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Gamma-linolenic acid, Dihommo-gamma linolenic, Eicosanoids and Inflammatory Processes

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ABSTRACT

Gamma-linolenic acid (GLA, 18:3n-6) is an omega-6 (n-6), 18 carbon (18C-) polyunsaturated fatty acid (PUFA) found in human milk and several botanical seed oils and is typically consumed as part of a dietary supplement. While there have been numerous *in vitro* and *in vivo* animal models which illustrate that GLA-supplemented diets attenuate inflammatory responses, clinical studies utilizing GLA or GLA in combination with omega-3 (n-3) PUFAs have been much less conclusive. A central premise of this review is that there are critical metabolic and genetic factors that affect the conversion of GLA to dihommo-gamma linolenic acid (DGLA, 20:3n-6) and arachidonic acid (AA, 20:4n-6), which consequently affects the balance of DGLA- and AA- derived metabolites. As a result, these factors impact the clinical effectiveness of GLA or GLA/(n-3) PUFA supplementations in treating inflammatory conditions. Specifically, these factors include: 1) the capacity for different human cells and tissues to convert GLA to DGLA and AA and to metabolize DGLA and AA to bioactive metabolites; 2) the opposing effects of DGLA and AA metabolites on inflammatory processes and diseases; and 3) the impact of genetic variations within the fatty acid desaturase (*FADS*) gene cluster, in particular, on AA/DGLA ratios and bioactive metabolites. We postulate that these factors influence the heterogeneity of results observed in GLA supplement-based clinical trials and suggest that "one-size fits all" approaches utilizing PUFA-based supplements may no longer be appropriate for the prevention and treatment of complex human diseases.

1. Introduction

Gamma-linolenic acid (GLA, 18:3n-6) is an omega-6 (n-6), 18 carbon (18C) polyunsaturated fatty acid (PUFA) found in human milk and several botanical seed oils (borage [~21% GLA], blackcurrant [~17%GLA] and evening primrose [~9%GLA]), and is typically consumed as a part of a dietary supplement. The scientific literature examining the clinical effects of GLA-containing supplements is both complex and confusing. While there have been numerous *in vitro* and *in vivo* animal models illustrating that GLA-supplemented diets attenuate various inflammatory responses, the clinical literature has been less conclusive (for a review, see (Fan and Chapkin, 1998)). The introduction of GLA supplementation strategies to achieve symptomatic relief of atopic dermatitis/eczema was historically preceded by the use of relatively large daily doses of oral linoleic acid (LA, 18:2n-6) containing oils. This was based on the premise that patients with atopic dermatitis/eczema had hallmark cutaneous signs of essential fatty acid deficiency and an impairment in PUFA biosynthesis at an early desaturase step (*FADS2*; Δ-6 desaturase) (Burr and Burr, 1929; Burr et al., 1932; Horrobin, 2000). It was hypothesized that GLA supplements could restore needed PUFAs and mitigate the disease.

Numerous studies primarily carried out in the 1980s and 1990s demonstrated that GLA-enriched botanical oils (evening primrose, borage, blackcurrant seed, and fungal-derived) had the capacity to relieve the signs and symptoms of several chronic inflammatory diseases, including rheumatoid arthritis (RA) and atopic dermatitis (Andreassi et al., 1997; Foolad et al., 2013; Kunkel et al., 1981; Leventhal et al., 1994, 1993; Lovell et al., 1981; Morse et al., 1989; Tate et al., 1989; Zurier et al., 1996). However, several more recent reviews and meta-analyses have questioned these earlier studies and raised doubts about the clinical effectiveness of GLA-enriched supplements particularly in the context of atopic dermatitis and RA (Bamford et al., 2013; Belch and Hill, 2000; Kitz et al., 2006; Macfarlane et al., 2011; Van Gool et al., 2004) (Table 1). A variety of issues complicate these studies including the fact that many of the

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Table 1
Effect of GLA-enriched oil supplements on various human disease from meta-analyses and recent studies.

Study	Disease[a] and study type[b]	Supplement[c]	Location	# Subjects	# Studies	Duration	Outcome	effect
Skin								
Morse et al. (1989)	Atoptic dermatitis (CO, parallel)	EPO (Epogam)	UK, Italy, Finland	311	9 (EPO)	4, 8, or 12 wk	Severity of symptoms	Reduced severity of symptoms
Van Gool et al. (2004)	Atoptic dermatitis (RCT, CO, CCT)	EPO, BO, BCO; 90–480 mg GLA/d (children); 132–720 mg GLA/d (adult)	Germany, Italy, UK, Canada, USA, Finland, Sweden, Switzerland,	1071	22 (total) BO (6) EPO (12) BCO (1)	3–24wk	Severity of symptoms	No effect
Bamford et al. (2013)	Eczema (AE, AD, AEDS) adult, children (RCTs)	EPO, BO	UK, Italy, Germany, India, NZ, Finland, Sweden, USA, Switzerland	1596	27 (total) 19 (EPO) 8 (BO)	3–24wk	Severity of symptoms	No effect
Morse and Clough (2006)	Atopic eczema	EPO (Efamol®)		1207	26	4–8wks	Severity of symptoms	Reduced severity of symptoms
Fiocchi et al. (1994)	Atoptic dermatitis, infants	EPO, 3 g oil/d	Italy	10	na	4wk	Lesion number; Severity of symptoms	Decrease number (trend); reduced severity of symptoms
van Gool et al. (2003)	Atoptic dermatitis, infants (RCT)	BO, 100 mg/d	Netherlands	118	na	6mo	Incidence in 1st yr; Severity of symptoms	No prevention benefit; reduced severity of symptoms (trend)
Kitz et al. (2006)	Atoptic dermatitis, infants	GLA, 40 mg/d	Germany	131	na	6 mo	Prevention	No effect
Kawamura et al. (2011)	Atoptic dermatitis, adult	GLA, 200 mg/d, oil of *Mucor circinelloides* in food	Japan	130	na	16wk	Trans-water loss; Nocturnal itching	No effect; decreased
Simon et al. (2014)	Atoptic dermatitis, children and adult (open study, non-controlled)	EPA, 4–6 g GLA/d	Switzerland	21	na	12wk	SCORAD[d] index	Plasma GLA content correlates with SCORAD
Arthritis								
Cameron et al. (2011) Macfarlane et al. (2011)	Rheumatoid arthritis (RCT, parallel, placebo controlled)	Herbal intervention 525–540 mg GLA/d	UK, USA	286 (total) > 90 (in 3 studies)	22 (total) EPO (2) BCO (1)	6mo	Morning stiffness; Pain	Decreased (2 of 3); no effect
Cameron et al. (2011) Macfarlane et al. (2011)	Rheumatoid arthritis	1400–2800 mg GLA/d	USA, Finland	> 111	EPO (1) BO (2) BCO (1)	6mo	Pain; Morning stiffness; Joint tenderness; Joint swelling;	Decreased; Decreased; Improvement; Decreased;
Asthma								
Arm et al. (2013)	Mild asthma, adults (randomized)	BO + EO (GLA, 1.67 g/d + SDA, 0.88 g/d)	USA	37	na	3wk	Basophil, Neutrophil leukotriene production (*ex vivo*)	> 50% decrease (basophil response); > 35% decrease (neutrophil response)
Ziboh et al. (2004)	Mild asthma, adults (randomized)	BO (2 g GLA/d)	USA	24	na	12mo	Neutrophil leukotriene production (*ex vivo*); Peak flow	> 20% decrease ($p < 0.05$); no effect

[a] CE, atopic dermatitis; AE, atopic eczema; AEDS, atopic eczema/dermatitis syndrome;
[b] RCT, randomized clinical trial; CO crossover; CCT, controlled clinical trial;
[c] BO, borage oil: BCO. Blackcurrant oil; EPO, evening primrose oil; EO, echium oil; GLA, gamma-linolenic acid; SDA, stearidonic acid;
[d] SCORAD, SCOing Atopic Dermatitis.