Dupuytren’s disease in type I diabetic subjects: Investigation of biochemical markers of type III and I collagen

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Abstract

Objective
To clarify whether biochemical markers of collagen type III and I metabolism show alterations in type I diabetic subjects with Dupuytren’s disease (DD) compared to those without DD.

Methods
DD was assessed in a total of 28 type I diabetic subjects, mean age 43.4 ± 9.5 (SD) and duration of diabetes 25.2 ± 9.7 years. Concentrations of aminoterminal propeptide of type III procollagen (PIIINP), carboxyterminal propeptide of type I procollagen (PICP) and carboxyterminal cross-linked telopeptide of type I collagen (ICTP) in serum and excretion of cross-linked N-telopeptides of type I collagen (NTX) and deoxypyridinoline crosslinks (DPyr) into urine were measured.

Results
The prevalence of DD was 32% (9 of 28 diabetic subjects). Average serum ICTP was 2.7 ± 0.8 µg/l in subjects without DD and 3.6 ± 1.2 µg/l with DD (p = 0.0276). No significant association between other collagen markers and DD was found. The reference intervals of PIIINP and ICTP were exceeded only in 1 and 2 subjects, respectively, and they both had DD.

Conclusion
The degradation of type I collagen might be increased in diabetic subjects with DD. The overall implication was that synthesis or degradation of type III and I collagen in diabetic subjects with DD did not differ enough from those without DD to reflect changes in the biochemical markers of type III and I collagen.

Key words
Dupuytren’s disease, carboxyterminal cross-linked telopeptide of type I collagen, carboxyterminal propeptide of type I procollagen, aminoterminal propeptide of type III procollagen, cross-linked N-telopeptides of type I collagen, deoxypyridinoline crosslinks of type I collagen.
Dupuytren’s disease and collagen markers in diabetic patients / P.E.T. Arkkila et al.

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Introduction

Dupuytren’s disease (DD) is a human affliction in which there is a progressive irreversible contraction of one or more fingers (1). DD is a spontaneously occurring, chronic and idiopathic thickening of the palmar aponeurosis leading to various degrees of flexion deformity of the fingers. The reported prevalence of DD in diabetic patients is higher than in control populations, varying from 2% to 63% depending on the patient’s age and ethnic origin (2, 3). Other conditions associated with DD include male gender, epilepsy and alcohol liver disease (3-8). The lesions of DD resemble normal scar tissue with fibroblastic proliferation and collagen accumulation (9). It has been shown that the nodules, contractures and apparently unaffected aponeurosis from patients with DD contain fibroblast-like cells, type III and I collagen, fibronectin and proteoglycans (10, 11). Exact histopathological alterations in DD lesions in diabetic subjects remain unknown, but connective tissue proliferation may be essential like in other hand abnormalities in diabetic subjects. Biochemical markers of type III and I collagen metabolism have become available. Type III collagen is derived from a procollagen, which has propeptide extensions at both ends of the molecule. Serum aminoterminal propeptide of type III procollagen (PIIINP) reflects synthesis and deposition of type III collagen (12). Some of the aminoterminal propeptides of type III are also liberated during tissue degeneration. Type I collagen is also derived from a procollagen, which has propeptide extensions at both ends of the molecule. The carboxyterminal propeptide (PICP) is liberated during the synthesis and deposition of type I collagen (13). Carboxyterminal telopeptide of type I collagen (ICTP), cross-linked via pyridinoline cross-links is liberated during the degradation of type I collagen (14). Urinary deoxypyridinoline crosslinks (DPyr) and N-telopeptides (NTX) of type I collagen have also been used for markers of type I collagen degradation (15, 16).

The aim of this study was to clarify whether biochemical markers of collagen type III and I metabolism show alterations in type I diabetic subjects with DD compared to those without DD.

Materials and methods

Patients and clinical examination

We evaluated in a cross-sectional study 28 type 1 diabetic men attending a diabetes outpatient clinic in Turku, Finland. All of the subjects were using both short- and long-acting insulin. Weight and height were measured and the body mass index (BMI) was calculated using the formula BMI = weight (kg)/[height (m)]². The subjects’ occupation (manual or intellectual) was recorded, as was the history of injuries, operations or infections in the upper extremities. Retinopathy and somatic peripheral symmetrical polyneuropathy (neuropathy) were assessed by the same methods as previously described (17).

The medical history of possible coronary heart or liver disease was recorded. The alcohol consumption and smoking history of the subjects were recorded. Alcohol consumption was defined as light, moderate or heavy if they consumed maximally one alcoholic drink per day, 2 to 3 drinks or more than 3 drinks per day, respectively. An ex-smoker was defined as a person who had smoked regularly at any time in the past.

The diagnosis of DD was made by one of the authors (P.E.T.A.) based on the observation of one or more of the following 4 features: a palmar or digital nodule, tethering of palmar or digital skin, a pretendinous band, and digital contracture. The same method was earlier used by Noble et al. (18). Limited joint mobility (LJM) was assessed by the method of Rosenbloom (19). Patients were asked to approximate the palmar surfaces of the fingers in a praying position, with the fingers fanned and the wrists maximally flexed. If the patient failed to approximate the palmar surfaces completely, the examiner attempted to extend the fingers passively. Equivocal or unilateral findings, or simply a sense of unlimited resistance was classified as “no LJM”. Failure of any joint to make contact was classified as LJM. All the patients were also studied by bilateral recording of the passive extension angle of the 3rd and 5th metacarpal-phalangeal (MCP) and wrist joints with a goniometer.
Biochemical methods

Blood samples for laboratory analysis were collected on the same day that the examination of the subjects, including the assessment of DD, was performed. Aminoterminal propeptide of type III procollagen (PIIINP), carboxyterminal propeptide (PICP) of type I procollagen and carboxyterminal cross-linked telopeptide of type I collagen (ICTP) in serum were determined with radioimmunoassays (Orion Diagnostica, Espoo, Finland). Excretion of deoxypyridinoline crosslinks (Dpyr) in urine was quantified with an enzyme immunoassay (Pyrilinks®D, Metra Biosystems, Inc., Mountain View, CA, USA). Excretion of cross-linked N-telopeptides (NTX) of type I collagen into urine was determined with an enzyme immunoassay (Osteomark®, Ostex International Inc., Seattle, WA, USA). Glycated hemoglobin in the blood (HbA1c) was measured by high performance liquid chromatography using a Variant™ analyzer (Bio-Rad Laboratories, Hercules, CA, USA). Alkaline phosphatase activity in serum was determined according to the SCE standard (Committee of Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiolog).

The investigation was conducted in accordance with the principles outlined in the Declaration of Helsinki. The protocol was approved by the Joint Ethics Committee of the University of Turku and Turku University Central Hospital and the patients gave their informed consent for the study.

Statistical methods

For the statistical analysis, Pearson’s χ²-test, one-way analysis of variance (ANOVA) and analysis of covariance were used (20). The results concerning continuous variables are given as means ± SD.

Results

Prevalence of Dupuytren’s disease

The prevalence of DD was 32% (9 of 28 diabetic subjects) (Table I). The duration of diabetes was longer in subjects with DD than in subjects without DD. DD was not associated with age, height, weight, BMI or HbA1c (Table I). No association with occupation was found. 56% of the subjects with DD were non-smokers, 22% smokers and 22% ex-smokers. The respective figures for subjects without DD were 47%, 47% and 5%. No significant difference was found in smoking habits between the groups (p = 0.2587).

Association with diabetic complications and related diseases

None of the subjects without retinopathy had DD. The prevalence of DD was 31% in subjects with background retinopathy and 71% in those with proliferative retinopathy. The association between DD and the severity of retinopathy was significant (p = 0.0126). Thirteen subjects had neuropathy (46%) and 6 of them (46%) had DD (p = 0.1394). The overall prevalence of LJM was 57.1%. Eight of 9 (89%) of subjects with DD also had LJM, whereas 8 of 19 (42%) subjects without DD had LJM (p = 0.0438).

None of the subjects had a history of coronary heart or liver disease. Serum alkaline phosphatase values were normal in all subjects. Four subjects were non-drinkers and the consumption of alcohol was light in the others. According to previous data, 2 subjects had macroalbuminuria (total urinary protein 0.4 and 0.5g/24 hrs), two subjects had microalbuminuria (30 and 33 µg/min) and in the others the albumin excretion rate was less than 20 µg/min. Only one subject had increased creatinine concentration (119 µmol/l).

Collagen markers and Dupuytren’s disease

No significant difference in average serum PIIINP or PICP was found in subjects with or without DD (Table II). Average serum ICTP was higher in subjects with DD than in subjects without DD (p = 0.0276) (Table II). There was no association between DD and urinary excretion of NTX and Dpyr (Table II).

Discussion

Histopathological data have shown that DD is characterised by cell proliferation and type I and III collagen deposition within the aponeurotic branches (11). Recently several biochemical markers of type I and III collagen have become available for clinical use. The present study was undertaken to clarify whether these markers show alterations in type I diabetic subjects with DD compared to those without DD. We wanted to study type I diabetic subjects, because the prevalence of DD is higher in those than in the healthy control population. They are also younger in age at the onset of DD than non-diabetic subjects and therefore fewer confounding factors of collagen metabolism exist (osteoarthritis or osteoporosis). We chose men instead of women for the present study to avoid the confounding effect of the higher risk for osteoporosis in women of this age group. Osteoporosis influences the biochemical markers of collagen and therefore different data could be expected in women,
Dupuytren’s disease and collagen markers in diabetic patients / P.E.T. Arkkila et al.

Table II. Concentrations of aminoterminal propeptide of type III procollagen (S-PIIINP), carboxyterminal propeptide of type I procollagen (S-PICP) and carboxyterminal cross-linked telopeptides of type I collagen (S-ICTP) in serum, and the excretion of cross-linked N-telopeptides of type I collagen per creatinine (U-NTX/Cr) and deoxypyridinoline crosslinks per creatinine (U-DPyr/Cr) according to the absence or presence of Dupuytren’s disease.

<table>
<thead>
<tr>
<th>Study group</th>
<th>No (n = 19; 67.9%)</th>
<th>Yes (n = 9; 32.1%)</th>
<th>Total (n = 28; 100%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-PIIINP (µg/l)</td>
<td>Mean ± SD</td>
<td>2.5 ± 0.7</td>
<td>2.9 ± 1.0</td>
<td>2.7 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>1.6 - 4.2</td>
<td>1.9 - 5.2</td>
<td>1.6 - 5.2</td>
</tr>
<tr>
<td>S-PICP (µg/l)</td>
<td>Mean ± SD</td>
<td>155.6 ± 42.3</td>
<td>133.1 ± 34.0</td>
<td>148.1 ± 40.5</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>94 - 214</td>
<td>86 - 170</td>
<td>86 - 214</td>
</tr>
<tr>
<td>S-ICTP (µg/l)</td>
<td>Mean ± SD</td>
<td>2.7 ± 0.8</td>
<td>3.6 ± 1.2</td>
<td>3.0 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>1.7 - 4.8</td>
<td>2.3 - 5.7</td>
<td>1.7 - 5.7</td>
</tr>
<tr>
<td>U-NTX/Cr (nmol/mmol)</td>
<td>Mean ± SD</td>
<td>39.4 ± 12.3</td>
<td>33.3 ± 10.8</td>
<td>37.3 ± 11.9</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>26 - 61</td>
<td>21 - 54</td>
<td>21 - 61</td>
</tr>
<tr>
<td>U-DPyr/Cr (nmol/mmol)</td>
<td>Mean ± SD</td>
<td>36.3 ± 8.2</td>
<td>34.6 ± 6.9</td>
<td>35.8 ± 7.7</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>16 - 53</td>
<td>23 - 43</td>
<td>16 - 53</td>
</tr>
</tbody>
</table>

Reference intervals in healthy adult men are: S-PIIINP: 1.7 - 4.2 µg/l; S-PICP: 38 - 202 µg/l; S-ICTP: 1.8 - 5.0 µg/l; and U-DPyr/Cr: 2.3 - 5.4 nmol/mmol.

especially those in the post-menopausal age group.

The main result of the present study was that the average serum ICTP was higher in subjects with DD than in subjects without DD, indicating that the degradation of type I collagen may be increased in subjects with DD. However, the overall implication was that synthesis or degradation of type III and I collagen in diabetic subjects with DD did not differ enough from those without DD to reflect changes in biochemical markers of type III and I collagen.

In the present study, only 2 subjects with DD had an elevated serum ICTP concentration. However, average ICTP activity was higher in subjects with DD than in those without DD. ICTP antigen is derived from fibrillar type I collagen and its release into the circulation is a direct measure of tissue destruction. Possible reasons for elevated serum ICTP in diabetic subjects with DD could be some type of destruction of the aponeurosis and connective tissue nearby. It is also possible that the development of DD causes a systemic reaction resulting in the attempt to decrease the accumulated overload of collagen, which may explain why DD seems to be milder in diabetic subjects.

There are several possible confounding factors which have to be considered when evaluating the association of serum ICTP with different metabolic and structural conditions. Several studies have shown increased ICTP concentrations in states associated with increased lysis of bone: multiple myeloma, osteolytic metastases, rheumatoid arthritis, immobilisation and osteoporosis (21-23). In the present study none of the subjects had overt osteoporosis, a history of bone fractures or immobilisation, Charcot neuroarthropathy, or symptoms suggestive of inflammatory arthritis or osteoarthritis. Our subjects’ physical exercise had been light or moderate for years and it is unlikely that physical activity had a significant influence on the biochemical markers in the present study. Alkaline phosphatase activity was also normal in all subjects, reflecting normal bone metabolism. ICTP is cleared from the blood by the kidneys (14). No evidence of renal failure existed in any of our patients.

Surgically excised specimens from patients with DD have shown increased amounts of type III collagen, even in the apparently unaffected aponeurosis, which indicates that the disease may have a broader involvement than is usually considered (10). Suggestive evidence for a systemic form of DD is also that bilateral involvement occurs in roughly 65% of patients and involvement of anatomic sites other than the palmar side of the hand (knuckle pads over thePIP joints, plantar fascia of the foot as inLedderhose’s disease, and the penis as in Peyronie’s disease) may exist in about 25% (24). Some studies including the present one have also shown an association between DD and long-term diabetic complications whose pathogenesis includes connective tissue alterations, but it has not been well demonstrated that DD in diabetes represents a general disease (25). Although DD would be a sign of a general disease, the amount of collagen involved seems to be too small to show alterations in the serum markers of collagen synthesis studied here.

It would be valuable to discover a marker that could identify DD subjects with a poor prognosis and who should be referred for surgery. Previously, serum concentrations of PIIINP and ICTP have been shown to provide prognostic information in rheumatoid arthritis and systemic sclerosis (26-28). Follow-up studies are needed to evaluate the possible prognostic value of procollagen markers in the prognosis of DD. It would also be interesting to follow the possible changes in these markers after surgery.

Conclusions

This study shows that the degradation of type I collagen may be increased in diabetic subjects with DD. The overall implication, however, was that the synthesis or degradation of type III and I collagen in diabetic subjects with DD did not differ enough from those without DD to reflect changes in the biochemical markers of type III and I collagen.

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Dupuytren’s disease and collagen markers in diabetic patients / P.E.T. Arkkila et al.

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