

TRANSPARENT SKIN AND OSTEOPOROSIS* A STUDY IN PATIENTS WITH RHEUMATOID DISEASE

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We have described elsewhere (McConkey, Fraser, Bligh, and Whiteley, 1963) an abnormality of the skin which we called transparent skin. In a number of patients, none of whom had rheumatoid disease, we found an association between transparent skin and osteoporosis. We suggested that both the transparency of the skin and the osteoporosis were the consequences of a disorder of connective tissue.

We now report a study of transparent skin and osteoporosis in patients suffering from a known disorder of connective tissue, rheumatoid disease.

Patients and Methods

The patients comprised 102 women aged from 40 to 78 years (mean 58.4); they had had arthritis from 1 to 50 years (mean 11.8).

67 had been treated with corticosteroids, usually prednisone. Where other preparations had been used the dose is expressed as the equivalent amount of prednisone. The total dose varied from 1.9 to 28.8 g. (mean 12.0); the duration of treatment from 10 to 84 months (mean 42), and the daily dose varied from 5 to 15.7 mg. (mean 9.5).

The skin on the dorsum of the hand in each patient was classified as transparent, opaque, or doubtful. In 57 patients we also measured the thickness of a fold of skin on the dorsum of the hand over the 4th metacarpal using a Harpenden caliper and measuring the skin fold three times in each patient. We also noted any purpura

of the "senile" or "steroid" type (Scarborough and Shuster, 1960; Shuster and Scarborough, 1961).

In the 74 patients who were x-rayed osteoporosis was diagnosed by the same criteria as before (McConkey, Fraser, and Bligh, 1962).

Results

Transparent Skin and Rheumatoid Disease.—Table I shows the prevalence of transparent skin in the 102 women with rheumatoid disease and in 200 women with other diseases. In each decade from 40 to 80 years, transparent skin was more common in the patients with rheumatoid disease.

Of the women with rheumatoid disease, 35 (mean age 58.5 years) had not received corticosteroids; in them the prevalence of transparent skin was 34 per cent. Table I shows that the highest incidence of transparent skin in the controls (in the eighth decade) was only 12 per cent. Thus the incidence of transparent skin is high in patients with rheumatoid disease, irrespective of treatment with corticosteroids.

Patients with transparent skin had usually had rheumatoid disease longer than those with opaque skin (mean duration 16.2 and 10.3 years respectively).

Transparent Skin and Corticosteroid Therapy.—To investigate whether corticosteroids contributed to the development of transparent skin, we compared the 67 women who had had corticosteroids with the 35 who had not had this treatment. The groups

* Based on a paper read to the Heberden Society on February 26, 1965.

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TABLE I
PREVALENCE OF TRANSPARENT SKIN IN 102 WOMEN WITH RHEUMATOID DISEASE
AND IN 200 WOMEN WITH OTHER DISEASES, BY AGE AND DIAGNOSIS

Age (yrs)	Rheumatoid Disease		Other Diseases	
	No. of Patients	Per cent. with Transparent Skin	No. of Patients	Per cent. with Transparent Skin
40-50	22	14	50	—
50-60	32	28	50	—
60-70	38	55	50	8
70-80	10	60	50	12
Total	102		100	

were well matched in age (mean 58·4 and 58·6 years) and in the duration of arthritis (mean 11·7 and 12·3 years). Table II shows how the patients were classified; there were more "doubtful" patients in the treated group than in the untreated group.

TABLE II
CLASSIFICATION OF 102 WOMEN WITH RHEUMATOID DISEASE ACCORDING TO THE APPEARANCE OF THEIR SKIN AND TREATMENT WITH STEROIDS

Appearance of Skin	Treatment			
	Corticosteroids		No Corticosteroids	
	No.	Per cent.	No.	Per cent.
Transparent	27	40	12	34
Opaque	29	43	21	60
"Doubtful"	11	16	2	6

To compare the prevalence of transparent skin in the two groups, we considered the results in two ways (a) when "doubtful" patients were classified as having transparent skin, and (b) when "doubtful" patients were classified as having opaque skin. The results are shown in Table III. The prevalence of transparent skin in patients who had had corticosteroids exceeded that in patients who had not, but the difference was not significant ($a: -0.20 > P > 0.10$, $b: -P \approx 0.70$). The prevalence of purpura, a recognized complication of corticosteroid therapy, was greater in patients who had had corticosteroids ($P \approx 0.02$).

TABLE III
PREVALENCE OF TRANSPARENT SKIN AND OF PURPURA IN WOMEN WITH RHEUMATOID DISEASE TREATED AND NOT TREATED WITH CORTICOSTEROIDS

Group of Patients	Treatment	No. of Patients	Transparent Skin (per cent.)	Purpura (per cent.)
(a) "Doubtful" patients classified as "transparent"	Corticosteroids	67	56.7	45
	No corticosteroids	35	40.0	20
(b) "Doubtful" patients classified as "normal"	Corticosteroids	67	40.3	45
	No corticosteroids	35	34.3	20

TABLE IV
TRANSPARENT SKIN, OSTEOPOROSIS, AND TREATMENT WITH CORTICOSTEROIDS IN 74 WOMEN WITH RHEUMATOID DISEASE

Skin	Treatment	No. of Patients	Mean Age (yrs)	Mean Duration of Arthritis (yrs)	Corticosteroids			Cases of Osteoporosis		Cases of Vertebral Fracture
					Total Dose (g.)	Duration of Treatment (mths)	Average Daily Dose (mg.)	No.	Per cent.	
Transparent	Corticosteroids	22	62.3	13.8	13.9	47.9	10.3	18	82	6
	No corticosteroids	8	64.0	11.9	—	—	—	4	50	—
Opaque	Corticosteroids	29	57.5	9.6	11.5	41.0	10.7	5	17	—
	No corticosteroids	15	57.2	10.1	—	—	—	1	7	—

Transparent Skin and Osteoporosis.—To study the relationship between transparent skin and osteoporosis, lateral radiographs of the dorsal and lumbar spine of 74 patients were assessed by two radiologists independently.

28 patients (38 per cent.) had definite osteoporosis, six with vertebral fractures. The radiologists disagreed, or were doubtful, about eleven patients (15 per cent.).

Table IV shows that osteoporosis was most common in patients with transparent skin who had had corticosteroids, all those with fractures being in this group. In this Table patients with "doubtful" skin and patients with "doubtful" bones were classified as normal. If either or both these groups of "doubtful" patients were classified as abnormal the figures did not alter materially.

The patients with transparent skin were older than the rest, but the difference in age does not account for the difference in the incidence of osteoporosis. Thus Table V shows the findings in patients who had had corticosteroids, and the 22 with transparent skin are compared with eighteen patients with opaque skin aged more than 55 years. Although the mean ages were similar, osteoporosis was much more common ($0.01 > P > 0.001$) in the patients with transparent skin. It is unlikely that the small differences in duration of rheumatoid disease and amount of treatment with corticosteroids could account for the large difference in the incidence of osteoporosis.

Skin-fold Thickness.—The thickness of a fold of skin on the back of the hand in 57 women with rheumatoid disease varied from 1.0 to 2.8 mm. In women with transparent skin the range was 1.0 to 1.7 mm. (mean 1.32) and in women with doubtful or opaque skin 1.3 to 2.8 mm. (mean 1.88). The figures agree with those we found before (McConkey and others, 1963). Thus transparent skin is usually thin skin, but the measurements in patients with opaque and transparent skin overlap.

We have considered further the patients in the range of overlap. There were 25 patients whose skin-fold measurements were between 1.3 and 1.7 mm.; eleven had transparent skin and fourteen had opaque or doubtful skin. Of the eleven with transparent skin, nine had osteoporosis, three of them with vertebral fractures. Of the fourteen with opaque skin, three had osteoporosis but none had vertebral fractures. These figures suggest that it is transparency, rather than thinness, of the skin which is associated with osteoporosis.

However, as transparent skin is usually thin skin, osteoporosis could have been predicted in these patients nearly as well from the skin-fold thickness as from the transparency. Of the 51 patients whose skin-fold thickness was known and who had been x-rayed, 21 had transparent skin; of these sixteen (76 per cent.) had osteoporosis. 26 had skin-fold measurements less than 1.6 mm.; of these sixteen (62 per cent.) had osteoporosis (Table VI).

Discussion

The prevalence of transparent skin and its relation to osteoporosis has been described before in patients

suffering from diseases other than rheumatoid arthritis (McConkey and others, 1963). We now show that transparent skin is commoner in women with rheumatoid disease, and usually affects patients who have had arthritis for many years. The finding supports the view that transparent skin is the consequence of a disorder of connective tissue.

Treatment with adrenal corticosteroids influences the connective tissue of the skin; the effects have been investigated in animals (Layton, 1951; Smith, 1962) and no doubt account for corticosteroid purpura in man. In our patients corticosteroids had certainly had an effect on the skin, for purpura was found more often in those who had had such treatment. There was no evidence that the corticosteroids had contributed to the development of transparent skin, though the effects of age and of the rheumatoid disease could have masked such an effect. Younger patients, receiving corticosteroids for a disease not associated with transparent skin, might provide an answer to this question.

There are also difficulties in assessing the contribution of corticosteroids to the development of osteoporosis in rheumatoid disease. Age and the rheumatoid disease itself are contributory factors which may be at least as important (McConkey and others, 1962). In the present study, the prevalence of osteoporosis in treated and untreated patients did not differ significantly, irrespective of whether the patients about whom the radiologists disagreed were regarded as normal or abnormal ($P \approx 0.10$ and $P \approx 0.20$ respectively). Yet all the patients with fractures were in the treated group and the data in Table IV also suggest that corticosteroids contributed to the osteoporosis.

TABLE V
TRANSPARENT SKIN AND OSTEOPOROSIS IN FORTY WOMEN WITH RHEUMATOID DISEASE TREATED WITH CORTICOSTEROIDS

Skin	No. of Patients	Mean Age (yrs)	Mean Duration of Arthritis (yrs)	Corticosteroids			Cases of Osteoporosis		Cases of Vertebral Fracture
				Total Dose (g.)	Duration of Treatment (mths)	Average Daily Dose (mg.)	No.	Per cent.	
Transparent	22	62.3	13.8	13.9	47.9	10.3	18	82	6
Opaque	18	61.9	9.8	11.8	41.7	10.6	5	28	0

TABLE VI
TRANSPARENT SKIN, SKIN-FOLD THICKNESS, AND OSTEOPOROSIS IN 51 PATIENTS WITH RHEUMATOID DISEASE WHO HAD BEEN X-RAYED

Skin	Number of Patients	Cases of Osteoporosis		
		Number	Percentage	Number with Vertebral Fractures
Transparent	21	16	76	5
Opaque	30	6	20	0
Skin-fold	< 1.6 mm. ..	26	62	5
	> 1.6 mm. ..	25	24	0

In our previous study of patients with rheumatoid disease, we found an association between osteoporosis and purpura (McConkey and others, 1962). In the present study the findings were similar; osteoporosis was commoner in patients with purpura (52 per cent.) than in patients without purpura (29 per cent.). However, there is also an association between purpura and transparent skin (McConkey and others, 1963). Table VII shows the results when the three variables are taken into account; patients with transparent skin are likely to have osteoporosis whether they have purpura or not.

The data on transparent skin and osteoporosis shown in Tables IV and V suggest a direct relationship. Transparent skin is usually thin skin. Osteoporosis was, in fact, found almost as often in patients with thin skin (skin-fold measurement less than 1.6 mm.) as in patients whose skin looked transparent. But when we compared groups of patients with opaque and transparent skin whose skin-fold thicknesses were similar, we found that osteoporosis was commoner in those with transparent skin. There must, therefore, have been some change in the skin, in addition to loss of substance, which made it look transparent and which was closely associated with osteoporosis.

This change in the skin can be recognized histologically. Dr. K. W. Walton has recently examined biopsy specimens of opaque and transparent skin of the same thickness, taken from pairs of patients matched for sex and age. The difference between opaque and transparent skin, which we shall describe fully when the work is complete, is most obvious in the collagen of the dermis.

This study of transparent skin in patients with rheumatoid disease supports the findings of our previous study of patients with other diseases. In both studies we found that transparent skin and osteoporosis were associated, that transparent skin is usually thin skin, and that it is its transparency, rather than its thinness, which is associated with osteoporosis. Transparent skin and osteoporosis are found together more often in patients with rheumatoid disease, a known disorder of connective tissue, than in patients with other diseases. Indeed transparent skin was found in about 35 per cent. of

patients with osteoporosis from any cause (unpublished observations), but in 22 of 28 (78.5 per cent.) of patients with osteoporosis and rheumatoid disease. Osteoporosis is probably not one disease but an accompaniment of a number of disorders with different causes; one type is associated with transparent skin. We suggest that when osteoporosis is accompanied by transparent skin a disorder of connective tissue underlies both phenomena.

Summary

The prevalence of transparent skin and its relationship to osteoporosis has been studied in 102 women, all over the age of 40, with rheumatoid disease.

Transparent skin was found more often in the 102 women with rheumatoid disease, whether they had had corticosteroids or not, than in 200 women with other diseases. The finding supports the view that transparent skin is the consequence of a disorder of connective tissue.

Women who had transparent skin had usually had arthritis for many years.

The prevalence of transparent skin in women who had and who had not had corticosteroids did not differ significantly; purpura, a known complication of corticosteroid therapy, was more common in the treated group. Thus corticosteroids had apparently not helped the development of transparent skin.

There was a close association between transparent skin and osteoporosis. Transparent skin is usually thin skin; osteoporosis was therefore nearly as common in women with thin skin (skin-fold < 1.6 mm.) as in those whose skin looked transparent. However, when we compared patients who matched in respect of skin-fold thickness, we found that osteoporosis was more closely associated with transparency than with thinness of the skin.

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TABLE VII
TRANSPARENT SKIN, PURPURA, AND OSTEOPOROSIS IN 74 WOMEN WITH RHEUMATOID DISEASE

Skin	Purpura			No Purpura		
	No. of Patients	Cases of Osteoporosis		No. of Patients	Cases of Osteoporosis	
		No.	Per cent.		No.	Per cent.
Transparent	18	13	72	12	9	75
Opaque	11	2	18	33	4	12

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Discussion

DR. OSWALD SAVAGE (*London*): I should like to ask about the diagnosis of osteoporosis if vertebral fractures are absent. We have found it impossible to get radiologists to agree with us, or among themselves, or to commit themselves, if vertebral collapse is not present. This is important, particularly with regard to steroid therapy. We have also been interested in steroid purpura, and have found that there is no particular connexion between this and vertebral collapse. When we last assessed steroid side-effects in 68 patients, 38 had steroid bruising and only one had vertebral collapse. What criteria were used for the diagnosis of osteoporosis if vertebral collapse was not present?

DR. MCCONKEY: Vertical trabeculation, fractures of end plates, and biconcavity of the vertebral bodies. Your point about purpura is interesting, because there is a partial relationship between purpura and transparent skin.

DR. V. WRIGHT (*Leeds*): This is tremendously important because it provides strong circumstantial evidence which may resolve the conflict between those who think osteoporosis is due to a calcium drain and those who think it has primarily to do with collagen. I should like to ask if you grade the transparency of the skin? What is your observer error in assessing the transparency? Have you looked for it elsewhere and have you done skin fold measurements? I should also be interested to know if you have any data on post-pregnancy osteoporosis. We have done stress-strain analyses on the skin of some of these patients, and these differ from those of rheumatoid arthritis.

DR. MCCONKEY: Osteoporosis is not a single disease but a number of conditions—one type is associated with transparent skin. In patients with osteoporosis, about 35 per cent. have transparent skin, but in those with rheumatoid arthritis and osteoporosis the figure is 80 per cent. We did not attempt clinical grading, but divided skins into either definitely "opaque" or "transparent", or "do not know". I do not know the observer error. Thin skin can be seen elsewhere, but more work on the histology is necessary. We have measured skin-fold thickness, but there are not many parts of the body where one can do this without including fat. I have no comment on post-pregnancy osteoporosis.

La peau transparente et l'ostéoporose. Une étude des malades atteintes de maladie rhumatoïde

RÉSUMÉ

On étudia la fréquence de la peau transparente et son rapport à l'ostéoporose chez 102 femmes, toutes âgées de plus de 40 ans et atteintes de maladie rhumatoïde.

La peau transparente fut trouvée plus souvent chez les 102 femmes atteintes de maladie rhumatoïde, avec ou sans traitement corticostéroïde, que chez 200 femmes atteintes d'autres maladies. Ce résultat vient à l'appui de l'hypothèse que la peau transparente est une conséquence d'un désordre du tissu conjonctif.

Les femmes à la peau transparente souffraient généralement de leur arthrite depuis plusieurs années.

La fréquence de la peau transparente chez des femmes traitées et non-traitées par des corticostéroïdes n'accusa pas de différence significative; le purpura, complication bien connue de la thérapie corticostéroïde, fut plus commun dans le groupe traité. Apparemment, les corticostéroïdes n'avaient pas contribué au développement de la peau transparente.

Il y eut une association étroite entre la peau transparente et l'ostéoporose. Une peau transparente est généralement une peau mince; l'ostéoporose fut donc presque aussi fréquente chez des femmes avec une peau mince (pli cutané <1,6 mm.) que chez celles dont la peau parut transparente. Toutefois, lorsqu'on compara les malades assortis selon l'épaisseur de leur peau, on trouva que l'ostéoporose fut plus associée à la transparence de la peau qu'à son épaisseur.

La piel transparente y la osteoporosis. Un estudio de enfermas reumatoides

SUMARIO

Se estudió la frecuencia de la piel transparente y su relación con la osteoporosis en 102 mujeres, de más de 40 años, sufriendo de enfermedad reumatoide.

La piel transparente fué encontrada más a menudo en las 102 mujeres con enfermedad reumatoide, tratadas o no con corticosteroides, que en 200 mujeres con otras enfermedades. Este resultado sostiene la hipótesis de que la piel transparente es una consecuencia de un disturbio del tejido conectivo.

Las mujeres con piel transparente sufrían generalmente de su artritis desde muchos años.

La frecuencia de la piel transparente en mujeres tratadas o no con corticosteroides no acusó diferencia significativa; el púrpura, complicación bien conocida de la terapia corticosteroide, fué más común en el grupo tratado. Aparentemente, los corticosteroides no habían contribuido al desarrollo de la piel transparente.

Hubo asociación estrecha entre la piel transparente y la osteoporosis. Una piel transparente es generalmente una piel delgada; la osteoporosis fué pues casi tan frecuente en las mujeres con piel delgada (pliegue cutáneo <1,6 mm.) que en las cuya piel pareció transparente. Sin embargo, al comparar las enfermas apareadas según la espesura del pliegue cutáneo, se vió que la osteoporosis fué más asociada a la transparencia de la piel que a su espesor.