UNIL | Université de Lausanne

Service de rhumatologie, médecine physique et réhabilitation

Mémoire de Maîtrise en médecine No 296

Prevalence of Joint Hypermobility and Joint Hypermobility Syndrome in a Swiss population with Chronic Low Back Pain.

Etudiante
Inês Caldeira da Silva

Tuteur
Dr. Pierre de Goumoëns, MER
Médecin associé, svce Rhumatologie
Hôpital Orthopédique

Co-tuteur
Dr. Yves Henchoz, PhD
svce Rhumatologie
Hôpital Orthopédique

Expert
Dr. Federico Balagué, PD
Médecin Chef adjoint
svce Rhumatologie
Hôpital Fribourgeois

Lausanne, le 13 novembre 2011

Table of contents

1.Abstract:

Objective. Joint hypermobility (JH) and Joint Hypermobility Syndrome (JHS) are often under-diagnosed and were never specifically assessed in a selected population of chronic low back pain (LBP). This study aimed to assess JH and JHS among a population with chronic LBP using the Beighton and the Brigthon criteria.

Methods. We conducted a retrospective cross-sectional study based on a prospective data base among 143 patients with non-specific chronic LBP. Patients were seen by the same rheumatologist, who looked for JH and JHS and took their medical history. Data were analysed using logistic regression.

Results. We found a JH prevalence of 33,3% (CI 95% 22.0-44.6) among women and 21,4% (11.7-31.2) among men, and for JHS, of 37,9% (26.0-49.8) among women and 30,9% (19.7-42.0) among men. JH was less frequent among people older than fifty ($P < 0.02$). JHS was more prevalent among Swiss individuals ($P < 0.01$) and among individuals having a non-manual job ($P<0.03$) compared to there opposites. Patients having an important limitation for daily living activities were four times more likely to have JHS. Degenerative spinal disorders were negatively associated with JH (OR 0.31 (0.13-0.73) and JHS (OR 0.31 (0.14-0.68).

Conclusion. A high prevalence of joint hypermobility was found in our population. JHS should be part of differential diagnosis in individuals with chronic non-specific LBP.

2.Introduction

2.1 Joint Hypermobility

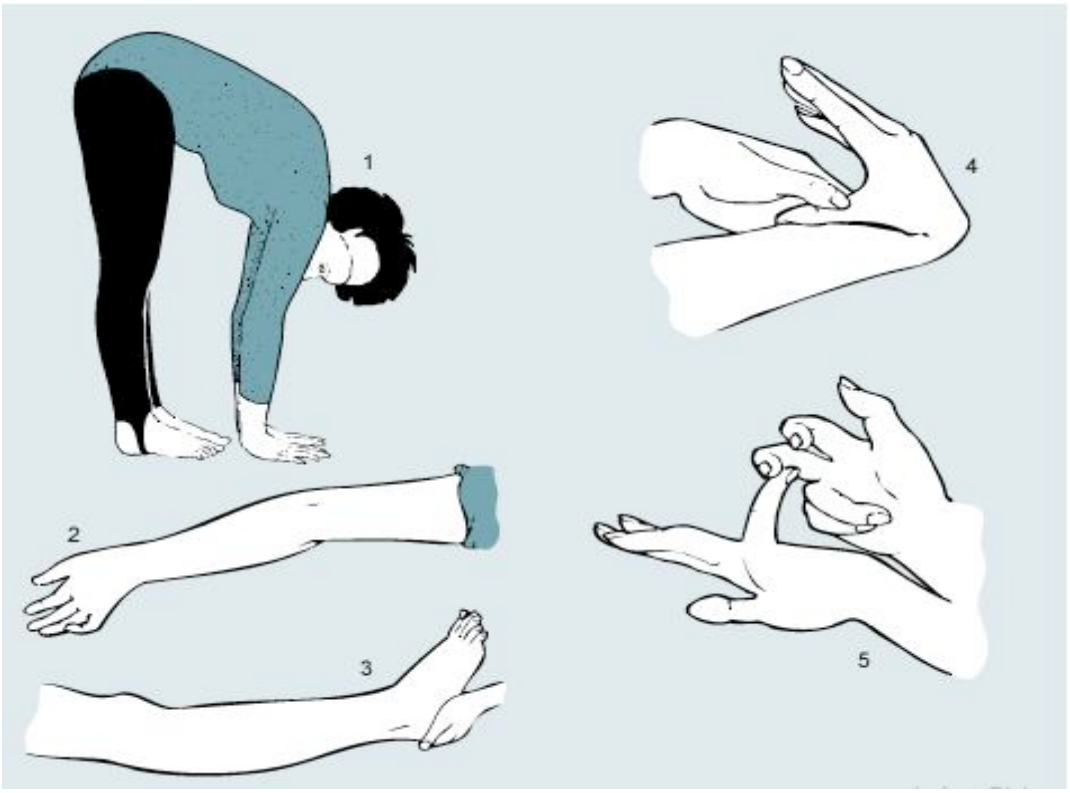
Joint Hypermobility (JH) used to only be seen as the normal upper end of a Gaussian distribution of joint range of movements (1), an opinion that has now changed. In most recent papers, a hypermobile joint is considered as one whose range of movement exceeds what is normal (2, 3).
The prevalence of JH depends on age, gender and ethnicity. It decreases with age, is about three times more frequent among women and is seen more often in African and Asians races compared to Caucasians (4). The prevalence of JH in Western populations has been shown as high as 10% by epidemiological studies and in other populations it has been recorded to be up to 25% (5, 6).

The conventional method to detect JH clinicaly is to apply the Beighton (1973) nine-point scoring system as shown on Table 1 (6). A score of four or more out of nine is usually the score accepted to diagnose « generalized » JH (4). Other former or less often used scoring systems exist (i.e. Carter and Wilkinson, Hospital del Mar criteria and Rotes-Querol) (7-9). There also is a four item questionnaire developed and validated by Hakim and Grahame (10).

Table 1. Beighton score (adapted from Grahame et al. Diagnostic criteria of BJHS, The Journal of Rheumatology, 2000)

The ability to:
1. Passively dorsiflex the 5th metacarpophalangeal joint to 90° or more
2. Oppose the thumb to the volar aspect of the ipsilateral forearm
3. Hyerextend the elbow to 10° or more
4. Hyperextend the knee to 10° or more
5. Place hands flat on the floor without bending the knees
One point can be acorded to each side, except for point 5. The maximum Total is 9 points
A score of at least 4/9 is enough to diagnose JH or «generalized» JH

Illustrations of the Beighton score taken from Alan HAKIM et Rodney GRAHAME, Best Practice & Research Clinical Rheumatology Vol. 17, No. 6, pp. 989-1004, 2003



2.2 Joint Hypermobility Syndrome

It is important to distinguish simple JH from the Joint Hypermobility Syndrome (JHS).

JHS was initially described in 1967, as the occurrence of musculoskeletal symptoms in the presence of hypermobility in individuals with no other cause explaining those symptoms (1).

JHS is now seen as a frequently overlooked and underdiagnosed multisystemic condition, belonging to the group of the heritable disorder of connective tissue (HDCT) (11). It shares overlapping features with the other major HDCT like Ehlers-Danlos syndrome (EDS) (12), Marfan syndrome (MS) (13, 14) and osteogenesis imperfecta (OI) (4). For some authors, JHS and EDS Hypermobile type (former type III) are clinically indistinguishable and considered as one and the same condition (2, 15-17). Others (18) call JHS «Benign Joint Hypermobility Syndrome» (BJHS) to denote a normal life expectancy and the absence of cardiac and arterial disorders (18) (unlike others HDCT like EDS vascular type or MS) (4).

Observation of families shows that the inheritance probably is autosomical dominant (1, 19, 20).

In 2003, a mutation in a non-collagenous molecule, tenascin-X, was identified in a subgroup of patients (mostly women),with JHS and with EDS hypermobile type (21). But the genetics of JHS remains poorly understood (19) and no genic or biochemical marker can be used to confirm the diagnosis (22).

Therefore, the diagnosis of JHS remains clinical, the accepted and validated (23) diagnosis criteria being the1998 revised Brighton criteria (24), illustrated on Table 2. The Brighton criteria consist of a set of major and minor criteria. They do not only include hypermobility, but also take into account other manifestations of tissue laxity, like skin striae, varicoce veins or myopia (25). These criteria have been demonstrated to have excellent specificity (93%) and sensitivity (93%) (24).

Table 2. The revised Brighton crireria (adapted from Grahame et al. Diagnostic criteria of BJHS, The Journal of Rheumatology, 2000)

To diagnose JHS are required the presence of:

- Two major criteria

- One major and two minor criteria

- Four minor criteria

- Only two minor criteria when a first degree relative is unequivocally affected

JHS is excluded by when Elhers Danlos syndrome (except the hypermobily type) or Marfan syndrome are present, as defined by the Ghent (14) and the Villefranche (12) criteria.

- Criteria Major 1 and Minor 1 are mutually exclusive, as are Major 2 and Minor 2.

Major criteria
1. A Beighton score of 4/9 or greater (either currently or historicaly).
2. Arthralgia for longer than 3 months in 4 or more joints.
Minor criteria
1. A Beighton score of 1, 2 or 3/9 (0,1,2 or 3 if aged 50 or older).
2. Arthralgia in 1-3 joints or back pain for 3 months or longer, the presence of spondylolysis / spondylolisthesis.
3. Dislocation or subluxation in more than one joint, or in one joint on more than one occasion.
4. Soft tissue rheumatism 3 lesions or more (e.g., epicondylitis, tenosynovitis, bursitis).
5. Marfanoid habitus (tall, slim, span/ height ratio > 1.03, upper:lower segment ratio < 0,89, arachnodactyly, (+Steinberg / wrist sign).
6. Abnormal skin: striae, hyperextensibility, thin skin, papyreceous scarring.
7. Eye sign: drooping eyelids or myopia or antimongoloid slant.
8. Varicose veins or hernia or uterine/rectal prolapse

Indeed, a wide range of symptoms and conditions can be associated with JH and JHS. Articular symptoms like arthralgia and fractures (26), premature osteoarthritis sometimes leading to chondrocalcinosis (27), chondromalacia patellae (28) and temporomandibular joint dysfunctions (29) have been reported. Low bone mass even in pre-menopausal women has also been associated with JH (30).

As a result of intrinsic weakness, or poor tensile strength, abdominal and pelvic viscera, as well as any other structure rich in collagen, may be affected (4): Genitourinary prolapse (31), skin striae or hyperextensibility (18) can occur.

Gastro-intestinal disturbances, often classified as functional gastro-intestinal disorders can also be present (32). Patients with JHS also manifest dysautonomia symptoms like fainting, palpitations or orthostatic intolerance more often than the rest of the population (33-35).

Anxiety disorders like panic attacks, social phobia and agoraphobia also occur, and have been significantly associated with JHS by studies from a Spanish team (36, 37).

2.3 Pain

Pain is the most common symptom (4, 38). Not all patients with JH experiences pain, as shown by Bravo and Wolff who did not find arthralgia in 43% of patients with JHS (22). For those who do it is often acute, recurrent and evolves into debilitating chronic pain (4, 38). Soft tissue injuries, like strains, tears or stress fracture are frequent. This tendency for injuries can be explained by an altered collagen, conducting to fragility of tissues like tendons, cartilage, bone and ligament (25) and similarly by the lack of proprioception linked with JHS, which probably adds to the likeliness of injury and secondary pain by favouring repeated microtrauma and prolonged abnormal joint positions (39-41).

Knowing this tendency for pain and injury, it is not surprising that a high prevalence of JHS is found in general rheumatology clinics. In this population, Grahame et al. (42) reported a prevalence of 46% among women and 31% among men in London, Bravo et al. (22) found a prevalence of 35% in Chile. The prevalence of JHS in the general population is currently unknown (4).

2.4 Low Back Pain and Hypermobility

2.4.1 Low Back Pain

Low back pain (LBP) consists of pain localised between the 12th rib and the inferior gluteal folds, acompaigned or not by leg pain. LBP is a very prevalent condition, the majority of cases being non-specific and self-limiting. Still, a small percentage of people will evolve to chronic and recurrent LBP with socio-economic consequences such as work impairment and prolonged sick leaves (43).

2.4.2 Back pain and Joint Hypermobility

People with JH also experience low back pain. A study among musicians (44), as well as another study (45) among industrial workers, both showed that individuals with an hypermobile spine (hands flat on the floor) were more likely to suffer from back pain. An Iraqui study (28), showed that among hypemobile (Beighton) individuals with chondromalacia patella, after knee pain, LBP was the most frequent complain (52%).

2.4.3 Back pain and Joint Hypermobility Syndrome

Some studies have already linked JHS with back pain. An Indian study (46), assessing the relationship between posture and pain among people with JHS, showed that LBP was the third most frequent pain complaint among individuals with JHS. Grahame et al. (42), reported a strong

association between mechanical back pain and JHS in both sexes. Among Omani women attending physiotherapy in a hospital center (47), 63% of the ones presenting with LBP had JHS.

The most similar paper to our study is the one from Howes et al. (48). It was a prospective study among 102 patients with back pain that also measured joint laxity. Since it was a study from 1971 and the validated Beighton and Brighton criteria did not exist, other methods to assess laxity were used. Spine x-rays were taken and analysed. In this paper the «loose back syndrome» was described for the first time. They found a higher prevalence of spine hypermobility among individuals without an anatomical explanation (x-ray) for their back pain. This situation was even more frequent among women. Pain had usually started in their teen years, was (invariabily) present in the low back and other joints were also hypermobile.

2.4.4 Spine and Hypermobility

A study from 1981 (26), in which spinal x-rays were analysed, showed a high prevalence (73%) of spinal anomalies like spondylolisthesis, pars interarticularis defect, transitional vertebrae at the lumbar sacral junction as well as scoliosis in the subgroup of people having a Beighton score of 5 out of 9.

A study from Bird et al. (49), looked at the link between spondylolisthesis and JH. Although they did not find a significant correlation, they still concluded that an association probably exists, and that spondylolisthesis probably is a consequence of back hyperlaxity. Moreover, spondylolisthesis as well as back pain (experienced for 3 months or longer) are part of the minor criteria used to diagnose JHS (24).

2.4.5 Back Pain in a Paediatric Population and Hypermobility

As to the association between JH or JHS and back pain in a child and teenage population, study results are conflicting. Most found no correlation between JH and back pain, but they sometimes used a higher Beighton cut-off point than usual (6/9 instead of 4/9) (50-53). One study showed a positive association between JH and back pain (54) . As to JHS, one study among a paediatric rheumatology population (already diagnosed with JHS), reported that LBP was their second commonest complaint (20).

3. Study Aim

Recent epidemiological studies on JH and JHS rarely took into account LBP complaints. Only one old study mentioned previously (48) examined individuals with back pain and searched for JH. To our knowledge, no study has measured the prevalence of JH and JHS among a population suffering from chronic non specific low back pain using the actual validated criteria (Beighton and Brighton). Therefore, we aimed to ascertain the prevalence of JH and JHS in a male and female Swiss population presenting with non-specific chronic LBP.

We hope to verify the following hypothesis:

1. To find a higher prevalence of JH and JHS in our chronic LBP population than the one found in the general population. To find a similar or even higher prevalence of JH and JHS in our population than the one found in the literature in a general rheumatology population.
2. Depending on the prevalence of JH and JHS we find, it could change the way in which we see and treat chronic LBP.

4.Material and Methods:

4.1 Patients Recruitment

A retrospective cross-sectional study based on a prospective database was conducted among 235 patients seen at the specialised back pain unit at Lausanne University Hospital (Switzerland). Only files of patients that had come for the first time to the consultation between the periods of the 10th may 2009 to the 10th October 2010 were selected. All files were found either on paper or on electronic versions.

4.2 Inclusion and Exclusion Criteria

Only patients having non-specific chronic LBP (>4 3 months) as a main complaint and coming for the first time to the back consultation were included. The exclusion criteria were the following: not having LBP as the main complaint or insufficient data being available. For instance patients complaining mainly of cervicalgia, brachio-cervicalgia or sciatalgia were not included.

4.3 Clinical Exam

All patients were seen by the same rheumatology and spine specialist (PdG), who conducted a detailed and systematic medical and personal history with each patient. A precise clinical back exam, as well as a general laxity exam was performed. When available, spine MRI or X-rays were analysed.

4.4 Patients History

Precise medical and personal history as well as family history was obtained. Socio-economic information like working status, education level or insurance claims were also obtained. Special attention was given to indication of obstructive sleep disorder and signs of anxiety or depression.

4.5 Hypermobility Assessment

Joint Hypermobility was assessed using the Beighton scoring system (6), considered positive when four or more out of the nine clinical points were present. Details of that scoring system are presented in Table 1 (previous pages). Since hypermobility signs decrease with age, for individuals being over fifty, the Hakim and Graham questionnaire (10) was also used additionally to the Brighton criteria. A positive questionnaire or an historical Beighton score of 4/9 was considered as having the same value as the clinical Beighton score in younger individuals (like it is accepted in the Brighton criteria) (24). Joint Hypermobility Syndrome was assessed using the 1998 revised Brighton criteria (cited before), presented on Table 2.

4.6 Data

Demographic and socio-economic data included sex, age, body mass index (BMI), marital status, education (primary, secondary, university), religion (Catholic, Protestant, other), origin (Swiss, other), employment category (Manual, non manual, half-manual), work status (full time, part time, off work/unemployed) and smoking status (non smoker, former smoker, smoker). Duration of LBP was defined as the time delay between symptoms occurrence and the date of the consultation with the specialist. Limitations in activities of daily living (ADL) was defined as the patient reporting any disturbances in all three following categories: house chores, driving or being a car passenger and sexual activity. Child abuse and neglect (CAN) was measured by taking detailed personal and familial anamnesis, using a genogram. Anxiety, depression, psychological diagnosis, possible microinstability[1], degenerative spinal disorder[2], health insurance conflict data were also collected.

[1] Here defined as sudden painful back spasme revieled by medical history, type I , II modifications and / or instability spondylophytes (according to the McNab X-Ray classification)
[2] Degenerative spinal disorders are here defined as spine arthrosis as well as disc herniations

4.7 Statistics

The sample size calculation was based on a margin of error for the prevalence estimates of 8%. In the absence of data, the sample size was calculated for a conservative prevalence estimate of 0.5. A multiple logistic regression model was constructed by incorporating as independent variables age, sex, and only those with $P<0.25$ in the analysis. Data analysis was performed using Stata 11.0 (Stata Corporation, College Station, Texas, USA). The significance level was set at 0.05.

4.8 Ethics

Ethical approval for the study was granted by the Ethics Committee of the University Medical School of Lausanne (Switzerland).

5.Results

5.1 Baseline characteristics

Of the 235 patients files from the selected period, 143 met the inclusion criteria and were statistically analysed. Table 3 presents baseline characteristics of the individuals included in the sample. Both genders were equally represented (70 women and 73 men). Thirty percent were older than 50 years. The majority of the individuals were married and catholic. About 53% had a Swiss origin and the rest were mostly Europeans, the second biggest origin group being people from Portugal (14%). The majority of patients had secondary education but did not go to University. Most patients had a manual profession. Despite their back pain, about 46% of the selected patients still worked full time on the day of the consultation. As to the duration of low back pain, a minority of patients had experienced it for less than a year (10,8%) but the majority of them had been suffering from it for more than 10 years (46,2%).

Table 3. Subjects' baseline characteristics.

Variable	n	%
Sex		
Women	70	49.0
Men	73	51.0
Age		
< 40 years	49	34.3
40-50 years	51	35.7
> 50 years	43	30.0
BMI		
Underweight	4	2.8
Normal weight	58	40.6
Overweight	48	33.6
Obesity	33	23.1
Marital status		
Single	39	27.5
Married	64	45.1
Divorced/Widowed	39	27.5
Education		
Primary	42	32.3
Secondary	55	42.3
University	33	25.4
Religion		
Catholic	59	49.2
Protestant	33	27.5
Other	28	23.3
Origin		
Swiss	74	52.9
Other	66	47.1
Employment category		
Non-manual	37	26.8
Manual	69	50.0
Half manual/half non-manual	32	23.2
Work status		
Full time	59	45.7
Part time	27	20.9
Off work / unemployed	43	33.3
Smoking		
Non smoker	52	36.9
Former smoker	34	24.1
Smoker	55	39.0
LBP duration		
< 1 year	14	10.8
1-5 years	33	25.4
5-10 years	23	17.7
> 10 years	60	46.2

BMI = body mass index ; LBP = low back pain

5.2 Univariate analyses

Table 4 shows JH and JHS prevalence according to socio-economic and demographic characteristics. In both conditions, the prevalence was slightly higher among women than among men. JH was found in 33.3% of women (confidence interval 22.0-44.6) and in 21.4% (11.7-31.2) of men. JHS was found in 37.9% (26.0-49.8) of women and 30.9% (19.7-42.0) of men. Clinical JH (Beighton score) was significantly less prevalent ($P < 0.02$) among people older than 50 years.

Another significant result ($P < 0.01$) is the fact that JHS was more prevalent in Swiss individuals than in individuals of other origins. There also was a positive correlation ($P < 0.03$) between having a non-manual job and the prevalence of the JHS.

Table 4. Joint hypermobility prevalence and joint hypermobility syndrome prevalence according to socioeconomic and demographic characteristics.

	JH prevalence				JHS prevalence			
Variable	n	% (95% CI)	OR (95%CI)	*P**	n	% (95% CI)	OR (95%CI)	*P**
Total	139	27.3 (19.8-34.8)			122	34.3 (26.2-42.5)		
Sex [§]								
Women	69	33.3 (22.0-44.6)	1.00		66	37.9 (26.0-49.8)	1.00	
Men	70	21.4 (11.7-31.2)	0.48 (0.22-1.05)	*0.066*	68	30.9 (19.7-42.0)	0.68 (0.33-1.42)	*0.305*
Age [¶]								
< 40 years	47	34.0 (20.2-47.9)	1.00		47	40.4 (26.1-54.7)	1.00	
40-50 years	50	32.0 (18.8-45.2)	0.87 (0.37-2.06)	*0.753*	46	34.8 (20.7-48.8)	0.77 (0.33-1.79)	*0.541*
> 50 years	42	14.3 (3.5-25.1)	0.28 (0.09-0.81)	*0.020*	41	26.8 (13.0-40.7)	0.51 (0.20-1.26)	*0.145*
BMI								
Underweight	4	50.0 (-7.1-107.1)	1.54 (0.19-12.59)	*0.683*	4	50.0 (-7.1-107.1)	2.07 (0.26-16.44)	*0.492*
Normal weight	57	36.8 (24.1-49.6)	1.00		56	30.4 (18.1-42.6)	1.00	
Overweight	47	19.1 (7.7-30.6)	0.59 (0.22-1.54)	*0.278*	45	35.6 (21.3-49.8)	1.67 (0.68-4.06)	*0.262*
Obesity	31	19.4 (5.1-33.6)	0.49 (0.17-1.45)	*0.198*	29	37.9 (19.8-56.1)	1.60 (0.61-4.21)	*0.343*
Marital status								
Single	37	35.1 (19.4-50.9)	1.00		36	38.9 (22.6-55.2)	1.00	
Married	62	22.6 (12.0-33.2)	1.26 (0.42-3.74)	*0.676*	61	32.8 (20.8-44.8)	1.14 (0.42-3.09)	*0.798*
Divorced/Widowed	39	28.2 (13.8-42.6)	2.06 (0.57-7.43)	*0.269*	36	33.3 (17.6-49.1)	1.26 (0.38-4.12)	*0.708*
Education								
Primary	40	22.5 (9.3-35.7)	1.00		39	25.6 (11.6-39.7)	1.00	
Secondary	55	25.5 (13.7-37.2)	1.03 (0.38-2.84)	*0.947*	50	38.0 (24.3-51.7)	1.67 (0.66-4.24)	*0.283*
University	32	40.6 (23.2-58.1)	2.66 (0.91-7.81)	*0.075*	32	43.8 (26.1-61.4)	2.25 (0.81-6.22)	*0.118*
Religion								
Catholic	58	22.4 (11.5-33.4)	1.00		56	35.7 (22.9-48.5)	1.00	
Protestant	33	30.3 (14.2-46.4)	1.70 (0.61-4.73)	*0.312*	32	40.6 (23.1-58.1)	1.31 (0.52-3.29)	*0.567*
Other	25	28.0 (9.8-46.2)	1.50 (0.49-4.56)	*0.478*	24	25.0 (7.1-42.9)	0.62 (0.21-1.83)	*0.384*
Origin								
Swiss	72	33.3 (22.3-44.4)	1.00		71	43.7 (31.9-55.4)	1.00	
Other	64	21.9 (11.6-32.2)	0.51 (0.23-1.15)	*0.103*	60	23.3 (12.4-34.2)	0.37 (0.17-0.80)	*0.011*
Employment category								
Manual	67	23.9 (13.5-34.3)	1.00		64	28.1 (16.9-39.3)	1.00	
Non-manual	37	35.1 (19.4-50.9)	2.00 (0.78-5.12)	*0.149*	36	50.0 (33.3-66.7)	2.71 (1.13-6.54)	*0.026*
Half manual/half non-manual	30	26.7 (10.4-42.9)	1.37 (0.46-4.04)	*0.568*	30	30.0 (13.2-46.8)	1.16 (0.43-3.14)	*0.771*
Work status								
Full time	58	27.6 (15.9-39.3)	1.00		57	35.1 (22.5-47.7)	1.00	
Part time	26	38.5 (19.2-57.7)	1.80 (0.64-5.10)	*0.265*	26	34.6 (15.8-53.5)	1.02 (0.37-2.78)	*0.970*
Off work / unemployed	42	21.4 (8.7-34.1)	0.80 (0.30-2.14)	*0.657*	38	34.2 (18.8-49.7)	1.04 (0.43-2.54)	*0.929*
Smoking								
Non smoker	50	32.0 (18.8-45.2)	1.00		52	25.0 (13.0-37.0)	1.00	
Former smoker	33	21.2 (6.9-35.5)	0.74 (0.25-2.18)	*0.586*	30	43.3 (25.1-61.5)	2.94 (1.07-8.04)	*0.036*
Smoker	54	25.9 (14.0-37.8)	0.68 (0.27-1.68)	*0.400*	50	38.0 (24.3-51.7)	1.84 (0.76-4.45)	*0.176*

JH = joint hypermobility; JHS = joint hypermobility syndrome; CI = confidence interval; OR = odds ratio, adjusted for age and sex; *Pearson's Chi-square test, adjusted for age and sex ; [§] = adjusted only to age; [¶] = adjusted only to sex; BMI = body mass index

Table 5 presents JH and JHS prevalence according to clinical characteristics. About 60% of the patients with JH and 85% of patients with JHS had been experiencing back pain for at least more than five years. The most significant result is the association between JH and degenerative spinal disorders. Among patients without degenerative spinal disorders, there was a higher prevalence of JH (46.8%, CI 32.2-61.3) and of JHS (54.5%, CI 39.5-69.6) than in patients with degenerative spinal disorders, with the following OR and p values: (OR 0.31, P < 0.007) for JH and (OR 0.31, P < 0.004) for JHS.

Table 5. Joint hypermobility prevalence and joint hypermobility syndrome prevalence according to clinical characteristics.

	JH prevalence				JHS prevalence			
Variable	n	% (95% CI)	OR (95%CI)	*P**	n	% (95% CI)	OR (95%CI)	*P**
Total	139	27.3 (19.8-34.8)			122	34.3 (26.2-42.5)		
LBP duration								
< 1 year	14	21.4 (-1.1-44.0)	1.00		12	16.7 (-5.6-38.9)	1.00	
1-5 years	31	22.6 (7.4-37.7)	1.14 (0.23-5.63)	*0.871*	32	25.0 (9.6-40.4)	1.75 (0.31-9.96)	*0.528*
5-10 years	22	31.8 (11.7-51.9)	1.66 (0.32-8.55)	*0.546*	21	47.6 (25.5-69.7)	4.82 (0.81-28.70)	*0.084*
> 10 years	59	28.8 (17.0-40.6)	2.06 (.046-9.34)	*0.346*	56	37.5 (24.6-50.4)	3.74 (0.70-19.84)	*0.121*
Health insurance conflict								
Yes	8	12.5 (-12.2-37.2)	0.57 (0.06-5.07)	*0.612*	8	25.0 (-7.4-57.4)	0.84 (0.15-4.53)	*0.836*
No	128	27.3 (19.5-35.2)	1.00		122	34.4 (25.9-43.0)	1.00	
Microinstability								
Yes	96	27.1 (18.1-36.1)	0.95 (0.41-2.20)	*0.898*	93	35.5 (25.6-45.4)	1.18 (0.53-2.62)	*0.688*
No	43	27.9 (14.2-41.6)	1.00		41	31.7 (17.2-46.3)	1.00	
Degenerative spinal disorder								
Yes	88	17.0 (9.1-25.0)	0.31 (0.13-0.73)	*0.007*	85	24.7 (15.4-34.0)	0.31 (0.14-0.68)	*0.004*
No	47	46.8 (32.2-61.3)	1.00		44	54.5 (39.5-69.6)	1.00	
Anxiety								
Yes	32	25.0 (9.6-40.4)	0.84 (0.32-2.22)	*0.725*	31	35.5 (18.2-52.8)	1.09 (0.45-2.63)	*0.852*
No	89	28.1 (18.6-37.6)	1.00		86	34.9 (24.6-45.1)	1.00	
Depression								
Yes	45	26.7 (13.5-39.9)	1.14 (0.47-2.72)	*0.775*	44	31.8 (17.7-45.9)	0.85 (0.38-1.90)	*0.691*
No	76	27.6 (17.4-37.9)	1.00		73	37.0 (25.7-48.3)	1.00	
Psychological diagnosis								
Yes	16	18.8 (-1.2-38.7)	0.60 (0.15-2.34)	*0.464*	17	23.5 (2.5-44.5)	0.53 (0.16-1.75)	*0.296*
No	107	28.0 (19.4-36.7)	1.00		101	36.6 (27.1-46.2)	1.00	
CAN								
Yes	29	31.0 (13.7-48.3)	1.11 (0.42-2.95)	*0.827*	28	39.3 (20.7-57.9)	1.17 (0.47-2.89)	*0.735*
No	98	27.6 (18.6-36.5)	1.00		95	34.7 (25.0-44.4)	1.00	
ADL limitations								
Yes	67	31.3 (20.0-42.7)	1.85 (0.72-4.72)	*0.199*	64	39.1 (26.9-51.2)	2.01 (0.84-4.78)	*0.114*
No	45	20.0 (8.1-31.9)	1.00		45	24.4 (11.6-37.3)	1.00	

JH = joint hypermobility; JHS = joint hypermobility syndrome; CI = confidence interval; OR = odds ratio, adjusted for age and sex; *Pearson's Chi-square test, adjusted for age and sex; LBP = low back pain; CAN = child abuse and neglect; ADL = activities of daily living

Table 6 presents multiple logistic regression analysis for JH and JHS according to socio-economic, demographic and clinical characteristics. The association between JH (OR 0.25, P < 0.011) and JHS (OR 0.17, P < 0.006) and degenerative spinal disorders was confirmed again. Individuals having an important limitation for ADL are four times more likely to have JHS than individuals having low back pain but experiencing less ADL limitations. According to our results patients being older than 50 years of age are less likely to be diagnosed with JH (OR 0.18, P < 0.030) and JHS (OR 0.11, P < 0.019) than younger individuals.

Table 6. Multiple logistic regression analysis for joint hypermobility and joint hypermobility syndrome according to socioeconomic, demographic and clinical characteristics.

	JH (n = 98)		JHS (n = 85)	
Variable	OR (95%CI)	*P**	OR (95%CI)	*P**
Sex				
Men	0.53 (0.20-1.44)	*0.212*	1.30 (0.41-4.07)	*0.655*
Age				
> 50 years	0.18 (0.04-0.85)	*0.030*	0.11 (0.02-0.70)	*0.019*
BMI				
Obesity	1.09 (0.31-3.90)	*0.890*		
Education				
University	1.13 (0.29-4.37)	*0.859*	1.12 (0.26-4.91)	*0.880*
Origin				
Other	0.77 (0.26-2.28)	*0.635*	0.77 (0.21-2.78)	*0.687*
Employment category				
Non-manual	2.92 (0.71-11.96)	*0.136*	3.27 (0.66-16.25)	*0.147*
Smoking				
Former smoker			0.69 (0.14-3.30)	*0.643*
Smoker			1.83 (0.54-6.27)	*0.335*
LBP duration				
5-10 years			3.68 (0.76-17.88)	*0.106*
> 10 years			3.24 (0.72-14.55)	*0.125*
Degenerative spinal disorder				
Yes	0.25 (0.09-0.73)	*0.011*	0.17 (0.05-0.60)	*0.006*
ADL limitations				
Yes	2.36 (0.82-6.82)	*0.113*	4.18 (1.23-14.14)	*0.022*

JH = joint hypermobility; JHS = joint hypermobility syndrome; OR = odds ratio; CI = confidence interval; *Pearson's Chi-square test; BMI = body mass index; LBP = low back pain; ADL = activities of daily living

6.Discussion

The main purpose of this study was to ascertain the prevalence of JH and JHS in a population suffering from chronic non-specific LBP and determine if JH and JHS are more frequent in certain subgroups of patients. We found a high prevalence of JH and JHS in our population. Among women, we found a prevalence of 33,3% for JH and of 37,9% for JHS. Among men, we found a prevalence of 21,4% for JH and of 30,9% for JHS. Our most significant result was the negative association between JH or JHS and degenerative spinal disorders. In our population, patients having degenerative spinal disorders were less likely to have JHS. We also found that individuals older than 50 years of age were less likely to be diagnosed with JH and JHS.

LBP of individuals having JH or JHS seams to last longer than LBP of individuals without JH or JHS. This observation can be considered as clinically important even though it did not reach statistical significance. These are all new information, since, to our knowledge, no recent studies have looked at JHS in individuals presenting LBP with the current validated criteria.

The non-randomized and retrospective nature of this study limits the conclusions that can be drawn from the data. However,data were prospectively collected by a single experimented rheumatology and back specialist (PdG) through a classical back consultation that systematically included JH and JHS diagnostic tests, thereby limiting potential bias. The prevalence of JHS is currently unknown in the Swiss or European general population so that no comparisons are possible. Also, imaging exams were not performed among all patients, which can influence the prevalence of degenerative spinal disorders. These limitations are counterbalanced by a rigourous methodology that enabled view missing data. Indeed, all positive diagnosis were verified by the rheumatologist and a second person (IC) by carefully analysing each patient's file.

The prevalence of JHS in a general Western or Swiss population is currently unknown but we can compare our results with the JHS prevalence in general rheumatology clinics. In 2004 Graham et al. (42) reported a JHS prevalence of 46% among women and 31% among men (England), which is

similar to our results (37,9% for women and 30,9% for men). We even found a higher prevalence of JH in our LBP population than Guma et al. (55) in their Spanish general rheumatology population (25%). We found a smaller prevalence of JHS than Clark et al. (47) found in their Omani female population (55%). Maybe Omani people are more likely to have JH and JHS, since we already know that ethnic variation exist. Also, we can say that the population of this study is not comparable to ours, since it consists exclusively of female patients, referred by orthopaedic surgeons to attend physiotherapy (and not a two gender rheumatology population like ours).

The prevalence of simple JH is estimated as high as 10% in a Western general population, which is two to three times less than the prevalence we found in our population (33,3% for women and 21,4% for men). Our results also confirm the general knowledge that JH is more frequent among women and that clinical signs of hypermobility diminish with age (4, 56). Since in this study we considered the questionnaire (10) or the anamnestic Beighton as having the same value as the clinical Beighton in patients older than 50, it is surprising that despite this precaution, we also found that JHS was less frequent at that age range. It might be explained by the fact that some patients are unaware of their own hypermobility as well as by memory bias.

As to the negative association between JH and JHS with degenerative spinal disorders, it can be surprising since degenerative spine disorders like spondylolisthesis are part of the diagnose criteria for JHS and should to be favoured by back laxity. On the other hand, our result are in accordance with the findings of Howes et al. (48). Indeed, for them the «loose back syndrome» was more frequent among individuals without anatomical findings on the spine x-ray. Also, in our study, imaging of the back was not available for all patients. Results might have been different if that was the case.

Even if it is not a significant association, it is interesting to discuss the fact that JH and JHS was more frequent among individuals having a non-manual job as well as people with a Swiss origin. We can easily imagine, that individuals with a manual job even without JH are still at greater risk of having mechanical LBP secondary to their heavy work. Also, even thought there is little data

available on the subject, there is a study from 1971 (56) that reported that children belonging to the higher income group were more lax jointed than those of the lower social classes. As non-manual jobs are the ones achieved by higher education and allowing for a higher income, this could be the first small step to a possible explanation for this result.

As to the racial prevalence disparity, it may be due to genetical differences since JHS is an inherited condition. Also, the two characteristics may reinforce each other, since non-Swiss individuals are more likely to work in the manufacturing sector than the service sector compared to Swiss individuals.[3]

[3] Swiss Federal Office of Statistics (homepage on the internet). Bern. Available from http://www.bfs.admin.ch

7. Conclusion:

In our Swiss population with chronic non-specific LBP, the prevalence of JH was higher than the one found in the general western population (around 10%) (5) and than the one found in a rheumatolgy clinic in Spain (55) . We also found a high prevalence of JHS, comparable to the one found in a general rheumatology clinic in England (42).

Therefore, we can only stress the importance for doctors to search for JH and JHS using the validated criteria (Beighton and Brighton), as well as the validated four item questionnaire from Hakim and Grahame in their daily practice. Especially when facing patients with unexplained chronic pain, including LBP.

A 2001 study from Graham et al. (57) showed that JHS was not well known even by rheumatology specialists. It is therefore not surprising that JHS is an under-diagnosed condition, only 1/20 people with JHS having the correct diagnosis (58).

Other studies (59-63), show that, in adults as well as in children, individuals with fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS) have a higher prevalence of JH and JHS.

For all those reasons, we support another authors opinion (17, 64), that it is important to consider JHS when or even before making the diagnosis of FMS or CFS.

Like other authors (16, 57), we think it is important to make doctors more aware of JHS. This effort should be made for different reasons.

First of all, for our patients benefit. Indeed like it is reported in the literature, living with JHS, especially without having been diagnosed is “painfull” (58, 65). Sometimes patients even start doubting themselves and to believe that the symptoms are only psychological (66). A recent study (67) even showed that female patients with EDS hypermobile type (comparable to JHS) even suffer from a greater burden than the ones having rheumaroid arthritis. Also, it usually takes about 10 years for the diagnosis to be made (68), and it is received with relief (66).

Beeing aware of and diagnosing JHS is also important for our public health system. Indeed, in 2005, LBP was the most prevalent health problem in Switzerland and was responsible for 6,1% of the total health care costs (69). Since classical treatments are ineffective or can even make the situation worse in individuals with JHS (4), diagnosing the subgroup of people having LBP secondary to JH is crucial. It means being able to give them appropriate treatment (4, 41, 46, 68) and help them recover. Early recognition and treatment prevents pain from becoming chronic and even more difficult to manage. It can also avoid work absenteeism, presenteism and their associated social consequences.

Is it not our duty as doctors, or future doctors, to avoid being so «fascinated» by fancy technologies and complicated diagnosis, that we forget simple clinical diagnosis which can have such a big impact on people's lives and public health?

8. Aknowledgments:

I would like to thank Dr. Pierre de Goumoëns and Dr. Yves Henchoz for helping me and supervising me during this year. Thanks to their availability and guidance, writing my master thesis was a pleasant and enriching experience.

9.Bibliography

1. Kirk JA, Ansell BM, Bywaters EG. The hypermobility syndrome. Musculoskeletal complaints associated with generalized joint hypermobility. Ann Rheum Dis. 1967 Sep;26(5):419-2
2. Grahame R. Joint hypermobility and genetic collagen disorders: are they related? Arch Dis Child. 1999 Feb;80(2):188-91.
3. Dolan AL, Hart DJ, Doyle DV, Grahame R, Spector TD. The relationship of joint hypermobility, bone mineral density, and osteoarthritis in the general population: the Chingford Study. J Rheumatol. 2003 Apr;30(4):799-803.
4. Hakim A, Grahame R. Joint hypermobility. Best Pract Res Clin Rheumatol. 2003 Dec;17(6):989-1004.
5. Silverman S, Constine L, Harvey W, Grahame R. Survey of joint mobility and in vivo skin elasticity in London schoolchildren. Ann Rheum Dis. 1975 Apr;34(2):177-80.
6. Beighton P, Solomon L, Soskolne CL. Articular mobility in an African population. Ann Rheum Dis. 1973 Sep;32(5):413-8.
7. Carter C, Wilkinson J. Persistent Joint Laxity and Congenital Dislocation of the Hip. J Bone Joint Surg Br. 1964 Feb;46:40-5.
8. Bulbena A, Duro JC, Porta M, Faus S, Vallescar R, Martin-Santos R. Clinical assessment of hypermobility of joints: assembling criteria. J Rheumatol. 1992 Jan;19(1):115-22.
9. Rotes-Querol J. [Articular laxity considered as factor of changes of the locomotor apparatus]. Rev Rhum Mal Osteoartic. 1957 Jul-Aug;24(7-8):535-9.
10. Hakim AJ, Grahame R. A simple questionnaire to detect hypermobility: an adjunct to the assessment of patients with diffuse musculoskeletal pain. Int J Clin Pract. 2003 Apr;57(3):163-6.
11. Grahame R. Heritable disorders of connective tissue. Baillieres Best Pract Res Clin Rheumatol. 2000 Jun;14(2):345-61.
12. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet. 1998 Apr 28;77(1):31-7.
13. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet. 1996 Apr 24;62(4):417-26.
14. Faivre L, Collod-Beroud G, Ades L, Arbustini E, Child A, Callewaert B, et al. The new Ghent criteria for Marfan syndrome: what do they change? Clin Genet. 2011 May 12.
15. Tinkle BT, Bird HA, Grahame R, Lavallee M, Levy HP, Sillence D. The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). Am J Med Genet A. 2009 Nov;149A(11):2368-70.
16. Grahame R. Time to take hypermobility seriously (in adults and children). Rheumatology (Oxford). 2001 May;40(5):485-7.
17. Bravo JF. [Ehlers-Danlos syndrome, with special emphasis in the joint hypermobility syndrome]. Rev Med Chil. 2009 Nov;137(11):1488-97.
18. Mishra MB, Ryan P, Atkinson P, Taylor H, Bell J, Calver D, et al. Extra-articular features of benign joint hypermobility syndrome. Br J Rheumatol. 1996 Sep;35(9):861-6.

19. Malfait F, Hakim AJ, De Paepe A, Grahame R. The genetic basis of the joint hypermobility syndromes. Rheumatology (Oxford). 2006 May;45(5):502-7.
20. Adib N, Davies K, Grahame R, Woo P, Murray KJ. Joint hypermobility syndrome in childhood. A not so benign multisystem disorder? Rheumatology (Oxford). 2005 Jun;44(6):744-50.
21. Zweers MC, Hakim AJ, Grahame R, Schalkwijk J. Joint hypermobility syndromes: the pathophysiologic role of tenascin-X gene defects. Arthritis Rheum. 2004 Sep;50(9):2742-9.
22. Bravo JF, Wolff C. Clinical study of hereditary disorders of connective tissues in a Chilean population: joint hypermobility syndrome and vascular Ehlers-Danlos syndrome. Arthritis Rheum. 2006 Feb;54(2):515-23.
23. Remvig L, Jensen DV, Ward RC. Are diagnostic criteria for general joint hypermobility and benign joint hypermobility syndrome based on reproducible and valid tests? A review of the literature. J Rheumatol. 2007 Apr;34(4):798-803.
24. Grahame R, Bird HA, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol. 2000 Jul;27(7):1777-9.
25. Grahame R. Joint hypermobility syndrome pain. Curr Pain Headache Rep. 2009 Dec;13(6):427-33.
26. Grahame R, Edwards JC, Pitcher D, Gabell A, Harvey W. A clinical and echocardiographic study of patients with the hypermobility syndrome. Ann Rheum Dis. 1981 Dec;40(6):541-6.
27. Bird HA, Tribe CR, Bacon PA. Joint hypermobility leading to osteoarthrosis and chondrocalcinosis. Ann Rheum Dis. 1978 Jun;37(3):203-11.
28. al-Rawi Z, Nessan AH. Joint hypermobility in patients with chondromalacia patellae. Br J Rheumatol. 1997 Dec;36(12):1324-7.
29. Westling L, Mattiasson A. General joint hypermobility and temporomandibular joint derangement in adolescents. Ann Rheum Dis. 1992 Jan;51(1):87-90.
30. Gulbahar S, Sahin E, Baydar M, Bircan C, Kizil R, Manisali M, et al. Hypermobility syndrome increases the risk for low bone mass. Clin Rheumatol. 2006 Jul;25(4):511-4.
31. Knuuti E, Kauppila S, Kotila V, Risteli J, Nissi R. Genitourinary prolapse and joint hypermobility are associated with altered type I and III collagen metabolism. Arch Gynecol Obstet. 2011 May;283(5):1081-5.
32. Zarate N, Farmer AD, Grahame R, Mohammed SD, Knowles CH, Scott SM, et al. Unexplained gastrointestinal symptoms and joint hypermobility: is connective tissue the missing link? Neurogastroenterol Motil. 2010 Mar;22(3):252-e78.
33. Gazit Y, Nahir AM, Grahame R, Jacob G. Dysautonomia in the joint hypermobility syndrome. Am J Med. 2003 Jul;115(1):33-40.
34. Hakim AJ, Grahame R. Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction? Rheumatology (Oxford). 2004 Sep;43(9):1194-5.
35. Bravo JF WC. Clinical study of Dysautonomia in 1226 patients with Joint Hypermobility Syndrome. Clin Rheumatol. 2008;14 (Suppl):S33 (Abstract).
36. Bulbena A, Gago J, Pailhez G, Sperry L, Fullana MA, Vilarroya O. Joint hypermobility syndrome is a risk factor trait for anxiety disorders: a 15-year follow-up cohort study. Gen Hosp Psychiatry. 2011 Jul-Aug;33(4):363-70.
37. Garcia-Campayo J, Asso E, Alda M. Joint hypermobility and anxiety: the state of the art. Curr Psychiatry Rep. 2011 Feb;13(1):18-25.

38. Grahame R. Pain, distress and joint hyperlaxity. Joint Bone Spine, Rev Rhum (Ed Fr). 2000;67:182-8.
39. Hall MG, Ferrell WR, Sturrock RD, Hamblen DL, Baxendale RH. The effect of the hypermobility syndrome on knee joint proprioception. Br J Rheumatol. 1995 Feb;34(2):121-5.
40. Sahin N, Baskent A, Cakmak A, Salli A, Ugurlu H, Berker E. Evaluation of knee proprioception and effects of proprioception exercise in patients with benign joint hypermobility syndrome. Rheumatol Int. 2008 Aug;28(10):995-1000.
41. Ferrell WR, Tennant N, Sturrock RD, Ashton L, Creed G, Brydson G, et al. Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. Arthritis Rheum. 2004 Oct;50(10):3323-8.
42. Grahame R. High prevalence of joint hypermobility syndrome in clinic referrals to a north London community hospital. Rheumatology (Oxford). 2004;43:suppl 2 : 91.
43. Krismer M, van Tulder M. Strategies for prevention and management of musculoskeletal conditions. Low back pain (non-specific). Best Pract Res Clin Rheumatol. 2007 Feb;21(1):77-91.
44. Larsson LG, Baum J, Mudholkar GS, Kollia GD. Benefits and disadvantages of joint hypermobility among musicians. N Engl J Med. 1993 Oct 7;329(15):1079-82.
45. Larsson LG, Mudholkar GS, Baum J, Srivastava DK. Benefits and liabilities of hypermobility in the back pain disorders of industrial workers. J Intern Med. 1995 Nov;238(5):461-7.
46. Booshanam DS, Cherian B, Joseph CP, Mathew J, Thomas R. Evaluation of posture and pain in persons with benign joint hypermobility syndrome. Rheumatol Int. 2010 May 20.
47. Clark CJ, Simmonds JV. An exploration of the prevalence of hypermobility and joint hypermobility syndrome in Omani women attending a hospital physiotherapy service. Musculoskeletal Care. 2011 Mar;9(1):1-10.
48. Howes RG, Isdale IC. The loose back: an unrecognized syndrome. Rheumatol Phys Med. 1971 May;11(2):72-7.
49. Bird HA, Eastmond CJ, Hudson A, Wright V. Is generalized joint laxity a factor in spondylolisthesis? Scand J Rheumatol. 1980;9(4):203-5.
50. Seckin U, Tur BS, Yilmaz O, Yagci I, Bodur H, Arasil T. The prevalence of joint hypermobility among high school students. Rheumatol Int. 2005 May;25(4):260-3.
51. Harreby M, Nygaard B, Jessen T, Larsen E, Storr-Paulsen A, Lindahl A, et al. Risk factors for low back pain in a cohort of 1389 Danish school children: an epidemiologic study. Eur Spine J. 1999;8(6):444-50.
52. Mikkelsson M, Salminen JJ, Kautiainen H. Joint hypermobility is not a contributing factor to musculoskeletal pain in pre-adolescents. J Rheumatol. 1996 Nov;23(11):1963-7.
53. Mikkelsson M. One year outcome of preadolescents with fibromyalgia. J Rheumatol. 1999 Mar;26(3):674-82.
54. El-Garf AK, Mahmoud GA, Mahgoub EH. Hypermobility among Egyptian children: prevalence and features. J Rheumatol. 1998 May;25(5):1003-5.
55. Guma M, Olive A, Holgado S, Casado E, Roca J, Forcada J, et al. Una estimacion de la laxitud articular en la consulta externa. Rev Esp Reumatol. 2001;28:298-300.
56. Wynne-Davies R. Familial joint laxity. Proc R Soc Med. 1971 Jun;64(6):689-90.
57. Grahame R, Bird H. British consultant rheumatologists' perceptions about the hypermobility syndrome: a national survey. Rheumatology (Oxford). 2001 May;40(5):559-62.

58. I. Knight HAB. A Patient's journey : Joint Hypermobility Syndrome. British Medical Journal. [Practice]. 2011 29 january;342:278-9.
59. Gedalia A, Press J, Klein M, Buskila D. Joint hypermobility and fibromyalgia in schoolchildren. Ann Rheum Dis. 1993 Jul;52(7):494-6.
60. Acasuso-Diaz M, Collantes-Estevez E. Joint hypermobility in patients with fibromyalgia syndrome. Arthritis Care Res. 1998 Feb;11(1):39-42.
61. Ofluoglu D, Gunduz OH, Kul-Panza E, Guven Z. Hypermobility in women with fibromyalgia syndrome. Clin Rheumatol. 2006 May;25(3):291-3.
62. Barron DF, Cohen BA, Geraghty MT, Violand R, Rowe PC. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. J Pediatr. 2002 Sep;141(3):421-5.
63. Nijs J, Aerts A, De Meirleir K. Generalized joint hypermobility is more common in chronic fatigue syndrome than in healthy control subjects. J Manipulative Physiol Ther. 2006 Jan;29(1):32-9.
64. Bravo JF. Joint hypermobility syndrome: the most frequent cause of pain in rheumatoligical practise? Interview by Zosia Chustecka. 2004.
65. Gurley-Green S. Living with the hypermobility syndrome. Rheumatology (Oxford). 2001 May;40(5):487-9.
66. Baeza-Velasco C, Gely-Nargeot MC, Bulbena Vilarrasa A, Bravo JF. Joint hypermobility syndrome: problems that require psychological intervention. Rheumatol Int. 2011 Sep;31(9):1131-6.
67. Rombaut L, Malfait F, De Paepe A, Rimbaut S, Verbruggen G, De Wandele I, et al. Impairment and impact of pain in female patients with Ehlers-Danlos syndrome: a comparative study with fibromyalgia and rheumatoid arthritis. Arthritis Rheum. 2011 Jul;63(7):1979-87.
68. Ross J, Grahame R. Joint hypermobility syndrome. BMJ. 2011;342:c7167.
69. Wieser S, Horisberger B, Schmidhauser S, Eisenring C, Brugger U, Ruckstuhl A, et al. Cost of low back pain in Switzerland in 2005. Eur J Health Econ. 2011 Oct;12(5):455-67.