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Osteoporosis, a unitary hypothesis of collagen loss in skin and bone

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Summary Progress in osteoporosis has been stultified by repetitive, statistic-driven studies and catechistic reviews; in the absence of concept and hypothesis research is aimless, and the trivial associations it continually reveals, has led to the cul-de-sac of multifactorialism. A return to hypothesis-led *research* which seeks major causal defects and the conclusive therapies that arise from them is essential.

The hypothesis proposed evolved from research into the mechanism of senile purpura. This predicted a causal loss of skin collagen that was contrary to contemporary opinion, but was confirmed when collagen was expressed absolutely, instead as a percentage or ratio: women have less collagen than men and it decreases by 1% a year in exposed and unexposed skin. Corticosteroids (which also produce shear purpura) reduce skin collagen and androgen and virilism increase it; growth hormone produces the greatest increase, and there is a decrease in hypopituitarism. All these changes in skin collagen correspond to changes in bone density, and the circumstances are too various for coincidence. This led to the hypothesis that the changes found in skin collagen also occur in bone collagen, leading to the associated changes in bone density; thus a loss of collagen in skin and bones with aging is the causal counterpart to loss of bone density in senile osteoporosis.

If this is correct then, as with aging, androgen and virilisation, corticosteroids, growth hormone and hypopituitarism, changes in bone density should correspond to systemic changes in skin collagen. This correspondence is found to occur in osteogenesis imperfecta and Ehlers-Danlos syndrome, two genetically discrete families of disordered collagen production, and other situations, e.g., scurvy and homocystinuria. A primary loss of collagen in osteoporotic bones is an essential prediction of the hypothesis; in fact this loss is well established but, inexplicably, it has been assumed to be secondary to the bone loss.

Because of the comparable changes in skin and bones, the hypothesis implies that skin collagen could be used to predict the state of the bones and their response to treatment. It also implies androgen should be an effective treatment of osteoporosis, and growth hormone even more effective (likewise, of course, skin aging). More importantly, skin collagen and the production of collagen by skin fibroblasts could be used for the assay and industrial development of more potent, if not less toxic treatments and prevention of loss of bone (and skin) substance.

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Introduction

The prevalence of osteoporosis has increased more than our understanding of its cause and treatment. Why? An outsider may see problems which have become too familiar to be noticed by workers in the field. I therefore present a hypothesis to explain lack of progress before presenting a different approach.

With a few, mostly recent, exceptions publications since 1960 have revolved in a slow spiral of fashion round the same interacting themes, periodically fortified by ''reviews'', the mind-closing, repetitive effect of which is to encourage the finding of new evidence that fits into the framework of old beliefs, and to tame and incorporate whatever does not. The underlying themes are too well known to require yet another repetition and, like the reviews that promote them, carry little of interest to the critical reader. Indeed, one of the Lancet's last series of reviews on osteoporosis [1—4], which provided yet another consolidatory exposition of the osteoporotic theme park, finally admitted the absence of solid aetiological evidence yet, curiously, found itself able to conclude ''osteoporosis... has no single cause'' and, worse still, is ''likely to have a heterogenous cause [2]''! Unfortunately that unthinking assumption is now commonplace (e.g. [5]).

Reviews are rarely intellectually neutral, and the packages of pre-conceptualised information they provide can mat the mind with cliché. And, sadly, they have helped mire osteoporosis in the morass of multifactorial causation, a contemporary belief destructive to research and understanding. In part, this belief relates to the contemporary muddle about the meaning of ''the cause'' of disease and the related absurdities of ''holism'' and stochastic chaos [5] — ideas which mate so well with relativist compromise; science does not dice with relativism. More prosaically, but equally dangerously, it also relates to the suffocation of research by a popular form of statistical epidemiology, which in turn elevates the inevitable finding of trivial associations into the lazy concept of multifactorial aetiology, that last resort of the intellectually destitute. Now it is not the time for a discussion of this muddle, or the reason for my certainty that, by contrast, all diseases that can be controlled (and we should maintain of interest, albeit of a different type in any that, perhaps, cannot) will be found to have single points of effective attack, notwithstanding the inevitable multiplicity of impinging influences. The role of the clinical scientist is to escape from the web of those impinging influences, those inevitable but minor ''factors'' that can always be found and promoted, and where possible to fly away on the wings of a therapeutic missile. The search for Erhlich's sublime bullets is still what the clinical researcher should aim at; they are devastatingly effective, and like discreteness of disease, make a lethal counter to the soggy multifactorial concept.

Need for conceptual base and therapeutic target; origin of hypothesis

Since none of what has been proposed for osteoporosis makes much of a mark when fired from the therapeutic gun [4], now must be the time to start again. In place of demineralisation and its congeners — from chalk to vitamin D via female sex hormones and exercise — all of which have so long been paraded despite their small (but, of course, real effect), I suggest that something closer to a single therapeutic target, if not an aetiological mechanism of osteoporosis, is *loss of bone collagen*. My case for this hypothesis arose from what happens to skin collagen with age, disease, and in response to hormones, and then noticing the remarkable correspondence of this to what happens in bone. As the skin changes are central to my hypothesis, but are not well known and, as we shall see, are still easily confused, I shall outline them first.

Changes in skin collagen with age correspond with osteoporosis

Skin thins and wrinkles with age; it may become brittle, tear and develop *senile purpura*. Long, long ago, I guessed from the initiation, shape and spread of the purpuric blotches of the condition that the mechanism was a loss of dermal collagen, which allows rupture of vessels by shear forces, followed by an unduly luxurious spread of the blood in the atrophic dermis [6]. This conflicted with the view held at the time (and proselytised by reviews that, fortunately, I came to read only after making my own observations and arriving at the conclusions they presented), that skin collagen was unchanged or actually increased with age [7]. This notion was based on the inappropriate use of relative expressions such as *percentages* and *ratios* to other tissue constituents [8,9]. The only absolute thing about such relative measures is they tell absolutely nothing about absolute changes in any particular

constituent. I find it extraordinary that this was not realised at the time and, more so, that the confusion persists. The conflict was easily resolved when skin collagen was expressed in *absolute* terms, most easily done for skin by relating it to an accurately obtained biopsy surface area (using a high speed punch to avoid distortion). In this way it was shown that skin collagen constitutes the bulk of dry dermal mass, and is lost at a rate of 1% a year throughout adult life [9]. That collagen concentration expressed as a percentage, or a ratio to an independent substance (hexosamine was all the rage in those dark distant days), was unchanged or increased [7] is, of course, irrelevant [8,9]. I present this in detail because it is essential to the argument that skin collagen content is measured in *absolute* terms (e.g., relative to surface area) and not the *relative* terms of percentages and ratios still used by some.

It is also important to my hypothesis that the absolute loss of skin collagen with age is the same in sun-exposed and unexposed skin [10], because it shows that this major component of skin ageing is intrinsic, and not, as some still appear to believe, caused by ultraviolet irradiation. The latter induces collagen cross-linking [11], which could well explain the greater brittleness of exposed skin and the localisation of certain lesions [10]. It is also essential to the argument that the rate of collagen loss is the same in men and women, but that as women start with less skin collagen than men, the changes of aging are apparent earlier in them. This sex difference in skin collagen content is apparent throughout adult life, and is equivalent to about 15 years of skin ageing [9].

Changes in skin collagen with hormones correspond to bone density

The parallel between these age and sex changes in skin collagen with the development of osteoporosis in men and women will be apparent. Of course, such a single finding could easily be coincidental; that it is not a coincidence is clear from similar findings in a number of diverse and unrelated situations. The first and most obvious of these is the effect of endocrine modulation. Skin collagen content is site specific in a way that suggests evolutionary adaptation [10]; furthermore individual variation is consistent between sites indicating an overall genetic control of its quantitative ''setting''. However, over and above these variations, hormones can profoundly alter skin collagen content: an increase was found with endogenous virilisation in women with hirsutes [11] and after androgen administration to patients with osteoporosis [13] in a dangerously small study, which nevertheless helped crystallise the present hypothesis; but the greatest increase was found in acromegaly [14] — and skin collagen decreased when growth hormone was decreased or absent in hypopituitarism. The greatest decreases occurred in Cushing's syndrome and glucocorticosteroid administration [15,16]. These different effects of hormones on total skin collagen correspond precisely to well-known changes in bone density, from the dense bones in acromegaly to the thinning with fractures in Cushing's syndrome and hypopituitarism. Because the dermis is mostly collagen, changes skin thickness can reflect collagen content; however their relationship is easily masked by independent changes in skin thickness due to variations in water content and density of collagen packing [9,14,15,17]. The same is true of the skin transparency despite the correlation found with osteoporosis in patients with rheumatoid arthritis and corticosteroid treatment [18].

Significance of correspondence: the hypothesis

As with ageing, therefore, there is a remarkable parallel between endocrine-induced changes in skin collagen and bone density. The notion that the changes in skin collagen with aging and those induced by hormones with totally different biological effects, sites and modes of action, could be related to similar changes in bone density by chance, cannot be seriously sustained. The mechanism underlying the changes in skin and bone must therefore be related. And since it is inconceivable that this relationship is one of the cause and effect (i.e., the absurdist notion that loss of bone density could itself cause loss of skin collagen, or vice versa), I can only conclude that both skin and bone are affected by a related if not the same process. In other words, the simultaneous loss of collagen in skin and density in bones is due to a defect common to both; this has to be the underlying causal relationship in the situations so far discussed. I therefore propose that with ageing, collagen is lost in the bones just as it is in skin — hardly surprising as the bulk of both consists of the same type I collagen — and this leads to the well-known features of loss of substance of the skin, the counterpart of

which is, loss of density of the bones — osteoporosis. Curiously enough, although this notion was formulated [19,13] it was never promoted.

Confirmatory predictions

Skin changes in genetic disorders of bone thinning

If my hypothesis is correct, certain predictions can be made: for example, in genetic disorders with widespread bone thinning, a comparable defect of skin collagen should also be found. Is it? Well it is indeed found in osteogenesis imperfecta, in which the considerable and widespread loss of tissue collagen first shown in skin [19] is now well established [20]. Thus, a disorder once considered to be primarily a particular loss of bone substance, shows a gross reduction of collagen in skin and other tissues; this further supports the hypothesis that loss of collagen may explain the loss of bone substance.

Bone changes in disorders of skin collagen

Acquired disease

What is the state of the bones in skin diseases such as localised scleroderma (morphoea), in which there is an increase in skin collagen? [21]. Sclerotic bone changes do occur, and this would fit the hypothesis; however, it is possible that these are a ''post-inflammatory'' consequence of the disease process. Systemic sclerosis is interesting rather than informative. Despite common assumptions to the contrary, direct measurement shows total skin collagen content is actually decreased [17]. There is an atrophic contracture which tightens the skin so that it cannot easily be lifted from the underlying tissue, and this, I believe, has been misinterpreted clinically as skin thickening [22]. But despite the measured reduction in skin collagen and observed thinning of the bones [23] in systemic sclerosis (note: scleroderma and systemic sclerosis are used interchangeably in many parts of the world), it would be unsafe to attribute this to the common cause of the hypothesis because bone thinning also follows disuse atrophy.

Genetic disorders

More important, therefore, than such acquired disorders where there may be an unrelated pathology, is the evidence from the Ehlers-Danlos syndrome, once thought to be primarily a disorder of skin hyper-elasticity, but now more properly understood as a widespread genetic defect of collagen production. In several of the genetic variants of the disorder there is a decrease collagen content of many organs, including skin and bone [24]; with this, as with aging and corticosteroid action [25], there is tearing of the skin and supportive (shear) purpura [6,26], together with osteoporotic bone thinning with spinal collapse and fractures.

Miscellaneous disorders with osteoporosis and a defect of collagen

There are a number in which the simultaneous occurrence would appear to be causal rather than coincidental. Of these I need only to mention the impaired collagen metabolism and osteoporosis of scurvy [27] and homocystinuria [28].

Bone collagen in osteoporosis

If my hypothesis is correct there must be a loss of bone collagen in osteoporosis, whether from ageing, corticosteroids or genetic and other diseases. But whilst, of course, it is well known that loss of bone collagen occurs in osteoporosis, remarkably, and inexplicably, this has been universally dismissed as secondary to the bone loss; indeed, it is usually relegated to a measurement to be made as an index of bone turnover and loss (e.g. [29,30]). Thus, the problem for my hypothesis is not whether or not collagen loss occurs in osteoporosis — it does — but whether, contrary to the accepted view, it is the primary defect as my hypothesis maintains. Clearly, this now needs testing.

Need for proof that collagen loss is the primary defect

Simple associative studies of skin collagen with bone collagen and density might be adequate to prove whether collagen loss is primary (there will be a temptation to use skin thickness and transparency because they are non-invasive, but for reasons already discussed, this would not be adequate evidence for proof, though these measurements could be useful in defined sequential assessments of treatment). However, the problem with such simple associative studies could arise if the proposed secondary loss of bone density follows so rapidly after the primary loss of bone collagen that it might appear to be concurrent. Thus, unless a decrease in bone collagen — whether measured directly as bone collagen

content or urinary output of collagen products — is found to precede loss of bone density at some, perhaps early, stage of the disease, temporal correlative studies may not be helpful. Although, nevertheless, such studies would need to be done, testing might have to be more sophisticated and critical — for example does collagen loss precede changes in bone density when the former process is extreme, e.g., fast or slow, as with corticosteroids and aging. In this respect, it might be found that changes in total skin collagen content are a predictor of subsequent changes in bone density. For reasons already discussed, skin thinning and translucency are not satisfactory measures as they do not necessarily correspond to total skin collagen.

Treatment and prophylaxis of osteoporosis with androgens and growth hormone

In contemporary medicine, the final arbiter of aetiological uncertainty is often therapeutic — remember the doubts about the role of the HIV virus before the ant-retroviral drugs or, on an altogether more trivial level, the role of the pityrosporum in seborrhoeic dermatitis before ketoconazole. Sadly, the crucially absent key to Koch's ideas at the time they were postulated only arrived later, with effective drugs. So far, apart from vitamin D, calcium and phosphates, the most often studied treatment is female gonadal hormones (see [4]). However, while it now seems desirable to study both skin and bone collagen changes with these hormones, the therapeutic prediction from skin collagen overwhelmingly favours the use of androgens [8,9,12] as in an early study [12]. Recently, there have been reports of osteoporosis with androgen deprivation treatment of prostatic cancer and its treatment with androgens [31], but whilst these effects are strong support for my hypothesis, an extensive, focused study of the effect of different androgens on both bone density and bone and skin collagen is now desirable. Until a dose-response and a clear measure of benefit and harm are established by clinical trial, the case for which is now clear, it is too soon to accept or dismiss their therapeutic potential.

But the response of skin collagen to hormones suggests that far and away the biggest improvement of osteoporosis could be expected from administration of growth hormone [14]. As with androgens, I believe my hypothesis, and the skin and bone changes on which it is based, already justify a full trial of this hormone. Although there have been a few human studies of replacement of a growth hormone defect, have indeed shown an increase in bone density following its use, more importantly this effect has now also been found in patients with idiopathic osteoporosis [32]. Of course, until full clinical studies are done — and as with androgen, a dose-response study establishes the dose required and the risk of harm — it is impossible to guess whether or not growth hormone can serve as a definitive therapy, or simply as therapeutic confirmation of a response predicted from the hypothesis, from which a more suitable agent can be developed.

Collagen production by skin and fibroblasts as bio-assay for drugs

I suspect that the most important consequence of my hypothesis could be less about mechanism than therapy. Drug development is an industrial process, depends both on the underlying concept and on the availability of a simple assay for the screening of potential agents for the desired property. Thus, arising from the hypothesis, it is proposed that the response of skin collagen and, more importantly, the in vitro production of collagen by fibroblasts, could be the crucial tool for the development and screening of new drugs and hormone analogues targeted for enhancing bone density and skin substance in osteoporosis and aging, as well as in prevention.

Other therapeutic possibilities

Beyond these considerations, the therapeutic argument develops easily into some obvious new therapeutic areas in both skin and bone — the former extend from the use of topical androgen by those anxious about skin ageing, to local injections of growth hormone for pugilists who cut easily. I also present three other examples: osteogenesis imperfecta, Ehlers-Danlos syndrome and the skin and bone atrophy that follow corticosteroids, and I mention these because, desirable though it may now be to try the effect of agents such as growth hormone in these situations, it could well be that, unlike in aging, the underlying genetic defect, or its consequences, will not allow the increased collagen production which is so apparent in normal tissues. Reversal of a defect does not always follow from exposure to its causal mechanism — which may well explain the disappointments of couch psychiatry. The consequences of corticosteroid action may be an example of this, because, although there

have been no studies of reversal of skin and bone collagen after stopping corticosteroids, dermal atrophy after local steroid injection is known to persist for years. Thus, even if my hypothesis is found tenable, its practical consequences will have to be tested in each pathological situation with its defects in skin and/or bone.

Summary and conclusions

I suggest that conceptual and therapeutic understanding of osteoporosis have failed to develop because research has used a rudderless statistical epidemiology instead of a hypothesis-led search for mechanism and treatment. From the correspondence between changes in total skin collagen with age and hormones it is proposed that the therapeutic target, if not ''primary'' defect in osteoporosis is a loss of bone collagen, to which bone thinning is secondary. Predictions from this hypothesis have been fulfilled in a number of situations, but others are proposed for testing. Meanwhile, there is a justification for an exploration of the clinically predictive value of the changes in skin collagen and clinical trials of hormones which increase its skin content, particularly androgens and growth hormone, in osteoporotic diseases as well as aging. It is suggested that the changes in total skin collagen (and, perhaps certain of its correlates) and more importantly its in vitro production by fibroblasts, could be used industrially as a pharmacological assay for the development of new treatments.

Finally, pleased though I would be if my hypothesis proved to be correct, even if it fails in the testing it would nevertheless have succeeded at a more fundamental level: since the idea will have to be considered if only to be refuted, this would achieve my objective, to promote engagement with the core philosophy of a hypothesis in clinical research.

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