patients achieving PASI 90, PASI < 3 and PASI 100 responses in the ixekizumab group. At week 48, a statistically significant difference in achieving PASI 90, PASI < 3 and PASI 100 response (100%, 100% and 75% of patients treated with ixekizumab achieved PASI 90, PASI < 3 and PASI 100, vs. 31%, 46% and 23% of patients treated with secukinumab respectively) was observed ($P = 0.01$; Fig. 1a). As for the EP group, it was not possible to confirm the efficacy of ixekizumab as previously reported[5]; on the other hand, secukinumab showed considerable efficacy, as 82% and 54% of patients achieved PASI 90 and PASI 100 at week 48 respectively (Fig. 1b). Regarding drug survival, in the PP group, most patients did not discontinue treatment during follow-up (Fig. 1c); in the EP group, statistically significant better results were achieved in the secukinumab group (Fig. 1d). Both treatments showed a reliable safety profile, with only one case of injection site reaction in an ixekizumab-treated PP patient. As EP and PP represent two uncommon subtypes of psoriasis, the small sample size collected could explain the overall low statistical power of our study. According to our data, secukinumab showed a lower efficacy in PP compared to data previously reported by Imafuku et al.[6] In contrast, for ixekizumab, PASI 90 and PASI 100 response rates at week 48 were higher than data reported in the UNCOVER-J trial.[5] As for the EP group, 83% of patients treated with secukinumab achieved a PASI 90 response by week 24 and this percentage is higher than what Weng et al.[7] previously described (PASI 90 at 24 of 30%). Although ixekizumab shows higher affinity for IL-17A – suggested to be the dominant cytokine in EP development – compared with secukinumab,[8,9] our patients treated with secukinumab displayed a better clinical response. In this regards, future studies are needed to unravel the mechanisms responsible for this occurrence. In conclusion, this study confirms the efficacy and safety of IL-17 inhibitors in PP and EP patients.

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The patients in this manuscript have given written informed consent to publication of their case details.

Conflicts of interest

The authors report no conflict of interest.

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All authors have contributed significantly to this publication.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Influence of menopause and hormone replacement therapy on epidermal ageing and skin biomechanical function

Dear Editor,

Skin ageing is accelerated during menopause; however, many women and healthcare professionals are insufficiently informed on the impact of menopause on skin.[1] Declining oestrogen detrimentally impacts the skin's extracellular matrix (ECM),

which provides strength, elasticity and resilience.[2] The relationship between dermal structural changes and altered skin function has been demonstrated by measuring the biomechanical properties of young, aged and photoaged skin in parallel with histological analyses.[3] Oestrogen levels also influence skin hydration, vascularity and pigmentation[4] and women report a greater incidence of skin dryness and sensitivity in relation to the menstrual cycle and menopause.[5,6] However, the specific biological mechanisms underlying these observations are poorly understood, as are the respective contributions of epidermal and dermal changes to skin biomechanics. Therefore, we explored how menopause and hormone replacement therapy (HRT) affect markers of epidermal and dermal ageing in relation to skin structure and biomechanical function, with a view to identifying targets for improvement of skin health at mid-life. Pre-menopausal women (Pre; $n = 7$), post-menopausal women, with (HRT; $n = 10$) and without HRT (Post; $n = 11$), and a group of age-matched men ($n = 29$) were recruited to the study. Menopausal status was self-reported and confirmed by serum oestrogen and follicle stimulating hormone levels. Skin structure was assessed via histological analyses of dermal ECM components (fibrillin, elastin, fibulin and collagen) in our female cohorts, which found few differences between groups, although total elastic fibre abundance was increased in the HRT vs. Post group ($P < 0.01$; /Fig. 1a). Epidermal thickness was reduced and *stratum corneum* (SC) thickness increased (Fig. 1b) in the Post vs. Pre group ($P < 0.05$), while SC thickness was partially normalised in the HRT group ($P < 0.05$ vs. Post group), supporting regulation of epidermal homeostasis and desquamation by female sex hormones. Cutometry was performed to assess skin biomechanical properties; in the Post group, total skin deformation (R0) was significantly reduced (Fig. 2a) when compared to the Pre group ($P < 0.05$), indicating a general reduction in elasticity. Increased viscoelastic/elastic ratio (R6) was found in the Post group vs. the Pre group (1.2-fold, $P < 0.01$; Fig. 1a) indicating extended stretch or creep following initial elastic deformation, and this again, was partially abrogated by HRT (~10% lower; $P < 0.05$ vs. Post group). No differences in other elastic parameters were found. Higher R6 correlated with lower serum oestrogen (Fig. 2c) and higher age (Fig. 2b) in women, but no correlation with age was found in men (Fig. 2b), suggesting skin viscoelasticity is specifically influenced by female hormonal ageing. In support of our findings, skin extensibility in peri-menopausal women has been found previously to increase whilst elasticity decreased, with some prevention by hormone replacement therapies.[7,8] No group differences in epidermal or dermal micromechanical stiffness were observed (not shown) when assessed by atomic force microscopy. However, a lower ratio of epidermis/SC thickness (Fig. 1d) was associated with higher R6 (Fig. 1e), suggesting skin viscoelastic changes at menopause may be influenced by alterations to epidermal morphology. Histological expression of epidermal CD44 (a receptor for hyaluronic acid) was also assessed due to its pleiotropic role in epidermal homeostasis and hydration. CD44 expression was reduced in the Post vs. the Pre group ($P < 0.05$; Fig. 1c), while no change in skin hyaluronic acid expression was found (not shown). As CD44 activation regulates keratinocyte differentiation and lipid biosynthesis,[9] epidermal lipids were quantified using mass spectrometry (UPLC-MS/MS). Ceramide abundance was found to be lower in Post vs. the Pre group ($P < 0.01$) and cholesterol was increased vs. Pre and HRT (both $P < 0.01$; Fig. 1f). This indicates that epidermal lipid synthesis is altered post-menopause and is susceptible to regulation by HRT. In summary, increased viscoelastic skin distension post-menopause is reversible by HRT, and may result from altered epidermal homeostasis and dermal morphology. Smaller R6 values are associated with improved skin condition, which is evident where decreased R6 is measured following the application of anti-ageing skin care routines.[10] Skewed CD44 expression and ceramide synthesis may contribute to declining epidermal barrier function and could represent key targets, beyond ECM rejuvenation, for improving skin function and appearance in mid-life.

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Conflicts of interest

MB and VLN are employees of Walgreens Boots Alliance; REBW is in receipt of consultancy fees from Allergan Ltd.; CEMG is a Co-Founder of CGSkincare Ltd.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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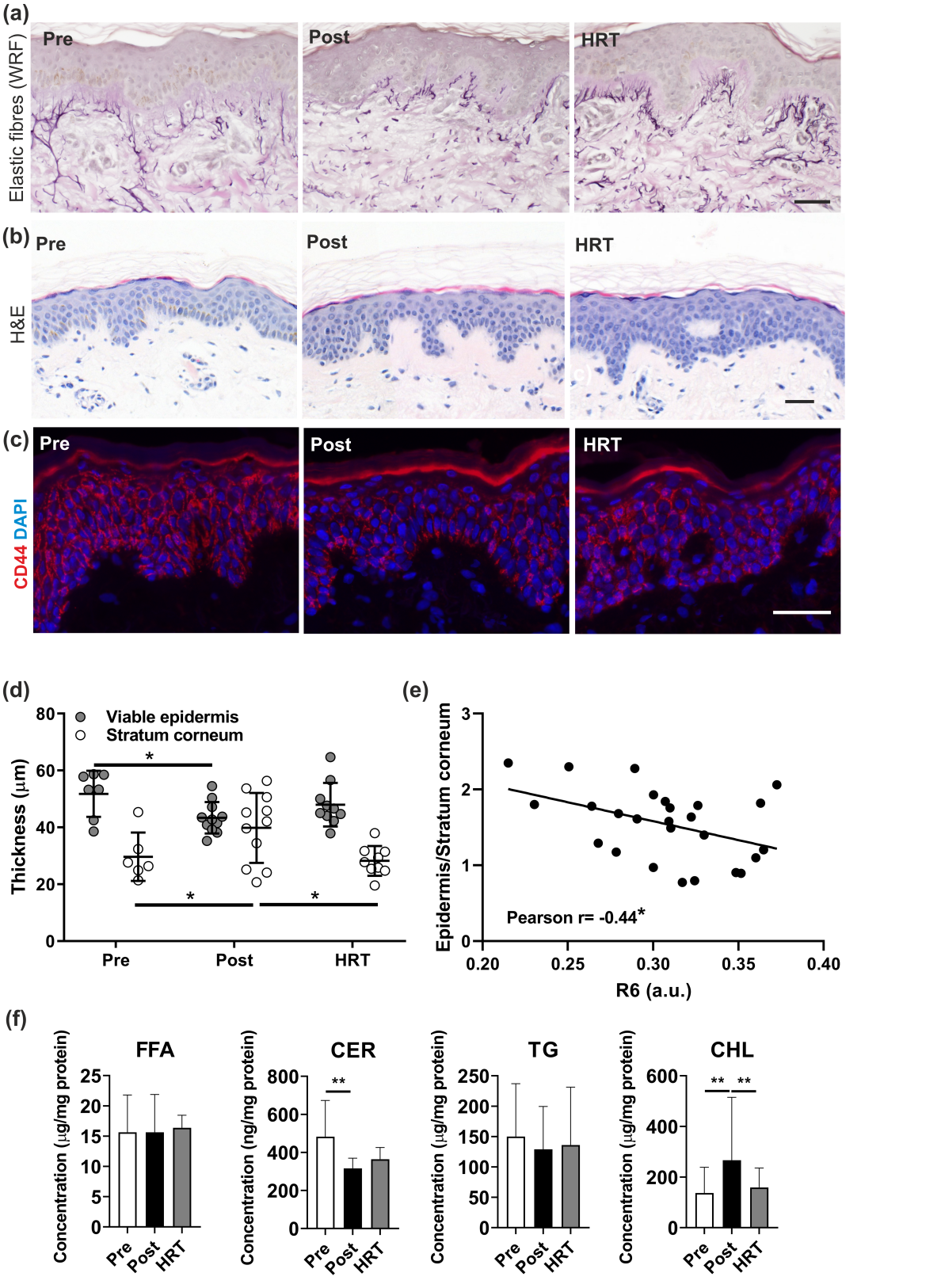

Figure 1 The dermal elastic fibre network was not significantly altered in post-menopausal women but epidermal morphology, CD44 expression and lipid biosynthesis was impacted by menopause and HRT. (a) The dermal elastic fibre network was assessed in biopsies from photoprotected skin of pre-menopausal (Pre; $n = 7$), post-menopausal (Post; $n = 11$) and post-menopausal women taking hormone replacement therapy (HRT; $n = 10$) groups using immunohistochemistry and immunofluorescence. Total elastic fibres were visualised using Weigert's resorcin fuchsin (WRF). (b) Epidermal morphology was assessed in H&E stained skin sections from photoprotected buttock skin of Pre ($n = 6$), Post ($n = 11$) and HRT ($n = 10$) groups and (d) thickness measurements of viable epidermis (nucleated cells) and *stratum corneum* were taken separately, and (e) the ratio calculated for each individual before correlation with the R6 cutometry parameter. (c) CD44 expression was assessed by immunofluorescence and (f) epidermal lipids quantified using UPLC-MS/MS. Data presented as mean ± SD. Statistical analysis by one-way ANOVA with Holm-Sidak's multiple comparisons and Pearson's correlation. *$P < 0.05$, **$P < 0.01$. Scale bar 50 μm.

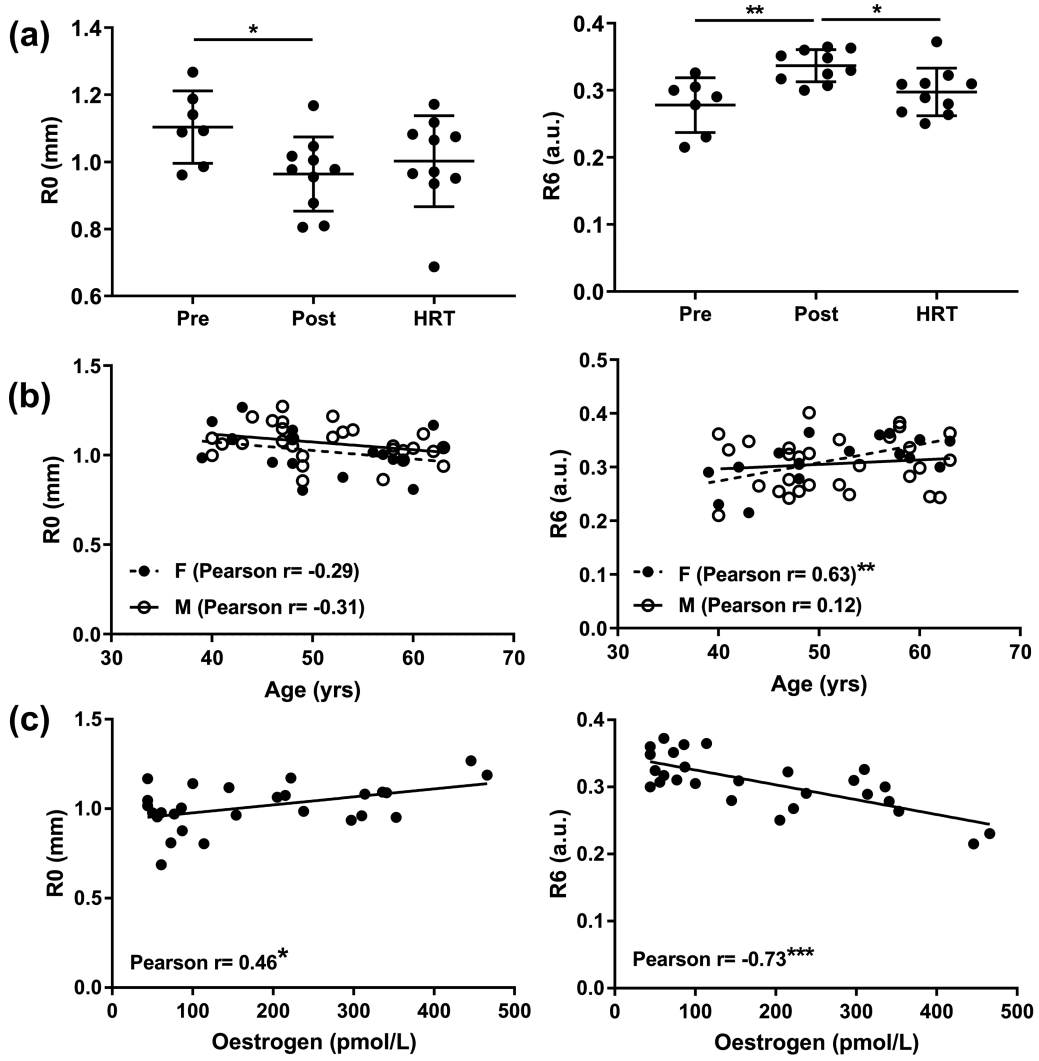

Figure 2 Increased skin viscoelasticity post-menopause is associated with increasing age and decreasing oestrogen levels. Using a Cutometer and 4-mm diameter probe the biomechanical properties of photoprotected buttock skin were measured and (a) mean time-strain curves generated for each group (Pre, $n = 7$; Post, $n = 10$; HRT, $n = 10$) prior to calculation of the different elastic measures (R parameters). From the curves: (a) R0 (total deformation) and R6 (viscoelasticity) were calculated and; (b) associations between age and cutometry parameters, R0 and R6, were assessed in females (F; $n = 17$: Pre $n = 7$ and Post $n = 10$) and in a group of age-matched males (M; $n = 29$). (c) Associations between serum oestradiol levels and R0 and R6 were also assessed in females ($n = 27$: Pre $n = 7$, Post $n = 10$, and HRT $n = 10$). Data presented as mean ± SD. Statistical analysis by Kruskal–Wallis test with Dunn's multiple comparisons (R0), one-way ANOVA with Holm-Sidak's multiple comparisons (R6) and Pearson's correlation, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

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Amplicon sequencing demonstrates comparable follicular mycobiomes in patients with hidradenitis suppurativa compared with healthy controls

Editor

Hidradenitis Suppurativa (HS) is a chronic inflammatory skin disease of the hair follicle defined by recurrent nodules, tunnels and extensive scarring involving the intertriginous regions.[1] Insight into the cutaneous microbiome in HS using high throughput sequencing (HTS) has provided novel data on the microbiological diversity of the skin.[2] Recently, several research groups have reported an association between HS lesions and certain Gram-negative anaerobic bacteria using HTS.[2] However, fungal analyses of HS skin samples are lacking.

We thus investigated the skin mycobiome in HS patients and healthy controls using high throughput amplicon sequencing of the highly conserved eukaryotic 18S ribosomal RNA gene.

We performed a case control study of 24 healthy controls and 30 patients with HS. Punch biopsy specimens (4 mm) from patients with HS (lesional and non-lesional (hair follicles)) and healthy controls were obtained and analysed using targeted 18S rRNA amplicon sequencing. Previously, these samples were analysed for bacteria using 16S rRNA gene amplicon sequencing, the results from which have previously been published.[3]

The mycobiome was characterized in 30 patients with HS (mean [SD] age, 46.9 [14.0] years; 19 [63% female]) and 24 healthy controls (mean [SD] age, 32.2 [12.0] years; 13 [54% female]), of which 19 samples from lesional skin, 23 samples from non-lesional skin and 17 samples from healthy controls with >0 fungal reads were included. The three most frequent species in HS and healthy controls were similar across all groups. The species were *Malassezia (M.) restricta*, *Saccharomyces cerevisiae* and *M. globosa*, respectively (Fig. 1). Lastly, the differential abundance plot shows that none of the most common species were significantly different between the three groups (Fig. 2).

Recently, a multi-centre study found both serologic IgG and IgA anti-*Saccharomyces cerevisiae* antibodies (ASCAs) associated with severe disease activity in HS.[4] The increased levels of ASCAs were suggested to constitute a potential biomarker in HS as it has been established in Crohn's disease.[5] However, in the perspective of our recent data, the potential increased levels of ASCAs in HS may rather be attributed to a dysbiotic HS gut mycobiome than a dysbiotic cutaneous mycobiome.

Furthermore, our study found no significant difference in the presence of various *Malassezia* species between sample types. This is noteworthy as the number of sebaceous glands have been found reduced in HS.[6] It has therefore been speculated that these characteristics of HS would limit the presence of lipophilic yeasts similar to for example reduced abundance of *Cutibacterium acnes*. However, our data suggest that the commensal colonization of *Malassezia* spp. is unaffected in HS.

Although none of the patients included in this study had been treated with antibiotics four weeks prior to sampling the result is also noteworthy in view of standard HS therapy where numerous broad-spectrum antibiotics often are prescribed. Although the participating patients had similar therapeutic experiences previously, we were unable to document long-term systematic changes of the skin mycobiome when sampling hair follicles.

Finally, the conclusion is limited to the skin sampled. Local differences may therefore exist mirroring the distribution of lesions. A potentially dysregulated immune response in HS may very well govern the growth of for example oral or

