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Letters to the Editor

Diabetic thick skin and stiff joints

Dear Sir,

In their review, Goodfield and Millard [1] list this condition under the rubric "Cutaneous features of vascular insufficiency", and term it "cheiro-arthropathy". They indicate that enthusiastic use of the test involving approximation of the palmar surfaces of the fingers leads to detection of abnormalities in many normal people, that the joint stiffness in the fingers is a result of stiffness of the skin, and that the lack of correlation with non-enzymatic glycosylation indicates that the browning reaction is not causal. Furthermore, they suggest that the association of limited joint mobility (LJM) with chronic complications may simply reflect the fact that all of these features are more likely in those with longer duration and poorer diabetes control. None of these notions is supportable, including the classification and terminology.

Firstly, considering the syndrome of LJM, particularly as it occurs in young patients [2], to be a result of cutaneous vascular insufficiency has no experimental basis. Biopsy study of the associated skin changes shows thickening of the dermis and epidermis with accumulation of collagen and loss of skin appendages, compared to control biopsies [3, 4]. Biochemical study does, indeed, fail to show that skin collagen glycosylation correlates with LJM [5, 6] or with microvascular complications [6]. Skin collagen glycosylation does, however, correlate with HbA_1 levels, reflecting the ketoamine link, an early step in the non-enzymatic browning reaction. Thus, glycosylation in the skin simply reflects recent diabetic control and not long-standing processes that would lead to abnormalities in the connective tissue. The stable end-products of the non-enzymatic browning reaction which are thought to be responsible for increased cross-linking, packing, and stiffening of collagen are fluorescent. Monnier et al. [6] demonstrated that fluorescence of skin collagen increased linearly with age, but that 95% of 41 Type 1 (insulin-dependent) diabetes patients had abnormal increases for age, and that the degree of skin collagen fluorescence correlated with the presence of retinopathy, nephropathy, *and* LJM.

The suggestion that cautious interpretation of LJM is needed because of its frequency in the normal population is in reference to a study [7] in older patients, in whom age and occupation-related changes in the finger joints confound interpretation, as does the presence of Dupuytren contracture. This is most definitely not the case in the young patients originally and subsequently reported by numerous investigators. Control populations of patients under 25 have been found to have an absence of any detectible limitation using the same techniques applied to age-comparable young people with diabetes having frequencies of limitation in the 30% range [2].

The authors suggest that LJM results from skin stiffness. This does not appear to be the case in youngsters with LJM, most of whom do not have clinically apparent thickened skin, but periarticular connective tissue thickening on radiographs and by palpation. Furthermore, extension is limited initially and flexion much later, if at all, the opposite of what would be expected if the predominantly dorsal thickening of the skin was responsible. Some investigators detect skin changes more frequently than LJM, either by palpation or ultrasound [8, 9]. Thus, if skin stiffness were the cause of the LJM, one would expect those with LJM to all have apparent skin stiffness. Buckingham et al. [8] found skin changes in 34% of patients without LJM, 70% with LJM, but, similarly to us [3], 100% of those with severe LJM.

The term cheiro-arthropathy is inadequate since other joints besides those in the hand are involved in this syndrome [3].

The suggestion that the association of limited joint mobility with the long-term complications of diabetes might simply reflect longer duration of diabetes and poorer diabetes control needs to be addressed. Although studies have not been carried out from the time of diabetes onset to demonstrate the relationship of control to the development of LJM, no relationship to metabolic control has yet been demonstrated, either using glycosylated haemoglobin levels or clinical criteria, in numerous controlled studies [2]. In our original report of the association of LJM with microvascular complications, half the population with greater than 4.5 years duration of diabetes had LJM and half of those with LJM had microvascular complications, in contrast to only 10 of 87 without LJM. Severity of LJM correlated directly with the frequency and severity of the microvascular disease; differences between LJM and non-LJM groups could not be accounted for by age or duration differences. Life-table analysis indicated an 83% risk for microvascular complications after 16 years of diabetes if LJM was present, in contrast to only 25% risk without LJM. The 95% confidence limits for these estimates were 70% to 96% and 6% to 45% [8]. This striking association has been confirmed by other investigators who controlled for duration effects [9, 11–13]. The suggestion that this is simply a duration effect has been made without comparisons to duration-matched control subjects nor the application of statistical methods to determine the interaction of duration with other factors [13]. In older patients, particularly those with Type 2 (non-insulin dependent) diabetes, the association of LJM and microvascular disease, although significant, is less striking [7, 15–17].

Yours sincerely,
A. L. Rosenbloom

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The skin in diabetes mellitus

Dear Sir,

We are grateful for the opportunity to reply to the letter from Dr. Rosenbloom. Our brief discussion of "thick skin and limited joint mobility [1]: cheiroarthropathy" was included under this rubric (and *not* simply as cheiroarthropathy) because the main point of discussion was the skin, with reference to the joints only as an association. Clinically obvious cutaneous changes due to thick skin occur principally in an acral distribution [2], and it was to this we addressed ourselves. The term cheiroarthropathy is well recognised, and correct, for the limited form of cutaneous involvement with stiffness of small joints that we, as dermatologists, recognise most commonly. We did not suggest that limitation of joint movement is caused solely by skin thickening, simply that they are closely associated; there is clearly thickening of other soft tissues that may be relevant.

The histological changes described in the skin of patients with diabetes are widespread [3] and are not limited to areas of clinical abnormality, where the changes are different only quantitatively. In our discussion of the general effects of diabetes on the skin, we drew attention to this and to the relationship of skin thickening to vascular abnormalities and aging, particularly to relative cutaneous ischaemia. Postural and gravitational features serve to localise vascular abnormalities, not just in diabetes, but also in systemic sclerosis [4], lipodermatosclerosis [5], and the vasculitic syndromes [6]. In the first two instances, where the microvascular disorder is chronic, ischaemia is associated with cutaneous sclerosis, and the histological appearances are very similar to those seen in diabetic thick skin. In addition, the striking relationship of thick skin (and Dr. Rosenbloom's LJM) to other microvascular complications of diabetes leads us to propose that the microvasculature holds the key to the cutaneous pathology, as it does to retinopathy, nephropathy and neuropathy.

Dr. Rosenbloom concedes that there is a lack of relationship between collagen glycosylation and LJM, and presumably to thick skin. The statistical relationship described by Monnier [7] showed a correlation coefficient *(r)* between joint stiffness and skin collagen fluorescence of 0.34. This may have struggled to significant levels, but the measure of dependance of one variable on the other (r^2), of 0.12, indicates that we must look elsewhere for causative association. If we were to accept the correlation, we would have to assume that it is skin collagen glycosylation that determines joint stiffness, since there is little evidence that glycosylation of other connective tissue is related directly or otherwise to that in the skin. We have not stated that the skin is the cause of the joint problem, and Dr. Rosenbloom is in error in assuming that we believe it to be so.

Dr. Rosenbloom raises an important point in the discussion of the interpretation of LJM. Our intention was to stress the dangers of generalisation of an observation to groups other than those in whom the original observation was made. The detection of LJM may possibly be of significance in a group of young diabetics with multiple complications of their disease but is of little specificity in the patients who make up the majority of those seen in clinical practice, i.e. the older diabetic, where age related changes in the vasculature and connective tissue confound the issue.

We accept that skin collagen glycosylation correlates with HbA_1 levels. If control is poor, and the duration of hyperglycaemia longer, it is self-evident that there is greater opportunity for the early step in