Clinical Research

Risk factors of limited joint mobility in type 1 diabetic adolescents: a two-center experience in Iraq

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ABSTRACT

BACKGROUND Limited joint mobility (LJM) is the most common joint-related complications in patients with diabetes mellitus (DM) and indicates the presence of microvascular complications. This study aimed to assess the frequency of LJM among adolescents with type 1 DM (T1DM), its risk factors, and the other microangiopathies.

METHODS In this cross-sectional study, 75 patients (adolescents between 10 and 17 years old) with T1DM were assessed for hand joint mobility using a prayer sign test. It was carried out from January 15 to June 1, 2022 in Baghdad city, Iraq. The patients' height, body mass index, blood pressure, glycated hemoglobin, and low-density lipoprotein (LDL) were recorded. Only 44 subjects were screened for diabetic nephropathy and 64 for diabetic retinopathy based on the eligibility criteria by the American Diabetes Association guidelines.

RESULTS Mean age was 13.60 (1.85) years, with a mean diabetes duration of 5.61 (2.87) years. LJM was found in 18 patients (24%). It was associated with a longer duration of diabetes ($p<0.001$), high LDL level ($p = 0.012$), diabetic nephropathy ($p = 0.04$), and diabetic retinopathy ($p<0.001$).

CONCLUSIONS The proportion of LJM was high among adolescents with T1DM, especially in those with a long duration of DM. It was associated with high LDL levels and diabetic microangiopathies (nephropathy and retinopathy).

KEYWORDS diabetic nephropathy, diabetic retinopathy, joints, low-density lipoprotein, type 1 diabetes mellitus

Limited joint mobility (LJM), also known as diabetic cheiroarthropathy, is characterized by hand stiffening caused by flexion contractures of the fingers as well as thickened, waxy, and tight skin.[1] It is listed as the most common joint-related complications in diabetic patients.[2] Type 1 diabetes mellitus (T1DM) children may develop LJM as early as a few months after the onset of the disease,[2] and the prevalence reaches a peak at 65% after 30 years of onset.[3] The distal and proximal interphalangeal joints are the first joints affected by LJM before the disease involves the metacarpophalangeal joints.[1] It can be classified into mild, moderate, and severe based on the number and type of joints involved. The disease progresses from mild to moderate to severe in 3 months to 4 years, with an average of 2 years.[4] Most patients are completely asymptomatic in the early stages.[1]

Skin fibrosis and a connective tissue elasticity loss that results in joint deformity are caused by nonenzymatic glycation of collagen, which renders it resistant to the actions of collagenase enzyme. These changes are linked to the duration of poor

glycemic control and microvascular complications,[5] and it might be a warning sign for the presence of other complications.[2] In a large study that involved 309 subjects aged 1–28 years, a positive association was found between the severity of joint limitation and diabetic microvascular complications.[6] LJM was also linked to retinopathy and proteinuria in diabetic children.[7]

Despite its association with microvascular complications of T1DM, less attention is paid to LJM. According to our knowledge, this was the first study in Iraq that highlighted LJM in T1DM adolescents. This study aimed to assess the frequency of LJM among adolescents with T1DM, its risk factors, and the other microangiopathies.

METHODS

This cross-sectional study was carried out from January 15 to June 1, 2022 in 75 diabetic patients who attended the Pediatrics Clinic of the National Diabetic Center of Al-Mustansiriyah University and the Pediatric Endocrinology Clinic at the Central Child Teaching Hospital in Baghdad city for follow-up. Any patient who attended the clinics during the study period and met the inclusion and exclusion criteria was included in this study. This study was conducted following the Declaration of Helsinki and was approved by the Ethical Committee of Al-Mustansiriyah University (IRB 1/2022 on January 2, 2022). Informed consent was obtained from every subject and their parents before being included in the study.

Inclusion criteria were T1DM patients, aged ≥10–17 years, and duration of DM ≥2 years. Patients with previous hand surgery or trauma, carpal tunnel syndromes, Dupuytren's contractures, tenosynovitis, scleroderma, or other deformities, whether diabetes-related complications or not, were excluded from this study. Data regarding age, sex, duration of diabetes, and daily insulin dose were achieved through a face-to-face interview with the patients in the presence of their parents. The weight and height measurements were taken while the subjects had light clothes and no shoes. The height Z-score was calculated following Center of Disease Control and Prevention (CDC) charts by an anthropometric calculator and categorized as tall (>+2 standard deviation [SD]), short (<−2 SD), or normal (−2 SD–+2 SD).[8,9] Body mass index (BMI) was plotted on CDC charts to achieve the percentile, categorized as underweight (<5th percentile), normal weight (≥5th–<85th percentile), and overweight or obese (≥85th percentile).[10]

During a relaxed seated position after 5 min of rest, a conventional mercury sphygmomanometer with appropriate cuff sizes was used to check the blood pressure (BP), with a second visit rechecking only if the initial measurement yielded abnormal high BP measurement. The average of these BP values was analyzed. BP tables were used to achieve the BP percentile. Patients were considered either normotensive (both systolic and diastolic BP <90th percentile), prehypertensive (BP between the 90th and 95th percentile), or hypertensive (systolic and/or diastolic BP ≥95th percentile).[11]

The same examiner used the Rosenbloom method on the prayer sign test to evaluate hand joint mobility for all patients without assessing its severity.[12] The patients were instructed to put both hands in a praying position with the fingers fanned and press the palmar surface of the interphalangeal joints and the palm together while the wrists were in a flexed position. If they failed to entirely approximate the palmar surface (a positive prayer sign), the examiner intervened by passively extending the fingers. Patients who showed a positive prayer sign after the examiner intervened were considered to have LJM.[13]

The glycemic control was evaluated by the mean of 3 to 4 values of glycated hemoglobin (HbA1c) using ion-exchange high-performance liquid chromatography, which were done every 3 months within a year before the study, and the mean was added in the analysis. A 12-hour overnight fasting serum sample was used to determine the low-density lipoprotein (LDL) levels by enzymatic colorimetric method. For children with DM, LDL cholesterol ≥100 mg/dl was considered high.[14]

From 75 patients, only 44 were screened for diabetic nephropathy and 64 for diabetic retinopathy since not all patients were eligible, as recommended by the American Diabetes Association guidelines. The diabetic nephropathy criterion was annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio (ACR) at puberty or aged >10 years, whichever was earlier, once the child had had diabetes for 5 years. Meanwhile, diabetic retinopathy included the first ophthalmologic examination that should be obtained once the child is ≥10 years of age and had had diabetes for 3–5 years.[15] Nephropathy was documented if, within 3–6 months,

two out of three early morning spot urine ACRs were high (>30 mcg/mg),[16] while the presence of diabetic retinopathy depended on fundoscopic examinations by ophthalmologists.

Statistical analysis was done using SPSS software version 27 (IBM Corp., USA). Comparisons between groups were performed using the student's *t*-test, while associations between categorical variables were determined using the Pearson chi-square and Fisher's exact tests. Significant differences were considered if the *p*-value was ≤0.05.

RESULTS

Of the 75 patients screened, 48 (64%) were female. The mean age was 13.60 (1.85) years (range 10–17 years), with a mean diabetes duration of 5.61 (2.87) years (range 2–14 years). The mean HbA1C level was 9.90 (1.42), ranging from 6.73 to 13.38%. Other characteristics of the patients are shown in Table 1.

Table 1. Characteristics of the subjects

Patients' characteristics	n (%)
Height Z-score, n = 75	
Tall (>+2)	0 (0)
Normal (−2 to +2)	58 (77)
Short (<−2)	17 (23)
BMI, n = 75	
Underweight (<5th percentile)	3 (4)
Normal (5th to <85th percentile)	53 (71)
Overweight & obese (≥85th percentile)	19 (25)
Systolic BP, n = 75	
Normal (<90th percentile)	57 (76)
Pre- or HT (≥90th percentile)	18 (24)
Diastolic BP, n = 75	
Normal (<90th percentile)	52 (69)
Pre- or HT (≥90th percentile)	23 (31)
LDL level (mg/dl), n = 75	
Normal (<100)	36 (48)
High (≥100)	39 (52)
Diabetic retinopathy, n = 64	
Present	12 (19)
Absent	52 (81)
Diabetic nephropathy, n = 44	
Present	31 (70)
Absent	13 (30)
LJM, n = 75	
Positive	18 (24)
Negative	57 (76)

BMI=body mass index; BP=blood pressure; HT=hypertensive; LDL=low-density lipoprotein; LJM=limited joint mobility

LJM was significantly associated with the long duration of diabetes (p<0.001), high LDL level (p = 0.012), diabetic nephropathy (p = 0.04), and diabetic retinopathy (p<0.001) (Table 2).

DISCUSSION

LJM is more frequently seen in patients with DM than in the general population.[3] The exact etiology of LJM is unknown, but tissue accumulation of advanced glycation end products (AGEs) may cause stiffness in the affected tissues. Connective tissue disorders, neuropathy, vasculopathy, or a combination of these problems may highlight the increased occurrence of musculoskeletal conditions in T1DM patients.[17] AGEs make cross-links with collagen in the skin, ligaments, and tendons, rendering them resistant to the collagenase enzyme. This mechanism could cause the development of LJM.[18–21]

In this study, LJM was positive in 24% of DM patients (Table 1), higher than the results reported by Clarke et al[22] (7%) and Traisman et al[23] (8.4%). However, this percentage is lower than Arkkila et al[24] (58%) or Duffin et al[25] (a positive prayer sign occurred in 35% of diabetic adolescents). Different ages of the samples may explain the varying results (8–17 years in Clarke et al[22] and 1–18 years in Traisman et al[23] and a mean age of 33.4 ± 10 years in Arkkila et al[24] and 11.5–20 years in Duffin et al[25]) and/or different methods used for evaluating LJM (table sign in Traisman et al,[23] goniometer in Arkkila et al,[24] and LJM in both hands and feet in Duffin et al[25]). The prevalence of LJM is varied among diabetes patients, depending on the methods used.[22] This emphasizes the need for the standardized criteria to define and diagnose LJM.

This study showed a significant association between LJM and the long duration of DM, as shown in Table 2. This finding is consistent with Amer et al[17] who concluded that joint limitation and stiffness in T1DM were strongly related to the duration of the disease and was the main generator for nonenzymatic glycosylation of collagens and tissues in small joints. This association is also documented by Clarke et al.[22] While a significant correlation between HbA1c and LJM was reported in a previous study,[17] Clarke et al[22] and

Table 2. Association between LJM and continuous and categorical variables

Variables	LJM		*p*	OR (95% CI)
	Positive, n (%) (N = 18)	Negative, n (%) (N = 57)		
Age (years), mean (SD), range	13.72 (1.84), 10.0–16.0	13.14 (1.82), 10–16	0.246*	
Duration of disease (years), mean (SD), range	7.81 (2.33), 4.0–12.0	4.92 (2.68), 2.0–14.0	**<0.001***	4.09 (1.480–4.289)
Insulin dose (IU/kg/day), mean (SD), range	1.17 (0.26), 0.6–1.6	1.05 (0.30), 0.4–1.5	0.13*	
HbA1c, mean (SD), range	10.23 (1.36), 7.4–12.13	9.80 (1.44), 6.73–13.38	0.264*	
Male sex	5 (28)	22 (39)	0.404†	
Height Z-score			0.332†	
Normal (−2 to +2)	12 (67)	46 (81)		
Short (<−2)	6 (33)	11 (19)		
BMI			0.525†	
Underweight (<5th percentile)	1 (5)	2 (4)		
Normal (5th to <85th percentile)	14 (78)	39 (68)		
Overweight & obese (≥85th percentile)	3 (17)	16 (28)		
Systolic BP			1.000†	
Normal (<90th percentile)	14 (78)	43 (75)		
Pre- or HT (≥90th percentile)	4 (22)	14 (25)		
Diastolic BP			0.146†	
Normal (<90th percentile)	10 (56)	42 (74)		
Pre- or HT (≥90th percentile)	8 (44)	15 (26)		
LDL (mg/dl)			**0.012†**	4.48 (1.312–15.299)
High (≥100)	14 (78)	25 (44)		
Normal (<100)	4 (22)	32 (56)		
Nephropathy, n = 44			**0.04†**	5.156 (0.977–27.204)
Present	15 (88)	16 (59)		
Absent	2 (12)	11 (41)		
Retinopathy, n = 64			**<0.001†**	14.33 (3.227–63.671)
Present	9 (50)	3 (7)		
Absent	9 (50)	43 (94)		

BMI=body mass index; BP=blood pressure; CI=confidence interval; HbA1c=glycated hemoglobin; HT=hypertensive; LDL=low-density lipoprotein; LJM=limited joint mobility; OR=odds ratio; SD=standard deviation
*Student *t*-test, $p \leq 0.05$ was significant; †Pearson chi-square and Fisher's exact tests, $p \leq 0.05$ was significant

this study (Table 2) failed to find a similar correlation. Moreover, the occurrence of LJM was not related to age, height, and BMI (Table 2).[17,22]

In accordance with a prior study,[17] no significant correlation was found between BP and LJM (Table 2). Although a significant correlation between LJM and greater systolic BP was found, the mechanism of this relationship was not described.[26]

A study on the development of LJM within 15 years in T1DM patients found that the alterations in joint mobility were not related to dyslipidemia.[27] In contrast, this study showed a significant association between high LDL levels and LJM (Table 2). An 8-year study by Lo et al[28] found that DM and accompanying hyperlipidemia were independent risk factors for adhesive capsulitis as a joint complication manifestation in adults with DM.

In this study, LJM was strongly associated with microvascular complications, namely nephropathy and retinopathy ($p = 0.04$ and $p<0.001$, respectively) (Table 2), similar to several previous studies.[2,17,29] However,

Clarke et al[22] found no relation between the presence of nephropathy or retinopathy with LJM. Differences in the study population and the study design (cross-sectional *versus* long-term prospective study) might have contributed to the discrepancy in the results. The association between LJM and microvascular complications may be attributed to their common pathological process that involves AGEs. High levels of oxidative stress and the development of AGEs are caused by intracellular hyperglycemia, with eventually increased generation of reactive oxygen species and subsequent activation of the inflammatory cascade leading to the production of numerous cytokines and growth factors causing hyperglycemia-induced vascular endothelium damage (microangiopathies).[30,31]

The main limitations of this study were relying on one observer and only using the prayer sign test, without examining other than hand joints, to determine LJM. Furthermore, fundoscopic examinations were done by different ophthalmologists. In conclusion, the incidence of LJM was high among T1DM adolescents, especially those with a long disease duration. It was significantly associated with high LDL levels and diabetic microangiopathies (nephropathy and retinopathy).

Conflict of Interest

The authors affirm no conflict of interest in this study.

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