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FATTY ACIDS IN DERMATOLOGY

Abbreviations

FA  fatty acid
EFA  essential fatty acid
PUFA  poly-unsaturated fatty acid
MUFA  mono-unsaturated fatty acid
SFA  saturated fatty acid
LA  linoleic acid (ω6)
GLA  gammalinolenic acid (ω6)
DGLA  dihomogammalinolenic acid (ω6)
AA  arachidonic acid (ω6)
αLA  alphalinolenic acid (ω3)
EPA  eicosapentaenoic acid (ω3)
DHA  docosahexaenoic acid (ω3)
PG  prostaglandins (PGE1/2/3)
LT  leukotrienes (LTB4/5)
PA2  phospholipase A2
Co  cyclooxygenase
Lo  lipooxygenase
TsupL  T suppressor lymphocyte

PUFA Nomenclature

PUFA can have special common names as «arachidonic acid» (AA) or «linoleic acid» (LA), particularly the most important. However, the scientific nomenclature includes names that are composed of two parts: one, lettered, indicating the number of carbon atoms and the number of double bonds, and another shorthand identification with numbers corresponding to the latter but also indicating the position of the double bond the closest to the methyl (CH₃) end. This location determines the family to which it belongs (9, 6 or 3).

Example with EPA (eicosapentaenoic acid):
**FATTY ACIDS IN DERMATOLOGY**

**Titles and Explanations of the Figures**

**Figure 1.** Origin and metabolic pathways of *PUFAs*.

*Figure 1* presents the origin of various fatty acids in the nature along with their metabolic pathways in the organism. This figure helps understanding the role of each fatty acid, the reason why some are essential, and the potential sources. It also helps understanding the following figure in which these metabolic pathways are presented in a simplified form.

**Figure 2A.** Principal properties of $\omega_6$ and $\omega_3$ *EFA*, and of their cofactors.

*Figure 2A* presents the different PUFA properties and interactions (including the EFA) within their simplified metabolic pathway.

**Figure 2B.** Synergistic effects of controlled *EFA* supplementation and benefits in dermatology ; the *MEGADERM* response.

*Figure 2B* presents the main influences of FAs in dermatology as it shows which metabolic pathways are favoured by the supplementation of EFAs included in MEGADERM. It explains the role of each MEGADERM’s FA and its subsequent advantage in dermatology, demonstrating the indissociable and major benefits of the two families $\omega_6$ and $\omega_3$.

**Figure 3.** Diagrammatic illustration of structural and functional benefits of an $\omega_6$ and $\omega_3$ combination depending on their ratio : the *MEGADERM* balance.

*Figure 3* is a theoretical diagrammatic illustration of the structural and functional benefits of an $\omega_6$ and $\omega_3$ combination depending on their ratio. It clarifies the purpose of respecting this ratio and shows the importance of large enough quantities of supplements to maintain this beneficial balance, whatever the diet of the animal is.
I. **PUFA AND EFA : WHO ARE THEY? WHERE DO THEY COME FROM?**

(Refer to Figure 1)

PUFA (poly-unsaturated fatty acids) are FA (fatty acids) that have a long chain with several double bonds.

They have multiple vital roles in the organism of animals as well as in plants. PUFAs are designed as EFA (essential fatty acid) when they cannot be synthesised *de novo* by the animal and therefore result in their necessary dietary requirement.

There are 3 principal families of PUFAs (ω9, ω6 and ω3) among which 2 are fundamental (ω6 and ω3).

In animals, each of these families have a different metabolic pathway.

The PUFA or EFA that are the first substrates of a metabolic pathway are designed as « parent FA ». Only plants possess the necessary enzymes (desaturases) to obtain the parent substrates of animals’ metabolic pathways. Only plants can indeed synthesise by desaturation, from a saturated FA of 18 carbon atoms (stearic acid), successively the parent of the ω9 family followed by the ω6 family and finally the ω3 family. The ω3 family has therefore a superior degree of unsaturation than the ω6 family, which itself has a superior degree of unsaturation than the ω9 family.

The parent substrates are therefore EFAs in animals and hence should be supplied by vegetable oils in their diet.

Plants can seldom transform parent PUFAs, hence vegetable oils cannot provide the metabolites of these FA. However, and exceptionally, some rare plants are capable of metabolising LA (linoleic acid ω6) and therefore contain GLA (gammalinolenic acid ω6).

Some “terrestrial” plants are particularly rich in LA and poor in αLA. The synthesis of αLA (alphalinolenic acid ω3), parent of the ω3 family, is on the other hand a major component of the metabolism of certain marine plants. This is why some fish are rich in ω3 FA and in particular in EPA (eicosapentaenoic acid ω3) and DHA (docosahexaenoic acid ω3) subsequent to the metabolic conversion of αLA in their organism. These ω3 FA can and therefore should be provided by fish oils. EPA is reversibly metabolised in DHA so the supply of one or the other of these FA is equivalent. On the other hand, the first metabolic conversions are irreversible all the way to AA for the ω6 family, and EPA for the ω3 family.

To conclude, LA, GLA and EPA (+ DHA) are fatty acids that are vital for animals. Supplementation in these FA may be considered only by providing properly selected vegetable oils for the ω6 family and certain fish oils for the ω3 family (EPA and DHA).
It is important to note here that the different metabolic pathways (ω3, ω6 and ω9) are well distinct as far as their substrates and products, but they competitively use common enzymatic systems. The outcome of this competition does not only depend on the amount of FA present but also of which families are competing: the greater the number of double bonds, the greater the affinity for the desaturase enzyme. This brings up fundamental consequences in how to influence the metabolic activities by supplementing the diet.
II. MAIN ROLES OF EFA

EFAs are at the same time cellular and intercellular components, and substrates involved in the metabolism of the animal. Their physiological role in the organism, in particular by their involvement in the inflammatory processes, makes them essential to life.

**EFA therefore have two principal roles that should not be disassociated.**

The first role is structural: they take part of the tissue structure, in particular in the skin. The second role is functional: they are involved in metabolic pathways (the eicosanoids cascades) and participate in the inflammatory reactions and their regulation.

Two types of EFA are specially involved in these two features: the EFAs of the \( \omega_3 \) family and the ones of the \( \omega_6 \) family. These two families are well distinct because animals cannot synthesise their parent FA and because the metabolites cannot switch to one or the other family (only plants have this ability). Nevertheless, these two metabolic pathways (\( \omega_6 \) and \( \omega_3 \)) are very closely connected by the fact that they use the same enzymatic systems, and therefore their metabolites of same level compete between each other. This bilateral influence depends of the ratio \( \omega_6: \omega_3 \).

As a result, it appears possible to favour certain steps of the EFA metabolic pathways by providing certain specific EFAs.

A. Structural Role

1. *Intercellular cohesion and superficial lipid film*

The \( \omega_6 \) parent FA (LA) is above all a major component of the epidermal intercellular cement. Indeed, LA is admitted to be a key component of the intercellular lipids, in particular of ceramides, which ensure the intercellular cohesion and limit water and nutrient losses (epidermal barrier function).

Furthermore, LA is an essential component of the superficial lipid film, which protects the skin from external chemical, physical or microbial injuries.

2. *Cell membrane fluidity*

PUFAs with 20 carbon atoms (C20), among which are found AA, DGLA and EPA, without any family consideration (\( \omega_6 \) or \( \omega_3 \)), are major structural components of cell membrane phospholipids. Their fluidity, due to the presence of double bonds, is a prerequisite to cell integrity (in particular for keratinocytes) in the skin and its appendages. The degree of fluidity is directly related to the degree of unsaturation of structural FA (\( \omega_9 \) to \( \omega_3 \)). Thereby, \( \omega_3 \) are of major benefit in skin and haircoat « nutrition ». 
B. Functional Role

1. \(\omega_6\) EFAs

The metabolic pathway of \(\omega_6\) EFAs produces pro-inflammatory mediators and «anti-inflammatory» mediators (eicosanoids).

The conversion of AA leads to pro-inflammatory mediators.

Even though LA and GLA are in fact precursors of AA, these FA have very beneficial effects on the skin condition as well as in modulating inflammatory processes. It is then important to emphasise here that the supplementation in LA (and GLA) has practically no effect on the production of AA, because GLA is quickly converted into DGLA (dihomogammalinolenic acid \(\omega_6\)) which itself is very slowly converted in AA. The amount of AA produced by these conversions when \(\omega_6\) FAs are supplemented is therefore very small (or even insignificant) compared to the amount provided by the carnivore diet of dogs and cats.

The principal strategy for encountering the results of an excessive conversion of AA does not consist in limiting its intake, but its metabolic followed by its structural utilisation in supplemented animals.

DGLA is preferentially converted into anti-inflammatory PGE1 (prostaglandins E1) and therefore competes the cyclo-oxygenase enzyme with AA, inhibiting the conversion of the latter into pro-inflammatory PGE2 (prostaglandins E2). PGE1 also inhibits the phospholipase A2 that releases AA from the cell membranes and makes it available to be metabolised. Another significant property of PGE1 is that it stimulates T suppressor lymphocytes and inhibits mastocyte degranulation. Thereby, it regulates IgE response and furthermore limits the hypersensitivity type I reactions that occur in allergic dermatitis.

2. \(\omega_3\) EFAs

The metabolic pathway of \(\omega_3\) produces «anti-inflammatory» mediators.

The principal activity of \(\omega_3\) EFAs is regulating the production of pro-inflammatory mediators issued from the \(\omega_6\) metabolic pathway. The presence of \(\omega_3\) turns the balance towards the production of less inflammatory (or even anti-inflammatory) mediators, synergistically with DGLA (\(\omega_6\)) and depriving inflammatory mediators issued from AA. This activity is due to competitions for enzymatic systems supported on the long term by a structural competition in the cell membranes.
As we have seen, PUFAs are substrates for the production of eicosanoid mediators that induce and regulate inflammation, mostly prostaglandins (PG) and leukotrienes (LT).

Two major groups of enzymatic systems are involved in PUFAs metabolism: the desaturases (that act very slowly) and the elongases (that act very quickly). The former suppresses 2 hydrogen atoms (-2H) creating a double bond, and the latter adds 2 carbon atoms, elongating the molecule. Each metabolic level has a different enzymatic system yet each of these are used by FA of same level but of different metabolic pathways.

Since enzymatic systems have a greater affinity for FA containing the most double bonds, for each step, ω3 FA are preferentially metabolised followed by ω6 and then ω9. That is why when ω3 and ω6 FA deficiency occurs, the conversion of ω9 FA increases, with negative consequences. Benefit can on the other hand be derived from this peculiarity when supplementing an excess of ω3 (EPA and DHA), which will favourably compete the enzymatic systems with AA (ω6), and therefore reduce the potential conversions of the latter. «Excess» is not meant as a flat amount but as decrease of the ω6:ω3 ratio hence favouring the metabolic conversions of ω3 to the detriment of those of ω6. An ω3 “metabolic overload” can therefore be obtained even with a smaller amount of ω3 than of ω6, like for example with a 5:1 ratio.

These metabolic systems readily waver between the different families.

This explains first why they can be balanced depending on certain amounts of supplemented EFA and in second, why different ω6:ω3 ratios have different effects.
III. THE RATIONALE OF EFA DIETARY SUPPLEMMENTATION

A. General Consequences of EFA Deficiencies

The skin is very susceptible to EFA deficiency, which leads to poor cutaneous and haircoat quality or even to severe scaling, epidermal hyperproliferation and impaired epidermal barrier function. Healthy animal support relatively well these deficiencies, which sole consequence is an altered haircoat quality. In subjects with dermatoses, EFA deficiency unquestionably aggravates the clinical signs and the poor cutaneous status.

Besides quantitative deficiencies, defects of the enzymatic systems lead on top to qualitative deficiencies in cats or in certain dogs with skin diseases.

A general EFA (therefore PUFA) deficiency leads to the incorporation of less unsaturated (ω9) or long chain saturated FA in the cell membranes (in particular in keratinocytes). The subsequent reduced cell membrane fluidity increases the tissue permeability and therefore the transepidermal water and nutrient loss.

Furthermore, an EFA deficiency or even a concentration imbalance of different FA, may alter the metabolic pathways and therefore enhance the inflammatory processes.

Broadly speaking, qualitative deficiencies may be induced by defects of the enzymatic function. The cat, for example, has a higher risk of PUFA deficiency because the activity of its desaturases is reduced. Enzymatic deficiencies may also be due to certain pathologic conditions as hypothyroidism, diabetes, liver disease, stress, etc. In these two latter cases, one of the reasons could be a Δ6 desaturase inhibition by cortisol (which secretion increases in stress) and in particular in liver disorders (older animals...).

A direct supplementation of GLA and EPA gains then all its importance in these pathologic conditions and in cats, and more particularly in those affected by allergic dermatitis, manifested by a miliary dermatitis, eosinophilic plaques or granulomas…

B. Main Therapeutic Perspectives of EFA Supplementation

Any apparently healthy subject, may benefit of a supplement that will compensate eventual imbalances, deficiencies or defects that do not cause obvious clinical signs.

Since EFA have many physiologic activities, their supplementation provides benefits in preserving an efficient immune defence and keeping the animal in good condition. It also has a major interest as preventing occurrence of dermatoses or as a cosmetic conditioner.
Furthermore, all dermatoses engender skin injuries whose structure and/or physiologic modifications can be improved by such supplementation. More particularly, a kerato-seborrheic status is linked to a high cutaneous concentration of oleic acid (AGMI $\omega_9$), which can be compensated the most advantageously and efficiently by a LA supplementation.

The clinical signs of allergic dermatitis are due as much to the structural modifications of the skin as to the inflammatory processes enhanced by type I hypersensitivity reactions. Hence, they represent a strong indication for an appropriate EFA supplementation.

EFA are known as well for their influence in many other metabolic activities involved in the regulation of miscellaneous organic functions that preserve the health of living beings.

In human medicine and aside from the dermatological field, the beneficial effects of EFAs, in particular the regulation of the production of inflammatory mediators, are exploited in many diseases as atherosclerosis, rheumatoid arthritis, asthma…

C. Fields of action in dermatology and required EFAs : $\omega_6$ or $\omega_3$?

1. Therapeutic strategies in dermatology

The ultimate aim of any dermatological treatment is to put an end to any clinical signs (symptoms and lesions). Accordingly, a double key strategy is necessary:

1°) restoring a perfect skin integrity is a prerequisite in all dermatological treatments. The structural role of EFA is of benefit for this objective.

2°) limit the outcome of inflammatory processes by strictly controlling the EFA supplementation and ratio in order to influence the metabolic pathways of PUFAs that are involved in this processes. The plan is to deprive the inflammatory process of its initial substrate (the AA) by inhibiting its potential metabolic conversions, and thereby deviating the metabolic pathways towards FAs that will produce anti-inflammatory (or less inflammatory) mediators instead of pro-inflammatory mediators.

These two strategies are necessary and indissociable to achieve this objective, and each of the two families, $\omega_6$ and $\omega_3$ participate in each of these two directions.

For full comprehension, it is important to remind that the FAs that compose membrane structural phospholipids are the ones that will be released later in order to be metabolically converted into inflammatory mediators in the eicosanoid cascades. Their presence in these membranes generates a substantive metabolic stock.

Each of the $\omega_6$ and $\omega_3$ metabolic pathways have a role in regulating the inflammatory processes, but their close interaction explains the complexity of their mechanism. Not only do these two families compete with the same enzymatic systems that are rate-limiting, but the latter also have a preference for FAs that contain the most double bonds, even if their concentration is lower. Therefore, for each enzymatic step, the choice of substrate ($\omega_6$ or $\omega_3$ ) is strongly influenced by variations of the $\omega_6:\omega_3$ ratio. The importance of supplementing each of these FA and maintaining a certain ratio between them is then capital. In order to utterly provide the two beneficial effects, a diet supplement should include substantial amounts of $\omega_6$ and $\omega_3$ FAs according to a certain ratio.
2. The required EFA for a structural beneficial effect

The double supplementation of ω6 and ω3 allows to perfectly restore the skin integrity taking into account the incorporation of LA in the intercellular cement as in the superficial lipid film, and of C20 FAs (DGLA and EPA) in the cell membranes. In fact, the integration of EPA in membrane phospholipids instead of AA provides not only a stock of EFA that produces anti-inflammatory mediators, but it also increases the fluidity and stability of cell membranes. This reinforces the epidermal function barrier. A supplement is more beneficial if it is limited in oleic acid (parent of the ω9 family) for this FA is an adverse structural component responsible of a loss of cell membrane fluidity.

3. The required EFA for a functional beneficial effect

Supplementation of ω6 (LA and GLA) and ω3 (EPA and DHA) is of benefit by influencing favourably the metabolic pathways of PUFAs hence producing anti-inflammatory mediators to the detriment of pro-inflammatory mediators.

- The first step is to favour the first steps of the ω6 metabolic pathways that produce DGLA, and more particularly the anti-inflammatory PGE1. This is achieved by supplying enough LA and direct GLA with limited αLA (ω3 parent EFA, which is a strong enzyme competitor). The functional role of LA is enhanced by the direct supply of GLA thus compensating eventual enzymatic (Δ6 desaturase) deficiencies. Even though these enzymes have less affinity for ω9 FAs, limited oleic acid is also beneficial by avoiding its competition with the ω6 metabolic pathway.

- A second step is to favour the metabolic conversion of EPA (and DHA). By competing with AA for the lipoxygenase and cyclooxygenase, they favourably deviate the eicosanoid cascade towards the production of PGE3 and LTB5 (anti-inflammatory), thus limiting the conversion of AA into PGE2 and LTB4 (pro-inflammatory).

D. Conclusion

The synergistic effects of ω6 and ω3 EFAs are beneficial as well in restoring the skin integrity as for providing an anti-inflammatory effect, by the control of PUFAs metabolic pathways. Other FA must be considered for their adverse effects.
Origin and metabolic pathways of PUFAs

ω 9 family

ω 6 family

ω 3 family

Stearic ac. 18 : 0
Oleic ac. 18 : 1 ω 9
Linoleic ac. LA 18 : 2 ω 6

Δ 6-desaturase (-2H)

Octadecadienoic ac. 18 : 2 ω 9
Gammalinolenic ac. GLA 18 : 3 ω 6

Δ 6-desaturase (-2H)

Eicosadienoic ac. 20 : 2 ω 9
Dihomoγamma linolenic ac. DGLA 20 : 3 ω 6

Δ 5-desaturase (-2H)

Eicosatrienoic ac. 20 : 3 ω 9
Arachidonic ac. AA 20 : 4 ω 6

Δ 5-desaturase (-2H)

Eicosatrienoic ac. 22 : 3 ω 9
Adranic ac. 22 : 4 ω 6

Δ 4-desaturase (-2H)

Docosatrienoic ac. 22 : 3 ω 6
Docosapentaenoic ac. 22 : 5 ω 6

Δ 4-desaturase (-2H)

Alphalinolenic ac. ω LA 18 : 3 ω 3
Octadecatetraenoic ac. 18 : 4 ω 3

Δ 6-desaturase (-2H)

Eicosatetraenoic ac. 20 : 4 ω 3
Eicosapentaenoic ac. EPA 20 : 5 ω 3

Δ 5-desaturase (-2H)

Docosapentaenoic ac. 22 : 5 ω 3
Docosahexaenoic ac. DHA 22 : 6 ω 3

Δ 4-desaturase (-2H)
Principal properties of \( \omega 6 \) and \( \omega 3 \) EFAs and of their co-factors

\( \omega 9 \) family  \( \omega 6 \) family  \( \omega 3 \) family

- Oleic ac.
- LA
- \( \text{GLA} \)
- \( \text{DGLA} \)
- mb AA
- \( \text{Free AA} \)
- EPA
- \( \alpha \text{LA} \)
- \( \text{PGE1} \)
- \( \text{PGE2} \)
- \( \text{PGE3} \)
- \( \text{LTB4} \)
- \( \text{LTB5} \)

- \( \text{PGE1} \), \( \text{PGE2} \), \( \text{PGE3} \), \( \text{LTB4} \), \( \text{LTB5} \) are proinflammatory mediators.
- \( \text{GLA} \), \( \text{DGLA} \), \( \text{Free AA} \), \( \text{EPA} \) are anti-inflammatory mediators.
Synergistic effects of ω 6 and the ω 3 = double role, structural and functional, for each family

Main actors and their favoured metabolic pathways

<table>
<thead>
<tr>
<th>Main actors and their favoured metabolic pathways</th>
<th>Effects</th>
<th>Benefits in dermatology</th>
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<tbody>
<tr>
<td>ω 9 family</td>
<td></td>
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<td>Oleag. ac.</td>
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| ω 6 family                                      |         |                         |
| LA                                              |         |                         |
| Zn⁺⁺                                            |         |                         |
| Δ-6-desaturase                                  |         |                         |
| VERY SLOW                                      |         |                         |
| DEFICIENT                                      |         |                         |
| GLA                                             |         |                         |
| Vit B6, B3                                     |         |                         |
| Vit H⁺⁺                                        |         |                         |
| Elongase                                        |         |                         |
| VERY QUICK                                      |         |                         |
| DGLA                                            |         |                         |
| Δ-5-desaturase                                  |         |                         |
| VERY SLOW                                      |         |                         |
| DEFICIENT                                      |         |                         |
| mb                                              |         |                         |
| AA                                              |         |                         |

| ω 3 family                                      |         |                         |
| GLA                                             |         |                         |
| Vit A, H⁺⁺                                      |         |                         |
| Cell injury                                     |         |                         |
| PA⁺⁺                                            |         |                         |
| DHA                                             |         |                         |
| Co                                              |         |                         |
| Lo                                              |         |                         |
| Lo                                              |         |                         |
| Free AA                                         |         |                         |
| Vit E                                          |         |                         |
| PGE1                                            |         |                         |
| PGE2                                            |         |                         |
| L sup T                                         |         |                         |
| PGE3                                            |         |                         |
| LTB4                                            |         |                         |
| LTB5                                            |         |                         |
| LTB5                                            |         |                         |

- LA : Improves the intercellular cement and superficial lipid film quality.
- GLA + EPA : Incorporate themselves into cell membranes:
  - Enhances membrane fluidity and stability
  - Storage of EFAs producing anti-inflammatory mediators
- GLA + EPA : Metabolites convert into anti-inflammatory mediators to the detriment of proinflammatory mediators
- GLA + EPA : Modulates IgE response and decreases hypersensitivity mechanisms (type I)

Haircoat quality
Reinforced skin integrity
Efficient epidermal barrier function
Helps control pruritus and inflammation

Proinflammatory mediators
Anti-inflammatory mediators
Diagrammatic illustration of structural and functional benefits of an $\omega_6$ and $\omega_3$ combination depending on their ratio.

Improvement of skin integrity: structural benefit.

Regulation of pruritus and inflammation: functional benefit.

With MEGADERM, what ever the animal’s diet is (among basic diets).

With an under-dosed supplement:
1°) absolute amounts are insufficient,
2°) uncontrollable variations of the physiologic ratio according to the diet.