# Limited Joint Mobility in Type 1 Diabetic Patients

## Associations with microangiopathy and subclinical macroangiopathy are different in men and women

DIETMAR FROST, MD
WOLFGANG BEISCHER, MD

**OBJECTIVE** — To study the relationship of limited joint mobility (LJM) in type 1 diabetic patients with microvascular complications, hypertension, and early atherosclerosis and to determine whether sex has an influence on possible associations.

**RESEARCH DESIGN AND METHODS** — A total of 335 consecutive unselected patients (191 women and 144 men), aged 14–40 years, were studied for LJM, retinopathy, nephropathy (stages III and IV), and hypertension. Standard laboratory tests were performed; the intima-media thickness (IMT) of the carotid arteries, which reflects the extent of early atherosclerosis, was measured by high-resolution ultrasound, and plaques were identified.

**RESULTS** — The frequency of LJM was 33.7% (29.8% in women and 38.9% in men). Subjects with LJM had a longer diabetes duration ($P < 0.001$) than those without (women 16.7 ± 9.1 vs. 10.3 ± 6.0 years; men 15.0 ± 9.0 vs. 9.4 ± 6.3 years). Age, $HbA_{1c}$, lipids, and systolic/diastolic blood pressure were not different between men and women with or without LJM. Men with LJM had a higher albumin excretion rate (37.1 vs. 13.1 μg/min, $P < 0.05$) than those without LJM and showed a higher risk of proteinuria (odds ratio 1.8, 95% CI 1.2–2.7; $P < 0.05$), retinopathy (2.4, 1.7–3.5; $P < 0.001$), and hypertension (1.7, 1.2–2.6; $P < 0.05$). The occurrence of these complications was not different between women with and without LJM, but only women with LJM had a greater IMT (0.59 ± 0.13 vs. 0.55 ± 0.10 mm, $P < 0.05$) and a higher risk of plaques (odds ratio 2.1, 95% CI 1.3–3.4; $P < 0.05$) than women without LJM. In a multiple logistic regression analysis, adjusted for age and diabetes duration, male sex independently predicted the presence of LJM. Moreover, LJM proved to be an independent predictor of retinopathy in men only.

**CONCLUSIONS** — LJM is an indicator of microvascular disease in men, and LJM is associated with early macrovascular disease in women.

*Diabetes Care* 24:95–99, 2001

Limited joint mobility (LJM), or diabetic cheiroarthropathy, is the earliest clinically apparent complication of diabetes in childhood and adolescence and can be found in ~30–50% of adult type 1 diabetic patients (and in patients with type 2 diabetes) (1–3). It typically begins with an extension deficit at the fifth finger on each hand and spreads radially, affecting interphalangeal and metacarpophalangeal joints. The inability of digital extension, usually painless and not disabling, is secondary to a thickening of the subcutaneous tissue, the flexor tendon sheaths, and sometimes the periarticular skin (4–6). The larger joints (elbow, knee, or foot) and the spine can also be involved.

From the Third Department of Medicine, Bürgerhospital Stuttgart, Stuttgart, Germany.
Address correspondence and reprint requests to Dietmar Frost, MD, Medizinische Klinik 3 Bürgerhospital, Zentrum für Innere Medizin, Tunzhofer Strasse 14-16, 70191 Stuttgart, Germany. E-mail: dfrost@buergerhospital.de.
Received for publication 24 March 2000 and accepted in revised form 3 October 2000.

**Abbreviations:** AER, albumin excretion rate; AGE, advanced glycation end product; IMT, intima-media thickness; LJM, limited joint mobility.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Several cross-sectional studies have shown an association between LJM and retinopathy (1,3,5); some also show an association between LJM and both micro- and macroalbuminuria (4,5,7). LJM has been regarded as an early marker for these complications. Some recent prospective studies questioned the role of LJM to predict microvascular diabetic complications in type 1 diabetic patients (8,9).

Little is known about associations between LJM and macrovascular disease. Whereas one study found significantly frequent cases of coronary heart disease and cerebrovascular disease in type 2 diabetic patients with LJM (2), there are nearly no data available on associations between LJM and macrovascular disease in type 1 diabetic patients.

According to earlier investigators, the appearance and the extent of LJM was not related to sex (5), but a more recent study reported that diabetic adolescents with LJM were predominantly male (10). Whether the associations between LJM and other diabetic complications were different among men and women was not addressed in previous studies.

The purpose of this study was *1*) to evaluate the relationship of LJM with early atherosclerosis, which can be reliably assessed by the measurement of the common carotid artery intima-media thickness (IMT) (11–15), and other diabetic complications in type 1 diabetic patients, and *2*) to determine whether possible associations differ between the sexes.

## RESEARCH DESIGN AND METHODS

### Patients

We prospectively studied 335 consecutive Caucasian patients with type 1 diabetes (191 women and 144 men), aged 14–40 years, who attended our hospital as inpatients or outpatients, had a diabetes duration of >2 years, and were treated with at least four daily insulin injections. There was no selection of patients in any other way. Atten-

**Table 1—*Characteristics of all 335 type 1 diabetic patients***

| Characteristic | No LJM | LJM |
|---|---|---|
| *n* | 222 | 113 |
| Age (years) | 27.9 ± 6.6 | 28.8 ± 7.6 |
| $HbA_{1c}$ (%) | 8.5 ± 2.3 | 8.8 ± 2.6 |
| AER (μg/min) | 12.5 (9.0–17.2) | 23.8 (14.7–38.4) |
| Cholesterol (mg/dl) | 195.0 ± 49.8 | 198.4 ± 47.6 |
| Triglycerides (mg/dl) | 105.0 ± 61.0 | 118.0 ± 86.9 |
| Systolic blood pressure (mmHg) | 116.9 ± 15.5 | 122.9 ± 15.3* |
| Diastolic blood pressure (mmHg) | 72.6 ± 11.3 | 76.4 ± 10.4* |
| IMT (mm) | 0.57 ± 0.12 | 0.60 ± 0.15* |

Data are means ± SD or geometric mean (95% CI). *$P < 0.05$ vs. subjects without LJM.

dance was a priority for the purpose of participating in a diabetes education program or achieving better metabolic control, i.e., aiming for a target $HbA_{1c}$ level <7.0–7.5%. All subjects gave their informed consent for the sonographic examination of the carotid arteries. The study was performed according to the principles of the declaration of Helsinki and was approved by the regional ethical committee.

LJM was assessed qualitatively by the same observer (D.F.) with the prayer maneuver; patients were asked to approximate the palmar surfaces of the fingers in a praying position with the fingers fanned and the wrists flexed (4,8). 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 resistance without limitation was classified as no LJM. The failure of any joint to make contact was classified as LJM.

A total of 12 patients were reexamined after ~3 months to assess the reproducibility of the LJM classification. At the time of the second examination, the observer was blinded to the results of the first LJM classification. Originally, five patients were classified as not having LJM and seven patients as having LJM, and on re-examination, an identical classification was found for each case.

In addition to the patients with established diabetes, we also assessed LJM in 40 subjects with recent onset of type 1 diabetes (24 men and 16 women, diabetes duration <1 year) to get a baseline frequency of LJM for this population.

We assessed the following patient characteristics: $HbA_{1c}$, using high-performance liquid chromatography (Bio-Rad Diamat) (normal range 4.3–6.1%); albuminuria or overt proteinuria, using the albumin excretion rate (AER) and the protein excretion rate in a 24-h urine collection (if the results were not within the normal range, the urine collection was repeated at least once after a minimum interval of 2 weeks); lipid status, using standard laboratory techniques to measure total cholesterol and triglycerides; and current smoking habit.

The patients were categorized according to the presence or absence of hypertension, nephropathy, or retinopathy. Hypertension was defined according to Doria et al. (16). It was considered to be present when at least three repeated measurements, taken with a standard cuff sphygmomanometer on different days in a seated position after a minimum rest period of 5 min, showed systolic blood pressure readings >140 mmHg or diastolic blood pressure readings >90 mmHg or if patients were receiving antihypertensive drug therapy. Nephropathy was defined according to Mogensen et al. (17) as stage III, microalbuminuria (AER >20 μg/min or >30 mg/24 h in at least two urine collections), or stage IV, overt proteinuria (>500 mg/24 h). Retinopathy was considered to be present if it was noted in any form by the ophthalmologist during a standardized examination of the fundus through dilated pupils.

## Sonographic examination

The IMT of the common carotid artery was measured in a section ~1–1.5 cm proximal the carotid bulb in an end diastolic frozen and zoomed B-mode picture by manually setting two pairs of calipers at the sites of greatest thickness from the leading edge of the first echogenic line (lumen-intima interface) to the leading edge of the second echogenic line (media-adventitia interface). We included the maximum IMT (i.e., to the greatest wall thickness from the right or left side) of each patient for evaluation, as previously published (18). The common carotid arteries and the internal and external branches were scanned cross-sectionally and longitudinally, and possible plaques were recorded. Plaques were defined as circumscribed wall thickenings >1 mm with increased density involving all layers of the wall (19,20). All of the ultrasound examinations were carried out by the same observer (D.F.), who was blinded to the patient's complication status at the time of the reading. We used an Ultramark 9 HDI sonographic system (Advanced Technology Laboratories, Bothel, WA) with a linear array wide-frequency probe (L 10-5 38 mm, 5–10 MHz) and an axial resolution of 0.3 mm.

To assess the reproducibility of the IMT measurement, a total of 20 subjects were examined by two independent observers twice on the same occasion (interobserver variability), and an additional measurement was carried out by one observer on a second occasion, separated by 7–14 days (intraobserver variability). The interobserver correlation was 0.97, and the intraobserver correlation was 0.98. The mean absolute differences were 0.04 ± 0.06 and 0.03 ± 0.06 mm, respectively, and the coefficient of the variation was 6.25% for both variabilities.

## Statistical analysis

The results for continuous variables are given as means ± SD unless expressed otherwise. Because the AER was not normally distributed, the values were log-transformed for analysis and are summarized in Tables 1 and 2 as the geometric mean with a 95% CI. The intergroup comparisons were done with the two-sided Student's *t* test for independent samples or nonparametrical tests (Mann-Whitney *U* test), when appropriate. The $\chi^2$ test was used to calculate the odds ratios for the presence of complications in patients with and without LJM. $P < 0.05$ was considered statistically significant.

A multiple logistic regression analysis for the presence of LJM was performed for all patients and performed separately for men and women. Additional logistic regression analyses were performed in the same manner for the presence of retinopathy and nephropathy. To eliminate any confounding effect of age and diabetes duration, these variables were taken into all models as covariates, then the other candidate variables were entered and stepwise excluded backwards until no entered candidate variable had a significance level >0.1. For all

**Table 2—*Characteristics of 191 type 1 diabetic women and 144 type 1 diabetic men***

| Characteristic | Women | | Men | |
|---|---|---|---|---|
| | No LJM | With LJM | No LJM | With LJM |
| *n* | 134 | 57 | 88 | 56 |
| Age (years) | 27.4 ± 6.6 | 28.8 ± 8.1 | 28.6 ± 6.4 | 28.9 ± 7.1 |
| Diabetes duration (years) | 10.3 ± 6.0 | 16.7 ± 9.1* | 9.4 ± 6.3 | 15.0 ± 9.0* |
| $HbA_{1c}$ (%) | 8.5 ± 2.3 | 8.8 ± 3.0 | 8.7 ± 2.3 | 8.8 ± 2.1 |
| AER (µg/min) | 12.1 (8.1–17.9) | 15.2 (8.4–27.6) | 13.1 (7.4–23.2) | 37.1 (17.5–78.8)† |
| Cholesterol (mg/dl) | 199.3 ± 51.0 | 200.2 ± 49.5 | 188.3 ± 47.5 | 196.5 ± 46.2 |
| Triglycerides (mg/dl) | 100.1 ± 58.0 | 104.5 ± 53.1 | 112.8 ± 65.2 | 131.2 ± 109.5 |
| Systolic blood pressure (mmHg) | 115.2 ± 14.6 | 118.5 ± 14.4 | 119.4 ± 16.6 | 126.5 ± 15.3 |
| Diastolic blood pressure (mmHg) | 71.6 ± 10.8 | 75.0 ± 9.0 | 73.9 ± 12.0 | 77.6 ± 11.5 |
| IMT (mm) | 0.55 ± 0.10 | 0.59 ± 0.13† | 0.59 ± 0.14 | 0.62 ± 0.16 |

Data are means ± SD or geometric mean (95% CI). *$P < 0.001$ vs. subjects without LJM; †$P < 0.05$.

statistical analyses, we used SPSS for Windows 7.5 (SPSS, Munich, Germany).

**RESULTS** — LJM was present in 113 of 335 (33.7%) type 1 diabetic subjects ( 38.9% men and 29.8% women; NS), whereas LJM was present in only 2 of 40 people (one man and one woman) with recent onset of type 1 diabetes (5%). The characteristics of patients with established diabetes with and without LJM were listed for all patients and for women and men separately in Tables 1 and 2. There were no differences regarding the smoking habits between subjects with and without LJM (smokers among women without LJM 34%, and with LJM 33%; smokers among men without LJM 44%, and with LJM 39%). Age, metabolic control (measured by $HbA_{1c}$), and lipids were not different between subjects with and without LJM, nor between men and women. Subjects with LJM had a highly significant longer diabetes duration ($P < 0.001$ in women and men). The AER was somewhat higher in subjects with LJM without reaching significance in the whole patient group, but when both sexes were evaluated separately, men with LJM had a significantly higher AER ($P < 0.05$) than men without LJM (no difference in women). Also, subjects with LJM had a significantly higher systolic and diastolic blood pressure and a greater IMT than subjects without LJM. The differences in blood pressure did not remain significant when men and women were evaluated separately, but women with LJM still had a significantly greater IMT ($P < 0.05$) than women without LJM, whereas the IMT difference between men with and without LJM was not significant.

The frequency of plaques, hypertension, and microvascular diabetic complications was not different between women with and without LJM (Fig. 1).

Men with LJM had significantly more frequent cases of hypertension (28.6 vs. 12.5%, $P < 0.05$), proteinuria (25.5 vs. 10.2%, $P < 0.05$), and retinopathy (48.2 vs. 14.8%, $P < 0.001$) than men without LJM, whereas there was no statistically significant difference in the frequency of microalbuminuria or the occurrence of plaques (Fig. 2).

The odds ratios for the presence of microvascular diabetic complications and hypertension showed no significant risk for women with LJM (retinopathy 1.3, 95% CI 0.8–2.0; nephropathy [combined stages III and IV] 1.4, 0.9–2.3; hypertension 1.0, 0.4–2.3), but were clearly significant in men with LJM, reaching 2.4 (95% CI 1.7–3.5) for retinopathy ($P < 0.001$), 1.8 (1.3–2.9) for nephropathy ($P < 0.01$), and 1.7 (1.2–2.6) for hypertension ($P < 0.05$). The relative risk for the presence of plaques in the carotid arteries, however, was only significant in women with LJM ($P < 0.05$) with an odds ratio of 2.1 (1.3–3.4), not in men (odds ratio 1.0, 0.6–1.9).

A multiple logistic regression analysis was performed to evaluate the effects of various parameters (including those listed in Table 2, and hypertension, retinopathy, nephropathy, smoking, and sex) on the presence of LJM. The analysis, performed for all patients, showed that besides diabetes duration and age, male sex proved to be the only additional independently predictive variable. When this analysis was repeated separately for women and men, diabetes duration and age were also independent predictors of LJM in both sexes, and smoking was an additional independent variable only in women. No other variables could be included in these logistic regression models.

In a similar multiple logistic regression analysis performed for the presence of retinopathy, LJM was an independent predictor only in men, whereas diabetes duration and hypertension independently predicted retinopathy in both sexes. The same multivariate analysis was also performed for the presence of nephropathy (stage III or IV), but LJM could not be included in this logistic regression model.

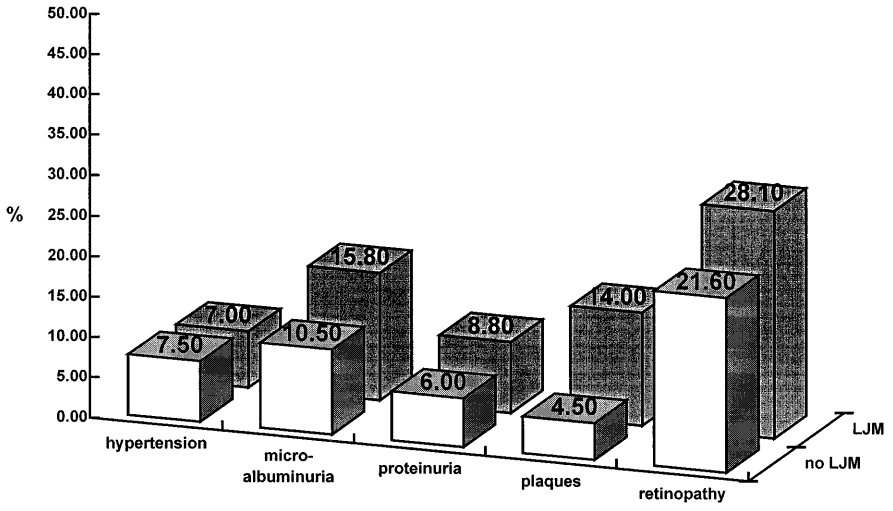


**Figure 1**—*Frequency of vascular diabetic complications and hypertension in 191 type 1 diabetic women with (■) and without (□) LJM.*

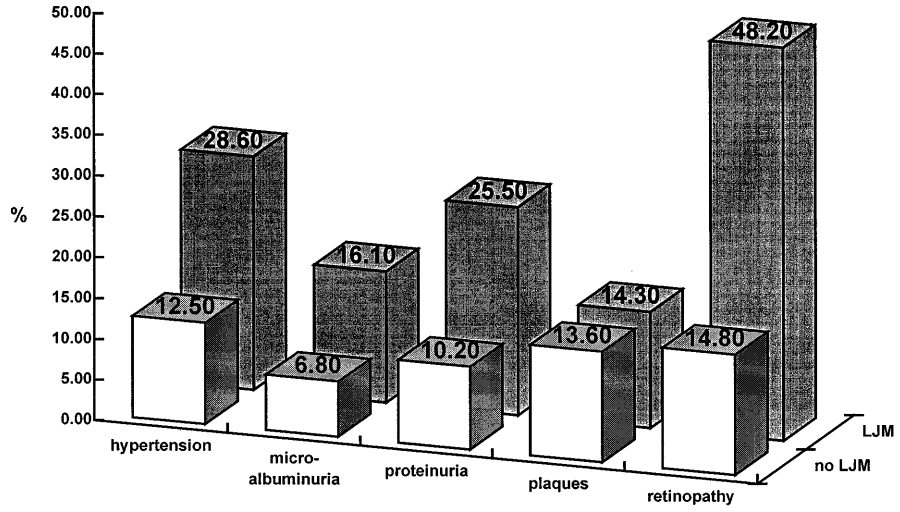


**Figure 2**—*Frequency of vascular diabetic complications and hypertension in 144 type 1 diabetic men with (■) and without (□) LJM.*

**CONCLUSIONS** — Associations between LJM and microvascular complications have been confirmed since the first description presented in diabetic children (4,5) and adult type 1 diabetic patients in several cross-sectional studies (1,7,21), but it remains unclear whether LJM only accompanies other diabetic complications or can also predict them (8,9) (perhaps only under certain conditions).

In many studies, the severity of LJM was classified according to the method of Rosenbloom et al. (4). These classifications were ideal for comparing the extent of LJM among different groups (21) and also within the same individual during the course of a study. Because we were primarily interested in the differences between subjects with and without LJM, we restricted our assessment of LJM to the qualitative test of the prayer maneuver (completed by passive finger extension), which discriminates between the presence and absence of LJM with excellent reproducibility and can be easily done without time-consuming examinations in a clinical setting (7,10).

This study was the first to evaluate possible associations between LJM and other complications separately for men and women. Whereas LJM occurred in nearly the same low frequency (~5%) in both sexes, in people with a recent onset of type 1 diabetes (who represent baseline conditions), we found that in a multiple logistic regression analysis, the male sex proved to be an independent predictor for the presence of LJM in patients with established diabetes.

Consistent with previous studies (5,8, 22), we found a strong association between LJM and diabetes duration in all of our patients, women and men alike. In addition, we found a striking difference between both sexes concerning the association of LJM with microvascular complications and hypertension. Men with LJM significantly more often had retinopathy, nephropathy, and hypertension than men without LJM, whereas these complications were similarly distributed among women with and without LJM. Also, a multivariate analyses, adjusted for age and diabetes duration, suggested that the role of LJM as an indicator of other complications seemed to be different in men and women. In addition to the predictive roles of diabetes duration and hypertension, LJM proved to be an independent predictor of retinopathy (but not of nephropathy) in men.

These results raise the question whether there are different conditions in type 1 diabetic men and women that lead to diabetic complications. By 1987, Borch-Johnsen et al. (23) had already described a male preponderance for the development of severe microvascular complications that is still unexplained but is supported by our present observations and by the results of Montana et al. (7), who also found a male predominance among their patients with microalbuminuria. In a previous report, we showed that in young type 1 diabetic subjects, the male sex was also a risk for more severe progression of early macrovascular lesions like intima-media thickening of the common carotid artery (18). Interestingly, Mitchell et al. (24) found a reduced palmar capillary blood flow only in type 1 diabetic men with LJM, which confirms suggestions that microvascular disease may be causally related to LJM, especially in men.

It has been hypothesized that the occurrence of LJM requires a genetic predisposition that could influence the formation of advanced glycation end products (AGEs). The stable AGEs are thought to be responsible for the increased cross-linking and stiffness of collagen in diabetic people; thus, AGEs are also likely to be responsible for the susceptibility to LJM and other diabetic complications (5,22,25–28). According to our results, this predisposition should be linked, especially to the male sex, perhaps because of different biochemical or hormonal pathways. However, the lack of differences in the occurrence of high AER, retinopathy, and hypertension between women with and without LJM might be because women, in general, have more flexible joints than men (29). This relatively increased joint flexibility in women might masque the influence of other factors, such as those mentioned above.

Only very few data are available on the associations between LJM and macroangiopathy. Arkkila et al. (2) found a higher risk for coronary heart disease and cerebrovascular disease in type 2 diabetic patients with LJM, but LJM in type 1 diabetic patients was not related to established macrovascular disease (1). We wanted to know whether there was a relationship between LJM and early (subclinical) macrovascular disease represented by intima-media thickening or the occurrence of plaques. Evaluating this issue for the first time in our study, we also found different results for both sexes. Only women with LJM had a significantly greater IMT and an approximate twofold risk for the presence of plaques compared with women without LJM, whereas there were no significant differences between men with and without LJM. Therefore, our findings suggest that there was only a relevant relationship between LJM and early atherosclerosis in type 1 diabetic women. One could speculate whether a similar relationship also exists in men but is masqued by their much more pronounced association between LJM and microvascular complications; however, this could only be revealed in a study population larger than ours. The association between LJM and early atherosclerosis might depend on the same type of under-

lying connective tissue abnormality in both conditions, probably due to the formation of AGEs (25,26,28).

It is a well-known fact that the occurrence and progression of retinopathy and nephropathy depend on metabolic control (30). This also seems to be the case for LJM, at least for its progression (22,27). Because the $HbA_{1c}$ values did not differ between both sexes at the time of the examination of our patients for this study, it is unlikely that our different results in men and women depend on differences in metabolic control. However, we could not refer to earlier $HbA_{1c}$ values of our patients, so we could not rule out that the long-term metabolic control, especially during the first years of diabetes, could have differed between the men and women.

Because this was a cross-sectional study, we could only draw conclusions for the relationship of LJM to other complications, not for a possible predictive role of LJM. We found that the function of LJM as an indicator of microvascular disease was linked to the male sex only. In women, LJM shows an association with early macrovascular disease. These obviously different effects of LJM in both sexes could explain the partially different or even contradictory results in some previous studies, and these effects should be taken into consideration during future prospective studies involving the elucidation of the role of LJM in the development of other diabetic complications.

**References**


1. Arkkila PET, Kantola IM, Viikari JSA: Limited joint mobility in type 1 diabetic patients: correlation to other diabetic complications. *J Intern Med* 236:215–223, 1994
2. Arkkila PET, Kantola IM, Viikari JSA: Limited joint mobility in non-insulin-dependent diabetic (NIDDM) patients: correlation to control of diabetes, atherosclerotic vascular disease, and other diabetic complications. *J Diabetes Complications* 11:208–217, 1997
3. Lawson PM, Maneschi F, Kohner EM: The relationship of hand abnormalities to diabetes and diabetic retinopathy. *Diabetes Care* 6:140–143, 1983
4. Rosenbloom AL, Silverstein JH, Legotte DC, Richardson K, McCallum M: Limited joint mobility in childhood diabetes indicates increased risk for microvascular disease. *N Engl J Med* 305:191–194, 1981
5. Brik R, Berant M, Vardit P: The scleroderma-like syndrome of insulin-dependent diabetes mellitus. *Diabetes Metab Rev* 7: 121–128, 1991
6. Ismail AA, Dasgupta B, Tanqueray AB, Amblin JJ: Ultrasonographic features of diabetic cheiroarthropathy. *Br J Rheumatol* 35: 676–679, 1996
7. Montana E, Rozadilla A, Nolla JM, Gomez N, Escofet DR, Soler J: Microalbuminuria is associated with limited joint mobility in type 1 diabetes mellitus. *Ann Rheum Dis* 54: 582–586, 1995
8. Arkkila PET, Kantola IM, Viikari JSA, Ronnemaa T, Vahatalo MA: Limited joint mobility is associated with the presence but does not predict the development of microvascular complications in type 1 diabetes. *Diabet Med* 13:828–833, 1996
9. McCance DR, Crowe G, Quinn MJ, Smye M, Kennedy L: Incidence of microvascular complications in type 1 diabetic subjects with limited joint mobility: a 10-year prospective study. *Diabet Med* 10:807–810, 1993
10. Duffin AC, Donaghue KC, Potter M, McInnes A, Chan AKF, King J, Howard NJ, Silink M: Limited joint mobility in the hands and feet of adolescents with type 1 diabetes mellitus. *Diabet Med* 16:125–130, 1999
11. Grobbee DE, Bots ML: Carotid artery intima-media thickness as an indicator of generalized atherosclerosis. *J Intern Med* 236:567–573, 1994
12. Salonen JT, Salonen R: Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation* 87 (Suppl. 2):II56–II65, 1993
13. Salonen R, Haapanen A, Salonen J: Measurement of intima-media thickness of common carotid arteries with high-resolution B-mode ultrasonography: inter- and intra-observer variability. *Ultrasound Med Biol* 17:225–230, 1991
14. Wendelhag I, Gustavsson T, Suurküla M, Wikstrand J: Ultrasonographic measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analyzing system. *Clin Physiol* 11:565–577, 1991
15. Wikstrand J, Wendelhag I: Methodological considerations of ultrasound investigation of intima-media thickness and lumen diameter. *J Intern Med* 236:555–559, 1994
16. Doria A, Warram JH, Krolewski AS: Genetic predisposition to diabetic nephropathy: evidence for a role of the angiotensin I-converting enzyme gene. *Diabetes* 43:690–695, 1994
17. Mogensen CE, Christensen CK, Vittinghus E: The stages in diabetic renal disease: with emphasis on the stage of incipient diabetic nephropathy. *Diabetes* 32 (Suppl. 2): 64–78, 1983
18. Frost D, Beischer W: Determinants of carotid artery wall thickening in young patients with type 1 diabetes mellitus. *Diabet Med* 15:851–857, 1998
19. Persson J, Stavenow L, Wikstrand J, Israelsson B, Formgren J, Berglund G: Noninvasive quantification of atherosclerotic lesions: reproducibility of ultrasonographic measurement of arterial wall thickness and plaque size. *Arterioscler Thromb* 12:261–266, 1992
20. Jensen-Urstad KJ, Reichard PG, Rosfors JS, Lindblad LEL, Jensen-Urstad MT: Early atherosclerosis is retarded by improved long-term blood glucose control in patients with IDDM. *Diabetes* 45:1253–1258, 1996
21. Schulte L, Roberts MS, Zimmerman C, Ketler J, Simon S: A quantitative assessment of limited joint mobility in patients with diabetes. *Arthritis Rheum* 36:1429–1443, 1993
22. Vukovic J, Dumic M, Radica A, Filipovic-Grcic B, Jovanovic V: Risk factors for expression and progression of limited joint mobility in insulin-dependent childhood diabetes. *Acta Diabetol* 33:15–18, 1996
23. Borch-Johnsen K, Nissen H, Salling N, Henrikson E, Kreiner S, Deckert T, Nerup J: The natural history of insulin-dependent diabetes in Denmark. II. Long-term survival: who and why. *Diabet Med* 4:211–216, 1987
24. Mitchell WS, Winocour PH, Gush RJ, Taylor LJ, Baker RD, Anderson DC, Jayson MI: Skin blood flow and limited joint mobility in insulin-dependent diabetes mellitus. *Br J Rheumatol* 28:195–200, 1989
25. Brownlee M: Glycation products and the pathogenesis of diabetic complications. *Diabetes Care* 15:1835–1843, 1992
26. McCance DR, Dyer D, Dunn JA, Bailie KE, Thorpe SR, Baynes JW, Lyons TJ: Maillard reaction products and their relation to complications in insulin-dependent diabetes mellitus. *J Clin Invest* 91:2470–2478, 1993
27. Silverstein JH, Gordon G, Pollock BH, Rosenbloom AL: Long-term glycemic control influences the onset of limited joint mobility in type 1 diabetes. *J Pediatr* 132: 944–947, 1998
28. Friedman EA: Advanced glycosylated end products and hyperglycemia in the pathogenesis of diabetic complications. *Diabetes Care* 22 (Suppl. 2):B65–B71, 1999
29. Seow CC, Chow PK, Khong KS: A study of joint mobility in a normal population. *Ann Acad Med Singapore* 28:231–236, 1999
30. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993