

# Osteoporosis, like skin ageing, is caused by collagen loss which is reversible

Sam Shuster 

Department of Dermatology, University of Newcastle upon Tyne, Newcastle upon Tyne NE1 7RU, UK

Corresponding author: Sam Shuster. Email: sshuster@btinternet.com

Emotion gives fact a hard ride; recently, I was travelling with a close, equally aged family member, who fell and suffered a femoral neck fracture. Surgical treatment is now exceptional, and all passed well; but what stayed is the remarkable simplicity of the occurrence and the grotesque complexity of its consequences, and that sent me back to find what had been learned about osteoporosis since the distant days of my own research interest. But the search left me disappointed; despite much new work, there was no defining mechanism, and nothing likely to improve on the marginal effect of exercise, Ca, D<sub>3</sub> and bisphosphonates. I was curious about the fate of my old idea that osteoporosis, like skin ageing, was caused by loss of collagen and should be reversible by growth hormone, perhaps with androgen. My disappointment on finding it had got nowhere, wasn't dented parental pride, but that it had not been *proved* to be incorrect. The possibility that it had been missed rather than dismissed, synergised with my painful family experience, and prompted this restatement of the hypothesis and commentary on its possible role, since the evidence for it, albeit ancient, still stands intact, unlike the family member who prompted it. More importantly, it offers what is still a novel approach, and could provide a major advance in the understanding and treatment of osteoporotic and ageing processes.

The original hypothesis arose from an unravelling of the mechanism of senile purpura,<sup>1</sup> which also explained corticosteroid purpura.<sup>2</sup> It was shown that dermal changes with age (and corticosteroids) allowed rupture of dermal vessels by shear force, and in the absence of normal dermal restriction, the extravasated blood spread widely (as did experimentally injected fluids), giving the lesions their characteristic appearance. This could only be caused by loss of the dermal collagen network; but, at the time, skin collagen was thought to be unchanged or increased<sup>3</sup> with age. To resolve this, new methodology was

developed, and this showed the misconception arose from the erroneous expression of collagen content relatively (to another constituent, or as a %), and when measured as an absolute quantity per skin surface area (using a high-speed punch for precision), all fell into place, and total skin collagen was shown to decrease incrementally with age<sup>4,5</sup> and corticosteroids.<sup>6,7</sup>

The loss is 1% per annum in men and women, although female skin has less collagen<sup>5</sup> – in the misogynistic terms of collagen content, female skin is some 15 years 'older' than that of men. The loss is not solar-induced, as was once believed, and is comparable in all body areas.<sup>4,5,8</sup> It is an intrinsic characteristic of collagen ageing and, therefore, a similar age loss with could be predicted in bone, which has the same predominant collagen type as skin. The story then took on more than a dermatological interest, and it was a short step to the idea that loss of collagen with age, occurring in bone, just as in skin, is the cause of osteoporosis in the elderly<sup>4,5,9,10</sup> (and its sex difference); likewise with corticosteroid and 'collagenolytic diseases such as Ehlers-Danlos syndrome, Marfan's syndrome'.<sup>4</sup>

Confirmation would require 'studies of the *absolute* collagen content of skin and bones',<sup>4</sup> but the simple first test was the predicted correlation between skin collagen and bone density. Total skin collagen content was measured in patients with various skin, endocrine and genetic conditions,<sup>4-13</sup> and they all confirmed the correlation, and with the causal strength of a dose–response relationship for age and oral corticosteroids. Patients with Cushing's syndrome had a greatly reduced skin collagen and bone density;<sup>7</sup> patients with acromegaly<sup>11</sup> had a massive increase in skin collagen (an effect missed when collagen was expressed as a percentage) and their bones were dense; in contrast, skin collagen content was reduced in patients with hypopituitarism<sup>11</sup> and their bones were thinned. The effect of androgen is

apparent from the similar sex difference in skin collagen and bone density,<sup>4,5,10</sup> the increased skin collagen in hirsute women<sup>12</sup> in whom osteoporosis is less frequent, and the osteoporosis induced by antiandrogens.<sup>14</sup>

Thus, when skin collagen was increased or decreased, there was an invariable correspondence with bone density. If the relationship is causal, the converse should be true, and patients with reduced bone density should have a reduction in skin collagen. That they do, was shown in patients with osteogenesis imperfecta,<sup>13</sup> also patients presenting with osteoporosis.<sup>10</sup> The evidence, therefore, from sources as diverse as ageing, endocrine, genetic and metabolic disorders is of a causal correspondence between skin collagen and bone density; and since bone density would not affect skin collagen, and vice versa, this can only result from an entity common – their identical predominant collagen subtype.

Thus the evidence supports the conclusion that systemic changes in bone density are causally related to bone collagen content – bone collagen loss is a cause not, as some believe, a consequence of osteoporosis; furthermore, a measure of this loss is given by skin collagen content. Although biopsy measurement of skin and bone collagen has not been done, post-mortem studies show a reduction of bone collagen with age<sup>15</sup> similar to found in skin;<sup>4</sup> measurement of skin collagen would therefore contribute to the understanding of unexplained loss of bone substance, e.g. in diabetes, scurvy and malnutrition, and its response to treatment.

It is a curious commentary on research into osteoporosis, that although the original hypothesis may have been missed, studies made since are unwittingly leading to back to it. Thus, the osteoporosis of homocystinuria is explained by a decrease in bone collagen, since the place of normal, mature collagen, which is cross-linked, is taken by its unlinked variety.<sup>16</sup> New studies will now be needed to define the role of mature cross-linked collagen and its un-linked variety, particularly when there are gross changes in total collagen, such as with corticosteroids<sup>6,7</sup> and human growth hormone.<sup>11</sup>

Any commentary on the current understanding of osteoporosis has to consider the role of bone mineralisation; and in this respect, the implication of the proposed causal relationship of osteoporosis to bone collagen is that collagen, rather than mineralisation, is critical for bone structure and strength. New evidence supports this idea,<sup>15,17</sup> and more studies of quantitative and qualitative differences in collagen content, cross-linkage, fibrillar form, arrangement and linear distribution in bones will be needed to test this further. Another testable

implication of the hypothesis is that mineralisation is secondary to collagen deposition. Indeed, it now appears that our historical attachment to a defect of mineralisation in osteoporosis (derived, perhaps, from osteomalacia, and the visual cliché of radiological density) has been a mechanistic and therapeutic distraction, and led to undue emphasis on calcium and vitamin D, and persistence with an ineffective therapy.

The therapeutic possibilities shown by the hypothesis and the evidence that led to it are perhaps the strongest reason for its reconsideration; and here, the most important finding is the considerable increase in skin collagen produced by human growth hormone. But whatever the weight of causal theory and laboratory evidence, proof must always be the clinical response; a key test would therefore be the therapeutic response of senile osteoporosis to human growth hormone (perhaps with androgen), as originally proposed.<sup>9,10</sup> This would be a fully controlled study, using clinical and radiological assessments, with measurement of the change in skin collagen content and thickness, and bone density and collagen content. Recently, there have been encouraging pilot studies<sup>18–20</sup> that support the original suggestion; but only the proposed fully controlled study will provide proof of concept.

Advance in the therapy of osteoporosis must consider its industrial development. Proof of concept is essential and is given by the proof proposed, which also provides the industrial essential of a therapeutic target and prototype bioassay. Thus, the increase in skin collagen produced by human growth hormone (and perhaps androgen) could provide the assay for the industrial development of agents that promote collagen deposition for treatment of osteoporotic disorders – and, inevitably, the cosmetology of ageing. The caveat is reversibility, and while the evidence suggests that age changes will be reversible, the response of corticosteroid osteoporosis to human growth hormone (and other collagen-promoting agents) can only be established by testing.

Dissatisfaction with the present understanding and therapy of osteoporotic disorders, led to this commentary on ideas arising from an old hypothesis that is still supported by the evidence, and can explain the findings of diverse new studies, made independently of it. It can serve as a core hypothesis that integrates and initiates experimental, diagnostic and therapeutic ideas, such as the diagnostic use of skin collagen for bone disease, the therapy of osteoporosis with growth hormone, and the industrial discovery of substances that augment skin collagen and therefore bone density. It is hoped this commentary on the mechanistic and therapeutic possibilities of the

hypothesis will encourage their development – and thereby perhaps, help others avoid the painful experience to which my family was recently exposed.

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**ORCID iD:** Sam Shuster  <https://orcid.org/0000-0002-6690-8869>

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