**Editorial: Lipids to support physiology and function: both quantity and quality are important**

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Complex lipids and their fatty acid constituents are found in every cell of the body and in many body fluids and secretions. They play structural, functional and metabolic roles that contribute to physiological homeostasis and to resilience in response to challenges, impacting cell, tissue and whole-body function and fitness, health and wellbeing, and ultimately disease risk. The number of possible lipid structures in any compartment or pool within the body is immense. For example, Quehenberger and Dennis [1] described an almost inconceivable complexity and diversity of “the human plasma lipidome”. In this compartment alone, the diversity of lipid species out numbers the combined count of amino acid, carbohydrate and nucleic acid species 3 to 1, and this is just the plasma, never mind tissue lipid species that do not circulate. Such complexity and diversity within any body compartment and of the possible relations in lipid species across body compartments clearly poses challenges to analysis, to better understanding of function and physiology, and to gaining insight into how differences and perturbations in lipid species relate to health and disease. Thankfully, advances in analytical capabilities and in molecular and cell biology are enabling new discoveries in the lipid field that aid our understanding of the important roles of complex lipids, fatty acids and fatty acid derivatives in physiology and “normal” function and in health and disease. Intriguingly (and unlike many other structural, functional and metabolic components of the body), blood, cell and tissue lipids are strongly influenced by the dietary intake of their precursors. This links dietary supply directly with the “lipidome” and provides a window of opportunity for preventative and therapeutic interventions through an altered diet, and through oral supplements and enteral and parenteral administration of components deemed to be helpful in particular population or patient groups. Hence, research in lipid metabolism and therapy is flourishing and playing an increasingly important role in identifying strategies for both preventing and treating human diseases.

For the first time, papers in the “Lipid metabolism and therapy” section of the journal have been spread across two issues and these papers represent the breadth of research in the field, including research relevant to the heart, liver, adipose tissue, skin and gut and involving diet, oral supplements and parenteral nutrition.

Despite decades of research, much remains to be learned about fatty acid and complex lipid metabolism in humans and its regulation. Cross et al. [2] provide an update on regulation of *de novo* lipogenesis (DNL; synthesis of fatty acids and their accumulation into triglycerides) which mainly occurs in the liver. They also review the experimental techniques that can be used to assess DNL in humans. DNL is promoted by insulin and so is regulated by nutritional state; DNL is increased post-prandially. Increasing carbohydrate intake increases DNL and it is now clear that fructose has a greater effect than glucose [3]; conversely restricting intake of free sugars decreases DNL [4]. The direct provision of fatty acids in the diet clearly provides substrate for triglyceride synthesis, although the impact of dietary fatty acids on DNL is modest compared with the contribution of carbohydrate. Nevertheless, some fatty acids play an important role in regulating DNL. This is most obvious for the long chain n-3 polyunsaturated fatty acids (PUFAs) which decrease the rate of DNL, mainly through actions on hepatic gene and protein expression, as also reviewed elsewhere [5]. N-6 PUFAs may have this effect also [6]. Recent research has reported that a high protein meal increases DNL compared to high fat meal [7]; this may be due to effects of specific amino acids on hepatic gene expression.

It has long been recognized that there are two kinds of adipose tissue in the body: white and brown, the former for general triglyceride (energy) storage, and the latter serving as a site for thermogenesis in cold environments. Further it has been tacitly assumed that each comprises a homogenous “kind” of fat tissue. However, it has recently become clear that not white adipose tissue (WAT) depots are the same, with clear metabolic differences between visceral and subcutaneous depots. Bilson et al. [8] discuss the most recent evidence identifying the presence of distinct white adipocyte subpopulations in WAT and how these may be altered with increasing adiposity and/or cardiometabolic disease. The identification of multiple adipocyte subpopulations has become possible using single-cell and single-nucleus RNA sequencing techniques. Different adipocyte subtypes appear to be functionally distinct and may have different roles in WAT function and in obesity-associated metabolic diseases. For example they appear to respond differentially to insulin and to have different capabilities for triglyceride storage and for mounting an inflammatory response. The authors highlight the need to explore any functional differences among adipocyte subpopulations and how such differences affect the tissue as a whole. This may uncover new targets for pharmaceutical and dietary interventions to reduce obesity-associated co-morbidities.

The skin contains a diverse array of lipids involved in its structure and as signalling molecules mediating homeostasis and inflammation. Nicolaou and Kendall [9] provide an update on skin lipids and new insights into approaches used for skin research including novel cell and tissue culture models. It is now recognised that skin surface lipids, some produced by the host (both skin cells and infiltrating immune cells) and some by resident microbes, maintain and regulate the skin microbiome as well as the epidermal barrier. Recent studies have expanded the understanding of epidermal production of ceramides [10], the role of eicosanoids and other lipid mediators on inflammation within the skin [11] and the role of n-3 PUFA-derived specialised pro-resolving mediators (SPMs) in regulating and resolving skin inflammation. The concentrations and/or compositions of many skin lipids are altered in disease and so skin lipids are an attractive therapeutic target for topical interventions or nutritional supplements.

Oxylipins are oxidised derivatives of PUFAs [12]. They are produced both enzymatically and non-enzymatically and are highly bioactive. Oxylipins include the eicosanoids produced from the n-6 PUFA arachidonic acid and from the n-3 PUFA EPA [13], and SPMs produced from EPA, docosapentaenoic acid and DHA [14]. Despite the research emphasis on these oxylipins, the oxylipins with the highest plasma concentrations are derived from linoleic and a-linolenic acids [15]. Many oxylipins are found in blood and tissues at very low concentrations [16] and detection of many is an analytical challenge [117]. Furthermore, reported concentrations can be highly variable [16]. Auekema and Ravandi [18] discuss the identified experimental and biological sources of variation in free (i.e., non-esterified) oxylipins. There are many experimental sources of variation which relate to sample handling, analytical technique and instrumentation, and post-analysis data handling. The impact of these can be minimised by using standardised protocols. Biological sources of variation include background diet (since diet is a source of substrates for oxylipin synthesis), medications, genetic variations (e.g., polymorphisms in genes encoding enzymes involved in biosynthesis of oxylipins), physiological state and presence of disease. Sex and age may also be sources of variation, but these are poorly explored to date.

There is significant evidence that higher intake of long chain n-3 PUFAs (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) and higher blood and tissue levels of EPA and DHA are associated with lower risk of cardiovascular disease in general and coronary heart disease in particular [19,20]. Trials of high dose EPA (and in some cases of EPA+DHA) show reduced risk of mortality and other “hard” clinical endpoints in at risk patients [20] and recent meta-analyses support that these n-3 PUFAs are of cardiovascular benefit [21,22]. Nevertheless, and despite showing an overall benefit on mortality, some trials report an increased risk of atrial fibrillation with long chain n-3 PUFAs [23]. Bork et al. [24] discuss this further. A meta-analysis suggests that supplemental long chain n-3 PUFAs increase risk of atrial fibrillation [25], and a recent large observational study reported a modestly increased risk of atrial fibrillation in habitual users of n-3 PUFA supplements [26]. Bork et al. [24] discuss candidate mechanisms for this potential adverse effect of n-3 PUFAs.

The gut microbiota is now thought to play an important role in host physiology, health and well-being including metabolic, immune and cognitive health [27]. Diet is one of the main determinants of the gut microbiota [28], and different dietary components and different diets per se result in different gut microbiota composition [29]. This is one important link between diet, physiology, and disease risk. Djuric [30] discusses recent findings on fat, fatty acids and other dietary components and gut microbiota, mainly referring to research in laboratory rodents. In rodents fed high-fat diets using lard or Western blend fats to induce obesity, switching to high-fat diets formulated to contain higher amounts of fiber or fiber-containing foods, plant extracts, long chain n-3 PUFAs or whole grains has beneficial effects on body weight, metabolic alterations, and the intestinal microbiota. Further research has suggested that changes in intestinal microbiota may in part mediate the beneficial health effects of these dietary factors. Many of the microbiota changes observed in animals fed the more healthful dietary components have also been observed in humans who follow healthful dietary patterns [31]. With regard to long chain n-3 PUFAs, recent studies indicate that they have a prebiotic-type action in humans resulting in changes in microbiota composition [32] that have been related to improvements in cardiovascular risk factors including lipid profile and inflammatory markers [33].

As mentioned above there is significant evidence that higher intake and higher blood and tissue levels of EPA and DHA are associated with benefits on disease risk factors and many clinical outcomes. However there are inconsistencies in the literature which often seem to relate to a) variations in EPA and DHA levels in any given body compartment or pool or b) to variations in the extent of the increase in EPA and DHA seen when their intake is increased. Obviously a smaller increase in EPA ad DHA levels would likely result in a smaller effect on physiology, biomarkers ad clinical outcome. This has been discussed elsewhere [34] and now Shaikh and Bazinet [35] provide an update focussing on the roles of background diet (e.g. intake of n-6 PUFAs), genetics (e.g. polymorphisms in FADS and APOE genes), gut microbiota and sex. Other factors to consider include age (both endogenous synthesis and body handling of EPA and DHA might change across the life course) and body fatness (adipose tissue provides a sink for EPA and DHA which might limit their availability to other pools) [36]. Also, differences in bioavailability of different forms and sources of EPA and DHA have been documented [37] and there may be variations in small intestinal handling of these fatty acids.

Emulsified lipids are included as part of intravenous nutrition support (parenteral nutrition) to provide a source of energy and of essential fatty acids. However, they may also provide fatty acids that influence metabolism, immunity, inflammation and hemostasis, so affecting patient outcomes. Long chain n-3 PUFAs (EPA and DHA) are suggested to have a role in patient support by beneficially altering metabolism and immunity and controlling adverse inflammation [38]; in this regard addition of fish oil, as a source of EPA and DHA, to blends of vegetable oils has been proposed to be of benefit to a range of pediatric and adult patients [39]. There are several recent meta-analyses supporting the use of lipid blends that include fish oil in hospitalised adult patients receiving parenteral nutrition [40,41], as well as supportive cost-effectiveness analyses [42]. One of the problems that can arise with long term lipid infusion is hepatic dysfunction, now termed intestinal failure associated lipid disease (IFALD), the characteristics of which are somewhat different between pediatric and adult patients. Miles [43] discusses recent developments around intravenous lipid emulsions (ILEs) and IFALD in children and adults. Cholestasis is the primary manifestation of IFALD in premature infants receiving ILEs, whereas in older children and adults, steatosis is predominant. These effects are likely related to both dose of lipid use (i.e., fat overload) and the composition of the lipid, including its fatty acid makeup, although phytosterols may also be involved [44]. Pure fish oil as well as ILEs with various combinations of soybean oil, medium chain triglycerides, olive oil and fish oil have been used in both children and adult on long term parenteral nutrition. Inclusion of fish oil has been shown to both prevent and reverse IFALD in premature infants [45], and in some reports to improve IFALD in adults. These effects may relate to the impact of long chain n-3 PUFAs on hepatic lipid metabolism as also discussed by Cross et al. [2].

Although much of the emphasis of fatty acid research remains on n-3 PUFAs, especially EPA and DHA, other fatty acids, including n-6 PUFAs, also have roles relevant to human physiology and health [46]. These include linoleic acid as a component of skin ceramides and linoleic and arachidonic acid as precursors of bioactive oxylipins involved in physiology. Linoleic acid also lowers plasm cholesterol when used as a replacement for saturated fatty acids. Despite this, and as discussed in previous editorials in the journal [47,48], n-6 PUFAs are often referred to as harmful components of the diet. Belury [49] updates on the linoleic acid literature. Recent evidence shows associations between higher dietary or blood levels of linoleic acid and lower risk of metabolic syndrome and cardiometabolic disease [50-53]. Furthermore, recent intervention studies report that adding linoleic acid to the diet

improves body composition, dyslipidaemia, and insulin sensitivity while reducing systemic inflammation and fatty liver. These effects probably relate to altered gene and protein expression, through effects of linoleic acid and its derivatives on transcription factors such as peroxisome proliferator activated receptors.

The articles featured in this year’s “Lipid metabolism and therapy” section highlight that exciting progress continues to be made in the area of complex lipids, fatty acids, lipid mediators (oxylipins), human physiology and human disease. There continue to be new understandings of effects, mechanisms of action and applications of the lipids and fatty acids under study and of relevant metabolic processes including DNL, PUFA interconversion [54] and oxylipin biosynthesis. The actions of fatty acids are widespread throughout the body and this section highlights effects in the liver, heart, skin and gut; there are of course effects elsewhere including in adipose tissue [55,56]. Observations that long chain n-3 PUFAs alter the gut microbiota provide a completely new mechanism of action for these fatty acids in beneficially affecting human physiology and health, while recent research on linoleic acid challenges the widely held view than n-6 PUFAs are by definition bad for us – in excess that might be true (depending on the definition of excess), but across the span of typical Western intakes, it appears that higher intakes are beneficial relative to lower. Recent trials have highlighted that long chain n-3 PUFAs might increase risk of atrial fibrillation, an effect of some concern that warrants further research. Nevertheless, it is worth noting that several studies that identify this effect also report an overall benefit of long chain n-3 PUFAs on cardiovascular outcomes [23], including reduced risk for stroke, the most serious medical consequence of atrial fibrillation. So far research on fatty acids is still mainly adopting a “one size fits all” approach; more research is needed on whether the interventions discussed herein work to different extents according to common differences among individuals such as sex, age, body fatness, ethnicity and so on, as well as genotype and perhaps gut metabotype. Research in this field must be conducted in manner that ensures that the scientific evidence base becomes as robust as possible in order that recommendations can be made with confidence that they will be of public and patient benefit.

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