Characterization of the Skin *In Vivo* by High Resolution Magnetic Resonance Imaging: Water Behavior and Age-Related Effects

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The age-related modifications of magnetic resonance imaging parameters in the skin have been studied *in vivo*. Modification of these parameters should provide important information about alterations in water structure and content in aged skin. Relaxation times, T1 and T2, and relative proton density, which corresponds to the mobile water proton fraction of tissues, have been measured on people under age 40 and over 70 on a sun-protected area. Results have confirmed *in vivo* skin layer differentiation through relaxation times performed in a previous study. Moreover, relative proton density quantification has shown that epidermal mobile water is at least twice as abundant as dermal mobile water.

No significant age-related T1 and T2 modification could be established, basically because of a large dispersion of values. The main result concerns the upper part of dermis (about 200 microns in thickness) which contains significantly more mobile water protons in chronologic aged skin than in young adult skin. This increase has been related both to an increase of total water content in dermis with age and to an apparent decrease of collagen and proteoglycan content. Associated with alterations of their structure, this decrease reduces macromolecular-water interaction sites. This finding has to be compared with ultrasound evaluation of aged skin, which is characterized by modifications of the echogenicity, related to collagen bundles size and density, in the outer part of dermis, too. Both of the imaging techniques tend to consider the outer part of dermis as one of the privileged sites of skin aging. *J Invest Dermatol 100:705–709, 1993*

Skin intrinsic aging has been extensively described in terms of morphologic changes [1] or connective tissue alterations [2,3], through histologic and clinical signs. Few of them mentioned the modification of water content or of water state during aging [2,4], except on the most superficial layer: the stratum corneum [5–7]. Nevertheless, because water constitutes some 70% of the skin weight, one would expect water properties to dominate many physical measures. In fact, it has been shown that the structural properties of proteins are to a great extent due to water-protein interactions and age-related modifications have been often discussed in terms of structural alterations resulting from biochemical changes. Therefore water studies should provide important information as far as macromolecular structural organization is related to protein-water interactions and thus is related to modifications of the mobile to restricted motion water ratio of the skin. Such studies have been carried out *in vitro*: on collagen fibers for instance [8], and some studies conclude to an increasing number of stabilized intermolecular crosslinks with age [9,10]. But clinical manifestations of aging cannot easily be related to data obtained on isolated fibers, disregarding the complex relationship of the proteins and their surroundings in living skin.

One recent technique, magnetic resonance imaging (MRI), appears to be a proper method of evaluating the behavior of water molecules *in vivo*. In addition to spatial localization, MRI furnishes multiparametric information: T1 and T2 proton relaxation times and relative proton density are intrinsic parameters of tissue that determine magnetic resonance (MR) signal intensity. As they are sensitive to both water content and water structure of biologic systems, MRI has the potential for non-invasive tissue characterization, allowing *in vivo* investigation of the motional behavior of biologic water in hydrated tissues. Thus, despite their limited use in clinical practice, relaxation times quantification has demonstrated some tissue specificity and the feasibility of water-compartment studies, particularly for brain and muscle tissues [11–14]. Its application to skin studies is more recent due to the high spatial resolution required for skin imaging [15–19], and thereby quantitative *in vivo* results are very few. We previously measured *in vivo* relaxation times of the different skin layers [20]. By using a specific imaging module we were able to differentiate the stratum corneum, the epidermis, and the dermis *in vivo* by their MR characteristics. To our knowledge, whether age affects these intrinsic parameters in the different skin layers has not yet been tested. In addition to T1 and T2 measurements, we evaluate in this study the relative proton density N(H), which describes the fraction of protons available for observations by MRI; these correspond to mobile water protons. Thus, it allows us to quantify modifications of the mobile water fraction in tissues on two populations of adult and aged persons.

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Abbreviations:
- MR: magnetic resonance
- MRI: magnetic resonance imaging
- N(H): mobile proton density
- RF: radiofrequency
- ROI: region of interest
- TE: echo time
- TR: repetition time

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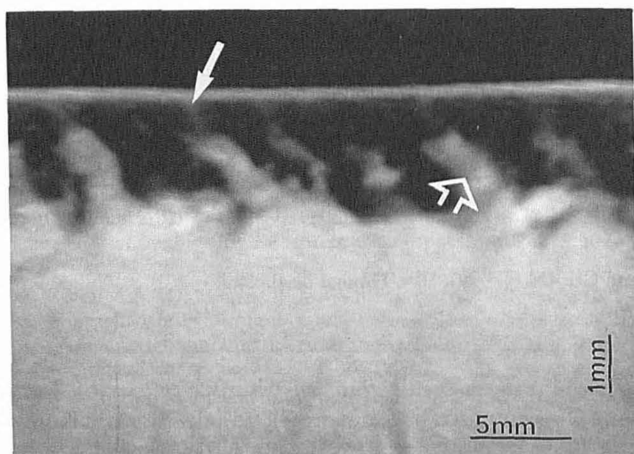

Figure 1. *In vivo* MRI of skin on thigh: the outer bright thin layer corresponds to epidermis, about 100 microns thick. Dermis appears as a darker layer about 1.6 mm in thickness. Cutaneous appendages such as pilosebaceous units (→) are grey inclusions in dermis and hypodermis invaginations (⇒) are bright. Hypodermis appears as a homogeneous bright area. *Horizontal bar,* 5 mm; *vertical bar,* 1 mm.

MATERIALS AND METHODS

Equipment The equipment has been extensively described in previous publications [16,17] and will therefore be briefly reviewed. A whole-body Signa system (GE Medical Systems, Milwaukee) operating at 1.5 Tesla was used. This equipment was modified to obtain high-resolution images by adding a specific surface gradient coil to achieve a pixel size of 70 microns in depth, and a small surface radiofrequency (RF) coil (3 cm in diameter) to improve the signal to noise ratio. Typical high resolution MR images of the skin were obtained with an 18×50 mm^2 field of view and a slice thickness of 3 mm, corresponding to a voxel dimension of $70 \times 390 \times 3000$ μm^3 (Fig 1). The sensitivity pattern of the surface RF coil has been checked to evaluate its influence on comparison of signal intensities between different skin layers. For our depth of interest, which concerns the very first millimeter of thickness away from the skin surface, the sensitivity decrease is less than 10% and not strictly depth dependent.

Subjects After medical examination two groups of healthy volunteers were involved in the study: ten young women (25 to 40 years; mean ± standard deviation, 32 ± 4) and ten elderly women (70 to 81 years; mean ± standard deviation, 74 ± 4). Informed consent was obtained in every case and the project was approved by the Hospital Ethical Committee.

Examination Procedure The image acquisition was performed on the dorsal face of the thigh, a rather sun-protected area that should reflect non-actinic aging. The thigh was stabilized relative to the module by means of straps and surrounding skin area was fixed with a double-sided adhesive tape on the module. All MR images were obtained at room temperature (21°C). The total examination time was about 70 min.

MRI Investigations The MR signal, S, is given as [21]

$$S = k\ N(H)\ \exp^{(-TE/T2)}(1 - \exp^{(-TR/T1)}), \qquad (1)$$

where k is a function of the instrument's receiver gain, N(H) is proportional to the mobile proton density, T1 and T2 are MR tissue relaxation times, and TE and TR are, respectively, echo time and repetition time. Relaxation time measurements were carried out by acquiring two sets of 2D spin echo images only varying TR for T1 measurements (TE = 16 ms, six values of TR ranging from 100 to 4000 ms) and only varying TE for T2 measurements (TR = 500 ms, five values of TE ranging from 16 to 70 ms). T1 and T2 were calculated by fitting to relation (1) the signal intensity S from a region of interest (ROI) measured in each of the spin echo images. It was performed using routine fit function of RS/Explore data analysis system (BBN Software Products Corporation). Data were adjusted by the Marquardt-Levenberg method to a monoexponential function and goodness of fit was checked for each curve during analysis.

T2 calculation has been also performed using a gradient echo sequence and results (unpublished data) are in good agreement with those previously published [20]. Nevertheless due to many potential sources of artifacts related to the gradient echo sequence, only T2 values obtained with the spin echo sequence are presented and discussed here.

A maximum signal intensity for each skin layer was computed according to relation (1) using signal intensity for infinite TR value corrected by T2 decay for each layer. The quantity thus obtained is still a function of the instrument's receiver gain, k, which is optimized for each subject. So the quantity N(H) must be normalized to obtain comparable N(H) values between subjects. On this purpose an external reference constant during the whole experimentation was introduced. This reference was simultaneously scanned with each subject and every subject's relative proton density was normalized to that of the external reference. It was made of a small glass tube filled with an Agar gel (5%) doped with $MnCl_2$ 0.06 mM with skin mimicking T1 and T2 values and mounted inside the RF coil, so that it could be visualized on each MR image.

It was also used to check both the accuracy and the long-term measurement reproducibility over a 6-month period. The accuracy of MRI results was obtained by comparing T1 and T2 values measured using the MR imager with T1 and T2 measured with a separate spectrometer (WM250, Bruker; 250 MHz). Finally, *in vivo* reproducibility was tested on one subject who was scanned twice, with an interval of 3 months between the two scans.

Image Analysis and Statistics A semi-automatic image analysis was used: the operator determines a region of interest (ROI) over the total skin thickness and the software first separates the hypersignal of epidermis from dermis. Besides, it eliminates inside dermis cutaneous appendages as pilosebaceous units and hypodermis inclusions that are in hypersignal, too. Finally, an outer layer (200 microns thick) was defined in dermis. The outer layer thickness was chosen with reference to another skin-imaging technique: ultrasonic imaging, which shows a subepidermal non-echogenic band on aged skin [22,23]. Thus relative proton density and relaxation times were determined on five areas: epidermis, outer dermis, inner dermis, total dermis (in each case without appendages), and hypodermis, in which a large ROI was manually selected. We took care that epidermis signal intensity was averaged on a minimum of 100 pixels. A ROI was also determined on the Agar gel phantom.

Differences in relaxation times and relative proton density values of different groups and skin layers were performed using Mann-Whitney tests and Wilcoxon signed-rank tests.

RESULTS

Measurement Accuracy and Reproducibility Accuracy (deviation from the true value) was periodically checked on the reference gel. Due to variation of T1 with field strength, T1 accuracy could not be directly measured by spectroscopy; concerning T2 measurements, accuracy was about 7%. The long-term reproducibility of the reference gel measurements with the spectrometer was 5% for T1 and 10% for T2 values. In the meantime, the reproducibility of the imager measures was 13% for T1 and 9% for T2. The long-

Table I. T1 and T2 Relaxation Times Mean Values of the Thigh Skin Layers[a]

	T1 (ms)		T2 (ms)	
Tissues	Young Subjects	Old Subjects	Young Subjects	Old Subjects
Epidermis	997 ± 100[b]	1060 ± 90	32 ± 2	32 ± 4
Outer dermis	1045 ± 236	977 ± 137	23 ± 2	24 ± 3
Inner dermis	856 ± 248	786 ± 160	31 ± 5	29 ± 3
Total dermis	897 ± 237	822 ± 158	29 ± 4	28 ± 2
Hypodermis	393 ± 53	388 ± 59	49 ± 2	47 ± 2

[a] Outer dermis corresponds to a subepidermal layer of 200 microns in thickness. Contribution of cutaneous appendages has been excluded from dermis measurements (see text). T1 and T2 are significantly different between epidermis and total dermis ($p < 0.01$) and between outer dermis and inner dermis ($p < 0.01$), but there is no significant difference between age groups.
[b] Mean ± standard deviation, $n = 10$.

term *in vivo* measurement reproducibility was assessed by repeating the scan on one subject after 3 months. The variation of T1 was 1% in epidermis and 3% in dermis; for T2, the variation was 3% in epidermis and 13% in dermis.

For each of the MR parameters, age groups are first compared for each of the skin layers. Then, skin layers are compared to each other for the overall population, with no age distinction.

T1 and T2 Determination Mean values and standard deviations for T1 and T2 relaxation times of the skin layers in young and elderly people are listed in Table I. Short T2 values, particularly for dermis (about 20 ms), and long T1 values about 1000 ms were obtained in epidermis and dermis. The distribution of individual T1 and T2 values in epidermis and in the different areas of dermis shows a large data dispersion as well as an overlapping between groups. Thus, no statistical difference according to age groups can be clearly established in any of the skin layers. Concerning hypodermis, mean T1 (about 400 ms) and T2 values (about 50 ms) are very similar for the two groups so that no significant difference according to age was found for this tissue.

By comparing skin layers to each other for the overall population (20 subjects), there are some statistical differences according to skin layers: both T1 and T2 relaxation times are significantly higher in epidermis than in total dermis ($p < 0.01$). Moreover, by comparing relaxation times within dermis, results show a lower T2 value and a longer T1 value ($p < 0.01$) in outer dermis than in inner dermis, for both young and elderly people.

Relative Proton Density Determination Mean relative proton densities, corresponding to the fraction of mobile water protons, are presented in Fig 2. Unlike T1 and T2 values, relative proton density may be used to discriminate age effect: in the outer dermis, the relative proton density is significantly higher for the elderly than for the young population ($p < 0.05$), whereas there are no statistical differences between young and old people in the other layers.

Concerning the difference among skin layers for the overall population, there are two significant results: first, the relative proton density is significantly higher in epidermis than in total dermis ($p < 0.01$). In epidermis, it is at least twice as large as the dermis relative proton density. Second, there is a significant difference between outer and inner dermis proton density ($p < 0.01$): the relative proton density is higher in the outer dermis than in the inner dermis. It should be noted that this difference exists for each subject; relative proton density is higher in epidermis than in dermis and is higher in outer dermis than in inner dermis in every case. Moreover, average difference between the two areas of dermis is 18%, which is more important than the RF surface coil sensitivity variations.

DISCUSSION

MR tissue characterization is mainly based on the visualization of differences in T1, T2, and relative proton density behavior. We attempted in our study to determine whether skin MR parameters vary with chronologic aging processes.

Considering the younger group, relaxation time mean values are consistent with those *in vivo* [18,20] or *in vitro* [24] values previously published; especially, MR parameter measurements are very reproducible in hypodermis, whatever the measurement protocol is [20,24].

Previous work has shown that epidermis and dermis could be well distinguished by their T2 relaxation times, which are longer in epidermis than in dermis; but this difference was not important enough to explain the MR contrast between these two layers [20]. N(H) is the third parameter that can explain MR contrast. As the total water content in these tissues does not significantly differ, difference in MR proton density could only be explained by a different mobile water fraction in these tissues. But this result was only a qualitative one. Relative proton density measurements allow one not only to confirm this hypothesis but also to quantify the fraction of mobile protons in epidermis and dermis; mobile water molecule fraction as measured by MRI is twice as much in epidermis as in total dermis. Moreover, the image analysis used in this study allows one to consider only the signal arising from dermis, avoiding contamination by cutaneous appendages. It is thus a true comparison between epidermis and dermis. As collagen represents 70% of the dry weight of dermis, the low mobile protons fraction in this tissue should be attributed to abundant water protons that are tightly bound to dermis collagen and thus have a restricted motion.

We also found a significant difference between the relative proton density of outer and inner dermis. Cells and glycosaminoglycans are proportionally more abundant in the superficial than in the deep dermis [25] and collagen fibers of the upper dermis are thinner and less closely packed into bundles than in deep dermis. Therefore collagen density should be proportionally lower in outer dermis, so that the proportion of collagen-water interaction sites would be reduced. Such a reduction could explain a higher mobile water fraction in outer dermis compared to inner dermis and hence the significantly higher relative proton density of outer dermis. This result is confirmed by a longer T1 relaxation time in the outer

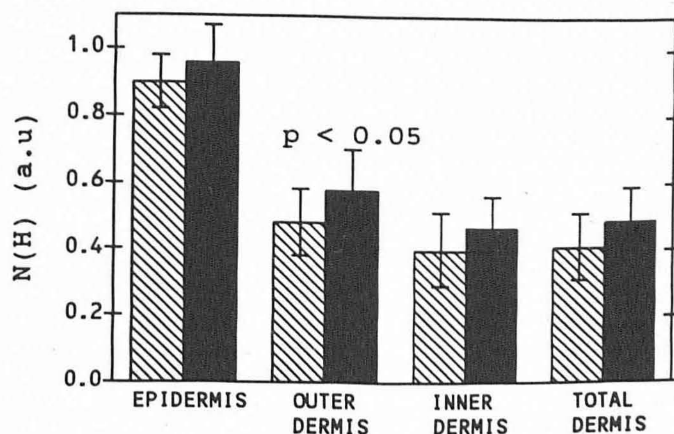

Figure 2. Relative proton density N(H) mean values of the thigh skin layers normalized with the external reference and thus expressed in arbitrary units. The outer dermis corresponds to a subepidermal layer of 200 microns in thickness. Contribution of cutaneous appendages has been excluded from dermis measurements by semi-automatic image analysis. Relative proton density, i.e., mobile water fraction, is significantly higher in epidermis than in dermis ($p < 0.01$) and is significantly higher in outer dermis than in inner dermis ($p < 0.01$). N(H) is significantly higher in aged outer dermis than in young outer dermis ($p < 0.05$). *Hatched columns,* young subjects; *solid columns,* old subjects. *Error bars,* standard deviation.

dermis than in the inner dermis, even if an unexpected shorter T2 value has been obtained in the outer dermis, which could be related to the fibril size distribution through dermis thickness.

Although relaxation time quantification has demonstrated some tissue specificities, the results are essentially characterized by a large dispersion of the relaxation time values concerning the age groups and thus we obtain no consistent age effect upon our relaxation time study. Regarding *in vivo* reproducibility results and external reference data, this inter-individual variation cannot be fully explained by instrumental inaccuracies. *In vivo,* the reproducibility is in the same range as data found in literature [12,21] and control measurements on the external reference Agar gel showed a long-term reproducibility of 9 and 13%, respectively, for T2 and T1. This is below the *in vivo* tissue relaxation time variations and this agrees with *in vitro* reproducibility measurements reported in literature [11,13,14,21]. Moreover, skin motions, which could be another measurement error, had been limited by fixing the surrounding skin area with a double-sided adhesive tape on the module. Furthermore, superimposition of images acquired at different times proved that no motion occurred during acquisition time. We believe, therefore, that the large standard deviations of relaxation times, which have been reported in other *in vivo* studies [14,21], reflect biologic variance in tissues. Thus differences according to age seem to be less important than inter-individual variations.

In contrast, it appears that MR proton density can be age-discriminant: the outer dermis relative proton density is significantly higher for old people. Such a difference could be explained either by an increase of total water content, or by a modification of the mobile to the restricted motion water molecules of outer dermis, as N(H) reflects only mobile protons. Concerning the variations of total skin water content with age, there are very few data in literature. Dermal water content would increase steadily with age, from about 60% to 65% between 20 and 70 years [2,4]. Concurrently, aging is marked by atrophy of the dermal collagen [2,26], owing to decreases in both collagen content and collagen density and also to a reduction in the amount of glycosaminoglycans [1,3,27]. Macromolecule decrease would result in a decrease of the fraction of water associated with the hydration layer of collagen. In addition, it has been shown that aged collagen becomes less soluble, stabilized intermolecular crosslinks increase [9,28], and collagen exhibits less capacity for swelling. This might also produce a higher mobile proton fraction. Therefore, each of the previous hypotheses, increase of total water content and modifications of mobile water molecules proportion, occurs in aging dermis and can explain a higher relative proton density in outer dermis of aged people. Nevertheless, it seems that the increase in relative proton density is more important than the total water content variation in the age range under study.

In this study, age-related effects on T1, T2 and mobile water fraction measurements have been carried out *in vivo* for the first time. Mobile proton density appears to be a more sensitive marker of aging than the relaxation times because of their great dispersion. MR proton density results are suggestive of a significant trend in mobile water fraction increase with aging in outer dermis. This result has to be related to ultrasound findings [22,23]; ultrasound examination has shown that the upper part of dermis is a sensitive marker of skin aging. This zone, which appears as a non-echogenic medium and is so-called sub epidermis non-echogenic band (SENEB), shows a progressive thickening with age. It reflects a relative increase in thin collagen bundles with regard to larger ones. Thus, ultrasonic imaging and MR imaging afford complementary and compatible information about the organization between collagen, glycosaminoglycans, and water in aged skin and present the upper part of dermis as one of the main sites of skin aging.

Moreover, MR proton density is a useful tool for characterization of the epidermis and dermis. The importance of collagen and glycosaminoglyans, the main dry constituents of dermis, on the structure of water has been quantified *in vivo*. Now, the contribution of each of these factors (collagen, glycosaminoglycans, and water content) on MR skin parameters has to be tested separately in further investigations to better understand which modifications are predominant in the alterations of water-macromolecular interactions of aged skin.

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PROGRAM ANNOUNCEMENT

The KAO Corporation of Japan in 1990 established awards of $50,000 each for two post-doctoral Ph.D. basic scientists or physicians who are destined for research careers in investigative dermatology, with special emphasis on basic science. The rationale of this award (the Thomas B. Fitzpatrick Research Award) is to bridge the critical gap between completion of training and stable support.

Many factors are considered in the final selection of the Fitzpatrick awardee — among them the scientific milieu, originality of research, quality of previous training, and evidence of potential for a career in research on the biology of skin.

This program has been continued for a second three-year period, with awards to be made for 1994–1995, 1995–1996, and 1996–1997. Interested applicants are encouraged to apply.

Awardees for July, 1993–June, 1994 are as follows:

Andrzej Antoni Dlugosz, M.D., Biotechnology Fellow, Laboratory of Cellular Carcinogenesis and Tumor Protection, National Cancer Institute (work on biochemical pathways regulating keratinocyte differentiation).

Walter M. Holleran, Pharm. D., Assistant Adjunct Professor, University of California, San Francisco (work on cutaneous biochemistry and homeostasis).

Application forms are available from Kao Scientific Committee, c/o Management Consultants, 395 E Essex Street (Suite 306B), Beverly, MA 01915. Application deadline is September 15th. Announcement of Awards will be in January, with funding in July.