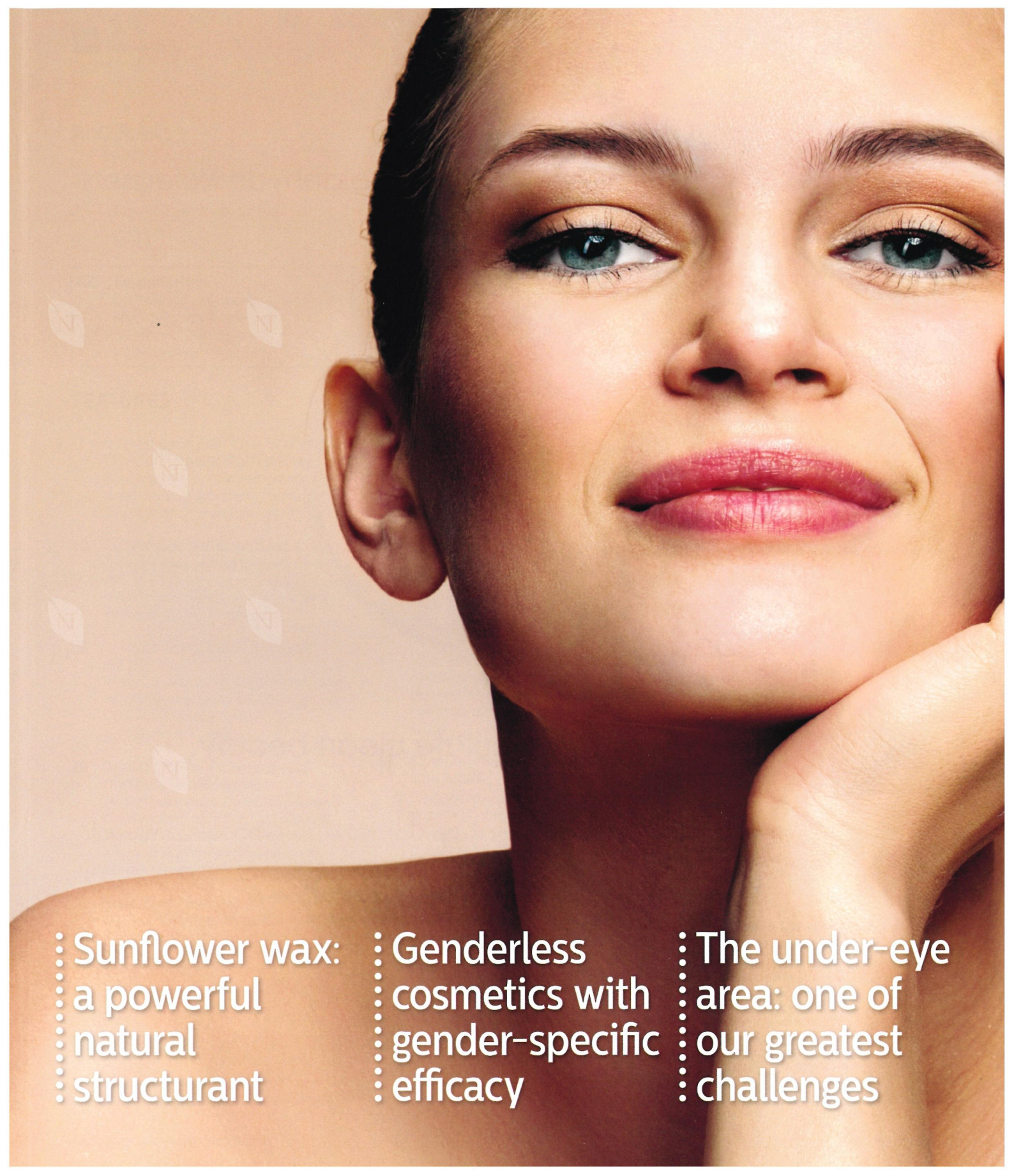


March 2021

GLOBAL

# PERSONAL CARE

INGREDIENTS • FORMULATION • MANUFACTURE



: Sunflower wax:  
: a powerful  
: natural  
: structurant

: Genderless  
: cosmetics with  
: gender-specific  
: efficacy

: The under-eye  
: area: one of  
: our greatest  
: challenges



# Genderless cosmetics with gender-specific efficacy

Emina Besic Gyenge, Stefan Hettwer, Brigit Suter, Barbara Obermayer – RAHN AG, Switzerland

Besides obvious gender differences in terms of anatomy, there are also certain gender-related variations in skin physiology. Studies have shown that levels of skin parameters such as hydration, sebum, skin pigmentation, and thickness are in general higher in men while rates of transepidermal water loss are higher in women.<sup>1</sup>

Skin is individual, not only when it comes to gender and age, but for each of us. Knowledge of physiological, chemical, and biophysical skin differences can help the cosmetic industry develop tailored cosmetic formulations. One non-gender-related common denominator that determines skin health, independent of gender, age, genetics or environment, is effective intracellular cleaning, the process known as autophagy.

Intracellular accumulation of damaged molecules, dysfunctional organelles and other impaired cellular components causes cellular ageing and dysfunction (garb'ageing). Keratinocytes and fibroblasts, the most important skin cells, lose their functional identity and this in turn is reflected in impairment of the skin barrier and a loss of firmness and elasticity of the skin. The maintenance of properly functioning autophagy in skin cells is therefore an effective strategy against garb'ageing. Chronological ageing and an unhealthy lifestyle are known factors that inhibit autophagy (Fig 1).

The presence of intracellular waste changes the structural organisation of the cells and it impedes cell signalling, transportation and metabolic

functions. Impaired skin homeostasis, shortened cellular lifespan, senescence and an insufficient energy supply are only a few of the cellular consequences. It can thus be assumed that stimulation of autophagy would be an excellent means of slowing ageing and would help detox the skin. Stimulation of autophagy in general and in skin can be achieved by exposure to metabolic stress, such as starvation, infection or high ROS levels. Intermittent fasting has recently come to enjoy increasing popularity in the fitness, beauty and wellness world. Evidently, extended fasting will activate autophagy. Likewise, physical activity also counteracts garb'ageing – unsurprisingly, couch potatoes age faster than active individuals, at least at the cellular level. However, a much more suitable approach in terms of a cosmetic treatment would be of course to use an active ingredient that would trigger the cellular waste management process.

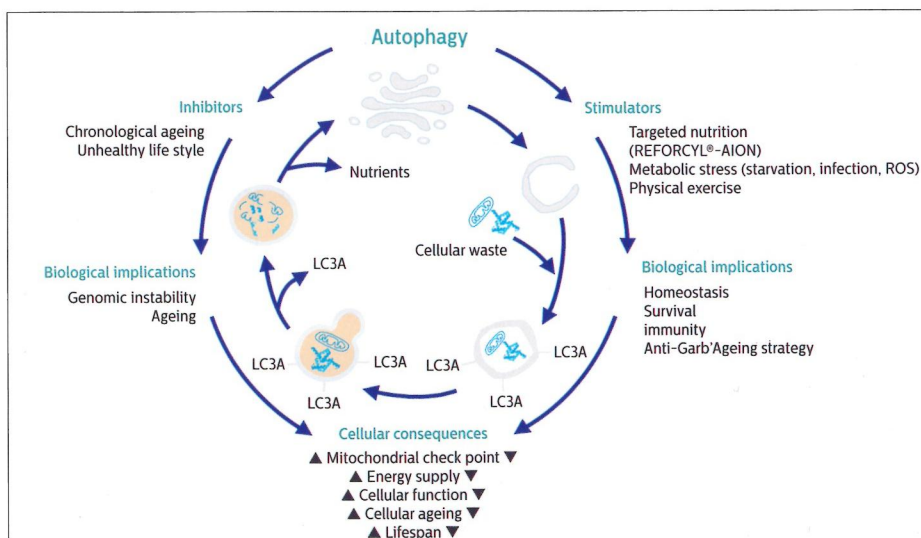
Reforcyl®-Aion's (INCI: Propanediol, Water, Cucurbita Pepo (Pumpkin) Seed Extract, Citric Acid) powerful ingredients (amino acids and saccharides - including sucrose and spermidine/spermine) are able to induce autophagy, supply the cells with optimal nutrition and rejuvenate and detox cells from within. Furthermore, it ensures that the process runs smoothly. Thus, there is not only measurable alleviation of undesirable effects such as a weakened skin barrier, poor hydration, loss of firmness and elasticity, but the results are visibly perceptible. As a preventive measure, it is

## ABSTRACT

Unisex was yesterday's trend - genderless beauty is here to stay. The definition of gender has become very fluid. It now goes beyond simply 'male' and 'female', taking the form of a desire for acceptance and empowerment in one's own person. Man, woman, transgender and those who fall under any other definitions of gender should be able not only to share fashion but also their lotions and potions. From the consumers' point of view, this makes cosmetics more practical and sustainable. Nevertheless, genderless cosmetics should not be defined in terms of non-binary fragrances but rather by their mode of action, which should adapt to the respective needs of various skin types.

However, where to start? Can genderless skin care truly cater to the distinct needs of male and female skin? Are there differences between male and female skin?

With this in view, our approach has been to develop Reforcyl®-Aion, an active ingredient with the capability to spring clean skin cells, activating and rejuvenating them, improving overall skin appearance and positively influencing the personal perception of beauty. Reforcyl®-Aion meets the individual needs of skin regardless of gender or age.



**Figure 1:** The basic elements of autophagy at a glance. Diagrammatic representation of the most important molecular pathways and factors that stimulate and inhibit autophagy.

advisable to start using such cosmetic formulations at a younger age. Nevertheless, the older one gets, the more important it becomes to employ these. Cellular garbage hoarding increases significantly with advanced age, while at the same time cellular activity and autophagy processes decline, causing unwanted skin deterioration. Safe triggering of autophagy seems to be the ideal anti-ageing and anti-garb'ageing approach. Reforcyl®-Aion helps cells to remember how to let go of unnecessary ballast and - even better - it creatively reuses unwanted and burdensome cellular material.

## Materials and methods

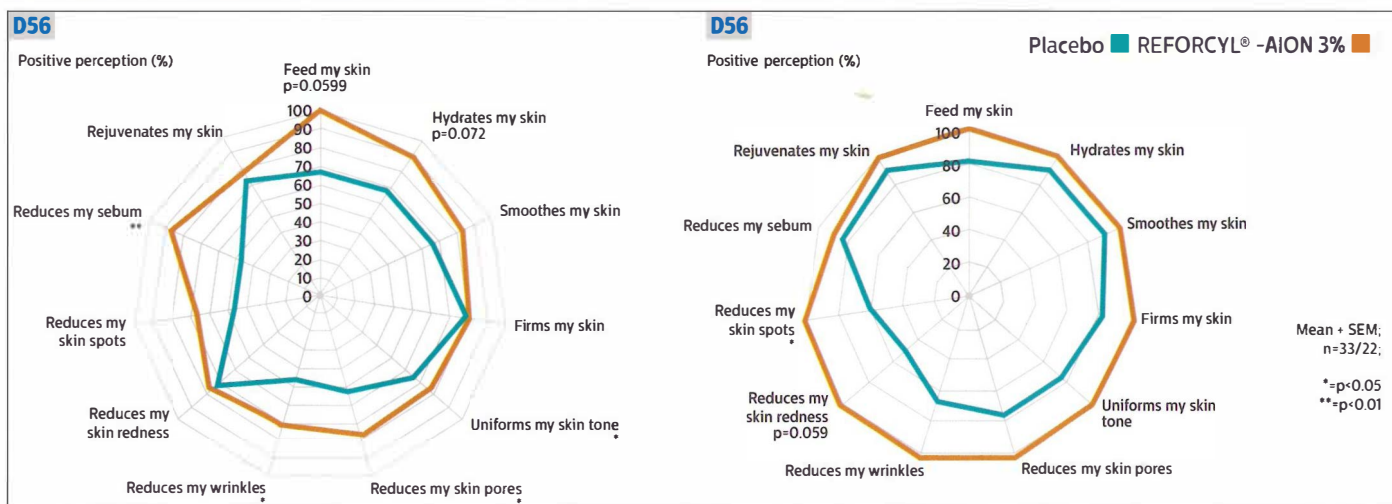
### Subjective perception and measured parameters

Our *in-vivo* study was performed in accordance with the principles of good laboratory practice (GLP), good clinical practice (GCP) and in compliance with the quality assurance system requirements. The study was also conducted in



## SUBJECTIVE PERCEPTION OF DIFFERENT SKIN CONDITIONS (FEMALE)

## SUBJECTIVE PERCEPTION OF DIFFERENT SKIN CONDITIONS (MALE)



**Figure 2:** Subjective perception by female and male subjects of various skin parameters after 56 days of topical application of 3% *Cucurbita pepo var. styriaca* extract or placebo.

accordance with the World Medical Association ethical principles defined in the Declaration of Helsinki. All study participants provided their written informed consent at the beginning of the study.

The effect that autophagy activation has on skin appearance was investigated in 55 subjects (female and male) with healthy, Caucasian skin aged 50 – 65 years.

In this study, personal perception together with photographic documentation (Visioscan), skin hydration, skin firmness and elasticity, skin desquamation, transepidermal water loss (TEWL), and skin sebum were assessed. Half of the subjects applied placebo while the other half applied the identical formulation containing 3% Reforcyl-Aion; all subjects used the corresponding preparations twice daily for 56 days. The Likert scale was employed for the subjective efficacy questionnaire. It was assumed that high scores equated to the subject being 'satisfied' with the results.

#### Statistics

All recorded parameters were subjected to unpaired Student's t-tests. The statistical values in black are the result of comparison with baseline status while the blue values are the result of comparison with placebo or vehicle control.

## Results and discussion

### Subjective perception

Female volunteers were selected so that their ages reflected that of the general average age at which there is onset of the menopause. Since the male andropause is not so well defined, we decided to select male panellists in the same age range as the females. The average age of females was 56.8 and that of males was 56.1 years. Assessed were eleven different skin parameters. The results were evaluated using a standard gender-specific approach (male and female) (Fig 2).

Personal perception is extremely important with regard to cosmetics. Our data show that our female and male subjects had differing perceptions of the results of placebo and verum treatment. Furthermore, it is also apparent that the females tended to have much more

differentiated opinions and even higher expectations in terms of each skin parameter, while the males were probably less 'trained/educated' in this respect. The male volunteers who used the 3% verum formulation were 100% satisfied in all but one parameter – 'sebum regulation'. Even so, 90% of male users reported positive impressions. The placebo volunteers were in general much less satisfied, irrespective of gender. Female users had, as said above, a much more differentiated view of effects on their skin. Despite this, in this context verum outperformed placebo in all parameters under investigation. It should be noted that 100% of volunteers reported that the nourishment of their skin was enhanced; at the same time, 90% were satisfied with skin hydration, while pore reduction, skin tone, sebum and wrinkle appearance were perceived as significantly improved.

*Cucurbita pepo var. styriaca* extract or better said its mode of action – autophagy activation – represents a factor that positively influences skin physiology across all individuals in common, whether female or male. Reactivation of the cellular self-cleaning process improves several skin parameters in parallel and leads to an overall improvement in skin appearance in women and men.

### Epidermal effects

Autophagy in the epidermis plays a dual role in skin barrier homeostasis. Firstly, long-lived and mostly quiescent stem cells require autophagy for intracellular homeostasis and for maintenance of their ability to supply functional progeny cells.<sup>2</sup> When all their metabolic activity in the stratum granulosum ceases, cells lose their organelles including the nucleus through autophagy, extrude lipids and proteins onto the cornified envelope scaffold, and this effectively seals the skin.<sup>3</sup> Finally, these layers of dead cells are shed off the surface and replaced by new cells. Holocrine secretion of sebum employs the same pathway and requires autophagy to function properly.

Desquamation levels increase with age in individuals of both genders due to the weaker adherence of corneocytes. But in general males

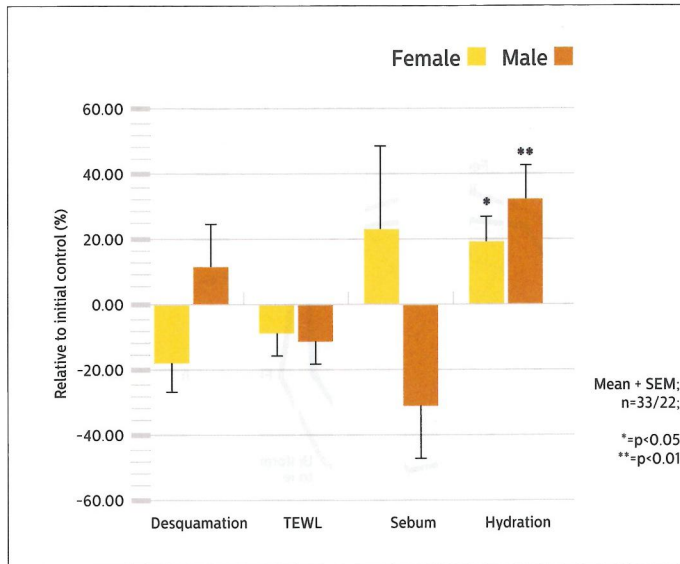
have a higher desquamation rate, suggesting that gender-specific hormonal factors probably influence this physiological phenomenon as well. Furthermore, older females tend to have higher desquamation rates in comparison with younger females, something that is not observable in males. This can also be explained by hormonal factors, especially those associated with the menopause.<sup>4,5</sup>

In our study, we were able to observe a gender-specific mode of action. Treatment with 3% verum decreased desquamation in females by up to 16% after 28 days, while desquamation in the males was increased by almost 25% (data not shown). By day 56, there was a decrease in female levels of up to 18% while in the males, the increase fell back slightly to 11% (Fig 3).

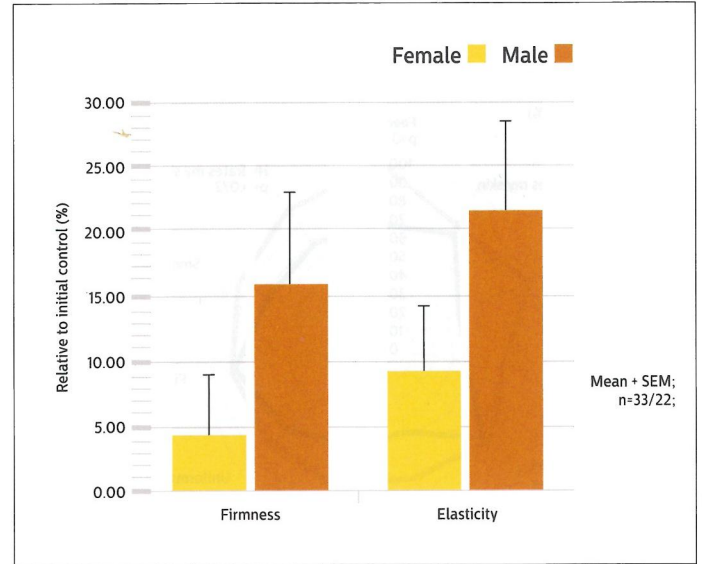
These results corresponded with the effects on levels of transepidermal water loss (TEWL) and sebum secretion. In general, alterations to the skin barrier and TEWL have been shown to correlate with skin ageing. An increase in TEWL indicates an impaired barrier function. Furthermore, TEWL is significantly lower in males than in females regardless of their age. In addition, TEWL is higher in post-menopausal females in comparison with those prior to the menopause.<sup>1</sup>

The results of measurement of TEWL showed that 3% verum treatment in females decreased TEWL by almost 15% after 28 days (data not shown) and by 10% after 56 days (Fig 3). These data indicate improvements to the skin barrier and are consistent with decreased skin desquamation. In the males, an initial increase of 11% was observed, which had decreased over 20% in total by day 56 (Fig 3). This suggests restructuring/reorganisation of the skin barrier.

Treatment with 3% verum resulted in gender-specific sebum regulation. In the females, sebum production increased by 23% in comparison with baseline, while in males, who in general have a greasier skin, sebum production decreased by almost 32% after 56 days of use (Fig 3). Placebo induced a sebum decrease in both gender groups; in women by up to 30% after 56 days (data not shown). Regulation of sebum helps improve the overall appearance of the skin and contributes



**Figure 3:** Epidermal skin parameter changes in females and males after 56 days use of 3% *Cucurbita pepo var. styriaca* extract.



**Figure 4:** Dermal skin parameter in females and males after 56 days of use of 3% *Cucurbita pepo var. styriaca* extract.

to an individual's satisfaction with their skin and general appearance.

Skin moisturisation is very important, especially in the meno- and andro-pausal life phases. Women experience a sudden drop in hormonal activity and suffer from dry skin, requiring special care in this period. From our data recorded for perception, we know that around 90% of our females and 100% of our males felt they had a more hydrated and nourished skin.

Measurements of hydration (Fig 3) revealed that hydration in women after 56 days use of 3% verum was increased by about 20% on average, while in the men the corresponding increase was greater than 30%. Placebo treatment resulted in a minor improvement of about 10% in both gender groups (data not shown). Differences between female and male skin hydration are due to the differences in stratum corneum thickness.<sup>1</sup> Men have in general a thicker stratum corneum resulting in a greater moisturisation effect. If we consider the results for subjective perception (Fig 2) and results of measurement, we can conclude that our panellists were able to feel and see the moisturisation effect irrespective of their gender.

### Dermal effects

During ageing, the dermis undergoes significant changes. The production of collagen and elastin decreases and degradation increases, leading to an overall reduction in collagen levels. This in turn hinders the mechanical interaction between fibroblasts and the ECM, and consequently leads to the deterioration of fibroblast function and further decreases in concentrations of dermal collagen and elastin. Furthermore, collagen fibres become thicker while bundles are disorganised. The numbers of cross-links between collagen increase, making the skin stiffer. Elastin is calcified and its turnover decreased. The associated deterioration of the dermis is characterised by the development of deep wrinkles and skin laxity.<sup>6</sup> This is due to the sudden hormonal changes that are more pronounced in women than in men. Various scientific studies have reported that the male dermis is 10-20% thicker than in the case of females.<sup>7</sup> Nevertheless, roughly

6% deterioration occurs in both sexes per life decade. Studies also report that women have a slightly better skin elasticity than men. Female skin is less distensible but has a greater ability to recover after stretching in comparison with male skin. This is due to the different orientation of the connective tissue. In females, the orientation of connective tissue is longitudinal; in males, there is diagonal intersection. This gender-dependent orientation of fascial bands, as one would expect, is particularly relevant when it comes to pregnancy in females.

According to our results, firmness and elasticity were improved to differing extents in both gender groups (Fig 4). In female panellists we observed an improvement in firmness by more than 4% in the verum group while there was a slight decrease in the placebo group (data not shown). Results of measurement of elasticity in the females were slightly improved in both treatment groups, demonstrating that autophagy-counteracting hormonal changes to this dermal parameter were not of particular relevance in the females. Nevertheless, a positive effect was still recorded. This finding goes hand in hand with the subjective perception of effects on skin firmness (Fig 2).

Male panellists showed an improvement of 15% in terms of firmness and 20% in terms of elasticity. Interestingly, results for both parameters in the men showed that mechanical stimulus initially played an important role in fibroblast stimulation. There were also significant improvements with use of placebo, but these completely disappeared following an additional 28 days of use while the effect in the verum group was maintained (data not shown).

### Conclusions

To tailor genderless skin care with gender-specific efficacy it is necessary to have extensive insights into skin physiology. Male and female skin have different skin physiology and, on top of that, they age differently. High life expectancy gives us an additional stage of life - a privilege that must be taken advantage of. Still, reaching post-menopause and -andropause brings some dramatic changes to our bodies, especially our

skin. Men begin to lose the beloved muscle mass they have built up over the years, which inevitably leads to sagging skin. Therefore, increased firmness and elasticity is one of the best things to achieve to counteract this. For women, this stage of life brings once again the rediscovery of the self, not only of the exterior, but also of the interior.

Reforcyl®-Aion activates autophagy, the ultimate upcycling and cleansing process for ageing cells, irrespective of gender. Autophagy not only cleans cells, but actively helps keratinocytes and fibroblasts regain their functional identity and improve the skin barrier, while there are also increases in collagen and elastin concentrations in the dermis. Improved skin hydration together with an increased skin thickness are the results. Gender-specific regulation of sebum completes the effect of an improved overall skin appearance. Reforcyl®-Aion is not only able to induce autophagy, but also provides the skin with healthy nutrition in the form of a rich cocktail of amino acids, proteins and saccharides. **PC**

### References

- 1 Rahrovan S, et al. Male versus female skin: What dermatologists and cosmeticians should know. *Int J Womens Dermatol* 2018; 4(3): p. 122-130.
- 2 Eckhart T, Tschachler E, Gruber F. Autophagic Control of Skin Aging. *Front Cell Dev Biol* 2019; 7: 143.
- 3 Koenig U, et al. Cell death induced autophagy contributes to terminal differentiation of skin and skin appendages. *Autophagy*, 2020. 16(5): 932-945.
- 4 Chaluk NE, et al. Morphological Characteristics of Residual Skin Surface Components Collected from the Surface of Facial Skin in Women of Different Age. *Ann Dermatol* 2017; 29(4): 454-461.
- 5 Harding CR, et al. Dry skin, moisturization and corneodesmolysis. *Int J Cosmet Sci* 2000; 22(1): 21-52.
- 6 Shin JW, et al. Molecular Mechanisms of Dermal Aging and Antiaging Approaches. *Int J Mol Sci* 2019; 20(9).
- 7 Branchet MC, et al., Skin thickness changes in normal aging skin. *Gerontology*, 1990; 36(1): 28-35.