Review

Lipidomic Profiles in Diabetes and Dementia

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Abstract. Lipids are a diverse class of hydrophobic and amphiphilic molecules which make up the bulk of most biological systems and are essential for human life. The role of lipids in health and disease has been recognized for many decades, as evidenced by the early identification of cholesterol as an important risk factor of heart disease and the development and introduction of statins as one of the most successful therapeutic interventions to date. While several studies have demonstrated an increased risk of dementia, including Alzheimer’s disease (AD), in those with diabetes mellitus, the nature of this risk is not well understood. Recent developments in the field of lipidomics, driven primarily by technological advances in high pressure liquid chromatography and particularly mass spectrometry, have enabled the detailed characterization of the many hundreds of individual lipid species in mammalian systems and their association with disease states. Diabetes mellitus and AD have received particular attention due to their prominence in Western societies as a result of the ongoing obesity epidemic and the aging populations. In this review, we examine how these lipidomic studies are informing on the relationship between lipid metabolism with diabetes and AD and how this may inform on the common pathological pathways that link diabetes risk with dementia.

Keywords: Alzheimer’s disease, diabetes mellitus, lipid metabolism, mass spectrometry, risk

DIABETES AND DEMENTIA

The dramatic increase in obesity over the past three decades, such that it is now at epidemic proportions in many countries around the world, has contributed substantially to an increase in the metabolic sequelae associated with obesity, which includes dyslipidemia, insulin resistance and type 2 diabetes (T2D). In 2013, there were an estimated 382 million people worldwide with diabetes mellitus, of whom almost half were undiagnosed [1]. A further 316 million have impaired glucose tolerance which is associated with dyslipidemia and risk of T2D. Globally the number of people with diabetes mellitus is expected to reach 592 million by 2035 [1].

Diabetes mellitus can be classified into several distinct categories. Type 1 diabetes (T1D) typically develops in early childhood as a result of an immune response against specific proteins, leading to the destruction of pancreatic islet β-cells, which produce the hormone peptide insulin, resulting in decreased insulin production and a persistent dysregulation of plasma glucose. The exact mechanism that triggers the immune response is not known but is believed to involve both environmental and genetic factors [2].
Insulin is the key hormone regulating the metabolism of fats and carbohydrates from the diet promoting the utilization of these nutrients in peripheral tissues such as liver and skeletal muscle as well as in the brain. Deficiency of this peptide leads to hyperglycemia or high blood sugar.

While T1D occurs early in life and is characterized by declining insulin availability, T2D is a metabolic disorder that typically occurs later in life resulting from insulin resistance, where the action of insulin is impaired. While the exact etiology and underlying mechanism is not fully known [3], the major risk factors for the development of T2D are obesity and dyslipidemia, which is characterized by increased central adiposity, elevated triglycerides and low density lipoprotein-cholesterol (LDL-C) and reduced high density lipoprotein-cholesterol (HDL-C) [4].

Alzheimer’s disease (AD) is a neurodegenerative disease resulting in loss of cognitive function. While traditionally AD pathology is associated with accumulation of Aβ peptide and tau hyperphosphorylation, the exact trigger and drivers for disease progression are not fully understood. The production of Aβ peptide is via the action of a family of secretases, membrane bound enzymes that cleave the amyloid-β protein precursor (AβPP). AβPP is firstly cleaved by the enzyme β-secretase, followed by further cleavage with the enzyme γ-secretase. This process leads to the production of Aβ peptides ranging in size between 37–43 amino acids in length. In an alternative pathway, AβPP can be processed via α-secretase, cleaving AβPP within the Aβ domain and thereby precluding the formation of Aβ peptides. Secretases are tightly associated with cellular membranes and while β- and γ-secretases are both located on and regulated by lipid rafts [5, 6], α-secretases, the enzyme in the non-amyloidogenic pathway, exerts its activity via non-lipid raft membrane domains [7].

Aβ accumulation has been the center of many theories of AD development, as mutations in several genes associated with Aβ production leads to early-onset AD, which accounts for a relatively small proportion of AD cases [8]. The majority of AD cases are of late-onset, typically >65 years of age, with no known trigger. Several factors have been identified to modify risk for development of late-onset AD, including age, diet, exercise, education background, family history and genetic risk factors [9–11].

It is now established that T2D is associated with poorer cognitive outcomes, especially in the elderly [12], and in the past decade, mounting evidence suggests T2D as a strong risk factor for dementia and AD [13]. The Rotterdam study reports an almost doubling of risk in those with diabetes [14], as was similarly reported in the Honolulu-Asia Aging Study [15]. While the exact link between diabetes and dementia is not fully understood, it is believed that the interplay between peripheral and brain insulin resistance, microvascular events, oxidative stress, chronic hyperglycemia, and dyslipidemia are strong cofactors in the increased risk of dementia and AD in T2D [16].

Dyslipidemia and insulin resistance are two mechanistic pathways that are associated with both diabetes and AD. Insulin resistance has been identified in AD brain [17] and the induction of brain insulin resistance in mice has promoted the phosphorylation of tau [18], while several groups have identified cognitive impairments in dyslipidemic mice [19, 20]. The overproduction of triglycerides and LDL commonly seen in dyslipidemia and diabetes is often attributed to over consumption of sugar and fat. Hypercaloric diets, particularly Western diets, typically contain high levels of fatty acids. This excess of fatty acids can be further exacerbated by de-novo lipogenesis driven by excess calories in the form of carbohydrates. With the onset of skeletal muscle insulin resistance, an early event in the progression towards T2D [13], the uptake of glucose into the liver is further increased enhancing de-novo lipogenesis. Within the liver these fatty acids can suffer one of several fates; they can be oxidized within the mitochondria to produce acetyl-CoA leading to ATP production, or they can be metabolized into glycerolipids (typically diacyl- and triacylglycerol) which are either exported from the liver in the form of very low density lipoproteins or stored within the hepatocytes as lipid droplets leading to hepatosteatosis, which in itself is associated with insulin resistance and increased risk of T2D. An alternate pathway for excess fatty acids is to flow into other lipid metabolic pathways including the formation of sphingolipid and glycerophospholipids (Fig. 1). The resulting dysregulation of these pathways is likely to be the main driving force behind the lipotoxicity associated with insulin resistance leading to T2D.

Detailed lipidomic studies are beginning to characterize these changes in the lipid composition of liver and in circulation, to more clearly define the effects of hypercaloric diets, not only on the resulting dyslipidemia and insulin resistance, but also on the underlying lipid metabolism. Such studies have been complemented by gene knockout studies to more clearly define the metabolic pathways involved in these processes [21].
A better understanding of the molecular changes to the lipidome in both T2D and AD may help to clarify the commonalities between the dysregulation of lipid metabolism and pathogenesis in each of these diseases and uncover the mechanistic links between T2D and increased risk of AD.

**LIPIDOMICS**

Lipids represent a broad range of small molecules that are associated with nearly all biological processes. While blood cholesterol typically refers to lipoprotein subpopulations such as LDL and HDL, cholesterol itself is a sterol that only makes up a portion of these lipoproteins. The six main categories of mammalian lipids are; fatty acyls, glycerolipids (i.e., triacylglycerol), glycerophospholipids, sphingolipids, sterols (such as cholesteryl esters) and phenols [22]. Each of these categories contains multiple classes and subclasses, each of which contains many individual molecular species [23, 24]. There are currently estimated to be many thousands of lipid species within mammalian systems. Lipoproteins such as LDL and HDL comprise of several hundred species of mostly glycerophospholipids, sphingolipids, glycerolipids and sterol lipids.

Lipidomics refers to the analysis and study of the individual lipid complement of biological systems which may be at a cellular, tissue or whole organism level. Over the past 20 years, advances in mass spectrometry and high pressure liquid chromatography have contributed to the rapid development in this field. Current lipidomic strategies typically rely on either shotgun based approaches (i.e., direct infusion into the mass spectrometer, without the use of chromatography) or chromatography based approaches coupled with mass spectrometry, typically using high pressure liquid chromatography, although gas chromatography or capillary electrophoresis are also used for more specialized analyses. Both these approaches have their advantages and limitations which have been discussed in recent reviews [25–28]. A second distinction in lipidomic strategies relates to the use of targeted or untargeted approaches; targeted analysis
relates to the foreknowledge of the lipid species to be analyzed and is typically performed using liquid chromatography coupled to a triple quadrupole mass spectrometer with one or more multiple reaction monitoring experiments tuned to a specific set of lipid species. Untargeted analyses, where the lipid species to be examined are not predetermined, is typically performed on a high-resolution instrument, with or without chromatography, and relies on scanning experiments to capture information on all lipid species within the detection capabilities of the instrument. Subsequent statistical analyses can identify those features of interest which can then be identified by a combination of exact mass measurement, fragmentation analysis and database searching.

While lipidomics has the capacity to examine hundreds to thousands of lipid species within a biological sample, cohort size is also critical to provide sufficient statistical power to identify associations with disease states or outcomes, independent of the many covariates known to be associated with the same outcomes that may influence lipid metabolism and homeostasis. In this context, maintaining assay performance and minimizing assay variance across the analytical process becomes of paramount importance and typically favors the targeted approach. Thus, much of the fine detail of lipid associations with disease states has come from the larger targeted lipidomic cohort studies as discussed below.

**LIPIDOMIC PROFILING IN DIABETES**

Given the established link between the dysregulation of lipid metabolism and T2D, it is not surprising that many studies examining the plasma lipidome have identified a strong relationship between circulating lipids and T2D. In a small cohort of 14 healthy and 13 diabetic patients, Haus et al. examined the levels of different ceramide species in human plasma; they found that diabetic patients had significantly higher concentrations of several ceramide species and conversely, they observed a strong inverse correlation between insulin sensitivity and these ceramide species [29]. Examining a cross sectional cohort of 14 subjects with T2D and 14 healthy lean controls, Lopez et al. identified several species of ceramide that were elevated in those with T2D [30]. A study examining lipoprotein subfractions also identified a positive association between ceramide in the LDL subfraction and insulin resistance [31]. These relatively small studies are supported by several others that have identified a negative correlation between muscle insulin sensitivity and ceramide levels [32, 33].

In a larger plasma lipidomic profiling study, Meikle et al. examined two cohorts comprising healthy individuals, individuals with prediabetes and with T2D. The cohorts represented a subset of the AusDiab Study \((n = 351)\), an Australian population based study, and the San Antonio Family Heart Study \((n = 1,076)\) a family based study of Mexican Americans [34]. In total, 259 lipid species of 1427 human plasma samples across both cohorts were profiled using liquid chromatography-tandem mass spectrometry. Ceramide species and their precursor dihydroceramide species, were again positively associated with T2D similar to the associations identified in previous studies. In the same study, phosphatidylethanolamine was also identified to positively associate with T2D and had positive correlations with both fasting blood glucose and 2-hour post load glucose levels. Phosphatidylethanolamines along with phosphatidylcholines and sphingomyelins make up the bulk of membrane lipids in most cells. Synthesis of phosphatidylcholine in the liver is by either de novo synthesis via the CDP-choline pathway [35] or remodeling of phosphatidylethanolamine via phosphatidylethanolamine N-methyltransferase (PEMT) [36]. Dysfunctional ratios of phosphatidylethanolamine to phosphatidylcholine have been identified in settings of obesity [37] and non-alcoholic fatty liver disease [38], which is typically associated with dyslipidemia and T2D [34]. PEMT\(^{-/-}\) mice lacking choline in the diets showed reduced phosphatidylcholine with elevated phosphatidylethanolamine and had severe liver dysfunction through cellular membrane dysregulation [39].

The de novo synthesis of ceramides occurs via the decarboxylation of serine and condensation with, commonly, palmitoyl-CoA. Further enzymatic action by 3-ketodihydrosphingosine, ceramide synthase and dihydroceramide desaturase produces the lipid ceramide [40, 41]. Ceramides are precursors to several more complex sphingolipids, including sphingomyelin and glycosphingolipids, and are believed to be one of the major lipid mediators in driving insulin resistance and lipotoxicity [42]. Ceramides are able to impair insulin stimulated glucose transport, through mechanisms involving AKT (protein kinase B) inhibition [43]. AKT is involved in many metabolic processes, but in the context of T2D, AKT is important in insulin induced translocation of GLUT4 (Glucose transporter type 4) which is important for glucose uptake into cells [44].
Alkylphospholipids are a subclass of glycerophospholipids with an alkyl chain attached to the sn1 position of the glycerol by an ether linkage. Alkenylphospholipids (plasmalogens) are a related class which contain a vinyl-ether linkage at the sn1 position. These lipids are generated through a complex biosynthetic pathway involving the peroxisome and endoplasmic reticulum [45]. Several species of alkyl- and alkenylphosphatidylcholines were identified to be negatively associated with T2D and prediabetes [34]. Lyso derivatives of alkylphosphatidylcholines, ether lipids without the sn-2 esterified fatty acid, were also negatively associated with T2D [34]. A recent study identified changes to the lipidome of HDL subpopulations, with decreases in choline plasmalogens associated with metabolic syndrome [46]. Due to the vinyl-ether bond, plasmalogens are more prone to oxidation and act as a sacrificial antioxidant in lipid membranes and lipoproteins [47, 48]. They have also been demonstrated to be involved in regulating cellular cholesterol metabolism [49] and AKT signaling [50].

**LIPIDOMIC PROFILING IN DEMENTIA**

There has been much interest to identify the relationship between lipid metabolism, dementia and AD. The potential role of lipids in disease pathogenesis is incompletely understood but may offer new treatment strategies and is an area of growing interest. In addition, the relatively weak treatment options currently available and the need to treat early in the disease process, have made the search for biomarkers, for early detection and risk assessment an important part of improving future treatment outcomes [51].

Lipids, comprise up to 66% of the dry weight of brain white matter, with a large proportion consisting of ether lipids [52]. One of the earliest studies examining brain ether lipids and AD examined the total plasmalogen lipid content of 9 control and 9 post-mortem AD brain samples [53]. As plasmalogens are susceptible to acid hydrolysis, they examined the total ethanolamine lipid content using thin layer chromatography with and without acid treatment to determine the overall plasmalogen levels in the examined brain region. There was a considerable decrease in the ethanolamine plasmalogen to non plasmalogen levels in the temporal cortex [53]. Han et al. examined brain tissues from age matched samples of 6 subjects at various stages of cognitive impairment, using shotgun lipidomics, it was identified that the level of cognitive impairment correlated with the decline of ether lipids, including plasmalogens in several brain regions including both white and grey matter [54].

Several mechanisms that link lower brain plasmalogen levels and susceptibility to AD have been proposed. In one study it was shown that vesicles comprised of ethanolamine plasmalogens, but not other diacyl phospholipids, reduced Aβ aggregation in an in vitro assay [55]. The formation of Aβ is dependent on β- and γ-secretases which are both expressed and regulated by lipid rafts [5, 6]; in contrast, α-secretases, the opposing enzyme in this pathway, is expressed and exerts its activity via non-lipid raft membrane domains [7]. Plasmalogens have been found to associate with lipid rafts [56] and are able to regulate membrane cholesterol, a deficiency in plasmalogens has been reported to reduce cholesterol esterification and clearance from the membrane [49, 57]. Elevated membrane cholesterol levels have been shown to enhance secretase activity [58], thus plasmalogens may play a role in maintaining cell membrane homeostasis and a decline in plasmalogens, which has been previously identified in AD, may drive Aβ production. Interestingly the association between plasmalogens and dementia has been found in the periphery as well. Goodenowe et al. examined the serum of 324 subjects (68 cognitively normal, 256 with probable dementia of the AD type) using liquid chromatography-tandem mass spectrometry focusing on several species of ethanolamine plasmalogens [59]. A strong negative association was found between circulating plasmalogens containing either docosahexaenoic acid or arachidonic acid with the Alzheimer’s disease Assessment Scale – Cognition (ADAS-Cog) score. This association was also observed in the immediate precursor to these species (alkylphosphatidylethanolamine) which is also peroxisome derived, however no association was seen for diacyl phosphatidylethanolamine species. Wood et al. also determined in a small AD cohort (n = 40) that patients with plasmalogen levels below the 75th percentile of the age matched controls (n = 66) showed progressive cognitive decline (increased ADAS-Cog score) over a 12 month period, whereas AD patients with normal plasmalogen levels did not show a decline in cognition [60].

Whether the plasmalogen pool in the periphery has any direct interaction with the brain or simply reflects cerebral plasmalogen metabolism and homeostasis remains to be determined. However, a study examining the role of plasmalogens in inflammation examined intraperitoneal injections of plasmalo-
Sphingolipids have also been found to associate with AD in multiple studies. Han et al. characterized the brain sphingolipid content of 22 subjects with known cognitive status (healthy to severe dementia), complex sphingolipids such as sulfatides, a sulfated sphingolipid abundant in white matter, were decreased in subjects with any dementia when compared to their healthy controls in both white and grey matter [63]. In contrast, ceramides were found to be elevated only in the white matter in subjects with higher clinical dementia ratings [63]. A more comprehensive study by Filippov et al. examined brain tissues of AD (n = 19), AD with other neuropsychological lesions (n = 6), non-AD dementia (n = 9) and healthy individuals (n = 6) [64]. Both lipidomics and gene expression studies were conducted, with ceramide found to be elevated for all dementia groups relative to the healthy controls. Interestingly, several genes associated with ceramide metabolism (ASMase, NSMase and GALC) were also upregulated in subjects with AD [64].

A study conducted by Mielke et al. identified associations between sphingolipids and AD in women. This study involved the lipidomic analysis of a subgroup from The Women’s Health and Aging Study II, consisting of 100 women who were followed up over 9 years [65]. Nineteen women developed probable AD during the follow-up period, as determined by the Diagnostic and Statistical Manual of Mental Disorders-IV criteria. Higher baseline circulating levels of ceramide and lactosylceramide were associated with increased risk of AD [65]. An earlier study with the same cohort identified associations between ceramide and other sphingolipids with onset of memory impairment [66]. A study examining the plasma samples of 26 AD patients and 26 cognitive normal controls also identified changes to sphingolipids, with elevated ceramide found in those with AD [67].

Recently, Mapstone et al. identified a series of phospholipids as a potential biomarker to predict AD [68]. Using untargeted metabolomics, they determined that a set of 10 metabolites, of which 8 were phospholipids, were able to distinguish those who are non-converters (people of normal memory who showed no cognitive decline, defined by memory composite scores) and those who become memory impaired over a 2-3 year time period, with an accuracy and sensitivity above 90% in two sets of independent samples. This set of phospholipids was characterized using direct infusion-tandem mass spectrometry and determined to be mostly diacyl- and alkylphosphatidylcholine [68]. While the above studies provide evidence on the link between lipid metabolism and AD, these preliminary findings need validation in larger well-characterized longitudinal cohorts of aging and AD such as the Australian Imaging Biomarkers and Lifestyle (AIBL) study of Ageing and the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort.

THE LIPIDOMIC INTERFACE BETWEEN DIABETES AND DEMENTIA

The studies highlighted above suggest that dysregulation of sphingolipid and phospholipid metabolism may provide a common link between diabetes, dementia and AD.

Ceramide

Ceramide has been consistently identified to associate with insulin resistance in the periphery [29–31, 34, 69] and it has been observed to be elevated in both the periphery [65, 67] and brain [63, 64] in those with AD. Lyn-Cook et al. used a high fat diet/T2D mouse model to demonstrate a potential role for circulating ceramide in mediating neurodegeneration through increased CNS oxidative stress [70]. Another study by the same group identified changes to insulin/IGF signaling combined with elevated Aβ and phosphorylated tau when treating neuronal cultures with short chain ceramides [71]. The inhibition of AKT by ceramide leads to several downstream effects including reduction of insulin-stimulated glucose [43], promotion of cell apoptosis [72] and...
reduced inhibition of glycogen synthase kinase 3 beta (GSK3β) [73]. Normally GSK3β is regulated by several kinases (including AKT) which is able to suppress its activity by phosphorylating certain sites on the enzyme. Increased GSK3β activity has been associated with complications such as insulin resistance [74] and has been identified to increase both Aβ production and phosphorylation of tau [75] (Fig. 2). Plasmalogens may also have an indirect interaction with GSK3β similar to that discussed earlier with ceramide. In a mouse model of plasmalogen deficiency, it was shown that AKT activation was impaired and phosphorylation of ser9 on GSK-3β was significantly reduced, leading to increased activity [76].

**Plasmalogen**

Plasmalogens play an important role in both the CNS and periphery. Lower circulating plasmalogen levels have been identified in both T2D and AD compared to healthy controls as described previously. Plasmalogens have been extensively studied as an endogenous anti-oxidant due to the susceptibility of the vinyl-ether bond to oxidation [77], which limits the propagation of the oxidation reaction to other lipids [78]. Plasmalogens also exhibit anti-apoptotic effects [50] and have been identified to be anti-inflammatory [61], where both cell death and inflammation are strongly associated with T1D, T2D and AD [79–82]. Interestingly, ceramides may be able to mediate plasmalogen hydrolysis in the brain, releasing arachidonic acid, a precursor to the pro-inflammatory eicosanoids [83].

**Sulfatides**

Sulfatides have been identified to be dysregulated in both T2D and AD. Sulfatides are formed from the sulfation of the sphingolipid cerebroside which is a ceramide attached to a glucose or galactose. Sulfatides are abundant in the myelin sheath and play important roles in maintaining its integrity and nerve signaling ability [84]. Sulfatide deficiency has been identified in very early stages of AD in the CNS and it was hypothesized that the degradation of sulfatides in AD, may lead to the elevation of ceramides and its downstream effects [63]. The apolipoprotein E gene has 3 major alleles, with the ε4 allele conferring the greatest risk of any gene for late onset AD [85]. An APOE knock in mouse study identified a sulfatide deficiency in the brains of mice with the ε4 allele [86]. While sulfatide is quite abundant in the CNS, sulfatides are localized to a much smaller proportion of the periphery. Sulfatide containing a palmitic acid (16:0) is predominately found in the pancreas and has been identified to be associated with insulin granules [87]. These sulfatides were reported to be decreased in a T2D mouse model [88] and polymorphisms to galactosylceramide sulfotransferase gene, an enzyme required for sulfatide synthesis, was identified to associate with insulin resistance [89]. Sulfatide may also play an immunomodulatory role [90], with anti-sulfatide antibodies being detected in those who develop T1D [91].

**Lipids in exosomes and insulin resistance**

The classes of lipids described above are also key constituents of exosomes, extracellular vesicles that
have been rapidly gaining interest in the context of AD and T2D. These vesicles may provide a mechanism for disease pathology and appear to be strong biomarkers for disease onset. Exosomes consist of a lipid bilayer enveloping lipids, proteins and RNA originating from certain cells and are highly enriched in plasmalogens, ceramides and other sphingolipids relative to their cells of origin [92]. Several recent reviews describe these vesicles in detail [93, 94]. Peripheral exosomes can be derived from neuronal cells [95] and exosomes containing insulin receptor substrates are a strong marker for brain insulin resistance and have been identified in the periphery in both T2D and AD patients [96]. Modifications to the lipidome has been reported to modulate the release of exosomes, for example incubation of PC-3 cells with plasmalogen precursors (1-O-hexadecylglycerol) has been shown to increase production of exosomes as well as modify its protein content [97]. Further to this, modifying the circulating levels of exosomes or their lipid content has shown promise in altering the pathology associated with AD in mouse models [98, 99].

**Dietary lipids**

It remains uncertain how peripheral lipids may influence or reflect the development and progression of AD. While the BBB inhibits free exchange of lipids and proteins between the central nervous system and the periphery, there are several lines of evidence to indicate that this is not absolute. Diet plays a major role in maintaining a healthy brain, with the brain lipidome containing the highest proportion of polyunsaturated fatty acids in the body. These polyunsaturated fatty acids (namely the omega-3 and omega-6 species) are derived from the diet and periphery, either directly or via essential fatty acid intermediates. As described earlier, the transport protein Mfsd2a was recently identified to be essential for the uptake of polyunsaturated fatty acids from the periphery to the brain [62]. Certain diets, such as the Mediterranean diet, appear to be beneficial in reducing risk of both AD and T2D [9, 100]. While several groups have reported a Western diet, high in saturated fats, as detrimental to the BBB [101, 102]. The dyslipidemia associated with T2D includes elevated triglycerides which have been found to negatively affect transport of leptin across the BBB [103]. In addition, dysregulation of brain and peripheral leptin signaling has been implicated in AD [104]. Together, these reports suggest that changes to the peripheral lipidome can influence the brain, with the dramatic shifts seen in T2D associated dyslipidemia, likely to be detrimental to brain health.

**Apolipoprotein E (APOE)**

The APOE ε4 allele is the biggest genetic risk factor for development of late onset AD [11]. APOE is found in several subsets of lipoproteins both in the periphery and brain and its main role is the transport of lipids between cells and tissues. In the brain, it plays an important role in providing cholesterol for repair of neuronal membranes with APOE ε4 being the least effective of the 3 common isoforms. While the mechanism by which the different APOE polymorphic alleles (ε2, ε3, and ε4) modify the risk of AD has not been fully defined, having a copy of the ε4 allele significantly increases risk while the ε2 reduces the risk of developing AD [85]. People with T2D carrying the APOE ε4 allele are at significantly greater risk of developing AD, more so than the sum of the risk contributed by T2D and APOE ε4 [105]. With the heavy involvement of APOE in cholesterol metabolism, one would expect changes to the lipidome with different APOE alleles While several studies have examined associations of blood cholesterol with different APOE alleles [106, 107], to date there have not been any published studies characterizing the associations between the lipidome and APOE genotypes. This will be an important area for future investigations.

**CONCLUSIONS AND FUTURE DIRECTIONS**

The studies described above provide evidence of an interplay between lipid species with both T2D and AD. Both diseases have complex potentially overlapping etiologies and pathology as evidenced by the increased risk of AD in those with diabetes.

Lipidomic studies have thus far identified several classes and subclasses of lipids which are altered in both T2D and AD and represent potential common mechanistic pathways acting in each disease. Elevation of ceramides and depletion of plasmalogens provide an interesting link between AD and T2D as they have been associated with insulin resistance, inflammation and cellular apoptosis. However, despite these commonalities, not all people with diabetes develop dementia and not all people with dementia have diabetes. There are many factors that may be involved in this apparent contradiction includ-
ing genetic protective factors; the preclinical phase of AD can take decades and T2D is also a strong risk factor for cardiovascular disease a major cause of death in the elderly. Thus, many people with T2D may not survive long enough to develop AD. Alternately, the site(s) of lipid dysregulation may also be a critical factor as may the environmental and/or genetic triggers for lipid dysregulation. While lipidomic studies have made substantial inroads into our understanding of the role of lipids and lipid metabolism in both diabetes and AD, further studies are required to better characterize these perturbations and to provide mechanistic understanding linking lipid metabolism to both T2D and AD.

Such studies may identify lipidomic biomarkers for risk assessment and early diagnosis of both T2D and AD and for monitoring disease progression and treatment. Importantly, understanding the role of lipid metabolism in disease onset and progression may also identify new therapeutic targets to modulate lipid metabolic pathways to prevent or slow disease onset and progression.

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