Connective Tissue Abnormalities in Diabetes Mellitus

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The vascular complications of diabetes mellitus are well recognised as a cause of morbidity and mortality. Both the macroangiopathy (in the form of the atherosclerotic plaque) and the microangiopathy (capillary basement membrane thickening) may be classified as connective tissue abnormalities since they are characterised by disturbances in the structural macromolecules of the extracellular matrix[1,2]. However, interstitial connective tissues such as the skeleton, joints and periarticular structures are also affected, although these complications have received little attention because they are less disabling. The rheumatological aspects have been previously reviewed[3,4] but clearer recognition of diabetic osteoporosis, the 'pseudo-scleroderma' of juvenile diabetes and the association with Dupuytren's disease, has stimulated investigation of the mechanisms underlying these connective tissue lesions. A wide range of syndromes are associated with diabetes (Table 1) and these fall largely into two groups: first, those characterised by reduced bone density (generalised or localised) and, second, those involving inappropriate deposition of connective tissue.

Table 1. Connective tissue manifestations of diabetes mellitus.

Skeleton
Osteoporosis
New bone formation — vertebral ankylosing hyperostosis
— hyperostosis frontalis interna
— osteitis condensans ilii
Joints
Neuropathic joint
Gout and pyrophosphate arthropathy?
Osteoarthrosis
Algodystrophy
Adhesive capsulitis of the shoulder
Shoulder-hand syndrome
'Forefoot osteolysis'
Transient juxta-articular osteoporosis of hip and knee
Skin and peri-articular tissues
'Pseudo-scleroderma' — tight, waxy skin
— limited joint mobility
— tenosynovitis
Carpal tunnel syndrome
Dupuytren's disease
Other fibromatoses — Peyronie's disease
— Ledderhose's disease
Developmental anomalies
Premature ageing syndromes
Congenital malformations

The Skeleton

Osteoporosis

Since the early autopsy study of Hernberg[5] much evidence that the insulin-dependent diabetic is at risk of generalised osteoporosis has accumulated. Objective measurements of forearm bone density by photon absorptiometry have demonstrated that bone mass is decreased by up to 20 per cent in young diabetics when compared with age- and sex-matched controls. This decrease in bone density is detectable early in the disease and is not related to its duration[6,7]. Furthermore, it has been suggested that the normal spurt in endosteal bone deposition at puberty is suppressed in diabetics[8]. In adult insulin-dependent diabetes the rate of bone loss is also maximal at or soon after diagnosis, and is correlated with the level of endogenous serum insulin[9].

The primary anabolic role of insulin and insulin-like growth factors is well documented[10]. Insulin stimulates nucleotide synthesis by osteoblasts *in vitro*[11], promotes the intracellular accumulation of amino acids in fetal membranous bone[12] and can restore circulating somatomedin levels in experimental diabetes[13]. Moreover, the hormone promotes bone collagen synthesis [12,14,15] and increases calcium deposition in the skeleton[16]. We conclude that insulin deficiency leads to net bone loss (either through failure of formation or increased resorption) and that replacement therapy is likely to diminish it. It remains to be seen whether early optimal therapy with an insulin continuous infusion pump can abolish this

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complication. Such a pathogenetic mechanism could explain why maturity-onset diabetics, who may have raised endogenous serum insulin levels, are spared[5] and may even have denser bone than age-matched controls[17].

The view that insulin deficiency is of primary importance in diabetic osteoporosis is supported by a study of streptozotocin-induced diabetes in rats[18]. Histology indicated reduced bone remodelling, with decreased osteoclasts and bone-forming sites, together with failure to assume a tetracycline label. Although serum calcium and phosphate concentrations were raised with increased urinary outputs, most biochemical changes were indicative of reduced bone turnover. Immunoreactive parathyroid hormone (iPTH) was not elevated and urinary cyclic AMP (a measure of PTH activity) was greatly decreased. Serum alkaline phosphatase and urinary hydroxyproline (indices of osteoblastic and osteoclastic function respectively) were reduced. Immunoreactive calcitonin (iCT) was increased, which may be construed as an attempt to minimise resorption of the already weakened bone. Insulin therapy corrected all the above abnormalities except the high urinary phosphate excretion.

A comparable study of human diabetic bone has not been published, but vitamin D and mineral metabolism have been investigated. Hypercalciuria and hyperphosphaturia in the presence of normal serum iPTH[8,19,20] are common and can be reversed by insulin[21,22]. A small reduction in serum total and ionised calcium[8] contrasts with their modest elevation in experimental diabetes in the rat[18]. Reduced serum concentrations of 1,25 dihydroxycholecalciferol ($1,25(OH)_2D3$) have been reported in the diabetic rat[23] and in juvenile diabetics[22,24], but the latter observation has not been confirmed[19,25]. In view of the suggestion that $24,25(OH)_2D3$ is an essential requirement for bone formation[26], the finding of reduced serum levels of this metabolite in the presence of normal concentrations of $25(OH)D3$ and $1,25(OH)_2D3$[25] is worthy of further investigation. Preliminary histological studies of diabetic human bone indicated a reduction in turnover[9,27]. This would not be compatible with the speculation that acidosis, which stimulates bone resorption, plays an important role[28].

Reference has already been made to the potential role of calcitonin in sedating osteoclasts and opposing bone resorption[29,30]. The increased level of serum iCT in experimental diabetes[18] is of interest, but it is not known whether its suppression by insulin therapy is primary or secondary. A close relationship between these two hormones is further suggested by the observations that patients with Paget's disease may develop reversible glucose intolerance when starting calcitonin (CT) therapy[31,32] and that CT can suppress pancreatic insulin output in man[33]. It is possible that insulin-calcitonin interaction may represent an unrecognised bone homeostatic mechanism.

From a carefully controlled study Heath *et al.*[34] concluded that '. . . any reduction of bone mass in diabetics that is revealed by sophisticated analysis is of no medical or economic importance to the patients or their physicians.' Nevertheless, although diabetic osteoporosis is frequently sub-clinical, a raised incidence of pathological fracture of the hip[35,36] and the foot[37] has been reported.

New Bone Formation

Whereas the skeleton of the juvenile-onset diabetic displays a tendency to rarefaction, that of the maturity-onset diabetic seems more prone to the inappropriate deposition of bone in certain sites[28]. Most attention has been paid to hyperostosis of the spine[38] but it also occurs elsewhere. In one study of 428 diabetics, hyperostosis was present in 25 per cent: as well as spinal involvement, hyperostosis frontalis interna, calcification of pelvic ligaments and osteitis condensans ilii were noted[39]. New bone formation around the hips, knees and wrists has also been recorded[4,40]. Hyperostosis frontalis interna is frequently accompanied by maturity-onset diabetes in Morgagni's syndrome[41].

Ankylosing hyperostosis of the spine occurs in 2-4 per cent of the normal population over the age of 40[42] and the prevalence of 13 per cent in diabetics (rising to 21 per cent in the age group 60-69 years) leaves little doubt that the association is genuine[43]. The condition is often symptomless and may be an incidental radiographic finding. There may be some back pain and stiffness, but sparing of the posterior spinal joints may account for the retention of good spinal movement[44]. It is characterised by bony outgrowths, which form anterior bridges between vertebrae, and sclerosis of the underlying vertebral cortex. Ossification occurs in adjacent connective tissue, commonly the anterior longitudinal ligament and the periphery of the intervertebral disc. The thoracic spine is most commonly involved, especially on the right, but the cervical and lumbar spines may also be affected. It is easily distinguishable from ankylosing spondylitis, which occurs in a younger age group in whom incapacitating early-morning stiffness and loss of spinal movements are more prominent. Radiologically, ankylosing spondylitis is characterised by 'squaring' of vertebral bodies, focal bone loss at ligamentous insertions and vertebral body osteoporosis. Intervertebral spaces are bridged by vertebral syndesmophytes rather than the curved, beak-like osteophytes of hyperostosis. The sacro-iliac joints are spared in hyperostosis in contrast to ankylosing spondylitis[4,38]; early reports of an association with HLA B27 have not been confirmed[45].

No adequate explanation of the association of diabetes and new bone formation has been offered. Growth hormone metabolism is normal[43]. The suggestion that diabetes and obesity are independently linked with spinal hyperostosis[46] has not been proved but exaggerated serum insulin responses to glucose challenge have been reported in non-diabetic cases[47]. It is possible that insulin and/or insulin-like growth factors in maturity-onset diabetes and obesity may promote new bone formation.

An autopsy study of 20 cases of ankylosing hyperostosis indicated that the initial event may be antero-lateral extension of the annulus fibrosus, with the formation of new bone in response to elevation of the periosteum[44].

These authors thought that the spinal changes were part of a generalised congenital or acquired abnormality of skeletal tissues but found no evidence to favour an association with diabetes. Some of the pathological changes in spinal hyperostosis can be better understood if it is remembered that the cells of the intervertebral disc may be considered as specialised chondrocytes with some of the properties of fibrocytes[48]. This could explain the tendency to endochondral ossification in the fibrous extension of the annulus and the adjacent anterior longitudinal ligament. Morphologically, the cells of the outer annulus resemble tendon cells rather than chondrocytes[49] and may respond to diabetes in a manner similar to that of mesenchymal cells in sites such as the palmar aponeurosis, viz. by proliferation and deposition of extracellular matrix. The factors which could stimulate fibroblast proliferation in diabetes remain to be identified but may include mast cell products[50] and compounds of low molecular weight which are present in diabetic serum[51].

The Joints

With the decline of neurosyphilis, diabetes has become the most common cause, outside lepromatous regions, of neuropathic joints. They have been well described[52]. Rudolf *et al.*[53] described seven insulin-dependent diabetic children with juvenile chronic arthritis. Since both diabetes[54] and rheumatoid arthritis[55] are strongly associated with HLA-DRW3 and DRW4, the occasional co-existence of the two conditions offers little surprise[56]. Several other rheumatic disorders have been linked to diabetes but the evidence is tenuous.

Gout and Pyrophosphate Arthropathy

It appears that non-obese diabetics run no greater risk of gout than the normal population, but a prospective study with age-, sex- and weight-matched controls has not been performed. Chronic glucose loading actually promotes uric acid excretion[57], and the onset of frank diabetes is accompanied by a fall in serum urate[58] and a reduction in the frequency and severity of attacks in patients with pre-existing gout[59]. Diabetes may be complicated by hyperuricaemia in ketoacidosis when ketone bodies inhibit the renal tubular secretion of uric acid[60].

However, obesity is an important cause of hyperuricaemia[61] and is probably the crucial link between hyperuricaemia, hyperglycaemia and hyperlipidaemia[62]. Although there have been reports of an increased prevalence of diabetes in gouty subjects[63,64], a study of glucose tolerance in weight-matched gouty and non-gouty subjects failed to demonstrate a difference[65]. In summary, frank diabetics who are not obese may be less likely to develop gout than normal subjects and it is probable that non-obese gouty patients do not have an increased tendency to diabetes.

In their initial description of pyrophosphate arthropathy McCarty *et al.*[66] noted an apparent association with diabetes but were unable to substantiate it in a later study[67]. In a survey of 105 consecutive patients with pyrophosphate arthropathy, Alexander *et al.*[68] were also unable to confirm an association. However, the actual prevalence of this type of arthropathy among diabetics has not been established.

Osteoarthrosis

It is obviously difficult to establish a relationship between such common diseases as osteoarthrosis and diabetes but a positive correlation has been documented in two controlled studies[69,70]. In the latter study not only was there a higher prevalence of osteoarthrosis in the group of young and middle-aged diabetics but joint damage started at an earlier age and was more severe than in controls. Experimental studies indicate that cartilage growth is depressed in diabetes[71,72] and there is diminished formation of sulphated proteoglycans[72-74], together with a reduction in the size of the high molecular weight proteoglycan aggregates[73-75]. Insulin has been shown to stimulate cartilage growth activity and proteoglycan biosynthesis[14,71,73] but although chondrocytes express insulin receptors under certain conditions[76,77] these effects are probably mediated through the somatomedins[71].

Both the structure and metabolism of hyaline cartilage are complex and it is not unreasonable to anticipate exacerbation of osteoarthrosis in diabetes. Nevertheless, osteoarthrosis is more than a simple depletion of chondroitin sulphate proteoglycan from the cartilage matrix[78] and until the significance of the matrix changes is understood it will be difficult to assign a certain pathogenetic role to diabetes.

Algodystrophy

A number of syndromes of unknown pathogenesis variously described as 'Sudek's atrophy', 'reflex sympathetic dystrophy', 'transient osteoporosis' and 'migratory osteolysis' have been grouped under the heading of algodystrophy[79]. They are characterised by pain and sometimes swelling of articular or peri-articular structures in which the severity of the pain may be disproportionate to the physical signs. Overlying vasomotor changes are common and mobility is limited. There may be increased urinary excretion of calcium and hydroxyproline, and early increased uptake of bone-seeking isotopes is almost invariable. Radiological changes of 'spotty' or diffuse osteoporosis are usually late developments. The natural course of these syndromes is spontaneous resolution, occasionally with fibrosis and contracture[80].

While trauma remains the most common predisposing cause of algodystrophy, a wide range of conditions and drugs also provides a fertile soil for its development (Table 2). Why diabetics are prone to algodystrophy is unknown. Of 108 consecutive cases, 8 were diabetic: 2 had shoulder-hand syndrome, 2 had knee involvement and in 4 the foot was affected[79]. The prevalence of diabetes in algodystrophy is said to be 7.4 per cent, but not all patients had glucose tolerance tests. Therefore the true prevalence may well be higher.

Table 2. Factors predisposing to algodystrophy[79,81,82].

Trauma	Barbiturates
Cerebrovascular disease	Isoniazid
Myocardial infarction	Ethionamide
The post-thoracotomy state	Cycloserine
Hyperthyroidism	Radio-iodine
Hyperlipidaemia	
Diabetes mellitus	
Electrocution	

Adhesive Capsulitis of the Shoulder and the Shoulder-hand Syndrome

In adhesive capsulitis there is painful restriction of all shoulder movements[83]. The thickened joint capsule is closely applied and adherent to the head of the humerus; arthrography demonstrates a marked reduction in volume of the gleno-humeral joint. There is increased periarticular uptake of 99m-technesium methylene-diphosphonate[84] and, later, bone demineralisation. Spontaneous recovery usually takes place within three years. The shoulder-hand syndrome may be considered a rarer but exaggerated species of adhesive capsulitis involving the whole upper limb, with striking vasomotor changes and oedema in the distal part[85].

In one study of 800 diabetic patients, 10 per cent had shoulder capsulitis compared with 2.5 per cent of non-diabetic controls[86]. Conversely, 28 per cent of patients with shoulder capsulitis had abnormal glucose tolerance tests as opposed to 12 per cent of age- and sex-matched controls attending a rheumatology clinic[80]. Capsulitis in diabetics is often multifocal and recurrent[80,86,87].

'Forefoot Osteolysis'

'Forefoot osteolysis' has been recognised as a distinct complication of diabetes but previous authors have failed to consider it as an example of algodystrophy[37,88-91]. It may be a presenting feature of diabetes but is more commonly recognised in a known case as a 'spotty' or generalised osteoporosis of the distal metatarsus and proximal phalanges. Pain is a variable feature and cutaneous erythema may be prominent. The inevitable exhaustive search for cellulitis or osteomyelitis, both known hazards of diabetes, fails to provide any evidence of infection. Arteriopathy and neuropathy are absent. Osteoporosis may be accompanied by juxta-articular erosions mimicking those of rheumatoid arthritis and gout[88,90]. These defects may proceed to complete lysis of the bone ends, although the articular surfaces may be preserved to a late stage. After a variable interval a perfect reconstruction of the bone and joint usually ensues.

Transient Juxta-articular Osteoporosis of Hip and Knee

In a study of 34 patients with algodystrophy of the hip, 5 had diabetes and the whole group of 34 patients showed an exaggerated serum triglyceride response to alcohol ingestion[82].

A connection between algodystrophy of the knee and diabetes has not been established, and the only report linking the two conditions is that of Doury *et al.*[79].

It is difficult to evaluate treatments of diseases that resolve spontaneously. Calcitonin therapy has been popular in Europe[79]. No reports of the treatment of diabetes-associated algodystrophy with calcitonin are available but in view of its ability to reduce endogenous insulin output[33] it should be used with caution.

Skin and Peri-articular Tissues

The tendency of diabetics to infection and ulceration of the skin, especially of the feet, is well recognised. Other dermatological features of diabetes include necrobiosis lipoidica and diabetic dermopathy[92], granuloma annulare[93] and reactive perforating collagenosis[94]. Within the last decade there has been increasing recognition of a condition involving both the skin and peri-articular tissues and grossly resembling scleroderma.

Diabetic 'Pseudo-scleroderma'

Most descriptions have concentrated only on the hand in juvenile-onset diabetes and have given rise to several synonymous terms such as 'diabetic hand syndrome', 'limited joint mobility' and 'juvenile diabetic cheiroarthropathy'. The clinical signs of thick tight waxy skin, tenosynovitis and restriction of joint movement are highly reminiscent of classical scleroderma but features such as Raynaud's phenomenon and telangiectasia are missing.

The thickening of the skin occurs principally over the dorsum of the hands[95-97] and there is histological evidence of dermal fibrosis and a dearth of sebaceous glands[95]. Seibold[97] found induration of the finger skin in 47 of 137 children (34 per cent) with insulin-dependent diabetes and in none of 52 controls. While severely affected children had loss of the transverse ridges on the dorsal skin, other signs suggestive of scleroderma were absent. Nevertheless, in six children sclerosis was present proximal to the metacarpophalangeal joints, which would fulfil the criteria for scleroderma established by the American Rheumatism Association[98]. Of the affected children 81 per cent also had skin thickening over the forefeet and toes.

A more obvious feature of diabetic 'pseudo-scleroderma' is contracture of joints. The reported prevalence of finger-joint contracture is between 8 and 42 per cent[95,97,99-101], and occasionally larger joints may be affected[97,101]. In the largest study, 30 per cent of 309 patients aged 1-28 years had contractures and one-third of these had dermal sclerosis[95]. No relationship to sex, insulin dosage or quality of metabolic control was found, but there was clearly an association with disease duration and microangiopathy[95,101]. A defective microcirculation may indeed prove to be the common denominator of classical scleroderma[102] and diabetic 'pseudo-scleroderma'. An evaluation of nailfold capillaries, which are morphologically abnormal in scleroderma[103] and excessively permeable in diabetes[104], has not yet been reported in diabetics with finger-joint contracture.

The limitation of joint movement most probably results from dermal and subcutaneous sclerosis, but fibrous thickening of the flexor tendon sheaths is almost certainly a contributory factor[97,105-107]. The molecular basis of the sclerosis remains obscure. Buckingham *et al.*[96] noted that the syndrome was accompanied by a high level of non-enzymatic glucosylation of haemoglobin A1 (a reflection of poor metabolic control) and skin collagen. Furthermore, the solubility of the skin collagen in acetic acid was reduced in two of their three patients, which suggests increased intermolecular crosslinking. This could diminish turnover of collagen fibres by inducing resistance to collagenase degradation[108,109]. Support for this concept has come from studies in diabetic rats in which there are increased amounts of lysine-derived crosslinks in the collagen of the tail tendons[110]. The first step in the formation of such crosslinks is the oxidative deamination of lysine and hydroxylysine residues in the chains of collagen: the reactive aldehydes formed undergo spontaneous condensation (Fig. 1: for

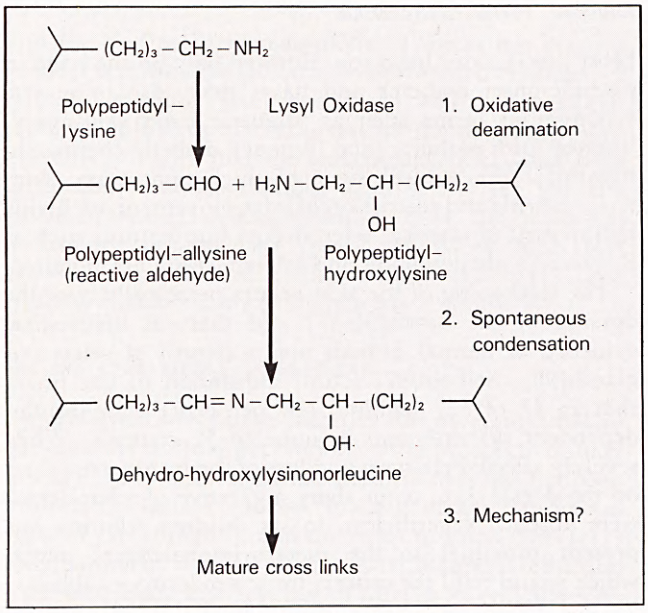

Fig. 1. *Formation of lysine-derived intermolecular crosslinks in adult dermal collagen.*

reviews,[111,112]). The deamination is controlled by the enzyme, lysyl oxidase, the activity of which may be increased in experimental diabetes[113]. Chang *et al.*[114] reported a reduction in the solubility of collagen from granulation tissue in diabetic rats compared with controls, and concluded that this reflected an increase in lysine-derived crosslinks because it could be prevented by the feeding of β-aminopropionitrile (an inhibitor of lysyl oxidase).

Nevertheless, not all experimental studies support the idea of enhanced crosslinking[115,116]. Studies *in vitro* clearly indicate that the increased non-enzymatic glucosylation of collagen reported in diabetes[96,117-120] may actually interfere with the crosslinking and maturation of collagen fibres[121]. To date there is no evidence of increased synthesis of collagen in the skin and subcutaneous tissues of diabetic animals[122], although skin fibroblasts from insulin-dependent diabetics appear to synthesise increased amounts *in vitro*[123].

Carpal Tunnel Syndrome

In a series of 379 patients with carpal tunnel syndrome, 63 (16.6 per cent) were found to be diabetic[124]. There is now convincing evidence that carpal tunnel syndrome may be caused by a primary deficiency of vitamin B6[125], and pyridoxine deficiency has been reported in diabetes[126,127]. The idea that deficiency of the vitamin underlies the association is attractive but unsupported by the only published study[128].

Dupuytren's Disease (DD)

The association of DD with diabetes has been noted on many occasions (Table 3), although its validity is not universally accepted[142]. This is to some extent a reflection of the high frequency of DD in the general population, especially the elderly[143,144]. Moreover, some studies (for example [137]) have focused on the contracture, i.e., the thickened band of palmar fascia and the flexion deformity, and have ignored less prominent features such as tethering of the skin and knuckle pads[143,144]. In this way a number of genuine cases of DD will have been missed.

Most observers agree that diabetics with DD tend to be older and to have had diabetes for a longer period than those without, but there is no evidence of the mode of treatment or the quality of control having any effect on the development of the hand lesions. However, the last point needs checking by an objective measurement of control such as glucosylated haemoglobin. The disease tends to be milder in diabetics[134,135] and few patients have symptoms. This is especially true of women[145]. In non-diabetics the lesions are mainly found in the little and ring finger-rays[130,146,147] but in the series of diabetics examined by Noble *et al.*[145] the middle and ring finger-rays bore the brunt of the disease.

Günther and Miosga[135] concluded that, as the proportion of diabetics with the condition increased with the increasing duration of hyperglycaemia (Table 4), DD was a late complication of diabetes. This interpretation may not be valid because their data indicate that 40 per cent of the cases of DD had had diabetes for less than ten years. Heathcote *et al.*[138] reported a corresponding figure of 57 per cent, and the proportion of diabetics with DD again rose with the duration of disease (Table 4). Since as high a proportion as 16 per cent of adult diabetics have the stigmata of DD at the time of diagnosis, the hypothesis that the fascial abnormality is a late complication is untenable[138]. A number of authors[133,136,137] have noted that DD may be linked to impaired glucose tolerance without overt diabetes. It would appear that DD must be considered a marker of the onset of carbohydrate intolerance, although it is not known what proportion of people with the disease will develop frank diabetes.

The tantalising nature of DD has provoked consider-

Table 3. Association of Dupuytren's disease and diabetes mellitus.

(a) Dupuytren's disease in diabetics

Patients	Prevalence			
	Diabetics		Matched Controls	
	No.	%	No.	%
Diabetic clinic[129]	8/500	1.6		
Diabetic clinic (>16 yr)[130]	6/200	3.0		
Diabetic clinic (>45 yr)[131]	117/475	25.0	84/500	17.0
Hospital patients[132]	34/268	13.0		
Diabetic clinic (>40 yr)[133]	83/400	21.0	27/500	5.0
Diabetic clinic[134]	224/716	32.0		
Diabetes Institute (>11 yr)[135]	96/1000	9.6	27/1000	2.7
Home for aged[136]	32/51	63.0		
Diabetic clinic (>16 yr)[137]	152/849	18.0		
General medical patients (>17 yr)[137]	17/110	15.0	9/1396	<1.0
Diabetic clinic (>16 yr)[138]	51/122	42.0	16/122	13.0

(b) Diabetes mellitus in patients with Dupuytren's disease

Patients	Prevalence			
	Overt DM		Reduced Glucose Tolerance	
	No.	%	No.	%
Volunteers (>50 yr)[139]	90/178	51		
Hospital patients[132]	41/193	13		
General medical clinic[140]	25/100	25	56/100	56
Hospital patients[141]	10/125	8		
Hospital patients[136]	44/94	47	16/94	17
Home for aged[136]	32/79	41	27/79	34

Table 4. Prevalence of Dupuytren's disease related to duration of diabetes.

	Duration of diabetes (yr)						
	0–5	6–10	11–15	16–20	21–25	26–30	30
Günther and Miosga (1972)[135]							
No. of patients	392	322	161	45	47	21	12
No. with DD	13	25	19	8	17	8	6
Percentage with DD	3	8	12	18	36	38	50
Heathcote *et al.* (1981)[138]							
No. of patients	62	22	14	12	6	3	3
No. with DD	19	10	6	8	5	2	1
Percentage with DD	31	45	43	67	83	67	33

able efforts to determine its pathogenesis. Gabbiani and Majno[148] described the occurrence in the nodules of modified fibroblasts ('myofibroblasts'), which resemble smooth muscle cells and are contractile[149]. Their proliferation and contraction might subject neighbouring fascial structures to intermittent tension, which results in work hypertrophy[150,151], and the presence of these cells in the dermis overlying Dupuytren's nodules[149] could explain the observed tethering of the skin. Myofibroblasts have also been reported in the nodules of Ledderhose's disease[149] and may be present in abnormal penile tissue in Peyronie's disease[152,153].

Biochemical studies on palmar fascia in DD indicate that there is active deposition of new connective tissue in the aponeurosis and that apparently uninvolved fascia is of abnormal composition. Increased amounts of type III collagen are present in the diseased fascia[154-156] and Brickley-Parsons *et al.*[155] were able to correlate the amount with the severity of the lesion. The greatest proportion of type III collagen was found in the nodules[155], which may reflect the effect of high cell density upon the pattern of collagen biosynthesis in fibroblasts[157]. The increased proportions of type III collagen and type I trimer[156] are characteristic of embryonic

collagen, and this immaturity is also seen in the glycosaminoglycan components of the connective tissue. Increased amounts of sulphated glycosaminoglycans, particularly chondroitin sulphate and dermatan sulphate[155,158-160], are present in Dupuytren's tissue, and are characteristic of immature tendinous structures[161]. The problem of relating these biochemical changes to the development of the contracture remains. From their detailed studies Brickley-Parsons *et al.*[155] concluded that the active reparative process in the palmar fascia resulted in a gradual approximation of the extremities of the lesion, akin to wound contracture. Why diabetes should promote these abnormalities has not been investigated, although increased biosynthesis of type III collagen in the skin of diabetic mice has been reported[162], and a high concentration of glucose stimulates the secretion of type III procollagen by fibroblasts *in vitro*[163].

Other Fibromatoses

Dupuytren's disease may co-exist with fascial thickening at multiple sites[164], notably the penis (Peyronie's disease) and the plantar fascia (Ledderhose's disease) . Both of these diseases have been described in diabetics[165-167] but because of their rarity it is impossible to say that this association is specific. In a group of 96 diabetics with DD, Günther and Miosga[135] found two patients with co-existent Peyronie's disease and two with Ledderhose's disease. Some cases of adhesive capsulitis of the shoulder, which have been linked to diabetes, may be examples of fibromatosis[165,168].

Developmental Anomalies

Premature Ageing

There are at least five major syndromes characterised by the appearance of premature ageing and three of these, metageria, pangeria (Werner's syndrome) and total lipodystropy, are associated with diabetes[169]. In the Hutchinson-Gilford progeria syndrome there is usually insulin resistance but not glucose intolerance[170,171]. The precise clinical features of these syndromes differ, but there is a general tendency to premature development of atherosclerosis with or without vascular calcification, atrophy of the skin, and generalised loss of subcutaneous fat, particularly on the limbs. In pangeria there is osteoporosis and patchy thickening of the skin, especially on the face and legs[172]. The linkage of these features suggests a widespread cellular defect of mesenchyme but the relationship to diabetes is obscure. Fibroblasts from progeric patients are less sensitive to the growth-promoting effects of insulin-like growth factors in plasma[173], which may account in part for the disordered development of connective tissues. For example, there is periarticular fibrosis in progeria[169] and increased solubility of skin collagen in pangeria[174]. In total lipodystrophy the subcutaneous adipose layer is replaced by acellular fibrous tissue[175] and this is reminiscent of the change in palmar subcutaneous tissue that is seen in Dupuytren's disease[160].

Congenital Malformations

It is well established that maternal diabetes is correlated with an increased risk of congenital malformations in the fetus[176]. The malformation most clearly associated with diabetes is the caudal regression syndrome in which there is femoral hypoplasia together with agenesis of the lower vertebrae. In the offspring of diabetic women the risk of its occurrence is increased 250-fold[176]. In another syndrome femoral hypoplasia may be accompanied by abnormalities of the face and upper extremities[177].

Caudal regression has been described in rats with streptozotocin-induced diabetes[178] in which there is both failure of ossification of the caudal vertebrae and defective fusion. These abnormalities can be prevented by careful control of blood sugar during the period of organogenesis[179,180]. Evidence from human studies also supports the association of congenital malformations with poor control during this period[181]. Glucose itself may be teratogenic[182], but other components in diabetic serum may be implicated[183]. Insulin can also produce skeletal defects in early embryos, but fetal hyperinsulinism is not thought to be the direct cause of the caudal regression syndrome[184]. In addition, growth retardation in early pregnancy[7-14 weeks) occurs in about one-third of the fetuses of insulin-dependent diabetic mothers[185] and appears to be linked to an increased incidence of congenital malformations[186].

Summary

A wide range of connective tissue disorders associated with carbohydrate intolerance has been reviewed. Although some insight into the cellular and molecular mechanisms of these disorders has been gained, it is still far from clear why diabetes should predispose to connective tissue problems.

There is little evidence that heredity plays a significant role, although there may be a genetic component in the development of diabetic 'pseudo-scleroderma'[101,187]. There have been two reports[188,189] of chromosomal defects in fibroblasts cultured from the palmar fascia of patients with DD, defects that were not present in unaffected skin fibroblasts from the same patients. Such cytogenetic lesions might accentuate the natural differences between fibroblasts from different sites[190] and contribute to the defective growth regulation found in some strains of diabetic fibroblasts[191-196]. The clinical observation that DD[138] and joint contractures[107] may precede the onset of overt diabetes is compatible with the existence of an underlying cellular defect.

The role of diabetic microangiopathy in the development of the connective tissue lesions also deserves more attention. There have been isolated reports of microangiopathic changes in osteoporosis[36] and adhesive capsulitis of the shoulder[168]. The limited joint mobility and skin thickening described by Rosenbloom *et al.*[195] were associated with an increased risk of microvascular complications, although others have disputed the association[101,197]. Moreover, from studies of hypertrophic scars and keloids[198], it has become evident that capil-

lary occlusion may induce hypoxic injury in connective tissues.

It has been claimed that tighter control of blood glucose may reduce skin thickness[199] and improve joint mobility[107]. Nevertheless, the degree of responsiveness of mesenchymal cell metabolism to insulin[200,201] or increased levels of glucose in extracellular fluid[202] is still far from clear.

Acknowledgements

A.J.C. was a recipient of an Arthritis and Rheumatism Council Travelling Fellowship in the Arthritis Unit, Massachusetts General Hospital, Boston, USA, during the preparation of this review, and also wishes to acknowledge the support of the King Edward's Hospital Fund for London and the Wellcome Trust.

J.G.H. holds a Career Development Award of the Juvenile Diabetes Foundation.

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