American Journal of Men's Health
September-October 1–5

DOI: 10.1177/1557988320969310
journals.sagepub.com/home/jmh
SAGE

Urological Aspects in Patients with Alkaptonuria: A Case-Control Study

Mohammed Suoub[1], Mohammed Alsbou[2], and Fadi Sawaqed[1]

Abstract

This study aimed to evaluate the urinary tract for dynamic function and stones and calcifications in patients with alkaptonuria. Thirty-eight patients were prospectively divided into two groups. Study group (A) involved 17 patients; the average age was 42 years. The control group (B) involved 21 patients; the average age was 37 years. All patients from the two groups underwent uroflowmetry assessment and ultrasonography for the kidneys and urinary bladder, and prostate in two phases (full bladder and empty bladder). Group A—Bladder volume ranged between 400 and 520 cc. The peak flow rate was between 7 and 23 mL/s, with an average of 18.6 mL/s. Flow rate curves shape were acceptable to the normal bell-shape curve in 11 patients. Seven patients (41%) had prostate calcification accounting for 5%–35% of prostate size. Group B—Bladder volume ranged between 290 and 510 cc. The peak flow rate was 8–27 ml/s, with an average of 20 mL/sec. Normal bell shape voiding curves were observed in 17 patients (80%). Four patients (19%) had prostate calcification accounting for 2%–12% of prostate size. Renal measurements on ultrasonography were the same in both groups. Patients with alkaptonuria developed prostate calcification at younger age; they have a slight but not statistically significant reduced peak urinary flow rate and post void residual urine.

Keywords

Alkaptonuria, urinary tract, stones, calcifications, bladder function, uroflowmetry

Received July 19, 2020; revised September 16, 2020; accepted October 6, 2020

Background

Alkaptonuria is one of four disorders originally defined by Archibald Garrod in his *Croonian Lectures* in 1902 (Garrod, 2002) as an inborn error of metabolism. Alkaptonuria is a rare congenital disease. It is inherited in an autosomal recessive pattern (Al-Sbou & Mwafi, 2012; Al-Sbou et al., 2012), with a 25% chance of disease in babies when both parents are affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier (Al-Sbou & Mwafi, 2012). This metabolism disorder has a very low incidence (1 in 250,000), and is equally prevalent in females and males, with higher morbidity and the more significant systemic effect observed in male patients. It has an earlier onset of arthritic symptoms with a higher degree of severity in males than in females.

A deficiency in hepatic enzymes, homogentisate types 1 and 2 dioxygenases, leads to an abnormality in the metabolism pathways of two amino acids (phenylalanine and tyrosine; La Du et al., 1958). These enzymes convert homogentisic acid (HGA) to maleylacetoacetic acid. Subsequently, this deficiency will lead to the accumulation of HGA. HGA is an intermediate substance excreted through the kidney glomeruli with urine. Its effect in the urinary tract system begins in the renal glomeruli and passes through the renal collection system to both ureters—urinary bladder and urethra—through the prostate gland (prostatic urethra; Kazancioglu et al., 2004; Nickavar & Azar, 2018).

[1]Department of Special Surgery, Faculty of Medicine, Mutah University, Karak, Jordan
[2]Alkaptonuria Research Office, Faculty of Medicine, Mutah University, Karak, Jordan

Corresponding Author:
Mohammed Suoub, MD, Department of Special Surgery, Faculty of Medicine, Mutah University, Karak 61710, Jordan.
Email: dr_suoub@yahoo.com

Patients are diagnosed with alkaptonuria if they have a higher concentration of HGA in their urine that turns urine into black color, if retained for a period of time, due to its oxidization with air. Oxidization of HGA leads to the production of melanin-like polymers and inflammation of large joints and the spine, causing arthritis. A dark pigmentation (bluish to blackish) is observed in cartilage and connective tissue (ochronosis; Fisher & Davis, 2004; Keller et al., 2005). Oxidization of HGA leads to the production of melanin-like polymers and inflammation of large joints and the spine, causing arthritis (Fernandez-Canon et al., 1996).

As alkaptonuria is a genetic disorder, homogentisate enzyme deficiency is present immediately after conception. Dark-stained diapers, the only very early sign, are noticed immediately after affected babies start to pass urine. However, most clinical symptoms usually present after the third decade of life.

The diagnosis of alkaptonuria is confirmed by gas chromatography-mass spectrometry analysis after identifying a significant amount of HGA in the urine (Al-Sarayreh et al., 2014). The amount of HGA excreted per day in individuals with alkaptonuria is usually 1–8 grams.

Genetic evaluation and counseling in alkaptonuria patients can be conducted in the form of a carrier testing for at-risk relatives (Fisher & Davis, 2004; La Du et al., 1958). Prenatal diagnosis for families at increased risk is possible if both HGA deficiency pathogenic variants in the family are known (Garrod, 2002).

Methods

We accessed 23 patients from the Jordanian Alkaptonuria Society patient registry, which lists 70 patients with alkaptonuria. Patients voluntarily agreed to be enrolled in this study and visit our clinic. They were contacted via telephone and home visits.

Our inclusion criteria for the study was male adult patients known to have alkaptonuria (whether on treatment or not). Six female patients with alkaptonuria were excluded from this study.

A prospective study of 38 patients was divided into two groups. Group A (the study group) involved 17 patients of an average age of 42 years (30–63 years). Group B (the control group) comprised 21 patients of an average age of 37 years (31–62 years). The control group matched with the ages of the members of the studied group, and members were randomly selected during a clinical visit for a medical condition unrelated to prostate or bladder disease. Urine cultures were conducted for all patients 72 hr before the study to exclude urinary tract infections. No patients had symptomatic urinary tract infection, fever, or positive urine culture, and none of them were on any medication related to prostate hyperplasia or dynamic bladder function.

All patients from the two groups underwent uroflowmetry for the peak flow rate (PFR), the shape of the flow rate curve, and the amount of voided urine using a flow rate machine (Life-Tech, module 1850UT). The normal flow curve was identified as smooth, unimodal, and bell-shaped, with peak flow reached in the first 30% of trace and within 5 s (3–10 s) from the start of the flow. The normal range of male PFR is 15–25 mL/s.

Ultrasonography for all patients in the two groups was conducted to evaluate both kidneys for renal cortical thickness, renal stones, cortical calcification and hydronephrosis, urinary bladder for volume in two phases (full and empty), and prostate gland for size, calcification, and prostatic urethra stones (using an ALOKA Prosound 2, model M00490 C ultrasound machine). Our reference range of normal bladder wall thickness was less than 4 mm. Bladder residual urine after voiding is deemed normal if it is less than 20% of the pre-voided amount of urine. Prostate calcification was calculated according to the percent of calcification in relation to prostate size. First, the size of the prostate is measured; then, calcification size is measured (if there is more than one calcification site, all sites are measured separately and added together) and divided over prostate size.

All patients in the two groups were asked to drink fluid over 2 hr before the study to ensure that a fair amount of urine was inside the bladder. Patients were asked to report any strong desire for urination to perform the tests. Ultrasonography and uroflowmetry were conducted in warm, comfortable conditions with maximum privacy to obtain a convenient result.

Results

Uroflowmetry

In group A, the mean pre-voided volume was 466 mL (400–520 mL), and the mean voided volume was 426 ml (350–500 mL). PFR was 7–23 mL/s, with a mean of 18.6 mL/s, and post void residual (PVR) was 10–120 mL with a mean of 33.5 mL/s. In this group, a normal flow rate curve shape was observed in 11 patients (65%); the other six patients had prolonged and extended PFR (see Table 1). In group B, the voided volume was 290–510 mL. PFR was 8–27 mL/s, with an average of 20 mL/s. A normal flow curve was observed in 17 patients (81%; see Table 2).

Ultrasonography

In group A, normal bladder wall thickness was measured in 14 patients, while three patients (21%) had bladder wall thickening of more than 4 mm. No patient had bladder wall calcification, tumors, or bladder stones. Sixteen patients (94%) completely emptied their bladders with no

Table 1. Age With Uroflow Rate, and Bladder, Prostate Ultrasound in Studied Group A (17 Patients).

Patient #	Age (Years)	Peak Flow Rate mL/s	Curve Shape	Pre-Void Urine Volume (mL)	Residual Urine (%)	Voided Volume (mL)	Percent of Residual Urine (%)	Prostate Calcification (% to Prostate Size)
1	30	21	Bell	480	20	460	4	0
2	30	19	Bell	450	10	440	2	0
3	31	22	Bell	490	20	470	4	5%
4	32	23	Bell	400	10	390	2	5%
5	32	21	Bell	510	10	500	2	0
6	33	21	Bell	480	20	460	4	0
7	35	20	Bell	490	30	460	6	0
8	41	16	Extended	440	50	390	11	0
9	42	20	Bell	490	20	470	4	0
10	42	18	Bell	490	10	480	2	0
11	44	19	Extended	420	10	410	2	10%
12	44	18	Extended	440	50	390	11	10%
13	44	19	Bell	470	10	460	2	0
14	48	21	Bell	520	40	480	7	0
15	55	15	Extended	440	70	370	16	20%
16	60	16	Extended	430	50	380	12	20%
17	63	7	Extended	490	140	350	29	35%

Table 2. Age, Urinary Flow Rate, and Bladder, Prostate Ultrasound in Control Group B (21 Patients).

Patient #	Age (Years)	Peak Flow Rate mL/s	Curve Shape	Pre-Void Urine Volume (mL)	Residual Urine (%)	Voided Volume (mL)	Percent of Residual Urine (%)	Prostate Calcification (% to Prostate Size)
1	31	24	Bell	480	10	470	2	0
2	31	25	Bell	510	30	480	6	0
3	32	27	Bell	490	10	480	2	0
4	33	23	Bell	510	20	490	4	0
5	33	24	Bell	390	10	380	3	0
6	35	23	Bell	480	35	445	8	0
7	37	22	Bell	470	20	450	4	0
8	38	22	Bell	490	40	450	9	0
9	39	21	Bell	490	30	460	7	0
10	41	23	Bell	290	20	270	7	0
11	42	19	Bell	490	40	450	9	0
12	44	22	Bell	350	5	345	1	0
13	44	21	Bell	380	30	350	9	0
14	44	24	Bell	370	20	350	6	0
15	46	17	Extended	480	10	470	2	0
16	49	22	Bell	290	30	260	12	0
17	49	17	Bell	310	15	295	5	0
18	52	22	Bell	390	20	370	5	5%
19	55	16	Extended	310	20	240	8	2%
20	61	14	Extended	400	90	310	29	12%
21	62	8	Extended	370	70	300	23	15%

significant residual urine, while only one patient (6%) had a significant amount of urine remaining after voiding (PVR was 29% of pre-voided urine). In this particular patient, the flowmetry curve was extended, and prostate calcification was observed and measured at around 35% (see Table 1). Seven patients (41%) from group A had prostate calcification accounting for 5%–35% of prostate size, while the other 10 patients did not show any calcification in the prostate gland. Patients reported that they developed prostate calcification at an average age of 47 years (31–63 years). In group B in the full bladder phase, only two patients showed bladder wall thickening, but no masses or bladder wall calcification were observed in the control group. Only one patient had significant residual

Table 3. Independent Samples *t*-Test.

	Group	Mean	*SD*	*p* value
Peak flow rate (m/s)	A	18.588	3.709	.11
	B	20.762	4.323	
PVR (mL)	A	33.529	33.155	.487
	B	27.381	20.410	
Percent PVR to pre-void volume (%)	A	0.071	0.071	.79
	B	0.077	0.068	
Percent of prostatic calcification (%)	A	0.062	0.101	.095
	B	0.016	0.041	

PVR = post void residual.

urine after voiding. The other 20 patients completely emptied their bladders. Prostate calcification was noticed in four patients (19%)—the percentage of prostate calcification accounting for 2%–15% of prostate size. Prostate calcification was detected at an average age of 57 years (52–62 years; see Table 2).

In order to determine whether there is a statistically significant difference between the two groups, the independent samples *t*-test was used to compare between the means. It showed no statistically significant difference for the PFR and PVR, *p* values were .11 and .49, respectively, in the two groups. The percentage of prostatic calcification to the prostate size was found to be higher in group A (mean 0.10%) compared with group B (mean 0.04%), though this difference was not statistically significant, $p = .095$ (Table 3). Assessment of renal size, cortical thickness, cortico-medullary differentiation was conducted as an indicator of renal function. This study did not conduct blood tests to assess renal function for the two groups. However, measurements on ultrasound of the two kidneys did not show any significant difference between the two groups that may indicate normal renal function. In the context of apparent renal cortical calcification, bladder volume ultrasonography did not reveal any significant differences between the two groups.

Discussion

This study evaluated the dynamic function of urinary bladder and urethra, and bladder and prostatic calcification in patients with alkaptonuria. The study group was compared with an age-matched control group. All alkaptonuria patients were previously diagnosed with the disorder. Dynamic bladder and prostatic urethral functions have not been evaluated before in alkaptonuria patients.

As we know from literature reviews and the progress of the disease, patients may develop calcification in the prostate gland and sometimes in the bladder wall (Sutor et al., 1970). These calcifications may affect bladder capacity and bladder contractility (dynamic function), and this effect may be detected in urine flow. Bladder capacity was normal in all evaluated alkaptonuria patients in this study in comparison to the control group. The flow rate was slightly lower in alkaptonuria patients than in control group patients, but there was no statistically significant difference between the two groups.

This study showed that the number of patients and percent of prostate calcification were higher in alkaptonuria patients than in the control group. However, the increase in prostatic calcifications did not affect flow of urine or increased residual urine volume The literature review indicated that alkaptonuria patients have prostatic calcification, which may present as prostatic urethral stones (Sutor et al., 1970) that may lead to bladder outflow obstruction and high pressure on the urinary bladder, subsequently leading to bladder wall thickening to the point of bladder decompensation and bladder hypotonia. Further, prostatic calcification is found to be significantly negatively correlated with total International Prostate Symptom Score (IPSS), IPSS voiding, and IPSS storage, and patients with prostatic calcification also had a significantly lower rate of improved outcome (47.9%) than those who did not (71.9%; Kuei et al., 2016). In this study, patients with alkaptonuria had a higher incidence of prostatic calcifications; moreover, they developed these calcifications at an earlier age than those in the control group.

There was only one article in the extant literature on prostatic stones and prostatic calcification compositions in patients with alkaptonuria (Sutor et al., 1970). The composition of the crystalline material present in five renal calculi and pieces of prostatic calculi from patients suffering from alkaptonuria was determined by the X-ray powder method. The urinary stones contain standard calculus constituents. Some pieces of the prostatic calculi comprise substituted calcite Ca (Mg, Mn) CO, a substance not reported hitherto in a calculus. The stones, which are very dark in color, also contain a small amount of the crystalline melanin-type oxidation product of HGA, and probably a more considerable amount of the pigment in a finely divided or amorphous state. (Fernandez-Canon et al., 1996).

The general effects of alkaptonuria on the urinary tract begin in the kidneys and progress to the urethra. It may

induce calcification and renal stones throughout the urinary tract; further, precipitation of some waste products inside renal glomeruli or renal tubules may result in renal damage and irreversible effects on the kidneys.

Measurements of renal size, cortical thickness, and cortico-medullary differentiation are good indicators of a normal renal function, in addition to blood investigations like serum creatinine, blood urea, urinalysis, and microscopy. For financial reasons, we could not run those tests; this could be done in future research. However, in this study, ultrasound measurements for the two kidneys did not show any significant difference between the two groups, which may indicate normal renal function.

Limitations of this study were that some patients had been on medical treatment for alkaptonuria for 1.5 years, while others were not on any medical treatment. Our patient group was not large enough to record a significant and valuable statistical difference between the studied and control group due to the rarity of alkaptonuria . The study may be continued for a more extended period of follow-up. Further, in addition to the control group, we may divide alkaptonuria patients into two groups: treatment and no treatment.

Conclusion

Patients with alkaptonuria developed prostate calcification at younger age; they have a slight but not statistically significantly reduce peak urinary flow rate and PVR urine.

Acknowledgments

The authors are very thankful to all associated personnel in any reference that contributed to the purpose of this research.

Authors' Contributions

All authors have read and approved the manuscript. MS collected, analyzed, and interpreted patient data. MA shared the literature review and collected and interpreted patient data; FS analyzed and interpreted patient data and was a major contributor in writing the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval and consent to participate

The study was approved by the Institutional Ethical Committee at the Faculty of Medicine, Mutah University, Reference Number: 201517. Written informed consent was obtained from all participants upon their visit to the clinic.

ORCID iDs

Mohammed Suoub https://orcid.org/0000-0002-6736-0946

Fadi Sawaqed https://orcid.org/0000-0002-5743-880X

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

Al-Sarayreh, S., Tarawneh, I., Alsbou, M., Albataineh, E., Al-Shuneigat, J., & Al-saraireh, Y. (2014). Measurements of homogentisic acid levels in alkaptonuria patients using an optimized and validated gas chromatography method mass spectrometry. *Jordan Journal of Biological Sciences*, *7*. doi:10.12816/0008238.

Al-Sbou, M., & Mwafi, N. (2012). Nine cases of Alkaptonuria in one family in southern Jordan. *Rheumatology International*, *32*(3), 621–625. doi:10.1007/s00296-010-1701-1.

Al-Sbou, M., Mwafi, N., & Lubad, M. A. (2012). Identification of forty cases with alkaptonuria in one village in Jordan. *Rheumatology International*, *32*(12), 3737–3740. doi:10.1007/s00296-011-2219-x.

Fernandez-Canon, J. M., Granadino, B., Beltran-Valero de Bernabe, D., Renedo, M., Fernandez-Ruiz, E., Penalva, M. A., & Rodriguez de Cordoba, S. (1996). The molecular basis of alkaptonuria. *Nature Genetics*, *14*(1), 19–24. doi:10.1038/ng0996-19.

Fisher, A. A., & Davis, M. W. (2004). Alkaptonuric ochronosis with aortic valve and joint replacements and femoral fracture: A case report and literature review. *Clinical Medicine & Research*, *2*(4), 209–215. doi:10.3121/cmr.2.4.209.

Garrod, A. E. (2002). The incidence of Alkaptonuria: a study in chemical individuality. 1902 [classical article]. *Yale Journal of Biology and Medicine*, *75*(4), 221–231.

Kazancioglu, R., Taylan, I., Aksak, F., Durak, H., Kumbasar, B., Yenigun, M., & Sar, F. (2004). Alkaptonuria and renal failure: A case report. *Journal of Nephrology*, *17*(3), 441–445.

Keller, J. M., Macaulay, W., Nercessian, O. A., & Jaffe, I. A. (2005). New developments in ochronosis: Review of the literature. *Rheumatology International*, *25*(2), 81–85. doi:10.1007/s00296-004-0498-1.

Kuei, C.-H., Liao, C.-H., & Chiang, B.-J. (2016). Significant intravesical prostatic protrusion and prostatic calcification predict unfavorable outcomes of medical treatment for male lower urinary tract symptoms. *Urological Science*, *27*(1), 13–16. https://doi.org/10.1016/j.urols.2015.01.003.

La Du, B. N., Zannoni, V. G., Laster, L., & Seegmiller, J. E. (1958). The nature of the defect in tyrosine metabolism in alcaptonuria. *Journal of Biological Chemistry*, *230*(1), 251–260.

Nickavar, A., & Azar, M. R. (2018). Alkaptonuria, a new association of distal renal tubular acidosis. *Saudi Journal of Kidney Diseases and Transplantation*, *29*(4), 997–999. doi:10.4103/1319-2442.239645.

Sutor, D. J., Wooley, S. E., & Křížek, V. (1970). The composition of calculi from patients with alcaptonuria. *British Journal of Urology*, *42*(4), 386–388. doi:10.1111/j.1464-410X.1970.tb04470.x.