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Musings about the role dietary fats after 40 years of fatty acid research☆

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A B S T R A C T

Since the 1950's nutrition recommendations have focussed on the replacement of saturated fats in the diet with polyunsaturated fats, a strategy that continues to this day. Despite supporting evidence from clinical trials for the advantages of Mediterranean diets, there has been less attention paid to the role of monounsaturated fats. It has been known for many years that diets high in linoleic acid (LA) compete for the incorporation of omega 3 fatty acids into tissues. What is also clear is that diets rich in LA are not free from concerns and the discovery of oxlams, oxygenated derivatives of LA, having potent inflammatory effects may help us question the dogma of LA rich diets. Given that dietary oleic acid a prime constituent of Mediterranean diets can be metabolised to Mead acid (ETrA) has in the past been a cause for concern, but new data showing the anti-inflammatory effects of ETrA suggest that there is a need for further research about the benefits of monounsaturated oils on human health. Finally, there is a need to re-examine how dietary fats are monitored in clinical studies. The current method of focussing on esterified fatty acids may be too insensitive to detect clinically important changes.

1. Introduction

It is some time since I received the Alexander Leaf Award and I thank Prof Susan Carlson and the ISSFAL Board for the tremendous honour they showed me by nominating me for this prestigious award. This award has special meaning for me as I was fortunate in knowing Dr Leaf and over the years had a number of energetic conversations with him. We shared a passion in wanting to see the potential benefits of omega 3 fats translated into clinical practice based upon adequately powered clinical trials. It is also special to me that I received the award in beautiful Vancouver and in Canada where I did my first degree and where I learned to love the complexities of biological mechanisms. Three of my children are Canadians and were present in the audience.

Dr Leaf is one of the many giants in the fatty acid field that it has been my pleasure to know including Ralph Holman, Hugh Sinclair, Andrew Sinclair, Martha Neuringer, Ricardo Uauy, Howard Sprecher, Bill Lands, Norman Salem, Susan Carlson, Hee Yong Kim and many more. Against the background of their achievements I feel unworthy.

I thought I would to try to map some areas of fatty acid research that we could do well to re-examine so that perhaps the early career scientists might find these challenging enough for them to help resolve in the future. Despite the huge amount of work done on dietary fats I feel that we have barely scratched the surface of this hugely important field.

1.1. *Saturated fatty acids*

I have lived through the era where saturated fatty acids were universally labelled as bad for health but this is now being re-evaluated. Nevertheless, saturated fats continue to be thought to be a cause of disease and poorly researched despite studies that have clearly shown that not all saturated fats are cholesterolemic and some are even poorly absorbed [1,2]. Thus fats such as dairy fat that have been labelled as 'saturated' even though they are also rich in monounsaturates (and even traces of omega 3 LCPUFA), are thought of as unhealthy and a cause of cardiovascular disease. This is despite the fact that systematic reviews of human studies show that intake of dairy fat has little or no relationship to CVD and cheese is often associated with CVD protection [3]. Strangely, saturated fats raise HDL (the "good") cholesterol and change LDL from small, dense (bad) to large LDL, which are mostly benign [4]. While there is little doubt that cholesterol levels can be reduced in some individuals by replacing saturates in the diet with unsaturates this rarely translates to a reduction in deaths [5,6]. There is an urgent need for large scale RCTs that do appropriately designed, well powered studies that have clinical outcomes rather than risk factors and surrogate markers. Whether meaningful studies investigating fatty acid interventions in relation to CVD can be done in the era of the wide use of statins is uncertain.

☆ "This paper is based on Dr. Gibson's Alexander Leaf Award lecture from the International Society for the Study of Fatty Acids and Lipids meeting in 2012"

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1.2. The replacement of saturated fats

In diets can be done by the addition of either monounsaturates or polyunsaturates. Historically, oils that were rich in linoleic acid (LA) were selected as a cheap alternative source of dietary fats and there is little doubt that LA-rich oils are effective in many people at lowering cholesterol levels when they replace saturated fats in the diets. Although early work [7] demonstrated that oils rich on monosunstaurates were also hypocholesterolemic, this line of work had been largely ignored until recently. As a result, the intakes of fats rich in LA have risen around the world as countries become morewesternised, in a manner similar to the United States [8].

There are a number of important issues relating to the huge increase in LA in the diet:

1. How much LA do we need in our diets?
   Historically the early animal work of Holman resulted in estimates of the amount of LA required to sustain a healthy life to be around 1–2% energy [9]. Following intense consultation the Academy of Paediatrics in the US define the minimum level of LA in infant formulas to be 3% energy. Many years ago Andrew Sinclair proved that like infants, adult humans exhibited skin rash in the absence of an adequate intake of the essential omega 6 fatty acid, LA [10]. Recently, the LA requirement has been re-examined in rats taking care to differentiate between LA and alpha linolenic acid (ALA) in the diets and it was found that an LA level of 1–1.5% energy provided all the omega 6 essential fatty acid needed for normal functioning and growth [11,12]. Nevertheless, most infant formulas contain levels 2–3 times the minimum amount recommended level and the LA intakes in the general US and Australian populations is the order of 4–6% energy [8,13].
2. Physiological effects of LA
   This is an under-researched area despite the fact that LA has long been claimed as healthy for humans due to its cholesterol lowering ability when replacing saturated fats in the diet. Worldwide we have seen a huge increase in the amount of LA consumed [8] as animal fats have been replaced by vegetable oils. The advisability of this has recently been questioned by Chris Ramsden and colleagues [5,6] since it has been discovered that LA in vivo and in vitro can give rise to derivatives called oxlams that are pro-inflammatory. A clinical trial has shown that replacing LA rich oils in the diet with low LA fats can reduce the incidence of severe headache and migraine [14,15] inferring that LA or its metabolites contribute to clinical outcomes with an inflammatory component. The challenge ahead is to see whether other clinical conditions can be improved by reducing LA intakes given that one of the basic 'truths' underpinning recommendations to include LA in diets, to reduce deaths from heart disease, has been brought under question by the reanalysis of two randomised trials [5,6].
   It is important to note that LA is the precursor of arachidonic acid (AA) which in turn can be metabolised by cyclooxygenases and lipoxygenases to give rise to a complex series of prostaglandins, leukotrienes, resolvins and protectins (collectively known as oxylipins) that have a range of biological activities. While the role of the prostaglandins has been well studied in humans, there is much less evidence about the role of the newer oxylipins in human health although studies are beginning to emerge [16,17].
3. Effects of dietary OA and its metabolite
   Oils rich in monounsaturates are readily available but few are low in LA. For example, the oil most commonly thought of as monounsaturated, olive oil, contains somewhere between 55 to 83% oleic acid (OA), and depending on its origin between 3.5 to 21% LA. High OA oils have been developed from genetic strains of safflower, sunflower and canola plants and well as by partially hydrogenating polyunsaturated plant oils. Macadamia oil is high in OA and has the lowest natural level of LA making it useful for dietary intervention studies [18,19].
   There is intense interest in the so called Mediterranean diets that are rich in the monounsaturated olive oil. Two large scale clinical trials for the prevention of heart disease [20,21] have fuelled interest in these diets although interpretation is made difficult since neither study involved a simple replacement of saturated fats with monounsaturated fats. Nevertheless, there is now a massive literature of the effect of Mediterranean diets on a range of human health outcomes and they have been extensively reviewed [22,23].
   Part of the biochemical rationale for the Mediterranean Diet rests in the replacement of saturated fats with monounsaturates like OA. It is not often appreciated that OA can also be unitised by the desaturase enzymes and can be converted to eicosatrienoic acid (ETrA, Mead Acid), which is the analogue of EPA and AA. Because even when diets are low in LA, the plasma lipids are still rich in oleic acid, ETrA can be readily formed and has been used as an index of essential fatty deficiency [9,10] and is seen negatively in terms of human health [24]. However, high OA diets can naturally result in elevated levels of ETrA in blood and levels of ETrA in rats have been shown to be independent of signs of EFA deficiency such as decreased growth and skin rash [9,12].
   Together with Les Clelend and Michael James we have had the opportunity of investigating some interesting aspects of ETrA. In a series of rat experiments we demonstrated that ETrA is anti-inflammatory [25,26]. Most importantly, we reported on the outcome of a patient who had had a gut resection and had refused intravenous fats over an extended period [27]. During this time she had successfully completed two pregnancies with the only clinical symptom a rash on her palms. At the time of assessment this subject had a level of ETrA in plasma phospholipids of nearly 20% while the LA level had dropped to less than 1% and AA level to less than 5% of the total fatty acids. Thus ETrA levels can be quite high in human without ill effects and even allows successful pregnancies. Further, ETrA has been shown in animals to inhibit the synthesis of inflammatory mediators [25,26].
4. High LA diets prevent synthesis and incorporation of Omega 3 fatty acids
   We have investigated the effect of a wide range of levels of LA and ALA on the apparent synthesis of DHA in rats [27]. It is clear that provided a minimal amount of ALA is present, the amount of DHA accumulated in plasma is regulated by the level of LA in the diet (Fig. 1). Similar results are clear from the work of Guesnet ([11], Fig. 2).

Omega 3 fats as a component of a healthy diet have been extensively

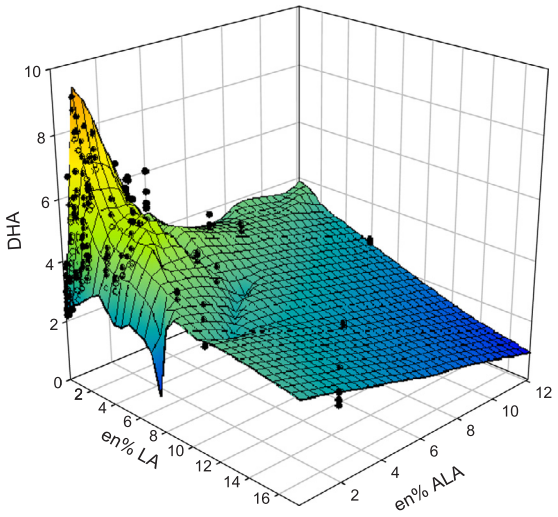

Fig. 1. Inter-relationships between LA and ALA of DHA accumulation in rats [28].