

Musculoskeletal Findings and Disability in Alkaptonuria

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ABSTRACT. *Objective.* To describe the musculoskeletal (MSK) findings in patients with alkaptonuria and to show which of these factors are associated with disability in this population.

Methods. This is a prospective cross-sectional MSK assessment of subjects. Participants included 53 patients with alkaptonuria across the life span, 22 female and 31 male, mean age 43.6 years (10–80 yrs), participating in a natural history study supported by the National Human Genome Research Institute (NHGRI). Assessments included objective measures of the MSK system (range of motion, radiographic assessment of joints and spine, etc.) and questionnaires including the Human Activity Profile (HAP), Health Assessment Questionnaire (HAQ), SF-36 health survey, and the Fatigue Assessment Instrument.

Results. There were 18 patients with kyphosis, 16 with scoliosis, 16 with marked reduction in range of motion of at least one major joint, 15 with joint replacements of major joints, 11 with tendon ruptures. A positive Schober's test was highly correlated with substantial functional loss and associated with disability as measured by the HAP ($p < 0.0001$), HAQ ($p < 0.0001$), and the physical component summary ($p < 0.0001$) of the SF-36 health survey. Severity of lumbar spine involvement had the greatest correlation with disability measures ($p < 0.0001$). All objective and subjective physical measures worsened with age.

Conclusion. Disability is common and severe in patients with alkaptonuria and correlates well with physical findings. Disability does not correlate with self-reports of mental competencies. Aging with alkaptonuria is associated with progressive disability. (First Release Sept 15 2006; J Rheumatol 2006; 33:2280–5)

Key Indexing Terms:

ALKAPTONURIA

FUNCTION

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Alkaptonuria is a rare autosomal recessively inherited inborn error of metabolism with an incidence of one in 250,000–1,000,000 live births¹. The absence of the enzyme homogentisate 1,2-dioxygenase causes massive accumulation of homogentisic acid. This compound oxidizes to form a darkly pigmented polymer that binds to connective tissue and bone. The resulting damage to the tissue, which turns brown or black, is called ochronosis. Ochronotic pigment is thought to irritate and accelerate the degenerative process in cartilage of the spine and large appendicular joints^{2–4}. Subjects develop kyphosis, stiff immobile joints, contractures, tendon ruptures, kidney stones, prostate stones, and heart valve deterioration and calcifications⁵. There is no overt inflammatory process.

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The natural history of the musculoskeletal (MSK) involvement in alkaptonuria varies significantly from person to person and is influenced by many factors. Some of these factors are difficult to discern because of late diagnosis. In addition, many symptoms of alkaptonuria are disregarded as routine aches, pains, and stiffness, attributable to overuse or aging. Consequently, suspicion of a significant disability or chronic, progressive condition is not raised. Alkaptonuria can be silent for decades before it becomes symptomatic; men develop symptoms at an average age of 37 years and women at 46 years¹. Patients are initially aware of, and later are limited by, joint and back stiffness and pain, radicular symptoms, and loss of range of motion (ROM). The low back is frequently the signal anatomical site, and onset of symptoms may be temporally associated with pregnancy or work-related "strain."

As the disease progresses, there may be joint contractures, joint space loss, and changes in alignment. Kyphosis and scoliosis may appear. Soft tissue problems may accompany bony abnormalities and be associated with joint effusions and tendon ruptures. The spine is more involved than the appendicular skeleton, and the distribution of joint involvement is more proximal than distal; proximal joints are also more severely involved⁶. Hip and shoulder symptoms usually occur after the fifth decade, at which time joint replacement is frequently performed to restore function and relieve pain. Patients with alkaptonuria are frequently referred to orthopedists with the presumptive diagnosis of osteoarthritis; the discovery of signifi-

cant articular ochronosis at the time of surgery often makes the diagnosis⁷.

The natural history of disability in alkaptonuria patients has been poorly documented. Usually, patients provide information based on their recall of pain or lost function, such as recent inability to play sports or perform specific types of physical labor. As they age, patients experience greater difficulty with self-care activities, as pain, deformity, decreased endurance, and/or loss of ROM intervene. Often, it is increasingly difficult to put on socks, bend forward from the waist, or place dishes on a high shelf.

While arthroplasty has been successful in providing pain relief and improving joint range and function, medical management of alkaptonuria has been unsuccessful. No dietary or supplemental treatment has reduced symptoms or slowed the progression of joint disease. Recently, however, a treatment trial of nitisinone demonstrated early promise⁸.

The natural history study we report here was undertaken to provide a better understanding of risk factors for disability. We performed a prospective, systematic, comprehensive, cross-sectional assessment of patients with alkaptonuria across the life span. We describe the MSK aspects of the alkaptonuria phenotype, functional limitations attributable to the disease, and the possible associations between the clinical findings and the functional disabilities.

MATERIALS AND METHODS

We examined all the individuals with alkaptonuria admitted to the NIH Clinical Center between 2000 and 2002. All patients were enrolled in a protocol approved by the National Human Genome Research Institute institutional review board, and all gave written, informed consent¹. Fifty-three subjects were given an examination involving a standard history and measurements of impairments and functional limitations. These included evaluations of ROM of all major joints^{9,10}, spinal flexion by Schober's test¹¹⁻¹³, standard radiographic assessments of joint involvement¹, which were scored according to severity, and identification of the presence or absence of kyphosis and scoliosis.

Functional measures included self-reported questionnaires, i.e., the Human Activity Profile (HAP) including the Adjusted Activity Score (HAP AAS)¹⁴, the Health Assessment Questionnaire (HAQ) including the Pain (HAQP) and Fatigue (HAQF) subscales¹⁵, a general health survey (SF-36)^{16,17}, and the Fatigue Assessment Instrument (FAI)¹⁸. The HAP is a 94-question survey assessing what patients are currently doing, have done but are no longer doing, and have never done, ranging in intensity from arising from a chair to running or jogging 3 miles. Each item on the survey represents an activity that requires a known metabolic equivalent (MET). The items cover a 10 MET range. The HAQ is an assessment of activities of daily living with ratings assessing if 20 specific activities can be performed without any difficulty, with some difficulty, with much difficulty, or not at all. The questionnaire also captures the use of aids or devices and whether or not assistance from another person is required, and it employs a visual analog scale for pain and fatigue. The SF-36 is a health status survey with 36 questions comprising 8 components: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. These components are combined into 2 summary measures which are the physical component summary (PCS) and the mental component summary (MCS). The FAI is a 29-question survey assessing statements of fatigue that are rated from completely disagreeing with the statement to completely agreeing with the statement. Sample statements in the FAI are, "I feel drowsy when I am fatigued," "when I am fatigued, I have difficulty concentrating," and "I experience prolonged fatigue after I exercise."

The eligibility criterion for the study was the confirmed diagnosis of alkaptonuria by laboratory measurement of the level of urinary homogentisic acid. Exclusion criteria included inability to travel to the research facility due to a medical condition, imminent danger of death, and age of less than 2 years.

Data were analyzed by using SAS statistical software. Spearman rank order correlation¹⁹ was used to correlate scores on Schober's test with functional questionnaire scores and age. Fisher's exact test²⁰ was used for associations between swimming and kyphosis or scoliosis. The Kruskal-Wallis test²¹ was used for associations between physical characteristics and activities, and functional questionnaire scores.

RESULTS

Fifty-three patients (22 female and 31 male) with a mean age of 43.6 years (range 10–80 yrs) participated in the study. Physical findings of the group are shown in Table 1.

Table 2 shows positive correlations between physical characteristics and age. The strongest correlations occurred between age and radiographic severity score and joint replacement ($p < 0.0001$). The presence of kyphosis, scoliosis, and total joint severity score were less strongly associated ($p < 0.05$). Schober's test, a measurement of spine flexion, had one of the strongest negative correlations (Spearman rank order

Table 1. Clinical profile of 53 alkaptonuria patients.

Physical Finding	No. of Subjects with Finding
Kyphosis	18 (7 M/9 F)
Scoliosis	16 (7 M/9 F)
30–50 yrs	7 (5 M/2 F)
> 50 yrs	9 (2 M/7 F)
ROM < 30% predicted	18 (12 M/6 F)
Shoulders	8 M/4 F
Hips	6 M/5 F
Knees	2 M/0 F
Joint replacement	15 (9 M/6 F)
Hips	6 M/2 F
Knees	8 M/5 F
Shoulders	3 M/1 F
Tendon rupture	11 (9 M/2 F)
Achilles	8 M/0 F
Quad	0 M/1 F
Shoulder	1 M/0 F
Wrist	1 M/0 F
History of swimming	27 (16 M/9 F)
History of manual labor	9 (8 M/1 F)

Table 2. Correlations of physical characteristics with age.

Physical Variables	Age, p
Kyphosis*	0.0465
Scoliosis*	0.0380
Joint replacement*	< 0.0001
Total spine severity*†	< 0.0001
Cervical spine severity*†	< 0.0001
Thoracic spine severity*†	< 0.0001
Lumbar spine severity*†	< 0.0001
Total joint severity	0.0271

* Kruskal-Wallis Test. † Radiographic findings.

correlation) with age of any of the measured characteristics ($p < 0.0001$, $r = -0.659$). As age increased, spine flexion decreased.

Table 3 shows the correlations between physical impairments and functional measures. As physical impairments worsened, physical function worsened; however, as total spine severity and cervical spine severity increased the SF-36 MCS improved. The strongest positive correlation occurred between lumbar spine severity and functional problems. All the physical measurements had positive correlations with the HAQ (high HAQ scores indicate worse function). All the physical measurements had positive correlations with HAQP, except joint replacement (severe impairments correlate with high HAQP scores). The HAQF measures did not correlate well with the physical measurements, except kyphosis and thoracic spine severity, which were positive correlations. The FAI measures (high FAI scores indicate more fatigue) correlated positively with thoracic and lumbar spine severity ($p = 0.0127$ and $p = 0.0131$, respectively). All the physical impairment measures had negative correlations with HAP AAS and SF-36 PCS (low HAP AAS and SF-36 scores indicate worse function). The SF-36 MCS positively correlated with joint replacement and cervical spine severity.

Schober's test had an inverse (negative) correlation with HAQ and HAQP scores. As spinal flexion decreased, Schober's score decreased. As function decreased, HAQ scores increased. The correlations between Schober's test with HAQ and HAQP were significant ($p < 0.0001$, $r = -0.54$; $p < 0.0053$, $r = -0.39$, respectively). This demonstrated loss of function with loss of spine flexion. Schober's test had a positive correlation with HAP AAS ($p < 0.0001$, $r = 0.52$) and SF-36 PCS ($p < 0.0001$, $r = 0.52$). Spinal flexion correlated with better physical performance. As well, Schober's test had an inverse correlation with the FAI measurement scores ($p = 0.027$, $r = -0.31$). Fatigue was associated with loss of spinal flexion.

The SF36 MCS did not correlate well with the physical impairments overall; however, the MCS score did increase with joint replacement and was statistically significant ($p = 0.02007$). It also increased with increased cervical spine severity ($p = 0.0377$).

The history of regular or routine seasonal swimming was correlated with less kyphosis and scoliosis and was statistically significant by Fisher's exact test ($p = 0.0109$ and $p = 0.0079$, respectively). Subjects with a history of swimming as a regular activity had higher values for MCS, role-physical, vitality, and mental health subscores in the SF-36.

Figure 1 shows the negative correlation between Schober's test scores and age ($p \leq 0.0001$). As age increased Schober's test scores decreased at a greater rate than normal¹.

Figure 2 presents the correlation between the subscore components PCS and MCS of the SF-36 Health Survey. There was a significant inverse correlation of PCS with age ($p \leq 0.00001$). Age and MCS were not significantly correlated.

Figure 3 shows the correlation between Schober's test scores and the subscore components PCS and MCS of the SF-36 Health Survey. There was a significant correlation of Schober's test scores with the PCS ($p \leq 0.0001$). As Schober's test scores decreased, self-reported scores on the PCS decreased.

Figure 4 shows a patient who has kyphosis with knee flexion contractures.

DISCUSSION

This cross-sectional study of 53 patients with alkaptonuria was undertaken to describe the natural history of the ochronotic disease process and to elucidate its impact on function. The wide range of ages (10–80 yrs) enabled us to assess the relationship between age and disability.

Much of the MSK and rheumatologic literature asserts that patients with alkaptonuria have significant disability, not unlike that of degenerative joint disease. Few objective data have been collected to describe the nature of the disability or its frequency in this population. Further, poor function has been considered to result from structural (anatomical) abnormalities. Data concerning impairments and functional problems are frequently obtained from large data sets, often compiled from multiple clinics or surveys. We collected primary, prospective, observational data, with measurements performed by 2 trained, experienced investigators (MP, LG). The information gathered was prospective and the instruments selected for evaluation were chosen because of their applicability to a MSK population, as documented in the literature.

Table 3. Physical characteristics and their correlations with disability.

Physical Measurement	Assessment, p						
	HAQ	HAQP	HAQF	FAI	HAP AAS	SF-36 PCS	SF-36 MCS
Kyphosis*	0.002	0.0016	0.0001	NS	0.002	0.0007	NS
Joint Replacement*	0.001	NS	NS	NS	0.0008	0.0058	0.0207
Total spine severity*†	0.0061	0.006	NS	NS	0.001	0.0042	NS
Cervical spine severity*†	0.0004	0.0062	NS	NS	0.0006	0.0066	0.0377
Thoracic spine severity*†	0.001	0.0005	0.0249	0.0127	0.0001	0.0002	NS
Lumbar spine severity*†	0.0001	0.0002	NS	0.0131	< 0.0001	< 0.0003	NS

* Kruskal-Wallis Test. † Radiographic findings. HAQ: Health Assessment Questionnaire; P: pain; F: Fatigue; FAI: Fatigue Assessment Instrument; AAS: Adjusted Activity Score; SF-36 PCS: Physical Component Summary; MCS: Mental Component Summary; NS: nonsignificant.

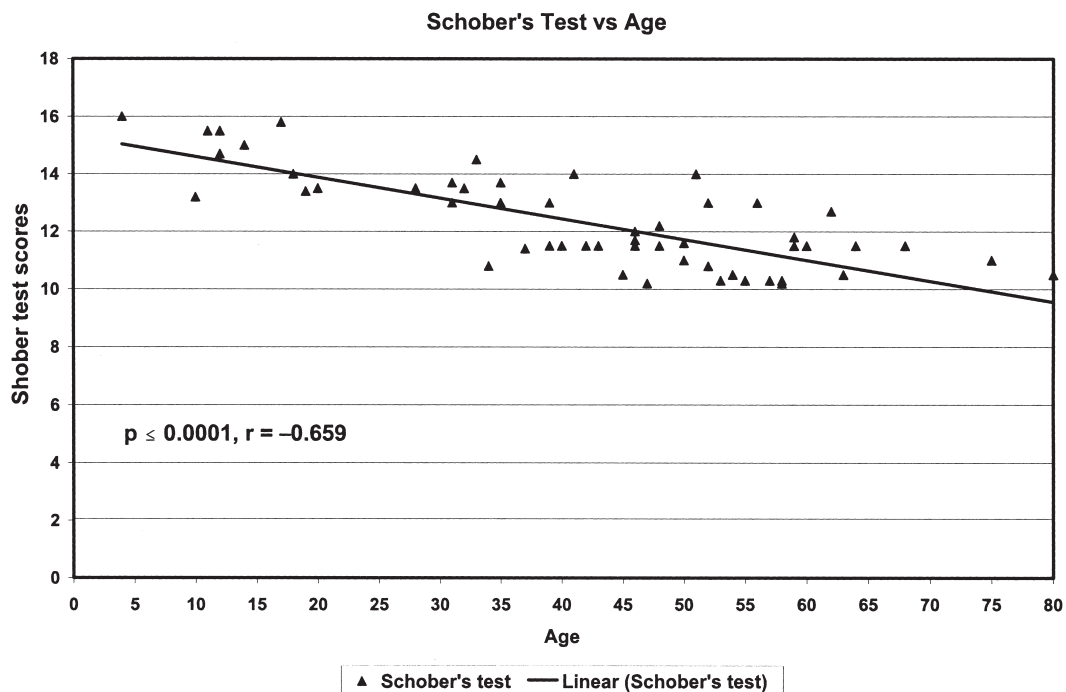


Figure 1. Correlation between Schober's test scores and age.

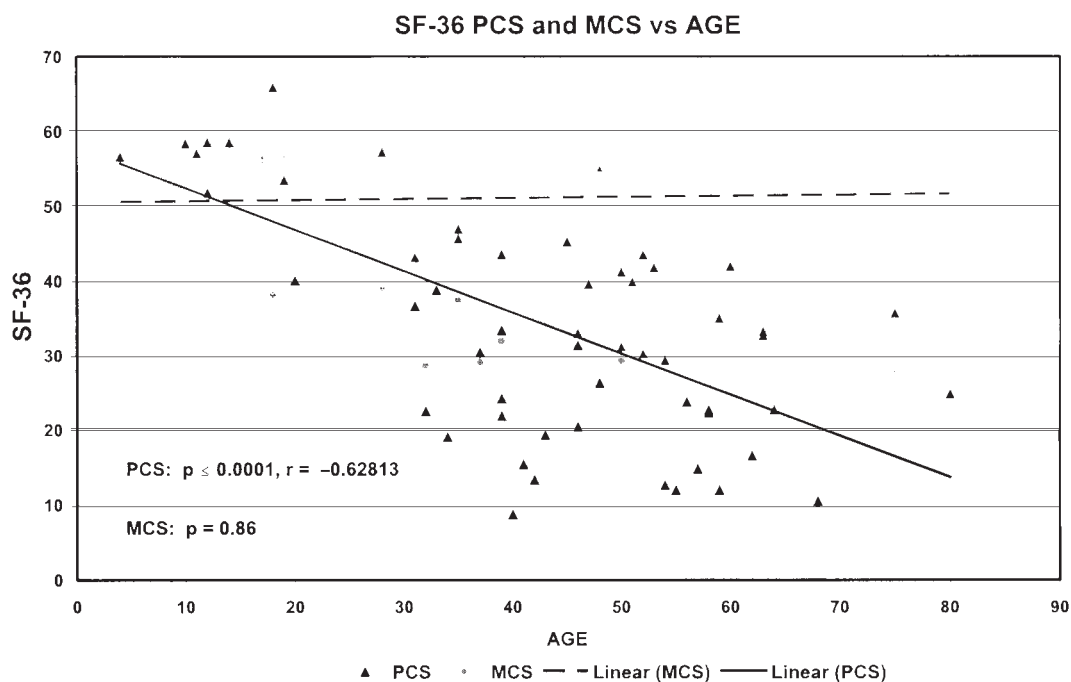


Figure 2. Correlation between age and SF36 PCS or MCS. There is a significant association of age with Physical Component Summary (PCS) but not with Mental Component Summary (MCS).

One of the highest risks for disability is age, and our study supports this observation. Our data show a strong correlation between age and most of the characteristics measured, with

one notable exception. More advanced age did not correlate with a lower mental component summary score as measured by the SF-36. The influence of aging on this cohort was main-

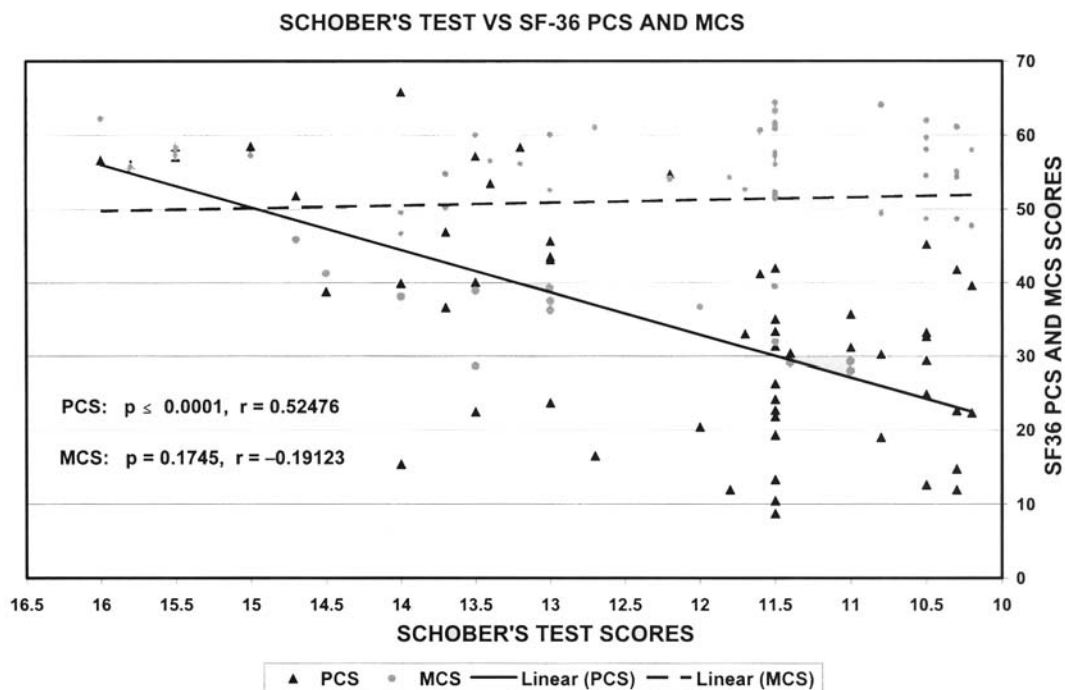


Figure 3. Correlation between Schober's test scores and SF-36 PCS and MCS. There is a significant correlation of Schober's test score and the PCS but not the MCS.



Figure 4. A 41-year old alkapttonuria patient with kyphosis and knee flexion contracture.

ly on measurements reflecting physical impairments. The patients with alkapttonuria reported here, however, were younger and more severely affected than other populations with similar impairments and disabilities. For example, 15 of our patients with alkapttonuria underwent joint replacement surgeries. Their average age, 53 years, was younger than the national mean of approximately 67 years²². Many of these

patients had played contact sports and incurred injuries typical for these activities. Such activity might have placed them at risk for future MSK problems, surgery, and tendon ruptures. Joint protection rehabilitative strategies, such as avoidance of contact sports, strength training programs, and proper coaching, or earlier surgical interventions (possibly arthroscopic), might mitigate some of the disabilities faced by this population. Future clinical trials would be needed to address these issues.

Alkaptonuria shares features with degenerative arthritis (osteoarthritis), as well as an inflammatory arthritis involving the vertebral column, ankylosing spondylitis. So it is illustrative of disabilities resulting from a chronic, progressive arthritic process. This group of patients suffers substantial limitation of spinal mobility. The severity of the spinal radiographs and the physical findings of limitation of forward flexion best correlate with measures of disability (HAQ, SF-36) and performance (HAP) in this population, suggesting that the structural problems are tightly linked to the more functional ones. That is, those persons with decreased forward flexion had poorer function, more fatigue, and lower performance levels. Only one person over 30 years of age had a PCS that was either normal or better than normal.

Interestingly, fatigue (FAI) did correlate with Schober's test and the thoracic and lumbar spine severity rating, but to a lesser degree than the other self-reported measures. It is not clear what fatigue self-reports are communicating; such reports are often poorly correlated with observed measures of performance that reflect physiological fatigue, such as VO_2 ;

correlations with self-reports of function and activity are reported to be poor^{23,24}. Nonetheless, this assessment may offer important information about patient perceptions of what they experience during daily routines, despite the poor correlation with many physical measures.

No treatment was involved in this study, but information provided by the patients did identify possible risk factors for disability or, conversely, decreased disability. For example, swimmers with alkaptonuria showed a trend toward higher vitality, physical role, and mental health scores of the SF-36, along with lower incidences of kyphosis and scoliosis. Since kyphosis and scoliosis correlated with lower performance, swimming may decrease disability. Studies designed to measure these relationships may help evaluate interventions designed to mitigate these risks.

The strongest associations identified for alkaptonuria patients were between spinal involvement and poor function. Treatment directed toward spinal mobilization and development of good truncal strength, relatively early in the course of the disease process, has the highest likelihood of improving functional outcome as an individual ages. Treatment trials would be needed to demonstrate the efficacy of such an approach.

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