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A mathematical model appraising the effect of metabolic control on joint mobility in young diabetic patients: a preliminary study

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Abstract

Objective. The impairment of glycemic control can induce limited joint mobility even in young type 1 diabetic (T1DM) patients. The aims of this study were to verify the presence of ankle joint mobility (AJM) deficits in young T1DM subjects and define a mathematical model of diabetes mellitus long-term effects on AJM.
Methods. AJM was evaluated using an inclinometer in 37 patients and 53 healthy, sex- BMI- and age-matched controls. To set up the mathematical model, we assumed that reduced metabolic control affects AJM according to a lognormal function: requiring some time for development of a reduction of joint mobility, which then persists for a long period, before fading out over time (if glycemic control has been recovered). A non-linear optimization determined the model parameters to achieve the best fit for a series of patients.
Results. Both plantar and dorsiflexion AJM was significantly lower in diabetic subjects than in controls (plantarflexion: 28.5°±7.5 vs 35.2°±6.5; dorsiflexion: 93.9°±16.0 vs 104.7±12.8; $p<0.01$). The defined model approximates the experimental data with good accuracy; after optimization, the lognormal curve obtained is in line with empirical estimates: lack of glycemic control needs to persist for at least a few months before producing a significant effect, that lasts up until one year. The fitting procedure indicated the optimal solution is p = (37; 30; 3:5; 6:7; 137); thus, the optimal _im(t) corresponds to the curve reported.
Conclusion. AJM was significantly reduced in young T1DM patients. The mathematical model represents the experimental data accurately.

Key words

Diabetes mellitus type 1, glycemic control, joint mobility, mathematical model.

Introduction

Diabetes mellitus (DM) is a metabolic disorder which has become one of the main global public health issues. It is estimated that almost 600 million of people in 2035 will be affected by DM due to its progressive increase (Guariguata et al., 2014; Lipsky et al., 2015).

Several epidemiological studies have shown that, even if there are significant regional differences, the incidence of type 1 diabetes (T1DM) has increased by about 2-5% over the last few years. Thus, the number of young patients affected by T1DM

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is increasing, representing about 5-10% of the total number of patients (Borchers et al., 2010; Mahaas et al., 2010; Guariguata et al., 2014).

Despite recent advances in patient care beginning at the pediatric age, diabetic patients may develop some chronic complications during their lifetime which are closely correlated with the quality of the metabolic control they maintain (Lindsay et al., 2005; Forbes and Cooper, 2013).

Some studies have reported that in young T1DM subjects, even if the incidence of limited joint mobility (LJM) shows a significant increase during the first years after disease onset, deterioration can be slower in adulthood. Therefore, the maximum prevalence of LJM is about 65% in subjects living with diabetes for longer than 30 years (Infante et al., 2001; Lindsay et al., 2005; Francia et al., 2015a).

Regular monitoring of a DM patient's condition is thus required, in order to provide early intervention. Joint abnormalities are one of the chronic diabetes-induced complications. The presence of stiff hand syndrome was first described by Lundbeack in the middle of the last century in adults and then by Grgic (1976) and Rosenbloom et al. (1981) in young patients with T1DM. Rosenbloom et al. (1981) published several studies reporting for the first time the prevalence of joint deficits, including those at the ankle, in young patients with T1DM and thus introducing the definition of limited joint mobility.

It has been further confirmed that both adults and young patients with T1DM can have a significant reduction of joint mobility at the ankle level (Francia et al., 2015a,b). The ankle joint has been extensively studied for the last 40 years in diabetic patients because of its important role in walking and because it is a distal joint which is particularly affected by diabetes (Mueller et al., 1989, 1995; Francia et al., 2014, 2015b). LJM is particularly dreaded as a major risk factor for the development of foot ulcers and for its possible correlation with other chronic complications induced by diabetes (e.g. vascular disease). Several studies have reported the relationship between joint mobility and other dysfunctions associated with diabetes in young T1DM patients: delay in sexual maturation, growth alterations, and early microvascular impairments such as retinopathy or nephropathy (Rosenbloom et al., 1981, 2015; Campbell et al., 1985; Zimny et al. 2004; Amin et al., 2005).

Factors predisposing to LJM occur from disease onset, and progressively worsen during its development (Abate et al., 2011; Rosenbloom et al., 2015). The main biochemical abnormality in DM patients' joint tissue is an excess of non-enzymatic glycosylation of collagen, with the production of advanced glycation and products (AGEs), which, in turn, lead to an increase in collagen cross-links. The increase in inter- and intra-molecular crosslinking of collagen fibers alters, in turn, the mechanical properties of these tissues, resulting in reduced elasticity and tensile strength which can cause mechanical stiffness (deGrot, 2004; Browlee, 2005; Snedeker and Gautieri, 2014). This alteration may negatively affect static and dynamic posture, progressively reducing the quality of movement. In turn, these effects may further induce anomalies in the patient's lifestyle (Mueller et al., 1989; Zimny et al., 2004; Francia et al., 2014).

However, no clear relationship has been identified between impaired metabolic control and joint mobility nor is the effect on joint mobility of impaired metabolic control over time understood.

The aims of this study were to verify the presence of both plantar and dorsiflex-

ion AJM deficit in young T1DM patients and to develop a mathematical model that would help understand the relationship between the level and duration of impaired metabolic control and the reduction in joint mobility. We believe that what we report can improve understanding of DM patients' overall condition, the disease effects on some tissues and functional skills as well as the prevention of physical and postural impairments.

Patients and methods

Patients attending the Meyer Children's Hospital in Florence, Italy, were consecutively enrolled for evaluation of plantar and dorsal flexion AJM by means of an inclinometer (Fabrication Enterprises Inc, White Plains, NY, USA) following the procedure reported in previous articles (Francia et al., 2015a,b, 2017).

A total of 37 patients with type 1 diabetes, 22 males and 15 females, were evaluated and compared with 53 healthy, age-, BMI- and sex-matched controls. Patients and controls ranged in age from 9 to 21 years. The main characteristics of the study participants are shown in Table 1. Patients with orthopedic and/or surgical foot complications were excluded. Data on age, sex, weight, height, body mass index (BMI, expressed as body weight in kilograms divided by height in meters squared, kg/m^2) diabetes duration, and presence of neuropathy were collected. The physical examination included foot inspection and evaluation of deformity. Hemoglobin A1c (HbA1c) was measured at baseline by high performance liquid chromatography (HPLC). Measured mobility was associated with previous measurements of glycosylated hemoglobin, extracted from the patient's health record, as required by the clinical protocol: measured every three months from the time of disease diagnosis.

It should be mentioned that HbA1c measurements reflect the overall degree of metabolic control over a period of 3 months (Saudek and Brick, 2009), thus, a vector of up to 20 values of glycosylated hemoglobin per patient was associated with mobility measurement.

All participants and parents or caregivers of the young subjects were informed about the study purpose and its experimental procedures before collecting written informed consent for enrollment in the study. The protocol and the consent forms were approved by the Ethics Committee of the Meyer Children's Hospital in Florence. The study was performed in accordance with the Helsinki declaration.

Determination of ankle joint mobility

To measure ankle range of motion (ROM), the patient was lying supine, with the subtalar joint in neutral position and the feet extending over the edge of the couch. The knee, corresponding to the evaluated ankle, was extended and positioned over a rigid support, 5 cm high.

The peak of plantar and dorsiflexion ROM was determined after marking the fifth metatarsal bone with a dermographic pen and positioning the inclinometer along the diaphysis of the bone, with one extremity positioned on the distal condylus. All measurements were performed by the same observer, who recorded the mean of three consecutive readings.

Mathematical model

The relationship between impaired metabolic control and measured mobility is described by a linear model. The model assumes that mobility is decreased, with respect to the physiological value, of a quantity linearly dependent from the entity of impairment of metabolic control with respect to the optimal value. For simplicity's sake, the model assumes that the effects of impaired control over time undergo a linear superimposition. In the temporal dimension, the impaired control causes a temporary decrease in mobility, represented by lognormal curve.

Summarizing, the mobility of a given subject p is expressed as:

$$m_p(t) = m_0 - \sum m_i\,(t)$$

where m_0 is baseline mobility, and m_i is the reduction in mobility caused by impaired control $g(t_i)$ at the time instant t_i. This function is, in turn, expressed as:

$$m_i(t) = \begin{cases} a(g(t_i) - g_0)lgn(t - t_i) & if\, g(t_i) > g_0 \\ 0 & oth\, erwise \end{cases}$$

where g_0 is the threshold glycemic index, and $lgn(t)$ is the normal curve, identified by the parameters m, s and defined as:

$$lgn(t) = \frac{e^{((t)-\mu)^2/(2\sigma)^2}}{\sigma\sqrt{2\pi}}$$

The parameters of the model (i.e. a, m_0, g_0, m, s) were estimated using a non-linear fitting procedure, based on a genetic algorithm, that determines the optimal parameter set corresponding to the best correspondence between measured motility and the model output [Francia et al., 2017].

The model reproduces the physiological knowledge on the effect of an impaired metabolic control, assuming that such impairment requires a certain amount of time to develop its effects. Once mobility is reduced, even when glycemic control is totally restored, the reduction lingers before the tissue can even partially recover its lost mobility. However, in order to reduce the number of free parameters and improve the stability of the numerical fitting procedure, the model assumes that if perfect metabolic control is re-established in the patient, his/her mobility will be fully restored.

Statistical analysis

Data are reported as the mean ± standard deviation (SD) or percentage, as appropriate. ROM values are expressed in degree and reported as the mean ± SD. Comparisons between groups were analyzed by ANOVA, using the Bonferroni correction for multiple comparisons. Frequencies were compared using the Chi-square method. Multiple regression analysis was performed using the AJM as the dependent variable

and all variables which appeared to be significantly correlated with joint mobility as confounding factors for univariate analysis. A two-tailed p value <0.05 was regarded as statistically significant. All calculations were performed using the SPSS system for Windows Version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Both plantar and dorsal flexion ankle joint mobility was significantly lower in diabetic subjects than in controls, (p<0.001), with an average 19.6% reduction of AJM in diabetic patients (Table 1).

We did not find a correlation between AJM and sex, BMI or age in both patient and control groups.

Control subjects were further subdivided into two groups: soccer players (CC group) and others (volleyball players and dancers, see table 2). Among the controls, soccer players had more significantly reduced dorsiflexion than other group members (p<0.001).

The model that best describes the relationship between glycemic control impairment and measured mobility corresponds to the parameter values $a = 37°$, $m_0 = 137°$, $g_0 = 6.7$, $m = 30$, $s = 3.5$; in this configuration the model explained about 50% of data variability. Furthermore, the curve describing the mobility reduction corresponds to the curve reported in Fig. 1. The curve has a strong similarity to expected physiological behavior, namely that metabolic control deficit takes several months to produce its maximum effect.

Table 1. Main characteristics and dorsal, plantar and total AJM (expressed as degrees) in T1DM patients and controls.

	Controls (n=53)	Type 1 diabetes mellitus patients (n=37)	P-Value*
Age (yrs)	13.8 ± 3.5	14.4 ± 3.5	NS
Gender (males/females)	31/22	22/15	–
Diabetes duration (yrs)	–	7.3 ± 3.7	–
BMI (Kg/m²)	19.4 ± 3.4	20 .0±3.2	NS
Neuropathy at baseline No. (%}	–	0	–
Plantar flexion (°-degree}	35.2 ± 6.5	28.5 ± 7.5	<0.001
Dorsal flexion (°)	104 .7 ± 12.8	93.9 ±16.0	<0.005
Total AJM(°)	140.0 ± 17.1	122.4 ± 20.7	<0.001

Compared to age-, BMI-and sex-matched controls . Values are mean ± SD.
*by one-way ANOVA.

Table 2. Main characteristics and dorsal, plantar and total AJM (expressed as degrees) in soccer player controls compared to all other controls.

	Group CC (soccer) (n=22)	**Group CNC (no soccer) (n=31)**	**P-Value***
Age (yrs)	12.0 ± 0.3	15.0 ± 4.1	<0,005
Gender (males/females)	22/0	9/22	–
BMI (Kg/m^2)	17.8±2.1	20.5 ± 3.7	<0,001
Plantar flexion (°-degree}	29.7 ± 4.4	39.2 ± 4.7	<0.001
Dorsal flexion (°)	98.4 ± 12.0	109.2 ± 11.4	<0.005
Total AJM(°)	128.1 ± 14.0	148.4 ± 13.9	<0.001

Values are mean± SD.
*by one-way ANOVA.

Discussion

This study indicates that our young T1DM patients had a significant reduction of ankle joint mobility, and associates the own AJM with the glycemic control maintained over the time through the definition of a mathematical model.

Today, although limited joint mobility in diabetic patients has not been fully explained, it is documented that reduced glycemic control is the main causal factor of increased stiffness of skin, joint capsule, ligaments and tendons (Mueller et al., 1989; Abate et al., 2011; Rosenbloom, 2015). The widespread occurrence of LJM in diabetic patients, with its significant clinical implications, is also well known (Delbridge et al., 1988). Unfortunately, LJM as a chronic complication of diabetes can be overlooked because it causes only a minor, although painful, disability (Benedetti and Noacco, 1976; Mueller et al., 1989; Abate et al., 2011; Rosenbloom et al., 2015; Zimny et al., 2015).

The assessment of joint mobility at the ankle level, in addition to providing important information on the DM patient's posture, movement quality and risk of developing foot ulcers, (as in adults and elderly patients), can also reveal how glycemic control maintenance has affected the health of the connective tissues - especially the periarticular ones (Mueller et al, 1989; Zimny et al., 2004; Francia et al., 2014).

Several studies on young patients with diabetes have reported and described a relationship between joint mobility deficits and the development of peripheral neuropathy and micro- and macrovascular complications, suggesting the presence of similar causal factors, in addition to stimulating physicians to be concerned about the increased risk of morbidity and mortality associated with LJM (Rosenbloom et al., 1981, 2015; Campbell et al., 1985; Jennings et al., 1989; Lu et al., 1993; Amin et al., 2005).

Consequently, the challenge of better understanding and monitoring the different responses of body tissues to the metabolic changes induced by diabetes is paramount. This is why one of the aims of this study was to create a mathematical model useful in the management of young patients with T1DM.

The assessment of HbA1c values is a commonly accepted procedure for monitoring glycemic control in clinical settings. This parameter measures the level of glycosylated hemoglobin in red blood cells that is correlated to the glucose control achieved in the previous 3 months. It has been fully confirmed that there is a strong relationship between glycemic control, HbA1c assessments and the risk of development and progression of the chronic complications induced by diabetes (Saudek and Brick, 2009; Rosenbloom, 2015).

Connective tissues exhibit different rhythms of extracellular matrix protein turnover. Collagen is the protein that determines the main tissue properties and its turnover is particularly slow, requiring up to several years. Consequently, this protein is exposed for longer times to glycemia changes caused by diabetes and persists in the extracellular matrix of periarticular tissues instead of being ascertained by the assessment of HbA1c (Snedeker and Guatieri, 2014; Rosenbloom, 2015). Therefore, we felt it important to define a mathematical model that could describe the relationship between maintained glycemic control as assessed by HbA1c and the diabetes effects on connective periarticular tissues through evaluation of ankle joint mobility. Our model assumes a linear superimposition of effects, and associates a decrease in metabolic control to reduced joint mobility with a lognormal shape. The model's parameters have been estimated using nonlinear fitting over a sample population.

Although the limited number of subjects in our study does not allow us to draw definitive conclusions, the proposed approach provides some insight into the possible relations between impaired metabolic control and reduced mobility. We are currently extending the dataset in order to perform a complete validation, possibly including other input data (i.e. patient age, sex, and time since disease diagnosis).

The realization of this study encountered difficulties involving direct investigation of the relationship between long term glycemic control and connective tissue glycosylation, the relationship between LJM and the condition of connective periarticular tissues and, finally, to the lack of consideration of LJM in the assessment and treatment of young diabetic subjects.

Ankle joint mobility reduction indicates a shift in foot plantar flexion due to the possible effect of diabetes on foot and leg muscle connective structures, progressing to a rigid foot posture in plantar flexion. Such alterations result in the inability to perform full ankle dorsiflexion, an impairment clearly exhibited by adult subjects with diabetic neuropathy and/or ankle equinus who are at risk of ulcers and an increased risk of falling (Salsich et al. 2000; Rao et al. 2007; Francia, 2014; Dallimore and Kaminski, 2015).

This condition causes a paradoxical situation: when patients are in a non-weight-bearing position they can have a typical rigid foot posture in plantar flexion while the ankle is forced in dorsiflexion when standing or during walking.

In this study it has not been necessary to consider the aging effects on joint mobility. Interestingly, 22 soccer players in the control group had a significant reduction of ankle joint mobility in plantar and dorsiflexion, similar to the diabetic patients, and more so than the others who played volleyball or danced. This result is worthy of further investigation.

The understanding and direct assessment of diabetes mellitus effects on periarticular connective tissues can contribute to improve treatment for patients who are subject to chronic complications such as those affecting the feet and vascular system.

Therefore, knowledge of this relationship could help to prevent diabetes effects, as well as provide insight into other factors having high impact on joint mobility such as sports like soccer, lifestyle activities or aging. These other factors could be considered in the definition of future mathematical models.

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