Milk and Insulin Growth Factor 1 (IGF1) – Implication in Acne and General Health

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VICTOR GABRIEL CLATICI1, OLIVIA GEORGESCU2, ANA MARIA VERONICA DRAGANITA3, ALIN LAURENTIU TATU4, SIMONA FICA1
1 University of Medicine and Pharmacy “Carol Davilla” Bucharest, Romania
2 Elias Emergency University Hospital – Bucharest, Romania
3 Dermatology Unit - Colentina Clinical Hospital, Bucharest, Romania
4 Dermatology Unit, Faculty of Medicine and Pharmacy, University Dunarea de Jos, Galati, Romania
*Corresponding author: Victor Gabriel Clatici, University of Medicine and Pharmacy “Carol Davilla”, Bucharest, Romania, Phone: 021/3161600 – 190, Fax: 021/3173052, Email: claticiv@yahoo.com

Abstract
Acne, which now is considered “epidemic” in Western countries, is estimated to affect 79-95% of the adolescent population and 40-54% of individuals older than 25 years. Social, psychological, and emotional impact of acne is similar to patients diagnosed with asthma, arthritis, epilepsy, and diabetes.

Keywords: acne, milk, insulin growth factor 1 (IGF1), general health, mTORC1, obesity, cancer, dietary intervention, biotechnology

1. Introduction
Acne pathogenesis is multifactorial and complex, including genetic factors, and is related to several key factors: excess sebum production by the sebaceous glands, follicular occlusion, hyper proliferation of Propionibacterium acnes bacteria, and inflammation.

High glycemic load diets (hyperglycemic carbohydrates) and increased consumption of dairy proteins are the major dietary factors of Western diet promoting the development or exacerbation of acne, by increasing insulin/insulin-like growth factor-1 signaling.

The connection between insulin growth factor (IGF-1) and acne is represented by the effects of IGF-1 on androgens secretion (both in ovaries and testis) and activation of 5α-reductase, which converts testosterone to the more potent dihydrotestosterone -DHT.

Moreover, IGF-1 inhibits hepatic synthesis of sex hormone-binding globulin resulting in increased bioavailability of androgens, and has an effect on acne pathogenesis.

IGF-1 is an important contributor to sebaceous gland growth and lipogenesis, increase the lipid production in sebocytes and promote acne by inducing hyperkeratosis and epidermal hyperplasia (regulating keratinocyte proliferation and apoptosis).
mTORC1 (the nutrient-sensitive kinase mammalian target of rapamycin complex 1), integrates nutrient signals, such as glucose (ATP/energy status of the cell), essential amino acids and growth factor signals (insulin, IGF-1, fibroblast growth factors).

mTORC1 is strongly involved in a lot of “disease civilization” like overweight, obesity, arterial hypertension, insulin resistance, type 2 diabetes mellitus, cancer, and Alzheimer’s disease.

The attenuation of whey protein-based insulinotropic mechanisms will be the most important future challenge for an interdisciplinary cooperation between medicine, nutrition research and milk processing biotechnology.

The connections between milk and acne are represented by the hormones presents in milk (testosterone precursors – androstenedione and dehydroepiandrosterone – sulfate – and 5a-reduced steroids, 5a-androstanedione and 5a-pregnanedione, which are DHT precursors) and by IGF-1.

Milk, because have in composition androgens, 5alpha reduced steroids and growths factors, exerts important effects on comedogenicity through interactions with IGF-1 pathway, stimulating sebum synthesis and accelerated the hyperkeratinization process of the pilosebaceous unit.

2. Acne: Epidemiology and Impact on Quality of Life

Acne, which now is considered ,,epidemic,, in Western countries, is estimated to affect 79-95% of the adolescent population and 40-54% of individuals older than 25 years. (L. CORDAIN & al. [1]) Others authors (E.H. SPENCER & al. [2]) confirm these results and estimated that 80-90% of American adolescents have acne.

Cordain et al (L. CORDAIN & al. [1]) found that acne is absent in Kitava islanders, which have a Paleolithic diet excluding dairy, sugar and grains. Non – Westernized diets is free of processed foods, cereal grains, dairy products, refined sugars, and is based on fresh fruits and vegetables, fish and seafood (L. CORDAIN [3]).

A lot of information confirms that epidemic acne in Western countries is the result of consumption of hyperglycemic carbohydrates / refined high glycemic index (high GI) and insulinotropic dairy (L. CORDAIN & al. [1], B.C. MELNIK [4])

A very important correlations found in cross sectional studies are about acne and insulin (C. SMITH & al. [5]), acne and preadolescent increase in body mass index (BMI) (M. ROLLAND-CACHERA [6]) and acne and IGF concentrations (C. SMITH & al. [5], S. CAPRIO & al. [7]).

Paleolithic diet, which means NO hyperglycemic carbohydrates and NO insulinotropic dairy, have both success in the prevention and treatment of acne, diabetes type 2 and cardiovascular diseases, according to some authors (B.C. MELNIK [4], L.A. FRASSETTO [8]).

In contrast with Western countries, acne remains rare in non-Westernized societies such as the Inuit (O. SCHAEFER [9]), Okinawan Islanders (P. STEINER [10]), Ache
hunter-gatherers, and Kitavan Islanders (L. CORDAIN & al. [1]), which suggest a life style impact on the acne (including diet).

Acne was absent in the Inuit population (living and eating in traditional manner) (O. SCHAEFER [9], E. BENDINER [11]) but its prevalence increased in the moment of changing the life style, including adoption of processing foods, beef and dairy (O. SCHAEFER [9], E. BENDINER [11]). The same increase of acne prevalence was noted in Okinawans after decreasing their starch intake and increasing consumption of animal products (P. STEINER [10]). On the contrary, in Zulu population, high acne prevalence are attributed to the migration into cities from rural villages (W.J. CUNLIFFE & al. [12]).

In contrast with the data reported by Spencer (E.H. SPENCER & al. [2]), a study of schoolchildren from Purus Valley, a rural region in Brazil showed that from 9955 children aged 6 to 16 years, only 2.7% had acne vulgaris (L. BECHELLI & al. [13]), which confirm the huge impact of life style (including diet) on acne prevalence.

Acne is not an insignificant problem (H.C. WILLIAMS & al. [14]) and is not a self-limiting disorder or a “cosmetic” problem. Some authors reported that social, psychological, and emotional impact of acne is similar to patients diagnosed with asthma, arthritis, epilepsy, and diabetes. (E. MALLON & al. [15])

Moreover, acne patients have much higher rates of clinical depression, anxiety, anger, suicidal thoughts, and even suicide itself (P. MAGIN & al. [16]-D.R. THOMAS [19]) and unemployment rates is significantly higher among adults with acne compared with matched – controls (W.J. CUNLIFFE [20]).

3. Acne: Pathogenesis and Link with Diet

Acne pathogenesis is multifactorial and complex (A. KATSAMBAS & AL. [21]), including genetic factors, and is related to several key factors such as excess sebum production by the sebaceous glands, follicular occlusion, hyperproliferation of Propionibacterium acnes (P. acnes) bacteria, and inflammation. (K. DEGITZ & al. [22], D.THIBOUTOT [23]).

Sebum production in association with hyperproliferation of follicular cells conduct to comedones development and occlusion (L.F. EICHENFIELD & al. [24]), and sebum production and secretion is stimulated by androgens. (D. THIBOUTOT [23], L.F. EICHENFIELD & al. [24]).

Acne is an androgen-dependent disease (D. DEPLEWSKI & al. [25]) but few studies have demonstrated a direct correlation between acne severity and plasma androgen levels (J. SHAW [26]), and variations in the clinical response to androgens suggests that the endocrine control of acne is complex. (M. LEVELL & al. [27])

Dihydrotestosterone (DHT), which act at androgen receptor on intranuclear level (R.L. ROSENFIELD & al. [28]) (sebaceous, hair, and ductal lining) of genetically predisposed pilosebaceous units (V. BATAILLE & al. [29]) contribute to development of acne.

Very interesting, the effect of the DHT is synergized by insulin like growth factor-1 (IGF-1) (L. CORDAIN [3], R.N. SMITH & al. [30]), and all the factors (genetics factors,
hormones, milk and dairy, high glycemic index food etc.) with effects on synthesis or level of IGF1 will have also impact on acne development.

From this point of view, hyperinsulinemia (and hyperinsulinemic diet) has been implicated in acne pathophysiology due to its association with increased androgen bioavailability and concentrations of IGF1 (L. CORDAIN [3], L. CORDAIN & al. [31]).

Hyperinsulinemic diet acts as a risk factor in the development of acne through influences on follicular epithelial growth, keratinization, and androgen – mediated sebum secretion (L. CORDAIN & al. [31]). In fact, some authors showed that sebum production is also stimulated by insulin (C.C. ZOUBOULIS & al. [32]) and IGF-1 (D. DEPLEWSKI & al. [33]).

The importance of androgens, insulin and IGF 1 in acne is confirm by the fact that higher serum androgen (D. THIBOUTOT & al. [34]), insulin (H. AIZAWA & al. [35]) and IGF-1 (H. AIZAWA & al. [36]) concentrations is associated with the presence of acne in women.

Regarding the link acne – diet, is important to say that acne is not related to obesity, but with Westernization of the diet (S. BOURNE & al. [37], R. WOLF & al. [38]). The glycemic index (GI), is a relative comparison of the potential of various foods or combination of foods to raise blood glucose, based on equal amounts of carbohydrate in the food (D.J. JENKINS & al. [39]). Glycemic load (GL) (glycemic index x the carbohydrate content per serving size) was introduced to assess the potential of a food to raise blood glucose, based on both the quality and quantity of dietary carbohydrate (S. LIU & al. [40]).

Evidence from studies showed that high glycemic load diets (hyperglycaemic carbohydrates) and increased consumption of dairy proteins (insulinotropic milk / dairy products) are the major dietary factors of Western diet promoting the development or exacerbation of acne, both promoting increased insulin/IGF-1 signaling (L. CORDAIN & al. [1], B.C. MELNIK [4], R.N. SMITH & al. [30], B.C. MELNIK [41]). Smith et al reported the association of acne with the ingestion of a high glycemic load diet, and the improvement occurring on a change to a higher protein, lower glycemic load diet. (R.N. SMITH & al. [30])

4. Milk and Acne

In 1949 Robinson (H.M. ROBINSON [42]) suggested an association between dairy intake and acne severity, based on 1925 subjects who kept strict food diaries. The first epidemiological evidence for an association between milk consumption and acne has been presented by the retrospective evaluation of women participating in the Nurses’ Health Study II (NHSII) (C.A. ADEBAMOWO & al. [43]).

Adebamowo et al (C.A. ADEBAMOWO & al. [43]) found that only skim milk showed a statistical correlation with acne and suggested that skim milk processing have some effects on factors involved in comedogenicity of the milk. Whey proteins are added to the formula of skim milk and possibly have an important effects in comedogenesis (C.A. ADEBAMOWO & al. [43, 44])

Milk have a low glycemic index but induces paradoxically an increase in IGF-1 levels, in specially skim milk intake, and bovine IGF 1 is identical with human IGF1 (B. MELNIK [45], J.W. BLUM & al. [46]) both having the ability to bind to the human IGF receptor.
Several studies have consistently shown that high milk consumption is associated with a 10%-20% increase in circulating IGF-I levels among adults and a 20%-30% increase among children (J. CADOGAN & al. [47] – R.P. HEANEY & al. [54]).

Most of the steroid hormones and growth factors produced by cows are identical to those produced by humans (V. GOFFIN & al. [55]) and dairy products contain at least 60 factors with possible influence on acne (I. KUROKAWA & al. [56]). Milk produced persistently by pregnant cows contains substantial amounts of steroids and androgen-precursors (F.W. DANBY [57, 58]).

Milk contains estrogens, progesterone, androgens, androgen precursors (including dehydroepiandrosterone-sulfate and androstenedione), 5-α-reduced steroids (including dihydrotestosterone, 5-α-pregnanedione and 5-α-androstane-19-ol) and bioactive molecules (such as glucocorticoids and IGF-1) (S. HARTMANN & al. [59] – A. DONNET-HUGHES & al. [61]). All of this components may have important effects on pilosebaceous units, and influence the development of acne by effects on comedogenesis.

5 α-pregnanedione and 5α-androstane-19-ol are precursors of dihydrotestosterone (DHT), the main acne stimulator, and the pilosebaceous unit present all the enzyme necessary to transform 5 α-pregnanedione and 5α-androstane-19-ol in DHT. (W. CHEN & al. [62]).

Dihydrotestosterone (DHT) is the 5α-reduced product of the testosterone (T) but there are also exogenous sources like milk and meat. (J.A. DARLING & al. [60], E. CHO & al. [63]). 5α-reductase, an enzyme present in the pilosebaceous unit mediates reduction of T in DHT but DHT may also reach the androgen receptor without the influence of 5α-reductase when the precursor molecules are already 5α-reduced. Milk contains at least 2 such molecules, 5α-androstane-19-ol and 5α-pregnanedione, (J.A. DARLING & al. [60]) and these are prime candidates as the long-term stimulants to pilosebaceous activity.

Milk is rich in iodine, which can conduct to acne. Iodine form milk results from supplementation of the animal’s diet and the use of iodine-based solutions in milking equipment (J.A.T. PENNINGTON [64]).

Skim and whole milk have a three – to six-fold higher GL and insulinotrophic response than predicted, based on the carbohydrate content of the milk. (G. HOYT & al. [65]). This reaction raise a hypotheses: “total milk consumption or total milk protein may have a greater influence on acne, compared with other carbohydrate foods.” (E.M. OSTMAN & al. [66]). So, dairy products raise IGF-I levels more than do meat and other sources of dietary protein (E. GIOVANNUCCI & al. [49]-I.S. ROGERS & al. [53]).

Milk is a strong promoter of mTORC1-mediated anabolic endocrine signalling (B. MELNIK [67]) by insulinotropic BCAAs (leucine, isoleucine and valine) and persistently elevated plasma levels of IGF-1.

Metabolic and endocrine factors involved in acne development can be affected by milk for at least two reasons, one is that milk has a high insulinenic index (G. HOYT & al. [65]) and the other one is the increased level of serum insulin and IGF-1 (C. HOPPE & al. [52], J.W. RICH-EDWARDS & al. [68], T. NORAT & al. [69], F.L. CROWE & al. [70]).
In conclusion, the most important mechanism of milk signalling for acne development is the postprandial fast up regulation of insulin secretion and the long-lasting increase in serum IGF-1 levels (B.C. MELNIK [4], B.C. MELNIK & al. [71]).

For the future, generation of less insulinotropic milk and milk products (insulinemic index <45) will have an enormous impact on the prevention of epidemic Western diseases like obesity, diabetes mellitus, cancer, neurodegenerative diseases and acne (B.C. MELNIK [72]).

5. Insulin Growth Factor 1 (IGF 1) and Acne

IGF-1 is structurally related to insulin and has specific metabolic effects mediated by IGF-1 receptors. It is present on almost every cell in the human body. In the skin, IGF-1 receptors are expressed by epithelial cells and sebocytes (E. HODAK & al. [73]), and by the follicular outer root sheath, sweat glands and the hair matrix. (R.L. ROSENFIELD & al. [74])

IGF 1 levels is influenced by hormones, nutrition, age, sex and genetic variability (R.J. CLEVELAND & al. [75], C.J. ROSEN [76]) and the majority of the circulating IGF 1 levels come from the liver, with more than 90% of circulating IGFs are bound to IGF-binding protein-3 (IGFBP-3) (B.C. MELNIK & al. [77]).

Increased Insulin / IGF-1 signaling (IIS) has been implicated to play an important role in most types of epithelial neoplasia (P.E. CLAYTON & al. [78], M. POLLAK [79]), including prostate, breast and colorectal cancers (G. FURSTENBERGER & al. [80], D.B. BOYD [81]).

Milk consumption is positively associated with higher plasma IGF-I levels (F.L. CROWE & al. [70], E. GIOVANNUCCI & al. [49], M.D. HOLMES & al. [50]), S. FRANKS [82]). Cow’s milk contains active IGF-1 and IGF-2 (another member of IGF family, with some differences in structure) (J.W. BLUM & al. [46]), with a special mention that bovine IGF-1 is identical to human IGF-1 (sharing the same amino acid sequences (A. HONEGGER & al. [83])), and both are able to bind to the human IGF receptor. (B. MELNIK [45], J.W. BLUM & al. [46]).

The connection milk – acne is supported by epidemiological and biochemical evidence, that revealed the effects of milk and dairy products as enhancers of insulin / IGF-1 signalling and acne aggravation (C.A. ADEBAMOWO & al. [43, 44], J.W. RICH-EDWARDS & al. [68], T. NORAT & al. [69], F.L. CROWE & al. [70], C.A. ADEBAMOWO & al. [84]).

Some studies have suggested that elevated levels of IGF-1 may play a role in the development of acne (Z. LARON & al. [85], R.G. ROSENFIELD & al. [86], M. POLAT & al. [87] – I. RIETVELD & al. [90]).

In 2109 number of European women, serum IGF-1 levels were positively related with the intake of milk (T. NORAT & al. [69]). Patients with acne had significantly higher IGF-1 and lower IGFBP-3 blood concentrations than the unaffected control subjects (Y. KAYMAK & al. [91]). In addition, increased serum levels of IGF-1 have been observed in adult women and men with acne (H. AIZAWA & al. [35], M. CAPPEL & al. [92]).
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Women with post-adolescent acne present high concentrations of IGF-I (B. KIENS & al. [93]) and are mildly insulin resistant (D.S. LUDWIG [94]). IGF-I has been shown to correlate with acne lesion counts in adult women (D. DEPLEWSKI & al. [33], H. AIZAWA & al. [35], M. CAPPEL & al. [92]) and raised the idea that increased insulin/IGF-1 signaling plays a most important role in acne pathogenesis (C. HOPPE & al. [95]).

IGF-1 stimulates the activity of 5α-reductase, which converts testosterone to the more potent dihydrotestosterone (DHT) (R. HORTON & al. [96]), and the effect of the DHT is likely synergized by (IGF-1) (L. CORDAIN [3], R.N. SMITH & al. [30]).

IGF-1 stimulates synthesis of androgens in both ovarian (J.F. CARA [97]) and testicular (J.S. DE MELLOW & al. [98]) tissues and inhibits hepatic synthesis of sex hormone-binding globulin (J.C. CRAVE & al. [99]) resulting in increased bioavailability of androgens (L. CORDAIN [3]).

Free IGF-1 and IGFBP-3 (both influenced by insulin) may promote acne by inducing hyperkeratosis (S.M. RUDMAN & al. [100]) and epidermal hyperplasia by regulating keratinocyte proliferation, apoptosis, and hyperkeratosis (in addition to hypersecretion of sebum) an initial step in the formation of a follicular obstruction (D.K. BOL & al. [101], S.R. EDMONDSO & al. [102]).

Normal sebaceous gland growth is also influenced by factors other than androgens, such as IGF-I (D. DEPLEWSKI & al. [33]), and insulin and IGF-1 have been demonstrated to stimulate hair follicle and sebocyte growth (R. ROSENFIELD [103, 104]). IGF-1, is the most important stimulus for mTORC1-driven sebaceous gland growth and lipogenesis (T.M. SMITH & al. [88, 105]), by increasing lipid production in sebocytes in vitro via the activation of IGF-1 receptor through multiple pathways (T.M. SMITH & al. [88]).

Sebum production is stimulated both by androgens (L.F. EICHENFIELD & al. [24], D. DEPLEWSKI & al. [25]) and insulin (C.C. ZOUBOULIS & al. [32]) and IGF-1 (D. DEPLEWSKI & al. [33]). IGF-1 via mTORC1 activation up-regulates the activity of sterol response element binding protein-1 (SREBP-1), the key transcription factor of lipogenesis (T. PORSTMANN & al. [106], T.R. PETERSON & al. [107], I. BAKAN & al. [108]), and it is likely that IGF-1 may mediate some of the effects of comedogenic factors, such as androgens, growth hormone, and glucocorticoids (D. DEPLEWSKI & al. [25]).

6. mTORC1 and General Health

mTORC1, the nutrient-sensitive kinase mammalian target of rapamycin complex 1, integrates nutrient signals, such as glucose (ATP/energy status of the cell), essential amino acids and growth factor signals (insulin, IGF-1, fibroblast growth factors (FGFs)) (K. INOKI & al. [109])

mTORC1 signaling stimulates gene transcription, translation, ribosome biogenesis, protein synthesis, cell growth, cell proliferation and lipid synthesis but suppresses the mechanisms of autophagy. (K. INOKI & al. [109] – X. WANG & al. [114]).

Increased mTORC1 signalling has been associated with obesity, type 2 diabetes and cancer (R.J. SHAW & al. [115], R. ZONCU & al. [116]) and the mTORC1 signaling pathway has become a major focus of human cancer research (P.T. BHASKAR & al. [110]).
Cordain et al. (L. CORDAIN & al. [1]) have suggested that acne belongs to the family of diseases of Western civilisation like obesity, type 2 diabetes mellitus and cancer and is a visible indicator of systemically exaggerated mTORC1 signalling (B.C. MELNIK [41, 67]).

Transcription factor SREBP (sterol regulatory element-binding factor) is one of the most important factor involved in lipogenesis and mTORC 1 is strongly involved in lipid biosynthesis (T. PORSTMANN & al. [106]) because stimulate the activity of SREBP-1. (K. DUVEL & al. [117], S. LI & al. [118]).

mTORC1 is strongly involved in a lot of “disease civilization” like overweight (increased BMI), obesity, arterial hypertension, insulin resistance, type 2 diabetes mellitus, cancer, and Alzheimer’s disease (C.G. PROUD [119]-S. ODDO [124]).

7. Perspectives

We are now 2000 years after Hippocrates wrote “Let food be your medicine, and let medicine be your food”, and we must do something!

The attenuation of whey protein-based insulinotropic mechanisms will be the most important future challenge for an interdisciplinary cooperation between medicine, nutrition research and milk processing biotechnology.

Acne, the mirror of exaggerated insulinotropic Western nutrition, is a most useful clinical and epidemiological indicator of appropriate or inappropriate human nutrition.

Dietary intervention in acne should thus (L. CORDAIN & al. [1]) decrease total energy, glucose and fat intake, (E.H. SPENCER & al. [2]) diminish insulin/IGF-1 signaling predominantly mediated by high dairy protein consumption, and (L. CORDAIN [3]) should limit the total leucine uptake predominantly provided by increased animal protein intake including meat and dairy proteins.

Epidemic acne is thus not a bagatelle but a constellation of exaggerated mTORC1 signalling, a metabolic deviation enhancing the risk for serious diseases of civilisation.

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