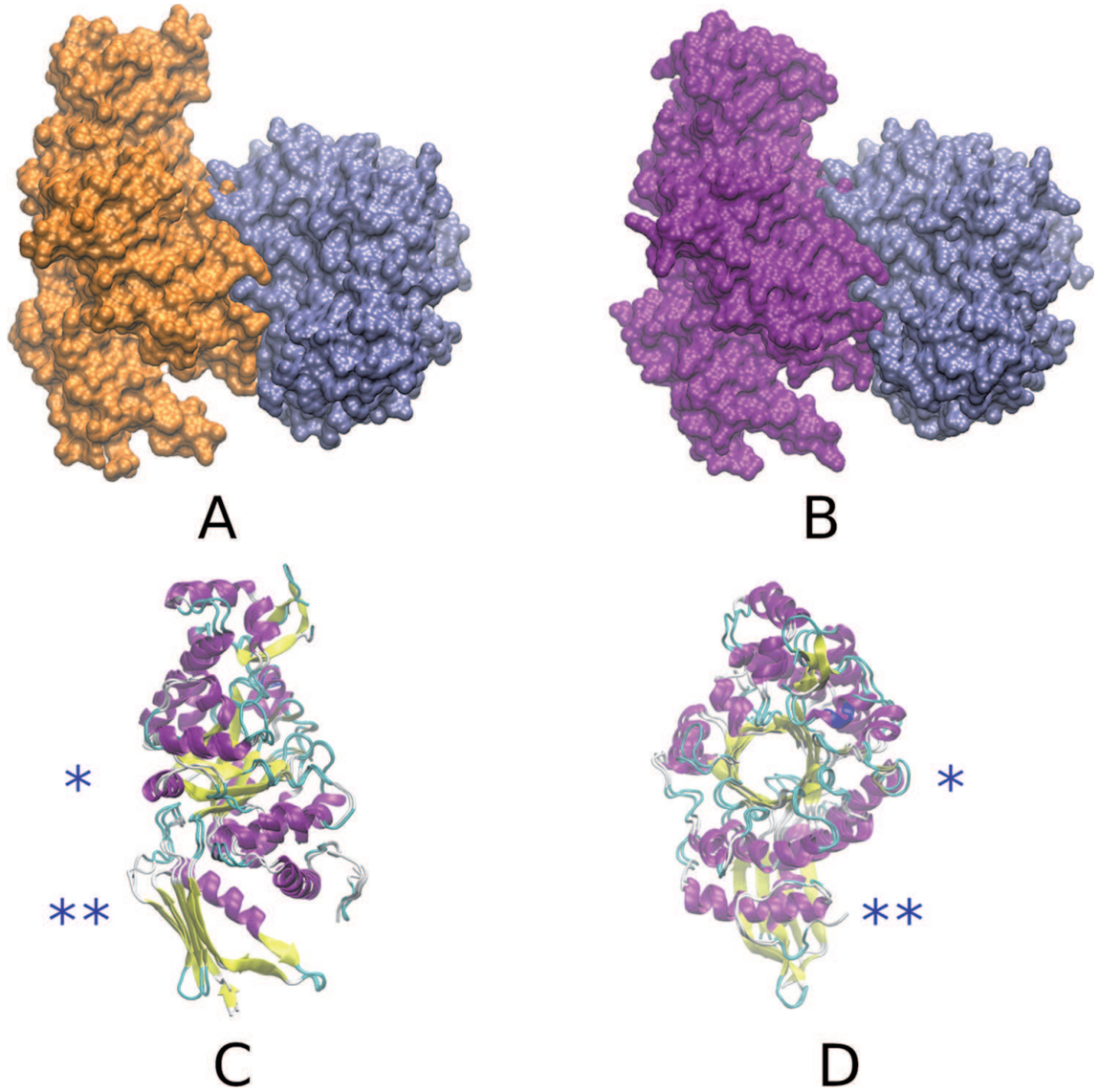

Figure 1.
Human β-hexosaminidase. A) Human β-hexosaminidase isoenzyme A structure (PDB ID: 2GJX) comprises two subunits from different genes. The subunit α (orange surface) is encoded by the HEXA gene (UniProtKB: P06865), and subunit β (blue light surface) is encoded by HEXB (UniProtKB: P07686). B) Hex isoenzyme A structure (PDB ID: 1NOU) comprises two β subunits (purple and blue light surfaces). C) Secondary structure representation of α and β subunits superimposed (helix in purple, β strands arrows in yellow, and turns/coil in cyan/white, respectively) in the same position that subunits orange and purple on A and B. Two CATH domains form both subunits; on the N-terminal, an α-β 2-layer sandwich architecture (**), followed the C-terminal by a catalytic α/beta-barrel fold architecture (*), the typical circular beta-barrel from the TPI enzymes. D) Secondary structure representation of α and β subunits superimposed rotated to see the α/β-barrel fold (*).

reactions to treatment. The antitumoral drug Imidazole Ketone Erastin increased the DAG, monoacylglycerol, and phospholipids, possibly through activation of the TAG hydrolysis enzyme (ATGL) in response to oxidative stress [86]. The CAPOX drugs employed in colorectal cancer treatment elicited differential levels of SM (d18:2/18:1), LysoPC (16:0/0:0), LysoPC (15:1(9z)/0:0), and Lyso PE (22:5/0:0) in responders versus non-responders [33]. In paclitaxel-resistant breast cancer, the forkhead box transcription factor M1 increased TG and PC, and decreased phospholipase D1 and lipid droplets [87]. In brain tumors, GPD1 displayed specific expression in brain tumor stem cells [88]. In general, lipid metabolism irradiation therapy (RT) disrupts

the regulation of lipogenic genes, decreasing LPCs and cholesterol [89]. Meanwhile, in patients with distal esophageal cancer, RT induced cardiotoxicity, detecting six metabolites, after a four-week RT therapy [17].

Similar effects have been observed in human cancer-derived cell lines. Oxaliplatin, a frequent first-line adjuvant therapy for colorectal cancer, altered TAG and phospholipid levels in HT29 cells [85]. Diclofenac altered the cell phospholipid metabolism and induced PUFA accumulation in a neuroblastoma-derived cell line, suggesting tumoricidal potential [90]. The experimental antitumoral drug T-3764518 induced lipidomic changes and suppressed PC desaturation indices in HCT-116 cells [10]. Another experimental drug, FTY720, induced elevated levels of sphingosine, causing apoptosis in leukemic natural killer cells [91]. When treated with inducers of sodium phenylbutyrate (SPB) and all-trans retinoic acid (ATRA), the glioblastoma-derived cell line U87-MG displayed an increase in saturated PCs (38:1), 816 m/z; PC (36:1), 788 m/z; (31:1), 725 m/z, and a decrease in saturated PCs (PC (32:0), 734 m/z). These modifications in the lipidomic profile have potential application in therapy personalization [64].

Not only cancer cells respond to treatment with lipid metabolism imbalances. The VEN/OL drugs increased Cer (C18, C22C, and C24) in patients with depression or bipolar disorder [41]. Statin therapy to treat atherogenic dyslipidemia induced LPC and LPI [92]. Astaxanthin treatment revealed the over-accumulation of myocardial Cer in cardiac fibrosis [93]. Leishmaniasis biomarkers predicted by machine learning and lipidomic profile, such as eotaxin, 11-HETE, and transforming growth factor-β, were useful in identifying potential treatment failure [43]. Older HIV+ Australian men on antiretroviral therapy displayed high lipid dysregulation, specifically in GM3 ganglioside and mon ohexosylceramides, previously identified as frailty biomarkers [94]. Eicosanoid concentration was an indicator of other lipidic alterations in asthmatic subjects with aspirin intolerance [95]. Obese patients with insulin-resistant hypertriglyceridemic hypertension treated with statins showed increased plasmalogen and PUFA levels and reduced PE and PG classes [96]. In obstructive sleep apnea patients, a five-lipid group comprising 25-cinnamoyl-vulgaroside, glycocholic acid, bilirubin, and two previously unreported lipid species changed significantly after continuous positive airway pressure treatment [60]. Canagliflozin treatment increased the amounts of prostaglandin E2 and resolvin E3 in the liver of obese mice used as a biological model to understand the NAFLD [97]. Saroglitazar, a PPAR α/γ agonist, protected patients against obesity, insulin resistance, and steatosis by reducing TG and modulating phospholipid levels. Meanwhile, Hepano, an Ayurveda formulation, did so by modulating phospholipids, Cer, and oxidized lipids [98]. The ELX/TEZ/IVA modulator therapy alters plasma SPH levels and Cer species in cystic fibrosis patients [62]. Systemic lupus erythematosus patients treated with antioxidants displayed an ordered lipid conformation that contrasted with that of untreated patients [50]. The experimental drug J147 used to treat AD, reduced plasma FFA levels [99]. Donepezil, an anti-dementia drug, and the traditional Chinese medicine herbal decoction prepared to treat AD caused modifications in 15 types of compounds derived from PC, SM, and LPC, which are now considered potential lipid biomarkers [100].

As noted in these works, the lipidome is highly sensitive to a wide range of stimuli, so there is vast potential for developing drugs that selectively target these modifications [2]. As Wolf and collaborators (2008) note, lipidomic tools offer a practical option for diagnosis and treatment monitoring in many diseases [101].

2.6 Lipidomics in response to diet: we are what we eat

Recent literature shows a growing interest in lipidome modifications derived from the diet. Pomegranate seed oil and bitter melon extract modify the lipidomic profile of the cardiotoxicity induced by the anti-cancerous therapies showing anti-carcinogenic or cardioprotective properties [102].

The effect of maternal diet supplementation with conjugated linoleic acids influenced the contents of micro-elements in the cardiac tissue of newborns significantly [103]. Orange juice-derived nanovesicles modified the lipidome, decreasing TAG levels [104]. Tangeretin, a flavonoid present in some fruits, reduced body weight gain and ameliorated hepatic steatosis, lowering FFA, DG, TAG, Cer, and Chol levels, as detected by hepatic lipidomic analysis [105]. The diet supplemented with Lactococcus lactis (subsp. cremoris) increased glucose tolerance, developed less liver fat and inflammation, and decreased the oxylipin levels [106]. Moreover, in humans, phytosterol- and ω-3-supplemented milk reduced the LDL-GPL and LPC, inducing cardioprotection in persons with dyslipidemia and metabolic risk [107]. Salmon consumption induced selective incorporation of n-3 PUFA into PC lipids in human plasma, reducing cardiovascular disease risk [108]. Finally, herbal decoctions as in the traditional Chinese [109] and Asian [110] medicine resulted in an improved lipidomic profile in several human

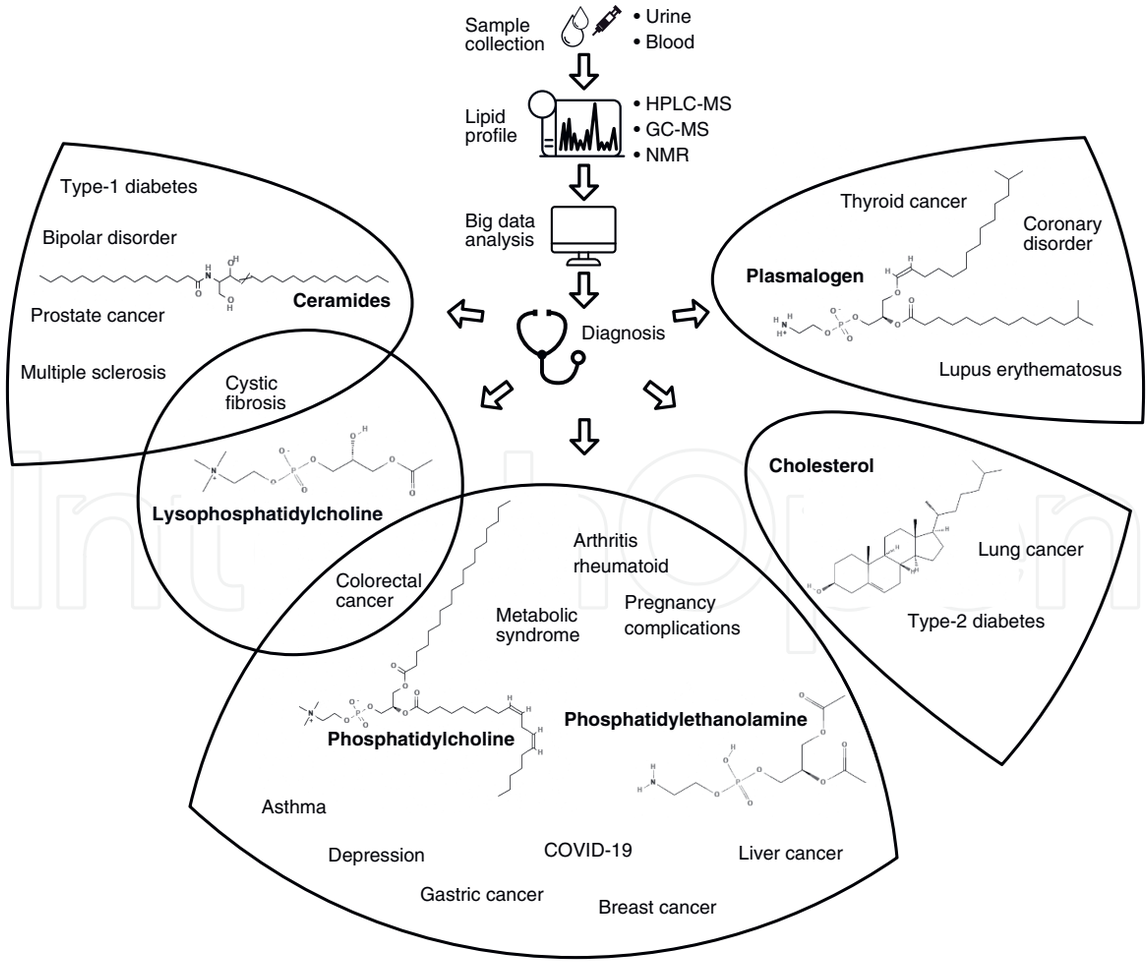

Figure 2.
The biological sample is obtained by noninvasive techniques such as blood and urine samples. Subsequently, the sample is analyzed by spectroscopic (NMR) and/or (mass spectrometry) techniques. Next, the results are compared with spectroscopic and/or spectrometric libraries. Soon, it will be possible to recognize the patients' lipid profile focused on the diagnosis or pharmacological treatment.

diseases. Together, these findings show that diet's therapeutic effects on the lipidome are evident in various human diseases. Ultimately, a clinical-chemical-bioinformatics method is proposed, using recurrent chemical techniques such as NMR [111] and mass spectrometry [112] , for the study of the lipidome in various human diseases (**Figure 2**).

3. Conclusions and perspectives

We live well into the era of big data and the discovery of biomarkers in various diseases through omics tools, such as lipidomics, which are currently in progress. Omics data is becoming increasingly essential for the diagnostic study and monitoring of human diseases and even in animals of economic importance. Therefore, lipidomics is suggested as a "gold standard" technique for the clinical and therapeutic part of this new era in clinical medicine. Finally, we agree with Hyötyläinen and collaborators (2017) [113], who reported that the lipidomic test must become inexpensive, and its added value concerning health economics needs to be demonstrated in a prospective setting.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

PC	phosphatidylcholine
LPC	lysophosphatidylcholine.
NAFLD	Nonalcoholic fatty liver disease.
DM	diabetes mellitus.
STBM	placental syncytiotrophoblast microvesicles.
PG	phosphatidylglycerol.
GPL	glycerophospholipids.
PI	phosphatidylinositol.
PS	phosphatidylserine.
PE	phosphatidylethanolamine.
SM	sphingomyelin.
Chol	cholesterol.
LPE	lysophosphatidylethanolamine.
LPI	lysophosphatidylinositol.
HDL-C	high-density lipoprotein-cholesterol.
DAG	diacylglycerol.
TAG	triacylglycerol.
FFA	free fatty acids.
FC	free cholesterol.
GPD1	glycerol-3-phosphate dehydrogenase.
CKD	chronic kidney disease.
ACLF	acute on chronic liver failure
CVD	cardiovascular disease.
AA	arachidonic acid.
EPA	eicosapentaenoic acid.

DHA	docosahexaenoic acid.
PUFA	polyunsaturated fatty acids.
LA	linoleic acid.
ALA	alpha-linolenic acid.
CAPOX	capecitabine/oxaliplatin treatment.
VEN/OL	venlafaxine and olanzapine treatment.
ENZA/AA	enzalutamide/abiraterone treatment.
MetS	metabolic syndrome.
15-LOX	15-lipoxygenase.
Cer	ceramide.
dhCer	dihydroceramide.
HexCer	hexoseceramide.
Hex	β-hexosaminidase.
GM2	disialotetrahexosylganglioside 2.
PPAR	peroxisome proliferator-activated receptors.
AD	Alzheimer's disease.
TD	Tay-Sachs disease.
ATGL	adipose triglyceride lipase.
NRP	not responder.
HETE	hydroxy eicosatetraenoic acid.
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2 of the genus Betacoronavirus.
SPH	sphingolipids.
LPA	lysophosphatidic acid.
mTLE-HS	mesial temporal lobe epilepsy-hippocampal sclerosis.
CE	cholesteryl ester.
CHD	Coronary heart disease.
ELX/TEZ/IVA	elexacaftor/tezacaftor/ivacaftor therapy.
GC-MS	gas chromatography coupled with mass spectrometer.
NMR H^1	proton nuclear magnetic resonance.
Q-trap	linear trap mass spectrometer.
TLC	thin layer chromatography.
HILIC	hydrophilic interaction liquid chromatography.
ESI	electrospray ionization.
MS/MS	tandem mass spectrometry.
LTQ	linear trap quadrupole mass spectrometer.
SIM	selected ion monitoring.
QTOF	quadrupole time-of-flight.
MRM	Multiple Reaction Monitoring.
Triple Q	triple quadrupole.
Q-orbitrap	quadrupole-orbiting trap.
HRMS	high-resolution mass spectrometer.
DESI	desorption electrospray ionization.
TIMS	thermal ionization mass spectrometry.
HPLC	high-performance liquid chromatography.
UHPLC	Ultra-HPLC.
nUHPLC	nano-HPLC.

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