SUMMARY: This document summarizes all claims made by Kyoku for Men™, which is a registered trademark of Kyoku Inc. (DBA: Kyoku Holdings LLC) located at 584 Broadway – Suite 506, New York, NY 10012, USA whose products are manufactured by RNA Corporation, an FDA approved & GMP (Good Manufacturing Practice) certified manufacturing facility located at 13570 Chatham Street, Blue Island, IL 60406, USA.

ABOUT KYOKU FOR MEN™

Kyoku for Men™ is the brand name under which Kyoku Inc. sells OTC acne & cosmetic products designed specifically for men’s skin. These products are designed to help men cosmetically improve the appearance of their skin as well as help get rid of acne blemishes, blackheads, whiteheads, and protect against UV damage from the sun.

FDA COMPLIANCE

In particular, 2 products of Kyoku for Men™ are regulated FDA OTC (Over The Counter) drugs approved for Human Use:

- SKN-WS 333: Daily Facial Cleanser
  - Contains 0.5% Salicylic Acid (Acne Medication)
- SKN-FC 901: Facial Moisturizer (SPF 15)
  - Contains Ethylhexyl Methoxycinnamate 7.5%, (Sunscreen), Octocrylene 5.0% (Sunscreen), and Butyl Methoxydibenzoylmethane 2.5% (Sunscreen)

Both products labeling follows the FDA Final Monograph for Topical Anti-Microbial Drug Products for Over-the-Counter Human Use 21 CFR part 333 subpart D & the FDA Final Monograph for Sunscreen Drug Products for Over-the-Counter Human Use 21 CFR part 352. The product labels are attached in Appendix 1 & Appendix 2 for reference & the appropriate monograph sections are attached in Appendix 3 & Appendix 4.

ABOUT DR. ASIM M. AKHTAR

Dr. Asim Munir Akhtar is a medical sciences researcher, not a licensed medical professional, and holds a PhD (also known as a Doctor of Philosophy or “DPhil”) from the University of Oxford located in Oxford, United Kingdom. Dr. Akhtar began his PhD studies immediately following graduation from the University of Illinois (Urbana, Champaign) in July of 2007. He completed his PhD studies at the University of Oxford by submitting his thesis, entitled “Molecular Magnetic Resonance Imaging of Vascular Inflammation using Microparticles of Iron Oxide” in 2010, which was met with critical acclaim from the University of Oxford for it’s insights into vascular inflammation in disease states such as Ischemia Reperfusion Injury, Atherosclerosis, and Multiple Sclerosis. Dr. Akhtar was awarded his doctorate by the Medical
Dr. Akhtar’s qualifications & thesis are available for public viewing via the following hyperlink: http://ora.ox.ac.uk/objects/uuid:12bf8e4f-2909-4715-a6fe-bf42d9d8355a and his CV is attached in Appendix 5.

In addition to being awarded the distinguished degree of “Doctor of Philosophy” by the Medical Sciences Division at the University of Oxford, Dr. Akhtar has published several peer-reviewed research articles within the field of vascular inflammation, as follows:


It should be duly understood that while Dr. Akhtar does possess an expertise in the field of vascular inflammation & disease states, he is not a licensed medical professional nor does he claim to be and his advice should not be taken as a substitute for professional advice or recommendations from a licensed doctor or dermatologist.

**IMPORTANT LEGAL DISCLAIMER FOR TESTIMONIALS, RISK, AND TYPICAL RESULTS FOR CUSTOMERS**

As with any treatment program, you assume certain risks to your health and safety by using Kyoku for Men™ products. Any form of acne treatment carries risks if used incorrectly, and Kyoku for Men™ is no exception. It is possible that you may make
your acne worse if instructions are not followed correctly or you overuse products in an attempt to make them work quicker or more effectively. Although thorough instruction is included with each product, realize that Kyoku for Men™ does involve some risk of a negative reaction to your skin. Kyoku for Men™ offers a 100% money-back guarantee — you can return the products for any reason if you are not satisfied with the results. However, we cannot guarantee your specific results in getting clear skin. It is possible that you will not see any results with these products – everybody’s skin and body is in fact different. Unique genetic and/or hereditary factors may play a role in your treatment. It is also possible that your acne may get worse. The stories and testimonials of the clients you see on this page are real and were taken from e-mails we receive to our customer service e-mail address. However, it must be disclaimed that these testimonials are not claimed to represent typical results with the products. They are meant as a showcase of what the most motivated and dedicated clients can do with these products. Your results may vary, and you may not get the same results when using the products due to differences in your individual history, genetics, and personal motivation. Dr. Asim Akhtar is not a medical doctor or dermatologist; however, he does hold a PhD from the University of Oxford in Clinical Medicine & Research, specifically in the field of vascular inflammation. His advice is not meant as a substitute for medical advice. Please consult your doctor before beginning use of this product if necessary and do consult a dermatologist if you have any negative reactions or your acne becomes worse. Results will vary, and you should not use this information as a substitute for help from a licensed professional.

HOW IS KYOKU FOR MEN™ SCIENTIFICALLY DESIGNED TO HELP ELIMINATE ACNE IN MEN’S SKIN?

Acne Vulgaris is a disorder of the pilosebaceous unit. The pathogenic factors of acne are, as follows: increased sebum secretion, follicular epidermal hypercornification, Propionibacterium acnes colonization and inflammation, which leads to a lowered oxygen environment where P. Acnes bacteria can colonize in the skin, leading to acne lesions. This is the clinically accepted pathogenesis of acne vulgaris.¹

In a double blind, peer reviewed clinical trial involving 914 acne patients (278 male and 636 female), male acne patients were found to have more inflammatory acne lesions as well as more acne lesions on their entire face than women. The proportion of inflammatory lesions over the total number of acne lesions was higher in male patients than in female patients. Similarly, sebum levels on the forehead were higher in male patients. In male acne patients, the sebum of the T-zone showed positive correlation with both the number of inflammatory lesions and the proportion of inflammatory lesions over the total number of acne lesions. All findings were statistically significant. With regard to sexual differences, male acne patients had more inflammatory lesions. Male acne patients also showed higher proportions of the inflammatory lesions.²

These results are in agreement with several other studies on the topic that have concluded that male patients experience more severe, longer lasting acne than their female counterparts due to inherent increased androgen / testosterone production and increased sebum (oil) levels on the skin. Therefore, one may surmise that inflammation and excessive oil production on the skin is higher in male patients, resulting in significantly greater acne lesions as well as acne severity.1-3

In another double-blind, peer reviewed clinical trial involving 242 acne patients and 188 control patients, researchers discovered that higher testosterone in men is a significant risk factor in the occurrence of adolescent acne. A higher 17-

3-OHP level aggravates the severity of male adolescent acne, while a higher estradiol level protects females against the onset of adolescent acne. All findings were statistically significant.4

Therefore, Kyoku for Men™ has used this research to create products for men’s unique skincare needs & acne profile. From data, we can see that reducing inflammation & oily skin is key to the reducing of acne in men. As its main acne fighting ingredient, Kyoku for Men’s™ product SKN-WS 333: Daily Facial Cleanser contains 0.5% Salicylic Acid, which is an FDA-approved OTC drug approved for human use to treat acne. Salicylic acid is the primary ingredient in aspirin; therefore, it is highly effective at reducing inflammation and treating acne by penetrating the follicle. It encourages the shedding of dead skin cells from within the follicle, helping keep the pores clear of cellular debris. This is how Kyoku for Men™ ‘penetrates men’s skin to help treat acne at its source,’ which the aforementioned research has shown is inflammation within the sebaceous glands. In this way, it reduces the number of pore blockages and breakouts on the skin. Therefore, Kyoku for Men™ sells this product primarily for men to reduce inflammation and treat their acne and includes it in every single acne treatment kit that it makes.

Our acne treatment kits also contain other, complimentary products that aid in the effectiveness of the main OTC acne treatment product, which is the Daily Facial Cleanser. The reason we have designed it this way is due to low acne patient adherence from irritation common in OTC acne treatments. Dryness or skin irritation may cause barrier disruption of the stratum corneum leading to increased transepidermal water loss (TEWL) and production of inflammation. Physicians recommend patients use moisturizers as adjunctive treatment of acne, especially when topical benzoyl peroxide, a topical retinoid, or salicylic acid is used.5 Moisturizers contain three main properties, which are occlusive, humectant, and emollient effects (Janamontri et al.). In Kyoku for Men’s™ SKN-FC 901: Facial Moisturizer (SPF 15), we have included ‘Soline,’ (INCI: Sunflower Oil Unsaponifiables) which is a cosmetic ingredient containing 90% unsaturated fatty acids (including 20% oleic acid and 60% linoleic aci) and 1% natural Vitamin E that aids in the reduction of TEWL

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and ‘soothes’ the skin. Our Facial Moisturizer SPF 15 is an OTC drug in it’s own right as a sunscreen. We had done this to protect the skin against mild sunburn, which often leads to inflammation and helps neutralize it. Similarly, our Facial Moisturizer contains Green Tea Leaf & Aloe Vera, which are herbal (non-medicated) oil-soluble anti-inflammatories. Furthermore, our Facial Moisturizer contains Advanced Delivery Technology, which we have called our ‘Microparticle Technology’ we acquired from Barnet Products Corporation called ‘Lecinol S-10.’ Lecinol S-10 is a hydrogenated phospholipid that can be used to create encapsulation or Liposomes of water-soluble or oil-soluble actives. This aids in the penetration of oil-soluble anti-inflammatories into the skin. Since men’s skin is thicker than women’s skin, we used this technology to help the anti-inflammatories absorb into the skin. The data for this ingredient is included in Appendix 6. This product is not meant to be an OTC Acne Treatment; however, it is sold in combination with our Daily Facial Cleanser as a cosmetic product to help skin recover from the drying effects of Salicylic Acid. We do not wish nor have we intended for this product to be any sort of NDA (New Drug Application) and all claims for this particular product are cosmetic and it is meant to be used alongside our Daily Facial Cleanser as combination therapy and help protect the skin against UV damage, which can in some cases lead to inflammation that is associated with acne.

Lastly, our kits also contain another cosmetic product SKN-MSQ 273: Lava Masque. This is a purely cosmetic product that contains several natural ingredients to help purify pores and detoxify skin through the use of a mineral-rich mud mask. This product is mean to be used as combination therapy alongside the Daily Facial Cleanser to help the appearance of the skin without further irritating it or causing additional inflammation, which can lead to even more acne. This product contains Phyko-AC, a complex of oligosachcharide (OGS) or marine origin and zinc (INCI name: Water & Hydrolized Algin & Zinc sulfate). Phyko-AC has been shown in studies sponsored by Barnet Corporation to reduce skin sebum levels (Data in Appendix 7). Also, this masque contains Atoligomer, a balanced cocktail of micro and macro minerals, which increases strength of the epidermis as per ex-vivo tests sponsored by Barnet Corporation (Data in Appendix 8). Finally, this product contains Volcanic Black Sand, which is a natural exfoliants that allows the removal of dead skin cells, oil, and ‘toxins’ to help improve overall appearance of the skin. This product is not meant to be an OTC Acne Treatment; however, it is sold in combination with our Daily Facial Cleanser as a cosmetic product to help skin recover from the drying effects of Salicylic Acid. We do not wish nor have we intended for this product to be any sort of NDA (New Drug Application) and all claims for this particular product are cosmetic. It is meant to be used alongside our Daily Facial Cleanser as combination therapy to help cosmetically improve the appearance of the skin.

I certify that all the statements made above are true to the best of my knowledge,

Dr. Asim M. Akhtar, PhD
Founder & CEO – Kyoku, Inc.
Directions

- Cover the entire affected area with a thin layer and rinse thoroughly twice daily.
- Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or directed by a doctor. Avoid application to once a day or
- If bothersome dryness or peeling occurs, every other day.

Drug Facts:

Active Ingredient: Salicylic Acid 0.5% w/w

Purpose: Acne treatment

Inactive Ingredients:


Warnings:

For external use only. When using this product skin irritation and dryness is more likely to occur if you use another topical acne medication at the same time. If irritation occurs, only use one topical acne medication at a time. Avoid contact with the eyes. If contact occurs, flush thoroughly with water. Stop use and ask a doctor if skin irritation or severe redness occurs.

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Other Information:

Store at room temperature.

Dermatologically Tested.

distributed by: Kyoku for Men
584 Broadway, New York NY, 10012 U.S.A.
www.kyokuformen.com

Salicylic Acid 0.5% Acne Medication.

100ml / 3.4 fl. oz.

SKN-WS 333: daily facial cleanser
[ginseng, camellia leaf, peppermint leaf, calendula, sunflower oil, and oat straw extract work together in penetrating pores to help treat acne breakouts, blemishes, oily skin, and clear blackheads & whiteheads, allowing skin to heal]

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Signature ___________________________ Date ________________

Warning: For external use only. When using this product avoid contact with the eyes. If contact occurs, flush thoroughly with water. Stop use and ask a doctor if rash or irritation develops and lasts. Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions: Use twice daily. 30 minutes before sun exposure. Reapply at least every two hours. Use Broad Spectrum SPF value of 15 or higher and other sun protection measures, especially from 10 a.m. - 2 p.m. when long-sleeved shirts, pants, and sunglasses. Children under 6 months of age, ask a doctor.

Other Information: Protect the product in this container from excessive heat and direct sun.

SKN-FC 901: facial moisturizer (SPF 15)
[bamboo, green tea leaf, aloe vera, plankton and vitamin E combine with Microparticle Technology to help stop men’s skin problems where they start while also providing sun protection]
subpart and each general condition established in § 330.1 of this chapter. (b) References in this subpart to regulatory sections of the Code of Federal Regulations are to chapter I of title 21 unless otherwise noted.

§ 333.303 Definitions.
As used in this subpart:
(a) Acne. A disease involving the oil glands and hair follicles of the skin which is manifested by blackheads, whiteheads, acne pimples, and acne blemishes.
(b) Acne blemish. A flaw in the skin resulting from acne.
(c) Acne drug product. A drug product used to reduce the number of acne blemishes, acne pimples, blackheads, and whiteheads.
(d) Acne pimple. A small, prominent, inflamed elevation of the skin resulting from acne.
(e) Blackhead. A condition of the skin that occurs in acne and is characterized by a black tip.
(f) Whitehead. A condition of the skin that occurs in acne and is characterized by a small, firm, whitish elevation of the skin.

§ 333.310 Acne active ingredients.
The active ingredient of the product consists of any of the following when labeled according to § 333.350.
(a) Resorcinol 2 percent when combined in accordance with § 333.320(a).
(b) Resorcinol monoacetate 3 percent when combined in accordance with § 333.320(b).
(c) Salicylic acid 0.5 to 2 percent.
(d) Sulfur 3 to 16 percent.
(e) Sulfur 3 to 8 percent when combined in accordance with § 333.320.

§ 333.320 Permitted combinations of active ingredients.
(a) Resorcinol identified in § 333.310(a) when combined with sulfur identified in § 333.310(c) the product is labeled according to § 333.350.
(b) Resorcinol monoacetate identified in § 333.310(b) when combined with sulfur identified in § 333.310(e) the product is labeled according to § 333.350.

§ 333.350 Labeling of acne drug products.
(a) Statement of identity. The labeling of the product contains the established name of the drug, if any, and identifies the product as an “acne medication,” “acne treatment,” “acne medication” (insert dosage form, e.g., "cream," "gel," "lotion," or "ointment"), or “acne treatment” (insert dosage form, e.g., "cream," "gel," "lotion," or "ointment").
(b) Indications. The labeling of the product states, under the headings "indications," the phrase listed in paragraph (b)(1) of this section and may contain any of the additional phrases listed in paragraph (b)(2) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in paragraph (b) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.
(1) "For the" (select one of the following: “management” or “treatment”) of acne.
(2) In addition to the information identified in paragraph (b)(1) of this section, the labeling of the product may contain any one or more of the following statements:
   (i) "Select one of the following: "Clears," "Clears up," "Clears up most," "Dries," "Dries up," "Dries and clears," "Helps clear," "Helps clear up," "Reduces the number of," or "Reduces the severity of") [select one or more of the following: “acne blemishes,” “acne pimples,” “blackheads,” or “whiteheads”] which may be followed by “and allows skin to heal.”
   (ii) "Penetrates pores to" [select one of the following: “eliminate most,” “control,” “clear most,” or “reduce the number of"] [select one or more of the following: “acne blemishes,” “acne pimples,” “blackheads,” or “whiteheads”].
   (iii) "Helps keep skin clear of new" [select one or more of the following: “acne blemishes,” “acne pimples,” “blackheads,” or “whiteheads”].
   (iv) "Helps prevent new" [select one or more of the following: “acne blemishes,” “acne pimples,” “blackheads,” or “whiteheads”] which may be followed by “from forming.”
   (v) "Helps prevent the development of new" [select one or more of the following: “acne blemishes,” “acne pimples,” “blackheads,” or “whiteheads”].
(c) Warnings. The labeling of the product contains the following warnings under the heading “Warnings”:

1. For products containing any ingredient identified in § 333.310. (f) “For external use only.”
   (ii) "Using other topical acne medications at the same time or immediately following use of this product may increase dryness or irritation of the skin. If this occurs, only one medication should be used unless directed by a doctor.”
   (2) For products containing sulfur identified in §§ 333.310(d) and (e). "Do not get into eyes. If excessive skin irritation develops or increases, discontinue use and consult a doctor.”
   (3) For products containing any combination identified in § 333.320. "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body.”
(d) Directions. The labeling of the product contains the following information under the heading “Directions”:
   (1) “Cleanse the skin thoroughly before applying medication. Cover the entire affected area with a thin layer one to three times daily. Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor. If bothersome dryness or peeling occurs, reduce application to once a day or every other day.”
   (2) The directions described in paragraph (d)(1) of this section are intended for products that are applied and left on the skin. Other products, such as soaps or masks, may be applied and removed and should have appropriate directions.
   (3) Optional directions. In addition to the required directions in paragraphs (d)(1) and (d)(2) of this section, the product may contain the following optional labeling: “Sensitivity Test for a New User. Apply product sparingly to one or two small affected areas during the first 3 days. If no discomfort occurs, follow the directions stated: (select one of the following: elsewhere on this label; ‘above,’ or ‘below.’)"
   (e) The word “physician” may be substituted for the word “doctor” in any of the labeling statements in this section.

David A. Kessler,
Commissioner of Food and Drugs.
[FR Doc. 91-19304 Filed 8-15-91; 8:45 am]
BILLING CODE 4160-01-M
TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE
PART 352 -- SUNSCREEN DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE
[STAYED INDEFINITELY]
Subpart B--Active Ingredients

Sec. 352.10 Sunscreen active ingredients.

The active ingredient of the product consists of any of the following, within the concentration specified for each ingredient, and the finished product provides a minimum SPF value of not less than 2 as measured by the testing procedures established in subpart D of this part:

(a) Aminobenzoic acid (PABA) up to 15 percent.
(b) Avobenzone up to 3 percent.
(c) Cinoxate up to 3 percent.
(d) [Reserved]
(e) Dioxybenzone up to 3 percent.
(f) Homosalate up to 15 percent.
(g) [Reserved]
(h) Menthyl anthranilate up to 5 percent.
(i) Octocrylene up to 10 percent.
(j) Octyl methoxycinnamate up to 7.5 percent.
(k) Octyl salicylate up to 5 percent.
(l) Oxybenzone up to 6 percent.
(m) Padimate O up to 8 percent.
(n) Phenylbenzimidazole sulfonic acid up to 4 percent.
(o) Sulisobenzone up to 10 percent.
(p) Titanium dioxide up to 25 percent.
(q) Trolamine salicylate up to 12 percent.
(r) Zinc oxide up to 25 percent.

[64 FR 27687, May 21, 1999] Effective Date Note:
At 67 FR 41823, June 20, 2002, § 352.10 was amended by revising paragraphs (f) through (n), effective Sept. 1, 2002. This amendment could not be incorporated because at 66 FR 67485, Dec. 31, 2001 the
effective date was stayed until further notice. For the convenience of the user, the revised text is set forth as follows:

(f) Ensolizole up to 4 percent.
(g) Homosalate up to 15 percent.
(h) [Reserved]
(i) Meradimate up to 5 percent.
(j) Octinoxate up to 7.5 percent.
(k) Octisalate up to 5 percent.
(l) Octocrylene up to 10 percent.
m) Oxybenzone up to 6 percent.
n) Padimate O up to 8 percent.

Links on this page:

4. http://www.fda.gov/MedicalDevices/default.htm
6. /scripts/cdrh/cfdocs/search/default.cfm?FAQ=true

Page Last Updated: 09/01/2014
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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U.S. Department of Health & Human Services

Links on this page:

4. http://www.fda.gov/MedicalDevices/default.htm
Asim Akhtar
Founder & CEO - Kyoku Holdings LLC
akhtar.asim@gmail.com

Summary
Currently, I'm the CEO & President of Kyoku for Men. I have a history in medical research, personal care product manufacturing, applied laboratory science, and direct marketing. I'm a passionate entrepreneur with a thirst for knowledge, thinking outside the box, meeting great people, building teams, innovating in the marketplace, never ending growth, and working with the people in our company so we all achieve our individual and collective goals.

Experience

**Founder & CEO at Kyoku Holdings LLC**

*August 2010 - Present (4 years 5 months)*

Started in 2010 by Dr. Asim Akhtar, Kyoku for Men is a men’s grooming & acne treatment brand that encompasses a variety of skincare products that help young men eliminate acne, breakouts, and oily skin that seem to come up especially during a specific time in a young man’s life. There are no other brands in the market today that address men’s acne in quite the way Kyoku for Men does – we literally invented the ‘male acne’ category. Here at Kyoku, we take skincare, acne, and our customer’s results very seriously – in fact, it’s all that we do. We want to make sure very single one of our clients goes on to become the best man he can be, from the inside out. Kyoku for Men has been featured in over 300+ pieces of press including GQ, Esquire, Men’s Health and has won several industry awards including ‘Best Face Wash’ by Men’s Health in 2012 and ‘Best in Shaving’ by GQ in 2011, to name a few. Kyoku products sell in 18 different countries in over 500 retail locations, including Barney’s, Macy’s, Boots UK, Shoppers Drug Mart Canada, and Douglas Pharmacies in Europe, to name a few. It’s been quite the journey and we hope to help even more men eliminate their acne and become the men they have always wanted to be in the future.

**Partner at RNA Corporation**

*January 2003 - Present (12 years)*

RNA Corporation, based out of Blue Island, IL is involved in the business of private label manufacturing of consumer goods, namely haircare and skincare.

*I recommendation available upon request*

Publications

**In Vivo Quantification of Vcam-1 Expression in Renal Ischemia Reperfusion Injury Using Non-Invasive Magnetic Resonance Molecular Imaging**

PLOS One  September 21, 2010
An approach to molecular imaging of atherosclerosis, thrombosis, and vascular inflammation using microparticles of iron oxide.

Atherosclerosis  March 2010

Authors: Asim Akhtar

The rapidly evolving field of molecular imaging promises important advances in the diagnosis, characterization and pharmacological treatment of vascular disease. Magnetic resonance imaging (MRI) provides a modality that is well suited to vascular imaging as it can provide anatomical, structural and functional data on the arterial wall. Its capabilities are further enhanced by the use of a range of increasingly sophisticated contrast agents that target specific molecules, cells and biological processes. This article will discuss one such approach, using microparticles of iron oxide (MPIO). MPIO have been shown to create highly conspicuous contrast effects on T2*-weighted MR images. We have developed a range of novel ligand-conjugated MPIO for molecular MRI of endothelial adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and P-selectin expressed in vascular inflammation, as well as activated platelet thrombosis. This review discusses the application of ligand-targeted MPIO for in vivo molecular MRI in a diverse range of vascular disease models including acute vascular inflammation, atherosclerosis, thrombosis, ischemia-reperfusion injury and ischemic stroke. The exceptionally conspicuous contrast effects of ligand-conjugated MPIO provide a versatile and sensitive tool for quantitative vascular molecular imaging that could refine diagnosis and measure response to treatment. The potential for clinical translation of this new class of molecular contrast agent for clinical imaging of vascular syndromes is discussed.

CCR2-mediated antiinflammatory effects of endothelial tetrahydrobiopterin inhibit vascular injury-induced accelerated atherosclerosis.

Circulation  September 30, 2008

Authors: Asim Akhtar

Vascular injury results in loss of endothelial nitric oxide (NO), production of reactive oxygen species (ROS), and the initiation of an inflammatory response. Both NO and ROS modulate inflammation through redox-sensitive pathways. Tetrahydrobiopterin (BH4) is an essential cofactor for endothelial nitric oxide synthase (eNOS) that regulates enzymatic synthesis of either nitric oxide or ROS. We hypothesized that endothelial BH4 is an important regulator of inflammation and vascular remodeling.

VCAM-1-targeted magnetic resonance imaging reveals subclinical disease in a mouse model of multiple sclerosis


Authors: Asim Akhtar

Diagnosis of multiple sclerosis (MS) currently requires lesion identification by gadolinium (Gd)-enhanced or T2-weighted magnetic resonance imaging (MRI). However, these methods only identify late-stage pathology associated with blood-brain barrier breakdown. There is a growing belief that more widespread, but currently
undetectable, pathology is present in the MS brain. We have previously demonstrated that an anti-VCAM-1 antibody conjugated to microparticles of iron oxide (VCAM-MPIO) enables in vivo detection of VCAM-1 by MRI. Here, in an experimental autoimmune encephalomyelitis (EAE) mouse model of MS, we have shown that presymptomatic lesions can be quantified using VCAM-MPIO when they are undetectable by Gd-enhancing MRI. Moreover, in symptomatic animals VCAM-MPIO binding was present in all regions showing Gd-DTPA enhancement and also in areas of no Gd-DTPA enhancement, which were confirmed histologically to be regions of leukocyte infiltration. VCAM-MPIO binding correlated significantly with increasing disability. Negligible MPIO-induced contrast was found in either EAE animals injected with an equivalent nontargeted contrast agent (IgG-MPIO) or in control animals injected with the VCAM-MPIO. These findings describe a highly sensitive molecular imaging tool that may enable detection of currently invisible pathology in MS, thus accelerating diagnosis, guiding treatment, and enabling quantitative disease assessment.—Serres, S., Mardiguian, S., Campbell, S. J., McAteer, M. A., Akhtar, A., Krapitchev, A., Choudhury, R. P., Anthony, D. C., Sibson, N. R. VCAM-1-targeted magnetic resonance imaging reveals subclinical disease in a mouse model of multiple sclerosis.

Skills & Expertise

Beauty
Retail
Luxury Goods
Marketing Strategy
Product Development
Marketing
Hair Care
Fragrance
Beauty Industry
Skin Care
Brand Management
Cosmetics
Management
FMCG
Consumer Products
Personal Care
Brand Development
Sales
Entrepreneurship
Business Strategy
Social Media Marketing
Strategic Planning

Education

University of Oxford
PhD, Cardiovascular Medicine, 2007 - 2010
University of Illinois at Urbana-Champaign
BsC, Medicine, Neurology & Psychology, 2003 - 2007
Title: Molecular magnetic resonance imaging of vascular inflammation using microparticles of iron oxide

Abstract:
One approach that has demonstrated success in the field of molecular imaging utilizes microparticles of iron oxide (MPIO) conjugated to specific antibodies and/or peptides to provide contrast effects on MRI in relation to the molecular expression of a specified target. The experimental aims of this thesis were 1) to investigate the ability of VCAM-1 and P-selectin targeted MPIO to detect the expression of VCAM-1 and P-selectin on the activated endothelium in vitro and in vivo in mouse models of renal and cerebral ischemia reperfusion injury, and 2) develop a novel contrast agent for imaging αvβ3-integrin expression in angiogenesis using

Digital Origin: Born digital
Type of Award: DPhil
Awardsing Institution: University of Oxford

Notes: This thesis is not currently available in ORA.

About The Authors
Asim M. Akhtar
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Faculty: Medical Sciences Division - Cardiovascular Medicine
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Advanced Delivery Technology
Lecinol S-10 and Net-LH

**Lecinol S-10**

**Product Intro**
A Hydrogenated Phospholipid that can be used to create encapsulations or Liposomes of water soluble actives. S-10 has also been tested to show an improved delivery of oil soluble actives.

**Formulation Guidelines**
- Lecinol S-10 must be added to the water phase in order to form an encapsulation
- Mix Water, Lecinol S-10 and Active into container
- Heat Phase up to 85°C and mix with Homogenizer
- Let cool to 75°C and Encapsulation will form
- NOTE THAT PRESERVATIVES ADDED TO THIS PHASE WILL NOT BE EFFECTIVE IN FINISHED FORMULA.

**Net-LH**

**Product Intro**
A proprietary mixture of a plant derived polymer, hydrogenated lecithin and surfactants. LH can encapsulate water soluble actives as well as isolating difficult materials making them easy to use.

**Formulation guidelines**
- Add LH to a Pre-phase (Water and LH, glycol can be added if applicable)
- Add water soluble active and water in a separate phase
- Disperse LH into water with homogenizer
- Once dispersed, add active phase with homogenizer (no heat required)
- Post add Pre-phase to batch with paddle mixer

Microscopic Pictures of Lecinol S-10 Generated
**Improved delivery of indomethacin with lecinol S-10 Liposome**

The pictures below demonstrate the difference between adding Lecinol S-10 to the water phase versus the oil phase. By adding S-10 into the water phase, we can see the encapsulation of copper PCA (Left), while in the oil phase we can see a blue color throughout the solution (right), signifying the copper PCA is not encapsulated.

**Lecinol S-10**

**Test Data**

Penetration of Lecinol S-10 into the skin

**Enhancement of Delivery of Oil-Soluble Anti-Inflammatory**

**Net-LH**

**Test Data**

Net-LH is a very helpful product when trying to incorporate materials that would typically be difficult to integrate into emulsions. By creating a pre-phase with Net-LH and the delinquent material, it can be post added with a paddle mixer. We have done several tests exemplifying the unique properties of Net-LH.

**Delinquent Product**

- **Calcium PCA**
  - Causes emulsions to loose viscosity and become unstable

- **Trehalose**
  - Has a tendency to change color of formula when it reacts with other actives
Amino Acid  Strong pungent odor
makes finished
formula unattractive

Benefit of creating a Pre-Phase with Net-LH:

<table>
<thead>
<tr>
<th>Delinquent Product</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium PCA</td>
<td>Does not affect overall viscosity or stability of formula</td>
</tr>
<tr>
<td>Trehalose</td>
<td>Does not react with other actives and does not change color of formula</td>
</tr>
<tr>
<td>Amino Acid</td>
<td>Covers odor so finished product is now acceptable</td>
</tr>
</tbody>
</table>
**Phyko-AC**

**DESCRIPTION**
Phyko-AC is a complex of an oligosaccharide (OGS) of marine origin and zinc. The oligosaccharide is obtained by controlled enzymatic depolymerization of membranous polysaccharides of laminaria digitata. It is formed by a chain of 2 uronic acids: mannuronic and guluronic.

The metal is chelated by adding zinc sulfate, and the OGS/metal ratio is optimized for maximum saturation.

**PROPERTIES**
Phyko-AC was tested in vitro and shown to reduce 5-Alpha Reductase activity. Phyko-AC also reduces P. acnes, S. areus and M. furfur (a fungi also known as P. ovale). Therefore, it is a candidate for acne treatment and dandruff reduction. Phyko-AC was tested in vivo at 3% for 1 month on 15 volunteers. Results show a very visible improvement in skin appearance.

**FORMULATION**
Phyko-AC is a yellow to honey colored cloudy liquid with a characteristic odor and a slight precipitate. The suggested use level is 1% - 3%. Please note that Phyko-AC forms a precipitate with ethanol (>10%). It is recommended that Phyko-AC be added to the formula at the end of the manufacturing process, at less than 35° C. Phyko-AC is water soluble.

**LEGISLATION**
INCI Name: Water & Hydrolyzed Algin & Zinc Sulfate

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Phyko-AC

IN VIVO TEST: REDUCTION OF CUTANEOUS ERUPTIONS

An in vivo test was performed on 15 subjects for one month. A gel containing 3% Phyko-AC was applied 3 times daily for 30 days. The pictures below demonstrate the improvement in the skin’s appearance.

PHYKO-AC IS A SEBUM REGULATOR

Twelve volunteers with inflammation on the forehead were treated twice daily for 28 days with a placebo (gel only) and a gel containing 5% Phyko-AC. Measurements were taken on Day 1 with a sebumeter in 2 symmetric areas. After the treatment period, sebum levels were measured again on the 2 areas. Results were expressed by a variation in sebum level (in μg/cm²) between Day 1 and Day 28. Results show a reduction in sebum levels for 67% of the volunteers, from -3 to -58 μg/cm². Observations were completed by subjective evaluation.
Atoligomer

**DESCRIPTION**

Atoligomer is a balanced cocktail of minerals in spray-dried (micromineral) form (size < 50μm). It is very rich in macro elements such as calcium, potassium, sodium and magnesium, and in trace elements such as iron, manganese, selenium and zinc. Macro elements and trace elements are the 2 parts of mineral elements which the body needs to grow and function satisfactorily. they are also beneficial to the skin.

Atoligomer makes it possible to restore the trace element equilibrium of the skin. Sea water contains 73 of the 92 elements in Mendeleiev’s classification system which are known to exist naturally in the body.

**FORMULATION**

The trace elements in sea water and in blood serum are very similar. Atoligomer increases fibroblast and keratinocyte vitality. Ex vivo tests show that Atoligomer strengthens the epidermis.

Atoligomer is a fine white powder. It can be used in foundations, pressed powders or masks. It can also be used in shampoos and bath products to replace sodium chloride in formulas. It can be used directly as a powder or re-solubilizer. Suggested use levels are as follows:

* In masks or wrappings, 5% -30%
* In emulsions, shampoos or bath products: 0.1% - 5%

Atoligomer works well with Barnet’s NET-WO and NET-LH, which are electrolytes / salt tolerant. Formulation assistance is available upon request.

**LEGISLATION**

INCI Name: Sea Salt
CAS #: 7647-14-5
ECOCERT Status: Complies with the ECOCERT Standard for natural ingredients.

Atoligomer has been authorized for food applications by French Food organizations, without any quantitative use.

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Atoligomer

**SEA WATER - BLOOD SERUM COMPARISON**

![Graph comparing sea water and blood serum](image)

**ATOLIGOMER INCREASES VITALITY IN HUMAN DERMAL FIBROBLASTS & KERATINOCYTES**

![Bar graphs comparing cellular vitality](image)

**RECONSTITUTED EPIDERMIS (EX VIVO TEST)**

- Reconstituted epidermis in a medium without minerals
- Reconstituted epidermis in culture in a saline medium with the 73 trace elements of Atoligomer. Atoligomer ensures excellent cohesion between the basal cells and the membrane, and between the keratinocytes of different layers.
Moisturizers for Acne
What are their Constituents?

LEENA CHULAROJANAMONTI, MD; PAPAPIT TUCHINDA, MD; KANOKVALAI KULTHANAN, MD; KAMOLWAN PONGPARIT, MD
Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

ABSTRACT
Acne is a chronic inflammatory disease of the pilosebaceous unit that affects almost all teenagers. Different treatments offer different modes of action, but aim to target acne pathology. Topical therapies, such as benzoyl peroxide, retinoids, antibiotics with alcohol-based preparations, and salicylic acid, can cause skin irritation resulting in a lack of patient adherence. Some physicians recommend patients use moisturizers as adjunctive treatment of acne, especially when either topical benzoyl peroxide or a retinoid is prescribed. Furthermore, some evidence shows that moisturizers can contribute independently to improve signs and symptoms of acne. Moisturizers contain three main properties, which are occlusive, humectant, and emollient effects. Currently, many moisturizers claim to be suitable for acne treatment. This article aims to provide a review of the active ingredients and properties of those moisturizers. Fifty-two moisturizers for acne were included for analysis. Most of the products (92%) have anti-inflammatory properties apart from occlusive, humectant, and emollient effects. Anti-acne medications, including salicylic acid, benzoyl peroxide, and retinol, were found respectively in 35, 10, and 8 percent of the moisturizer products containing anti-inflammatory properties. More than half of the products contain dimethicone and/or glycerin for its moisturizer property. Aloe vera and witch hazel are botanical anti-inflammatories that were commonly found in this study. Scientific data regarding some ingredients are discussed to provide a guide for physicians in selecting moisturizers for acne patients.


DISCLOSURE: The authors report no relevant conflicts of interest.
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<td>9. Caprylic/capric triglyceride</td>
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<td>14. Cocoa butter</td>
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<td>15. Coconut oil</td>
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<td>19. Cyclopentasiloxane</td>
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<td>20. Decyl oleate</td>
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<td>21. Dimethicone</td>
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<td>22. Ethylhexylpalmitate</td>
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<td>24. Glycerin (glycerol)</td>
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<td>26. Glycyrrhetinic acid</td>
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<td>27. Grape seed oil</td>
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<td>28. Green tea extract</td>
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<td>29. Honey</td>
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<td>30. Hyaluronic acid</td>
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<td>31. Hypericum perforatum (St. John’s wort)</td>
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<td>32. Jojoba oil</td>
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<td>33. Isohexadecane</td>
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<td>34. Isopropyl myristate</td>
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<td>35. Lactic acid</td>
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<td>36. Lanolin (wool alcohol)</td>
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<tr>
<td>37. Lecithin</td>
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<td>38. Licochalcone A</td>
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</table>

**TABLE 1. Active ingredients in moisturizers for acne**

- OCCLUSIVES: Serves to retain moisture in the skin by creating a barrier.
- HUMECTANTS: Hydrates the skin by attracting and retaining moisture.
- EMOLLENTS: Softens and smoothes the skin.
- ANTI-INFLAMMATORY: Reduces inflammation and irritation.
- OIL-REDUCING: Helps control oil production.
not been combined with other ingredients are not greasy. The second property of moisturizers is humectant, which attracts water from the dermis to epidermis. Examples of humectants are glycerin (glycerol), sodium lactate, ammonium lactate, hyaluronic acid, sorbitol, urea, and alpha hydroxyl acids.  

The other property of moisturizers is emollient, which smooths skin by filling space between skin flakes with a droplet of oil. Emollients include a vast array of compounds ranging from esters to long chain alcohols, such as isopropyl isostearate, caster oil, propylene glycol, octyl stearate, and dimethicone. One ingredient of moisturizers can have more than one property, such as dimethicone, which has both occlusive and emollient properties. Other ingredients including topical medications for acne and botanical anti-inflammatory substances are sometimes added to moisturizers for acne.

Currently, many moisturizers that are available either over the counter or online claim that they are suitable for acne treatment. The current study was designed to investigate the active ingredients and properties of those moisturizers.

MATERIAL AND METHODS

The authors used the key words “moisturizers” and “acne” to search for moisturizers that are available online. Only moisturizers that claimed they are suitable for acne, blemishes, and pimples were selected to identify their ingredients and properties. The same inclusion criteria were used for moisturizers that are available over the counter. Each moisturizer with its corresponding ingredients was entered into a Microsoft Excel (Seattle, Washington) spreadsheet and then evaluated for their ingredients and properties.

RESULTS

Fifty-two products were included for analysis. Table 1 demonstrates the active ingredients and their properties that the authors were able to identify in the products. Some ingredients also have an oil-reducing property, which may be suitable for oily skin. Ninety-two percent (48/52) of the products have anti-inflammatory properties apart from occlusive, humectant, and emollient effects. Table 2 demonstrates a list of the products and their ingredients that do not contain anti-inflammatory properties. Anti-acne medications, including SA, BP, and retinol were found, respectively, in 35 percent (17/48), 10 percent (5/48), and 8 percent (4/48) of the moisturizer products containing anti-inflammatory effects (Tables 3 and 4). Twenty-two of 48 products (46%) contained other anti-inflammatory substances without anti-acne medications (Table 5). More than one-half of all products contain dimethicone and/or glycerin for their moisturizing properties. Aloe vera and witch hazel, botanical anti-inflammatories, were commonly found in the products as well.

DISCUSSION

Topical therapies, including SA, BP, retinoids, and antibiotics are effective in managing acne, but are associated with local adverse effects, such as irritation and dryness. A concomitant use of moisturizers can enhance efficacy, alleviate dryness, and improve skin comfort. The study by Laquieze et al showed that using moisturizers...
provided a significant improvement in skin dryness and comfort to the patients who were treated with oral or topical isotretinoin. From the study described herein, the authors found that SA was the most common anti-acne medication added in the moisturizers for acne. SA has comedolytic effects by breaking down follicular plugs because of its lipophilic nature and anti-inflammatory capability by affecting arachidonic acid cascade.7–10 However, SA is likely to cause local skin peeling when used at concentrations of 2% or more.11 Thus, moisturizing properties in the products can relieve the irritation effect of SA. O’Goshi et al12 demonstrated an increase in skin hydration of the skin of swine after applying 10% SA in petrolatum once daily for five days. The continuous effect was also detected over two weeks after cessation of application.12
Similarly, BP and retinols are regarded as irritative agents. BP has greater activity than topical (iso)tretinoin against inflammatory lesions while retinoids work well for comedolytic effects and decrease sebum excretion.  

Although the concentration of BP used for acne is limited by local skin irritation, there were no significant differences in frequency and severity of irritation between the use of 5% and 2.5% BP.  

The study by Matsunaga et al showed that the adjunctive use of a moisturizer (Cetaphil®, Galderma Laboratories, L.P.) improved local tolerance of adapalene gel.  

Dimethicone and glycerin were the most common ingredients found in the products. Dimethicone and cyclomethicone are silicone derivatives and usually used in oil-free facial moisturizers. The term “oil-free” implies that this substance does not contain either mineral oil or vegetable oil. Dimethicone reduces TEWL without a greasy feel and contains both occlusive and emollient properties. It is suitable for acne and sensitive patients as it is noncomedogenic and hypoallergenic. Cyclomethicone is a thicker silicone that has similar properties as dimethicone. The authors found that other ingredients, such as petrolatum, lanolin, and mineral oil, were occasionally added in the 52 products analyzed, as they have some drawbacks for acne-prone skin. The use of lanolin is limited by odor, expense, and the fact that it is a common cause of allergic contact dermatitis.  

Mineral oil is a lightweight inexpensive oil that is odorless and tasteless. One of the main concerns for its use is that it is comedogenic. However, there are different grades of mineral oil, including industrial grade and cosmetic grade. Some experts believe that cosmetic grade mineral oil is

<table>
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<tr>
<th>ACTIVE INGREDIENTS</th>
<th>PRODUCTS</th>
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<tbody>
<tr>
<td></td>
<td>5</td>
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<tr>
<td><strong>ANTI-INFLAMMATORY</strong></td>
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<tr>
<td>Aloe vera (Aloe barbadensis)</td>
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<td>Chamomile (Matricaria recutita)</td>
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<tr>
<td>Cucumber extract</td>
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<tr>
<td>Licochalcone A</td>
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<tr>
<td><strong>SALICYLIC ACID</strong></td>
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<tr>
<td>Tea tree oil (Melaleuca alternifolia)</td>
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<tr>
<td>Vitis vinifera (grape seed extract)</td>
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<tr>
<td>Witch hazel (Hamamelis virginiana)</td>
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<tr>
<td>Zinc gluconate</td>
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Products
5. Aveeno Clear Complexion Daily Moisturizer (Johnson and Johnson); 6. Burt’s Bees Natural Acne Solutions Daily Moisturizing Lotion (Burt’s Bees); 7. Philosophy Clear Days Ahead Oil-Free Salicylic Acid Acne Treatment and Moisturizer (Philosophy); 8. Neutrogena Oil-Free Anti-Acne Moisturizer (Johnson and Johnson); 9. Yves Rocher Pure System Soin Stop Imperfections Stop Blemish Lotion (Yves Rocher); 10. Pevonia SpaTeen Blemished Skin Moisturizer (Pevonia); 11. Acne Treatment Exfoliating & Rejuvenating Acne Treatment Gel/Non-Greasy Moisturizer (DermaCosmic); 12. AHSR Day – acne protective moisturizer (Oregon Aesthetic Technologies, Inc.); 13. Hope in a Bottle - oil-free moisturizer and acne treatment (Philosophy); 14. Clean & Clear Oil-Free Dual Action Moisturizer (Johnson and Johnson); 15. Aubrey Organics – clarifying therapy moisturizer-cream treatment for acne-prone skin (Aubrey Organics); 16. Clean & Clear Acne Control Moisturizer (Johnson and Johnson); 17. Clean & Clear Essentials Moisturizer Oil-Free Anti Acne Cream won’t clog pores (Johnson and Johnson); 18. Dr. Somchai Face & Body Anti Acne Lotion prevent breakouts oiliness (SS Manufacturing Co., Ltd.); 19. Clear-n-Smooth Anti-Blemish Cream (Hawknad Manufacturing Industries, Inc.); 20. L’Oreal Men Expert Pure & Matte Acne Striker Moisturizer (L’Oreal); 21. Vichy Normaderm Tri-activ Anti-Imperfection Hydrating Care (Vichy Laboratories)
### TABLE 4. Moisturizers containing benzoyl peroxide or retinol

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<td><strong>MOISTURIZER EFFECT</strong></td>
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<td>Betaine</td>
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<td>Butylene glycol</td>
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<td>Caprylic/capric triglyceride</td>
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<td>Cetearyl alcohol</td>
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<td>Cetyl alcohol</td>
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<td>Cholesterol</td>
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<td>Cyclopentasiloxane</td>
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<td>Dimethicone</td>
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<td>Ethylhexylpalmitate</td>
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<td>Glycerin (glycerol)</td>
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<td>Grape seed oil</td>
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<td>Propylene glycol</td>
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<tr>
<td>Sodium hyaluronate</td>
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<tr>
<td>Sodium pyrrolidone carboxylic acid (PCA)</td>
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<td>Sorbitol</td>
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<tr>
<td>Sunflower seed oil (Helianthus annuus)</td>
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<tr>
<td>Vitamin E</td>
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<td>Zinc oxide</td>
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<tr>
<td><strong>ANTI-INFLAMMATORY</strong></td>
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<tr>
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<td><strong>BENZOYL PEROXIDE</strong></td>
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<td>Bisabolol</td>
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<tr>
<td>Marigold (Calendula officinalis)</td>
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<tr>
<td>Niacinamide/nicotinamide/vitamin B3</td>
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<tr>
<td><strong>RETINOL</strong></td>
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<tr>
<td>Tea tree oil (Melaleuca alternifolia)</td>
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<tr>
<td>Vitis vinifera (Grape seed extract)</td>
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<tr>
<td>Witch hazel (Hamamelis virginiana)</td>
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</table>

**Products**

22. Clinique Acne Solutions Clearing Moisturizer Oil-Free (Clinique Laboratories); 23. Augustus BioMed All-in-One Acne Cream + Moisturizer with Vitamin E (Augustus BioMed Skin Care LLC); 24. Paula’s Choice Clear Line Extra Strength Acne Fighting Treatment – Moisturizer Lotion (Paula’s Choice); 25. Acnezine Revitol Acne Moisturizing Cream (Revitol); 26. Acnezine Revitol Moisturizing Cream (Revitol); 27. IQ Natural “Sensitive” Acne Moisturizer w/ DMAE & MSM Anti-Acne Cream (IQ Natural); 28. Murad Anti-Aging Acne Moisturizer SPF 20 Facial Treatment Products (Murad); 29. ICI Natural Skincare Anti-Acne Moisturizer (ICI Natural); 30. Neutrogena Healthy Skin Anti-Wrinkle Anti-Blemish Treatment (Johnson and Johnson)
<table>
<thead>
<tr>
<th>ACTIVE INGREDIENTS</th>
<th>PRODUCTS</th>
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<tr>
<td>ALMOND OIL</td>
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<td>BUTYLENE GLYCOL</td>
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<tr>
<td>CAPRYLIC/CAPRIC TRIGLYCERIDE</td>
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<td>CETEARYL ALCOHOL</td>
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<td>CETEARYL ISONONANOATE</td>
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<td>CETYL ALCOHOL</td>
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<td>COCOA BUTTER</td>
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<td>CYCLOPENTASILXANNE</td>
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<td>JOJOBA OIL</td>
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<tr>
<td>LACTIC ACID</td>
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<td>LECITHIN</td>
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<td>OCTYLDODECANOL</td>
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<td>SACCHARIDE ISOMERATE</td>
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<td>SODIUM HYALURONATE</td>
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<td>SQUALANE</td>
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<td>STEARIC ACID</td>
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<td>STEARYL ALCOHOL</td>
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<td>SUGARS</td>
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<tr>
<td>VITAMIN E</td>
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</table>

Table 5 continued on next page
Glycerin is the most effective humectant available to increase stratum corneum hydration. If the concentration of glycerin is too high, it will create a sticky feeling on skin. Hyaluronic acid and sodium pyrrolidone carboxylic acid (PCA), which are humectants, may be used in addition to glycerin to decrease stickiness. It should be noted that application of a humectant alone can increase TEWL. For example, glycerin (glycerol) can increase TEWL by 29 percent. Thus, a humectant agent is usually combined with an occlusive ingredient when used as a moisturizer. The authors found that glycerin (humectant) and dimethicone (occlusive agent) were usually used in combination in the 52 products analyzed.

**TABLE 5 continued. Anti-inflammatory moisturizers without anti-acne medications**

<table>
<thead>
<tr>
<th>ACTIVE INGREDIENTS</th>
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<tr>
<td>Aloe vera (Aloe barbadensis)</td>
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<td>Cucumber extract</td>
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<td>Glycyrrhetinic acid</td>
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<td>Green tea extract</td>
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<td>Licochalcone A</td>
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</tr>
<tr>
<td>Marigold (Calendula officinalis)</td>
<td>√</td>
</tr>
<tr>
<td>Niacinamide/ Nicotinamide/ Vitamin B3</td>
<td>√</td>
</tr>
<tr>
<td>Shea butter (Butyrospermum parkii)</td>
<td>√</td>
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<tr>
<td>Tea tree oil (Melaleuca alternifolia)</td>
<td>√</td>
</tr>
<tr>
<td>Vitis vinifera (Grape seed extract)</td>
<td>√</td>
</tr>
<tr>
<td>Witch hazel (Hamamelis virginiana)</td>
<td>√</td>
</tr>
<tr>
<td>Zinc gluconate</td>
<td>√</td>
</tr>
</tbody>
</table>

Products:
31. Weleda Baby Calendula Face Cream (Weleda); 32. Dr. Somchai Acne Prevention Moisturizer (SS Manufacturing Co., Ltd.); 33. Yes To Daily Balancing Moisturizer, Tomatoes (Yes To); 34. Cetaphil Dermaclean Moisturizer SPF 30 (Gelderma); 35. Acne.org Moisturizer with Licochalcone (Acne.org); 36. Dermaflage Acne Moist Moisturizer (Dermalogica); 37. Neutrogena Acne Stress Control, 3-in-1 Hydrating Acne Treatment (Johnson and Johnson); 38. Mentholatum Acne Oil Control Moisturizer SPF15 (The Mentholatum Company); 39. End-Zit Blemish Control Moisturizer for Treatment of Acne (ABBE Laboratories); 40. Coral Actives Moisturizer for Acne Prone Skin (Erma LABS); 41. Therapeutic Acne Moisturizer (Emerge Skin Care); 42. Blissoma Solutions Natural Skincare (Irie Star); 43. SpaGlo Vitamin B Day Cream for Acne Control (SpaGlo Beauty); 44. Acne Ceticals Moisturizer by Raw Skin Ceticals (RawSkinCeticals); 45. Happy Me Skincare Natural Acne Healing Moisturizer (High Concept Events); 46. Herbal Natural Cucumber Whitening Nourishing Moisturizing & Anti-Acne Cream (Thanyaporn, Thailand); 47. Organix Ever Clear: TeaTree (acne treating) Facial Products (Vogue International); 48. PAN Cosmetics Acnicare Cream Anti-Acne & Blemish Oil Control Anti-Comedone (PAN Cosmetic); 49. Anti Acne Cream for Oily Skin with Natural Antibacterial Extracts (Swissorganics); 50. Papulex Isocorrexion for Acne Prone Skin (Sinclair Pharma France); 51. Eucerin DermaPURIFYER Hydrating Day Care (Beiersdorf); 52. Oriental Princess Acne Control Moisturizing Cream (O.P. Natural products co., LTD).
Metals and botanical extracts are sometimes added in the moisturizers for their anti-inflammatory properties. Ginkgo biloba, green tea, aloe vera, allantoin, and licochalcone are botanical anti-inflammatory agents that are commonly used in the current market. Aloe vera and witch hazel, which were found commonly in this study, also have skin-soothing properties. The anti-inflammatory effect of aloe vera results from inhibition of cyclooxygenase in the arachidonic pathway. The concentration of aloe vera should be at least 10 percent in order to have a moisturizing effect. Witch hazel is commonly used as an astringent in people with oily skin. Its high tannin content obtained by steam distillation of the plant may cause astringent action. Hamamelis ointments, known as witch hazel ointments, are used as acne cosmecceuticals.

Currently, there are many metals, such as zinc, copper, selenium, aluminum, and strontium, that are used in cosmecceuticals. Well-established scientific data support the anti-inflammatory and wound healing benefits of zinc. Alkaline phosphatase requires multiple zinc ions, which are involved in adenosine monophosphate metabolism. This action has a role in restraining an inflammatory response.

In conclusion, the authors aim was to investigate the ingredients and properties of moisturizers claimed to be suitable for use in acne patients. Some scientific data regarding the properties and mechanisms of action were provided to aid physicians in selecting a suitable moisturizer for their acne patients.

REFERENCES

Higher 17α-Hydroxyprogesterone Levels Aggravated the Severity of Male Adolescent Acne in Northeast China

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Department of Dermatology, 1st Hospital of Chongqing Medical University, Chongqing, and Department of Dermatology, No. 1 Hospital of China Medical University, Shenyang, China; Department of Dermatology, Mount Sinai Medical Center, New York, N.Y., USA

Key Words
Androstenedione · Dehydroepiandrosterone sulfate · Testosterone · Estradiol · 17α-Hydroxyprogesterone · Adolescent acne

Abstract
Background: The relationship between serum hormone levels and adolescent acne is not fully clarified. Objective: To determine the relationship between levels of androstenedione, dehydroepiandrosterone sulfate (DHEA-S), testosterone, estradiol and 17α-hydroxyprogesterone (17-OHP) with adolescent acne in Northeast China. Methods: A transversal study included 242 acne cases and 188 controls. All data were analyzed using SPSS version 17.0. Results: Androstenedione and testosterone levels were significantly higher (p < 0.0001) in the cases than in the control group. In males, the difference in 17-OHP levels was statistically significant (p < 0.0001), as well as between mild and severe acne cases (p = 0.002). The estradiol level was significantly different (p < 0.0001) between cases and controls in females. Conclusion: Higher androstenedione and testosterone levels are significant risk factors in the occurrence of adolescent acne. A higher 17-OHP level aggravates the severity of male adolescent acne, while a higher estradiol level protects females against the onset of adolescent acne.

Introduction
Acne is one of the most common skin diseases in adolescents [1]. The pathogenesis of acne includes ductal hypercornification, enhanced sebaceous gland activity, colonization by Propionibacterium acnes and inflammation [2]. Androgens impair the skin barrier function and cause epidermal hyperplasia and follicular hyperkeratosis, and consequently result in the onset of acne [3]. In addition, it was reported that applying estrogen could prevent the multifactorial processes of acne [4, 5]. However, the association between serum hormone levels and acne has been hotly debated. To further explore and confirm the relationship between hormone levels with adolescent acne in Northeast China, we determined the lev-
els of androstenedione, dehydroepiandrosterone sulfate (DHEA-S), testosterone, estradiol and 17α-hydroxyprogesterone (17-OHP) in the cases with adolescent acne and healthy adults as controls.

Subjects and Methods

Subjects
The study population consisted of 124 males and 118 females with acne, and 98 males and 90 females were randomly selected as controls. All the participants were between the ages of 17 and 25 years and were recruited from the outpatient clinic of the Department of Dermatology, No. 1 Hospital of China Medical University. The controls accompanied the acne patients to the outpatient clinic.

Methods
Blood specimens were collected from the patients and controls from Northeast China. All subjects signed the informed consent, and the study was approved by the Ethical Committee of the Hospital. Blood specimens were taken between 8 and 9 a.m. to exclude same-day variations. The severity of acne was assessed according to Pillsbury's diagnostic criteria: grade 1, comedones and occasional small cysts confined to the face; grade 2, comedones with occasional pustules and small cysts confined to the face; grade 3, many comedones and small and large inflammatory sites on the face, and grade 4, many comedones and deep lesions tending to coalesce and canalize, and involving the face and the upper aspects of the trunk [4]. In our study, mild acne was defined as grades 1 and 2, and severe acne as grades 3 and 4. The levels of androstenedione, DHEA-S, testosterone, estradiol and 17-OHP were determined by chemiluminescence immunoassay. The process was as follows: first, we prepared the serum (blood sample: centrifuged at 2,800 g for 5 min); then, sampling, chemiluminescence reaction and putting out the results were done automatically by the Siemens Immulite® 2000 in the laboratory.

Statistical Analysis
All data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, Ill., USA), and p < 0.05 was considered as statistically significant. The 5 variables we measured belonged to the continuous data, which were calculated as means with standard deviations, or medians with interquartile ranges. Comparison between two groups was performed by an independent sample t test and correlation analysis.

Results

Serum Hormone Levels in Acne Patients and Controls by Gender
The results of serum hormone levels were depicted in table 1. In both the male and female groups, the levels of androstenedione and testosterone were significantly higher in acne cases than those in controls (all p < 0.0001). In males the level of 17-OHP was significantly higher in...
the acne cases than those in controls (p < 0.0001). In females, the difference in estradiol levels between the acne patients and controls was statistically significant (p < 0.0001). In both the male and female patients, there was no significant difference in the level of DHEA-S.

Serum Hormone Levels in Male/Female Acne Patients by Severity

Only in male patients were the levels of 17-OHP found to be significantly different (p = 0.002) between patients with mild and severe acne (table 2).

Discussion

Acne is a most common dermatological disease with a high incidence in adolescents [6, 7] and has significant psychological and physical impacts on youngsters [8]. Hamilton [9] first reported that androgen was involved in the pathogenesis of acne in the early 1940s. Since then, the association between androgen and acne has become the focus of research.

At present, various literatures present different conclusions on the relationships between androgen and acne. Our study showed that the levels of androstenedione and testosterone were significantly higher (p < 0.0001) in adolescent acne cases than those in controls. This result was consistent with some reports in the literature. Lawrence et al. [10] reported a higher level of testosterone was found in women with severe acne, and Darley et al. [11] reported a 60% increase in the level of testosterone in patients with late-onset or persistent acne. Gonzaga da Cunha et al. [12] reported 54.56% of the patients had hyperandrogenism, and the levels of DHEA were most frequently elevated. Our result was inconsistent with that of Gonzaga da Cunha et al. [12] concerning DHEA-S and the study of Ginsberg et al. [13] in which 48% of acne patients were found to have elevated DHEA-S levels. Our study found DHEA-S levels were of no statistical difference between the acne patients and controls, in agreement with the study of Palatsi et al. [14] in which the levels of DHEA-S in acne cases did not significantly differ from those in controls. We considered the difference might be associated with age and the ethnicity of the selected cases.

We found that the estradiol level was significantly different (p < 0.0001) between female acne cases and controls. This result was underreported in the literature and consistent with the report of Arora et al. [15] that the lower serum estrogen level was observed in patients with acne vulgaris. In addition, a few clinical trials indicated that topical application of antiandrogens had demonstrated efficacy and effectiveness in acne treatment [16–18]. The trials mentioned above indirectly supported our findings. Placzek et al. [19] reported that 17-OHP levels were significantly higher (p = 0.01) in male acne patients than in the controls. In addition, it was reported that an elevated level of 17-OHP was found in male acne patients compared to unchanged 17-OHP levels in controls [20, 21]. Our study demonstrated that the 17-OHP level with adolescent acne was significantly higher in the male patients than in controls (p < 0.0001), and in patients with mild acne grades than in those with severe acne grades (p = 0.002). Our study further indicated that higher 17-OHP levels might exist as an important risk factor in the pathogenesis of acne and an aggravating factor in the severity of male adolescent acne. Although our study showed the level of 17-OHP was not statistically significantly different between the acne patients and controls in females, serum concentrations of 17-OHP after adrenocorticotropic stimulation (17-OHP$_{2}$O) should be investigated in women with persistent acne in adult life [22].

Our survey was carried out in the outpatient clinic of the Department of Dermatology, No. 1 Hospital of China Medical University. Part of the participants visited doctors in other hospitals, therefore it is difficult to follow up these young people. This point was considered as the study limitation. In conclusion, our study demonstrated that there were significant differences in the serum hormone levels between the patients with adolescent acne and controls. High levels of androstenedione and testosterone may serve as risk factors, while lower estradiol levels count as a protective factor in the pathogenesis and onset of adolescent acne. Elevated levels of 17-OHP aggravated the severity of adolescent acne in male patients. Our studies may provide valuable information for clinicians in the prevention and treatment of acne.

Acknowledgments

This work was supported in part by grants from the Program for Changjiang Scholars and Innovative Research Team in University (State Education Ministry, IRT0760, and Education Department of Liaoning Province, 2006T133, 2008T193, LR201040). We express our gratitude to all those who participated in this study as well as those who helped enroll subjects.

Disclosure Statement

Conflicts of interest: none declared.
References

Facial sebum affects the development of acne, especially the distribution of inflammatory acne

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‡Department of Dermatology, Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Seoul, Korea
*Correspondence: S.W. Youn. E-mail: swyoun@snu.ac.kr

Abstract

Background The increased sebum secretion has been considered as one of the pathogenic factors of acne.
Objective The goal of this study was to assess the correlation between the casual sebum level and the severity of acne using objective measuring methods in a large acne patients group. We also investigated the influence of age or gender on the correlation.
Methods A total number of 914 acne patients were recruited. The standard digital photographs were taken, and the acne lesions were counted as comedones or inflammatory lesions. The casual sebum level was measured using the Sebumeter SM 815. The correlation analysis was performed.
Results The casual sebum level showed positive correlation with the number of acne lesions. The casual sebum level markedly influenced the number of inflammatory lesions and the acne lesions located in the U-zone. In the young acne patients, the casual sebum level showed significant correlations in the U-zone, whereas in the old acne patients, there were significant correlations in the T-zone. The male acne patients were more influenced by the casual sebum level.
Conclusion This was the first study to report the significant correlations between the casual sebum level and the number, proportion and location of acne lesions in a large acne patients group, using an objective, bioengineering method. Moreover, we also found that the influence of sebum was prominent on the inflammatory lesions. In addition, both age and gender influenced the correlation between the casual sebum level and the acne.

Conflict of interest
The authors have no conflict of interest to declare.

Funding sources
This study was supported by grant 02-2010-027 from Seoul National University Bundang Hospital.

Introduction
Acne is a disorder of the pilosebaceous unit. The pathogenic factors of acne are, as follows: increased sebum secretion, follicular epidermal hypercornification, Propionibacterium acnes colonization and inflammation. Previous studies have found the positive correlation between the sebum secretion and acne. However, the population samples of previous studies were small or the method to evaluate the acne severity was a subjective grading system. Moreover, the sebum measurement methods were not standardized. Recently, a meta-analysis study was performed to investigate the relationship between the sebum secretion and acne severity. It revealed that the sebum excretion rate was in a linear relationship with the acne severity.

In this study, we performed correlation analysis between the casual sebum level (CSL) and the number of acne lesions, according to clinical types. We also investigated the influence of several parameters, such as the type of acne lesions, the patients’ age and gender on the relationship between the CSL and the acne. This is the first objective, quantitative study evaluating the severity of acne and its topographical correlation of CSL in a large population sample.

Materials and methods

Subjects
A total of 914 patients (278 male and 636 female), who visited the Seoul National University Bundang Hospital between 2004 and
2009, and were clinically diagnosed as acne vulgaris, were retrospectively included in this study. The study was approved by the Institutional Review Board of our hospital study (B-1006-103-115).

Clinical photography and lesion counting
We took three standard clinical photographs (i.e. an anterior view of the entire face and both lateral views) of identical compositions. The photographs of the face were divided into two parts: the T-zone (forehead, nose and chin) and the U-zone (both cheeks). One dermatologist counted the acne lesions of both the T-zone and the U-zone as either comedones (TCom or UCom) or inflammatory lesions (TInf or UInf) using the ImageJ software (Rasband WS, Image, U. S. National Institutes of Health, Bethesda, MD, USA).12 The acne lesions of the whole face was calculated: comedones on the whole face (WCom = TCom + UCom); inflammatory lesions on the whole face (Winf = TInf + UInf); total acne lesions in the T-zone (TTotal = TCom + TInf); total acne lesions in the U-zone (UTotal = UCom + UInf); and total acne lesions on the whole face (WTotal = WCom + Winf). The inflammatory lesion proportions of the T-zone (TInf/TTotal), the U-zone (UInf/UTotal) and the whole face (Winf/WTotal) and the proportion of comedones, inflammatory lesions and total acne lesions located in the T-zone (TCom/WCom, TInf/WInf, and TTotal/WTotal respectively) was also calculated.

Measurement of the CSL
We used the Sebumeter® (SM 815; Courage and Khazaka, Cologne, Germany) to measure the CSL, as previously shown.2,13,14 In measuring the sebum, the CSL or the sebum excretion rate is used. The CSL is the amount of surface sebum.15 The amount of surface sebum is dependent on the amount of excreted sebum from the sebaceous glands and the amount of washed-out sebum from the surface. In this study, the CSL was measured. The mean of the measured CSL was calculated in specific areas as follows: the high sebum secreting zone (T-zone; forehead, nose, chin), the low sebum secreting zone (U-zone; both cheeks) and the whole face (forehead, nose, chin and both cheeks).

Statistical analysis
We performed the Student’s t-test to compare the clinical features between young vs. old or male vs. female groups. We also used the Pearson’s correlation test to find the correlation between the clinical features and the CSL. Data were expressed as the mean ± SD, and a P-value of <0.05 was considered as statistically significant.

Results
Demographics
The mean age of the patients was 22.6 ± 6.86 years, and the mean age of onset was 17.0 ± 5.66 years. The mean disease duration was 5.62 ± 5.46 years. We divided the acne patients into men vs. women and young (age <25) vs. old (age ≥25) groups for further evaluation.

The mean age of the men (n = 278) and women (n = 636) acne patients was 20.02 ± 5.57 and 23.71 ± 7.07 years respectively. The mean age of onset was 16.01 ± 4.78 and 17.37 ± 5.97 years respectively. The mean acne duration was 4.00 ± 3.71 and 6.33 ± 5.93 years respectively. The mean age of the young (age <25; n = 616) and old (age ≥25; n = 298) acne patients was 18.86 ± 3.79 and 30.29 ± 5.17 years respectively. The mean age of onset for these groups was 15.02 ± 3.49 and 20.96 ± 7.04 years, respectively, and the mean acne duration was 3.84 ± 3.04 and 9.32 ± 7.22 years respectively.

CSL affects the number of inflammatory lesions
The mean number of acne lesions for each investigated zone was summarized in Table 1. There were more comedones than inflammatory lesions in both the T-zone and the U-zone. The proportion of inflammatory lesions was higher in the U-zone than in the T-zone.

The mean CSL of the forehead, nose, chin, left cheek and right cheek was 192.37 ± 113.48 µg/cm², 218.05 ± 129.04 µg/cm², 189.80 ± 120.72 µg/cm², 121.89 ± 112.21 µg/cm², and 115.90 ± 106.88 µg/cm² respectively. The mean CSL of the T-zone, U-zone and the whole face was 200.07 ± 92.33 µg/cm², 118.90 ± 100.04 µg/cm², and 167.60 ± 86.44 µg/cm² respectively. The CSL of the nose was the highest. The CSL of the T-zone was higher than that of the U-zone.

The correlation analysis between the CSL and the number of acne lesions was summarized in Table 2. In the T-zone, the CSL correlated with the number of inflammatory lesions (r = 0.119, P < 0.001). In the U-zone, the CSL positively correlated with the number of comedones (r = 0.079, P = 0.016), the inflammatory lesions (r = 0.120, P < 0.001) and the total number of acne lesions (r = 0.110, P = 0.001). The CSL of the whole face showed positive correlation with the number of inflammatory lesions (r = 0.148,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The mean number of acne lesions (a) and the proportions of acne lesions (b)</th>
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<tbody>
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<td>(a) Type of acne lesions</td>
<td>T-zone</td>
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<tr>
<td>Comedone</td>
<td>11.42 ± 10.56</td>
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<tr>
<td>Inflammatory lesion</td>
<td>7.90 ± 8.64</td>
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<tr>
<td>Total lesion</td>
<td>19.32 ± 16.91</td>
</tr>
<tr>
<td>(b) Proportions of acne lesions</td>
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<tr>
<td>TInf/TTotal</td>
<td>0.40 ± 0.21</td>
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<td>UInf/UTotal</td>
<td>0.44 ± 0.17</td>
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<td>Winf/WTotal</td>
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<td>TCom/WCom</td>
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<td>TInf/WInf</td>
<td>0.36 ± 0.23</td>
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<tr>
<td>TTotal/WTotal</td>
<td>0.39 ± 0.20</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD.
The CASL influenced differently between young and old patients

Old acne patients had less comedones and inflammatory lesions than young acne patients (Table 3). However, the proportion of inflammatory lesions or the proportion of lesions located on the T-zone was not different between the two groups (data not shown).

Comparing the CSL of the young and old acne patients, there was no significant difference except in the chin; the CSL of the chin was higher in the old patients group \( (P = 0.041) \).

The correlation between the CSL and the acne lesions of the two groups (i.e. old vs. young) was summarized in Table 4. In the T-zone, the CSL of the old acne patients showed positive correlation with the inflammatory lesions \( (r = 0.216, P < 0.001) \), the total number of acne lesions \( (r = 0.152, P = 0.009) \), and the proportion of inflammatory lesions over the total number of acne lesions located in the T-zone \( (r = 0.216, P < 0.001) \).
The male acne patients were more influenced by the CSL

The age and the age of onset in male acne patients were significantly younger than that of the female acne patients. Moreover, the acne duration in male patients was significantly shorter than that found in female acne patients. The clinical characteristics were also different between male and female acne patients (Table 5). The male acne patients had more inflammatory lesions. We also found that the male acne patients had more acne lesions in both the U-zone and the whole face. In contrast, the female patients had more comedones in the T-zone. The proportion of inflammatory lesions over the total number of acne lesions was higher in the male acne patients. Conversely, both the proportion of comedones and the total number of acne lesions located in the T-zone were higher in the female acne patients.

Comparing the CSL of the male and female acne patients, there was no significant difference except the CSL of the forehead which was higher in the male acne patients ($P = 0.038$).

The correlation between the CSL and the acne lesions of the two groups (i.e. male vs. female) was summarized in Table 6. In male acne patients, the CSL of the T-zone showed positive correlation with both the number of inflammatory lesions ($r = 0.174, P = 0.004$) and the proportion of inflammatory lesions over the total number of acne lesions ($r = 0.169, P = 0.005$). Similarly, the CSL of the U-zone was positively correlated with the number of comedones ($r = 0.149, P = 0.013$), the number of inflammatory lesions ($r = 0.171, P = 0.004$), the total number of acne lesions ($r = 0.175, P = 0.003$) and the proportion of inflammatory lesions over the total number of acne lesions ($r = 0.132, P = 0.002$). In female acne patients, there was positive correlation between the CSL of the T-zone and the number of inflammatory lesions over the total number of acne lesions ($r = 0.158, P = 0.008$) and the proportion of inflammatory lesions over the total number of acne lesions ($r = 0.188, P = 0.002$).

### Table 5 The characteristics of the male and female acne patients

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>278</td>
<td>636</td>
<td></td>
</tr>
<tr>
<td>Acne lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_{Com}$</td>
<td>10.15 ± 8.56</td>
<td>11.97 ± 11.29</td>
<td>0.008*</td>
</tr>
<tr>
<td>$T_{Inf}$</td>
<td>8.98 ± 7.73</td>
<td>7.44 ± 8.97</td>
<td>0.013*</td>
</tr>
<tr>
<td>$T_{Total}$</td>
<td>19.13 ± 14.46</td>
<td>19.40 ± 17.88</td>
<td>0.809</td>
</tr>
<tr>
<td>$U_{Com}$</td>
<td>17.99 ± 12.82</td>
<td>17.31 ± 14.41</td>
<td>0.496</td>
</tr>
<tr>
<td>$U_{Inf}$</td>
<td>17.56 ± 14.65</td>
<td>12.97 ± 11.59</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>$U_{Total}$</td>
<td>35.54 ± 25.24</td>
<td>30.28 ± 23.25</td>
<td>0.002*</td>
</tr>
<tr>
<td>$W_{Com}$</td>
<td>28.14 ± 18.08</td>
<td>29.28 ± 21.06</td>
<td>0.436</td>
</tr>
<tr>
<td>$W_{Inf}$</td>
<td>26.54 ± 19.48</td>
<td>20.40 ± 17.69</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>$W_{Total}$</td>
<td>54.69 ± 34.24</td>
<td>49.68 ± 34.24</td>
<td>0.042*</td>
</tr>
<tr>
<td>$T_{Inf}/T_{Total}$</td>
<td>0.46 ± 0.20</td>
<td>0.37 ± 0.21</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>$U_{Inf}/U_{Total}$</td>
<td>0.47 ± 0.16</td>
<td>0.43 ± 0.17</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>$W_{Inf}/W_{Total}$</td>
<td>0.47 ± 0.13</td>
<td>0.41 ± 0.14</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>$T_{Com}/W_{Com}$</td>
<td>0.37 ± 0.17</td>
<td>0.41 ± 0.22</td>
<td>0.003*</td>
</tr>
<tr>
<td>$T_{Inf}/W_{Inf}$</td>
<td>0.36 ± 0.21</td>
<td>0.36 ± 0.24</td>
<td>0.904</td>
</tr>
<tr>
<td>$T_{Total}/W_{Total}$</td>
<td>0.37 ± 0.17</td>
<td>0.40 ± 0.21</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD.

* $P < 0.05$.

### Table 6 The comparison of the Pearson’s correlation coefficients of the casual sebum level and the acne lesion count between the male and female acne patients in the T-zone (a), U-zone (b) and whole face (c)

<table>
<thead>
<tr>
<th></th>
<th>The Pearson’s correlation coefficients of the T-zone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>(a) Correlations in the T-zone</td>
<td></td>
</tr>
<tr>
<td>$T_{Com}$</td>
<td>0.026 (0.663)</td>
</tr>
<tr>
<td>$T_{Inf}$</td>
<td>0.174 (0.004)*</td>
</tr>
<tr>
<td>$T_{Total}$</td>
<td>0.109 (0.071)</td>
</tr>
<tr>
<td>$T_{Inf}/T_{Total}$</td>
<td>0.169 (0.005)*</td>
</tr>
<tr>
<td>(b) Correlations in the U-zone</td>
<td></td>
</tr>
<tr>
<td>$U_{Com}$</td>
<td>0.149 (0.013)*</td>
</tr>
<tr>
<td>$U_{Inf}$</td>
<td>0.171 (0.004)*</td>
</tr>
<tr>
<td>$U_{Total}$</td>
<td>0.175 (0.003)*</td>
</tr>
<tr>
<td>$U_{Inf}/U_{Total}$</td>
<td>0.132 (0.028)*</td>
</tr>
<tr>
<td>(c) Correlations in the whole face</td>
<td></td>
</tr>
<tr>
<td>$W_{Com}$</td>
<td>0.101 (0.093)</td>
</tr>
<tr>
<td>$W_{Inf}$</td>
<td>0.184 (0.002)*</td>
</tr>
<tr>
<td>$W_{Total}$</td>
<td>0.158 (0.008)*</td>
</tr>
<tr>
<td>$W_{Inf}/W_{Total}$</td>
<td>0.188 (0.002)*</td>
</tr>
</tbody>
</table>

Data presented as Pearson’s correlation coefficient ($P$-value).

* $P < 0.05$. 
inflammatory lesions ($r = 0.097, P = 0.014$). Similarly, the number of inflammatory lesions of the U-zone correlated with the CSL of the U-zone ($r = 0.083, P = 0.035$). The CSL of the whole face showed positive correlation with the number of inflammatory lesions ($r = 0.126, P = 0.002$) and the proportion of inflammatory lesions ($r = 0.128, P = 0.001$).

**Discussion**

This is the first correlation study between the CSL and the number of acne lesions in a large acne patients group. We found statistically significant correlations between the CSL, and either the numbers of comedones or the inflammatory lesions. We also found that the CSL correlated with the proportions of acne lesions. Our results supported the previous concepts that the sebum secretion is the major pathogenic factor in the development of acne.

Among the key elements of acne pathogenesis, the positive correlation between the sebum secretion and acne was shown. Furthermore, the aggravation of acne after the high glycemic diets was thought to be associated with the increased sebum production. Moreover, the treatment with the sebum reducing medications has been used to treat the acne. The previous experimental studies suggested that sebum was associated with both the initiation of inflammation and the formation of comedones. The previous study reported the statistically significant correlation between the sebum secretion and either the inflammatory or non-inflammatory lesions. However, that study could not find significant correlations in most facial regions, possibly due to the small subject size. In this study, the number of acne lesions showed statistically significant correlation with the CSL in a large sample of acne patients. We also found that the CSL influenced acne differently, according to the type of acne lesions. The most important finding in this study is that the number of significant correlations of the CSL with inflammatory lesions was greater than that of correlations with the comedones; the Pearson’s correlation coefficients of the inflammatory lesions were also higher than those of the comedones. The CSL was also positively correlated with the proportion of inflammatory lesions over the total number of acne lesions. These results suggested that the CSL had a strong influence on the development of inflammatory lesions. In addition, the influence of the CSL was different according to the affected area of the face. Although the mean CSL of the T-zone was higher than that of the U-zone, the number of significant correlations of the CSL with the U-zone was greater than that of the T-zone. These results suggested that the numbers of acne lesions on the U-zone were more influenced by the CSL.

The clinical features were different in young vs. old acne patients. Thus, the old acne patients had a smaller number of comedones, inflammatory lesions and total acne lesions. These results are in accordance with previous reports. In the young acne patients, the significant correlations were found in the U-zone, whereas the significant correlations of the old acne patients were found in the T-zone. Furthermore, as the CSL increased, more acne lesions were found in the U-zone of the young acne patients, whereas the more inflammatory lesions were found in the T-zone of the old acne patients. These results suggested that the influence of CSL is stronger on the U-zone in the young acne patients and the T-zone in the old acne patients.

**With regard to the sexual difference**, the male acne patients had more inflammatory lesions. Male acne patients also showed higher proportions of the inflammatory lesions. These results are in agreement with those from other studies that have concluded that male patients had more severe acne. In both male and female acne patients, the number of inflammatory lesions was correlated with the CSL. However, in the male patients, the CSL of the U-zone showed significant correlations with the comedones, the total number of acne lesions and the proportion of inflammatory lesions. Moreover, the Pearson’s correlation coefficients were higher than those found in female acne patients. These results suggest that the male acne patients are more influenced by the CSL than the female acne patients.

Based on the newly found significant correlation between the CSL and the number of acne lesions, the approach to the acne patients can be adjusted. When grading the acne patients, those with a high proportion of inflammatory lesions may suggest that they have high CSL and it is better to select the modalities that can reduce the sebum secretion. From our results, the U-zone acne lesions of the young patients and the T-zone lesions of the old patients would show improvement with the sebum reduction treatment, such as isotretinoin. Accordingly, this sebum reduction may directly impact on the severity of acne in the male acne patients. Conversely, in the female acne patients, sebum reducing modalities would show less improvement, because the acne of female patients is less influenced by the sebum secretion. Therefore, we suggest that the treatment with antibiotics should be considered in the female acne patients.

In conclusion, the CSL showed significant correlation with the clinical features of acne in our study; thus, the number of lesions as well as the proportion and location of lesions, were influenced by the CSL. In addition, the clinical features of either young or male acne patients were strongly influenced by the CSL. According to these results, the inflammatory lesions of acne patients could be a clinical indicator of high CSL. The objective assessment of the skin type by measuring the CSL can be helpful in selecting the treatment modalities for acne. Further studies focusing on the relationship between reduced sebum secretion after treatment and the improvement of acne lesions will advance the understanding of the pathogenic role of sebum in the development of acne.

**References**

Acne sans *P. acnes*

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Abstract

Acne vulgaris is a common disease that carries an enormous financial and psychosocial impact. Androgens, excessive sebum production, ductal hypercornification, changes in the microbial flora, as well as inflammation and immunological host reactions are considered the major contributors to acne pathogenesis. Despite extensive research on acne pathogenesis, the exact sequence of events and their possible mechanisms leading to the development of a microcomedone and its transformation into an inflamed lesion has remained unclear.

There is a significant amount of *in vitro* evidence suggesting a possible pathogenetic role for *Propionibacterium acnes* in comedogenesis as well as inflammation in inflammatory acne. However, the microbiological data from non-inflamed as well as inflamed acne lesions, cultured individually, do not entirely support the hypothesis that these micro-organisms are actually responsible for their initiation. There appears to be comedones and inflamed lesions in which there is no clear evidence of *Propionibacterium acnes* involvement. Considering this microbiological data, alongside the *in vitro* evidence, we have tried to delineate the possible sequence of events and their mechanisms, leading to the development of a microcomedone and its transformation into an inflamed lesion. Based on the available literature we have analysed the evidence of both non-inflamed as well as inflamed acne lesions occurring in the absence of *Propionibacterium acnes* from the pilosebaceous follicles. We propose that the development of an inflamed acne lesion depends on an imbalance between the pro-inflammatory and anti-inflammatory pathways rather than the incitement of inflammation by *Propionibacterium acnes*.

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Conflict of interest

None.

Introduction

Acne vulgaris is a multifactorial, pleomorphic skin disease of the pilosebaceous follicles (PSFs) characterized by a variety of non-inflamed (open and closed comedones) and inflamed (macules, papules, pustules and nodules) lesions. Microcomedones (earliest subclinical lesions) are thought to be the precursor lesions that can then develop into non-inflamed and/or inflamed lesions. Although a common disease, the aetiology of acne is not yet fully elucidated and is thought to be a multifactorial process. Androgens, excessive sebum production, hyper-proliferation and abnormal differentiation of the follicular infundibulum, changes in the microbial flora, as well as inflammation and immunological host reactions are considered the major contributors to acne pathogenesis.

The controversial role of *Propionibacterium acnes* in the initiation of non-inflamed and inflamed acne lesions

The role of *Propionibacterium acnes* (*P. acnes*) in acne has long been a very controversial topic. The microbiological data obtained from comedones, cultured individually, suggest that *P. acnes* may not be involved in the initiation of these lesions. This data has been recently reviewed by Shaheen and Gonzalez.¹ However, there is a considerable amount of *in vitro* data suggesting a possible pathogenetic role for this micro-organism in comedogenesis. Nevertheless, none of the previous reviews on acne pathogenesis has tried to incorporate the existing microbiological data with the *in vitro* evidence to explain the possible role of this microorganism in the evolution of non-inflamed acne lesions.²⁻⁴ Likewise, the involvement of *P. acnes* in the initiation of inflammation in inflamed lesions is still a matter of debate. Two distinct phenotypes of *P. acnes* (type I and II), corresponding to phylogenetically distinct clusters or lineages, have been identified.⁵ Interestingly, *P. acnes* type I was isolated from the majority of acne lesions in one study, favouring the hypothesis that a specific *P. acnes* phenotype might be more common in acne patients.⁵ Similarly, based on multilocus sequence analysis of various housekeeping and virulence factor genes, Lomholt and Kilian⁶ also identified three phylogenetically different groups of *P. acnes* (I–III). They also found a subdivision of group I (I-1) to be significantly associated with moderate to severe acne. The difference in
the production of various virulence factors was thought to be responsible for this association.\textsuperscript{6} This viewpoint has been recently supported by the finding that strain specific differences in the genome of various \textit{P. acnes} groups do exist.\textsuperscript{7} This along with a wealth of other \textit{in vitro} evidence (discussed later), showing various ways in which \textit{P. acnes} can be involved in inflammation, suggests a possible role for this organism in inflammatory acne. However, even with such compelling data, this by no means proves that \textit{P. acnes} is involved in the initiation of inflamed acne lesions. The question regarding the involvement of \textit{P. acnes} in the initiation of inflammation cannot be answered without looking at the microbiological data obtained from inflamed acne lesions, cultured individually. This data, as reviewed by us recently, showed that \textit{P. acnes} is never isolated from 100\% of inflamed lesions and that various investigators also found a proportion of these lesions to be sterile.\textsuperscript{1} It is important to understand that although the organism is isolated from the skin surface, its normal habitat is the PSF.\textsuperscript{8} As \textit{acne} is a disease of the PSFs, inflammation in an inflamed acne lesion cannot be assumed to be initiated by \textit{P. acnes} particularly when the PSF is confirmed to be sterile or not colonized by this micro-organism.

\textit{Propionibacterium acnes} may be a bystander in the development of inflamed acne lesions

Based on the observation that patients with severe acne, compared with mild acne and normal controls, have higher levels of antibodies to \textit{P. acnes}, it has been proposed that hypersensitivity to \textit{P. acnes} may be responsible for the variation in acne severity.\textsuperscript{9,10} However, in both these studies no statistical analysis was done to ascertain whether or not there was any significant difference in the antibody titres between normal controls, mild/moderate acne and patients with severe acne. Provision of this data could have been more informative in drawing conclusions regarding the role of these antibodies in acne pathogenesis (i.e., whether pathogenic or consequential). In contrast, Ingham \textit{et al.}\textsuperscript{11} found no significant difference in the antibody titres to \textit{P. acnes} in patients with mild or moderate acne compared with normal controls. They only found patients with severe acne, compared with normal controls, to have significantly higher titres of antibodies to this micro-organism. Furthermore, patients with severe acne do not harbour significantly larger numbers of \textit{P. acnes} than those with milder disease.\textsuperscript{12,13} Thus, it is possible that the increased antibody titres to \textit{P. acnes} in severe acne patients, is due to an increased exposure of these individuals to the immunogen as a result of their disease \textit{per se}. Likewise, cell-mediated immunity to \textit{P. acnes} cannot be solely held responsible for the initiation of inflammation in all acne patients as it has been shown to occur late in the chain of events.\textsuperscript{14} Moreover, the improvement seen with the use of antibiotics, such as tetracycline, may partly be explained by their anti-inflammatory effects.\textsuperscript{15} Together this evidence suggests that \textit{P. acnes} may be merely a bystander and not an active participant in the development of inflamed acne lesions.

Although a number of different reviews have been published on acne pathogenesis, none of them gave a clear cut sequence of events and mechanisms leading to the development of a non-inflamed lesion followed by its progression to an inflamed one.\textsuperscript{2–4} The aim of this review is to propose a possiblestepwise mechanism to explain this process. We have also tried to incorporate the \textit{in vitro} evidence, regarding the pathogenic potential of \textit{P. acnes}, to explain its possible role in the evolution of non-inflamed as well as inflamed acne lesion. Moreover, in line with the microbiological data, we have retained the viewpoint that both comedogenesis and inflammation may occur in the absence of \textit{P. acnes}.

\textbf{Comedogenesis}

Comedones result from abnormal proliferation and differentiation of ductal keratinocytes.\textsuperscript{16} Hyper-proliferation has been confirmed by demonstration of an increase in the Ki-67 labelling of ductal keratinocytes.\textsuperscript{17} This fact is further substantiated by the presence of keratins 6 and 16 (keratin markers of hyper-proliferation) in comedones.\textsuperscript{18}

\textbf{Androgens, PPARs and seborrhoea}

The role of androgens in acne vulgaris and the beneficial effect of anti-androgen therapy are well established. Acne development begins at the time of adrenarche when the adrenal glands start producing dehydroepiandrosterone sulphate (a precursor for testosterone).\textsuperscript{19,20} Androgen-insensitive subjects do not produce sebum and do not develop acne.\textsuperscript{21} Acne patients have also been found to have a higher density of androgen receptors\textsuperscript{22} and increased activity of type 1 5α-reductase enzyme\textsuperscript{23} which might support the hypothesis of end-organ sensitivity in these patients. In addition, anti-androgen therapy reduces sebum excretion rate (SER) and improves acne.\textsuperscript{24}

The risk of acne vulgaris in relatives of patients with acne, as compared with controls, is significantly higher suggesting hereditary influences.\textsuperscript{25} Interestingly, evidence of direct genetic association of acne with androgen abnormalities has been observed. CYP17-34C/C homozygote Chinese men have been found to be at a significantly increased risk of developing severe acne.\textsuperscript{26} This gene encodes cytochrome P450c17α which is one of the key enzymes in androgen biosynthesis. Moreover, neonatal acne has been found to be associated with familial hyperandrogenism.\textsuperscript{27} It seems likely that acne is a polygenic disorder and that different genes, accounting for either increased concentration and/or sensitivity to androgens, may be responsible for the development of acne in an individual.

As mentioned earlier, acne patients have increased end-organ sensitivity to circulating androgens. Although androgens have a proliferative effect on cultured human\textsuperscript{28} and SZ95 sebocytes,\textsuperscript{29} they have only a minimal effect on SZ95 sebocyte differentiation.\textsuperscript{30} PPAR ligands, on the other hand, have been shown to be the master regulators of lipid metabolism.\textsuperscript{30,31} In addition to the androgen receptors, PPARs are abundantly present in human sebaceous...
glands. Taken together, these findings may explain the increase in sebaceous gland size with associated seborrhoea seen in acne patients at puberty.

Acne patients are also known to have a low sebaceous linoleic acid (LA, C18:2,9,12) level, which returns to normal with a concomitant decrease in SER, after treatment with anti-androgens. These results indicate that the proportion of LA in sebum is influenced by SER. A low concentration of linoleate in sebum has been proposed to cause follicular hyperkeratosis and decreased barrier function. It is, therefore, understandable that an increased sensitivity to androgens, in acne patients, may lead to a low sebaceous linoleate concentration as a consequence of increased SER, resulting in comedogenesis. Indeed, the severity of acne has been found to be related to the rate of sebum excretion. Adding more weight to the LA theory is the fact that topical LA has been shown to cause a significant reduction in the size of follicular casts and microcomedones in acne patients.

In addition, androgens have been shown to significantly stimulate the proliferation of keratinocytes co-cultured with beard dermal papilla cells via the production of insulin-like growth factor-1 (IGF-1) by the dermal papilla cells. Thus, it is possible that androgens may also influence epithelial turnover in the follicular infundibulum via the production of IGF-1, which acts as a paracrine growth factor. Interestingly, serum IGF-1 levels have been found to be positively correlated with the number of comedones in females with clinical acne. IGF-1 has also been shown to stimulate lipid production in human SEB-1 sebocytes by an increased expression of sterol response element-binding protein-1, a transcription factor that regulates numerous genes involved in lipid biosynthesis. Thus androgens can cause seborrhoea in acne patients not only by their direct proliferative action on the sebocytes but also via IGF-1, which stimulates lipogenesis in the sebaceous glands.

**Interleukin-1α**

Results from essential fatty acid deficient mice have shown mRNA levels for epidermal IL-1α to be elevated several-fold over controls. Disruption of the skin permeability barrier and the body's attempt to repair it was postulated to be responsible for this increase. Elevated IL-1α has been reported in comedones in acne patients. Furthermore, IL-1α has been demonstrated to cause hypercornification of the follicular infundibulum, which can be blocked by IL-1 receptor antagonists. Therefore, we propose that low sebaceous LA levels (an essential fatty acid), in acne patients, may cause disruption of the cutaneous permeability barrier of the follicular infundibulum. This may lead to increased epidermal IL-1α production, resulting in comedogenesis.

In summary, it is highly probable that androgens may play an important role in comedogenesis. They may not only stimulate keratinocyte proliferation but may also lead to seborrhoea by their direct and indirect action (via IGF-1) on the sebocytes. These two androgen mediated effects may, therefore, explain the development of comedones in acne patients. Our proposed mechanism may also explain the microbiological data which suggests that comedogenesis can occur in the complete absence of *P. acnes* from the PSFs.

**Propionibacterium acnes colonization of comedones**

Keeping in mind the above-mentioned hypothesis regarding the role of androgens in the initiation of comedogenesis, the fact that *P. acnes* has been found to colonize significantly more comedones compared with unaffected follicles can be explained as follows:

**Follicular micro-environment**

The micro-environment of individual PSFs, whether normal or acne affected, is thought to be important for colonization by micro-organisms. Follicular pH, water availability and oxygen as well as carbon dioxide tension are some of the possible parameters that might differ from one PSF to another and may determine microbial colonization.

**Innate immunity**

More recently, innate immunity has received a lot of attention because of its potential role in protecting surface epithelia from microbial colonization and invasion. Apart from secreting lipid-rich sebum onto the skin surface, sebocytes can also provide an innate immune defensive function. This has been supported by the observation that various antimicrobial peptides (e.g. cathelicidin, Psoriasin, human β defensin (hBD)-1 and 2 and histone H4) are produced by these cells. These antimicrobial peptides have been found to have antimicrobial activity against *P. acnes*, in vitro.

It is prudent to mention herein that the actual concentration of these antimicrobial peptides released by human sebaceous glands remains unknown. It is possible that the concentration of these antimicrobial peptides having an antimicrobial activity in *vitro*, is not achievable in *vivo*. However, these antimicrobial peptides demonstrate additive or synergistic functions when combined. It is therefore possible that the total antimicrobial activity in sebocytes is due to all antimicrobial peptides acting together.

Although antimicrobial peptides are extensively studied, other protection systems also exist. Free fatty acids (FFAs) are ubiquitous on the human skin surface, possessing intrinsic antimicrobial activity predominantly against gram-positive bacteria. Moreover, they can further strengthen the cutaneous innate immunity by upregulation of hBD-2 by sebocytes. Lastly, synergistic antimicrobial activity of hBD-2 and lauric acid (C12:0) has been demonstrated against *P. acnes*, in *vitro*.

When all these findings are considered together we can hypothesize that in addition to the follicular micro-environment the synergistic antimicrobial activity of the various antimicrobial components secreted from sebocytes, may also determine colonization of the normal and acne affected PSFs. This innate defence mechanism may be defective in acne patients and, along with a
favourable follicular micro-environment, may be responsible for the significantly greater colonization of comedones (by \textit{P. acnes}) compared with the unaffected follicles.\textsuperscript{44,45} Changes in the skin surface FFAs can be postulated as one of the possible mechanisms for such a defect. It is, therefore, possible that a lower LA level in acne patients may be one of the factors responsible for a defective innate immune mechanism in these patients.\textsuperscript{33} However, this matter is still unresolved and more research is needed to test this hypothesis.

**Potentiation of comedogenesis after \textit{Propionibacterium acnes} colonization**

After colonization, \textit{P. acnes} can potentiate comedogenesis by various mechanisms (Fig. 1). It is known that \textit{P. acnes} produces lipases which hydrolyse triglycerides, thereby releasing FFAs. These FFAs have been found to be comedogenic in the rabbit ear model.\textsuperscript{56} Oxidized squalene is another substance that has been found to be comedogenic in the rabbit ear model.\textsuperscript{57} \textit{P. acnes}, through its production of porphyrins, may act as a catalytic agent in the oxidation of squalene.\textsuperscript{58} This, along with the fact that keratinocytes stimulated by \textit{P. acnes} have been shown to produce significantly more IL-1\alpha compared with unstimulated keratinocytes, might signify other potential pathways through which \textit{P. acnes} may be involved in comedogenesis.\textsuperscript{59}

Compared with normal controls, aberrant α6 integrin expressions have been demonstrated around clinically normal follicles and early inflamed lesions of acne patients.\textsuperscript{60} Integrins are postulated to be important in the proliferation and differentiation of keratinocytes.\textsuperscript{61} \textit{P. acnes} has been shown to induce the expression of β1, α3, α6, αVβ6 integrins and filaggrin on epidermal cells, \textit{in vitro}.\textsuperscript{62} This may be another possible mechanism by which \textit{P. acnes} may aggravate comedogenesis.

Lastly, \textit{P. acnes} has been shown to increase the production of IGF-1 by keratinocytes.\textsuperscript{63} This can then activate IGF-1R, mostly located in the basal layer of the epidermis and also induced by \textit{P. acnes}, leading to proliferation of the keratinocytes and an increase in filaggrin expression through a paracrine pathway.\textsuperscript{63} This can potentially be another mechanism by which \textit{P. acnes} can potentiate comedogenesis.

**Inflammation**

**Sub-clinical inflammation**

The next question which needs to be answered is exactly what initiates inflammation, if not \textit{P. acnes}? Compared with the control follicles obtained from non-acne patients, clinically normal skin of acne patients has been shown to have increased numbers of T cells and macrophages in the perifollicular and papillary dermis.\textsuperscript{60} Furthermore, expression of E-selectin and vascular adhesion molecule-1 was also found to be upregulated, with the dermal concentration of IL-1\alpha reported to be three times higher in this clinically normal skin.\textsuperscript{60} All these data suggest that sub-clinical inflammation exists in acne prone areas, even if it appears clinically normal, in people suffering with acne.

Many cells, including keratinocytes and fibroblasts, function as sources of IL-1.\textsuperscript{64} In Ser252Trp-FGFR2 mutated osteoblasts (mesenchymally derived cells) in patients with Apert syndrome, an

![Figure 1](image-url)
increase in the expression of IL-1α has been reported. Androgens are thought to be involved in FGF2 production (by dermal fibroblasts) which then binds mesenchymal isoform FGFR2c receptors. It is possible that increased androgen sensitivity in acne patients may lead to increased FGF2 production by dermal fibroblasts. FGF2 produced as a result of this stimulation may lead to increased IL-1α production by these fibroblasts via an autocrine effect. This may explain the higher dermal concentration of IL-1α, noted in the clinically normal skin of acne patients.

The IL-1α is a pro-inflammatory cytokine which can upregulate the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1. Therefore, it is possible that the increased expression of IL-1α, both in the dermis as well as epidermis (mechanism explained under comedogenesis), will not only contribute to comedogenesis but may also result in the initiation of non-specific sub-clinical inflammation, demonstrated in the clinically normal skin of acne patients. More recently, upregulation of IL-6 and TNF-α in cultured human sebocytes after addition of Dihydrotestosterone has also been demonstrated. These pro-inflammatory cytokines may also play a role in the sub-clinical inflammation mentioned above.

**Clinical inflammation**

The transition from sub-clinical to clinical inflammation might depend on an imbalance between pro-inflammatory and anti-inflammatory pathways that are activated as a result of this local stress.

**Activation of the cutaneous equivalent of the central hypothalamic-pituitary-adrenal axis**

The hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role in terminating the stress response and buffering tissue damage, in response to any systemic stress. This process involves production and release of corticotropin-releasing hormone (CRH) followed by production and secretion of proopiomelanocortin (POMC) derived peptides (adrenocorticotropic hormone, ACTH and α-melanocyte stimulating hormone, α-MSH). ACTH induces production and secretion of the powerful anti-inflammatory protein cortisol, which terminates the stress response and buffers tissue damage. The presence of corticotropin-releasing hormone (CRH), its binding protein (CRHRBP) and corticotropin-releasing hormone receptor type 1 (CRHR-1) and 2 (CRHR-2) has been confirmed in human sebaceous glands, in vivo, suggesting that a complete CRH system exists in sebocytes. Moreover, a functional CRH- proopiomelanocortin (POMC)-corticosteroid axis organized similarly to the HPA axis has been demonstrated in epidermal melanocytes, dermal fibroblasts and human hair follicles.

The CRH expression in the hypothalamic cells can be modulated by various pro-inflammatory cytokines (Tumour necrosis factor-α (TNF-α), IL-1β and IL-6). These cytokines may also modulate its expression in the skin. Thus, the sub-clinical inflammation evident in the clinically normal skin of acne patients may lead to increased cutaneous production of CRH. Indeed, CRH expression has been found to be greatly increased in acne involved skin compared with non-involved and normal skin. As α-MSH peptides, produced locally, as a result of this CRH stimulation of the cutaneous CRH-POMC-corticosteroid axis also modulate the expression of its receptor (MC-1R), this may explain the increased expression of MC-1R in the sebaceous glands of lesional skin of patients with acne vulgaris.

Although CRH can induce cutaneous inflammation by causing mast cell degranulation, it might also act as an anti-inflammatory agent by increasing the local production of steroids. Likewise, α-MSH has also been shown to exert anti-inflammatory actions by inhibition of IL-1α mediated IL-8 secretion from SZ95 sebocytes and by suppressing TNF-α and IL-1β gene expression following an ischaemic cerebral event in mice. Furthermore, it has also been demonstrated to induce the production of IL-10 by human peripheral blood monocytes in vitro. IL-10 is a regulatory cytokine that acts to harness the release of several pro-inflammatory cytokines.

In brief, activation of the cutaneous CRH-POMC-corticosteroid axis may activate both pro-inflammatory and anti-inflammatory pathways that when working in conjunction with other pro-inflammatory pathways (discussed below) may determine the development of a clinically inflamed lesion.

**Substance P and human β-defensins**

Substance P (SP), another important pro-inflammatory neuropeptide, has also been found to be over expressed in dermal nerves around the sebaceous glands of acne patients. Recently, IL-1α was found to upregulate SP expression in the dorsal root neurons from mature rats. This may be another pro-inflammatory pathway that is activated as a result of sub-clinical inflammation seen in the clinically normal skin of acne patients.

Further, antimicrobial peptides hBD-1 and hBD-2 have been found to be upregulated in lesional skin from acne patients. hBD-2 does not only possess antimicrobial activities but also acts as a chemoattractant for mast cells and induces histamine release and prostaglandin D2 production from these cells as well. Moreover, human β-defensins are also chemotactic for immature dendritic cells and memory T cells. Pro-inflammatory cytokines e.g. TNF-α can modulate hBD-2 expression and, therefore, may explain its upregulation in acne lesions.

It is evident that various pro-inflammatory and anti-inflammatory pathways are activated as a result of sub-clinical inflammation, seen in the clinically normal skin of acne patients. We hypothesize that an imbalance between these pathways may lead to the development of clinical inflammation in inflammatory acne (Fig. 2). Interestingly, an in vitro study has shown that acne patients produce significantly less IL-10 from monocytes, in response to P. acnes stimulation, as compared with healthy controls. It is possible that the production of IL-10 by monocytes, in response to α-MSH, in acne patients may also be impaired: this is a pro-inflammatory cytokine which can upregulate hBD-2 expression and, therefore, may explain its upregulation in acne lesions.
may be one of the anti-inflammatory pathways that can be defective in these patients.

Our proposed mechanism signifies that the presence of *P. acnes* in PSFs is not necessary for the development of clinical inflammation in acne patients. This may therefore explain the sterility or absence of *P. acnes* from a significant proportion of inflamed acne lesions as reported by various investigators.1

**Potentiation of inflammation by *Propionibacterium acnes* and other intrafollicular contents**

As explained above, clinical inflammation in an acne lesion may develop in the complete absence of *P. acnes* from the PSFs. However, micro-organisms (from colonized follicles) and other intrafollicular contents may further intensify this inflammation.

*Propionibacterium acnes* and/or its products, after being released into the dermis, may intensify the inflammatory process by its antigenic,9,11,89 enzymatic,90–92 complement activation93,94 and chemotaxtactic activities.95,96 (Fig. 3). Moreover, *P. acnes* can also lead to the production of pro-inflammatory cytokines/chemokines by keratinocytes59,97 (IL-1α, TNF-α, granulocyte/macrophage colony-stimulating factor and IL-8), sebocytes98 (CXCL8, synonymous with IL-8) and peripheral blood mononuclear cells99 (IL-1β, TNF-α, and IL-8). Lastly, *P. acnes* can also enhance expression of antimicrobial peptide hBD-2 in sebocytes and keratinocytes.97,98

![Diagram](image_url)

**Figure 2** Proposed mechanism for the aetiopathogenesis of acne vulgaris and its association with *Propionibacterium acnes* (*P. acnes*). DHT, Dihydrotestosterone; IL, Interleukin; CRH, Corticotropin-releasing hormone; MSH, Melanocyte stimulating hormone; ACTH, Adrenocorticotropic hormone; hBD-2, Human beta defensin-2; SP, Substance P; TNF, Tumour necrosis factor; IGF-1, Insulin-like growth factor-1.
is obvious that hBD-2 (an antimicrobial peptide containing pro-inflammatory properties) and all the other pro-inflammatory cytokines/chemokines mentioned above, may also intensify inflammation in acne patients.

Propionibacterium acnes secretory protein called Christie-Atkins-Munch-Peterson factor and acid sphingomyelinase, which is released from the host cells in the presence of P. acnes, are cytotoxic to keratinocytes and macrophages, in vitro. Furthermore, P. acnes can lead to the formation of reactive oxygen species, especially superoxide anions, by keratinocytes. These may be other potential mechanisms explaining the involvement of P. acnes in inflammatory acne. Last but not least, P. acnes can also exaggerate inflammation in acne by the induction and activation of toll-like receptors 2 and 4. After rupture of the duct it is likely that other intrafollicular contents like FFAs, keratin and hairs may also contribute to the inflammation.

**Conclusion**

We conclude that androgens, sebaceous lipid abnormalities and key cytokines such as IL-1α may play an important role in the initiation of comedogenesis. Although acknowledging the significant supportive evidence on the role of P. acnes in acne pathogenesis, we propose that P. acnes may not be central to the initiation of inflammation in inflamed acne lesions. Rather, an imbalance between the pro-inflammatory (CRH by causing mast cell degranulation, SP and hBD-2) and anti-inflammatory pathways (steriodogenesis and α-MSH production as a result of cutaneous CRH-POMC-corticosteroid axis activation) may be more important in this context. This hypothesis may be tested by comparing the pro-inflammatory and anti-inflammatory effects of these different pathways in patients with either predominantly comedonal or inflammatory acne.

There is no doubt that the in vitro evidence for the role of P. acnes in acne pathogenesis is compelling. However, it cannot be taken as a proof of its involvement in the initiation of non-inflamed and inflamed acne lesions. We have attempted to take a balanced view of most of the available evidence, including the microbiological data, and shown that the central role of P. acnes in the initiation of acne lesions is not yet irrefutable. If P. acnes is not isolated from a significant number of acne-affected PSFs (whether inflamed or non-inflamed) the organism cannot be held responsible for the initiation of pathological changes in these lesions. The story on the role of P. acnes in acne pathogenesis must therefore be viewed as still evolving.

**References**

39 Cappel M, Mauger D, Thiboutot D. Correlation between serum levels of insulin-like growth factor 1, dehydroepiandrosterone sulfate, and dihydrotestosterone and acne lesion counts in adult women. Arch Dermatol 2005; 141: 333–338.
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54 Wille JJ, Kytomies A. Palmitoleic acid isomer (C16:1delta6) in human skin sebum is effective against gram-positive bacteria. Skin Pharmacol Appl Skin Physiol 2003; 16: 176–187.


76 Theoharides TC, Singh LK, Boucher W et al. Corticotropin-releasing hormone induces skin cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. Endocrinology 1998; 139: 403–413.


