Butterfly Effect – the Concept and the Implications in Dermatology, Acne, and Rosacea

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ABSTRACT

Acne and Rosacea are chronic inflammatory skin diseases with an increasing frequency and an important negative impact on the quality of life, which are associated with a large number of false myths regarding causes and treatment. The butterfly effect is associated with chaos theory, and it is a concept originated in meteorology, which represents the dependence on initial conditions.

Keywords: butterfly effect, dermatology, acne, rosacea, skin care, diet, public health, chronic disease.

I. The butterfly effect – definition of concept, the author of concept and the use in general life

The butterfly effect (in chaos theory) represents the sensitive dependence on initial conditions, that is, a very small change in one state of a deterministic nonlinear system is associated with large differences in a later state.

Edward Lorenz coined the term, and “the butterfly effect” was derived from the metaphorical example in which the details of a tornado were influenced by minor perturbations such as flapping of the wings of a distant butterfly. Lorenz discovered the effect when he observed that runs of his weather model with a very small change in initial conditions had created a significantly different outcome.

The idea that small causes may have large effects in general and in weather specifically has been earlier recognized by the French mathematician and engineer Henri Poincaré and the American mathematician and philosopher Norbert Wiener.

The idea that one butterfly could eventually have a far-reaching ripple effect on subsequent historic events made its earliest known appearance in A Sound of Thunder, a short story about time travel, written by Ray Bradbury in 1952.
II. The butterfly effect and dermatology

On 12 May 2018, we performed a search on PubMed about “butterfly effect” and “dermatology”, and “butterfly effect” and “acne” and “butterfly effect” and “rosacea”, respectively, but all returned 0 results; therefore, we started to develop the possibility to use “the butterfly effect” in dermatology, particularly in acne and rosacea management.

III. Acne and the butterfly effect

1. Acne definition

Acne, characterized by androgen-induced increased sebum production, follicular hyperkeratinisation, inflammation and altered adaptive immune response, is a chronic inflammatory disease of the pilosebaceous unit (1) with an important negative impact on the quality of life.

Acne is characterized by a prolonged course, a pattern of recurrence or relapse, manifestation as acute outbreaks or slow onset, and a psychological and social impact that affects the individual’s quality of life (2). These are the features used by the World Health Organization (WHO) to define the chronicity of diseases, and now acne is considered to be a "chronic disease".

2. Acne frequency

Acne represents the most common diagnosis made by dermatologists (3), and unfortunately, a common misconception among medical and lay communities is that acne is a self-limited teenage disease and thus, it deserves not the same attention as that paid to a chronic disease (4, 5). Importantly, adult patients with acne, mostly women, comprise the majority of visits (61.9%), with adolescents (peak age 15–17 years) presenting in 36.5% of visits (6), showing that acne occurs very frequently in adulthood.

3. Acne impact on quality of life

“There is no single disease which causes more psychic trauma, more maladjustment between parents and children, more general insecurity and feelings of inferiority and greater sums of psychic suffering than does acne vulgaris” (7).

The impact of acne is comparable to that of systemic disease processes such as diabetes, asthma, arthritis, and epilepsy (8), and the change in the skin appearance may give rise to a changed body image that, in turn, is known to lead to anger, fear, shame, anxiety, depression, embarrassment, and bullying and stigmatisation within peer groups (9).

The negative effects of acne are represented by lack of confidence, social withdrawal, feelings of insecurity and inferiority, limited employment opportunities, functional and interpersonal difficulties at work, and suicidal tendencies, and the treatment must start as soon as possible, in order to prevent both physical and psychological scars.

4. Acne and myths

Patients often have misconceptions about factors exacerbating acne that may influence their treatment-seeking behaviour (10), and the most common myths and misconceptions are usually connected with etiology of acne and its treatment (11).

Misunderstanding and misinformation is associated with the beliefs that poor hygiene, hormones, diet, cosmetics, infection or stress are the factors that exacerbate acne in teenagers (10, 12).

Patients use “acne treatments” (cleansers, acne pads, masks, cover-up products, acne lotions, etc.) before seeking medical attention. It was reported that 74% of such patients waited more than 1 year before medical consultation (12). Unfortunately, delay in obtaining adequate treatment for acne has been shown to increase the risk of scarring (13). The remedies for acne management were provided by a family member in 42.4% of cases, a pharmacist in 10%, and by a dermatologist in only 7.2%.

In addition, excessive cleansing can lead to disruption of the epidermal barrier, increased transepidermal water loss (TEWL), roughened and irritated skin, increased bacterial colonization, increased comedonal formation, secondary irritant contact dermatitis, and burning and stinging. These negative effects caused by harsh soaps and aggressive cleansing make many prescription topical AV medications less tolerable (14). The direct effect of improper skin care in acne patients is lower adherence to treatment and failure of therapy. Finally, the perceptions and beliefs about acne have practical implications in management, adverse effects, expense and potential psychological sequelae.

5. Acne – causes and pathogeny

Pathogenesis of acne in adult women is complex, involving androgens in addition to other...
important factors such as sebum production, follicular plugging, genetics, Propionibacterium acnes, diet, smoke, stress medications, innate immunity, and alterations in follicular keratinization and differentiation (15).

Sebaceous glands possess the enzyme machinery for the production of hormones (i.e., 5-α-dihydrotestosterone, vitamin D, corticotropin-releasing hormone) and proinflammatory cytokines (IL-1α, TNF-α, IL-6 and IL-8) express a variety of receptors, including those for sex steroids, retinoic acid (isotypes α, γ) and retinoid X receptors (isotypes α, β, γ), peroxisome proliferator-activated receptors, liver-X receptors, histamine, prostaglandins, corticotropin-releasing hormone, neuropeptides, growth hormone, IGF-1 and melanocortin-1, and thereby, they function as independent endocrine organs (28), and are also an important part of the innate immune system, expressing Toll-like receptors 2, 4, 6 and CD14, or producing a variety of antimicrobial peptides like human β-defensins, cathelicidin or antibacterial lipids such as sapienic acid or other monounsaturated fatty acids (16).

Acne exposome represents a new concept that is defined as the sum of all environmental factors influencing the occurrence, duration and severity of acne (17). Exposome factors interact with the skin barrier, sebaceous gland, innate immunity and cutaneous microbiota (18) and have a direct impact on the response and frequency of relapse to treatments.

Nutrition, medication, occupational factors (including cosmetics), pollutants, climatic factors, and psychological and lifestyle factors (17) represent the main exposome in acne.

6. Acne and nutrition
Food is a conditioning environment that shapes the activity of the human genome, and the “milk and sugar” combination is the inseparable and most common food items in Western societies.

In mammals, milk signaling is generally limited to the physiological nursing period, except the Neolithic Homo sapiens, who introduced milk consumption 8,000-10,000 years ago into his food chain (19).

Two major compounds of Western diet have been identified to drive acne pathogenesis, hyperglycaemic carbohydrates (high Glycemic Load) and insulinotropic milk/dairy products, both promoting increased insulin/insulin-like growth factor-1 (IGF-1) signalling (20, 21).

The impact of diet in acne is highlighted by the fact that acne is absent in populations consuming less insulinotropic palaeolithic diets that exclude grains, milk, and dairy products and exhibit much lower insulin/IGF-1 signalling (20, 22).

Increased insulin/IGF-1 signaling mediated by consumption of hyper-glycemic carbohydrates and insulinotropic milk and dairy products has been associated not only with the pathogenesis of acne, but also with other diseases of civilization (23, 24).

IGF-1 is able to stimulate 5-α-reductase, adrenal and gonadal androgen synthesis, androgen receptor signal transduction, sebocyte proliferation, sebum production, and lipogenesis, affecting acne development (25).

There is evidence that a low glycaemic load diet can reduce the size of sebaceous glands and the sebum, decrease inflammation and total lesion counts, and diminish the expression of pro-inflammatory interleukin-8, all showing a positive influence on the clinical course and intensity of acne and sebum production (26, 27).

The Western diet is characterized by a high glycaemic load and increased levels of milk/dairy protein, containing abundant amounts of branched-chain amino acids (leucine, isoleucine, and valine), and able to overstimulate a kinase termed mammalian target of rapamycin complex 1 (mTORC1). The activation of mTORC1 signalling is involved in both acne pathogenesis and insulin resistance (21, 28). mTORC1 is the growth factor and nutrient-sensitive kinase that is activated by growth hormones such as insulin and IGF-1 and amino acids, predominantly by the BCAAs leucine, isoleucine, and valine (29).

The pathogenesis of age-related diseases of civilization such as obesity, T2DM, insulin resistance, metabolic syndrome, cancer, neurodegenerative diseases and early aging has been related to persistently increased activation of the nutrient-sensitive kinase mammalian target of rapamycin complex 1 (mTORC1) (29).

Basically, from Western diet we have five major pathways that activate mTORC1:
1) growth factors (insulin and IGF-1);
2) sufficient cellular energy (glucose, ATP);
3) availability of amino acids – BCAA;
4) presence of glutamine;
5) availability of saturated fatty acids (palmitic acid) (28, 29).
7. What we can do now?

International estimates suggest that 17–40% of people with acne consult either a general practitioner (GP) or a dermatologist (30), and the first step is to bring more patients with acne to medical consultation before the development of physical and psychological scar.

Another important step – from a dermatologist point of view – is to educate other clinicians and patients that acne is a chronic disease (5), and not just a self-limited disorder of teenagers. Spending time dispelling myths and explaining that most treatments will not cure is worthwhile and might improve adherence.

Increasing patients’ knowledge about their skin disease and treatment can stimulate participation in treatment decision making, which may have positive effects on patient satisfaction, compliance and health outcomes.

Management should comprise safe treatment, reduction of psychological burden through emotional and social support, and clarifying popular misconceptions about the disease.

Treatment should start as early as possible to reduce the risks of scarring or adverse psychological effects. It should be aimed at reducing non-inflammatory lesions that may be precursors to inflammatory lesions, improving existing inflammation and reducing the \( P. acnes \) population.

It is important for the dermatology practice to efficiently provide an office visit experience that is highly educational and includes the integration of proper skin care and product selection along with medication selection and proper use (31).

A skin care product dedicated to acne patients may provide a protective barrier from pollution, restore microbiome equilibrium to prevent overabundant bacteria (including \( P. acnes \)) colonization and control disease severity and postinflammatory pigmentation (32).

Proper skin care provides adjunctive value to the medical regimen and can reduce local tolerability reactions associated with topical medications; a complete management for maintaining the structural and functional integrity of the epidermal barrier includes cleansing, medicating, moisturizing, and photoprotection (31).

The goals of cleansing in patients with acne are to gently cleanse the skin and prepare it for the absorption of topical therapies and avoid skin irritation and dehydration, minimize or reverse the damage to the skin barrier that is seen with many acne therapies and maintain skin pH, and reduce the proliferation and inflammation associated with \( P. acnes \).

Acne is a disease of Western civilization, which is closely related to Western lifestyle factors, especially exposure to Western diet, and acne vulgaris belongs to the family mTORC1-driven diseases of civilization (33, 34).

Acne appears to be a visible indicator of systemically exaggerated mTORC1 signalling, an unfavourable metabolic deviation on the road to serious mTORC1-driven diseases of civilisation, especially overweight (increased BMI), obesity, arterial hypertension, insulin resistance, type 2 diabetes mellitus, cancer, and Alzheimer’s disease (29).

Dietary intervention in acne must decrease total energy, glucose and fat intake, diminish insulin/IGF-1 signaling predominantly mediated by high dairy protein consumption, and limit the total leucine uptake (meat and dairy proteins).

Acne is obviously the visible outcome of imbalanced nutrigenomics induced by Western diet, the maximized form of neolithic nutrition, which exaggerates insulin/IGF-1 signaling. Therefore, dermatologists have the great opportunity to introduce dietary and metabolic interventions in acne, so as to prevent more serious mTORC1-driven diseases of civilization such as obesity, diabetes, and cancer.

Dietary attenuation of overstimulated mTORC1 signalling may not only improve acne, but may also prevent the march to more serious chronic mTORC1-driven diseases of civilisation.

Public health issues in acne are represented by frequency of disease, costs for medical care and health systems, negative impact on quality of life, antibiotic resistance of \( P. acnes \), associated morbidity (35, 36).

IV. Rosacea and the butterfly effect

Rosacea is a chronic and common skin condition characterized by specific signs and symptoms located mainly on the convex areas of the face (cheeks, nose, forehead, chin) such as facial erythema, dilated vessels, inflammatory lesions (papules and pustules), hypertrophic lesions named phyma, sometimes accompanied by ocular irritation, with a potential important impact on the individual’s emotional wellbeing.

The pathophysiology of rosacea continues to remain unclear, but it is believed that genetic fac-
tors, immune system dysregulation, abnormal neurovascular signaling and dysbiosis of commensal skin organisms may be the key promoters of rosacea (37).

Triggers of rosacea include sun exposure, hot temperatures, exercise, feelings of embarrassment or anger, spicy foods, alcohol consumption. Some of these triggers act directly to trigger vasodilation, while other factors such as Demodex or its endosymbionts act via different mechanisms, with an ultimate increase in skin inflammation (38).

In one patient survey conducted by the National Rosacea Society, 78% of all subjects had altered their diet, and 95% of this group reported subsequent reduction in flares. Trigger foods were represented by capsaicin containing foods (spices, pepper, hot sauce), cinnamaldehyde containing foods (cinnamon citrus, chocolate, tomatoes), heat related foods (hot beverages such as tea or coffee) and alcohol (various hard liquor, wines) (38).

Capsaicin and high temperatures can induce vanilloid receptors activation, which results in inflammation and vasodilation (39, 40), and cinnamaldehyde activates TRPA1 (an ankyrin receptor) which induces flushing by neurogen vasodilation.

Rosacea patients may be advised to consider fiber-rich (prebiotic) diet measures to promote a healthy gut microbiome and also to avoid trigger factors or learn simple methods to control them.

Patients need simple recommendations and advice to prevent a flare of rosacea: to replace their steaming mug of coffee with iced coffee, avoid exercise outside when it is too hot (if inside, a fan or air conditioner should be used), use sunscreen to protect the skin outdoors, and learn ways to calm oneself before stress results in a rosacea flare-up (deep breathing exercises).

Endosymbionts of Demodex have been identified as triggers of inflammation in rosacea, respectively Bacillus oleronius (41), Bacillus simplex, which was isolated from Demodex folliculorum in a patient with primary demodicosis, Bacillus pumilus positive culture confirmed by mass spectrometry was found in a patient with rosacea and D. folliculorum (42), and also Bacillus cereus from Demodex was isolated from a patient with steroid induced rosacea-like facial dermatitis.

Extensive topical corticosteroid use leads to increased mite populations and thus, what might often be known as demodicosis or rosacea might be steroid-induced rosacea-like dermatitis.

Importantly, a better detection of Demodex presence is required – clinically spinuloso-filiform spicules, whitishyellow follicular plugs; by dermoscopy – features of Demodex: follicular plugs and Demodex tails – and ≥ 3 tails on a dermoscopic area are considered specific for Demodex or by its endosymbionts (MALDI–TOF Spectrometry).

The first step in rosacea management is education about trigger and “avoidance policy” in order to prevent a flare as well as active detection of Demodex presence.

V. Discussions and conclusions

From the authors’ point of view, “the butterfly effect” associated with Acne and Rosacea is represented by education about these chronic inflammatory skin diseases, with emphasis on myths and skin care, because the power of false myths keep patients away from medical care; also, correct and individualized skin care is associated with a better adherence to treatment and results.

Dermatologists have the great opportunity to introduce dietary and metabolic interventions in acne so as to prevent more serious mTORC1-driven diseases of civilization like obesity, diabetes, and cancer.

We were unable to find any previously published reports on the presence and role of „butterfly effect” in Dermatology.

At the moment of our article submission, we did not find any kind of PubMed reference on „the butterfly effect” and Dermatology, Acne and Rosacea, respectively, and our article represents the first published paper on the subject, concept which could be associated with other diseases such as psoriasis, atopy or immunology and cytokines. To assess possible correlations between subtypes of acne or rosacea, dermoscopy features, microbiome and others, further research with large study samples is needed to explore „the butterfly effect” in Dermatology, but also as an expanded concept to all the fields of medicine.

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