Sebum Production

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M.A. Farage et al. (eds.), *Textbook of Aging Skin*,
DOI 10.1007/978-3-662-47398-6_33

Abstract

Sebum produced by sebaceous glands is progressively altered during its transit in the sebaceous duct. Sebaceous gland dynamics involves four successive features including sebum productive and storage, sebum delivery at the skin surface, and the sebum resorption by the stratum corneum. The excretion rate at the skin surface is indeed different from the secretion rate by the gland. The skin microbiome is globally influenced by sebum that promotes anaerobic and lipophilic microorganisms. The lipid composition of sebum exerts profound influences on epithelial tissues.

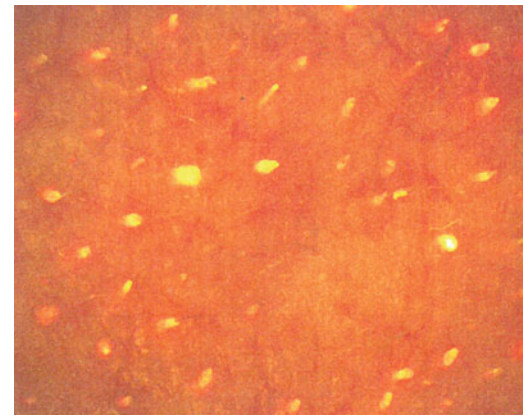

Fig. 1 Fluorescent follicular openings under Visiopor® examination

Introduction

Sebum is produced exclusively by the sebaceous glands. It serves as a vehicle for odors involved in sexual and social attraction. By a similar mechanism, the newborn child commonly recognizes his/her mother's body odor. The reciprocal recognition between the newborn and the mother likely develops during the first weeks of life when the sebaceous glands are active in the newborn. In addition, it is noteworthy that the individual sebum-driven scents of each human being are commonly detected by dogs on the skin and clothes. Other volatile compounds corresponding to pheromones are produced by mammalian skin in a mixture of apocrine sweat and sebum. In addition, sebum brings vitamin E, the α-melanocyte-stimulating hormone (α-MSH) isotype, and other various compounds to the stratum corneum (SC).

Sebum interferes with the skin microbiome [1]. In particular, it is fungistatic to dermatophyte species. Tinea capitis caused by *Microsporum* or *Trichophyton* spp. typically occurs only before puberty when sebum production is minimal to absent. In addition, sebum exhibits some bacteriostatic properties. By contrast, sebum promotes the growth of specific anaerobic and lipophilic microorganisms and parasites including *Propionibacterium* spp. [2], *Staphylococcus epidermidis*, *Malassezia* spp., and *Demodex* mites [3]. Interestingly enough, some specific follicular bacteria, particularly *Propionibacterium acnes*, release porphyrins that are identifiable by their fluorescence [4, 5]. They are seen clinically using a special camera (Visiopor, CK Electronic, Cologne, Germany) revealing fluorescent follicular ostia (Fig. 1). Other fields of biology are influenced by sebum. The high squalene content in sebum supposedly represents, after resorption, a substrate for cholesterol and vitamin D synthesis by the epidermis.

Plasticity and cohesion between corneocytes are somewhat related to the sebum amount. Sebum protects the skin and the hair shaft from damage induced by mild acid solutions and friction. Indeed, combing and hairdressing generate friction effects on the cuticular cells. Skin and hair surfaces that are primarily hydrophobic and paradoxical become more wettable by a series of sebum components including free fatty acids [6]. In fact, surface wettability is involved in various protective functions of the SC including biocenosis preservation, smoothness, resiliency, and barrier effect to various xenobiotics.

Sebum production shows large interindividual differences. Nonetheless, there are global influences of age and gender. In adults, the critical period in life regarding sebum production begins after menopause and andropause. In older subjects, the sebum flow at the skin surface usually runs dry. In a global perspective aging of the sebaceous glands appears quite complex.

Seborrhea in Cosmetic Perspective

Sebum production shows large interindividual variations as well as intraindividual fluctuations with age. Any excess in sebum output defines seborrhea that leads to unpleasant cosmetic aspects, and possibly fuels specific disorders. Most seborrheic subjects exhibit both greasy hair and oily skin on the forehead and nose. However, some relative differences are possibly found between these locations. After wiping or washing the skin, the sebum coating is often quickly restored. Hence, seborrhea commonly represents a matter of concern to the affected individual.

Observing the skin under ultraviolet light (Visioscan, CK Electronic, Cologne, Germany) discloses specific subclinical or faint mosaic patterns of perifollicular melanosis [7]. Typically, speckled perifollicular melanotic rims (SPMR) are disclosed on the face and scalp of seborrheic individuals (Fig. 2), in particular those with androgenic alopecia [7]. SPMR are evidenced well before the development of distinct patterns of photodamage-related melanosis. In addition, SPMR are absent in children when sebaceous glands are quiescent. It is also absent in nonseborrheic parts of the body, including sun-exposed areas. It has been postulated that SPMR on the seborrheic skin resulted from the melanocyte activation by α-MSH produced by the follicular infundibulum and present in sebum [7].

Greasy hair has lost its natural luster, and it looks dull, darker, and moist. Hair shafts are weighted down with leaking sebum which makes them adherent and flattens all hairstyles in thick masses on the scalp. They are hard to comb. Sebum appears to exert similar effect as a humid environment on hair hold. Sebum is left on the fingers and clothes. When feeling the oily tresses of sticky hairs, their limpness is perceptible, and it is difficult to separate the individual hairs. The possibility to render translucent a piece of paper helps to distinguish sweaty and greasy hair. On heating, an aqueous impregnation disappears rapidly by evaporation, while lipids remain. It should be noted that sustained sweating may be associated with increased seborrhea.

A scaly dermatitis is commonly present on seborrheic scalp. This condition is sometimes associated with pruritus or slight discomfort during the days preceding a shampoo. While these symptoms disappear with a regular shampoo, dandruff become more visible, since scales are no longer stuck to the scalp by sebum, and they are more easily shed on to the clothes and pillow.

Structure of the Sebaceous Gland

Mature sebaceous glands are holocrine lobulated structures distributed all over the skin except on the palms and soles (Fig. 3). Apart from

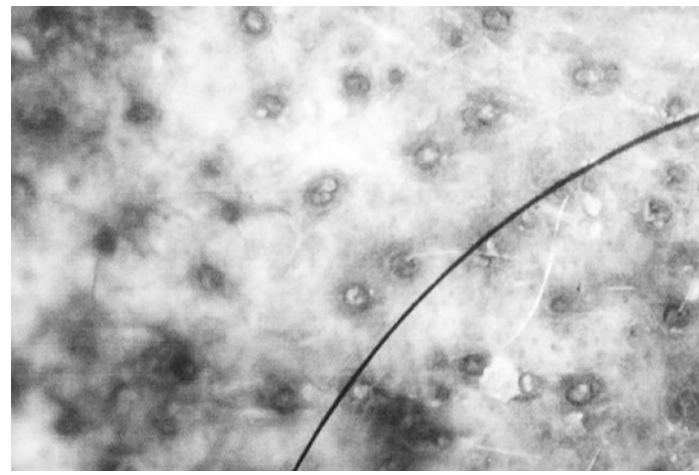

Fig. 2 Speckled perifollicular melanotic rims under Visioscan® examination

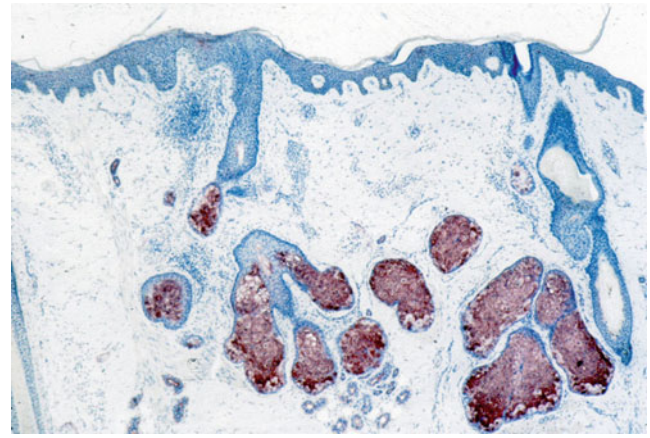

Fig. 3 Sebaceous glands highlighted by an anti-EMA (epithelial membrane antigen) antibody

specialized sites such as the eyelids and prepuce, sebaceous glands open indirectly at the skin surface via the hair follicle [8, 9]. The density of sebaceous glands differs from site to site on the body, being higher on the face and scalp followed by the back, chest, abdomen, arms, and legs. The face contains about 300–1,500 glands/cm^2, the scalp about 300–500 glands/cm^2, and other sites present 100 glands/cm^2 or less.

Three distinct types of pilosebaceous follicles are identified according to the volume of the sebaceous glands and the size of associated hairs. They are termed terminal hair follicle, vellus hair follicle, and sebaceous follicle, respectively. Terminal hair follicles are present on the scalp and beard region in men. The corresponding hair shaft is thick, and the sebaceous gland is of medium to large size reaching about 1 mm^3. Vellus hair is found over the entire body surface except on the palms, soles, and areas with terminal hair follicles. In vellus hair follicle, the hair shaft is short and thin, and the sebaceous gland is tiny when present. The sebaceous follicle is only found in humans. The gland is quite large, whereas the hair shaft is miniature and does not reach the skin surface.

The holocrine process of sebum production begins with the proliferation of basaloid undifferentiated cells located at the periphery of the acini as well as in transglandular partitioning epithelial strands. During sebocyte maturation and lipid synthesis, cells enlarge up to 150-fold in volume, and they express the epithelial membrane antigen (EMA). They move toward the ostia of the glands. Finally, the cell wall ruptures. The lipid content and the cellular remnants form the sebum that is discharged into the sebaceous duct and further to the pilosebaceous infundibulum and finally to a hair follicle opening (skin pore) [8, 9].

The pilosebaceous infundibulum forms a reservoir which commonly contains a sizable amount of sebum. The overall transit time of sebocytes takes about 2–3 weeks within the gland and a further week or so through the follicular reservoir before reaching the SC surface. The SC acts as a sponge trapping part of the sebum and eventually resorbing it [10, 11]. In these respects, the bulk of lipids present at the skin surface depends on so many variables that it does not directly reflect the metabolic events taking place in the glands themselves.

Lipid Composition of the Sebum

Skin surface lipids originate from two distinct sources, namely, the keratinizing epithelium and sebum. The composition of lipids from these two origins greatly differs. Native sebum is composed of triglycerides, wax esters, squalene, and cholesterol esters (Table 1). In mature sebocytes, vacuoles almost filling the cytoplasm contain two components that appear clearly distinct on electron microscopy. One looks opaque, cloudy, and osmium positive, probably enriched in squalene.

Table 1 Average lipid composition of sebum (%)

Component	Native sebum	Skin surface
Triglycerides	57	30–40
Wax esters	25	22–25
Squalene	15	12
Cholesterol esters	3	7
Diglycerides	0	2
Free fatty acids	0	16–25
Ceramides	0	2

The other component appears translucent and osmium-negative reflecting the presence of saturated lipids. Heparan sulfate contributes to the sebaceous gland morphogenesis [12].

Synthesis of the various components of sebum involves two different pathways including (a) squalene synthesis following the classical mevalonate and farnesyl pyrophosphate route and (b) fatty acid [13] and wax ester synthesis. Cholesterol is only present in trace amounts in native sebum because it is part of the structural compounds of the cell rather than to the sebum itself. Indeed, sebocytes do not contain the required enzymatic equipment for synthesizing cholesterol from squalene. Wax esters or squalene is generally a marker of sebum excretion helping to differentiate the sebum contribution from epidermal lipids.

Fatty acids of the triglycerides are varied, corresponding to either saturated or unsaturated compounds that are branched or not. They show straight hydrocarbon chains with even or odd numbers of carbon atoms. Wax esters contain the longest chains, with the C16 and C18 fatty acids being the most abundant.

During its transit up to the skin surface, the sebum composition is altered by oxidative processes and biodegradation partly induced by specific microorganisms [6]. Indeed, triglyceride hydrolysis by bacterial lipases gives rise to free fatty acids and mono- and diglycerides. At the skin surface, epidermal lipids are admixed with the sebum forming a spotty or continuous lipid film. In adults, the relative contribution of epidermal lipids over the SC is minimal in areas rich in sebaceous glands, although it affects the surface lipid composition on the limbs and trunk away from the midline. On the scalp and forehead, for example, epidermal lipids amount to 5–10 μg/cm^2 of the skin, whereas sebum is present at 100–700 μg/cm^2 [14].

Quantitative variations in sebum production following drug intake (e.g., retinoids, antibiotics, etc.) are likely associated with subtle changes in its molecular composition which in turn possibly alter the infundibulum cornification and be a key factor for comedogenesis.

Sebum Excretion and Spreading

Sebaceous gland dynamics involves four basic distinct and successive steps represented by sebum production (a secretion rate function), storage (a volume function), skin surface output (a delivery rate function), and SC permeation (an influx rate function). The oily appearance of the skin and hair results from an excess of sebum excretion, spreading and interacting with sweat, SC, and the hair.

On the scalp, sebum often appears as discrete droplets emerging from follicular outlets, and partly as a surface coating. The droplets are unevenly spread on the hair. In seborrheic subjects, the whole hair shaft appears to be fully coated with sebum. On the skin surface, sebum is usually accumulated in the follicular funnels from where it flows out. Sebum permeates the superficial layers of SC, but a homogenous film is only found in seborrheic subjects. Sebum migration occurs between contiguous hairs or in a swatch, due to capillary forces. After degreasing hairs, the initial refatting rate reaches about 2–3.5 mm/min.

Methods for Sebum Excretion Measurement

Subjective methods for evaluating skin and hair greasiness are available based on tactile and visual scales. Their correlation with an overall rating into five classes (very dry, dry, medium, greasy, very greasy) is convenient. These assessments are

useful for the appraisal of sebum-controlling products.

Objective measurements of the sebum excretion provide better evidence of greasy skin and hair. Over the years, a wide variety of ingenious methods have been developed for measuring the amount of sebum excreted at the skin surface and present on the hair [6]. Indeed, scalp and hair sebum amounts must be distinguished because they commonly differ. Estimating the amount of scalp sebum needs a miniature sampling method, and the hair must be shaved 24–30 h before measurement. The sebum amount present at the skin surface is conveniently measured in vivo using photometric assessment and lipid-sensitive tapes. A reproducibility of about 10 % and a sensitivity threshold in the 5 μg range of lipid amounts are usually considered to be satisfactory [6].

Sebum production and secretion are not measurable in the gland itself. In contrast, sebum excretion at the skin surface after its transit within the storage and delivery units corresponding to the infundibulum reservoir is routinely measured. Several major methods contributed over the years in the evaluation of certain parameters quantifying the sebum bulk and rheology. It should be kept in mind that components of the excreted sebum are partly trapped as any xenobiotic by the SC. Hence, part of sebum is free inside the infundibulum and at the skin surface, while another part permeates onto the SC before eventually being metabolized and further resorbed.

Photometric Method

The basic principle of the photometric method relies on the fact that opalescent glass, sapphire plate, or lipid-sensitive tapes of a given opacity to light become translucent when their surfaces are coated with lipids. The photometric procedure is time-saving and highly reproducible and does not require specially trained scientific staff.

The Sebumeter® SM810 (CK Electronic) is a device that has reached popularity [6]. Sebum is absorbed into a piece of matted plastic strip 0.1 mm thick placed on a roller which is manually rewound before each measurement. The probe is pressed under constant pressure against the skin surface. Pitfalls arise from skin microrelief and roughness impairing the close contact between the probe and the SC. After the probe has been in contact with the skin surface for 30 s, measured by an internal timer, it is placed back into the main unit of the Sebumeter®. Transparency of the plastic film is measured by a photocell linked to a microprocessor after the emitted light has passed back and forth through the strip. It is acknowledged that the measures are in good agreement with the actual amount of lipids present on the strip. In fact, it is estimated that an average of about 40 % of total skin surface lipids is absorbed with one sampling. The digital readout displayed as $\mu g/cm^2$ gives the estimated total amount of lipids on the skin. In order to get valid data, it is necessary to take several samples within a given area in order to avoid the problematic heterogeneity in sebaceous gland activity. However, the calculated amounts are possibly underestimated when seborrhea is intense due to a saturation effect of the plastic strip.

The photometric method yields a single global estimate of the casual bulk of lipids present on a given surface of the skin at one point in time. The test area is large compared to the size of the ostia of sebaceous follicles. Thus, any difference between the activities of individual sebaceous follicles remains impossible to assess through this method. A few overactive sebaceous follicles releasing a large amount of sebum contribute to a disproportionate large effect on measurements.

Sebum-Sensitive Tape Method

The method using standardized hydrophobic lipid-absorbent tapes relies on opaque, open-celled, microporous polymeric films [6, 15, 16]. It is considered as complementary to and as useful as the photometric method [6, 17, 18]. The tape material has to be affixed to the skin by gentle pressure ensuring the elimination of any air bubbles. When the sebum-sensitive tape is placed on a

skin area possibly moved by muscles, the investigator should periodically check that the uniform contact between tape and SC is maintained throughout the test.

Two proprietary tapes are currently available. One type is the regular Sebutape® (Cuderm Corp., Dallas, Texas) characterized by the presence of an adhesive coat on one side of the tape designed to adhere tightly to the SC. Such adhesive coat likely impairs the swift penetration of sebum into the tape. The other type of lipid-sensitive tape is designed to be applied for only a very short time to the skin surface without interfacing any adhesive coating. These commercially available tapes are the Instant Sebutape® (Cuderm Corp.) and the Sebufix® (CK Electronic).

Depending on the study design, the skin is prepared or not prior to the timed collection by removing sebum from the skin surface. The collection time should be determined according to the type of tape. With the regular Sebutape®, the adhesive interposed between the lipid-sensitive film and the skin is a limiting factor to the transfer of lipids. This is of importance when the rate of sebum excretion is low and/or when the duration of the test is short. On the other hand, a saturation effect occurs on regular Sebutape® when evaluating intense seborrhea during a test period beyond about 30 min. The amount of sebum collected over uninterrupted period of time is in fact lower than the addition of shorter sebum collections for a similar cumulative period of time. This is associated with confluence of sebum droplets and inaccuracy in identifying each spot as a single sebaceous follicle. These features are the main reasons why sebum samplings longer than about 30 min should be avoided when using regular Sebutape®. When using one of the uncoated sebum-sensitive tapes, a contact time of 30 s or so is appropriate.

During the procedure, each follicular outlet enriched in sebum pours out lipids which fill pores of the tape rendering it focally transparent. The size of the clear spots is proportional to the amount of sebum delivered. The number of spots reflects the number of sebum-rich follicular ostia. These parameters are conveniently evaluated by visual inspection alone. Looking at samples against a black background in reflectance mode results in a black and white pattern that can be assessed using an ordinal scale. The method allows to obtain a rough but reasonable estimate of skin greasiness without requiring sophisticated equipment.

Better quantitative assessments are achieved using computerized image analysis [16–21], which represents the most sensitive and accurate method (Fig. 4) when offering the possibility of recording the number and size of individual spots and calculating the mean and total area of spots (TAS). The free sebum content of follicular reservoir is conveniently assessed using Sebufix® tapes affixed onto a recording video camera working under ultraviolet light illumination (Visioscan VC 98®, CK Electronic). Computer-assisted image analysis provides proper readings [21]. A

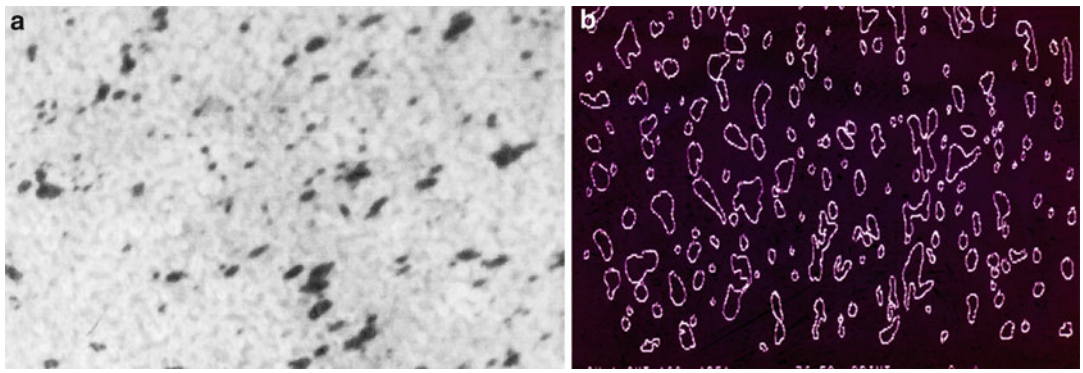

Fig. 4 Aspect of a computerized image from a lipid-sensitive tape. (**a**) The *black dots* represent the sebum output at the follicular orifices. (**b**) Higher magnification of the *dots* allowing measurements of sizes and shapes

built-in microprocessor providing such information is present in the device.

A photometric evaluation obtained by measuring the intensity of light transmitted through the samples is an alternative rapid approach [19] and is roughly equivalent to the TAS value obtained by image analysis. A variant is represented by reflectance colorimetric assessment of the samples placed against a colored background [20]. However, such overall quantitative approaches lose one of the main benefits of the lipid-absorbent tape method, namely, the evaluation of sebum excretion at single individual sebaceous follicles.

A similar quantitative method was designed aiming at collecting data any time during the tape application onto the skin [21]. The basic principle relies on the measurement of the color modifications of the tape that occur when it becomes transparent. It shifts the natural "white" color of the tape to a color closer to that of the skin itself. Reflectance colorimetry is conveniently expressed as DE*ab. The benefit of such an approach is the ability to obtain multiple measurements without removing the tape and therefore to explore a continuous reading of the kinetics of sebum output.

There are some limitations to the proper interpretation of the data. Some are specifically related to the material itself. Sebum spots are subject to changes in their size and transparency depending on storage time and temperature. At 20 °C or so, they should be evaluated at a defined time after removal, preferably within 24 h. When immediate evaluation is not possible, storage in a freezer at −30 °C is advisable.

Combined Methods

When using lipid-sensitive tapes alone, the interpretation of the number and size of lipid droplets with regard to the sebaceous glands is occasionally uncertain. In fact, it is not valid to ascribe a single follicular outlet to each spot, particularly when the latter is large. In order to solve such uncertainty, a two-step method was designed [11]. Before removing the sebum-sensitive tape from the skin, its outlines are delineated on the SC with an ink mark. In a second step, a cyanoacrylate skin surface stripping [22] using a cyanoacrylate-coated polyester film (3S-Biokit, CK Technology, Visé, Belgium) is collected from that site. The CSSS conveniently exhibits follicular casts and microcomedones [6, 8, 22, 23]. The ink marks of the outlines of sebum-sensitive film are harvested on this material. The skin surface stripping and the corresponding lipid-sensitive tape are then exactly superposed using the ink imprint as an adjusting mark. This dual material is examined under the microscope and processed in a computerized image analyzer. This method allows simultaneous assessment of the size of lipid droplets and that of the corresponding follicular ostia and microcomedones [17].

A surrogate method relies on examination using a video camera working under ultraviolet light illumination (Visioscan VC98®, CK Electronic). A frame designed to precisely attach and locate the camera is first affixed onto the test site. The aspect of the skin surface and follicular outlets is recorded. In a second step, a Sebufix® is interposed between the SC and the camera. The picture of lipid droplets is recorded after a 45-s collection. The comparison of both pictures identifies sebum-poor and sebum-rich follicles [21, 23].

Quantitative Parameters of Sebum Excretion

The various sampling procedures of sebum provide information about a series of specific parameters. As a rule, the values obtained for these parameters commonly differ among subjects by a tenfold coefficient, but each value is a representative of a given subject in a precise environment.

Sebum Casual Level

Sebum casual level (CL) is defined as the lipid amount present at equilibrium when the skin surface remains untouched for several hours. It is a

global estimate of skin greasiness. For practical reasons, most researchers record CL generally after a 4-h lag time following uncontrolled removal of the sebum film from the skin surface. It is expected but uncertain that such CL measurement reflects a plateau value. CL is not recommended as a single parameter for in-depth studies of the sebaceous system. Therefore, CL is believed to represent a rough estimate of a constant value for each normal adult. In contrast, interindividual variations are large as shown by CL ranging from 100 to 700 μg/cm^2 on the forehead of healthy subjects. Similar wide variations are found on the scalp.

Sebum Excretion Rate

Sebum excretion rate (SER) refers to the amount of sebum excreted on a given skin area during a defined period of time [6]. The duration of the collection period is important because SER progressively decreases over the first hours after degreasing the skin. SER of the first hour sampling from the forehead usually ranges from 0.5 to 2.5 μg/cm^2/min. On the scalp, it varies from 0.1 to 0.8 μg/cm^2/min. TAS values yielded by the lipid-sensitive tape method represent a surrogate of SER evaluations.

SER is expected to be roughly correlated with CL. A linear relationship is commonly yielded between four successive 1-h SER and TAS measurements at least in the medium range of severity of seborrhea. The correlation is lost when the sebum output is either very low or quite high. This finding indicates that these parameters are related to the delivery of the pool of sebum already secreted by the gland and stored in the sebum reservoir corresponding to the distal portion of pilosebaceous duct. Thus, it is clear that an initial 3–4-h collection is a measurement of sebum excretion rather than sebum secretion.

Sebum Replacement Time

Sebum replacement time appears to be a cumbersome parameter difficult to manage. It refers to the expected time duration needed to recover CL after sebum removal from the skin surface. It has been reported to take about 4 h in subjects with sebum excretion in the medium range.

Density in Sebum-Enriched Reservoirs

The number of spots over a lipid-sensitive tape is a rough indicator of the density of follicular reservoirs enriched in sebum. Such a figure is usually lower than the number of sebaceous glands present on that area of the skin. This information can be confirmed by staining CSSS for lipids. The sebum delivery at a given follicular ostium represents a clue for the presence of an actively secreting sebaceous gland. It occasionally represents the site of a follicular reservoir passively filled by the sebum coming from the skin surface. It is clear using the combination of lipid-sensitive tape and CSSS that many follicular ostia neither store sebum nor represent a route for sebum outflow. It is also possible that one single droplet corresponds to a merging of several smaller ones. The size of the follicular outlet at the skin surface is not correlated with the presence or absence of sebum [17].

Instant Sebum Delivery

SER and TAS decrease almost linearly during the initial hours of collection time. Calculating the regression line for the cumulative data at hourly intervals allows to extrapolate a theoretical value for instant sebum delivery (ISD) at T0. This parameter supposedly reflects the spontaneous leakage of free sebum from the follicular reservoirs. ISD is not always correlated with SER. Information similar to ISD is provided by the Sebufix® tape applied to the skin for a few seconds.

Follicular Excretion Rate

The slope of the above-mentioned regression line between cumulative TAS over time has been coined follicular excretion rate (FER). It is a

measure of the delivery rate of sebum from the follicular reservoirs. FER is frequently related to the first hour TAS value, although physiological influences and some topical compounds interfere with such a relationship.

Factors Affecting Sebum Excretion

Physicochemical Regulation

SER and FER are influenced by the physicochemical characteristics of sebum. Environmental and skin temperatures and the balance between the sebum molecular components affect the viscosity and rheology of lipids at the skin surface [24]. This could explain in part some chronobiological variations in SER and FER including seasonal fluctuations [25–27] as well as the influence of the ovarian cycle [28, 29] and perhaps other chronobiological rhythms of unknown periodicity. A circadian rhythm has been suggested for sebum output being optimal in the midmorning and minimal during late evening and early morning hours [29].

The width of follicular ostium greatly influences sebum rheology. There is an inverse relationship between the fluid flux and the fourth power of the radius of the tube in which the fluid passes through. Hence, variations in corneocyte accumulation and swelling at the lips of follicular outlets, occurring during the ovarian cycle or after occlusion, probably influence sebum rheology [28, 29].

Skin surface energy phenomena result from molecular interactions. They are involved in sebum and sweat dispersion. Sweating is indeed an important confounding factor in rating sebum excretion. Even in dry-skinned subjects, intensive or continuous sweating increases the CL. The sebum of seborrheic subjects appears as an oily and homogeneous fluid barely emulsified with water at ordinary temperatures. However, in some instances, it can be emulsified with sweat though it generally takes several hours.

The theory of a continuous sebum excretion is opposed to the concept of a discontinuous excretion with a feedback control by the CL. SER appears to decline progressively as CL returns to its initial value. This observation supported the hypothesis of a feedback mechanism controlling sebaceous excretion by the lipid film developed on the skin surface. This concept was further strengthened by the fact that the amounts of sebum collected at constant time intervals seem to increase with the number of degreasing procedures. Sebum excretion stops spontaneously even in highly seborrheic subjects if the area, although isolated, remains uncovered. However, the plateau effect in excretion kinetics is only apparent and due to the sebum spreading over a larger surface or to its permeation into the upper layers of the SC. It is concluded that the initial phase of sebaceous secretion is likely continuous or fluctuating as a result of the combination of chronobiological rhythms. Any feedback mechanism from CL could only affect the sebum excretion thus modifying sebum storage rather than sebum production.

Shampoos dedicated to greasy hair are commonly used as sebum-controlling products for the scalp. Some chitosan-derived molecules hinder sebum coating of the hair shaft. Particles of dry shampoos adhere to the hair, retain lipids, and exert electrostatic forces repulsing the hair shafts. Frequent regular shampoos do not appear to increase the sebum output on the scalp and do not influence the sebum coating of the hair. By contrast, cationic polymers and silicone oils used in some shampoos facilitate sebum spreading. Regreasing studies on the scalp and hair show general differences according to the level of greasiness. Hair sebum amount is typically lower than the accumulation of scalp sebum. Scalp CL recovers completely after 1–4 days following hair washing, at least for greasy hair types [30], and the aspect remains fairly constant in the following days. Scalp SER has been reported to progressively increase until 24 h after shampooing when it reaches its maximum value.

Hormonal Regulation

The human skin, in particular the sebaceous glands, receives, produces, and coordinates hormone activation and inactivation through various

molecular signals. The involved physiological mechanisms belong to the endocrine, paracrine, juxtacrine, autocrine, and intracrine hormonal repertoire.

Free testosterone and 3α-dihydrotestosterone (DHT) are considered to exert a major boosting and dose-related effect on sebocyte proliferation and sebum secretion in man [31]. The levels of type 1 isoform of 5α-reductase are significantly higher in sebaceous glands than in other skin structures [31, 32]. Cells of the infundibulum are also reported to be sensitive to the same hormones. In women, the most important androgen is Δ^4-androstenedione, which is produced by adrenal gland and ovaries. It is possibly converted into testosterone, but it has some intrinsic androgenic activity. The 5α-androstane-3β, 17β-diol compound is a potent androgen and is the main metabolite of testosterone in the back and scalp skin. Other androgen precursors of purely adrenal origin such as dehydroepiandrosterone (DHEA) explain sebaceous development in the fetus, in the newborn, and in the prepubertal years [33]. DHEA is converted into androstenedione and testosterone inside the sebocytes. By contrast, conversion of DHEA sulfate to DHEA only occurs with the assistance of monocytes exhibiting steroid sulfatase activity. The amount of circulating androgens is important to consider. However, the local production of sexual steroids provides autonomous control adjusting sexual steroid metabolism according to the body area. Facial and scalp sebocytes are particularly involved in this mechanism.

The glucocorticoid receptor is another nuclear steroid receptor present in sebocytes. Glucocorticoids have been reported to stimulate sebocyte proliferation [31].

The second group of nuclear receptors, namely, the thyroid receptor family, encompasses different soluble receptors in sebocytes. They correspond to the thyroid hormone receptor isotype β1, the estrogen receptor β, the retinoic acid receptor (RAR) isotypes α and γ, retinoid X receptor (RXR) isotypes α, β, and γ, and the peroxisome proliferator-related receptor (PPAR) isotypes α, δ, and γ. PPAR ligands augment the androgen stimulation of sebocyte differentiation [34].

Estrogens exert the opposite effect of androgens but with a much weaker potency. However, any decrease in size and excretion of sebaceous glands is only achieved with high doses of estrogens that are nonphysiological in women and feminizing in men. It is thus unlikely that normal estrogen levels play any role in inhibiting sebaceous gland activity. Following estrogen suppression, administration of testosterone restores sebum secretion. Estrogens at sebum-suppressive doses have been shown to reduce plasma and urine levels of testosterone. They also inhibit gonadotropin-releasing hormone synthesis and 5α-reductase activity.

There is no established relationship between the growth rate of vellus hairs and sebum excretion. By contrast, the intensity of seborrhea and severity of evolving androgenic alopecia are often related. In this condition, GH and IGF-1 might play a role.

Neuropeptide Regulation

A neurovegetative nerve plexus surrounds the sebaceous gland, but acetylcholine and adrenaline do not seem to influence sebum secretion. Sympathectomy has no effect on the level of surface lipids. A localized neurological lesion conversely induces seborrhea in the involved site. Several types of neuropeptide receptors are present in sebocytes. They include the μ-opiate receptor which binds β-endorphin, the vasoactive intestinal polypeptide (VIP) receptor, the neuropeptide Y receptor, and the calcitonin gene-related peptide (CGRP) receptor.

Psychotropic drugs, often dopamine inhibitors, increase sebaceous secretion considerably. The same observation is present in Parkinson's disease [35] perhaps due to high α-MSH serum levels. During treatment with levodopa, seborrhea decreases, although the drug is inactive on sebaceous excretion in normal subjects.

Ethnic, Gender, and Age Effects

Some specific attributes related to sebum excretion have been ascribed to ethnic groups [36]. Such observation awaits for confirmation.

As a consequence of the diversity of hormonal signals, sebum excretion varies according to age, gender, and the perimenopausal period [37–39]. At any given age in men and women, both sebum excretion and secretion rates differ between individuals over a wide range. In addition, there is a huge overlap between data gained in both genders. Hence, it is not the amount of circulating androgens, but rather the receptivity of the target tissues that accounts for interindividual differences in sebum excretion. It is clear that other additional factors are likely to be involved.

SER and FER values remain high in men until the eighth decade. In women the rates remain unchanged until menopause. During the perimenopausal period, seborrhea either increases or steadily decreases with age. Using the lipid-sensitive tapes, it is possible to distinguish distinct patterns according to age and physiopathological conditions [36]. The size of follicular reservoirs and pores shows no tendency to shrink with age.

A series of endocrine imbalances and a few drug treatments aiming or not at direct or indirect hormonal effects affect the activity of sebaceous apparatus. The most potent inhibitor of sebum excretion is the synthetic retinoid 13-*cis*-retinoic acid or isotretinoin, which at oral doses of 0.1–1 mg/kg/day inhibits sebum production by up to 80 % within 6–8 weeks. Isotretinoin reduces cell renewal and lipid formation in the sebaceous gland. Isotretinoin reduces not only SER but also the follicular reservoir, and both remain significantly suppressed for up to 1 year after therapy. Topical products are far less potent although of cosmetic interest [40, 41].

Conclusions

The current knowledge of sebaceous gland physiology and sebum rheology on the glabrous skin, scalp, and hair shaft has made some progress, leading to the introduction of new antiseborrheic agents. This breakthrough was made possible through the development of qualitative and quantitative methods for measuring the amounts of excreted sebum and evaluating its lipid composition.

Seborrhea on the scalp and forehead possibly represents a single phenomenon or be part of a more complex system of multiple disturbances. As an interesting index of neuroendocrine physiology, it plays an increasing role in the understanding of biology, mainly due to the reliability of its measurement.

The sebum flow is altered with aging. In any study in this field, ethnicity, age range, gender, adequate skin profile, and test area on the body must be appropriate for a relevant design. The environmental conditions including seasons, relative humidity, and temperature should be controlled. In addition, skin temperature affects sebum rheology. A number of other physiological parameters modulate sebum excretion, and some of them are responsible for chronobiological variations. Despite clever experimental designs, it should be stressed that panelists, subjective perceptions, clinical gradings, and biometrological measurements are not always matched.

Several objective methods have been devised for measuring the greasiness of skin, most of which involve the collection of sebum once it runs off the sebaceous apparatus. Preconditioning the skin by prior removal of sebum from the skin surface is a common procedure. Part of the sebum present inside the follicular reservoir is potentially ignored by measurements. Uncontrolled depletion of the sebum pool impedes collection of reliable data.

Conceptually, aging of the sebum production in women begins in the perimenopausal period after menopause. It is obvious in men well after entering the andropause period. In both genders, the early changes are often erratic, and they progressively evolve to a reduction of the sebum flow.

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