

URINARY CHOLESTEROL IN CANCER SCREENING

DIETER JÜNGST, M.D.

MARGARETE OSTERHOLZER, M.D.

ROLAND TAUBER, M.D.

HANS JOSEF KARL, M.D.

From the Departments of Medicine 2 and Urology,
Klinikum Grosshadern University of Munich, F.R. Germany

ABSTRACT — *Cholesterol determinations in morning urine samples were taken in 235 selected patients with a positive test for microscopic hematuria. Values ranged from 0.2 to 76.0 mg (median 5.5) in 23 patients with urologic malignancies and from 0.1 to 33.4 mg (median 1.1) in 38 patients with various benign diseases of the kidney or urogenital tract. In the 28 patients with urinary tract infections and 146 subjects without evidence of disorders of the kidney and the urogenital system, urinary cholesterol excretion was usually normal (0.1 to 1.9 mg; median 0.35). Using 1.0 mg urinary cholesterol per morning urine as a cutoff point, sensitivity for urologic carcinomas is about 80 per cent with a comparable high specificity of 90 per cent. Therefore, subsequent measurements of urinary cholesterol in populations with microscopic hematuria could define two groups, one with high prevalence and one with low prevalence of urologic malignancies. The less complicated colorimetric instead of gas-liquid chromatographic determination of urinary cholesterol can be recommended as a screening test for urologic carcinomas in populations with microscopic hematuria.*

Since the event of the polarizing microscope, birefringent or anisotropic crystals are well recognized components in the urinary sediment of patients with a variety of diseases, especially the nephrotic syndrome.¹⁻³ This anisotropic material is apparently composed largely of cholesterol esters with a smaller proportion of free cholesterol.⁴ However, the quantitative determination of cholesterol in urine has received comparatively little attention. Reports in the literature⁵⁻¹⁶ have indicated that patients with benign and malignant diseases of the kidney or the urogenital tract frequently have marked elevations of cholesterol in their urine. Based on these studies it was suggested that the determination of urinary cholesterol may be of possible value in the diagnosis of urogenital carcinomas, especially of the prostate, kidney, and bladder.

The objective of a recent study was to determine whether or not this method could be used as a screening test in large numbers of patients.¹⁷

A high predictive value (0.23) of a positive urinary cholesterol test result (exceeding the upper 3 SD limit) and the presence of urologic neoplasms in males was apparently due to patient selection. Therefore, because of the low prevalence of urologic carcinomas in an average population, this method has not been recommended as a primary screening test.

The present study was carried out to investigate the possibility of whether urinary cholesterol determinations could be successfully applied in preselected populations with an increased prevalence of urologic carcinomas due to a positive test result for microscopic hematuria.

Material and Methods

The study included a total of 235 patients, 119 males with an age range of fifty to eighty-two years (median 63.4) and 116 females with an age range of fifty to seventy-nine years (median 58.6). Criteria for selection were an age above

TABLE I. Urinary cholesterol in patients with urologic carcinomas and microscopic hematuria

Diagnosis	Tumor Stage/Grade	Cholesterol (Mg)/ Morning Urine
Carcinoma of bladder	T ₁ N ₀ M ₀ G ₁	13.1
	T ₂ N ₀ M ₀ G ₂	11.1
	T ₁ N ₀ M ₀ G ₁	8.6
	T ₁ N ₀ M ₀ G ₁	6.3
	T ₁ N ₀ M ₀ G ₁	6.3
	T ₂ N ₀ M ₀ G ₂₋₃	4.3
	T ₃ N ₁ M ₀ G ₂	1.4
	T ₁ N ₀ M ₀ G ₀	1.2
	T ₃ N ₁ M ₁ G ₃	12.3
	T ₃₋₄ N ₂ M _X	1.3
	T ₂ N ₁ M _X G ₂	0.7
	T ₂ N ₁ M ₁ G ₂₋₃	0.8
	T ₂₋₃ N ₀ M ₀ G ₃	0.4
Carcinoma of prostate	T ₂ N ₀ M ₀ G ₁	14.2
	T ₁ N ₀ M ₀ G ₂	76.0
	T ₂ N ₀ M ₀ G ₁	2.4
	T ₂ N ₁ M _X G ₃	0.2
	T ₃ N ₁ M _X G ₂	5.7
Carcinoma of kidney	T ₂ N ₀ M ₀ G ₁	8.8
	T ₂ N ₀ M ₀	52.3
	T ₃ N ₁ M _{1d}	2.8
	T ₁ N ₀ M ₀	0.9
	T ₂ N ₁ M _X	5.5

fifty years and a positive test result for microscopic hematuria in the urinary sediment. These data were provided by the central institute of clinical chemistry and read from computer charts. The diagnoses of the investigated patients were usually not known at the date of the urinary cholesterol analyses which were performed exclusively on morning urine samples. Patients with urethral catheters, suprapubic fistula, or macroscopic hematuria were excluded from the study.

Analysis of urinary cholesterol

Urinary cholesterol was analyzed in 2 by 1-ml aliquots of morning urine samples and expressed as mg cholesterol/sample considering the total volume. After extraction with 8 ml chloroform/methanol(3:1) and centrifugation, 5.0 ml chloroform were removed and dried under a stream of nitrogen.

The residue was hydrolyzed with 0.5 ml ethanolic 0.5 N KOH at 60° C for sixty minutes and reextracted with 6 ml n-hexane. A total of 5 ml extract was used for subsequent gas-liquid chromatography. The dried residue was dissolved in 0.1 ml of the internal standard solution (10 mg 4-androstenedione/dl iso-octane). Two to

3 µl were injected on a 1.80 m, 1%-XE-60 column, i.d. 2 mm, temp. const. 220° C, and measured by flame ionization detectors.

Quantitation was performed due to the peak height ratio, since alterations of cholesterol/4-androstenedione concentrations gave a linear response. The specificity of the method was confirmed by simultaneous mass-fragmentometric analysis in selected samples. Using this method an intra-assay variance of 5.6 per cent and an inter-assay variance of 10.4 per cent was calculated with an average recovery exceeding 90 per cent. A less complicated colorimetric determination of cholesterol in the dried hexane extracts is possible but was not used in this study.

Results

After completing the urinary cholesterol analysis, the evaluation of the clinical records revealed the presence of known urologic malignancies in 23 of 235 selected patients with a prevalence of 15.9 per cent in males and 3.4 per cent in females. Data on these patients including tumor stage and grade and the results of urinary cholesterol determinations are illustrated in Table I. In 38 patients various benign diseases of the kidney and the urogenital tract were present, and in 28 patients infections of the bladder had been diagnosed. In 146 patients with microscopic hematuria, clinical records revealed no evidence of diseases of the urogenital system. They consisted of 34 with endocrine and metabolic disorders, 43 with cardiovascular, 41

TABLE II. Urinary cholesterol in patients with benign diseases of kidney and urogenital tract or other internal disorders and microscopic hematuria

Diagnosis	n	Cholesterol (Mg)/ Morning Urine	
		Range	Median
Adenoma of kidney	1	1.8	1.8
Adenoma of prostate	3	0.2-4.4	2.3
Urolithiasis	12	0.1-9.6	1.1
Renal insufficiency (cause unknown)	5	0.2-7.2	0.9
Nephrotic syndrome	4	0.3-33.4	4.2
Renal cyst	3	0.1-10.4	0.8
Glomerular, tubular and vascular diseases of kidney	10	0.2-4.4	0.6
Infections of bladder	28	0.1-1.7	0.4
Other internal diseases	146	0.1-1.9	0.3

with gastrointestinal, 15 with respiratory, and 13 with hematopoietic diseases. The ranges and medians of the urinary cholesterol determinations in several groups of these patients are presented in Table II.

The correlation of sensitivity and specificity for urologic carcinomas at various cutoff points from 0.1 to 5.0 mg cholesterol in morning urine is given in Figure 1.

Comment

Hyperexcretion of urinary cholesterol in association with urologic malignancies has been observed in several studies and was thought to be of value in the diagnosis of these diseases.⁵⁻¹⁶ In a prior study, positive test results, using the upper 3 SD limit as cutoff point, have been obtained in 13 of 430 male patients and in 9 of 545 female patients above fifty years old.¹⁷ There was no evidence of neoplasias or diseases of the kidneys and urogenital tract at the date of the urinary cholesterol analysis.

After further investigation, 2 carcinomas of the bladder and 1 carcinoma of the kidney were diagnosed in the male group while in female patients no malignancies could be detected. In most cases, however, nonmalignant diseases of the kidney and the urogenital tract seemed to be responsible for the measured increments of urinary cholesterol. The high predictive value (0.23) of a positive urinary cholesterol test result, and the presence of urologic neoplasms in the male group, was obviously due to patient selection, since comparable results could not be expected in a normal population as well as in cancer screening.

Urinary testing for occult blood, usually by microscopic analysis, is a simple method which will result in an increased prevalence of urologic carcinomas in the average population. This method has a diagnostic sensitivity of about 45 to 70 per cent for these malignancies and increases the low prevalence from about 0.1 to 1 to 2 per cent in males and from 0.02–0.03 to 0.2–0.3 per cent in females above forty years old. The low predictive value of a positive test for occult blood (0.002–0.02) and the presence of urologic malignancies clearly diminish the value of this method as an effective screening test.

The presented results demonstrated that subsequent measurements of urinary cholesterol in populations with microscopic hematuria could be advantageous in defining high-risk and low-risk groups for urologic carcinomas. For the given problem, the most practical cutoff value for the

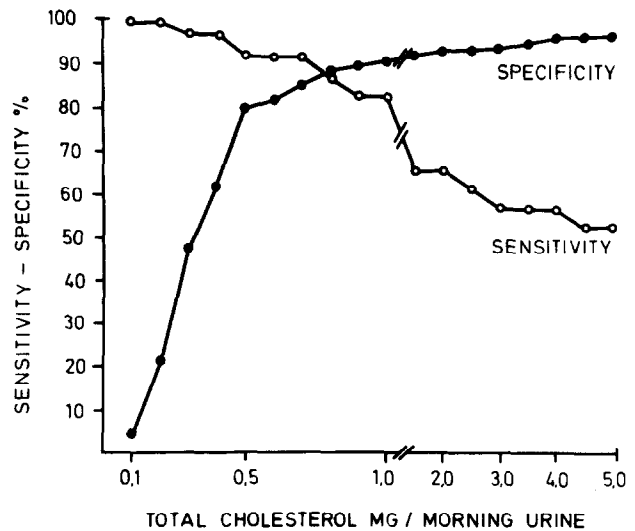


FIGURE 1. Correlation of sensitivity and specificity of cholesterol in morning urine for urologic carcinomas in population with microscopic hematuria.

urinary cholesterol method is 1.0 mg/morning urine. At this cutoff point, sensitivity for carcinomas of prostate, kidney, or bladder with associated microscopic hematuria is about 80 per cent with a comparable high specificity of 90 per cent. Therefore, subsequent measurements of urinary cholesterol in populations with microscopic hematuria, which could be revealed in cancer screening, would increase the prevalence of urologic carcinomas in positive cases (exceeding 1 mg cholesterol/morning urine sample) about eightfold.

The less expensive and complicated enzymatic assay of urinary cholesterol in the dried hexane extracts can be recommended as a secondary screening test for urologic carcinomas in selected populations with microscopic hematuria.

Marchioninstr. 15
8 München 70, F.R. Germany
(DR. JÜNGST)

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