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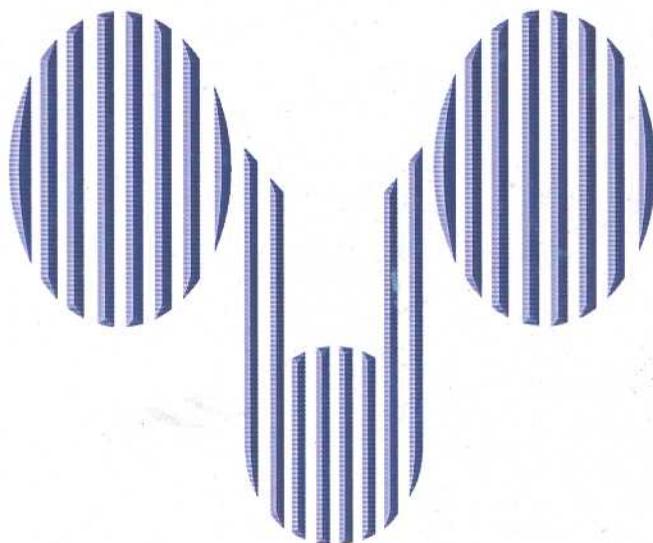
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BRAZILIAN JOURNAL OF UROLOGY

EDITOR'S COMMENT

The September - October 2000 issue of the *Brazilian Journal of Urology* presents outstanding contributions from USA, Europe, and Brazil.

Doctors Rassweiller from Heilbron and Eisenberger from Stuttgart, Germany, present on page 463 a critical analysis on management of staghorn calculi after 250 cases. A total of 197 patients were treated with the new technologies in a five-year period and compared to 83 patients who underwent open surgery for complicated nephrolithiasis prior to the introduction of ESWL and endourology. The introduction of minimally invasive techniques has completely changed the management of complex stones. However, the multimodal minimally invasive therapy of complex renal stones requires an individual treatment plan for each patient depending on stone burden and distribution, anatomy of the collecting system, and the composition of the calculus. Doctor Preminger from North Caroline, USA, one of the most recognized world experts on stone disease, provided an Editorial Comment on this article.

Doctor Tiselius from Karolinska Institute, Stockholm, Sweden, authored on page 452 a comprehensive up-to-date presentation on stone incidence and prevention. The average lifetime risk of stone formation has been reported to be in the range of 5-10% with a considerable geographical variation. In Europe it was estimated that stones form in 2,000 persons of a population of one million. Of these patients, 500 (25%) will require active stone removal. It was also showed that as many as 75% of the patients suffers the risk of repeated stone formation during a follow-up period of 20 years. The recurrent nature of stone disease makes it important not only to remove stones from the urinary tract and to assist in the spontaneous passage of stones, but also to offer these patients an appropriate metabolic care.

Doctor Lancina and co-workers from La Coruña, Spain, performed a comprehensive metabolic evaluation on 106 single calcium stone formers, and on 394 recurrent calcium stone formers (170 mild and 224 severe forms of the disease), page 479. The authors found that recurrent stone formers present more frequently hypercalciuria and alkaline urine, and also excrete in urine more calcium than first-time stone formers. Recurrent stone formers had first stone occurrence younger than single stone formers. The authors concluded that calcium stone formers with high level of calcium in urine or with alkaline urine pH are associated with a high recurrence rate and require constant clinic watchfulness with selective medical therapy for preventing new stone formation.

On page 488, Doctor Böhle from Medical University of Luebeck, Germany, one of the world leading researchers on Bacillus Calmette-Guérin (BCG) in superficial bladder carcinoma, presents the most recent knowledge on this form of immunotherapy. Although the BCG's mode of action has not been fully elucidated yet, the author provided a conclusive overview on this complex field and gave detailed information on several aspects of relevance for the understanding of the involved immune mechanisms.

EDITOR'S COMMENT - *continued*

Doctor Alvarez-Alvarez and colleagues from Vigo, Spain, reported on page 503, their experience on prostate needle biopsy specimens that contained foci of atypical small acinar proliferation (ASAP) but not diagnosed for malignancy. Among 1,345 prostate needle biopsies, 39 cases (2.89%) showed foci of ASAP. Of these, 10 (52.63%) were later found to have adenocarcinoma, with a mean Gleason score of 6.28. Forty-two percent of cases with uncertain diagnosis and 63.6% from the probably malignant group were carcinomas. The authors concluded that the recommended clinical attitude after a diagnosis of ASAP must be careful patient follow-up considering the repetition of biopsy after few months. Doctor Bostwick, from Virginia, USA, one of the world experts on prostate pathology, provided an important Editorial Comment on this article.

On page 510 Doctor Luján and co-workers from Madrid, Spain, reported the Spanish contribution to the European Randomized Study of Screening for Prostate Cancer (ERSPC). At a Spanish center, 2,416 men were included in the screening arm, and 264 biopsies were performed. The authors performed biopsies when PSA ≥ 3.0 ng/ml (rectal examination is not considered to indicate biopsies in these cases). Fifty-four prostate cancers were detected (47 localized, 5 locally advanced, and 2 metastatic); overall, detection rate was 2.24%. The authors suggested that screening detects more cancers at an early stage. Nevertheless, it is necessary to wait at least for 10 years of follow up to verify if a significant benefit, with regard to prostate cancer mortality reduction, is achieved.

Doctor Martins and colleagues, from Ribeirão Preto, Brazil, studied on page 516 the incidence of carcinoma of the prostate in 1,079 volunteers from a community population. Two hundred and thirty-five volunteers with PSA greater than 4.0 ng/ml, positive digital examination or both were referred to prostate biopsy. Of the 136 (57.6%) men who agreed with the biopsy, 27 (2.5%) had tumor and 10 (0.9%) had isolated prostatic intraepithelial neoplasia (PIN). Thirteen of the cancer patients were submitted to radical prostatectomy, which revealed that 61.5% of them had tumor stage lower than pT3.

On page 535 Doctor Telöken and co-workers from Porto Alegre, Brazil, demonstrated that a period of 10 weeks of hypercholesterolemic diet induced increase in the thickness of rabbit penile tunica albuginea and an increase in the blood levels of cholesterol and testosterona.

Dr. Francisco J.B. Sampaio

Editor-in-Chief

STONE INCIDENCE AND PREVENTION

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ABSTRACT

The recurrent nature of stone disease makes it important not only to remove stones from the urinary tract and to assist in the spontaneous passage of stones, but also to offer these patients an appropriate metabolic care.

The average lifetime risk of stone formation has been reported to be in the range of 5-10% with a considerable geographical variation. The annual incidence varies between 0.1 and 0.4% and it is roughly estimated that in Europe stones form in 2000 persons of a population of one million. Of these patients 500 (25%) will require active stone removal. It has been shown in some series that as many as 75% of the patients suffers the risk of repeated stone formation during a follow-up period of 20 years.

In almost all reports on stone composition there is a striking predominance of calcium oxalate stones with or without calcium phosphate (70-80%). The remaining 20-30% of the stones are composed of magnesium ammonium phosphate (struvite), carbonate apatite, uric acid, ammonium urate and cystine. Stones composed of struvite and carbonate apatite are usually referred to as infection stones and also ammonium urate stones are in most cases associated with urinary tract infection. Cystine stones are found in 1-2% of the patients, whereas uric acid stones are subject to the most pronounced geographical variation. Recurrent stone formation is a common problem with all these types of stones and recurrence prevention thus is an important part of the medical care of patients with stone disease.

The intention of this paper is to discuss some metabolic risk factors and preventive treatment of stone disease and also to describe a few simple principles that can be followed in the clinical routine.

Key words: kidney, calculi, metabolic disease, factors, risk, incidence
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INTRODUCTION

Formation of concrements in the urinary tract is a pathologic condition that afflicts people in most parts of the world with a high prevalence. Urolithiasis thus causes a pronounced strain to the health care system. The recurrent nature of the disease makes it important not only to remove stones from the urinary tract and to assist in the spontaneous passage of stones, but also to offer these patients an appropriate metabolic care.

EPIDEMIOLOGICAL CONSIDERATIONS

The average lifetime risk of stone formation has been reported to be in the range of 5-10% with a

considerable geographical variation (1,2). The annual incidence varies between 0.1 and 0.4% (3,4) and it is roughly estimated that in Europe stones form in 2000 persons of a population of one million (5). Of these patients 500 (25%) will require active stone removal. There are various figures in the literature on the risk of recurrent stone formation and it has been shown in some series that as many as 75% of the patients suffers the risk of repeated stone formation during a follow-up period of 20 years. Based on epidemiological studies in Swedish stone patients there was an expected recurrence rate of 70% after 10 years when those patients were considered who had formed at least 2 stones before the follow-up period (6). After 5 years, about 50% had formed new stones. In contrast

only less than 30% of the first time stone formers presented with recurrent stones during the following 10 years (7,8).

There is obviously a pronounced variation in the severity of the disease and in a recent review Strohmaier pointed out that the fraction of patients who formed more than 3 stones was only 11-14% (9). For interpretation of therapeutic results it is of importance to realize that the average individual annual rate of stone formation is in the range of 0.15 to 0.20 (9,10).

In almost all reports on stone composition there is a striking predominance of calcium oxalate stones with or without calcium phosphate (11). Approximately 70-80% of the stones has this composition. The remaining 20-30% of the stones are composed of magnesium ammonium phosphate (struvite), carbonate apatite, uric acid, ammonium urate and cystine. Stones composed of struvite and carbonate apatite are usually referred to as infection stones and also ammonium urate stones are in most cases associated with urinary tract infection. Cystine stones are found in 1-2% of the patients, whereas uric acid stones are subject to the most pronounced geographical variation. In Scandinavian countries uric acid stones occur with a frequency of not more than 4-5%, while the frequency might be as high as 30-40% in the Mediterranean and Arabic countries. Recurrent stone formation is a common problem with all these types of stones and recurrence prevention thus is an important part of the medical care of patients with stone disease.

For the preventive treatment of patients with stone disease it is fundamental to be as selective as possible. Thereby it is necessary to take into consideration the stone composition, the expected risk of recurrent stone formation for the individual patient and the abnormalities that are responsible for or might have contributed to the stone formation. In order to be successful in this regard it is important to take a careful medical history in order to identify those patients for further evaluation that are most likely to benefit from preventive measures. The intention of this paper is not to give a complete review of the world literature of metabolic risk factors and preventive treatment but rather to describe a few simple principles that can be followed in the clinical routine.

CATEGORIES OF STONE FORMERS

It is important that a program for evaluation and treatment of stone patients take the various aspects mentioned above into consideration. The factors responsible for formation of non-calcium stones are well identified and so are the therapeutic principles. The formation of calcium stones is unfortunately less well understood and this fact is of obvious concern because in most populations calcium stones constitute more than 70-80% of all stones.

For the therapeutic efforts, attention has to be paid to the variable course of the disease. It is thus necessary to adapt the evaluation and treatment to the presentation of the disease in the individual patient. In this regard, it is very helpful to subgroup the stone-formers in the categories depicted in Table-1 (12-14).

Table 1 - Definitions of different categories of stone formers.

Non Calcium Stones	
INF	Infection stone disease
UR	Uric acid or ammonium urate stone disease
CY	Cystine stone disease
Calcium Stones	
S ₀	First time stone former without residual stone or fragments
S _{res}	First time stone former with residual stone or fragments
Rm ₀	Recurrent stone formers with a mild disease (long intervals between episodes of stone formation). No residual stones or fragments
Rm _{res}	Recurrent stone formers with a mild disease with residual stones or fragments
Rs	Severe disease. Frequent stone formation. Specific risk factors.

The number of patients in each category certainly is subject to a considerable variation from one geographical area to another, not only because of differences in stone incidence but also because of differences in principles for stone removal (2).

If the reasons for stone formation have not been eliminated, the rate of recurrent stone formation that occurs in patients with non-calcium stones, that is cystine, uric acid and infection stones, is so high that stone preventive treatment always should be considered. Treatment of these patients in most cases can be started following only a few specific analyses. For calcium stone patients who form stones of pure calcium oxalate, mixtures of calcium oxalate and calcium phosphate, or pure calcium phosphate, the situation is different inasmuch as in average only 25-30% of the patients can be expected to form another stone within a 10-year period (6,8).

For Swedish stone formers, and with generous application of shock wave lithotripsy for stone removal, it was noted that of patients presenting with a stone problem 55% were first time stone formers (S) and 45% recurrent stone formers (R). Although 8-10% of the first time stone formers will form new stones during the coming 5 years and 25-30% during 10 years, it is usually not possible at this stage to predict who will become a recurrent stone former and who will not (5).

It is difficult to derive exact figures for the fraction of patients belonging to each category but the figures in Table-2 might serve as a rough guide. For these data, the author have referred to category Rs those patients who had formed at least 4 stones or had an annual frequency of stone formation of at least 0.3. The definition of category Rs can otherwise be left to the discretion of the reader. In this respect, it is important to also include the patient's attitude. If the patient is not interested in preventive measures there is of course no meaning to proceed with an extensive metabolic evaluation.

The reason for making a distinction between S and Rm patients with (res) and without (o) residual stone material is that the latter group theoretically is at greater risk of new stone formation (see Table-1, for classification).

Irrespective of their previous history of stone formation, patients with specific risk factors are re-

ferred to category Rs and treated accordingly. The following risk factors should be noticed in this regard: 1)- Start of stone disease before the age of 25; 2)- Pronounced family history of stone formation; 3)- Single kidney; 4)- Presence of brushite (calcium hydrogen phosphate) in the stone; 5)- Disease or medication known to be associated with stone formation; 6)- Anatomical abnormalities that have not been surgically corrected.

Despite our incomplete understanding of the exact mechanisms of calcium stone formation, a number of risk factors and abnormalities have been identified in stone formers. It is important to utilize this knowledge and the available tools in order to counteract new stone formation in those patients who are likely to benefit from such a treatment. For this purpose we need a program for identification of risk factors of stone formation in the individual patient, a program that take into account not only the mechanisms of stone formation but also the variability by means of which the disease presents (15-18).

According to the data in Table-2 approximately 20% of the calcium stone patients ($Rs + Rm_{res} + S_{res}$) should be offered a biochemical risk evaluation. It can be assumed that about half of these patients (10%), will be considered for pharmacological stone prevention (5,9).

Table 2 - Approximate fractions of calcium stone formers in each category.

Category	Percent
S_0	51
S_{res}	4
Rm_0	29
Rm_{res}	2
Rs	14

EVALUATION OF RISK FACTORS

Stone Analysis

Knowledge of which salts that build up the stone is of fundamental importance for correct decisions regarding the preventive treatment. In every patient steps should be taken so that at least one stone

can be analyzed for its composition. The recommended methods for stone analysis are x-ray diffraction or infrared spectroscopy.

Unfortunately a stone is not retrieved from every patient and conclusions have to be made from indirect evidence. A positive urine culture and a high pH might reflect a condition typical for formation of an infection stone. A positive cystine test (Brand's test; sodium nitroprusside reaction) is diagnostic for cystinuria. Uric acid stones develop in acid urine and although this process can occur at a completely normal metabolism of urate, a high blood level of urate supports the diagnosis.

Medical History

Information on the previous medical history is of great help in the further work-up procedure. It is necessary to know if the current stone is the only one that the patient has formed and if not, how many stones there have been. The age at which the initial stone was diagnosed might give a clue to the severity of the disease and it also gives a possibility to calculate the frequency of stone formation. The latter estimate is not always easy to derive and the stone age index (SAI) might serve the same purpose. SAI is calculated as follows: $100 \times [\text{total number of stones formed} / \text{age of the patient}]$ (7). A high SAI is associated with a higher prospective recurrence risk than a low index. This is in accordance with the observations that patients with a history of more than one stone have a higher future recurrence risk than those who have formed only one stone (19).

Information on previous surgical procedures for stone removal as well as on any other disease the patient might suffer from is important. We know that abnormalities in intestinal function associated by malabsorption give a high risk of stone formation. Other causes of stone disease are hyperparathyroidism, hyperthyroidism, Cushing's disease, hyperuricosuria due to chemotherapy of malignant diseases, renal tubular acidosis and immobilization.

Some forms of medication can contribute to stone formation for example: acetazolamide, calcium supplements taken between meals, vitamin D, indinavir (resulting in indinavir precipitation) and possibly very large ($> 4\text{g}$) doses of ascorbic acid.

Radiographic Examination

A plain x-ray film together with a pyelography usually is the standard procedure for description of the current stone situation in terms of size and number of concrements. The plain film of kidney, ureter and bladder (KUB) gives the necessary information on whether the kidney is stone free or has residual stones or fragments after treatment or after an acute stone episode. This step in the work-up of the stone forming patient also discloses any contributing anatomical abnormalities. Moreover, the radiographic image of the stone can be used for conclusions on the stone composition.

BIOCHEMICAL ANALYSES

Blood Analyses

A limited set of samples should be part of the early examination of all patients with stone disease. It thereby is recommended to measure the plasma concentrations of either calcium and albumin or ionized calcium. This analytical step makes it possible to diagnose or rule out hyperparathyroidism as a cause of stone formation. It is the author's routine to measure the parathyroid hormone level only in those patients who have an albumin-corrected calcium level of 2.6 mmol/litre or higher. Furthermore, creatinine should be measured as a rough estimate of kidney function. Plasma urate also should be included in the analysis. It is of note, however, that an increased creatinine occurs together with a high urate. Analysis of potassium also might be motivated particularly for patients treated with diuretics, because hypokalemia is one cause of hypocitraturia.

Spot Urine Analysis

A spot urine sample is useful for the diagnosis of bacteriuria and cystinuria. In cases of unknown stone composition, microscopic examination of the urinary sediment can give valuable clues. Although information of the pH level is of great importance, random spot urine is of doubtful value in this respect. To tell anything about the acidification of urine the measurement has to be made in a fasting morning sample. The 8-hour night urine collection is another way to get a standardized estimate of the pH level (see below).

A spot urine sample should be analyzed in all patients, but when the stone composition is known its major purpose is to demonstrate the presence or absence of bacteria.

Analysis of Urine Collections

The major risk factors for calcium stone formation are supersaturation with calcium oxalate, calcium phosphate or both salts. Moreover it has been demonstrated that stone-forming urine very often is deficient in its inhibiting power with regard to crystal growth and crystal aggregation. Although promotion of nucleation and crystal-cell interaction probably also are of importance, there are no methods by means of which these variables easily can be assessed.

Urine analysis for demonstration of risk factors of calcium stone-formation is only indicated for patients belonging to categories R_s , $R_{m_{res}}$ and S_{res} (see Table-1). The rational for including the latter 2 categories is that the combined presence of residual fragments or stones and a high supersaturation occasionally might call for preventive measures irrespective of the previous stone history.

Analysis of urine composition can be carried out in 24-hour urine samples as well as in samples collected during shorter periods of the day. It is the author's preference to split the 24-hour collection in one 16-hour daytime sample and one 8-hour night sample. Repeated sampling in at least two collections is recommended (12, 20).

16-hour Urine

The 16-hour urine produced between 6:00h and 22:00h should be collected in a bottle containing 20-30 ml of 6 mol/l of hydrochloric acid. This acidification is necessary to maintain the calcium salts in solution and to prevent ascorbic acid from being oxidized to oxalate. The 16-hour urine sample should be analyzed for its content of calcium, oxalate, citrate and creatinine. The additional analysis of magnesium and phosphate makes it possible to get approximate estimates of the ion-activity products of calcium oxalate and calcium phosphate (11,21-25). Although the individual urine variables are useful for selecting the appropriate form of treatment, it is the combined effect in terms of super-

saturation (ion-activity product) that gives us an idea of the risk of crystallization.

The following formulas can be used to derive approximate estimates of the ion-activity products by inserting the recorded urine volumes, and there is no doubt that the urine volume is of fundamental importance for the supersaturation with both calcium oxalate and calcium phosphate. The volumes recorded in the urine samples, however, do not necessarily reflect the normal situation. Estimates of the ion-activity product of calcium oxalate therefore have been standardized to a 24-hour urine volume of 1.5 litres (16-hour volume = 1 litre):

$$\text{AP(CaOx)-index}_s = \frac{A \cdot \text{Calcium}^{0.84} \cdot \text{Oxalate}}{\text{Citrate}^{0.22} \cdot \text{Magnesium}^{0.12} \cdot \text{Volume}^{1.03}}$$

For the 24-hour period $A = 1.9$ and $V = 1.5$ litres and for the 16-hour period $A = 2.3$ and $V = 1.0$ litre (11).

The index thus obtained corresponds numerically to $10^8 \cdot \text{AP}_{\text{CaOx}}$ (where AP_{CaOx} is the ion-activity product of calcium oxalate).

In a similar way is it possible to derive an estimate of the ion-activity product of calcium phosphate (AP_{CaP}). In addition to standardized volumes of 1.5 and 1.0 litres for the 24-hour and 16-hour periods, respectively, the pH is set to 7.0:

$$\text{AP(CaP)-index}_s = \frac{B \cdot \text{Calcium}^{1.07} \cdot \text{Phosphate}^{0.70} \cdot (\text{pH } 7 - 4.5)^{6.8}}{\text{Citrate}^{0.20} \cdot \text{Volume}^{1.31}}$$

In this formula, B should be set to 0.003 for a 16-hour sample and to 0.0027 for a 24-hour sample. The AP(CaP)-index_s approximately corresponds to $10^{15} \cdot \text{AP}_{\text{CaP}}$ (where AP_{CaP} is the ion-activity product of calcium phosphate) (11).

It is of note that there is a relationship between AP(CaP)-index_s derived from analysis of voided urine and AP_{CaP} in the distal part of the distal tubule, where the initial nucleation of CaP might take place (26).

It has been shown that patients with a high AP (CaOx) index_s have a higher recurrence rate than those with a low index (7). A higher rate of recurrent stone formation in patients with more advanced biochemical abnormalities was recorded also in other studies (16).

8-hour Urine

The urine produced between 22:00h and 6:00h is collected in a bottle containing 10 ml of 0.3 mol/l sodium azide as a preservative to avoid bacterial growth. Provided this sample is delivered to the laboratory within the first few hours after completion, it gives a good opportunity to measure pH in a standardized way. Moreover, the sample gives an idea of the night urine volume. The 8-hour urine sample also with advantaged can be used for urate analysis.

Because the 8-hour urine sample does not contain any destructive preservative, it opens the possibility to measure inhibitory properties as well as the risk of crystallization (27-30). Such procedures are, however, not commonly used in most laboratories and these analyses will not be further considered in this paper.

RECURRANCE PREVENTIVE TREATMENT

Calcium Stones

The recurrence prevention can be carried out at 3 different levels: 1)- General advice regarding fluid intake and diet; 2)- Specific advice regarding fluid intake and diet; and 3)- Pharmacological treatment.

General Advice

Without sufficiently supersaturated urine there will be no risk of crystallization and without crystals, no stones will develop. The easiest way to reduce urine supersaturation is to keep the fluid intake at a level so that the 24-hour urine flow is at least 2000 ml (31-34). The patient should be advised to refrain from excessive intake of animal protein that is to avoid eating meat products every day (33). There should be no restriction in calcium intake unless this is at a very high level (12), and the minimal daily requirement of 800-1000 mg (20-25 mmol) should

be fulfilled. There is usually no need to restrict oxalate intake, but if dark chocolate and nuts are commonly ingested snacks, such a habit should be stopped. General advice is given to patients in categories S₀ and Rm₀.

Specific Advice

This type of advice has the purpose of correcting one or several abnormalities recorded in urine. The analytical findings provide the basis for this regimen.

The drinking habits should be adapted to a urine volume required for an AP (CaOx) index of 1.5 or less. The 24-hour volume necessary for this can be calculated from the AP (CaOx)-index_s. For example with an AP(CaOx)-index_s of 2.65 obtained from analysis of the 16-hour urine sample, a 24-hour urine volume of about 2.6 litres would be necessary to get an AP(CaOx)-index of 1.5.

The limit of 1.5 has been chosen because experiments have shown that an AP_{CaOx} of 1.5-1.7 was enough for calcium oxalate crystallization, induced by calcium phosphate (35). There are no experimental data available to select a corresponding limit for AP(CaP)-index_s, but a value of 50 had at least some discriminating power when stone-formers and normal subjects were compared (7). Both AP(CaOx) index_s and AP(CaP) index_s are useful parameters in the follow-up. They are excellent tools for recording the therapeutic effects on the risk of forming urine critically supersaturated with these salts.

It is highly important to teach the patients that the fluid intake should be evenly ingested during the day and that an abnormal loss of water needs to be replaced by an extra load of fluid.

Animal protein increases urinary calcium, oxalate and urate and decreases pH and citrate. It is therefore obvious that in the presence of such findings a careful dietary history should be taken and the necessary corrections made. In patients with a urinary pattern reflecting an excessive intake of animal protein, meat and sausage should be avoided 2-3 days a week.

Restrictions in oxalate intake is usually without meaning in patients with a normal urinary

oxalate, but intake of oxalate-rich food stuff should be restricted if the oxalate excretion is above normal, as for instance in patients with enteric hyperoxaluria. The latter group of patients might benefit from calcium supplements which, however, always should be taken together with meals.

Details regarding the dietary influence on urine composition and the effects of dietary manipulations is extensively summarized elsewhere (33).

Pharmacological Treatment

Extensive reviews of the literature have shown that thiazides, alkaline citrate and allopurinol are the only useful pharmacological agents for calcium-stone prevention (12,36). Although there is no definitive proof that a selective treatment is superior to a non-selective treatment, there is no proof for the opposite view either (5). When the literature was scrutinized, patients treated in a selective manner had a lower recurrence rate than those who were treated non-selectively (5,37). According to these observations, it is recommended that pharmacological treatment should be instituted selectively according to the principles outlined in Table-3 (12).

During the last years, treatment with citrate has become very popular. The reasons for this is that hypocitraturia is a common abnormality in calcium stone formers and, moreover, the fact that citrate influences a number of important steps in the crystallization process (38-41). Recent results have shown that a single evening dose of sodium potassium citrate is not sufficient to effectively prevent recurrent stone formation (42). Potassium citrate should be chosen instead of sodium potassium citrate in order to avoid the hypercalciuric effect of sodium.

For patients who need a calcium reducing treatment and do not tolerate thiazides, orthophosphate might be an alternative. The problem with phosphate treatment is, however, that the side effects are bothersome and that this drug has to be administered at least three times daily.

Potassium-magnesium citrate represents a new and promising alternative form of treatment but this preparation is not yet universally available (43), and it remains to be shown that this form of treatment is superior to treatment with potassium citrate.

It is usually wise to start a recurrence preventive regimen with conservative measures and to

Table 3 - Principles for recommended pharmacological treatment of patients with calcium stone disease.

Biochemical Abnormality	Recommended Treatment
High calcium excretion	Thiazide + potassium or Thiazide + potassium + magnesium (Orthophosphate in case of thiazide intolerance)
High oxalate excretion (moderately increased)	Oxalate restriction
Enteric hyperoxaluria	Oxalate restriction + calcium supplements (together with meals) + alkaline citrate Reduced intake of fat might be useful.
Primary hyperoxaluria	Pyridoxine can be tried. These patients should be treated by a specialist on primary hyperoxaluria
Low citrate excretion	Alkaline citrate (potassium citrate)
Low pH	Alkaline citrate
High urate excretion	Allopurinol
High phosphate excretion	Restricted intake of animal protein
Low magnesium excretion	Magnesium oxide or magnesium hydroxide supplements
No abnormality	Alkaline citrate

institute pharmacological therapy only when the conservative approach for some reason fails. The compliance to the long-term treatment regimens necessary for these patients is low.

In order to maintain compliance at a reasonable level it is necessary to see these patients regularly and to check the therapeutic effect by repeated follow-up examination of urine composition and stone formation.

In the literature there are very few controlled studies of sufficient duration to provide a solid basis for conclusions on the real efficacy of the various forms of preventive treatment. In Table-4 the data from recurrent stone formers treated in a selective way have been used to derive an approximate average estimate of the stone free rate after 3 years (5). The stone free rates obtained from patients treated selectively, which varied between 77 and 86%, were obviously better than those 49 to 73% recorded in patients treated in a non-selective way. The expected stone free rate in an untreated group of recurrent stone formers is about 65% (7).

Table 4 - Approximate average stone free rate after 3 years for patients treated selectively and non-selectively. The figures were obtained by recalculation of literature data (ref. 5).

Form of Treatment	Percent of Stone Free Patients Treated Selectively	Percent of Stone Free Patients Treated Non-selectively
Thiazides	86	73
Alkaline citrate	78	72
Allopurinol	85	68
Dietary advice	77	49

Uric Acid

The determinants for precipitation of uric acid are a low pH, a small urine volume, a high urinary urate or any combination of these variables. The risk of uric acid crystallization can be reduced by an increased pH. This is accomplished with alkaline citrate. Both sodium potassium citrate (5g twice or three times daily) and potassium citrate (6.5 mmol twice or three times daily) are acceptable alternatives. The 24-hour urine volume should be at least 2000 ml. In case of hyperuricosuria, allopurinol should be part of the therapeutic regimen.

Uric acid stones can be dissolved with a similar treatment. In these cases allopurinol (300 mg once daily) should always be given. Sodium potassium citrate and potassium citrate should be given in doses higher than those used for prevention (7.5g 3 times daily and 10 mmol 3 times daily, respectively). The duration of this treatment depends on the stone volume but at least 2-3 months are usually required.

Cystine

The genetic defect in cystine stone formers causes an abnormal excretion of the aminoacids cystine, lysine, ornithine and arginine. The solubility of cystine increases with increasing pH and with dilution of the urine. The basic therapeutic steps are generous fluid intake giving a urine volume of at least 3000 ml per 24-hour and an alkalinization of urine to pH 7.5 if possible.

The cystine concentration should be lower than 300 mg or 1.25 mmol per litre and the currently most used compound to achieve this goal is α -

mercaptopropionyl-glycine (Thiola®), the administration of which ideally should be determined by the diurnal excretion pattern of cystine.

Treatment of cystine stone formers is a difficult and delicate task that with advantage should be managed by someone who has particular experience and expertise in this field.

Infection Stone

Radical clearance of stone material is a mainstay for treatment of these patients. Long-term (3-6 months) of low-dose antibiotics helps to eradicate the infection after stone removal. Prevention

of struvite and carbonate apatite precipitation can be accomplished by acidification of urine either with ammonium chloride or with methionine. The author has successfully used intermittent acidification with 1g of ammonium chloride 3 times one day each week.

CONCLUDING COMMENTS

Risk evaluation and preventive treatment of patients with stone disease have been a neglected area during recent years. One reason for this is the opinion by many urologists that stones better were removed with the new convenient methods than treated medically. There are, however, several problems with this attitude. The new methods, which are neither completely without risk nor without cost, have not reduced the recurrence risk. On the contrary, about 25-30% of patients treated with shock wave lithotripsy is left with residual fragments in their kidneys and these patients are thus potential candidates for new stone problems. Of all stone-formers 70-75% pass their stones during an acute stone episode, where methods for active stone removal usually have no place. Finally, the risk of being afflicted by an unannounced stone colic means a real threat to these patients.

It thus makes sense that steps should be taken to offer patients with urolithiasis an individualized preventive care in proportion to the severity of their disease. Undoubtedly there are serious shortcomings both in terms of our knowledge of the mechanisms of stone formation and the preventive possibilities. There are, however, some obvious risk factors that can and should be corrected in patients with a severe disease. It is important to detect these abnormalities with a rational system for biochemical evaluation and to make attempts to overcome the problem of a low compliance. One prerequisite for being successful in this respect is to give these demanding activities an appropriate place within the frame of everyday urologic practice.

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MANAGEMENT OF STAGHORN CALCULI: CRITICAL ANALYSIS AFTER 250 CASES

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ABSTRACT

Objectives: Based on long-term experience with over 250 patients and the review of the literature we want to focus on the state of the art management of complicated nephrolithiasis. This includes the application of extracorporeal shock wave lithotripsy (ESWL) and endourology as well as the remaining indications for open surgery.

Material and Methods: A total of 197 patients were treated with the new technologies in a five year period and compared to 83 patients who underwent open surgery for complicated nephrolithiasis prior to the introduction of ESWL and endourology. Two-hundred and forty-seven patients (186 respectively 61) could be followed over a period of up to 42 months to analyze the pattern of stone-clearance by passage of fragments, recurrent stone formation and urinary tract infection.

Results: Stone distribution (borderline vs. staghorn stones) was similar in both groups with a higher percentage of complete staghorn stones in the open surgery-group. Blood transfusion rate (37% vs. 10%) was significantly higher after open surgery, whereas the rate of minor side effects did not differ in both groups. Also major complications were observed at a similar rate (7 vs. 8%) as well as hospital stay (17.2 vs. 15.4 days). Stone-free rate at discharge after open surgery is significantly higher than after ESWL and endourology (80 vs. 31%). In contrast to this, the stone-free rate after 42 respectively 36 months does not differ significantly (72 vs. 60%). The majority of the remnants after the modern techniques were asymptomatic (CIRF), whereas the recurrence rate after surgery is significantly higher (20% vs. 7%). Additionally, the reduction of urinary tract infection (UTI) rate is better after the modern approach (0.51 vs. 0.32 = UTI after/UTI before).

Conclusions: The introduction of minimally invasive techniques has completely changed the management of complex stones. Open surgery is only preferable in case of giant staghorns requiring numerous percutaneous procedures along with ESWL, after failure of the modern techniques or in cases necessitating additional surgical reconstruction. However, the multimodal minimally invasive therapy of complex renal stones requires an individual treatment plan for each patient depending on stone burden and distribution, anatomy of the collecting system, and the composition of the calculus.

Key words: kidney, kidney calculi, lithotripsy, percutaneous nephrolithotomy, surgery

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INTRODUCTION

More than 20 years after the clinical introduction of extracorporeal shock wave lithotripsy (ESWL) and endourological techniques, such as ureteroscopy (URS) and percutaneous nephrolithotripsy (PCNL) (1-3), the treatment of urolithiasis has changed completely. Whereas in the seventies and the be-

ginning of the eighties of the last century, the majority of renal and ureteral stones have been removed by open surgery (4-7), in the new millennium the latter has become a very rare event at least in European, Japanese and Anglo-American centers. The widespread use of ESWL resulted in a significant decrease of patients suffering from renal stones and consecutively an increase of ureteral stones from 10-20% to

30-40% in our treated stone population (8,9). Additionally, we do not see as many complicated renal stones as we have been treated with the new multimodal minimally invasive techniques in the eighties and early nineties (Table-1). We have therefore observed an increase in ureteroscopy but a decrease in percutaneous stone surgery.

Table 1 – Change of indications: personal experience at three stone centers (Stuttgart, Mannheim, Heilbronn).

	1984	1990	1999
Localization			
Caliceal stones	35%	43%	46%
Pelvic stones	42%	20%	13%
Staghorn stones	8%	3%	1%
Ureteral stones	15%	34%	40%
Treatment Modality			
ESWL	64%	79%	78%
PCNL	20%	5%	2%
URS	11%	15%	20%
Open surgery	9%	1%	0.1%

There are several reasons to explain this situation: 1)- the minimal morbidity associated with the new treatment modalities has significantly improved the compliance of the patients to undergo early therapy of their stone disease; 2)- the wide-spread use of diagnostic ultrasound has increased the early detection rate of urinary calculi; 3)- the new generation antibiotics (i.e. gyrase inhibitors) allow more effective treatment of urinary tract infections, particularly with respect to urease-splitting bacteria (i.e. proteus), and 4)- the possibility of multiple treatments in case of recurrent stone formation (i.e. by ESWL) without a significantly enhanced risk of deterioration of renal function or increasing technical difficulties, like in the era of open surgery, has improved the prognosis of our stone patients.

Nevertheless, even today we still see complex renal stones requiring more than a simple extracorporeal shock wave lithotripsy or an ureteroscopic stone removal. In the following, based on our own experience and the review of the literature we want to focus on the state of the art management of com-

plicated nephrolithiasis, emphasizing all existing minimally invasive techniques. However, in addition the remaining indications for open surgery in the new millennium will be presented.

DEFINITION OF COMPLEX RENAL STONES

Complicated nephrolithiasis consists of a variety of stone-bearing situations depending on: 1)- the stone burden and distribution; 2)- the anatomy of the collecting system; 3)- the stone composition; 4)- the renal function; 5)- associated urinary tract infection.

The majority of complex renal stones are staghorn calculi, but also multiple stones behind infundibular stenosis or in a caliceal diverticulum may be complicated. Moreover, stones in renal abnormalities, such as horseshoe-kidney, medullary sponge kidneys, are most frequently difficult to manage (9). Finally, reduced renal function and/or infection of the renal collecting system always represents a challenge for the treating urologist. However, in the following we want to focus on the management of staghorn stones.

STAGHORN CALCULI

Definition

Principally, staghorn calculi are defined as branched stones in the renal collecting system. However, as mentioned before, there are several different constellations, within this entity. This has been taken into consideration by the more complex definition of Rocco et al. (10) or the PICA-classification of Griffith et al. (11). For the modern management of such stones three factors are of major importance to decide the optimal treatment: 1)- the overall stone burden; 2)- the localization of the stone burden (i.e. which and how many calyces are involved); 3)- the anatomy of the collecting system (i.e. a dilated collecting system).

Based on this, several authors have introduced a relatively simple definition (Table-2) distinguishing between borderline stones, partial and complete staghorn calculi (12). Of course, the stone bur-

Table 2 – Classification of staghorn stones.

Stone Classification	Description	Rocco (10)	Griffith (11)
Borderline	filling the pelvis and one calyx	C2,C3	P1 IC1
Partial staghorn	filling the pelvis and two or more calyces	C4	P1 IC2
Complete staghorn	filling of the entire renal collecting system (> 80%)	C5	P1 IC3

den can be calculated more exactly using the area on the kidney-ureter-bladder (KUB) x-ray plan film, as proposed by Lam et al. (13). This was extremely useful in the evaluation of different therapeutic approaches, however in the daily routine the above mentioned classification proved to be sufficient.

Treatment Options

Whereas in former times, only the modification of the open renal surgery, i.e. anatomic versus radial nephrolithotomy (4,7), was discussed and even conservative management was optioned (14), nowadays a multimodal approach has been developed to minimize morbidity of the treatment and aiming at optimal long-term results. This may include: 1)- extracorporeal shock wave lithotripsy with or without indwelling stent; 2)-percutaneous nephrolithotomy using different devices for stone disintegration; 3)-the combination of both techniques as a planned procedure; 4)- retrograde ureteroscopic stone disintegration using a holmium laser; 5)- open surgery (i.e. anatomic or radial nephrolithotomy, sinusoidal pyelolithotomy).

Staghorn stones are unquestionably an indication for interventional therapy, since all reports following conservative treatment showed a substantially increased rate of nephrectomy (up to 50%) and an increase in associated morbidity (i.e. dialysis); in

many cases (up to 28%) the disease resulted in death (5,14). Of course, the choice among the listed treatment modalities mainly depends on the specific finding of the staghorn stone (i.e. stone classification) (15). On the other hand, further factors such as the age of the patient or the function of the stone-bearing kidney may be important (Table-3). Finally, it has to be emphasized that these criteria do not allow exact discrimination in every case.

Criteria of Success

The goal of any of these procedures is to carry the patient stone-free. However, with the introduction of ESWL particularly in case of larger calculi or stones in the lower caliceal group, even more than 40% of persisting fragments have been accepted (16,17), because in the majority of cases (90%) these asymptomatic fragments proved to be clinically insignificant (CIRF). This means, that these fragments did not induce early stone recurrence, which was different to the presence of residual stones in the era of open surgery, particularly in case of infected calculi. This may be attributed to the improved generations of antibiotics, but also to the fact, that the fragmented calculi are better treatable resulting in some residual sterile fragments after ESWL (16,17). Nevertheless, any patient with a treated staghorn stone requires a short consequent follow-up (18).

Table 3 – Criteria for choice of treatment for staghorn calculi.

Criteria	ESWL-Monotherapy	PCNL-Monotherapy	Combination (ESWL & PCNL)
Stone burden	minor	major	major
Distribution of stone load	peripheral	central	central + peripheral
Renal collecting system	narrow	dilated	narrow / dilated
Radiopacity	sufficient	(in-)sufficient	sufficient
Chemical composition	No cystine	-	-

MANAGEMENT OF STAGHORN CALCULI

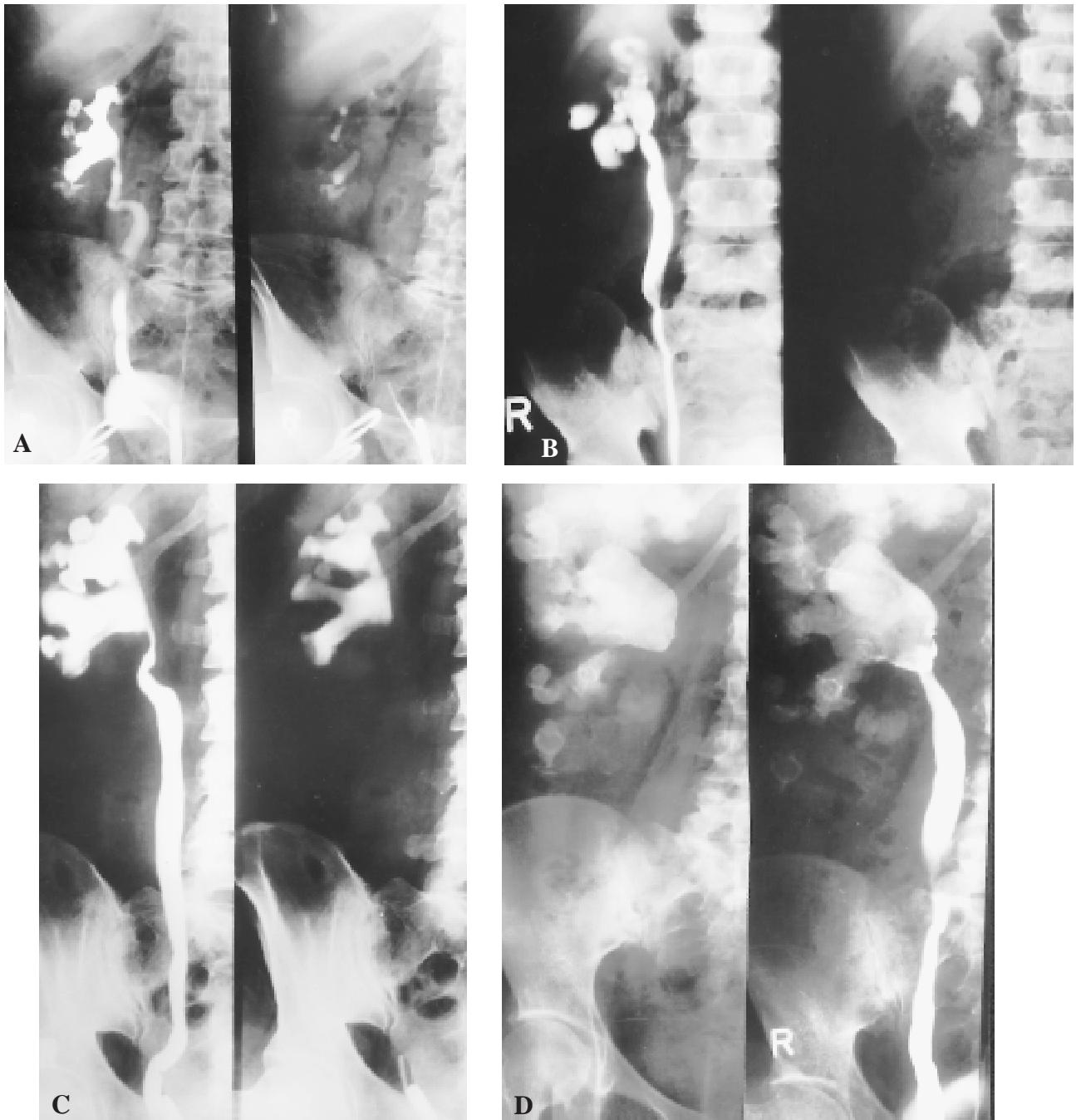


Figure 1 – Staghorn stones - Indications for the different procedures: A) ESWL-monotherapy: partial staghorn stone (calcium-oxalate-dihydrate) in the right kidney involving the pelvis and lower caliceal group together with filling of the middle and upper caliceal group; B) PCNL-monotherapy: borderline stone (calcium oxalate-monohydrate) filling one lower pole calyx with an dilated collecting system (right side), easy removable by one-stage PCNL via a single percutaneous tract; C) Combination: complete staghorn stone (struvite) on the right side with a dilated collecting system. Percutaneous debulking of the lower pole calyces and pelvis is followed by ESWL for fragmentation of the upper pole part; D) Open surgery: complete giant staghorn stone (calcium oxalate monohydrate) multiple stones in all calyces. Stone removal requires an extended pyelotomy plus multiple radial nephrolithotomies. Additionally there was an UPJ-stenosis requiring pyeloplasty.

Indications for ESWL-Monotherapy

Extracorporeal shock wave lithotripsy should be performed in case of minor stone burden, peripheral stone load (i.e. multiple stone-filled calyces) and a narrow renal collecting system. Moreover, patients with enhanced risk (i.e. cardiosclerosis, respirators problems) or other difficulties related to percutaneous surgery (i.e. children, urinary diversion) have to undergo ESWL alone (Figure-1A; Figure-2).

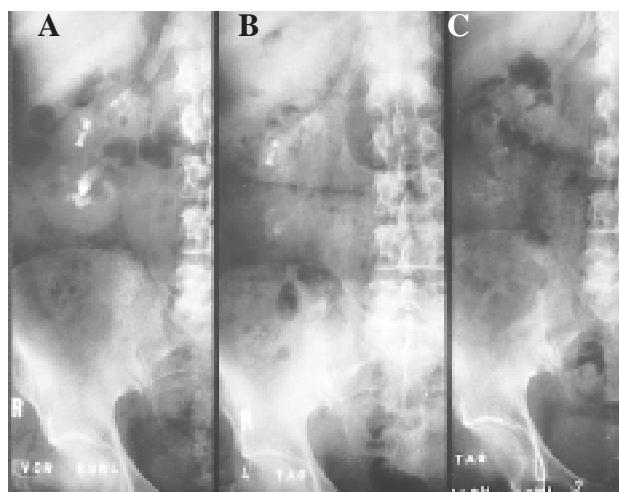


Figure 2 – ESWL-monotherapy for partial staghorn stone: A) KUB prior to ESWL; B) KUB 4 days after the first ESWL-session treating the pelvic part and lower caliceal group; C) KUB after the second session treating the upper caliceal group. Only some stone dust is left in the upper and lower calyx.

Indications for PCNL-Monotherapy

The percutaneous nephrolithotomy in single session can be successfully applied for cases of major stone burden with central (= pelvic) stone load in an enlarged (= dilated) collecting system (i.e. borderline, and partial staghorn calculi) (Figure-1B). Furthermore, slightly opaque or shock wave resistant calculi (i.e. cystine) are candidates for PCNL alone (Figure-3).

Indications for the Combination

The combination of ESWL and PCNL, principally started by the percutaneous approach, is applied for all cases of major stone burden (i.e. partial and complete staghorn stones) (Figure-1C) with cen-

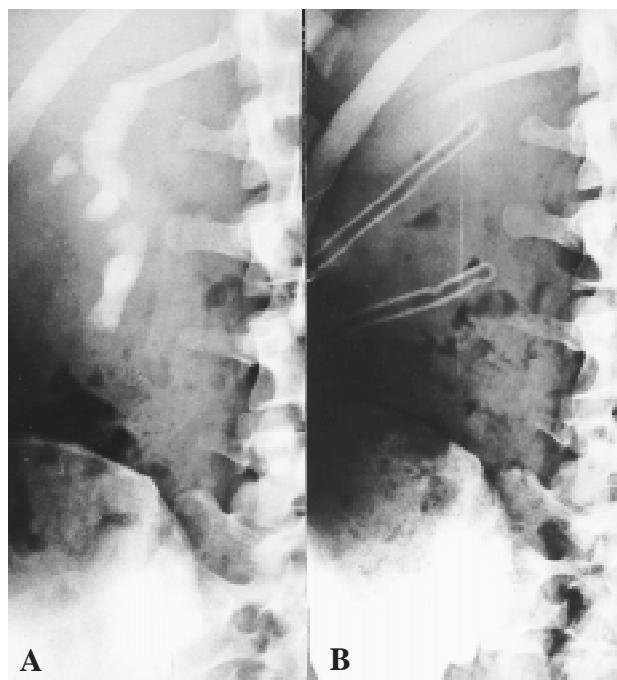


Figure 3 – PCNL-monotherapy for a partial staghorn stone: A) KUB prior to PCNL shows filling of the upper and lower calyces with a cystine stone; B) Complete stone removal via two percutaneous tracts.

tral and peripheral stone load. The rationale for the combination therapy is to reduce the morbidity of the PCNL, which is carried out in the majority of cases via one lower pole tract, and the use of ESWL selectively for disintegration of those calculi (parts of the staghorn stone) that cannot be reached with the nephroscope (Figure-4).

Indications for Open Surgery

Surgery is a potential treatment option for any staghorn for several reasons. The stone can be removed by a single procedure with comparable stone-free rates. Therefore, some authors still advocate open surgical removal in case of complete staghorn stones (19-22). However, there is the problem of loss of renal function after such extensive surgical interventions like anatrophic intersegmental pyelolithotomy, which has been reported in the range of 30-50% (23). Overall, the residual stone rate after open renal surgery is about 15%, with a 30% stone recurrence rate over 6 years and a 40% risk of urinary tract infections (16,19-25).

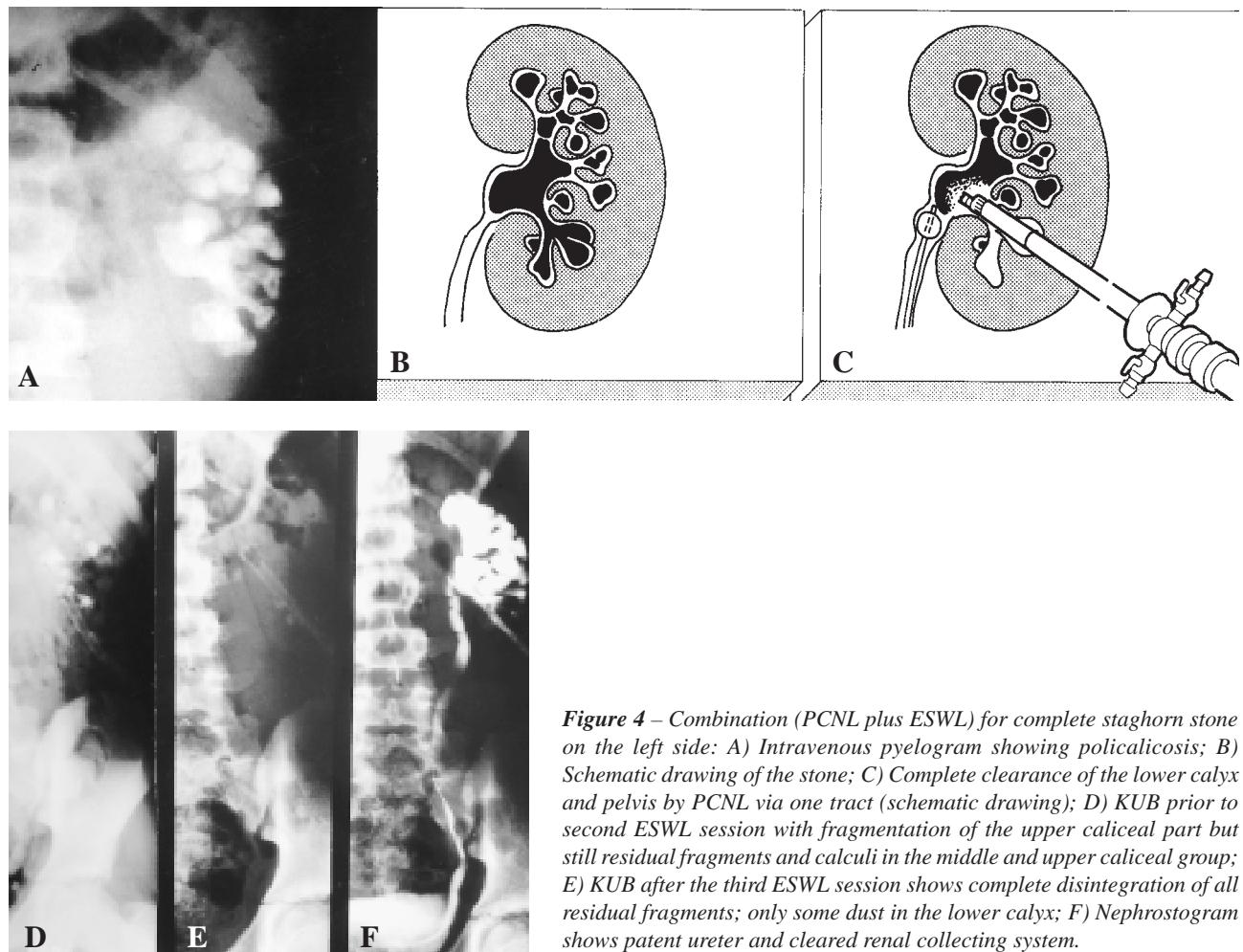


Figure 4 – Combination (PCNL plus ESWL) for complete staghorn stone on the left side: A) Intravenous pyelogram showing policalicosis; B) Schematic drawing of the stone; C) Complete clearance of the lower calyx and pelvis by PCNL via one tract (schematic drawing); D) KUB prior to second ESWL session with fragmentation of the upper caliceal part but still residual fragments and calculi in the middle and upper caliceal group; E) KUB after the third ESWL session shows complete disintegration of all residual fragments; only some dust in the lower calyx; F) Nephrostogram shows patent ureter and cleared renal collecting system.

We have therefore restricted the indications for open surgery to those cases with giant stone burden that cannot be reached endoscopically nor by a considerable number of ESWL-treatments or if additional reconstructive surgery (i.e. calicoureterostomy, pyeloplasty) is required, Figure-1D (25). Nephrectomy of non-functioning kidneys can be performed laparoscopically (26-27).

Therapeutic Approach

Independently to the following procedure, every patient with a staghorn stone requires antibiotic prophylaxis (i.e. gyrase inhibitors) at least 2 days prior to the intervention. In our series 38% of the patients presented with urinary tract infections prior to the treatment (25), 51% of whom were *Proteus mirabilis*.

ESWL-Monotherapy

The techniques of extracorporeal shock wave lithotripsy have been described in detail previously (28-31). In case of a larger stone (> 2 cm) we recommend the insertion of a double J-stent prior the procedure. This avoids obstruction of the ureter by formation of a steinstrasse, but does not inhibit the passage of fragments along the stent (13). Staghorn stones should be first treated at the pelvic part to enable passage of fragments, thereafter the upper and middle calyces are focussed leaving the lower pole untreated to avoid that fragments fall into the lower calyces from where further passage may be prolonged (Figure-3). Depending on the energy setting of the machine, the number per session should not exceed 4000 impulses. The interval between each treatment should be at least 2 days.

PCNL-Monotherapy

This is performed as a one-stage procedure with the patient under general anesthesia using a retrograde balloon occlusion catheter placed at the uretero-pelvic junction (12,25). Access is usually through the lower pole posterior calyx with removal of the lower caliceal and pelvic stone burden. In case of major stone burden, we always place an Amplatz sheath down the percutaneous tract. This allows removal of larger stone fragments and reduces the risk of pelviocaliceal influx. Only in selective cases (i.e. stones less suitable for ESWL, i.e. cystine), we recommend the puncture of an additional calyx to achieve complete stone clearance in a single PCNL-session (Figure-3). Another option to access stone burden in upper and middle calyces may be the use of a flexible cystoscope together with a holmium or dye laser introduced via the Amplatz sheath.

Combination

In the combined approach, we principally recommend to start with a debulking PCNL via the lower pole posterior calyx. The puncture of the kidney is performed under combined sonographic and fluoroscopic control. On occasion, multiple tracts (maximum 3) can be made, in case of massive stone burden (i.e. in the upper dilated calyx).

Open Surgery

Whereas in our earlier experience the technique of clamping and cooling was used (32,33), we have recently preferred the technique of radial nephrotomies with intraoperative color-duplex-sonography (7). Other options include extended pyelolithotomy, anatrophic nephrolithotomy or posterior lower nephrolithotomy. Nowadays, we would not put the same emphasis to achieve complete stone clearance, because minor residual stones can be treated effectively with ESWL.

Own Experience

Patients

Some of our personal experience with the multimodal minimally invasive management of staghorn calculi has been published previously (12,25,33).

In this paper, we want to focus on long-term results in comparison to those obtained by open surgery. A total of 197 patients were treated with the new technologies in a 5-year period and compared to 83 patients who underwent open surgery for complicated nephrolithiasis prior to the introduction of ESWL and endourology. Two hundred and forty-seven patients (186 respectively 61) could be followed over a period of 36 respectively 42 months to analyze the pattern of stone-clearance by passage of fragments, recurrent stone formation and urinary tract infection.

Distribution of Treatment

In correlation to the increasing stone burden and complexity of the cases, the percentage of ESWL-monotherapy decreases from 45% for borderline stones to 2% in case of a complete staghorn. PCNL is most frequently performed (28%) for management of partial staghorn calculi, whereas the combination is applied in 74% of all complete staghorns. For borderline stones only 6% of the patients required more than 3 sessions compared to 10% for partial and 21% for complete staghorn stones. Open surgery was performed in 7% for partial and in 11% for complete staghorn calculi. Overall, 53 patients were treated by ESWL-monotherapy, 56 by PCNL-monotherapy, and 77 had a combination of both techniques (Table-4).

Treatment Data

Thirty-seven percent of patients with “borderline” and 35% of patients with partial staghorn calculi presented with urinary tract infection prior to treatment, in contrast to 50% with complete staghorn stones. A detailed analysis of all relevant data is listed on Tables-4, 5 and 6. Three or more sessions were necessary in 24% of all patients, ranging from 0% (PCNL-monotherapy) to 54% (combination). This was because maximally two PCNL-sessions were performed for stone removal. Any further parts of the stone that could not be treated effectively received ESWL.

Blood transfusions were required in 10% of the patients, in no case after ESWL-monotherapy, but in 17% after the combination, mainly because of the increased technical difficulties of percutaneous nephrolithotomy.

MANAGEMENT OF STAGHORN CALCULI

Table 4 – Clinical results in the modern management of complex renal stones.

Criteria	ESWL (n = 53)	PCNL (n = 56)	PCNL & ESWL (n = 77)	All (N = 186)
Borderline stones	44 (83%)	25 (45%)	18 (23%)	87 (47%)
Partial staghorn	7 (13%)	26 (46%)	30 (39%)	63 (34%)
Complete staghorn	2 (4%)	5 (9%)	29 (38%)	35 (19%)
2nd session	13 (25%)	15 (28%)	77 (100%)	105 (56%)
3rd session	3 (6%)	–	27 (35%)	30 (16%)
> 3 sessions	1 (2%)	–	14 (18%)	15 (8%)
Blood transfusion	–	5 (9%)	13 (17%)	18 (10%)
Auxiliary measures	19 (36%)	9 (17%)	11 (14%)	39 (21%)
- Ureterorenoscopy	3 (6%)	1 (2%)	7 (9%)	11 (6%)
- Open surgery	2 (4%)	2 (4%)	1 (1%)	4 (2%)
Minor complications	23 (44%)	22 (39%)	41 (52%)	86 (45%)
- Colic	12 (23%)	4 (7%)	12 (15%)	28 (15%)
- Fever	11 (21%)	18 (32%)	29 (37%)	56 (30%)
Major complications	5 (10%)	4 (7%)	4 (4%)	13 (7%)
- Septicemia	3 (6%)	1 (2%)	1 (1%)	5 (3%)
- Bleeding	1 (2%)	2 (4%)	2 (2%)	5 (3%)
- Others	1 (2%)	1 (2%)	1 (1%)	3 (1%)
Mean hospital stay (d)	11.6	12.9	19.8	15.4

Table 5 – Follow-up results after management of complex stones.

Criteria	ESWL (n = 53)	PCNL (n = 56)	PCNL & ESWL (n = 77)	All (N = 186)
Stone-free at discharge	6 (11%)	35 (63%)	17 (22%)	58 (31%)
Remants in kidney	32 (60%)	21 (37%)	57 (74%)	110 (59%)
Remnarts in ureter	15 (29%)	–	3 (4%)	18 (10%)
Stone-free after 36 m.	35 (66%)	40 (71%)	37 (48%)	112 (60%)
Asymptomatic remnants (CIRF)	11 (21%)	10 (18%)	25 (33%)	46 (25%)
Symptomatic remnants (SIRF)	3 (6%)	2 (4%)	10 (13%)	15 (8%)
Recurrence	4 (8%)	4 (7%)	5(6%)	13 (7%)
UTI (at hospitalization)	14 (26%)	20 (36%)	31(40%)	65 (35%)
UTI (after 36 m.)	6 (11%)	4 (7%)	11(14%)	21 (11%)

UTI = urinary tract infect; CIRF = clinically insignificant fragments; SIRF = significant residual fragments.

Auxiliary measures have to be performed in 21% of all patients, ranging from 14% after the combination to 36% after ESWL-monotherapy. Nowa-

days, this figure could be even higher, since we recommend the prophylactic insertion of a double-J stent prior to ESWL-monotherapy. However, only 8%

needed curative auxiliary measures (31), such as ureteroscopy or open surgery.

Forty-five percent of the patients experienced minor side effects like colic or fever. Whereas colics have been more frequently associated with ESWL-treatment, postoperative fever occurred increasingly after PCNL. In contrast to this, major complication have been observed only in 7% of all patients, including perirenal hematoma after ESWL, bleeding after PCNL, colon perforation after PCNL, and pulmonary embolism.

The mean hospital stay amounted to 15.4 days ranging from 11.6 to 19.8 days.

Follow-up Data

The mean follow-up of our study was 36 months. Thirty-one percent of all patients were stone-free at discharge ranging from 63% after PCNL-monotherapy to 11% after ESWL-monotherapy. However, after a 3 years period, 60% of the patients (48 to 71%) became stone-free, depending mainly on the complexity of the treated stone (Figure-5). Twenty-five percent (21 to 33%) of all patients had still clinically insignificant residual fragments (CIRF), and only 8%

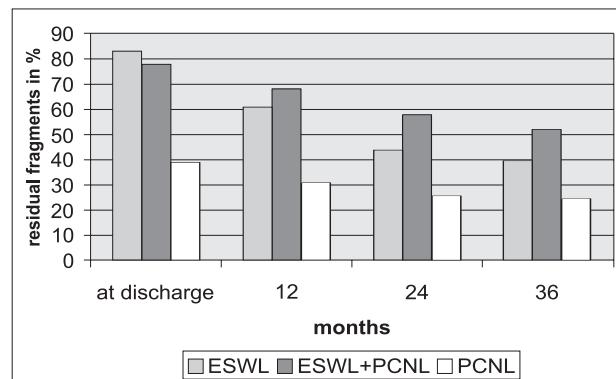


Figura 5

(4 to 13%) had symptomatic fragments mainly associated with UTI (Table-5). The overall recurrence rate amounted to 7% independent on the treatment group. Only 11 % suffered still from urinary tract infection compared to 35% at hospitalization (Table-5).

Comparison with Open Surgery

Our series of open surgery was performed prior to the introduction of ESWL and Endourology.

The stone distribution in terms of borderline vs. staghorn stones was similar in both groups, but

Table 6 – Modern management of complex stones. Comparison of results with open surgery.

Criteria	Open Surgery (n = 83)	Modern Management (N = 186)	
Borderline “stones”	40 (48%)	87 (47%)	
Partial staghorn	16 (19%)	63 (34%)	
Complete staghorn	27 (33%)	35 (19%)	
Blood transfusion	31 (37%)	18 (10%)	(p < 0.05)
Nephrectomy rate *	12 (14%)	3 (2%)	
Minor complications	28 (39%)	86 (45%)	n.s.
- Colic	-	28 (15%)	
- Fever	27 (33%)	56 (30%)	
- Wound problems	5 (6%)	-	
Major complications	6 (8%)	13 (7%)	n.s.
- Septicemia	3 (4%)	5 (3%)	
- Bleeding	-	5 (3%)	
- Others	3 (4%)	3 (1%)	
Mean hospital stay (d)	17.2	15.4	

* In 9 cases due to poor function, in 3 instances due to septicemia. n.s. = not statistically significant.

the percentage of complete staghorn stones was higher in the open surgery group (Table-6). The blood transfusion rate (37% vs. 10%) was significantly higher after open surgery, whereas the rate of fever and other minor side effects did not differ in both groups. Also major complications were observed in a similar rate (7 vs. 8%) as well as hospital stay (17.2 vs. 15.4).

In the follow-up of both groups, there are further significant differences (Table-7): the stone-free rate at discharge after open surgery is signifi-

cantly higher than after ESWL and endourology (80 vs. 31%). In contrast to this, the stone-free rate after 42 respectively 36 months does not differ significantly (72 vs. 60%) but is in favor of the open approach (Figure-6). It is to be noted, on the other hand, that the majority of the remnants after the modern techniques represent CIRF, whereas the recurrence rate after surgery is significantly higher (20% vs. 7%). Additionally, the reduction of urinary tract infection rate is better after the modern approach (0.51 vs. 0.32 = UTI after/UTI before), Table-7.

DISCUSSION

The surgical management of urinary stone disease has undergone dramatic changes and seen the implementation of technological innovations that are unsurpassed in the field of urological surgery over the past 20 years. Before these advancements, open surgery was the only surgical option for nephrolithiasis. In the current era, the first question in the management of any stone usually is whether the situation is amenable to ESWL. This should come

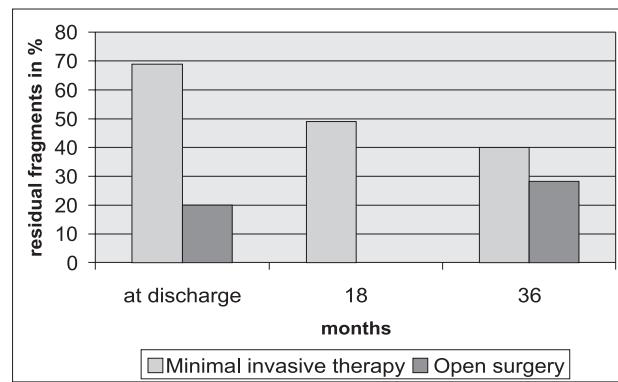


Figura 6

Table 7 – Modern management of complex stones. Comparison of follow-up results (1984-1987) with open surgery (1981-1983).

Criteria	Open Surgery (n = 61)	Modern Management (N = 186)	
Stone-free at discharge	49 (80 %)	58 (31%)	p < 0.05
Remants in kidney	12 (20 %)	110 (59%)	
Remants in ureter	-	18 (10%)	
Mean follow-up (months)	42	36	
Stone-free	44 (72 %)	112 (60%)	n.s.
Asymptomatic remnants (CIRF)	2 (3%)	46 (25%)	p < 0.05
Symptomatic remnants (SIRF)	3 (5%)	15 (8%)	n.s.
Recurrence	12 (20%)	13 (7%)	p < 0.05
UTI (at hospitalization)	35 (57%)	65 (35%)	
UTI (after follow-up)	18 (30%)	21 (11%)	
UTI after/UTI before	0.51	0.32	p < 0.05

UTI = urinary tract infect; CIRF = clinically insignificant fragments;

SIRF = significant residual fragments.

as no surprise because of the ease of use and noninvasive nature of the procedure. The real issue is whether the excellent results obtainable with this technology in case of small stones translate into successful treatment when targets are complex stones such as staghorn calculi. The patient demand and the desire to avoid painful incisions and long recovery periods, and finally the pressure to provide cost-effective care with shorter hospitalizations after surgery have created a treatment philosophy that defines success as the ability to eradicate the stone with the least invasive modality.

Guidelines for the Treatment of Staghorn Calculi

In this situation, particularly in case of complex stones, urologists have to define the indications for selection of the best procedure for treat the individual stone. The Nephrolithiasis Clinical Guidelines Panel of the American Urological Association reviewed 110 articles concerned with staghorn calculi resulting to the following guidelines (18). The committee believed that a newly diagnosed staghorn was an indication for active treatment. Percutaneous stone removal, followed by ESWL or repeat PCNL, should be used for most patients with struvite staghorns. Neither ESWL-monotherapy nor open surgery should be used as first-line treatment for staghorns in most patients.

As options PCNL and ESWL are equally effective in treating small-volume staghorns when the renal anatomy is normal or near normal. Also as an option, open surgery is appropriate therapy when the staghorn cannot be managed by any reasonable number of PCNL and ESWL sessions, i.e. in case of a giant staghorn. Nephrectomy is a reasonable option for a poorly functioning stone-bearing kidney.

This summary is in accordance with our previously stated indications (Table-3). It reflects, however, the limitations of further clarifications mainly due to the lack of prospective randomized studies as well as an accepted way to describe staghorns in the literature. We therefore believe that it is important to focus further on the comparison of the different treatment strategies for staghorn stone in the

literature. For this purpose, the changing treatment philosophy and consecutively the criteria of therapeutic success have to be addressed.

Treatment Philosophy

As stated before, the introduction of the new technologies resulted to the philosophy to treat the stone most effectively with minimal invasiveness and morbidity for the patient. This includes the amount and severity of complications associated with the applied procedures, length of hospitalization and disability, and initial stone-free rates. However, the ultimate goals of therapy in this specific group of patients should include the long-term stone-free rates, minimizing the rates of recurrent stones and infection, and the preservation of renal function (16,34).

Morbidity of the Treatment

The morbidity of open surgery have been reported extensively in the literature (4,6,21,22,35-40) including fever (26-29%), blood transfusions (14-70%), pneumothorax (5%), recurrent bleeding (4%), septicemia (1%), urinoma/fistula (1%), embolism (2%), flank abscess (2%), flank pain (16%), flank bulge (5%), incisional hernia (2%) and wound infections (4%) with a postoperative hospital stay ranging from 11 to 16 days.

Using the modern approach (3,12,13,15, 25,37-45), the morbidity mainly is associated to percutaneous surgery with the need of blood transfusions (5-53%), fever (12-64%), septicemia (2-4%), pneumothorax (2%), A-V malformation requiring superselective embolization (1%), flank abscess (1%), and colon perforation (1%). The hospital stay ranged between 9.5 and 18 days.

Our own experience with both methods (Tables-6 and 7) correlates with these data. There is no doubt, that due to the complexity of the disease both approaches are associated with significant side effects. On the other hand, there is sufficient evidence that the overall peri- and postoperative morbidity of ESWL and endourology is significantly less compared to the open approach. The fact that the modern techniques require multiple treatment sessions (2.8 vs. 1 session) (18) does not represent a disadvantage, be-

cause it has an impact neither on morbidity nor on the hospital stay.

The differences between both approaches are even more pronounced with respect to the long-term complications. Whereas the time to normal activity ranged between 44 to 54 days after open surgery, this was only 21 to 30 days after ESWL plus endourology (38-40). Complete loss of renal function was seen in 2-8% after open surgery associated with a nephrectomy rate of 7-14%. Based on these, earlier calculations considered an overall dialysis rate of 5% of all patients with urolithiasis (46,47). The nephrectomy rate in our series was only 2% using the modern approach, and in a follow-up period of 3 years there was no further need of renal ablation due to delayed loss of renal function (Tables-6 and 7). In our personal experience with almost 20 years of multimodal minimally invasive stone management there have been only casuistic cases of stone-related dialysis in the eighties, however, not a single remembered case in the last ten years. This underlines the possibilities of ESWL and endourology to treat and also retreat patients with complicated stone disease without a significant risk of loss of renal function.

Residual Fragments

When open surgery was the standard treatment for the management of renal calculi, the presence of residual fragments suggested a failed procedure, even those remaining fragments were small. Because residual calculi may act as a nidus for recurrent stone formation, complete stone removal was the principal goal of therapy. The introduction of extracorporeal shock wave lithotripsy, however, shed a new perspective on this century-old concept, minimizing the importance of postprocedural residual fragments.

Nevertheless, in the last decade the main goal of PCNL and ESWL treatment was to achieve a complete stone-free status ignoring the fact that more and more patients benefit from successful stone disintegration but with minor asymptomatic residual fragments, the so called “clinically insignificant residual fragments” = CIRF (Table-5). Of course, the acceptance of this change of therapeutic endpoints would have a major impact on treatments strategies for all complex stones. Some authors do not accept the CIRF-

theory in case of complex stones because the majority of calculi are associated with infection of the urinary tract and consist of struvite with a high risk of persisting infection and stone recurrence (19). This is true for open surgery: the stone free rates at discharge are significantly higher (80-93%) than after the modern techniques (19-37%). However, after 3 months these figures are rising up to 67-78%. Our long-term experience after three years revealed an overall stone-free rate of 60%, which was not statistically significant from the 72% stone-free rate after open surgery. Subsequently, the recurrence rate was significantly higher after open surgery (20% vs. 7%) (Table-7).

Infection

Moreover, about 3 quarters (46 of 61) of the residual fragments were asymptomatic (= CIRF) in our series, which has been found recently by other authors, too (42). In both series, more than 50% of stones consisted of struvite, however, the rate of urinary tract infection could be significantly reduced (i.e. from 35% to 11%). The ratio UTI after/UTI before was significantly higher after open surgery than when using ESWL and endourology (0.51 vs. 0.32) (Table-7). There may be several reasons to explain these finding: 1)- residual fragments are better reachable for antibiotic drugs than residual stones which still may contain bacteria; 2)- the quality of antibiotics (i.e. gyrase inhibitors) has improved; 3)- the operative trauma to the collecting system as well as to the renal parenchyma is significantly less after PCNL plus ESWL than after open surgery.

Anatomical criteria of the lower caliceal system (i.e. length of the caliceal neck, pelvic-caliceal angle) may help to predict the chance of complete stone clearance (48,49). Nevertheless, one has to accept the fact, that even in case of complex stone the majority of residual fragments after extracorporeal shock wave lithotripsy are or may become clinically insignificant (= CIRF) and only about 10-15% require further treatment (= SIRF). This has been in accordance to a recent review of the literature concerning more than 14,000 patients (50).

In contrast to this, persisting infection still remains one of the main problems after open surgery.

Even in a recent study Rocco et al. revealed a 21% UTI-rate in their follow-up (22).

Perspectives

In summary, the introduction of minimally invasive techniques has also completely changed the management of complex stones. Open surgery is only preferable in case of giant staghorns requiring numerous percutaneous procedures along with ESWL, after failure of the modern techniques or in cases necessitating additional surgical reconstruction. Even stone-bearing non-functioning kidneys can be removed laparoscopically in most situations. The majority of long-term studies show almost similar stone-free rates, but lower percentages of stone recurrence and urinary tract infections when using ESWL and endourology. In addition, the number of dialysis cases because of progressing nephrolithiasis is trending towards zero. However, the multimodal minimally invasive therapy of complex renal stones requires an individual treatment plan for each patient depending on stone burden and distribution, anatomy of the collecting system, and the composition of the calculus (Table-3).

Recently ureterorenoscopic techniques have been introduced for the management of staghorn stones based on the holmium laser technology (51). However, at present, we feel that such techniques have only limited indications because of the problems with removal of stone burden, intrarenal influx in case of infected stones, as well as with respect to the prolonged operating time. On the other hand, there may be reasonable indications for flexible ureterorenoscopy, i.e. in the treatment of calculi behind caliceal neck stenosis (52).

Finally, as mentioned before, we have to face the upcoming problem of adequate training and education in the surgical management of complex renal stones. This affects both, the percutaneous and open surgical techniques. The frequency of staghorn stones has declined dramatically in our daily routine, which is in accordance with other centers in Europe and United States. None of the existing centers - except those in stone-belt areas - is currently able to reproduce the large series of the eighties. On the other hand,

increasing reports of extensive use of the modern techniques are presented from countries, which previously had only limited access to ESWL and endourology, i.e. in Eastern Europe, India, (52). The main problem of training represents the difficulty and complexity of these procedures, albeit percutaneous or open surgery. This situation is similar to the training of laparoscopy and retroperitoneoscopy. Therefore, we feel that such complex stone cases should be concentrated to a few centers of expertise, which then could also provide adequate training for urologists with special interests in this field.

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EDITORIAL COMMENT

The authors present their extensive experience in the contemporary management of staghorn calculi. Having been leaders in the minimally invasive management of staghorn calculi, including shock wave lithotripsy and percutaneous techniques, this manuscript provides an excellent overview of endoscopic and shock wave-related approaches to the management of complex renal stones.

Comparing almost 200 patients who had undergone contemporary minimally invasive management of symptomatic staghorn calculi to more than

80 patients who had undergone open nephrolithotomy, this study finds that minimally invasive techniques offer reliable, safe and efficacious options for the management of complex renal calculi. The results and suggestions offered in the current manuscript are comparable to the recommendations introduced in the American Urological Association's Nephrolithiasis Guidelines report on the management of staghorn calculi (1). In essence, small-volume staghorn calculi in a non-dilated collecting system can be managed in many cases with shock wave lithotripsy monotherapy. However, for large volume staghorn calculi, a percutaneous approach either as monotherapy or in conjunction with shock wave lithotripsy should provide stone-free rates comparable to that of open surgery. Moreover, these minimally invasive approaches offer the benefits of decreased blood loss, decreased growth of residual fragments as well as a more rapid return to normal activity.

The authors stress that the minimally invasive techniques of shock wave lithotripsy and percutaneous nephrolithotomy have replaced open stone surgery for the management of all but the most complex of staghorn calculi. Finally, the authors note the importance of adequate training in various endoscopic techniques, which will provide the Urologist the ability to manage complex renal and ureteral stone disease.

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METABOLIC ALTERATIONS AND CLINICAL EVOLUTION IN URINARY CALCIUM STONE FORMERS

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ABSTRACT

Purpose: To identify significant differences in metabolic alterations in single and recurrent calcium stone formers.

Materials and Methods: From August 1993 to January 1999, a comprehensive metabolic evaluation was performed as an outpatient basis on 106 single calcium stone formers (49 male and 57 females), and on 394 recurrent calcium stone formers (170 mild and 224 severe form of the disease), 177 males and 217 females. The patient collected a 24-hour urine specimen on the 2nd and 3rd day of the restricted diet (400-mg/d calcium). The 24-hour urine samples were analyzed for total volume, calcium, phosphate, uric acid, creatinine, sodium, potassium, oxalate, magnesium and citrate. On 4th day, a venous blood sample was analyzed for creatinine, calcium, phosphate, uric acid, sodium, potassium and magnesium. In a spot urine sample, density, pH and ammonium were measured. Then, the patient taken 1g of elemental calcium and collected urine over a 4-hour period to measure calcium and creatinine.

Results: In recurrent stone formers it was observed more frequently hypercalciuria ($p < 0.05$) and alkaline urine ($p < 0.05$), excreting in urine more calcium ($p < 0.05$) than first-time stone formers. Recurrent stone formers had first stone occurrence younger ($p < 0.001$) than single stone formers. Hypercalciuria was observed in 36.9% of single, 41.7% of mild and 51.4% of severe stone formers. Alkaline urine was observed in 3.5% of mild and 3.6% of severe stone formers, but in no single stone formers. 24-hour urine calcium was 169 ± 82 mg in single, 183 ± 89 mg in mild and 192 ± 98 mg in severe stone formers. The mean age for the first stone occurrence was 43.7 years in single, 40.4 years in mild and 34.6 years in severe stone formers.

Conclusions: The calcium stone formers with high level of calcium in urine or with alkaline urine pH are associated with a high recurrence rate and require a constant clinic watchfulness with selective medical therapy for preventing new stone formation.

Key words: urolithiasis, calculi, metabolism, risk factors, calcium

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INTRODUCCIÓN

La litiasis urinaria puede ser considerada una enfermedad crónica que evoluciona por fases de actividad clínica de frecuencia variable, provocando malestar en el paciente y una merma en su calidad de vida y, al mismo tiempo, genera un coste elevado al precisar el paciente cuidados médicos repetidos. Un 75% de los cálculos son de composición cálcica y por medio del estudio metabólico-mineral se descubren factores causales en un 80-90% de los pacientes

(1) como hipercalciuria, hiperparatiroidismo primario, hiperoxaluria, hiperuricosuria, hipocitraturia, hipomagnesuria, cambios en el pH urinario y baja ingesta de líquidos.

Los progresos conseguidos en los últimos años en el tratamiento de la litiasis urinaria, con la introducción de los procedimientos endourológicos y la litotricia extracorpórea por ondas de choque, ha supuesto un cambio radical en el abordaje terapéutico de esta patología, consiguiendo una gran eficacia con una significativa menor morbilidad, mejor tole-

rancia y una reducción considerable de la convalecencia. Sin embargo, el impacto causado por estas nuevas modalidades terapéuticas ha supuesto una desviación de la atención sobre la necesidad de evaluar los factores de riesgo implicados en la formación de los cálculos con el fin de establecer medidas profilácticas para evitar la recidiva litiasica. La profilaxis médica es posible, eficaz y menos costosa que cualquier otra terapéutica de intervención sobre el cálculo y, desde luego, supone un beneficio real para el enfermo porque le evita el sufrimiento de un cólico nefrítico y de un posible tratamiento activo. El cálculo no es más que la expresión final de un trastorno subyacente: sobresaturación urinaria de sustancias cristalizables, déficits de inhibidores de la cristalización, presencia de nucleantes heterogéneos, zonas de urodinámica reducida o lesión anatómica de la vía urinaria. El desconocimiento y, por tanto, la falta de resolución de estos factores nos conducirán, en muchos casos, a una indeseable recidiva. Los avances producidos en los últimos años nos han permitido controlar médica mente estos disturbios metabólicos en la mayoría de los pacientes, muchas veces con simples recomendaciones higiénico-dietéticas. Con programas de profilaxis médica se ha podido reducir considerablemente la recurrencia hasta un nivel por debajo del 25% a largo plazo (2).

La reducción de nuevos episodios litiasicos supone un beneficio incuestionable para estos pacientes, pero cabe también preguntarse si estos programas de profilaxis médica deben proponerse a todos los pacientes de forma indiscriminada o quizás a un reducido grupo con marcada tendencia a la recidiva. Se sabe que, con simples medidas higiénico-dietéticas. Hasta un 60% de pacientes con litiasis cárctica idiopática no forman nunca un nuevo cálculo después del primer episodio (the stone clinic effect) (3). Por tanto, resulta del todo beneficioso poder reconocer aquellos factores metabólicos que están especialmente relacionados con una evolución clínica maligna de la litiasis. De esta forma, nos permitiría seleccionar a los pacientes que deben ser sometidos a una vigilancia especial bajo un programa de profilaxis médica selectiva. Con ello conseguiríamos frenar la tendencia a la recurrencia mejorando, por tanto, el estado de salubridad de estos pacientes y reduciendo,

de forma notable, los costes que ocasionan las intervenciones médicas por atención en cada episodio litiasico (4).

En el presente trabajo estudiamos la relación que existe entre el grado de severidad clínica en pacientes con litiasis urinaria cárctica y los factores metabólicos de riesgo litogenético implicados en cada paciente para determinar el papel que tiene cada trastorno metabólico en la evolución clínica de los pacientes.

MATERIAL Y MÉTODOS

En el período de tiempo comprendido entre Agosto de 1993 y Enero de 1999 fueron sometidos a estudio metabólico-mineral 500 pacientes con litiasis urinaria cárctica, 226 varones (45.2%) y 274 mujeres (54.8%) con una edad media de 47.4 años y un rango de 75 a 20 años. Los criterios de inclusión para el estudio fueron: pacientes de ambos sexos con edad entre 20 y 75 años, pacientes con al menos un episodio de litiasis cárctica (cálculos de oxalato y/o fosfato cárxico) basando la composición del cálculo en criterios analíticos y/o clínicos y la realización del estudio metabólico-mineral bajo el entorno del programa informático original Emusys siguiendo siempre la misma metodología. Los criterios de exclusión considerados fueron: errores metodológicos en cualquier fase del estudio metabólico-mineral, pacientes con insuficiencia renal (creatinina sérica superior a 1.5 mg%), pacientes sometidos a tratamientos reductores de la litogénesis urinaria en los últimos 6 meses, presencia de infección urinaria en el momento del estudio metabólico-mineral, cálculos de tamaño superior a 30 mm de diámetro mayor, presencia de alteraciones morfológicas de la vía urinaria de carácter litogenético (tanto congénitas como adquiridas), presencia de cuerpos extraños en vía urinaria, pacientes con antecedentes de cirugía reconstructiva del aparato urinario, cirugía con derivaciones urinarias (internas o externas) o trasplante renal.

Según la severidad en la evolución clínica de la litiasis en cada paciente se dividieron en tres grupos: pacientes de severidad clínica mínima (SCM), leve (SCL) y severa (SCS) (Tabla-1). Los criterios de

Tabla 1 – Grupos de litiásicos según el grado de severidad clínica de la litiasis

	Total	Sexo		Edad (años)	
		Varón	Mujer	Media	Rango
SCM	106	49	57	43.8	68-20
SCL	170	75	95	46.8	75-20
SCS	224	102	122	49.5	75-20

SCM: litiásicos monoepisódicos; SCL: litiásicos recurrentes leves; SCS: litiásicos recurrentes severos

selección seguidos para el grupo de SCM fueron haber padecido un solo episodio litiásico con cálculo único, para el grupo de SCL fueron haber padecido de 2 a 3 episodios litiásicos y/o tener cálculos múltiples (de 2 a 4 cálculos) de localización uni o bilateral y, finalmente, para el grupo de SCS fueron haber padecido más de 3 episodios litiásicos y/o tener cálculos múltiples (más de 4 cálculos) de localización uni o bilateral.

El proceso de estudio metabólico-mineral evoluciona de forma fásica, de acuerdo a un protocolo establecido en régimen completamente ambulatorio que hemos descrito en otras publicaciones (5). Se le pide al paciente que siga durante 3 días una dieta hipocálcica (400 mg de calcio) libre en purinas. Se deberá ir colecciónado la orina formada en 24 horas durante el segundo y tercer día desde el comienzo de la dieta hipocálcica. Un frasco de recolección contiene 20 ml de ácido clorhídrico fumante al 37%. Se pide al paciente que ingiera una cantidad similar de agua durante los dos días de recogida. Al cuarto día de comenzada la dieta hipocálcica, se le practica al paciente una extracción de sangre en ayunas y se recoge orina fresca recién emitida acude. Una vez centrifugada la muestra de sangre, en una alícuota se procede a la determinación de forma automatizada en un autoanalizador de creatinina, ácido úrico, calcio, fósforo y magnesio. En otra alícuota se determinan con un aparato de electrodos selectivos el sodio, potasio, cloro y carbónico total. Con la orina fresca recogida, en una muestra se determinan pH, densidad, acidez titulable, amonio y estudio del sedimento, y otra muestra se envía al laboratorio de Microbiología para examen bacteriológico.

En cuanto a las orinas recogidas durante 24 horas, se anota el volumen total de orina emitida (Diuresis). En la muestra de orina con el frasco acidificado se determina calcio, fósforo, oxalato, magnesio y citrato, mientras que en la muestra de orina del frasco sin acidificar se determina creatinina, sodio, potasio, cloro y ácido úrico. Los métodos analíticos empleados en estas determinaciones son los mismos que los referidos para las muestras de sangre, excepto para la determinación del citrato que se realiza de forma manual (método enzimático de la citrato liasa). El mismo día que el paciente acude al laboratorio, y una vez que se ha hecho la extracción sanguínea y se ha recogido orina recién emitida, se le somete a una prueba de sobrecarga oral de calcio (1 g) recogiendo la orina formada durante las siguientes 4 horas, tras recomendarle una ingesta de 500-1.000 ml de agua durante ese período, donde se anota el volumen de orina emitido y se determina calcio y creatinina.

Tras el registro de estas determinaciones en sangre, orina recién emitida y orina de 24 horas postdieta hipocálcica y orina de 4 horas postsobrecarga cálcica, se procede al cálculo de una serie de indicadores y cocientes que el programa informático original Emusys ejecuta automáticamente facilitando enormemente el trabajo del laboratorio. En orina de 24 horas se calcula la excreción de creatinina, calcio (Ca), calcio/Kg de peso (Ca/Kg), fósforo (P), oxalato (Ox), ácido úrico (Au), magnesio (Mg), citrato (Ct), sodio, potasio y cloro; aclaramiento de creatinina y de ácido úrico (Cau); reabsorción tubular de calcio (RTCa) y de fosfato (RTP), cociente calcio/creatinina (Ca/Cr), fósforo/creatinina (P/Cr), oxalato/creatinina (Ox/Cr), ácido úrico/creatinina (Au/Cr), citrato/creatinina (Ct/Cr), magnesio/creatinina (Mg/Cr), sodio/creatinina, potasio/creatinina y cloro/creatinina. En orina de 4 horas se calcula excreción de creatinina y de calcio, cociente calcio/creatinina y aclaramiento de creatinina.

Las alteraciones metabólicas consideradas son la hipercalciuria (Hca), hiperoxaluria (Hox), hiperuricosuria (Hur), hipocitraturia (Hct), hipomagnesuria (Hmg), acidosis tubular renal distal (ATRd), cambios en el pH urinario y bajo volumen de orina (Bdiur) (inferior a 1.200 ml durante 24 horas). La hipercalciuria se divide en los subtipos

absortiva (Hcab), renal (Hcrn) y resortiva (Hcrs). La hipercalciuria absortiva puede ser de tipo I (HcabI), II (HcabII) o III (HcabIII) de Pak. La hipercalciuria resortiva puede ser secundaria a hiperparatiroidismo primario (HPTP) o de otro origen (Hcrm). La hiperoxaluria se divide en absortiva (Hoab) y endógena (Hoed). La hiperoxaluria absortiva puede ser dietética (Hoad) o entérica (Hoet). La hiperuricosuria se divide en los tipos entero-renal (Huer) y endógena (Hued). Los cambios del pH de orina pueden ser de tendencia ácida (pHac) (pH inferior a 5.3) o de tendencia alcalina (pHal) (pH superior a 6.0). Los criterios seguidos para el diagnóstico de estas alteraciones metabólicas han sido expuestas en otras publicaciones (5).

Para el tratamiento estadístico de los datos se emplea el programa informático SPSS. Para comparar las frecuencias de las distintas variables categóricas entre los grupos de estudio se aplica la prueba del Ji-cuadrado (C^2), considerando el p-valor de Pearson y el p-valor de la razón de verosimilitud. La corrección de Yates y la prueba de Fisher fueron aplicadas en los casos necesarios. Para comparar los valores de las distintas variables continuas entre los grupos de estudio se aplica el análisis de la varianza de un factor (ANOVA-Oneway). Si se detectan, con este test, diferencias significativas entre algunas de las variables numéricas se aplica la prueba de Scheffé para averiguar en cuáles grupos del estudio se daban esas diferencias. Cuando se detecta significación estadística al comparar las variables de los grupos de estudio se expresa por p-valor de $p < 0.05$, $p < 0.01$ o $p < 0.001$. En caso de no encontrar diferencias significativas se expresa por NS.

RESULTADOS

El 20% de los pacientes del grupo SCM, el 34.6% del grupo SCL y el 34.7% del grupo SCS refirieron tener parientes próximos que habían tenido o tenían urolitiasis, no siendo estadísticamente significativa la diferencia en la frecuencia.

En la Tabla-2 se muestra el porcentaje de alteraciones metabólicas en el total de pacientes litiásicos de los grupos SCM, SCL y SCS. Algunos pacientes tienen más de una alteración. Se encontraron

Tabla 2 – Alteraciones metabólicas en los grupos de litiásicos

	SCM	SCL	SCS	P (c2)
Hca	36.9%	41.7%	51.4%	< 0.05
Hox	18.8%	18.9%	12.5%	NS
Hur	25.5%	28.2%	19.2%	NS
Hct	8.5%	7.6%	10.7%	NS
Hmg	4.7%	4.1%	5.4%	NS
pHac	33.0%	28.2%	25.0%	NS
pHal	0.0%	3.5%	3.6%	< 0.05
ATRd	7.5%	8.8%	7.1%	NS
Bdiur	2.8%	8.8%	7.1%	NS
Normal	18.9%	14.7%	18.3%	NS

Hca: hipercalciuria; Hox: hiperoxaluria; Hur: hiperuricosuria; Hct: hipocitraturia; Hmg: hipomagnesuria; Phac: pH ácido; Phal: pH alcalino; ATRd: acidosis tubular renal distal; Bdiur: Baja diuresis; P (c2): p valor para Ji-cuadrado.

Tabla 3 – Subtipos de alteraciones metabólicas en los grupos de litiásicos

	SCM	SCL	SCS	P (c2)
Hcab	33.0%	35.2%	36.2%	NS
HcabI	9.4%	8.2%	10.3%	NS
HcabII	17.0%	22.9%	17.9%	NS
HcabIII	6.6%	4.1%	8.0%	NS
Hcrn	2.0%	1.2%	5.4%	< 0.05
Hcrs	1.9%	5.3%	9.8%	< 0.01
HPTP	1.9%	1.2%	5.8%	< 0.05
Hcrm	0.0%	4.1%	4.0%	< 0.05
Hoab	11.3%	11.8%	7.6%	NS
Hoad	11.3%	11.2%	7.6%	NS
Hoet	0.0%	0.6%	0.0%	NS
Hoed	7.5%	7.1%	4.9%	NS
Huer	23.6%	24.7%	17.0%	NS
Hued	1.9%	3.5%	2.2%	NS

Hcab: hipercalciuria absortiva; HcabI: hipercalciuria absortiva tipo I; HcabII: hipercalciuria absortiva tipo II; HcabIII: hipercalciuria absortiva tipo III; Hcrn: hipercalciuria renal; Hcrs: hipercalciuria resortiva; HPTP: hiperparatiroidismo primario; Hcrm: hipercalciuria resortiva de otro origen. Hoab: hiperoxaluria absortiva; Hoad: hiperoxaluria absortiva dietética; Hoet: hiperoxaluria entérica; Hoed: hiperoxaluria endógena; Huer: hiperuricosuria entero-renal; Hued: hiperuricosuria endógena; P (c2): p valor para Ji-cuadrado.

ron diferencias estadísticas significativas en la Hca ($p < 0.05$) con mayor porcentaje de casos en el grupo SCS (51.4%) que en el grupo SCL (41.7%) y SCM (36.9%), y en la pHal ($p < 0.05$) con predominio en el grupo de SCS (3.6%) y SCL (3.5%) con respecto al grupo SCM (no se registró ningún caso). Según muestra la Tabla-3, dentro de las Hca se observaron diferencias significativas en los subtipos Hcrrn ($p < 0.05$), con una frecuencia del 5.4% en el grupo SCS contra el 2.0% del grupo SCM y el 1.2% del grupo SCL, y en la Hcrs ($p < 0.01$) con predominio también en el grupo SCS (9.8%) contra el 5.3% del grupo SCL y el 1.9% del grupo SCM. Asimismo, dentro del tipo Hcrs, se observaron diferencias en la forma HPTP ($p < 0.05$), con predominio en el grupo SCS (5.8%) contra el 1.9% del grupo SCM y el 1.2% del grupo SCL, y en la forma Hcrm ($p < 0.05$) con una frecuencia de 4.1% en el grupo SCL y de 4.0% en el grupo SCS (4.0%) contra ninguno caso en el grupo SCM. No hubo diferencias significativas en los otros subtipos.

Tabla 4 – Parámetros bioquímicos en orina en los grupos de litiásicos

	SCM	SCL	SCS	P ANOVA
Diuresis, ml/24 h	1995 ± 466	1943 ± 554	1917 ± 420	NS
PH	5.4 ± 0.5	5.6 ± 0.7	5.6 ± 0.6	< 0.05
Ca, mg/24 h	169 ± 82	183 ± 89	192 ± 98	< 0.05
Ca/Kg, mg/Kg/d	2.3 ± 1.0	2.6 ± 0.9	2.9 ± 1.5	< 0.05
Ca/Cr	0.14 ± 0.06	0.15 ± 0.08	0.16 ± 0.08	NS
RTCa	98.3 ± 0.9	98.0 ± 1.0	98.0 ± 1.0	< 0.05
P, mg/24 h	875 ± 367	867 ± 27	882 ± 371	NS
P/Cr	0.74 ± 0.30	0.74 ± 0.33	0.72 ± 0.28	NS
RTP	77.3 ± 11.5	77.3 ± 11.9	76.4 ± 10.9	NS
Ox, mg/24 h	32.4 ± 17.3	33.9 ± 17.1	31.3 ± 16.2	NS
Ox/Cr	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	NS
Au, mg/24 h	653 ± 251	652 ± 274	610 ± 229	NS
Au/Cr	0.54 ± 0.16	0.53 ± 0.18	0.51 ± 0.18	NS
Cau, ml/minuto	10.5 ± 4.4	10.6 ± 5.3	10.1 ± 5.1	NS
Ct, mg/24 h	641 ± 256	649 ± 261	611 ± 268	NS
Ct/Cr	0.56 ± 0.27	0.57 ± 0.29	0.52 ± 0.25	NS
Mg, mg/24 h	89.2 ± 37.0	93.7 ± 36.5	88.2 ± 40.6	NS
Mg/Cr	0.07 ± 0.03	0.08 ± 0.03	0.07 ± 0.03	< 0.05

Valores expresados como media y desviación estándar. Ca: cálculo; P: fóforo; Ox: oxalato; Au: ácido úrico; Ct: citrato; Mg: magnesio; Cr: creatinina; RTCa: reabsorción tubular de calcio; RTP: reabsorción tubular de fosfato; Cau: aclaramiento de ácido úrico; P ANOVA: p valor para análisis de la varianza de un factor.

encias significativas ($p < 0.001$) entre el grupo SCS (34.6 años de media) y SCL (40.4 años de media) y SCM (43.7 años de media) respectivamente. Sin embargo, no existen diferencias entre el grupo SCM y SCL.

En la Tabla-4 se muestran los valores de los parámetros bioquímicos que fueron observados entre los tres grupos de pacientes litiasicos. Se encontraron diferencias estadísticamente significativas en pH de orina ($p < 0.05$), con menor valor en el grupo SCM (5.4 contra 5.6 de los otros grupos), en Ca ($p < 0.05$), con valores más elevados en el grupo SCS (192 contra 183 y 169 del grupo SCL y SCM, respectivamente), en Ca/Kg ($p < 0.05$), con mayor valor también en el grupo SCS (2.9 contra 2.6 y 2.3 del grupo SCL y SCM respectivamente), en RTCa ($p < 0.05$), con menor valor en el grupo SCS y SCL (98.0 contra 98.3 del grupo SCM), y finalmente en Mg/Cr ($p < 0.05$) con nivel más bajo en el grupo SCS y SCM (0.07 contra 0.08 del grupo SCL). No se encontraron diferencias significativas en los otros parámetros.

De acuerdo al sexo, en los hombres no se encontraron diferencias en ningún parámetro bioquímico. En las mujeres se encontraron diferencias en Ca ($p < 0.05$), con nivel superior en el grupo SCL y SCS (186 y 183 respectivamente contra 157 del grupo SCM), en Ca/Cr ($p < 0.05$), con mayor valor en el grupo SCL y SCS (0.18 y 0.17 respectivamente contra 0.15 del grupo SCM), en RTCa (< 0.05), con menor valor en el grupo SCL y SCS (97.9 y 98.0 respectivamente contra 98.2 del grupo SCM) y en Mg/Cr ($p < 0.05$) con nivel inferior en el grupo SCS (0.07 contra 0.08 y 0.09 del grupo SCM y SCL respectivamente).

DISCUSIÓN

La historia natural de la enfermedad litiasica aún no ha sido bien establecida. Son pocas las series publicadas sobre la frecuencia de alteraciones metabólicas observadas en pacientes con litiasis recurrente y con litiasis monoepisódica. El HPTP supone un factor de riesgo considerable para la recidiva al punto de que los pacientes con litiasis e HPTP en el momento del diagnóstico tienen un 50% de posibilidades de tener un episodio litiasico en el fu-

turo, consiguiéndose reducir significativamente la formación de nuevos cálculos en estos pacientes después de practicar la paratiroidectomía, aunque existen algunas discrepancias en estos resultados. Robertson et al. (6) comprueban que los pacientes con hiperoxaluria tienen mayor frecuencia de cristaluria de oxalato cálcico que aquellos con hipercalciuria llegando a la conclusión de que la concentración de oxalato en la orina es uno de los factores más determinantes para la solubilidad del oxalato cálcico. Cualquier incremento del oxalato urinario sería un factor crítico para la cristalización del oxalato cálcico. Algunos autores reportan que los pacientes litiasicos con hiperuricosuria tienen mayor tasa de recurrencias que los que tienen otras alteraciones metabólicas, precisando de mayor número de tratamientos intervencionistas por su litiasis. Sin embargo, Ettinger (7) encuentra que, aunque el porcentaje anual de recurrencias es mayor para los que tienen hiperuricosuria que hipercalciuria, esta diferencia no es estadísticamente significativa.

Se considera que los pacientes litiasicos con ATR distal tienen una tendencia a formar cálculos mayor que los pacientes litiasicos con otros trastornos metabólicos (8). El bajo volumen de orina parece ser el factor de riesgo más importante identificado. Para Harvey et al. (9) es la alteración metabólica más frecuentemente observada entre 3.473 pacientes litiasicos de diferentes regiones de EEUU. Los pacientes con litiasis cálcica que han tenido un primer episodio litiasico solamente recurrirán un 27%, después de un período de seguimiento de 5 años, simplemente aconsejándoles aumentar la ingesta de líquidos y corrigiendo sus hábitos dietéticos (the stone clinic effect). Cupisti et al.(10) comparan un grupo de 73 pacientes varones adultos con litiasis cálcica (51 recurrentes y 22 monoepisódicos) observando hipercalciuria en 31.4% y 27.6% respectivamente, hiperoxaluria en 7.8% de recurrentes y ningún caso en monoepisódicos, hiperuricosuria en 19.6% y 9% respectivamente e hipocitraturia en 31.4% y 4.5%, respectivamente. De acuerdo a estos resultados, la hipocitraturia es más frecuente, de forma significativa, en el grupo de pacientes recurrentes respecto al grupo de monoepisódicos.

En el presente estudio, la hipercalciuria se observa más frecuentemente en los pacientes con litiasis recurrente que en los monoepisódicos. Asimismo los tipos de hipercalciuria renal y resortiva, tanto el HPTP como otras causas distintas a HPTP, también son más frecuentes en los pacientes con litiasis recurrente. Estos resultados son concordantes con los reportados por otros autores en cuanto al HPTP aunque Cupisti et al. (10) comprueban una frecuencia similar de hipercalciuria entre los recurrentes y monoepisódicos. Nosotros no pudimos observar una mayor frecuencia de hiperoxaluria en los pacientes recurrentes contradiciendo las observaciones que tradicionalmente se han referido a cerca del mayor potencial litogenético del oxalato respecto al calcio. La mayor parte de estos estudios fueron realizados con técnicas *in vitro* pero queda por demostrar el verdadero papel del oxalato en estudios *in vivo*. En nuestro estudio, la frecuencia de hiperuricosuria no fue un factor diferenciador entre litiásicos y recurrentes y, por tanto, estos resultados están en contraposición con los reportados por otros autores y son más concordantes con los comunicados por Ettinger (7) & Cupisti et al. (10). Tampoco hemos observado que la hipocitraturia y la ATR distal sean más frecuentes en los litiásicos recurrentes como han revelado otros estudios.

Asimismo son pocas las series publicadas sobre los niveles de excreción urinaria de calcio, oxalato, ácido úrico, citrato y magnesio en pacientes con litiasis recurrente y con litiasis monoepisódica que pretendan establecer diferencias entre estos dos grupos de pacientes litiásicos. Se han venido refiriendo mayores niveles de calciuria y oxaluria y menores niveles de citraturia y magnesuria en los pacientes litiásicos recurrentes que en los que han tenido un solo episodio litiásico. Tiselius (11) comprueba que los niveles de calciuria y oxaluria estaban incrementados en los pacientes recurrentes respecto a los pacientes con un solo episodio litiásico, 445 ± 65 contra 469 ± 53 mmol/mol Cr de calcio y 21.9 ± 1.3 contra 35.8 ± 16.6 mmol/mol Cr de oxalato en orina respectivamente, aunque estas diferencias no fueron significativas estadísticamente. Strauss et al. (12) estudian una serie de pacientes con litiasis cálcica recurrente que son sometidos a profilaxis médica

con carácter prospectivo. Observan que 57 pacientes recidivan, permaneciendo libres de cálculos 189 pacientes después de un período de seguimiento de 4.3 ± 2.2 años. Comparando los pacientes que recurrieron con los que no, encuentran que los recurrentes tenían, de forma significativa, un mayor nivel de calciuria durante el tiempo de profilaxis (2.79 ± 1.08 vs 2.39 ± 0.98 mg/Kg peso/24 horas, $p < 0.04$) y el incremento del volumen urinario era menor respecto al que tenían al comenzar la profilaxis (-0.02 ± 0.48 vs 0.23 ± 0.54 litros/24 horas). Ljunghall & Danielson (13), en un minucioso estudio, siguen a 54 pacientes que han tenido un primer episodio litiásico durante un período de 8 años sin profilaxis médica, observando recurrencia en el 53% de los casos. En todos los pacientes se realizó determinación de calcio, oxalato, ácido úrico, magnesio y volumen de orina en orina de 24 horas cuando tuvieron el primer episodio litiásico. Sólo observaron diferencias significativas, entre los que recurrieron y los que no recurrieron, en el nivel de calciuria que era superior entre los que recurrieron (7.4 ± 2.9 y 2.43 ± 0.08 mmol/24 h respectivamente, $p < 0.05$).

En el referido estudio de Cupisti et al. (10) encuentran diferencias significativas en el nivel de citrato, más bajo en los recurrentes (2.06 ± 1.04 mmol/24 horas) que en los monoepisódicos (3.20 ± 1.18 mmol/24 horas, $p < 0.001$). Los niveles de calciuria, oxaluria, uricosuria y el volumen de orina eran similares entre los dos grupos de pacientes. Trinchieri et al. (14) no encuentran diferencias significativas en la frecuencia de trastornos metabólicos observados en pacientes monoepisódicos y litiásicos, aunque el nivel de calciuria es significativamente más alto en recurrentes (264 ± 144 mg/24 horas) que monoepisódicos (230 ± 121 mg/24 horas). Borghi et al. (15) seleccionan 199 pacientes que han tenido un único episodio de litiasis cálcica. De estos, a 99 pacientes (grupo 1) se pide un incremento en la ingesta de agua sin variar sus hábitos dietéticos mientras que en los otros 100 pacientes (grupo 2) no se le da ninguna instrucción especial. Despues de un período de seguimiento de 5 años comprueban que la orina basal de los pacientes que recurrieron tenía una mayor concentración de calcio. En el grupo 1 el nivel de calciuria en los recurrentes era de 326 ± 140 en comparación

con 233 ± 106 mg/24 horas de los que no habían recurrido ($p < 0.005$) y en el grupo 2 era de 313 ± 113 contra 249 ± 107 mg/24 horas respectivamente ($p < 0.01$). Ninguna diferencia era observada en los otros parámetros bioquímicos (oxalato, ácido úrico, citrato, magnesio, pH).

En general, los resultados de nuestro estudio son concordantes con los comunicados por otros autores. La mayoría coincide en encontrar niveles mayores de calciuria en los pacientes con litiasis recurrente respecto a los pacientes con litiasis monoepisódica, a excepción de la serie de Cupisti et al.(10). Nuestros resultados también corroboran los de otros autores al no encontrar diferencias significativas en los niveles de oxaluria, uricosuria, citraturia y magnesuria entre litiásicos recurrentes y monoepisódicos salvo contadas excepciones, como la reportada por Cupisti et al. (10) en donde encuentran niveles inferiores de citraturia en la orina de pacientes con litiasis recurrente en relación con pacientes con litiasis monoepisódica.

CONCLUSIONES

Los trastornos metabólicos discriminantes entre los grupos de pacientes litiásicos monoepisódicos y recurrentes fueron la hipercalciuria y el pH de orina con tendencia alcalina. Los subtipos de hipercalciuria, renal y resortiva, a su vez fueron trastornos discriminantes pero no lo fue la hipercalciuria de subtipo absorbiva. Teniendo en cuenta el sexo de los pacientes, en las mujeres fue significativamente más frecuente la hipercalciuria de subtipo renal pero, sin embargo, el volumen de orina fue significativamente inferior en las mujeres recurrentes que monoepisódicas. Los presencia de antecedentes familiares de urolitiasis en los pacientes litiásicos no tuvo carácter pronóstico en la evolución de su enfermedad. En el grupo de pacientes con litiasis recurrente, la existencia de niveles altos de calcio en la orina fue el factor más determinante respecto al grupo de pacientes con litiasis monoepisódica. La edad de comienzo de la enfermedad litiásica fue significativamente inferior en los pacientes con varios episodios litiásicos que aquellos con un episodio único.

Los pacientes litiásicos con niveles elevados de calcio en la orina o/y un pH urinario con tendencia alcalina constituyen un grupo especial de alto riesgo de recurrencia. Estos pacientes precisan de una vigilancia clínica frecuente y permanente. La profilaxis médica tendrá como objetivo la reducción de la calciuria o/y pH urinario hasta niveles de normalidad. Las medidas simples de corrección de los hábitos dietéticos y el incremento de la ingesta acuosa pueden ser insuficientes para el control de la recidiva en estos pacientes y, por tanto, se recurrirá a la administración de fármacos siempre que sea preciso para normalizar el nivel de calciuria y pH urinario.

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RECENT KNOWLEDGE ON BCG'S MECHANISM OF ACTION IN THE TREATMENT OF SUPERFICIAL BLADDER CANCER

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ABSTRACT

Intravesical Bacillus Calmette-Guérin (BCG) against superficial bladder carcinoma recurrences is regarded as the most successful immunotherapy to date. However, the mode of action has not been fully elucidated yet. The aim of this review is to provide a conclusive overview on this complex field and to give detailed information on several aspects of relevance for the understanding of the involved immune mechanisms.

The BCG-induced inflammation after intravesical immunotherapy in patients obviously differs from non-specific inflammation by its quality and its subclinical duration. The pronounced infiltration of the bladder wall by immunocompetent cells together with the secretion of cytokines into the urine point toward the intense local immune activation after BCG. In-vitro models of BCG-induced cytotoxicity have shown powerful and selective effector mechanisms. Orthotopic animal models gave valuable information, confirming and extending ex-vivo and in-vitro data. These approaches led to a hypothesis of BCG-induced tumor control, which will be the platform for further improvements of this highly effective anticancer immunotherapy.

Key words: BCG, bladder neoplasms, immunotherapy, mycobacterium bovis, mechanism
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INTRODUCTION

In 1976, Morales, Eidinger & Bruce were the first to report on successful treatment of superficial bladder cancer (SBC) with BCG (1). Since then, BCG became the treatment of choice for high-risk superficial bladder cancer in most countries of the world and is given at an annual rate of approximately 1 million. Intravesical BCG therapy is regarded as the most successful immunotherapy to date (2,3) and not only is superior to intravesical chemotherapy with regard to the recurrence rate of SBC (4-6) but also beneficially acts on the progression rate of this tumor (7-9) and, obviously, also positively influences survival in high-risk patients (8,9).

Ever since the immuno-activating properties of BCG were discovered, investigations have been carried out to ascertain the functional mechanism. All investigations to date have shown that not one single functional mechanism, but a whole series of immu-

nological phenomena are involved. For this reason, the following contribution is only able to provide an overview of the most important findings from this interesting area of research.

GENETIC BACKGROUND OF BCG

What is BCG? The life attenuated *Bacillus Calmette-Guérin* (BCG) vaccine for the prevention of disease associated with *mycobacterium tuberculosis* was derived from the closely related virulent tubercle bacillus *mycobacterium bovis* (10). Although the BCG vaccine has been one of the most widely used vaccines in the world for over 40 years, the genetic basis of BCG attenuation had never been elucidated. The current vaccine was originally developed by Calmette and Guérin who passaged a strain of *M. bovis* 230 times in vitro between 1908 and 1921. The resulting vaccine was thought to have struck a balance between reduced virulence and preserved im-

munogenicity. However, because of the inability to preserve viable bacteria (such as by freezing), this live vaccine required continued passage, eventually resulting in a profusion of phenotypically different daughter strains that are collectively known as BCG. By the time lyophilized seed lots of BCG vaccines were created in the 1960s, these vaccines had been separately propagated through about 1,000 additional passages (depending on the daughter strain), usually under the very conditions that effected the original attenuation. To better understand the differences between *M. tuberculosis*, *M. bovis* and the various BCG daughter strains their genomic compositions were

Table 1 – Genetic information about distribution of deletions (RD) in virulent *M. bovis* and BCG strains. Parentheses after *M. bovis* indicate how many strains of virulent *M. bovis* are missing the genetic element (modified after reference 11).

Deletion Region	Strains where Missing
RD1	All BCG strains
RD2	BCG-strains: -Danish, -Prague, -Glaxo, -Frappier, -Connaught, -Phipps, -Tice, -Pasteur
RD3	<i>M. bovis</i> (3/8)
RD4	<i>M. bovis</i> (8/8)
RD5	<i>M. bovis</i> (8/8)
RD6	<i>M. bovis</i> (8/8)
RD7	<i>M. bovis</i> (8/8)
RD8	BCG-Frappier, BCG-Connaught
RD9	<i>M. bovis</i> (8/8)
RD10	<i>M. bovis</i> (8/8)
RD11	<i>M. bovis</i> (8/8)
RD12	<i>M. bovis</i> (8/8)
RD13	<i>M. bovis</i> (4/8)
RD14	BCG Pasteur
RD15	<i>M. bovis</i> (8/8)
RD16	BCG-Moreau

studied recently by performing comparative hybridization experiments on a DNA microarray (11). By this method 11 regions of a virulent *M. tuberculosis* strain were found that were absent from one or more virulent strains of *M. bovis*. Five additional regions representing 38 open reading frames were present in *M. bovis*, but absent from some or all BCG strains. This was seen as evidence for the ongoing evolution of BCG strains since their original derivation. Furthermore, contemporary BCG vaccines were compared to their progenitor strain. Because this strain was lost during World War I, the origin of current BCG vaccines could only be inferred through an evolutionary approach. Behr et al. (11) curated a collection of BCG daughter strains representing this global dissemination for the purpose of performing genomic comparisons. Altogether 16 regions were found as deleted in BCG strains as compared to virulent TBC. Of the 16 deletion regions, nine are missing from BCG and all virulent *M. bovis* strains tested, two are missing from BCG and some of the strains of *M. bovis*, one is missing from all BCG strains, and four are missing only from certain BCG strains (Table-1).

To further address the differences specific to BCG the authors assumed that regions of a virulent TBC present in *M. bovis* strains and absent only from BCG were deleted during the derivation and maintenance of BCG vaccines in various vaccine facilities around the world. If this was true, then regions of *M. bovis* missing from BCG strains would indicate unidirectional genetic events from which the phylogeny of BCG strains can be inferred. Because some BCG daughter strains were obtained directly from the Institute Pasteur while other strains were derived from another vaccine facility, it was possible to reconstruct the genealogy of BCG strains and determine when and where BCG specific deletions occurred (Figure-1). In comparison with *M. bovis*, all BCG vaccines lack one region (RD1) that presumably was lost during the 1908-1921 attenuation (10). Another deletion (RD2) occurred at the Institute Pasteur between 1927 and 1931. A further deletion (RD14) specific to BCG-Pasteur indicates an event in 1938, and before the lyophilization of BCG Pasteur 1173 in 1961. The losses of RD8 in Montreal (between

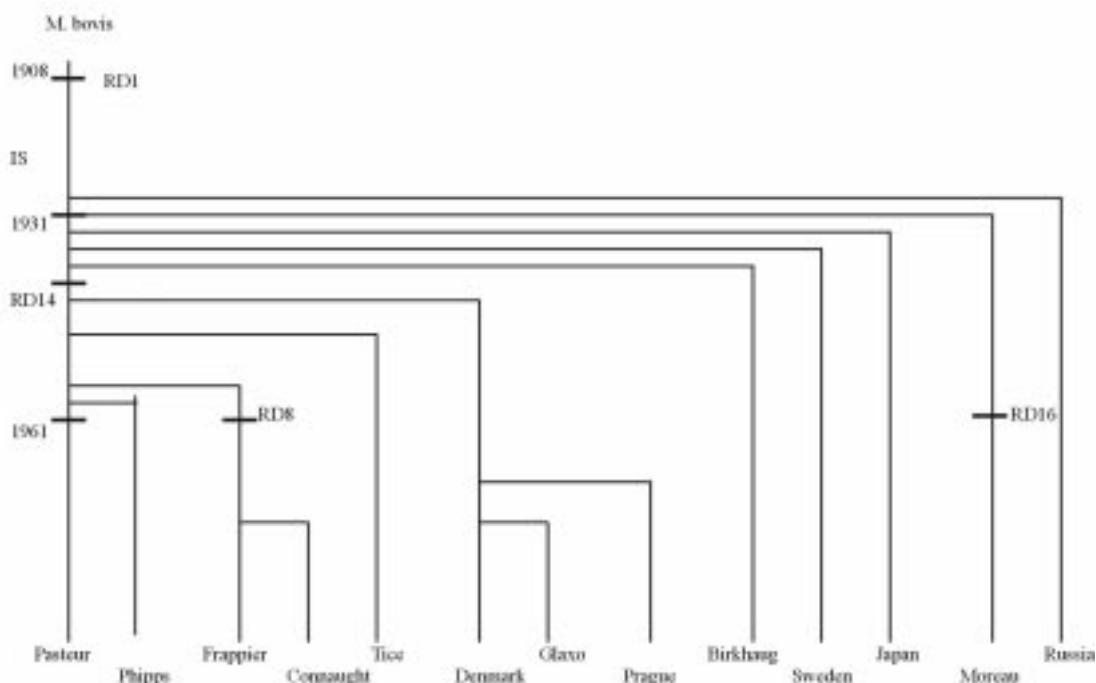


Figure 1 – Genetic genealogy of BCG (modified after reference 11). RD: region of genetic deletion; IS: insertion element.

1937 and 1948) and RD16 in Uruguay or Brazil (after 1925) indicate that ongoing evolution of BCG strains was not confined to Institute Pasteur. A historical review of the BCG literature revealed reports of decreasing virulence in the Institute Pasteur at various times, consistent with the documented ongoing evolution (11).

Thus, BCG significantly differs from *M. bovis*, from which it was originally derived. Attenuation led to the elimination of most virulence genes, which made BCG a famous vaccine against tuberculosis and a well-known immunostimulant with a very advantageous risk-to-benefit ratio.

ANIMAL EXPERIMENTS: BACKGROUND AND DEVELOPMENT

Old et al. were able to observe the inhibition of growth of implanted sarcomas, carcinomas and ascites tumors in mice following pre-treatment with BCG (12). The systematic work of Zbar et al. at the National Cancer Institute, USA, was of vital importance to the further development of BCG applications in oncology (13-17). Using the model of a guinea pig

hepatocarcinoma, Zbar et al. were able to demonstrate that administration of tumor cells with BCG leads to a significant inhibition of tumor growth. Intralesional injections of BCG led to involution of tumors already formed, and also of the lymph node metastases. Furthermore, animals that had become tumor-free after treatment with BCG had developed immunity to the hepatocarcinoma, as re-administration of tumor cells led to no further tumor growth.

From their investigations, Zbar et al. have devised basic rules for the optimum immunotherapy of tumors with BCG (14-17): 1)- localized tumors respond to BCG immunotherapy better than generalized tumors; 2)- the tumor mass must be as small as possible before commencement of immunotherapy; 3)- a direct contact of long duration between the tumor cells and the BCG should be ensured; 4)- in the animal experimental models tested, the optimum effective dose of BCG for local or intratumoral application was 10^6 - 10^8 colony forming units (CFU).

Similar favorable results were reported by Baldwin & Pimm on rat sarcomas (18) and by Bartlett et al. (19,20) on spontaneously originating

or carcinogenically induced murine tumors. The growth-inhibiting effect of the BCG treatment of mice, rat and guinea pig tumors has been observed in numerous other investigations. In many cases, systemic pre-treatment (prophylaxis) was already found to lead to a significant inhibition of tumor growth. Sparks et al. were able to demonstrate that an intralesional BCG injection before surgical removal of the spontaneously originating metastasizing mammary adenocarcinoma in rats not only significantly extended the median survival time, but that a significant number of animals remained tumor-free over the long term (21). Therefore, after primary therapy of the tumor had been carried out, BCG therapy was able to eliminate the occult minimal residual tumor ("minimal residual disease").

From these investigations, it was concluded that high doses (10^6 - 10^8 CFU) of living BCG microbes were necessary to produce an anti-tumor effect. Differences between the various BCG strains were found in some studies, but it was not possible to determine conclusively whether the different therapy results in animal experiments were attributable to this (22,23).

INTRAVESICAL IMMUNOTHERAPY IN THE RODENT BLADDER MODEL

Using the orthotopic bladder carcinoma model in mice, Ratliff et al. could significantly contribute to the explanation of the mode of action of intravesical immunotherapy. By means of implantation of syngeneic bladder carcinoma cells into the bladders of normal, immunocompetent mice, these authors examined an animal model which was very close to reality and which was highly relevant for intravesical therapy. These authors were able to establish the significance of fibronectin for the adhesion of BCG to the bladder wall (24-28) Ratliff et al. initially conducted investigations into the binding of BCG to various surfaces. They were able to show that BCG adheres *in vitro* almost selectively to fibronectin-coated wells. This binding could be inhibited using fibronectin antibodies, and also by soluble fibronectin (26,27). No differences were seen when comparing various commercially available BCG preparations (26). Furthermore, the authors were able

to establish in animal experiments (24) that BCG is retained in the mouse bladder after instillation only if the bladder wall had been damaged by either physical or chemical means before instillation. This binding could be inhibited by soluble fibronectin or anti-fibronectin antibodies. Moreover, it was evident that after inhibition of BCG binding, the typical delayed-type hypersensitivity (DTH) reaction did not occur and that no anti-tumoral activity was generated. From these investigations, it was possible to conclude that, at least in animal experiments, fibronectin is essential for the binding of BCG to the bladder wall.

Guinan et al. established a quantitative difference in the cellular infiltrate of the urinary bladder wall after intravesical instillation of thiotepa and BCG (29). They postulated a T-cell dependent functional mechanism, which Ratliff et al. were able to prove. Athymic nude mice who did not form T-cells were not able to generate a BCG-induced tumor defense, which then became possible after the transfer of homologous T-cells (30).

These results were further confirmed in an animal model by Ratliff et al. who showed, using immunocompetent mice, that the depletion of both CD4⁺ (T-helper) cells and CD8⁺ (T-suppressor) cells completely inhibited the BCG-induced anti-tumoral effect on implanted bladder tumor cells (31). In this system, CD4⁺ and CD8⁺ cells appeared to be necessary for producing a DTH immune response.

INVESTIGATIONS IN HUMANS: EX-VIVO

While it was initially suspected that a non-specific effect within the context of an eroding cystitis provided a therapeutic momentum for the effect of BCG (32) most authors nowadays agree to an involvement of the immune system. In our systematic investigations on patients treated with BCG we were able to demonstrate the local immune response in the bladder by immunohistological analysis of the infiltrating cellular subpopulations (33) and of local cytokines determined directly in the bladder wall (34), as well as by examining the patients' urine with regard to cytokine secretion (35). In this way, we characterized both the acute and also the long-term

persisting local immune response of patients to the intravesical immunotherapy.

Immunohistology

Biopsies from the bladder wall before and after BCG were analyzed by means of immunohistology by several groups (29,36-47).

To give an insight into the development of the local inflammatory response against BCG, data from our analyses are given here. During routine follow-up, "cold-cup" biopsies were obtained before instillation and immediately after the sixth instillation, and then at three-monthly intervals. Before therapy, such biopsies showed relatively few mononuclear cells in the bladder. The local ratio of T-helper/T-suppressor cells in the bladder wall before the start of therapy was about 1:2. After the sixth instillation of BCG, a massive inflammatory reaction of the entire bladder wall ensued. In all biopsies, aggregates of immunocompetent cells which had developed under the treatment could be detected, corresponding with the so-called BCG-induced granulomas (41,48) (Figure-2)

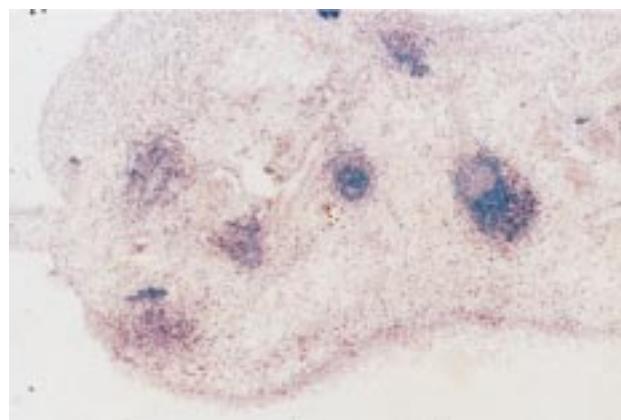


Figure 2 – Biopsy of a urinary bladder 3 months after intravesical BCG therapy. Typical picture with several suburothelial BCG-induced granulomas visible.

These follicle-like structures were found almost exclusively in the highly vascularized submucosa. The infiltrate of mononuclear cells in the bladder wall consisted mainly of T-cells after completion of the intravesical BCG therapy, with a distinct predominance of CD4⁺ (so-called T-helper/inducer) cells compared with CD8⁺ (so-called T-suppressor/

cytotoxicity) cells in the granuloma (Figure-3). The ratio of CD4⁺/CD8⁺ T-cells detectable in the submucosa was 2:1, which represents a reversal of the original ratio found in the normal bladder. The immunohistological characteristics remained unchanged through later examinations at 6, 9 and 12 months after start of therapy.

These investigations point to a stimulation of the local immune system in the bladder which differs significantly from non-specific cystitis in terms of its duration and also in qualitative terms: while in the case of non-specific cystitis, or even of cystitis induced by cytostatic drugs, a mainly granulocytic infiltration is found, an almost exclusive increase in mononuclear, immunocompetent cells (lymphocytes and macrophages) was found after BCG treatment. Increased number of immunocompetent mononuclear cells could be detected to express so-called activation markers (IL-2-R and HLA-DR). This infiltrate of activated cells persists for at least 12 months, mainly in suburothelial granulomas.

The numbers of infiltrating mononuclear cells into the bladder wall was also measured by Honda et al. (49), who found lymphocytes and $\gamma\delta$ cells significantly increased after treatment compared with numbers before treatment (although the correlation with regard to $\gamma\delta$ cells was not statistically significant). The localization of pro-inflammatory cytokines was measured by immunohistology (50). Among the few patients studied no single cytokine or cytokine profile was associated with clinical response to BCG therapy. Bladder-wash derived lymphocytes were studied by Bruno et al. (51). The addition of BCG on bladder-wash derived lymphocytes expanded in-vitro enhanced their proliferation suggesting that this population was sensitized against BCG. This hypothesis was confirmed by analysis of T cell receptor restriction patterns showing that bladder lymphocytes from patients under BCG were oligoclonal. Bladder-wash derived lymphocytes were also analyzed by the group from Esuvaranathan (52). They found an increasing trend in the percentage of CD 3⁺ T cells with each weekly intravesical instillation and the proportion of CD 3⁺ T cells expressing the $\gamma\delta$ T cell receptor was significantly higher in patients receiving standard dose BCG than those receiving low dose BCG.

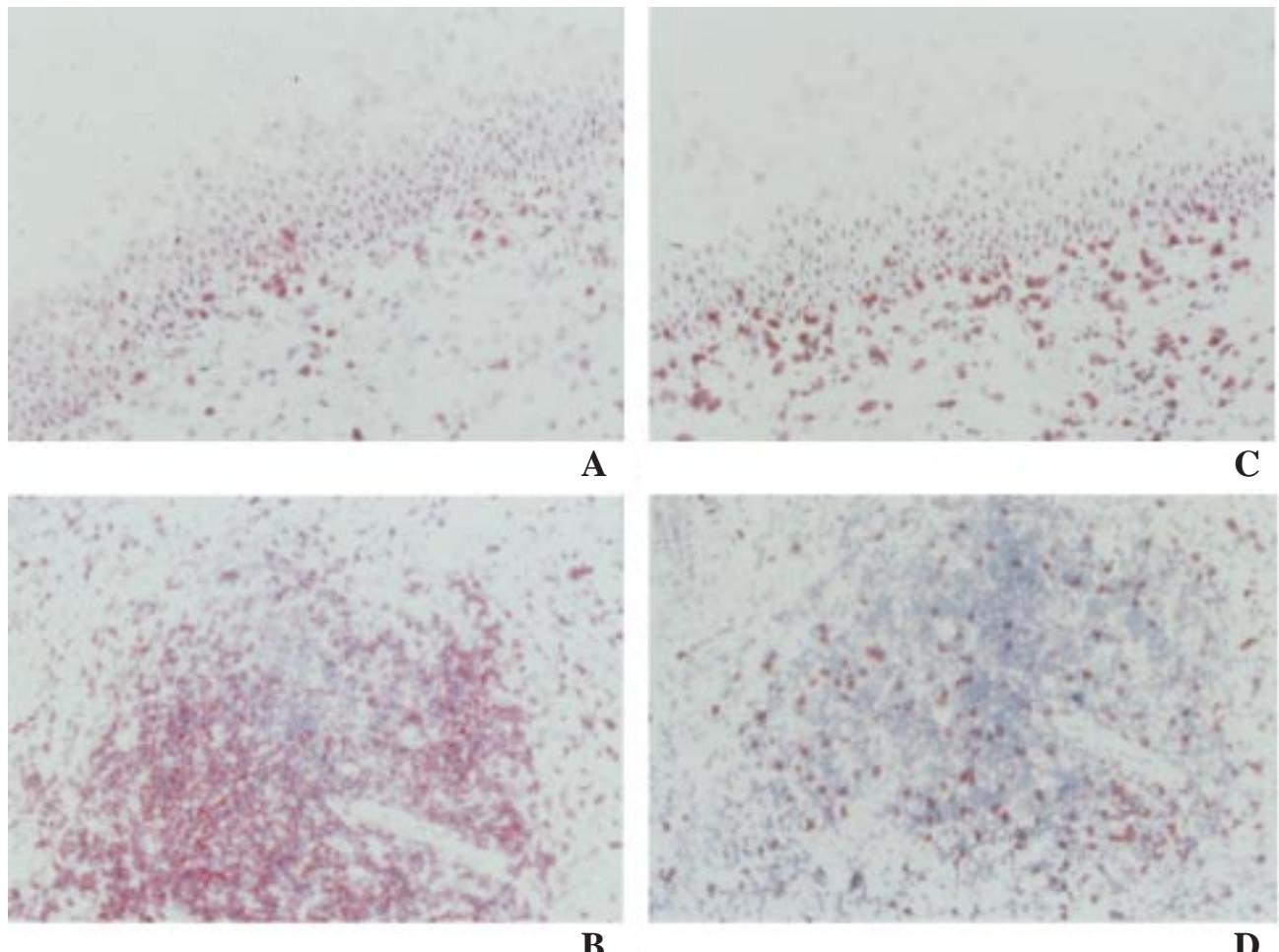


Figure 3 – Dynamics of the immune reaction after BCG. Biopsies of a normal urinary bladder (upper row) compared to biopsies from BCG-treated bladders (lower row). A and B, staining against CD4⁺ T-helper cells; C and D, staining against CD8⁺ T-suppressor/cytotoxic cells. Before therapy, only relatively few immunocompetent cells (A,C) are visible. After BCG, abundant mononuclear cells are visible within granulomas (B,D), with a clear predominance of T-helper cells (B) as compared to T-suppressor/cytotoxic cells (D).

Cytokine Secretion into the Urine

Further investigations to determine the secretion of cytokines into the urine were performed from others and from our group (35,53-57). Within 24 hours after BCG instillation, considerable quantities of inflammatory cytokines such as interleukin (IL-1), interleukin-2 (IL-2) and tumor necrosis factor (TNF) were found in the urine(35). The cytokine titers in the urine differed considerably from one patient to another after BCG instillation - both with regard to the temporal maximum and the total level of 24-hour secretions. Significantly elevated values were detected only 2 hours after the instillation of BCG, with a maximum

after 2-8 hours. The elevated titers returned to normal within 24-hours. In the control group, consisting of patients with non-specific cystitis, only minute amounts of cytokines could be detected in the urine of individual patients. Comparison of the 2 groups showed a highly significant difference between the BCG group and the control group. These investigations confirmed the results of others with regard to IL-2 secretion (58) and furthermore described for the first time the secretion of IL-1- β and TNF into the urine of patients after BCG treatment. The presence of IL-1 in the urine of healthy and febrile subjects has already been demonstrated (35,59). However, the secretion of IL-2 and TNF fol-

lowing BCG treatment represents a qualitatively and quantitatively very different reaction compared with non-specific cystitis. Neither IL-2 (58,60) nor TNF have been found in the urine of healthy individuals and IL-2 has been detected in the urine of patients with non-specific cystitis in minute amounts only. IL-2 is mainly produced by activated T-helper cells. It acts specifically in the proliferation and differentiation of T-lymphocytes. Its effect on tumor cells is mainly based on the generation of lymphokine-activating killer cells (LAK cells). TNF- α is mainly formed by activated macrophages (61,62) and, alongside other effects, possesses both a direct cytotoxic effect on tumor cells as well as an inhibitory effect on the vascularization of tumors, imposing macroscopically as a hemorrhagic necrosis (12).

A special attention was paid by some groups to interleukin-8 (IL-8) due to its rapid onset in the immune response to intravesical BCG (57,63). Due to its appearance already after the first instillation and its stability, IL-8 seemed an attractive candidate for investigation of its prognostic value for clinical response to BCG. However, in analyzing the predictive potency of IL-8 Rabinowitz et al. (64) found no association between the direction of change in interleukin-8/creatinine ratio and response to intravesical BCG making this cytokine probably not an useful marker for predicting the response to BCG.

Analysis of Peripheral Blood Parameters

Few groups have looked at the antibody response against BCG or against defined mycobacterial antigens after BCG intravesical therapy with regard to systemic immune activation and the possible inherent specificity of this immune response (65-69). In an early study, van der Sloot et al. have characterized the antibody response in the urine and peripheral blood after BCG (66,70).

Zlotta et al. looked into the proliferative T cell response to mycobacterial antigens of bladder carcinoma patients before any treatment to detect possible cross-reactivity between mycobacterial antigens and tumors (71). They showed that patients with superficial bladder carcinoma demonstrated an increased lymphoproliferation against mycobacterial antigens before intravesical BCG as compared to control subjects, suggesting indeed a possible existence

of bladder carcinoma antigens cross-reactive with mycobacterial antigens (67-69). Furthermore, the serum antibody response against several heat shock proteins was analyzed in patients receiving BCG (68) showing indeed an antibody response against various heat shock proteins.

A very interesting way of predicting the response to BCG was found by Kempfer et al. from Israel (72). These authors analyzed the induction of interleukin-2 and interferon- γ mRNA in peripheral blood mononuclear cells during BCG treatment. They could show that independent of tumor type, induction of interleukin-2 mRNA was observed for patients who responded with remission, but not for those who relapsed ($p = 0,0001$). Multivariate logistic analysis showed that inducibility of IL-2 mRNA was the discriminating parameter, which yielded a predictive value of 97 % for remission.

The relevance of all these phenomena with regard to the anti-tumoral efficacy of BCG was not clarified until further, in vitro investigations had been carried out, which gave a complex picture on the mode of action of BCG.

IN VITRO INVESTIGATIONS

The ex-vivo investigations described above have resulted in a substantial qualitative and quantitative characterization of the local immune response to intravesical BCG therapy in humans. This reaction represents a complex immune response of the body to the local BCG instillation. Further analysis of these phenomena as possible effector mechanisms against bladder tumors required dissection of the immune response into several individual events, and it was necessary to investigate these events in vitro independently of one another (73).

The Direct Cytotoxic Activity of BCG

In order to rule out the possibility that BCG, as in the case of cytostatic drugs, acts purely as a cytotoxic agent, the direct cytotoxic activity of BCG towards bladder tumor cells was investigated (73,74): co-incubation of increasing concentrations of BCG with several target cell lines showed no significant cytotoxicity. Thus, under the known clin-

cal conditions, a direct cytotoxic effect of BCG on bladder tumor cells can be ruled out as a major functional principle.

Humoral Mechanisms

A further possible mechanism was addressed by Popas et al. (75), who suggested that BCG might activate anti-angiogenic pathways. The group collected urine samples and determined the urinary output of anti-angiogenic IP10 and interferon-gamma during 12 post-treatment hours. In all cases, significant titers of these chemo- and monokines were detected. The in-vitro response to stimulation of human transitional and endothelial cells with BCG or interferon confirmed these data. The results suggested that anti-angiogenesis might indeed be a further factor of BCG's mode of action. The next step downwards was analyzed by a Swedish group (76). As cytokines may induce nitric oxide (NO) by the enzyme nitric oxide synthase (NOS) and as NO exerts cytotoxic effects in tumor cells, this mechanism was further analyzed with regard to BCG. Induction of NOS activity in the human urinary bladder after BCG treatment was determined and the presence of NOS was localized in urothelial cells by immunohistochemistry. NO was shown to exert cytotoxic effects on bladder cancer cells. Therefore, NO might be involved in cytotoxicity induced by BCG.

Cellular Mechanisms Involved in BCG Immunotherapy

Unstimulated mononuclear cells. Immuno-competent cells can be found in the bladder wall even before BCG instillation - albeit in considerably smaller numbers. In order to clarify the extent to which these non-stimulated immune cells (whose cytotoxicity resides mainly in the natural killer (NK) cell fraction) are able to kill urothelial carcinoma cells, the cytotoxicity of these cells was investigated (77,78): all five urothelial carcinoma cell lines tested were virtually resistant. These findings also underline the value of results obtained from cell lines for the *in vivo* situation in humans resistant to unstimulated NK cells. The cell line used as a control, the erythroleukaemia cell line K562, known to

be NK-sensitive, showed a distinct sensitivity in the same experiment. Not only those bladder tumor cell lines quoted, but also short-term cultures of newly resected papillary bladder tumors showed the same resistance to non-activated immune cells (79), which is an indication of the inability of the immune system without adequate stimulation to control a tumor once it has become established.

Lymphokine-Activated Killer Cells (LAK Cells)

Through co-incubation with IL-2, immune cells can be stimulated to produce so-called lymphokine-activated killer (LAK) cell cytotoxicity. As IL-2 could be detected in the urine as well as in the bladder wall after BCG treatment, it appeared possible that these killer cells were generated. For this reason, the cytotoxicity of LAK cells towards bladder tumor cells was tested. The results of these investigations showed that a marked cytotoxicity towards bladder tumor cells could be induced by IL-2 and IFN- γ (77,80). This mechanism can therefore be considered as a possible functional principle for intravesical immunotherapy using BCG.

BCG-Activated Killer Cells (BAK Cells)

In order to demonstrate further BCG-induced effects on immunocompetent cells, activation by BCG itself was tested (74,81): after pre-incubation of immune cells with BCG over several days, it was possible to induce a considerable degree of cytotoxicity to all bladder tumor cell lines tested so far (82). We named this apparently autonomous BCG-activated killer cell phenomenon "BAK" cytotoxicity. Further experiments showed that only living BCG bacteria were able to induce BAK cells, whereas dead bacteria or cell-free fragments were ineffective - corresponding to the situation *in vivo*. Also, a dose and time optimum was determined for BCG efficacy *in vitro*.

Characterization of BAK Cells

Further characterization of the effector cells was the next step taken in our investigations (82,83). The cytotoxicity of LAK cells shows a well-known maximum after 2-3 days of stimulation with IL-2

(84), while BAK-cell cytotoxicity continued to increase to day seven. In contrast to LAK cells, BAK cells could not be generated from CD4⁺- and CD8⁺-depleted cell populations. Because of these and other differences, it was concluded that BAK cells represent a different cell population and are activated via a different route than LAK cells. Experiments followed in which this unique cytotoxic BAK effector cell was further characterized: we were able to demonstrate that neither macrophages nor CD4⁺ T-cells come into question as effector cells, but that cells expressing CD8⁺ and CD56⁺ antigens on their surface are responsible for this BCG-induced cytotoxicity. The induction of BAK cytotoxicity, on the other hand, is apparently very complex, as all detectable mononuclear subpopulations, also those in the bladder wall, play a part: both the depletion of CD4⁺ and CD8⁺ cells and the depletion of macrophages prevents, concentration dependent, the generation of BAK cells (85).

To understand BCG-induced activation of effector lymphocytes more precisely we investigated the lytic pathways of human BAK cells and compared BAK cell cytotoxicity with LAK cell cytotoxicity (86). Perforin and Fas Ligand (FasL) are the major cytolytic molecules of cytotoxic lymphocytes. Our results demonstrate that BAK- and LAK cells showed an increased expression of perforin and FasL as compared to unstimulated controls. Killing of T-24 bladder tumor cells by BAK and LAK cells was predominantly mediated via perforin as demonstrated by a drastically reduced lysis in the presence of specific inhibitors. In contrast, lysis and membrane disintegration of target cells by BAK and LAK cells could not be blocked with an inhibitory anti-FasL antibody. We concluded that cellular mediators of BCG effector mechanisms, such as BAK and LAK cells, kill their targets via perforin and independent of the FasL-pathway. This has potential clinical relevance as BCG-therapy would not be impaired by FasL-resistance of target cells, which recently has been described for some tumors. As perforin is the cytotoxic effector molecule typically used by Natural Killer (NK) cells, these data suggested involvement of these effector cells in the mode of action of BCG. We further elucidated the

role of NK cells in BCG-induced cellular cytotoxicity (87): Magnetic depletion experiments and fluorescence-activated cell sorting revealed that NK cells were the major effector cell population in vitro, indeed. To confirm the role of NK cells in vivo we studied a syngeneic orthotopic murine bladder cancer model and compared BCG-immunotherapy in C57BL6 wild-type mice, NK-deficient beige mice and mice treated with anti-NK1.1 monoclonal antibody targeting NK cells. Four weekly instillations of viable, commercially available BCG significantly prolonged survival in wild-type mice with bladder cancer as compared to control mice treated with solvent alone. In contrast, BCG-therapy was completely ineffective in NK-deficient beige mice, and mice treated with anti-NK1.1 monoclonal antibody. Altogether, these findings suggested a key role for NK cells during BCG-immunotherapy.

CONCLUSION

A complex local immune response involving humoral and cellular immune mechanisms is induced by BCG in the human bladder (Figure-4). Long-term follow-up examinations showed a predominance of the T-helper/inducer cell population and the persistence of inflammatory (Th1-type) cytokines within

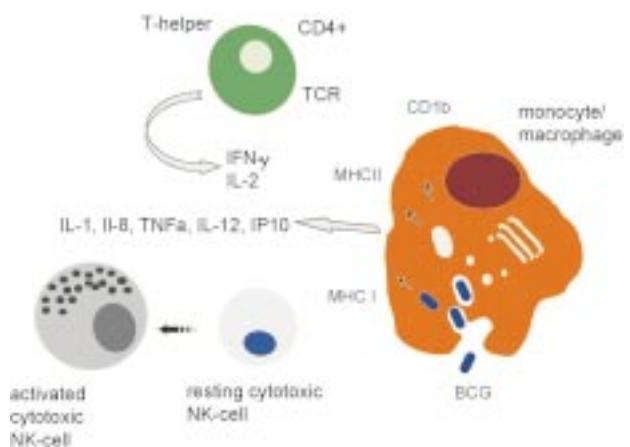


Figure 4 – Hypothesis of the mode of action of BCG against bladder carcinoma: Supported by CD4⁺ T-helper cells, BCG mycobacteria induce a Th1-polarized cytokine secretion in macrophages/macrophages. These cytokines activate resting Natural Killer (NK) cells, which kill their malignant target via perforin.

the bladder wall. These sub-clinical local inflammatory signs persist for a long time within the so-called BCG-induced granulomas, which might have an important role in the recurrence-free status of the patient. The function of this prolonged inflammation seems to provide immature effector cells with a continuous level of activating cytokines (such as IL-2, Ifn- γ , and Il-12). In vitro, at least two cellular cytotoxic effector mechanisms had been determined. Next to the well-known LAK-cell cytotoxicity, a further cytotoxic phenomenon could be characterized, which was termed "the BCG-activated killer (BAK) cell phenomenon". Recent investigations convincingly proved that the effector cells involved are activated NK cells, which are known to selectively kill malignant targets. Thus, the search for effector mechanisms involved in BCG immunotherapy has opened a new and exiting field.

An important clinical aspect of these investigations is to decipher which part of the complex immune response is involved in the killing of the tumor, and which parts contribute to the side-effects involved with BCG immunotherapy. Enhancing the former and suppressing the latter reaction would lead to an even more effective therapy.

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ATYPICAL SMALL GLANDS IN PROSTATE NEEDLE BIOPSIES. DIAGNOSTIC VALUE OF CLINICOPATHOLOGICAL PARAMETERS

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ABSTRACT

Background: The purpose of this study was to report our experience on prostate needle biopsy specimens that contained foci of atypical suspected acini but not diagnosed for malignancy.

Material and Methods: We reviewed all the prostate needle biopsies performed at our institution between January 1988 and June 1999. Cases diagnosed as atypical with suspected malignancy and without previous histopathological diagnosis of prostate carcinoma were re-evaluated and several clinicopathological data were assessed. A comparison was made between eventually malignant and benign groups. For all cases the histological diagnostic suspicion was separated into 3 groups (probably benign; uncertain; probably malignant).

Results: 39 (2.89%) patients showed foci of atypical small acinar proliferation (ASAP). On review, 19 cases were found to have an adequate follow-up. Of these, 10 (52.63%) were later found to have adenocarcinoma, with a mean Gleason score of 6.28. Forty-two percent of cases with uncertain diagnosis and 63.6% from the probably malignant group were carcinomas. Proteinaceous eosinophilic secretions ($p = 0.006$) and acute inflammation ($p = 0.02$) were more frequent in patients with subsequent benign biopsies. Follow-up low PSA value was significantly associated with a benign outcome ($p = 0.04$).

Conclusions: The right clinical attitude after a diagnosis of ASAP must be careful patient follow-up considering the repetition of biopsy after few months.

Key words: prostate, atypia, needle biopsy, adenocarcinoma, hyperplasia, prostatic intraepithelial neoplasia (PIN)
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INTRODUCTION

The number of prostate needle biopsies has remarkably increased during the last few years. This increase is mainly explained by the development of screening programs for prostate cancer based on serum prostate-specific antigen. The use of thinner gauge needles to obtain biopsy specimens achieves smaller tissue cores than formerly, and makes it relatively common to see problematic lesions such as some acini containing atypical architectural or cytological features that represent a diagnostic challenge for the pathologist, because either the number of glands is small, or these are placed at the edge of the core and have artifacts that obscure the nuclei, or the degree of architectural atypia

is not concordant with the cytological one (1-6). For all cases that do not fulfil all of the diagnostic features of adenocarcinoma, the acronym ASAP (Atypical Small Acinar Proliferation) has been applied (2-7). This entity includes 1.5-10% of all prostate needle biopsies in the different series reported (1-9). The aim of this study was to report our experience on this issue at a general hospital, and to correlate the clinicopathological findings in these patients with their following evolution.

MATERIALS AND METHODS

We reviewed the prostate needle biopsies carried out at the POVISA Medical Center (Vigo, Spain) for all patients diagnosed as having "atypical

Table 1 – Clinicopathological data from patients with ASAP.

	n = 38 Patients	Intensity (0-3)†
Age	71.94 years (53-86)	
Initial PSA (n = 28)	12.43 ng/ml (2.3-42)	
Follow-up PSA (n = 10)	9.45 ng/ml (2.29-23.4)	
Abnormal DRE (n = 33)	25 (75.7%)	
Number of cores	3.78 (2-6)	
Number of foci	1.36 (1-4)	
Number of glands per foci	15.69 (3-37)	
Fibrosis	3 (7.89%)	
Atrophy	17 (44.73%)	
High grade PIN	7 (18.42%)	
Nucleomegaly	35 (92.1%)	1.52
Nucleolomegaly	25 (65.78%)	1.05
Proteinaceous eosinophilic secretions	27 (71.05%)	1.07
Intraluminal mucin	8 (21.05%)	0.28
Crystalloids	6 (15.78%)	0.23
Amphophilic cytoplasm	29 (76.31%)	1.13
Acute inflammation	11 (28.94%)	0.39
Chronic inflammation	25 (65.78%)	1.13

DRE: digital rectal examination, †: when available

glands with suspected malignancy” between January 1988 and June 1999, and without previous histopathological diagnosis of prostatic adenocarcinoma. In each of these cases, several clinical features (age, digital rectal examination -DRE- before the first biopsy with ASAP, and initial serum prostate specific antigen -PSA-) and histopathological features related to prostatic adenocarcinoma (7) (number of cores, number of atypical foci, number of acini per focus, high grade prostatic intraepithelial neoplasia -PIN-, atrophy of the parenchyma, fibrosis, amphophilic cytoplasm, nucleomegaly, nucleolomegaly, luminal eosinophilic secretions, intraluminal mucin, crystalloids, acute inflammation and chronic inflammation) were reviewed. The latter eight histological data were quantified as follows: 0 = none present; 1 = mild; 2 = moderate; 3 = severe. Nuclear and nucleolar size was evaluated by comparison with adjacent benign glands.

For all cases the suspected diagnosis was separated into 3 groups (probably benign; uncertain; probably malignant) before knowing the patients progress, in order to correlate this evaluation with the final diagnosis.

Subsequent prostatic specimens were reviewed when available, and the interval from the first biopsy until said review, serum PSA and Gleason score when an adenocarcinoma existed were recorded. A comparison was made between patients who finally were or were not malignant. Statistical analysis was performed using a 2-tailed Fisher exact test for bimodal variables and a nonparametric Mann-Whitney U test for continuous variables.

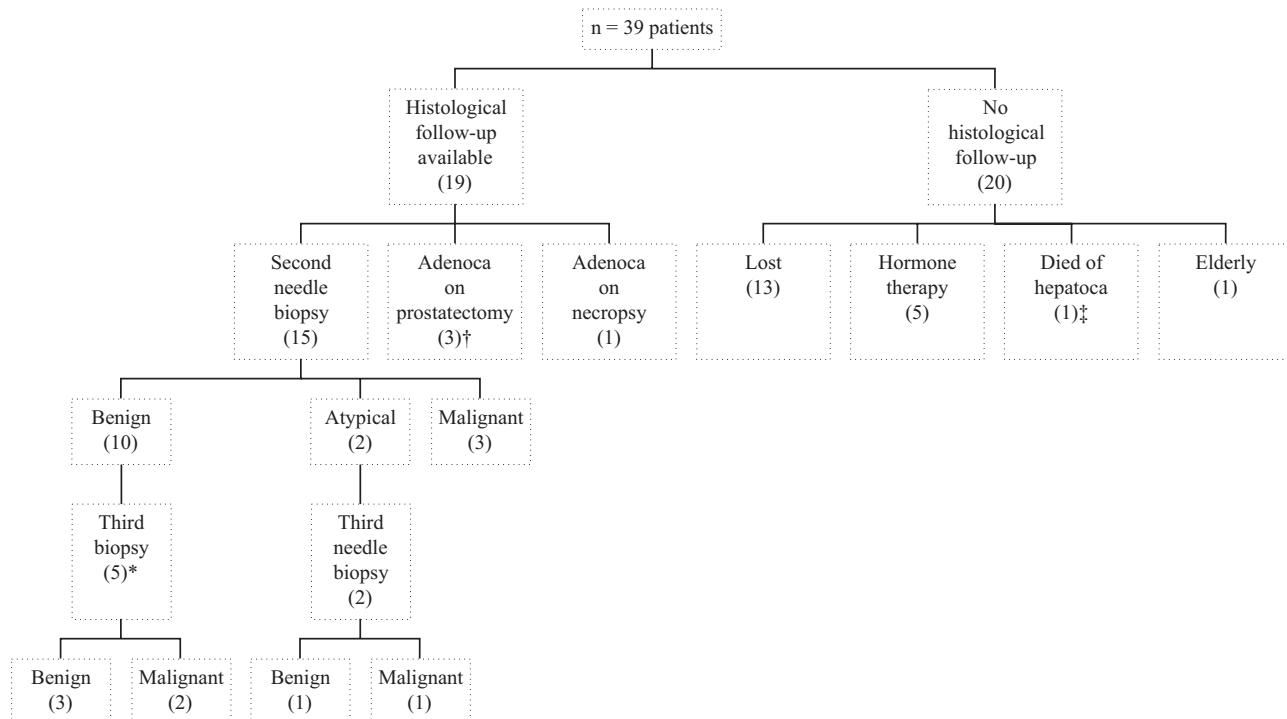
Immunohistochemistry was undertaken in cases where progress data and valid specimens were available using cytokeratin 34bE12 (DAKO; 1:50).

RESULTS

During the 10-year period that covers this review, 1,345 prostate needle biopsies were performed in our hospital, of which 48 (3.56%) were diagnosed as “atypical glands with suspected malignancy” (Figures 1 to 3). After review, 6 (12.5%) were reclassified as malignant (one had an ASAP focus and a contralateral adenocarcinoma), 2 (4.16%) were artifactual and the specimen could

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Table 2 – Progress data from patients with ASAP.



*: 3 transurethral resections and 2 needle biopsies; †: pathological stage pT3N0, pT3cN1 and pT3N1; ‡: necropsy not conceded

not be evaluated, and 1 (2.08%) was considered to be benign. The remaining 39 patients (2.89% of all prostate needle biopsies) had a mean age of 71.94 years (53-86). There were available histological specimens for 38 of the 39 patients, whose clinicopathological features are presented in Table-1.

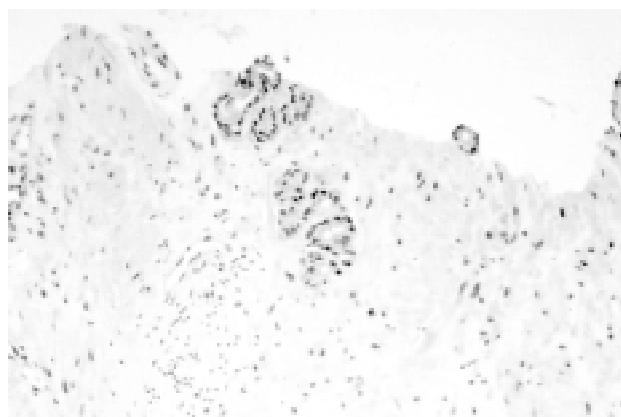


Figure 1 – Small focus of ASAP near the edge of a needle biopsy specimen (HE, X10).

From the 19 patients with available histological follow-up (Table-2), 10 (52.63%) were finally diagnosed as adenocarcinoma, with a mean Gleason sum of 6.28 (range: 4-9). Mean time between the first and second needle biopsy was 101.8 days (3-346), and between the second and third one were 200.8 days (10-474).

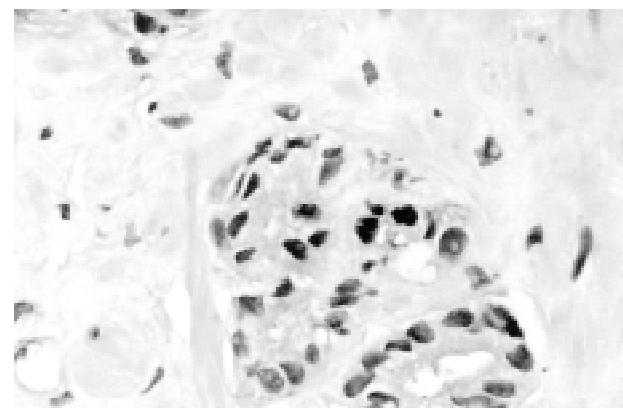


Figure 2 – Same specimen as Figure-1 showing uniform, small glands with increase in nuclear size and some nucleoli. The patient was finally diagnosed as adenocarcinoma (HE, X40).

Table 3 – Clinicopathological data from patients with ASAP (excluding ASAP + PIN), according to their final evolution.

	Benign (n = 8)	Malignant (n = 8)
Age	73 years	69.7 years
Initial PSA	‡9.6 ng/ml (3.1-21.8)	†11.29 ng/ml (3.79-25)
Follow-up PSA	‡7.81 ng/ml (2.29-17.3)	∅13.92 ng/ml (4.9-23.4)
Abnormal DRE	5 (62.5%)	*6 (85.71%)
Number of cores	4.5 (3-6)	*3.85 (3-5)
Number of foci	1.25 (1-2)	*1.28 (1-3)
Number of acini	14.5 (9-24)	*19.77 (10-37)
Nucleomegaly	8 (100%)	*7 (100%)
Nucleolomegaly	4 (50%)	*5 (71.42%)
Proteinaceous secretion	8 (100%)	*2 (28.57%)
Intraluminal mucin	2 (25%)	*1 (14.28%)
Crystalloids	1 (12.5%)	*1 (14.28%)
Amphophilic cytoplasm	6 (75%)	5 (71.42%)
Fibrosis	1 (12.5%)	*0
Atrophy	5 (62.5%)	*1 (14.28%)
Acute inflammation	4 (50%)	*0
Chronic inflammation	6 (75%)	*4 (57.14%)

PSA: prostate specific antigen; DRE: digital rectal examination

‡: n = 6; †: n = 5; ∅: n = 4; *: n = 7

A comparison was made between patients who finally were and were not malignant (Table-3). Lower follow-up PSA value ($p = 0.04$), proteinaceous secretion ($p = 0.006$) and acute inflammation ($p = 0.02$) were significantly more frequent in the benign group. No statistically significant differences were noted for the other variants.



Figure 3 – High magnification microphotograph with glands showing a greater variation in size and intraluminal eosinophilic secretions. The patient was finally diagnosed as non-malignant (HE, X40).

All cases were divided for review into 3 groups (probably malignant; uncertain; probably benign). After excluding the cases of ASAP + PIN, 7 cases were considered uncertain, 1 probably benign and 8 probably malignant. 3 cases from the first group (42.85%) and 5 from the third (62.5%) were adenocarcinomas. The patient considered as probably benign was finally diagnosed as not malignant.

Immunohistochemistry with 34βE12 cytokeratin was performed in the 19 cases with progress data available. 15 cases were negative, 10 being malignant (66.66%) and 5 (33.33%) non-malignant. 4 cases were positive for basal cells, all being non-malignant.

DISCUSSION

The term ASAP is an useful designation to classify lesions made up by a small number of acini that do not fulfil all the histological criteria of adenocarcinoma but that are worrisome because of their atypia, or for being located at the periphery of the core with crush artifact so that it is impossible to

evaluate nuclear characteristics (1-4,6). Nevertheless, histological or cytological findings are useless to reliably differentiate these lesions from a focal adenocarcinoma, and this decision must rely on the pathologists' criteria and experience. In fact, some authors believe that over 50% of ASAP are tangentially biopsied adenocarcinomas (1). None of our foci disappeared on step levels, another possible cause of ASAP diagnosis (2).

The diagnosis of atypical acinar proliferation, with suspected malignancy must be interpreted as the uncertain tumorous nature of the lesion. Histological data such as the existence of a florid inflammatory reaction or atrophic glands in the vicinity would make us think of a benign lesion, although malignancy should not be excluded. It is advisable to take a careful stand in order to avoid false malignant diagnosis. In our laboratory, a minimum of 9 sections of every core were studied, a seriation that we consider necessary to drastically reduce the chances of an incorrect diagnosis.

After review we excluded 9 from the 48 initial cases diagnosed as ASAP (6 considered to be adenocarcinomas, 2 artifacted and 1 benign). The reevaluation of some biopsies by the same observers who initially diagnosed them may be due to the improved definition of some concepts in prostatic pathology over the past years (3).

The degree of nuclear and nucleolar size increase was moderate and mild, respectively. 65.78% patients presented chronic and 28.94% acute inflammation in the parenchyma not related with foci of ASAP. Proteinaceous intraluminal secretions and acute inflammation were more frequent in patients who finally had a benign biopsy than in those who evolved to carcinoma (statistically significant differences). No significant differences were noted for the other histological variables.

In our series, 51.28% (20/39 cases) of patients with ASAP did not undergo a second biopsy, an average similar to other reports (1-4,6,10), so it would be reasonable to assume that we are not taking into account some patients with a high likelihood of having a tumor. It is noteworthy that 5 patients with an elevated serum PSA and abnormal DRE (3 elderly, 1 refused re-biopsy and 1 with bad health) were treated

with hormonal therapy and 3 were submitted to prostatectomy after diagnosis of ASAP without subsequent biopsies.

Ten patients (52.63%) were found to have adenocarcinoma, although only 3 were diagnosed on the second needle biopsy and 3 needed a third one. The average time interval between ASAP diagnosis and the second needle biopsy was 101.8 days, a short enough period to consider it unlikely that the tumor was not present at the time of the first biopsy. After excluding the 3 patients with ASAP foci and coexistent high-grade PIN from the group, 50% (8 cases) of patients finally underwent adenocarcinoma. In the largest series, 34-60% of patients with ASAP showed tumor (1-6,11-13), and 3-9 % were still atypical (1,2,11) on subsequent biopsies. The right clinical attitude after a diagnosis of ASAP must be patient follow-up with repetition of biopsy after some months (1,2,4,8,11,14). This could detect 90% of tumors after the second biopsy and 99% after the third one (1). It is important to emphasize that a benign biopsy after ASAP does not exclude tumor: in our series, 2 patients with this evolution showed carcinoma on the third biopsy. We found that the follow-up PSA value was lower in men with subsequently benign biopsies than in those who were malignant (7.81 vs. 13.92 ng/ml, p = 0.04), so its measurement may be useful for the follow-up of these patients.

Immunohistochemistry using cytokeratin 34 β E12 may assist in placing ASAP into benign or malignant categories (15), above all when a positive stain exists, because it nearly definitely facilitates a diagnosis of non-malignancy. Its negativity does not exclude this same diagnosis, because the histology of the atypical foci may be not so clear as to be able to base oneself on this technique for a diagnosis of malignancy (2,5,10).

The differential diagnosis for ASAP must be posed with morphologically similar entities, such as atypical adenomatous hyperplasia (AAH), basal cell hyperplasia (typical and atypical), sclerosing adenosis, atrophy, postatrophic hyperplasia or hyperplasia of mesonephric remnants (16). The diagnosis of AAH must be reserved to proliferation of small acini, most often in the transition zone, placed at the edge of areas with nodular hyperplasia, and

can rarely be performed on a needle biopsy (4,5). Moderately differentiated prostate adenocarcinomas, such as some ASAP foci, show atypical glands crowded without intermingled stroma that usually have a wide variation in size and shape, so the Gleason score would be 3 or more. In fact, the mean Gleason sum of adenocarcinomas after ASAP seen in our series was 6.28; similar to some others previously reported (1-3). In a prospective study of 156 patients with minimal cancer or ASAP (6), Iczkowski et al. found 10 significantly different histological features that could help to differentiate the two groups.

Cases were separated into 3 groups (probably malignant, uncertain, probably benign), according to suspected histological malignancy, and before knowing data on patients' progress. After excluding the cases of ASAP + PIN for the aforementioned, 42.8% of cases with an uncertain diagnosis and 63.6% from the probably malignant group were adenocarcinomas. These data seem to support a certain predictive value of this stratification of the level of suspected histological malignancy (11), although the limited number of cases that we present may influence this affirmation.

ASAP should be kept in mind to avoid false diagnosis of adenocarcinoma, and to induce urologists to repeat the biopsy in cases with atypical acini not related to inflammation, atrophy or former biopsy areas. The interobserver level of consensus in ASAP is barely sufficient (1,3), although the description of new series with cases of this hereto little-known entity will probably help us to achieve a greater diagnostic concordance.

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EDITORIAL COMMENT

More prostate biopsies are being performed than over before, often in men with minimal or marginal indications. The early dividend of screening and biopsy includes downward migration of stage, grade, and cancer volume. Later dividends will likely in-

clude a decline in recurrence and death rates. The increase in number of biopsies has also generated great interest in the two known histopathologic risk factors for prostate cancer: atypical small acinar proliferation (ASAP, or "suspicious") and high grade prostatic intraepithelial neoplasia.

The current study expands our understanding of the diagnosis of ASAP ("suspicious"), an uncomfortable and unsettling finding for the pathologist, urologist, and, ultimately, the patient. Yet, prostate biopsy is prone to sampling variation, and in a small but significant number of cases (2.9% in this study), the findings fall short of the diagnosis of malignancy. What should the pathologist report? It is imprudent to render an unequivocal diagnosis of cancer without absolute confidence in the biopsy findings, yet the alternative diagnosis of "benign" might be a serious under-diagnosis. The authors note that additional biopsies in patients with ASAP reveal cancer in about half of cases, indicating that this is an important (and reproducible) risk factor that warrants clinical attention. It is critical that the pathologist not overuses this diagnostic category, but we have not seen this in our experience. The urologist and patient is best served by reports that provide as definitive a diagnosis as possible; in occasional cases, the pathologist is "absolutely positively uncertain", and this suspicion in prostate biopsies is best summed up as ASAP.

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DATA OF SPANISH CONTRIBUTION TO THE EUROPEAN RANDOMIZED STUDY OF SCREENING FOR PROSTATE CANCER (ERSPC)

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ABSTRACT

Introduction and Objectives: The benefit of routine screening for prostate cancer (PCa) in terms of mortality reduction is controversial. In this paper, we report the Spanish contribution to the European Randomized Study of Screening for Prostate Cancer (ERSPC).

Material and Methods: Seven countries are ERSPC participants: Holland, Finland, Belgium, Italy, Sweden, Portugal and Spain. Men between 45 and 70 years old are randomly (1:1) allocated in: 1)- Screening group (PSA and transrectal ultrasound guided biopsy if elevated), and 2)- Control group (no diagnostic tests). At our center we perform biopsy when PSA ≥ 3.0 ng/ml (rectal examination is not considered to indicate biopsies). Prostate cancer-specific mortality is recorded and the two groups are compared with regard to this point.

Results: To date there are 143,256 recruited men (all centers). At our center, 2,416 men were included in the screening arm, and 264 biopsies were performed. Fifty-four PCa were detected (47 localized, 5 locally advanced, and 2 metastatic). Overall, detection rate was 2.24%. Eighteen radical prostatectomies were performed (with 44.4% of extracapsular pathologic stage), 12 radiotherapy, 9 watchful waiting, and 8 awaiting treatment. To date, there were 37 deaths, none of them due to PCa.

Conclusions: Although these data are preliminary, it seems that screening detects more cancers at an early stage. Anyway, it is necessary to wait at least for 10 years of follow up to verify if a significant benefit, with regard to prostate cancer mortality reduction, is achieved.

Key words: prostate, prostatic neoplasms, screening, prostate-specific antigen, biopsy
Braz J Urol, 26: 510-515, 2000

INTRODUCCIÓN

El cáncer de próstata (CaP) es la neoplasia más común entre los varones americanos (1). A incidencia en 1997 en nuestro área sanitaria fue de 32 varones/100.000 personas/año (Getafe, Madrid, España). En España es la segunda causa de muerte por neoplasia en el varón tras el cáncer de pulmón y fue la responsable de 28.1 fallecimientos / 100.000 varones / año en 1997 (2).

Actualmente sabemos que el CaP se presenta, en cuanto al pronóstico y tratamiento, en dos formas: limitado a la glándula y potencialmente curable, y avanzado cuya supervivencia no ha sido mejorada por las alternativas disponibles en la actualidad (3).

La elevada incidencia y la no desdeñable mortalidad por esta enfermedad, así como la disponibilidad de medios aparentemente eficaces de diagnóstico y tratamiento (en estadios precoces) hacen muy atractiva la posibilidad de generalizar el cribaje o "screening" entre la población masculina ya que, de ser estas estrategias válidas, la mortalidad por CaP podría verse reducida. No obstante, este hecho no ha sido todavía demostrado (4) y algunas cuestiones son todavía objeto de controversia. Para despejar esta incógnita es necesaria la existencia de estudios randomizados.

El el presente artículo mostramos los datos disponibles hasta la fecha de nuestra contribución al Estudio Randomizado Europeo para el Screening del Cáncer de Próstata (ERSPC).

MATERIAL Y METODOS

El ERSPC comenzó su andadura en 1.994 y está formado actualmente por centros de siete países: Rotterdam (Holanda), Helsinki y Tampere (Finlandia), Amberes (Bélgica), Florencia (Italia), Göteborg (Suecia), Lisboa (Portugal) y Madrid (España). El Servicio de Urología del Hospital Universitario de Getafe (Madrid) es el único centro que contribuye a este estudio por parte de España. Este estudio recluta varones sanos entre 55 y 70 años, distribuyéndolos aleatoriamente (randomización 1:1) en 1)- grupo Screening, y 2)- grupo Control, siendo el objetivo principal de este estudio es comparar la mortalidad cáncer-específica entre los dos grupos mencionados. Los varones incluidos en el grupo Screening son sometidos a determinación sérica de antígeno específico prostático (PSA), con o sin tacto rectal (TR) inicial, según el protocolo de cada Centro. Por el contrario, los varones randomizados en el grupo Control no reciben atención diagnóstica ni terapéutica alguna dentro del estudio. Son automáticamente excluidos del estudio (no randomizados) los varones con esperanza de vida estimada inferior a 10 años.

En nuestro Centro se ha procedido (desde principios de 1996) a la invitación mediante carta a varones supuestamente sanos con edades comprendidas (en el momento de la randomización) entre los 45 y los 70 años, procedentes del censo poblacional. En los pacientes del grupo Screening con PSA sérico de 3.0 ng/ml o superior se indica biopsia sextante, dirigida mediante ecografía transrectal (ECOTR) con un aparato Siemens Sonoline SI-450 y transductor transrectal biplanar de 7.5 MHz. El TR y la ECOTR son realizados sólo en los enfermos biopsiados durante el procedimiento, y no constituyen per se indicación de biopsia.

Los pacientes del grupo screening con un PSA inicial elevado y biopsia negativa son sometidos a nueva evaluación (“rescreen”) al cabo de 1 año con una nueva determinación de PSA, realizando biopsia sextante si este es igual o superior a 3 ng/ml.

Periódicamente se obtienen los listados de fallecimientos producidos en nuestro Hospital (único de referencia en nuestro Área Sanitaria), así como en el resto del Área, procedente del Ayuntamiento de Getafe. Siempre que esto es posible, se obtiene también información acerca de la causa de la muerte, mediante copia de informes o certificados de exitus o de necropsia, en el caso de realizarse esta.

RESULTADOS

Actualmente se han reclutado 143.256 individuos entre todos los centros participantes. En nuestro Centro se han invitado a participar en el programa a 18.612 varones. Un total de 5.271 han acudido respondiendo a la invitación, de los cuales 993 fueron rechazados por diversos motivos (sintomatología significativa del tracto urinario inferior, esperanza de vida inferior a 10 años, tratamiento con anticoagulantes, entre otras causas). Finalmente, se han reclutado hasta la fecha 4.278 pacientes (2.416 en el grupo Screening, y 1.862 en el Control), con una tasa de aceptación del 28.3%.

Las edades medias de los varones reclutados en nuestro estudio fueron de 58.5 años (grupo Screening) y 58 años (grupo Control). Se llevaron a cabo 2.416 determinaciones de PSA en la primera visita, donde se realizó biopsia a 166 varones, de los cuales 12 (7.2%) presentaron un TR anormal, y 25 (15.1%) mostraron alguna anomalía en la ECOTR. Un total de 193 varones fueron reevaluados al cabo de un año (rescreen) por presentar un PSA elevado

Tabla 1 – Distribución de la población estudiada según niveles de PSA. Cánceres detectados y tasa de detección.

n = 2.416	n	Cánceres Detectados/ Biopsias Realizadas	Tasa de Detección
PSA < 3.0 ng/ml	2152	-	-
3.0 - 10 ng/ml	242	31 / 146 (21.2%)	12.8%
> 10 ng/ml	22	9 / 20 (45%)	40.9%

Tabla 2 – Distribución de la población estudiada según niveles de PSA en evaluaciones posteriores (rescreen). Cánceres detectados y tasa de detección. El tiempo transcurrido entre evaluaciones se encontró entre los 169 y los 434 días, media 298 días

n = 225	n	Cánceres Detectados/ Biopsias Realizadas	Tasa de Detección	
PSA	< 3.0 ng/ml	60	- / -	-
	3.0 - 10 ng/ml	147	10 / 85 (11.8%)	6.8%
	> 10 ng/ml	18	3 / 13 (23.1%)	16.7%

Tabla 3 – Características de los cánceres detectados y tratamientos efectuados.

	n	Tratamiento Efectuado
Estadio clínico	Localizado	47
	Localmente avanzado / regional	5
	Metastásico	2
Gleason score	2,3,4	8
	5,6	27
	7	10
	8,9,10	9

en la visita inicial y el tiempo transcurrido entre evaluaciones se encontró entre los 169 y los 434 días, con una media de 298 días.

En total (primera evaluación + rescreen) se han realizado 264 biopsias, detectando 54 CaP. En la Tabla-1 ofrecemos los datos correspondientes de la distribución de la población estudiada en cuanto a rangos de PSA, biopsias realizadas y tasa de detec-

ción en la primera ronda del programa. En la Tabla-2 ofrecemos los mismos datos, referentes a las evaluaciones posteriores (rescreen) realizadas en los varones del grupo screening.

De los 54 CaP detectados, 47 fueron clínicamente localizados, 5 localmente avanzados y 2 con metastasis (Tabla-3). La tasa global de detección fue, por tanto, de 2.24%. De los 47 pacientes

Tabla 4 – Rendimiento diagnóstico de los distintos tests empleados.

	S	E	VP+	VP-	CaP detectados	Biopsias/cáncer	área ROC
PSA	1	0.94	0.24	1	40	166/40 (4.15)	0.972
TR	0.15	0.95	0.50	0.78	6	12/6 (2)	0.551
DPSA	0.75	0.64	0.40	0.89	30	75/30 (2.5)	0.696
ECOTR	0.40	0.93	0.64	0.83	16	25/16 (1.56)	0.664

PSA = antígeno específico prostático; TR = tacto rectal; DPSA = densidad de PSA; ECOTR = ecografía transrectal; S = sensibilidad; E = especificidad; VP+ y VP- = valores predictivo positivo y negativo; Área ROC = área bajo la curva ROC.

con estadio clínico localizado, 18 se sometieron a prostatectomía radical (con hasta un 44.4% de estadio patológico extracapsular), 12 a radioterapia, 9 en observación y 8 en espera de tratamiento.

En cuanto al rendimiento de los distintos tests diagnósticos empleados en el transcurso del programa (Tabla-4), el PSA consiguió una mayor sensibilidad para la detección del CaP, siendo las otras alternativas inaceptables desde este punto de vista (dejan sin diagnosticar un número importante de tumores, sin conseguir además un ahorro significativo de biopsias).

Hasta la fecha han fallecido en nuestro Hospital un total de 37 varones: 24 del grupo Screening y 13 del Control. Sólo en uno de ellos se había detectado un CaP, y esta no fue la causa de la muerte. Dicho de otro modo, no se produjeron exitus por CaP. Los fallecimientos producidos pueden desglosarse en: 24 por tumores (no CaP) (64.9%), 4 por patología cardiovascular (10.8%), 1 por traumatismo (2.7%), y 8 con causa no especificada (21.6%).

DISCUSIÓN

En este estudio hemos observado una mayor detección de cánceres con estadio clínico localizado, en comparación con nuestra experiencia previa a este programa de screening. Este hecho ha posibilitado el ofrecer un tratamiento supuestamente curativo a un mayor número de pacientes.

No obstante, ya es conocido que cuando los tests empleados en los programas de screening (habitualmente PSA y TR) se utilizan de modo indiscriminado, el número de cánceres diagnosticados se eleva considerablemente. Además, estos serán de estadios más precoces (reducción del estadio o “stage-shift”), con una mayor proporción de tumores órgano-confinados (5,6). En cualquier caso, este hecho no es suficiente por sí solo para probar una reducción en la mortalidad por CaP.

Otro sesgo a tener en cuenta en todo programa de screening es el “lead-time bias”. El error consiste en que el tiempo de “supervivencia” extra obtenido en los programas de screening puede deberse simplemente a que estos tumores son detectados antes (en estadios iniciales de su historia natural, con

todavía mucho tiempo por transcurrir hasta un desenlace fatal) y no a un aumento real del tiempo de supervivencia.

Aunque existe algún estudio randomizado que afirma que esta reducción de la mortalidad cáncer-específica es un hecho (7), el debate sigue abierto (8). En la actualidad se encuentra en marcha el estudio randomizado europeo para el screening del cáncer de próstata (ERSPC), en el que nuestro Centro participa (9).

Con la evidencia actual disponible, incluso con análisis de decisión que asumen las bondades de la detección precoz (entre otras, que el cáncer órgano-confinado es sinónimo de curación) el screening tan sólo aportaría 17 días de esperanza de vida adicionales en hombres entre 50 y 69 años (como máximo 3 años si consideramos sólo los candidatos a tratamiento agresivo entre 50 y 59 años). Además, esta supervivencia añadida disminuiría exponencialmente con la edad (10).

También deben colocarse en el lado opuesto de la balanza los efectos adversos sobre la calidad de vida de los pacientes que, sin duda, el screening produce (11). Por ello, es necesario explicar a los pacientes interesados en el screening del CaP los potenciales pros y contras de esta actitud y, si es posible, incluirlos en los estudios randomizados en marcha hasta que exista una evidencia científica sólida a este respecto.

Tampoco en este estudio pueden extraerse conclusiones con respecto a la mortalidad de la población estudiada y sus causas, debido al escaso seguimiento (apenas cuatro años). La prolongada historia natural del CaP (12) nos indica que aún no ha transcurrido el tiempo suficiente para esperar un número importante de fallecimientos por CaP. Por ello, el análisis de mortalidad deberá realizarse con un mínimo de 10 años de seguimiento.

En cuanto al rendimiento de los tests empleados en nuestra experiencia, el PSA es el único test que permitió detectar un número aceptable de tumores. Ni el TR aislado, la ECOTR, o DPSA alcanzaron una sensibilidad suficiente para ser empleados por sí solos como criterio de biopsia, dejando sin diagnosticar un número excesivo de cánceres.

CONCLUSIONES

A tenor de los resultados obtenidos, parece que el programa de screening favorece la detección de cánceres en estadio localizado. No obstante, debido al escaso tiempo transcurrido desde el reclutamiento no podemos adelantar si este hecho supone una reducción en la mortalidad cáncer específica de la población estudiada. Será necesario llegar al menos a los 10 años de seguimiento para despejar esta incógnita.

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Miembro del European Randomized Study of Screening for Prostate Cancer (ERSPC)

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COMENTÁRIO EDITORIAL

Nos últimos anos o rastreamento do câncer de próstata tem sido realizado no mundo inteiro, demonstrando que entre homens voluntários com mais de 50 anos, cerca de 2% deles apresentam câncer de

próstata no momento do rastreamento. Além disto o tumor é localizado em quase 90% destes, demonstrando que o rastreamento implica em diagnóstico precoce do tumor.

Contudo, os benefícios em termos de redução da morbidade e mortalidade neste grupo de pacientes não está demonstrado, havendo dúvida em relação ao custo/benefício no rastreamento desta neoplasia.

O ERSPC (European Randomized Study of Screening for Prostate Cancer) que está em fase de recrutamento, mas que já conta após seis anos com quase 150.000 homens cadastrados, é um projeto ambicioso que poderá ajudar a responder estas dúvidas nos próximos anos. Esse artigo preliminar

relata a contribuição espanhola para esse projeto multicêntrico europeu.

O ERSPC usa como único critério de rastreamento os níveis séricos de PSA acima de 2.9 ng/ml, sem considerar necessário toque retal. Sabidamente a associação toque retal/PSA tem melhor sensibilidade que o PSA isoladamente. Possivelmente, pacientes com PSA abaixo de 2.9, que é o ponto de corte desse estudo independente da idade, poderão ter câncer de próstata, especialmente se tiverem menos que 60 anos.

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SCREENING FOR CARCINOMA OF THE PROSTATE IN VOLUNTEERS

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ABSTRACT

Objectives: To study the incidence of carcinoma of the prostate in a community population and to evaluate parameters such as prostatic specific antigen (PSA) and digital rectal examination (DRE).

Material and Methods: Prostate carcinoma first round screening was planned for community men between 40 and 70 years old. One thousand and seventy-nine volunteers were evaluated by DRE and PSA. Two hundred and thirty-five volunteers with PSA greater than 4.0 ng/ml, positive DRE or both were referred to prostate biopsy in sextant guided by transrectal ultrasound.

Results: Of 136 (57.6%) men that agreed with the biopsy 27 (2.5%) had tumor and 10 (0.9%) had isolated prostatic intraepithelial neoplasia (PIN). No men under 50 years had cancer but in 2 of them, PIN was detected. The sensitivity, specificity and positive predictive value for total PSA and DRE were respectively: 81.4%, 92.7% and 24.1%, and 74.0%, 94.4% and 27.4%. Clinical staging showed disease confined to the gland in 92.5% of patients. Thirteen of these patients were submitted to radical prostatectomy, which revealed that 61.5% of them had tumor stage lower than pT3.

Conclusions: The incidence of prostate cancer detected in this first round screening program is within the range previously reported. The PSA cut-off at 4.0 ng/ml for this community showed sensitivity, specificity and predictive positive values within the range published by many centers.

Key words: prostate; prostatic neoplasms; prostatic specific antigen, screening
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INTRODUÇÃO

A incidência do câncer prostático (CP) aumenta a partir da 5a. década, depende da raça, da herança não mendeliana e é afetada por fatores ambientais (1,2). Assim, rastreamento populacional obtido em um país pode não corresponder à realidade de outros, seja ele passivo (pacientes procuram espontaneamente o médico devido a sintomas) ou ativo (voluntários são induzidos a fazer os exames através de campanhas independente da existência de sintomas). O rastreamento do CP na população brasileira, visa fundamentalmente conhecer a incidência da doença, os valores do antígeno prostático específico (PSA) que possam ser considerados normais, tais como o PSA segundo a idade e a raça.

Neste artigo, apresentaremos os resultados de um rastreamento ativo para detecção dessa neoplasia na cidade de Ribeirão Preto, São Paulo, realizado em junho de 1997.

MATERIAL E MÉTODOS

O rastreamento do CP foi programado para homens da faixa etária entre 40 e 70 anos. Fez-se uma campanha publicitária preliminar com duração de 1 mês na imprensa leiga, com painel em estandes e distribuição de panfletos em pontos de grande movimento. Todos foram convidados à comparecer ao ambulatório do hospital para a avaliação inicial. Neste dia, fez-se a coleta de sangue para dosagem do PSA e o toque retal (TR). O PSA foi dosado em amostras frescas de soro com “kits” da DPC-IMMULITE®.

Os voluntários com alteração da próstata ao toque (aumento da consistência ou nódulos) e/ou PSA > 4.0 ng/ml, foram submetidos a biópsia prostática em sextante, guiada por ultra-som transretal. Fragmentos prostáticos adicionais foram removidos de nódulos suspeitos ao ultra-som. O material assim obtido foi submetido a exame histopatológico. Os demais voluntários foram informados por carta dos resultados da avaliação e orientados a fazer exames periódicos anuais.

Foram avaliados 1079 homens, alguns com idades acima da faixa preestabelecida, que também foram estudados por interesse epidemiológico. Indicou-se biópsia em 235 (21.7%), mas apenas 136 aceitaram.

Os portadores de CP submeteram-se a exames de imagem para estadiamento (mapeamento ósseo, tomografia computadorizada abdominal e/ou ressonância magnética abdominal e endo-retal). Para os pacientes com doença clinicamente localizada (3) e com expectativa de vida maior de 10 anos, indicou-se a prostatectomia radical. Para aqueles que não aceitaram esta opção, ou com risco anestésico alto, sugeriu-se a radioterapia. Naqueles com doença disseminada propôs-se a terapia anti-androgênica.

Para a avaliação estatística empregou-se a análise de variância dos parâmetros obtidos que foi efetuada através de computador. O nível de significância usado foi de 95%.

RESULTADOS

A Tabela-1 apresenta a distribuição dos voluntários e os resultados histológicos das biópsias. A proporção número de voluntários sujeitos à biópsia

por tumor diagnosticado foi 5/1. Esse índice variou com a faixa etária indo de 23/1 na 6a. década à 2/1 na 9a. década de vida. A incidência global de CP foi de 2.5%. Não foi detectado câncer em homens abaixo de 50 anos, mas a partir daí a incidência aumentou com a idade, variando de 0.5% na faixa dos 50-59 anos à 25% naqueles com 80 anos ou mais. Em 2 voluntários com menos de 50 anos detectou-se PIN.

A Tabela-2 mostra a distribuição dos voluntários entre as faixas de 40 e 90 anos segundo a cor e incidência de câncer. A indicação de biópsias em relação às diversas amostras ocorreu nas seguintes proporções: brancos: 195/852 (22.8%), mulatos: 29/146 (19.8%), negros: 10/58 (17.2%) e amarelos: 1/23 (4.3%). As proporções entre homens com biópsia indicada e as realizadas, segundo a cor, foram: brancos: 195/111 (56.9%), mulatos: 29/20 (71.4%) e negros: 10/4 (40%). Os 4 portadores de neoplasia acima dos 80 anos eram brancos. A idade média dos brancos, mulatos e negros foi 57.8 ± 6.9 anos e não houve diferença estatística entre as idades das 3 amostras ($p = 0.13$). Também não houve diferença estatística na incidência de câncer entre brancos, mulatos e negros ($p = 0.09$).

A Tabela-3 correlaciona a incidência de câncer com as alterações do toque e do PSA. Através de seus dados e desconsiderando-se os 99 pacientes que deixaram de fazer as biópsias, pôde-se estimar a sensibilidade, a especificidade e o valor preditivo positivo do PSA total, que foram respectivamente: 81.4%, 92.7% e 24.1%; assim como do toque retal: 74.0%, 94.4% e 27.4%. Três pacientes com câncer apresentaram PSA < 2.5 ng/ml e o menor valor do PSA em paciente com adenocarcinoma foi 1.4 ng/ml.

Tabela 1 – Distribuição dos voluntários por faixa etária, número de biópsias realizadas e anatomo-patologia.

Idade	N	No. Biópsias	HPB*	N	Câncer Gleason			PIN**	Grau		
					< 5	5-6	≥ 7		1	2	3
40 – 9	271	10	8	0	0	0	0	2	1	0	1
50 – 9	376	23	21	2	1	1	0	1	0	1	0
60 – 9	304	66	46	13	7	4	2	5	4	0	1
70 – 9	12	29	20	8	3	5	0	2	2	0	0
80 –	16	8	4	4	1	2	1	0	0	0	0
Total	1079	136	99	27	12	12	3	10	7	1	2

* Hiperplasia prostática benigna; ** Neoplasia intra-epitelial

Tabela 2 – Distribuição dos pacientes segundo a cor, faixa etária e incidência de câncer prostático.

Idade	COR*								Voluntários com Câncer					
	B		M		N		A		B		M		N	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
40 - 9	210	77.6	45	16.7	13	4.8	3	0.9	0	0.0	0	0.0	0	0.0
50 - 9	283	75.2	53	14.1	29	7.7	11	3.0	1	0.4	1	1.8	0	0.0
60 - 9	245	79.6	41	13.4	13	4.2	5	2.8	11	4.5	1	2.4	1	7.6
70 - 9	100	90.0	6	5.0	3	2.5	3	2.5	7	7.0	1	6.6	0	0.0
80 -	14	87.5	1	6.2	0	0.0	1	6.2	4	14.2	0	0.0	0	0.0
Total	852	78.9	146	13.5	58	5.3	23	2.1	23	2.7	3	2.0	1	1.7

* B: branca; M: mulata; N: negra; A: amarela

Tabela 3 – Correlação entre câncer prostático, nível de PSA e achado do toque retal (TR).

PSA ng/ml	TR+ Câncer +		TR+ Câncer -		TR- Câncer +		TR- Câncer -		TOTAL	
	N	%	N	%	N	%	N	%	Câncer +	Câncer -
Até 4.0	5	11.2	40	88.8	0	0	0	0	5	11.2
4.1 - 10.0	5	35.7	9	64.3	2	4.3	45	95.7	7	11.5
> 10.1	10	71.4	4	28.6	5	31.3	11	68.7	15	50.0
Total	20	27.4	53	72.6	7	15.9	56	84.1	27	19.9
									109	80.1

Nos 136 pacientes sujeitos à biópsia mediou-se o volume prostático pelo ultra-som transretal para cálculo dos valores médios da densidade do PSA (PSAD) dos pacientes com câncer, PIN e sem qualquer dessas alterações, que foram respectivamente: 0.36 ± 0.32 , 0.17 ± 0.20 e 0.11 ± 0.08 . O estudo estatístico mostrou diferença significante entre esses valores ($p < 0.05$). O menor valor do PSAD de 2 portadores de câncer, do grupo de 47 voluntários com PSA entre 4.1 e 10.0 ng/ml e sem alteração ao toque retal, foi 0.13. Caso se aplicasse para o grupo o PSAD ≤ 0.12 como critério de exclusão, 15 (31.2%) deles não seriam submetidos à biópsia sem que houvesse omissão de diagnóstico. Se o critério de exclusão fosse o nível mais aceito de PSAD ≤ 0.15 , 22/47 (46.8%) não seriam sujeitos à biópsia, mas 2 destes tinham CP que não seria diagnosticado. Já no grupo de 45 pacientes com alteração ao toque retal e PSA ≤ 4.1 ng/ml o menor valor do PSAD foi 0.07.

Outro critério estudado visando a redução da indicação de biópsias desnecessárias foi a simulação feita fixando o valor de corte do PSA segundo a faixa etária, conforme proposição de Oesterling et al. (4). Usando-

se essa proposta, em 32 voluntários acima de 60 anos a biópsia não seria indicada, mas haveria indicação de biópsia em 16 pacientes adicionais abaixo dessa idade. Se esse critério fosse usado, 2 portadores de câncer acima de 60 anos não teriam o tumor diagnosticado.

Em 19 homens (13.9% das biópsias) a histologia mostrou prostatite crônica: em 11 deles não havia alteração da consistência prostática, mas o PSA estava acima de 4.0 ng/ml; nos 8 restantes o toque era suspeito de câncer, mas o PSA era menor que 4.0 ng/ml. Neste grupo, 2 tinham câncer associado, 2 PIN e os 15 restantes tinham HPB.

A Tabela-4 contém dados sobre o PSA em brancos, mulatos e negros, sendo que os amarelos não foram analisados devido seu pequeno número. Foram excluídos os pacientes que não compareceram para biópsia ou com CP, prostatite ou PIN. Dados de mulatos e negros na faixa 70-90 anos também foram desconsiderados devido ao número muito reduzido. O estudo estatístico comparativo do PSA entre brancos, mulatos e negros revelou os valores respectivos de significância para as diversas faixas etárias: 40-9 ($p = 0.8$), 50-9 ($p = 0.5$) e 60-9 ($p = 0.12$).

Tabela 4 – Parâmetros do PSA (ng/ml) segundo a faixa etária e a cor em pacientes sem câncer prostático, PIN e prostatite.

Cor	N	Mínimo	Quartil 25%	Mediana	Quartil 75%	Percentil 95%	Máximo
Branca							
40 - 9	210	0.04	0.5	0.8	1.3	2.2	3.9
50 - 9	283	0.10	0.5	0.9	1.5	2.3	3.8
60 - 9	245	0.01	0.7	1.2	2.6	3.6	4.0
70 - 9	100	0.39	0.8	1.5	2.3	3.3	3.8
80 -	9	0.30	1.0	1.2	1.8	1.8	3.2
Mulata							
40 - 9	45	0.26	0.5	0.9	1.1	1.5	2.1
50 - 9	53	0.16	0.7	1.0	1.6	2.2	3.2
60 - 9	41	0.25	0.5	1.0	1.4	2.5	3.3
70 - 9	6	-	-	-	-	-	-
80 - 9	1	-	-	-	-	-	-
Negra							
40 - 9	13	0.58	0.6	1.1	1.3	1.3	1.3
50 - 9	29	0.22	0.6	0.8	1.3	2.2	2.6
60 - 9	13	0.50	1.8	1.5	1.8	3.0	3.5
70 - 9	3	-	-	-	-	-	-
80 -	0	-	-	-	-	-	-

Níveis de significância (valores de *p*) da comparação do PSA em brancos, mulatos e negros: 40-9: 0.8; 50-9: 0.5 e 60-9: 0.12.

O estadiamento clínico dos portadores de câncer foi: T1c - 5 (18.5%), T2a - 4 (14.8%), T2b - 10 (37.0%), T2c - 5 (18.5%), T3a - 1 (3.7%) e T1cNxM1 - 2 (7.5%). Dos 27 pacientes com câncer, 7 tinham mais de 75 anos e 2 eram coronariopatas graves e foram tratados com radioterapia. Os 2 com doença disseminada foram tratados com orquiectomia. Dos 16 restantes, 13 foram submetidos à prostatectomia radical tendo sido encontrados os seguintes estádios patológicos (com estádios clínicos correspondentes): 1 pT1 (T1c), 3 pT2a (2 T2a e 1 T1c), 2 pT2b (2 T2b), 2 pT2c (2 T2b), 3 pT3a (2 T1c e 1 T2b) e 2 pT3c (1 T2c e 1 T3a). Portanto, dentre os pacientes operados, o carcinoma estava confinado à próstata em 61.5% dos casos, e nos demais a neoplasia ultrapassava a cápsula prostática, sendo que num destes encontrou-se margem cirúrgica positiva. Três dos pacientes com doença clinicamente localizada e com condições cirúrgicas optaram pela radioterapia.

DISCUSSÃO

O não comparecimento para biópsia de 42% dos casos com indicação é uma taxa elevada, mas isso ocorreu também em outros estudos recentes, como o da Áustria, no qual 52% dos voluntários com indicação deixaram de comparecer (5). Nada obstante, deve-se considerar que esse fato interfere no resultado e subestima a incidência da neoplasia.

A incidência de CP na população estudada foi de 2.5%, e no grupo entre 50 e 70 anos, foi de 2.9%. Ainda que com os fatores de erro resultantes da omissão de biópsias, a incidência encontrada está dentro do intervalo de variação (1.5 a 4.1%) relatado na literatura (5-7). A incidência de PIN, de 0.9%, também é comparável à encontrada em países ocidentais desenvolvidos (7). Os portadores de PIN de alto grau devem ser submetidos a novas biópsias.

O estadiamento encontrado nos portadores de câncer neste rastreamento ativo também é compa-

rável à literatura (5-7), ao contrário do que ocorre quando pacientes sintomáticos procuram avaliação prostática (8).

Dados do IBGE obtidos junto à Prefeitura Municipal apontam 462.578 habitantes residentes no município no ano de 1997. Se considerarmos o censo demográfico municipal, em que cerca de 43% da população é referida como de idade superior a 40 anos, não mais que 1% da população masculina alvo compareceu para os exames. Por outro lado, se considerássemos a média do censo nacional, em que a população nesta faixa etária é inferior a 12%, o índice de comparecimento subiria para 4% aproximadamente. Em qualquer das hipóteses, deve-se salientar que o impacto da campanha foi pequeno para a população alvo, apesar da divulgação na mídia. Se a amostra fosse representativa da população, o que não se pode afirmar com segurança, mais de 90% dos homens portadores de neoplasia permaneceram sem o diagnóstico, e, portanto sem a oportunidade de tratamento, o que mostra a limitação de uma campanha isolada sobre a saúde da população, nas condições do estudo. Para se atingir maior eficiência seriam necessárias outras campanhas ou então a mudança da abordagem. A simulação efetuada, assim como os próprios resultados, não se aplicam automaticamente a outros países, ou mesmo regiões do Brasil, em razão das variações demográficas e ambientais.

Não encontramos diferença na incidência de câncer entre brancos, negros e mulatos. Na literatura há evidências da maior incidência da neoplasia em negros (1,6). Essa discordância pode ser casual ou devida a outros fatores. Chama a atenção em nossa amostra que o percentual de voluntários negros e mulatos é bem inferior ao de brancos e essa desproporção pode levar a distorções. É interessante ressaltar que em nossa amostra, na década dos 40 anos a proporção de negros e mulatos é de 21.5% enquanto que na dos 70 anos ela cai para 7.5%. Essa queda possivelmente reflete a composição censitária regional, seja por aumento mais recente da miscigenação, seja por menor longevidade de negros e mulatos motivada por doenças e dificuldades sociais, ou por ambas.

A proporção de 5 homens submetidos à biópsia para cada câncer diagnosticado é semelhante

à referida para populações européias e norte-americana (5-7). Esse dados sugerem que os critérios de indicação da biópsia prostática propostos para aqueles países também podem ser aplicados na região deste estudo. Essa hipótese é reforçada ao se comparar a sensibilidade, a especificidade e o valor preditivo positivo do PSA e do TR com a de outros estudos (4,6,7). Nada obstante, vale ressaltar que o valor preditivo positivo do PSA varia na literatura de 11 a 33 % (6,7), mas o referencial mais comum do parâmetro está entre 29 e 33% (6,7), enquanto que neste trabalho foi de 24.1%. Isso pode ser casual, mas é conveniente analisar com mais detalhes os dados do PSA, pois há referências de que sofre influência racial (1).

Nosso estudo não demonstrou diferença significante nos valores do PSA das amostras de brancos, mulatos e negros não portadores de câncer, PIN ou prostatite. Por outro lado, pode-se observar pela Tabela-4 que a dispersão (percentil 95%) observada em brancos, mulatos e negros é parecida. Esses dados contradizem os de Morgan et al. (1) que encontraram percentil 95% em negros norte-americanos muito maior que a de brancos, como segue (por faixa etária, em ng/ml): brancos: 40-49: 2.1; 50-59: 3.6; 60-69: 4.3 e 70-79: 5.8; e, negros: 40-49: 2.4; 50-59: 6.5; 60-69: 11.3 e 70-79: 12.5. Nossos dados em brancos, mulatos e negros são parecidos com os dos brancos norte-americanos. Deve-se alertar, todavia, que embora nossa amostra de brancos seja grande, a de mulatos e negros é pequena, o que indica a necessidade de novos estudos. Também não se deve desconsiderar que a miscigenação racial existente no Brasil, onde muitas vezes se confunde posição social com cor da pele, pode comprometer cientificamente os dados encontrados. E, é por essa razão que estamos empreendendo outro estudo, agora com marcadores genéticos capazes de identificar a ascendência racial, em uma comunidade nordestina. Mas, essa abordagem embora seja de grande interesse científico teria pequena aplicação prática, pois não seria factível rotineiramente em consultórios. Apesar das limitações científicas na identificação das raças do presente estudo, é esta a situação que se apresenta ao urologista em sua prática diária. E, nestas circunstâncias, e talvez por isso mesmo, esses resultados preliminares

parecem apontar para níveis de PSA semelhantes para as raças estudadas.

A simulação feita com corte do PSA por faixa etária reduziria a indicação de biópsias em 11.7% dos casos, mas com omissão do diagnóstico em 2 deles (7.4%), o que significa um aumento da sensibilidade do teste, mas com redução da especificidade na faixa acima dos 60 anos. A adoção desse critério também geraria dificuldades pelo aumento das indicações de biópsias em pacientes abaixo dos 60 anos, com PSA entre 2.5 e 4.0 ng/ml. A indicação de biópsias em pacientes com esses valores de PSA é polêmica, apesar de haver referências sugerindo incidência de câncer em 15 a 20% desses casos quando seguidos durante 5 anos (6).

Embora haja artigos mostrando que a elevação do PSAD se associa a maior incidência de câncer e aumento do estádio tumoral, há dúvidas sobre sua importância (9). Há a necessidade do ultra-som para a medida do volume prostático (o que seria um problema em larga escala), pode haver erro de medida do volume prostático e a produção do PSA pode variar de um tumor para outro. Não há consenso sobre o nível de corte (9). Em nossa amostra, caso se tivesse adotado o critério de exclusão da biópsia em voluntários sem alteração ao toque, e PSA entre 4.1 e 10.0 ng/ml, aqueles com PSAD < 0.12, cerca de 1/3 dessa amostra deixaria de ser biopsiada sem que ocorresse omissão no diagnóstico de câncer. Entretanto, se fosse adotado o nível de corte mais aceito, de 0.15, ter-se-ia redução de 45.8% das biópsias, mas com omissão de diagnóstico de câncer em 2 pacientes.

Dos 45 pacientes com alteração exclusiva do TR, encontrou-se câncer em 5, em 3 dos quais o PSA estava entre 1.4 e 2.5 ng/ml. Isso mostra a importância do TR no rastreamento, pois se não tivesse sido feito, o diagnóstico seria omitido em 19.2% dos casos com PSA < 4.1 ng/ml e em 11.5% com PSA < 2.5 ng/ml. Mas, há sugestões de se evitar o TR e o ultra-som em pacientes com PSA < 1.1 ng/ml (7) porque o câncer é muito raro nesta situação. Em nossa amostra, 4 voluntários apresentavam esse nível de PSA e nódulo prostático ao toque e em nenhum deles a biópsia revelou neoplasia. Seria o caso de se questionar o dogma da indicação automática de biópsia em pacientes com TR alterado e condicionará-la ao valor do PSA maior que 1.0 ng/ml?

Há controvérsias na literatura sobre a conveniência da realização de rastreamentos populacionais para o diagnóstico do CP por causa dos custos, das dúvidas sobre a história natural do tumor, de outros problemas de saúde dos pacientes (comuns na idade em que é detectado), da inconsistência científica sobre o melhor tratamento da doença localizada na glândula e do desconhecimento sobre o impacto na sobrevida da população (5,6,10). Para tentar responder a essas dúvidas há alguns estudos prospectivos de longo prazo como o PIVOT - Prostate Intervention Versus Observation Trial (10) e o ERSPC - European Randomized of Screening for Prostate Carcinoma (7). A experiência neste Hospital Universitário Público, que ofereceu seus arquivos para defesa de Tese em outra Universidade (8), abrangendo o período de 1982-97, mostrou que de 116 pacientes com CP que procuraram a instituição espontaneamente por sintomas, e manejados predominantemente com conduta conservadora (somente 13 foram submetidos à prostatectomia radical), 110 (94.9%) apresentavam doença disseminada ou evoluíram com metástases. Essa experiência de 15 anos, de se diagnosticar os pacientes sintomáticos que passivamente procuram o atendimento não oferece bons resultados, e contrasta com o diagnóstico do CP quando realizado durante o rastreamento populacional.

CONCLUSÕES

O rastreamento para o CP em 1079 homens mostrou incidência de neoplasia em 2.5% deles, e PIN em 0.9%, resultados esses comparáveis aos referidos em campanhas semelhantes em países desenvolvidos do mundo ocidental. Não foi encontrada diferença na incidência de câncer entre brancos, mulatos e negros. Os critérios para indicação de biópsia prostática na população da região do estudo parecem compatíveis com os propostos na literatura internacional, embora os valores médios, medianos e percentil 95% do PSA em brancos, negros e mulatos não portadores de câncer, prostatite ou PIN pareçam semelhantes.

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EDITORIAL COMMENT

In this study, the authors stated that no difference on incidence of cancer was observed among white, black or mixed men. No statistical difference of PSA mean values was noted among normal whites ($n = 847$), blacks ($n = 58$) and mixed ($n = 147$) on the following age ranges: 40-49 years ($p = 0.8$), 50-59 ($p = 0.5$) and 60-69 ($p = 0.12$). PSA median values and 95% percentile for normal men of these three groups also shared similarities. PSA mean, median and 95% percentile values for whites, blacks and mixed people share similarities. The authors affirm that these data are in contradiction with data established elsewhere and deserve further studies.

It is important to remember that in countries like Brazil, on which occurred extensive and intensive miscegenation, the racial data must be analyzed with extreme caution.

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LEIOMYOSARCOMA OF THE KIDNEY**DUARTE N. BARRADAS, D. ARAÚJO, A. PIMENTA**

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ABSTRACT

Introduction: Sarcomas of the kidney are rare and constitute 1 to 3% of all malignant renal tumors. By definition, renal sarcomas are malignant mesenchymal tumors of the kidney, with a variety of histological types. Leiomyosarcoma is the most common (60%). Clinical presentation and diagnosis of these tumors are unspecific.

Case Report: A 49 years-old woman was admitted with flank pain and hematuria. The laboratory studies and the thorax x-ray were normal. Ultrasound and CT confirmed a left renal tumor, and a radical nephrectomy was performed. Immunohistochemistry confirmed a leiomyosarcoma. It revealed focal positivity for muscle-specific actin. Two years later metastatic disease in both lungs and liver was diagnosed. The patient underwent chemotherapy, without remission of the disease. One year later the patient is alive and with good health.

Discussion: The treatment of choice for leiomyosarcoma of the kidney is radical nephrectomy. The use of chemotherapy and radiotherapy is controversial and the overall prognosis is poor. Despite radical nephrectomy, the tumors have aggressive clinical course and early local and distant recurrence is common. Prognosis is generally poor, with survival less than 2 years. There are some good prognosis factors: complete excision of the tumor with negative margins, low histological grade and tumor less than 5 cm.

Key words: kidney, kidney neoplasms, leiomyosarcoma**Braz J Urol, 26: 523-525, 2000****INTRODUÇÃO**

Os sarcomas do rim são entidades raras e de mau prognóstico, representando 2 a 3% das neoplasias malignas do parênquima renal (1). Entre os tumores de origem mesenquimatosa, o leiomiossarcoma é o tipo mais frequente (60%), sendo mais raros o angiossarcoma, o fibrossarcoma, o rabdomiossarcoma e o histiocitoma fibroso maligno.

A primeira descrição de um leiomiossarcoma renal foi realizada por Berry, em 1919 (2). A incidência do leiomiossarcoma é ligeiramente maior no sexo feminino (1.5/1.0), ocorrendo geralmente entre a 4^a e a 6^a décadas de vida, afectando por igual ambos os rins, sendo 7% bilaterais.

Os autores relatam um caso de um leiomiossarcoma renal, focando aspectos relacionados com

o comportamento biológico, o tratamento e o prognóstico.

RELATO DO CASO

Mulher de 49 anos, recorreu ao serviço de urgência por dor lombar esquerda e episódios de hematúria total com evolução de 3 meses. Após a realização de ultra-sonografia e tomografia axial computadorizada (TAC) (Figura-1) que demonstraram a existência de uma neoformação renal esquerda, foi realizada nefrectomia radical. O estudo imunocitoquímico demonstrou franca positividade para o SMA (actina específica do músculo liso), permitindo o diagnóstico de leiomiossarcoma de baixo grau de malignidade (Figura-2).



Figura 1 – Tomografia computadorizada do abdômen demonstrando neoplasia renal esquerda.

Dois anos e quatro meses após a cirurgia a doente notou o aparecimento de um nódulo com cerca de 3 cm de diâmetro, localizado na intersecção da linha médio-clavicular direita com o sulco mamário.

A citologia após biópsia aspirativa mostrou tratar-se de metástase do carcinoma anteriormente diagnosticado. A TAC tóraco-abdomino-pélvica revelou metástases pulmonares e hepáticas (Figura-3).

A doente realizou 2 ciclos de quimioterapia (adriamicina, ifosfamida e dacarbazina) sem remis-

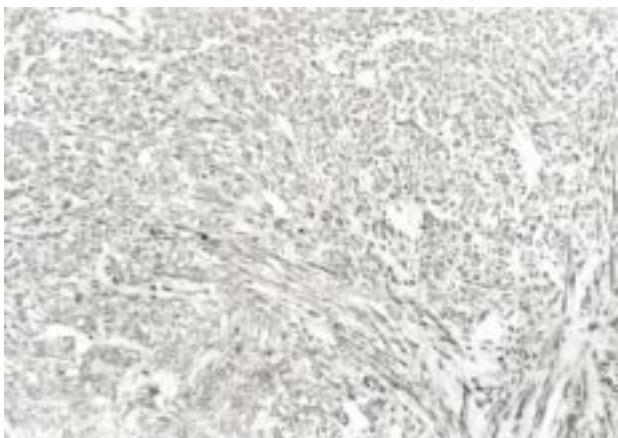


Figura 2 – Fotomicrografia do estudo imuno-histoquímico do tumor renal, demonstrando franca positividade para o SMA (actina específica do músculo liso, X100).

são da doença. Um ano após o tratamento, a paciente mantém-se clinicamente estável e sem deterioração do seu estado geral.

DISCUSSÃO

O Leiomiossarcoma renal é uma neoplasia maligna com diferenciação muscular lisa. A sua estrutura microscópica não difere do resto dos leiomiossarcomas de outras partes do organismo havendo-se estabelecido critérios estruturais e imunohistoquímicos para melhor orientação do seu prognóstico (tamanho celular, atipias, necrose e actividade mitótica), demonstrando-se os métodos imuno-histoquímicos mais fiáveis que os convencionais para determinar o potencial maligno destes tumores.

Clinicamente a dor é o sintoma mais freqüente (55%), seguido de massa palpável (33%), perda de peso e hematúria (16.5%).

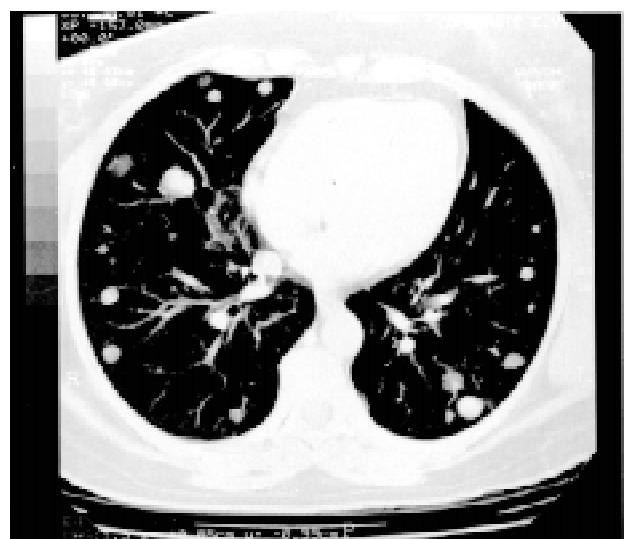


Figura 3 – Tomografia computadorizada do tórax evidenciando metástases pulmonares bilateralmente.

Os meios complementares de diagnóstico utilizados no estudo das massas renais (ultra-sonografia, urografia intravenosa e TAC) não são conclusivos para este tipo de tumor. A arteriografia sugere o diagnóstico ao proporcionar imagens de uma massa volumosa periférica hipovascular, mas não oferece elementos seguramente patognomônicos. O diagnóstico definitivo é anatomo-patológico.

A recidiva do leiomiossarcoma é habitualmente local. A metastização é mais rara (via hematogênica - pulmão, fígado e osso) e normalmente durante os 3 primeiros anos pós-nefrectomia.

O tratamento é sempre cirúrgico - nefrectomia radical. A quimioterapia parece aumentar a sobrevida. A radioterapia não altera a evolução e emprega-se apenas com fins anti-álgicos e paliativos, embora alguns autores preconizem que a radioterapia externa no leito cirúrgico pode prevenir a recidiva tumoral (3).

O prognóstico é em geral reservado, com sobrevidas inferiores a 2 anos. Foram indicados como fatores de melhor prognóstico a exérese completa do tumor com margens livres, o baixo grau histológico e tumor com diâmetro inferior a 5 cm.

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CONCOMITANT RENAL AND SPLENIC INFARCTION

SIDNEY ABREU, HOMERO ARRUDA, JOSÉ CURY

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ABSTRACT

Introduction: Some organs, such as kidney and spleen, are supplied by end-arteries that irrigate well-defined parenchyma segments. When these arteries are occluded at any point, an infarct area with posterior fibrosis and loss of function may develop.

Case Report: A 73 year-old female patient was referred for severe left flank and left upper quadrant abdominal pain for 48 hours associated with malaise and fatigue. Physical examination showed dehydration, heart rate of 100 beats/min with an irregular rhythm. Left upper abdominal palpation revealed pain. Laboratory analysis showed: lactic acid dehydrogenase = 2500 UI/ml, creatinine = 1.4 mg/ml, electrocardiography demonstrated typical atrial fibrillation, the abdominal CT scan showed no enhancement areas of spleen and left kidney. The patient was submitted to analgesia and systemic anticoagulation therapy. After 6 days the patient reported complete relief of symptomatology and was discharged.

Discussion: The kidney and spleen, like the brain, are the most common organs that have infarctions caused by cardiac embolus. Coronary artery diseases and valvopathies are found in 30% of patients with renal infarction, while cardiac arrhythmia is found in 55%. The most frequent arrhythmia is atrial fibrillation. The incidence of renal infarction in an autopsy study was 1.4%, whereas the clinical diagnosis was made in only 0.014% of the studied patients. To our knowledge, there are only six reported cases of concomitant renal and splenic infarctions. This diagnosis should always be considered in patients with severe flank and left upper quadrant abdominal pain, with previous history of cardiac illness.

Key words: kidney, spleen, infarction, arrhythmia

Braz J Urol, 26: 526-527, 2000

INTRODUÇÃO

Defini-se como infarto uma área de necrose isquêmica de um tecido ou de um órgão. O infarto freqüentemente é causado por redução súbita da irrigação arterial ou, ocasionalmente, por oclusão do sistema venoso.

Alguns órgãos, como o rim e o baço, apresentam um fluxo arterial através de artérias terminais, que irrigam segmentos bem definidos do parênquima, e portanto susceptíveis a este evento. Quando uma destas artérias é ocluída, em qualquer ponto, se desenvolve uma área de infarto “anêmico” com posterior fibrose e perda de função do órgão (1). Aqui relatamos um caso de infarto concomitante de rim e baço.

RELATO DE CASO

Paciente feminina de 73 anos apresentou-se com queixa de dor forte, tipo cólica, em flanco e hipocôndrio esquerdo há 48 horas. Queixava-se ainda de adinamia e náuseas. Antecedentes pessoais de hipertensão arterial e diabetes tipo II.

Ao exame físico: Encontrava-se desidratada, afebril, freqüência cardíaca de 100 bpm, ritmo cardíaco irregular. Dor a palpação profunda em flanco e hipocôndrio esquerdo, sem sinais de peritonite.

Exames laboratoriais: leucócitos = 11000 (3 segmentados, 56 bastões); desidrogenase lática = 2500 UI/ml; creatinina = 1.4 mg/ml; urina I = 55 leucócitos; Rx tórax = área cardíaca aumentada; eletrocardiograma = fibrilação atrial; tomografia computadorizada de

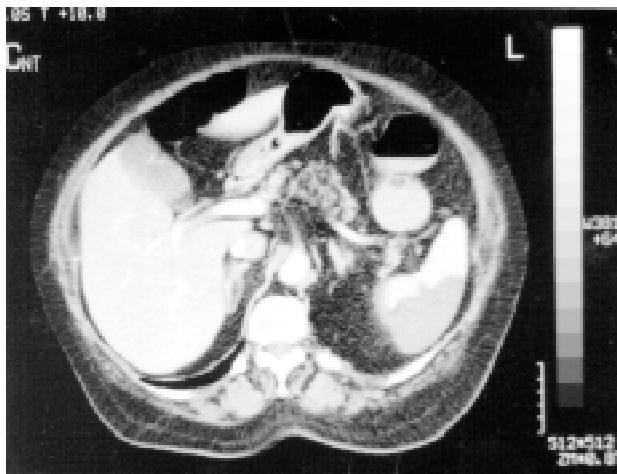


Figura 1 – Tomografia computadorizada de abdome demonstrando infarto do segmento posterior do baço.

abdome = ausência de impregnação pelo contraste em áreas segmentares do rim e do baço (Figuras-1,2).

A paciente foi submetida a hidratação, analgesia e anticoagulação sistêmica. O ecocardiograma evidenciou presença de um trombo intra-ventricular, como fonte emboliogênica. Após 6 dias de hospitalização, a paciente referiu completo alívio dos sintomas e recebeu alta hospitalar.

DISCUSSÃO

O rim, assim como o baço e o cérebro são os locais onde freqüentemente ocorrem infartos secundários a êmbolos cardíacos. Coronariopatias e valvulopatias são encontradas em até 30% dos pacientes acometidos por infarto renal. Enquanto que arritmia cardíaca está presente em 55% destes pacientes, a fibrilação atrial é a arritmia mais comum (2). Outras causas que podem ocasionar o infarto renal são: trauma abdominal fechado, manipulação durante arteriografia e injeção intravenosa de cocaína. Estudos de autópsia mencionam uma incidência de 1.4% de infarto renal. No entanto, o diagnóstico clínico prévio só foi realizado em 0.014% dos casos estudados (3). No caso de infartos esplênicos, devem ser pesquisadas causas como anemia falciforme e endocardite infecciosa.

É do nosso conhecimento que apenas 6 casos de infarto renal e esplênico concomitantes foram reportados na literatura, com as respectivas causas: 2 – fibrilação atrial crônica, 1 – defeito no septo atrial, 1 – doença car-

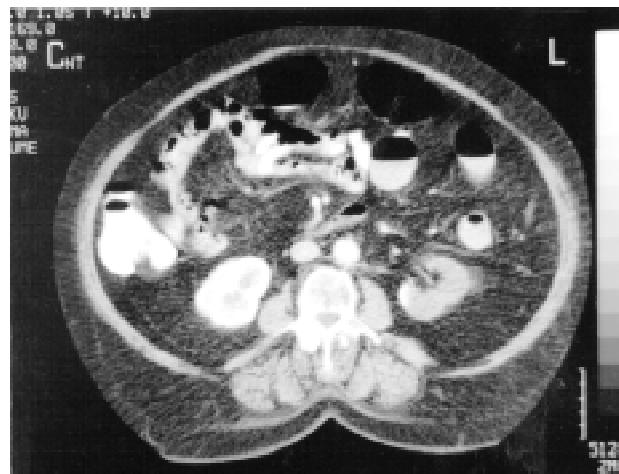


Figura 2 – Tomografia computadorizada de abdome evidencian- do ausência de impregnação pelo contraste no rim esquerdo.

díaca reumática, 1 – endocardite infecciosa e 1 – lúpus eritematoso sistêmico com anticorpo anticardiolipina.

Assim, este diagnóstico deve ser considerado em pacientes com dor severa no quadrante abdominal superior esquerdo e história prévia de patologia cardíaca, especialmente fibrilação atrial.

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TRAUMATIC TESTICULAR DISLOCATION

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ABSTRACT

Introduction: Testicular dislocation is an unusual complication of pelvic trauma. We discuss the mechanism, classification, diagnosis and factors, which influence treatment and prognosis of this entity.

Case Report: A 30-year-old male, victim of a motorcycle accident, presented at physical examination with the left hemiscrotum empty. A painful mass was palpable in the inguinal subcutaneous region, near the external ring. Surgical therapy was instituted 2 months and 15 days after injury. The testis was repositioned inside the scrotum and orchiopexy was performed.

Discussion: The traumatic testicular dislocation can be undetected at the time of the initial injury. Dislocations are usually inguinal and sometimes are bilateral. Spermatic cord lesions and testis rupture may also be associated. Early closed reduction with surgical orchiopexy is recommended since there is limited morbidity with operative exploration. Repositioning of the testis in the scrotum ensures cure when the testis is still viable.

Key words: testis, testicular, dislocation, trauma

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INTRODUÇÃO

A luxação de testículo é uma consequência rara de trauma escrotal (1-3). O primeiro caso foi relatado em 1809, em Paris, em um soldado atropelado por uma carroça (2,3). Há aproximadamente 37 publicações sobre o assunto na literatura, acumulando aproximadamente um total de 120 casos descritos. Relatamos 1 caso de luxação à esquerda do tipo inguinal superficial.

RELATO DO CASO

Paciente de 30 anos que após acidente de motocicleta apresentou hematoma perineal, que foi drenado após 6 dias em outra instituição. Passou a notar a ausência do testículo esquerdo e uma massa na região inguinal (Figura-1). Procurou nosso serviço aproximadamente 2 meses e 15 dias após o trauma.

Foi submetido à exploração inguinal esquerda sob anestesia peridural. O testículo estava no tecido subcutâneo, entre tecido fibrótico e aderências (Figura-2). Foi individualizado e fixado ao escroto. O paciente evoluiu bem.



Figura 1 – Pré-operatório. Ausência de testículo em hemi-escroto esquerdo e massa palpável na região inguinal.



Figura 2 – Transoperatório. Testículo individualizado na tela subcutânea da região inguinal esquerda.

DISCUSSÃO

A luxação de testículo geralmente é resultado de traumas tipo queda-à-cavaleiro, principalmente, em motocicletas e atropelamentos, ocorrendo menos freqüentemente as rupturas (1,2). O movimento da roda sobre o períneo ou quando o períneo é forçado contra o tanque de motocicletas parecem ser os prováveis mecanismos (3). Manifestações comuns são: dor, náuseas, vômitos, sensibilidade no testículo luxado, e vazio escrotal (1).

As luxações podem ser superficiais e internas. As primeiras podem ser inguinais superficiais (50%), pélvica (18%), peniana (8%), perineal (4%), e crural (2%) enquanto as internas podem ser canaliculares (8%), abdominais (6%), acetabular (4%) e femoral (0% - teoricamente possível). O sítio da luxação depende da direção da força e do caminho de menor resistência. As luxações canaliculares e abdo-

minais geralmente associam-se à hérnias inguinais indiretas ou à testículo atrofiado (2).

O diagnóstico pode ser retardado por edema e hematomas escrotais. Descreveu-se luxação tardia, provavelmente por avulsão do gubernaculum testis, expansão de hematoma e posição supina, agindo conjuntamente para a luxação. A força necessária para a redução não cirúrgica pode causar dano adicional ao testículo (2).

O ultra-som e a fluxometria com Doppler permitem o estudo da integridade da túnica albugínea e da simetria do fluxo sanguíneo, para descartar ruptura e torção testicular (2,3).

Ocorrendo ruptura das túnicas do cordão espermático um orifício em “casa de botão” dificulta a redução fechada (2,3).

Considerando-se a baixa morbidade da exploração cirúrgica e a importância de garantir a integridade do testículo justifica-se a cirurgia precoce (2). Biópsias transoperatórias tem mostrado ausência de espermátides, diminuição de espermatogônias e aumento relativo das células de Sertoli (3).

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ANOMALIES OF THE TESTIS, EPIDIDYMIS AND VAS DEFERENS IN NORMAL HUMAN FETUSES AND IN PATIENTS WITH CRYPTORCHIDISM

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ABSTRACT

Objectives: To compare the incidence of anomalies of the testis, epididymis and vas deferens in human fetuses without congenital abnormalities and in cryptorchidic patients.

Material and Methods: We studied bilaterally 276 testes, epididymides and vas deferens taken from 138 fresh human fetuses between 10 and 35 weeks after conception and 64 testes taken from 49 patients with cryptorchidism. The testicular anomalies were divided into anomalies of number and position; the epididymal anomalies were divided into anomalies of detachment, obliteration, number and position, and the vas deferens anomalies were divided into anomalies of obliteration and number.

Results: Of the 276 fetal testes studied, 190 (68.84%) were positioned in the abdomen, 36 (13.04%) in the canal, 48 (17.39%) in the scrotum and 2 testes, epididymides and vas deferens (0.72%) were absent. We found 3 cases (1.08%) of epididymal detachment. Of the 64 cryptorchidic testes, 37 (57.8%) were in the canal, 16 (25%) in the internal ring, 8 (12.5%) in the external ring and 4 (6.2%) were in the abdomen. We found epididymal detachment in 19 testis (29.6%).

Conclusions: The anomalies of the testes, epididymis and vas deferens are rare, found in less than 2% of the cases in fetuses without anomalies. The epididymal anomalies are more frequent in cases of cryptorchidism.

Key words: testis, epididymis, vas deferens, anomalies, cryptorchidism

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INTRODUÇÃO

O testículo humano se origina a partir de um espessamento do epitélio celomático na região medial do ducto mesonéfrico, entre a quarta e a sexta semanas pós-concepção (1,2). Durante o período fetal os testículos migram do abdômen em direção ao escroto, atravessando a parede abdominal pela região do canal inguinal. As teorias mais aceitas para explicar a migração testicular são: a)- aumento da pressão intra-abdominal (3,4); b)- desenvolvimento do gubernáculo testicular (5,6); c)- estímulos hormonais (gonadotrofina coriônica e testosterona) (7-9); d)- estímulos provenientes do nervo gênito-femoral (6,8,9).

As anomalias testiculares podem ser divididas em 2 grupos: a)- anomalias de número, divididas em agenesia (unilateral ou bilateral) e testículo ex-

tra-numerário e b)- anomalias de posição, divididas em criptorquidia e ectopia (1,2). A infertilidade é muito frequente nos pacientes com anomalias testiculares (1,2).

O epidídimo, o ducto deferente, a vesícula seminal e os ductos ejaculatórios se originam a partir do ducto mesonéfrico. O desenvolvimento deste sistema ductal termina em torno da décima terceira semana pós-concepção (2). As anomalias destas estruturas anatômicas também são prevalentes em pacientes com infertilidade, ocorrendo com freqüência em pacientes com criptorquidia e com fibrose cística (10,11).

Existem muitos estudos em crianças, feitos durante intervenções cirúrgicas (orquiodopexias, hérnia e hidrocele) e em pacientes com infertilidade que mostram a incidência de anomalias do testículo, epidídimo e do ducto deferente. (12-14).

São poucos os trabalhos que mostram a anatomia normal do testículo, do epidídimo e do ducto deferente em adultos e crianças (15-17). As pesquisas que mostram a incidência das anomalias destes órgãos durante o período fetal humano são raras (15). Trabalhos mostrando a incidência de anomalias testiculares, epididimárias e deferenciais em pacientes criptorquídicos e em fetos humanos sem anomalias congênitas feitos simultaneamente são inexistentes na literatura.

O objetivo deste trabalho é fazer um estudo comparativo em pacientes criptorquídicos e em fetos humanos analisando a incidência de anomalias do testículo, epidídimo e do ducto deferente nessas duas populações.

MATERIAL E MÉTODOS

Foram estudados 276 testículos, epidídimos e ductos deferentes provenientes de 138 fetos humanos sem anomalias congênitas do trato genito-urinário e 64 testículos, epidídimos e ductos deferentes provenientes de 49 pacientes criptorquídicos submetidos à orquidopexia.

Todos os fetos estavam em bom estado de conservação, sem nenhuma malformação congênita detectável. Os fetos apresentavam idade variando entre 10 e 35 semanas pós-concepção, idades estimadas pelo critério do tamanho do maior pé (12,18-22). Os pacientes com criptorquidia apresentavam idade variando entre 1 ano e 6 meses e 15 anos (média de 6.4 anos).

Os testículos foram considerados abdominais quando situados acima do anel inguinal interno, inguinais quando localizados entre o anel inguinal interno e o anel inguinal externo e escrotais quando localizados abaixo do anel inguinal externo.

As anomalias testiculares foram divididas em anomalias de número (anorquia ou poliorquia). As anomalias epididimárias foram divididas em anomalias de obliteração (da cabeça, do corpo ou da cauda) (Figura-1); disjunção (da cabeça, da cauda ou total) (Figura-2); número (duplicação ou agenesia) e ectopia (canal ou abdominal). As anomalias do ducto deferente foram divididas em anomalias de obliteração (segmento curto, segmento longo ou agenesia) e número (duplicação ou agenesia).

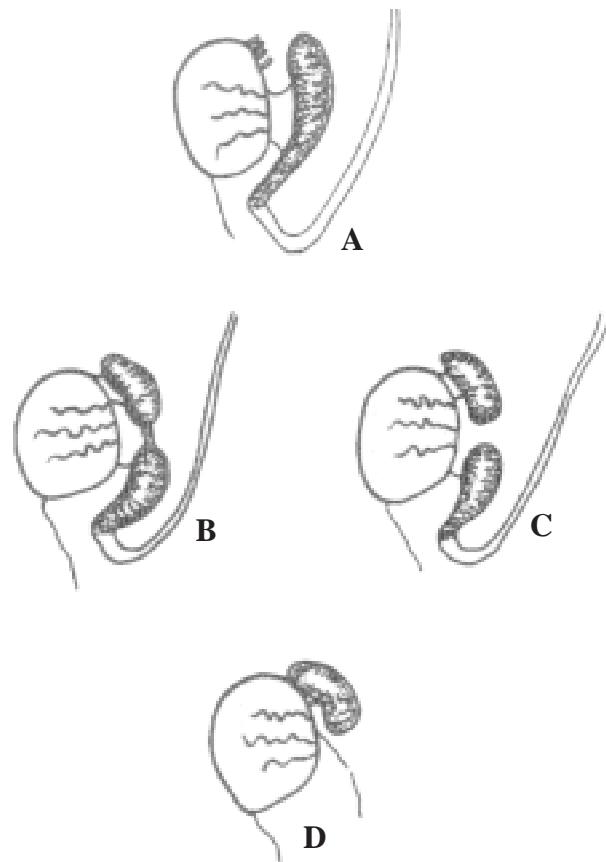


Figura 1 – Anomalias epididimárias de obliteração; A)- obliteração dos ductos eferentes; B)- obliteração do corpo do epidídimo; C)- corpo do epidídimo separado em 2 porções e D)- agenesia da metade final do epidídimo.

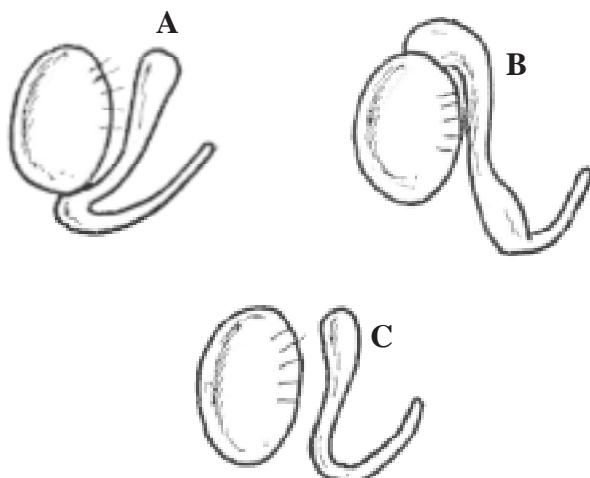


Figura 2 – Anomalias epididimárias de disjunção; A)- disjunção da cabeça do epidídimo; B)- disjunção da cauda do epidídimo; C)- disjunção total do epidídimo.

RESULTADOS

Dos 276 testículos fetais estudados 190 (68.84%) estavam no abdômen, 36 (13.04%) na região inguinal e 48 (17.39%) no escroto. Em 1 feto - 02 casos (0.72%) - os testículos, os epidídimos e os ductos deferentes estavam ausentes. Além dos casos de agenesia bilateral nós encontramos anomalias epididimárias de disjunção em 3 casos (1.08%), não encontramos anomalias de obliteração do epidídimos ou do ducto deferente. Os 4 fetos com anomalias testiculares e epididimárias estão listados na Tabela-1. Na Tabela-2 estão evidenciadas as anomalias epididimárias nos fetos e na população com criptorquidia.

Tabela 1 – Fetos com anomalias. SPC - semanas pós-concepção; TD - testículo direito; TE - testículo esquerdo.

Idade	TD	TE	Órgão	Anomalia	Lado
23 spc	abdômen	abdômen	epidídimos	Disjunção Cauda	esq
23 spc	-	-	testículo	Agenesia	bilateral
27 spc	abdômen	abdômen	epidídimos	Disjunção - cabeça	direito
28 spc	escroto	escroto	epidídimos	Disjunção Cauda	direito

Tabela 2 – Incidência das anomalias epididimárias nos fetos e nas crianças com criptorquidia. Em toda amostra fetal ocorreram anomalias em 5 casos (1.81%); na amostra dos pacientes com criptorquidia as anomalias epididimárias ocorreram em 19 casos (29.6%).

Anomalia	Agenesia	Disjunção cauda	Disjunção cabeça	Disjunção total	Total de casos
Feto	2	1	2	0	5
Crianças	0	11	4	4	19

Dos 64 testículos criptorquílicos estudados, 37 (57.8%) estavam no canal inguinal, 16 (25%) no anel inguinal interno, 8 (12.5%) no anel inguinal externo e 4 (6.2%) eram abdominais. Não encontramos nenhum caso de agenesia testicular ou testículo extra-numerário, no entanto 3 (4.7%) dos testículos criptorquílicos eram atróficos. Encontramos anomalias de disjunção epididimária em 19 casos (29.6%). Não encontramos anomalias de número ou de obliteração do ducto deferente e do epidídimos.

Para comparação das duas populações foi utilizado o teste estatístico do qui-quadrado.

DISCUSSÃO

A criptorquidia é uma das anomalias congênitas mais freqüentes, com incidência de 0.8 a 5% nos recém-nascidos masculinos (2,23-25). As anomalias testiculares de número são raras. A ausência de um ou de ambos os testículos ocorre em cerca de 3% dos pacientes com criptorquidia (1,2).

Existem 3 teorias para explicar a anorquia: a)- ausência de desenvolvimento testicular durante o período fetal; b)- interrupção do suprimento vascular do testículo durante o período fetal e c)- atrofia causada por torção testicular intra-útero (1,2). Dos 138 fetos, observamos apenas 02 casos (no mesmo feto) de anorquia

(0.72%). Dos 49 pacientes criptorquílicos não encontramos nenhum caso de anorquia. Esses dados confirmam que esta anomalia é extremamente rara tanto nos pacientes criptorquílicos como na população normal.

As anomalias epididimárias estão freqüentemente associadas à criptorquidia - 36 a 79% dos casos (12,13,17) e com à infertilidade em adultos (10). Existem muitos estudos feitos em pacientes criptorquílicos e com infertilidade que mostram a incidência das anomalias epididimárias nestes distúrbios.

Turek (17) em um estudo com crianças normais mostrou que as anomalias epididimárias estão presentes em 4% dos casos. Nós em um estudo prévio com 73 fetos humanos sem anomalias congênitas, mostramos que as anomalias epididimárias estavam presentes em 2.75% dos casos.

A incidência de anomalias epididimárias foi (com significância estatística) maior na população com criptorquidia. Este estudo confirma que as anomalias epididimárias são raras na população sem anomalias congênitas.

As anomalias do ducto deferente são responsáveis por cerca de 1 a 2% dos casos de infertilidade no homem, estando associadas em 65 a 95% dos pacientes com fibrose cística (10,11). Os estudos das anomalias do ducto deferente são raros. Encontramos agenesia do ducto deferente em 2 casos (0.72%) entre os fetos e nenhuma anomalia desta estrutura foi encontrada na população com criptorquidia.

Concluímos que: 1)- a anorquia é uma anomalia muito rara, tanto nos pacientes com criptorquidia como nos fetos; 2)- as anomalias do epidídimos são freqüentes nos pacientes com criptorquidia e raras nos indivíduos sem anomalias congênitas e 3)- as anomalias do ducto deferente são muito raras, ocorrendo apenas em associação com a anorquia e a agenesia epididimária.

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HYPERCHOLESTEROLEMIA IN RABBIT INDUCES INCREASE IN THICKNESS OF THE PENILE TUNICA ALBUGINEA

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ABSTRACT

Introduction and Objective: Hypercholesterolemia and other vascular risk factors for atherosclerosis are commonly associated with impotence. The main purpose of this study is to determine the possible effects of the hypercholesterolemic diet in the following parameters: a)- the thickness of rabbit penile albuginea tunica; b)- surface of smooth muscle cells in the corpora cavernosa; c)- blood analysis of cholesterol and testosterone.

Methods: Twenty-seven, 8 weeks old New Zealand male rabbits were randomly divided into 3 groups: group-1: the animals were treated with standard diet (low cholesterol) during 10 weeks; group-2: the animals were treated with hypercholesterolemic diet (high cholesterol) during 5 weeks; group-3: the animals were treated with hypercholesterolemic diet during 10 weeks. After the period determined, the animals were sacrificed and the penises were dissected. The morphologic characteristics of the penis and the blood levels of cholesterol, triglycerides and testosterone were determined. The morphometric analysis was performed with the aid of a computed system.

Results: The main penile size in the control group (group-1) was 2.45 cm, in group-2 was 2.54 cm, and in group-3 was 2.56 cm. There was no statistically significant difference between the groups. The main thickness of the penile tunica albuginea and the surface of smooth muscle cells were 767.1 μm and 139834 μm^2 in the control group, 810.2 μm and 142344 μm^2 after 5 weeks with hypercholesterolemic diet and 1045.3 μm and 145345 μm^2 after 10 weeks with hypercholesterolemic diet, respectively. The statistic analysis showed increase in the tunica albuginea after 10 weeks in the animals with hypercholesterolemic diet. The blood levels of cholesterol and testosterone were 100 mg/100 ml and 168.4 ng/dl in the control group, 103.4 mg/100 ml and 217 ng/dl after 5 weeks with hypercholesterolemic diet and 314.1 mg/100 ml and 1097 ng/dl after 10 weeks with hypercholesterolemic diet, respectively.

Conclusion: A period of 10 weeks of hypercholesterolemic diet induced increase of the thickness of rabbits penile tunica albuginea and increase in the blood levels of cholesterol and testosterone.

Key words: penis; corpus cavernosum; hypercholesterolemia; tunica albuginea; rabbits

Braz J Urol, 26: 535-540, 2000

INTRODUÇÃO

A ereção peniana é um fenômeno multifatorial que envolve vários sistemas. Fatores que alteram qualquer um destes, podem contribuir para a disfunção erétil. Os principais fatores de risco envolvidos são o fumo, diabetes, hipertensão arterial sistêmica e hipercolesterolemia (1). Entretanto, dúvidas existem sobre a fisiopatogenia da disfunção erétil orgânica. A incidência de impotência masculi-

na orgânica atinge índices de 50% na população com 50 anos (1), porém estes valores vão aumentando nos grupos mais velhos.

O aumento na freqüência de impotência com a idade tem sido associada às alterações arteroscleróticas nas artérias do pênis (2). Estudos em animais têm demonstrado diminuição do relaxamento dos vasos sanguíneos da musculatura lisa dos corpos cavernosos, decorrente de alterações no endotélio dos vasos, causados pela hipercolesterolemia (3). O me-

canismo da disfunção do endotélio, assim como os efeitos da hipercolesterolemia na musculatura lisa e na túnica albugínea do corpo cavernoso não foram completamente elucidados.

A túnica albugínea peniana é uma espessa e não distensível bainha que envolve os corpos cavernosos. Possui papel importante no mecanismo de ereção e afecções desta túnica podem ser responsáveis por quadros de disfunção sexual (4).

O propósito deste estudo é demonstrar os efeitos da dieta hipercolesterolêmica nas características morfométricas do pênis de coelhos.

MATERIAL E MÉTODOS

O estudo foi desenvolvido no período de janeiro a agosto de 1999.

Animais: foram utilizados 27 coelhos machos da raça Nova Zelândia, com idade de 80 dias no início do experimento. Foram divididos, de forma randomizada, em 3 grupos:

Grupo-1: composto por 7 coelhos que receberam durante 10 semanas dieta purina padrão para a idade e raça.

Grupo-2: composto por 10 coelhos que receberam durante 5 semanas dieta hipercolesterolêmica.

Grupo-3: composto por 10 coelhos que receberam durante 10 semanas dieta rica em colesterol.

Dieta: Dieta purina era composta por ração rica em sais minerais e proteínas, com baixos índices de colesterol.

A dieta hipercolesterolêmica constitui-se de ração purina acrescida de 0.5% de colesterol puro e 4% de gordura animal, foi preparada semanalmente pelos pesquisadores.

Foi fornecido aproximadamente 150 gr de ração/ diariamente para cada coelho e água livremente.

Experimento: Os animais receberam durante o período pré determinado a dieta para cada grupo. Após, foram anestesiados com tiopental intraperitoneal (5 mg/100 gr de peso) e coletado sangue venoso da orelha para dosagem sérica de testosterona total, colesterol total e triglicerídos. Foram sacrificados no mesmo momento, com 5 ml de cloreto de potássio a 10% intra cardíaco. Realizado, então, amputação peniana ao nível das glândulas de Cowper. O

pênis foi pesado com balança eletrônica e mensurado através de um paquímetro (3 medidas). Após coloração com hematoxilina e eosina foram quantificadas a espessura da túnica albugínea e a área correspondente a musculatura lisa do corpo cavernoso. Para tal foi utilizado o computador Leica 500 para a análise morfométrica. Este consta de um software que permite a avaliação histomorfométrica quantitativa e qualitativa. A lâmina histológica em estudo é demonstrada no monitor do computador. Marca-se a extensão que deseja-se mensurar, através de uma régua que é apresentada na barra de ferramentas do software, e obtém-se o valor da medida. Na mensuração da albugínea, o procedimento foi repetido em 3 locais diferentes da túnica, e realizado uma média aritmética para aproximar-se mais fielmente do valor real da sua espessura no animal em estudo. A área correspondente ao músculo liso foi avaliada da seguinte forma: selecionou-se a cor que representava o músculo na coloração utilizada e solicitou-se a mensuração desta área. O procedimento foi repetido 3 vezes e realizado média aritmética dos resultados.

Análise estatística: a comparação envolvendo variáveis independentes foi feita utilizando o teste do Qui quadrado com fator corretivo de Yates. Para identificar contraste entre grupos foi utilizado teste de Duncan. Os resultados foram considerados significativos quando $p < 0.05$.

RESULTADOS

Os resultados estão dispostos a seguir conforme os grupos delineados previamente na metodologia:

Grupo-1 (grupo controle) (Tabela-1)

Os animais tiveram um aumento do peso corporal total de aproximadamente 620 gr no final do experimento. A média do comprimento e peso penianos foi 2.45cm e 0.46 gr, respectivamente. A média da área correspondente ao músculo liso do corpo cavernoso foi $139834 \mu\text{m}^2$ e da espessura da albugínea foi $767.1\mu\text{m}$ (Figura-1). A dosagem sérica da testosterona foi 168.4 ng/dl, o colesterol total 100 mg/100 ml e os triglicerídos 98.2 mg/100ml (médias).

Grupo-2 (5 semanas de dieta hipercolesterolêmica) (Tabela-2)

HYPERCHOLESTEROLEMIA AND RABBIT TUNICA ALBUGINEA

Tabela 1: Grupo controle

	Peso do Pênis							Hormônios			
	Pré (gr)	Pós (gr)	Peso (gr)	Tamanho (μm)	TA (μm)	Corpo Cavernoso (μm ²)	T (ng/dl)	Colesterol Total (mg/100ml)	HDL (mg/100ml)	LDL (mg/100ml)	Tg (mg/100ml)
1	2600	3500	0.40	2.5 x 0.5	830.0	133752	217.0	100.0	< 10	92.3	88.3
2	2700	3500	0.40	2.3 x 0.6	760.2	139875	201.0	100.0	< 10	76.0	70.0
3	2800	3300	0.53	2.5 x 0.7	803.3	139000	118	100.0	< 10	76.0	70.0
4	3000	3500	0.55	2.7 x 0.5	684.7	143210	186.0	100.0	15.4	96.9	92.5
5	2500	2900	0.34	2.1 x 0.5	753.2	142137	189.0	100.0	< 10	61.0	145.0
6	2600	3500	0.52	2.7 x 0.6	794.4	135789	150.0	100.0	10.5	92.0	92.3
7	2700	3100	0.50	2.4 x 0.7	743.0	145075	118.0	100.0	19.7	93.9	129.0

TA = túnica albugínea; T = testosterona; Tg = triglicerídio

O aumento médio do peso neste grupo, no final do estudo, foi de 1070 gr. A média do comprimento e peso penianos foi 2.54 cm e 0.48 mg, respectivamente. A área do músculo liso e a espessura da túnica albugínea foi 142344 μm² e 810.2 μm, respectivamente. A média da dosagem da testosterona foi 217 ng/dl, o colesterol total 103.4 mg/100 ml e os triglycerídios 114.6 mg/100 ml.

Grupo-3 (10 semanas de dieta hipercolesterolêmica) (Tabela-3)

A média do aumento do peso dos animais foi 920 gr, do comprimento peniano foi 2.56cm e o peso do pênis foi 0.47gr. A área média do músculo liso do corpo cavernoso e a espessura da albugínea foi 145345 μm² e 1045.3μm (Figura-2), respectivamente. O valor médio da testosterona foi 1097ng/dl,

Tabela 2 – Grupo que recebeu durante 5 semanas dieta rica em colesterol.

	Peso do Pênis							Hormônios			
	Pré (gr)	Pós (gr)	Peso (gr)	Tamanho (μm)	TA (μm)	Corpo Cavernoso (μm ²)	T (ng/dl)	Colesterol Total (mg/100ml)	HDL (mg/100ml)	LDL (mg/100ml)	Tg (mg/100ml)
1	2600	3200	0.53	2.3 x 0.5	805.3	145625	180.0	123.0	19.8	117.8	76.6
2	2900	3300	0.61	2.4 x 0.65	905.4	139856	209.0	105.0	11.9	293.9	196
3	2500	3000	0.70	2.5 x 0.6	798.3	138998	169.0	86.0	13.7	87.0	96.1
4	2600	3400	0.56	2.1 x 0.6	799.8	142152	291.0	102.0	18.4	103.6	100.0
5	3000	3500	0.57	2.5 x 0.6	802.6	140201	186.0	139.0	17.7	157.3	70.0
6	3000	3500	0.61	2.5 x 0.6	810.3	129878	256.0	98.0	15.3	102.5	100.2
7	2400	2900	0.52	2.4 x 0.6	823.2	148999	245.0	107.0	12.4	104.2	102.3
8	2600	3100	0.54	2.3 x 0.5	745.2	133654	236.0	90.0	13.8	204.3	95.3
9	2700	3100	0.68	2.2 x 0.6	805.0	151020	259.0	100.0	15.3	178.9	112.4
10	3100	3500	0.72	2.5 x 0.6	806.0	153057	139.0	116.0	11.2	100.2	197.1

TA = túnica albugínea; T = testosterona; Tg = triglicerídio

Tabela 3 – Grupo com dieta rica em colesterol por 10 semanas.

	Pênis						Hormônios				
	Pre (gr)	Pós (gr)	Peso (gr)	Tamanho (μm)	TA (μm)	Corpo Cavernoso (μm ²)	T (ng/dl)	Colesterol Total (mg/100ml)	HDL (mg/100ml)	LDL (mg/100ml)	Tg (mg/100ml)
1	2800	3200	0.64	2.8 x 0.5	1051.2	142356	1119.0	225	45.1	165.9	70.0
2	2600	3300	0.5	2.3 x 0.5	985.3	148769	1500.0	>500	23.7	442.5	169.0
3	2800	3800	0.45	0.22x0.7	998.2	138596	1136.0	>500	25.1	438.1	184.0
4	3200	4300	0.45	2.2 x 0.6	1122.3	135789	927.0	250	35.5	195.9	92.7
5	3000	4300	0.45	2.0 x 0.7	1054.2	149563	934.0	133	25.9	91.8	76.2
6	2600	4000	0.46	2.2 x 0.5	945.3	142345	1500.0	224	32.9	176.6	72.2
7	3000	3200	0.50	2.5 x 0.5	1098.5	148963	873.0	208	10.3	203.4	74.3
8	2800	3100	0.50	2.8 x 0.5	1048.9	145236	907.0	124	30.9	79.1	70.0
9	2600	4100	0.25	2.0 x 0.5	1054.0	157015	980.0	477	10.0	471.2	98.8
10	2800	4100	0.58	2.3 x 0.6	1095.0	145017	1094.0	>500	13.8	425.2	305.0

TA = túnica albugínea; T = testosterona; Tg = triglicerídio

do colesterol 314.1 mg/100 ml e triglicerídios totais 122.2 mg/100 ml, respectivamente.

A análise estatística comparativa entre os grupos não evidenciou alterações significativas no peso e comprimentos penianos; assim como, na área correspondente ao músculo liso cavernoso e dosagem de triglicerídios. Houve aumento significativo ($p < 0.05$) na espessura da túnica albugínea somente após 10 semanas de dieta rica em colesterol. Os níveis de

testosterona e colesterol total foram significativamente maiores neste mesmo grupo.

DISCUSSÃO

Este estudo demonstra os efeitos da dieta rica em colesterol no pênis de coelhos, colaborando com outras pesquisas que vêm surgindo, que procuram esclarecer a fisiopatogenia da disfunção erétil masculina.

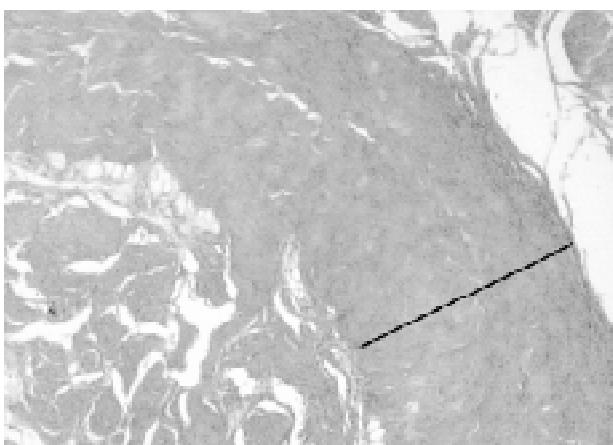


Figura 1 – Corte da tunica albuginea do pênis de animal do grupo controle, que recebeu somente dieta purina, demonstrando a espessura da albugínea - 794.4 μm (HE, X 400).

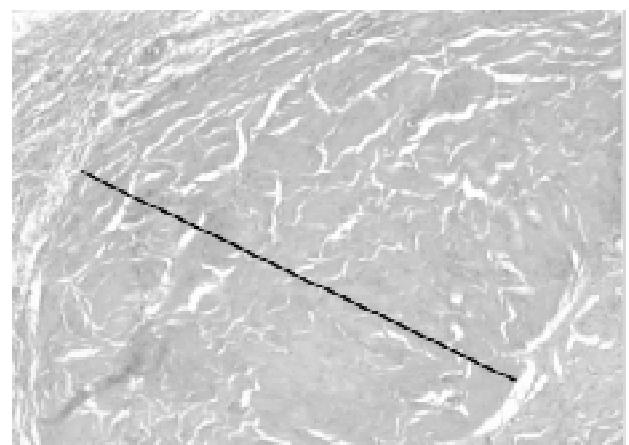


Figura 2 – Corte da tunica albuginea do pênis de animal do grupo-3, que recebeu dieta hipercolesterolêmica durante 10 semanas, demonstrando albugínea espessada – 1054.2 μm (HE, X 400)

Jünemann, em recente trabalho, avaliou a ação da dieta hipercolesterolêmica no pênis, demonstrando uma diminuição da membrana basal e diminuição dos contatos da membrana entre as células, interferindo com a transmissão intercelular da excitação (1). Constatou também uma diminuição da área correspondente a musculatura lisa cavernosa, fato este não identificado neste estudo, talvez pelo método de mensuração utilizado pelos autores, microscopia óptica associada a computador Leica neste e eletrônica naquele. Este mesmo estudo demonstrou, associado as fibras musculares diminuídas, um aumento da densidade do tecido conectivo do corpo cavernoso (1). Comparativamente, detectamos em nossa pesquisa, aumento da espessura da túnica albugínea após 10 semanas de dieta acrescida de colesterol, podendo corresponder a ação do colesterol no tecido conectivo, tornando-o mais denso, com perda da distensibilidade.

Recentemente, tem ocorrido um crescente interesse pelo estudo da forma estrutural e funcional da túnica albugínea, bem como seu papel no mecanismo da ereção peniana (4,5). Tais fatos ainda não foram totalmente compreendidos, necessitando ainda estudos maiores nesta área.

A túnica albugínea é formada por fibras elásticas e colágeno, estando envolvida com o mecanismo da ereção, participando das etapas de extensibilidade, complacência e venoclusão (6). As fibras colágenas possuem elasticidade limitada devido a sua configuração molecular, as elásticas, as quais são compostas de elastina e microfibrilas, podem alongar-se até 150% a mais do seu tamanho inicial (7). Defeitos nestas fibras alteram a hemodinâmica e complacência do pênis, podendo levar à disfunção erétil (8).

Demonstramos, pela análise morfométrica, espessamento da albugínea na vigência de níveis elevados de colesterol. Seria o espessamento um dos fatores responsável pelo mecanismo da disfunção erétil em homens hipercolesterolêmicos?

A hipercolesterolemia estimula a produção de testosterona tanto pela glândula supra-renal quanto pelo testículo (9,10). Elevados níveis de testosterona associados ao aumento do colesterol sérico parecem piorar o mecanismo de relaxamento endo-

telial, porém este comportamento não foi reproduzido quando analisado independentemente a ação da testosterona e do colesterol sobre os vasos sanguíneos (11). Neste estudo constatamos aumento da testosterona no grupo com alterações da albugínea, havendo então um mecanismo direto ou indireto da testosterona, quando em níveis supra fisiológicos, em induzir espessamento da túnica?

Ao longo do tempo tem-se procurado determinar a fisiopatogenia da disfunção erétil com o intuito de poder melhor tratar os indivíduos que possuem incapacidade de obter relações sexuais satisfatórias. Frente a isto, estudos experimentais comparando diferentes fatores de riscos e suas alterações no pênis têm colaborado para este fim, portanto devem ter sua prática estimulada.

CONCLUSÃO

A dieta hipercolesterolêmica, por um período mínimo de 10 semanas, foi responsável pelo aumento dos níveis séricos de testosterona e do colesterol total. Houve também um espessamento significativo da túnica albugínea que envolve os corpos cavernosos. Não constatamos alterações na área correspondente ao músculo liso do corpo cavernoso ou diferenças no peso e comprimento penianos.

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UROLOGICAL SURVEY

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MISCELLANEOUS

¿Qué idioma hablará MEDLINE el próximo milenio?

Escandón MAS, Gutián CG, Fernández MMG

Arch Esp de Urol, 53: 93-99, 2000

Qual será o idioma da MEDLINE no próximo milênio?

Objetivo: Analisar a evolução idiomática da Medline desde sua criação em 1966 até o presente, tanto no nível global quanto na área urológica, e extrapolar o futuro idiomático e de informação biomédica nos próximos 15 anos.

Métodos: O número total de artigos publicados, tanto na Antiga Medline de 1960-1965, quanto na atual 1966-1999, foi analisado por ano, idiomas e países de origem. O mesmo estudo foi realizado, centrando-se no campo da urologia.

Resultados: Desde sua criação, 75% dos artigos são publicados em inglês. Essa influência foi aumentando, paulatinamente, desde 1966, quando era somente 53% até 1999 quando passou a 89%, com aumento de 1% ao ano. Esses dados se reproduzem igualmente nos artigos urológicos. Os trabalhos indexados em idioma inglês aumentou, aproximadamente, 400% desde 1966, ao passo que os escritos em outros idiomas diminuíram cerca de 40%. Alguns países como Alemanha, Holanda e Japão publicam a maioria de seus artigos em inglês.

Conclusão: mantendo-se a evolução atual, a Medline irá publicar somente artigos escritos em inglês a partir de 2014.

Comentário Editorial

O número de citações de artigos brasileiros é muito reduzido, mesmo nas revistas nacionais. Os artigos publicados em 1999, em 2 revistas urológicas brasileiras de diferentes estilos, o Jornal Brasileiro de Urologia (JBU) e Urologia Contemporânea (UC), foram analisados quanto às suas referências bibliográficas. O total de artigos publicados foi 139, e apenas 7.3% citações se referiam a autores nacionais.

A dificuldade para localizar, e a escassez ou total ausência das revistas brasileiras no contexto das publicações indexadas, são fatores que explicam, pelo menos em parte, a ausência de referências nacionais.

A criação de um Índice Médico Brasileiro, sob a responsabilidade da Associação Médica Brasileira e suas associadas, informatizado e distribuído às bibliotecas sob a forma de CD-ROM, será a estratégia mais adequada para contornar esse obstáculo.

As citações nacionais devem ser incrementadas nas revistas brasileiras, através das comissões editoriais de nossas revistas, que devem estimular as citações de artigos nacionais, como também lutar pela indexação de nossas revistas.

Os dados oferecidos pelo artigo revisado são assustadores, e mostram a necessidade de mudança urgente, dado o perigo iminente de desaparecermos por completo do cenário mundial.

Dr. Nelson Rodrigues Netto Jr.

ONCOLOGY

Dilema en el tratamiento del angiomiolipoma

Ikari O, D'Ancona CAL, Prando A, Rodrigues-Netto Jr N

Arch Esp Urol, 53: 425-429, 2000

O dilema do tratamento do angiomiolipoma renal

Objetivo: Revisar a experiência com os angiomiolipomas renais.

Casuística e Métodos: O total de 27 pacientes, 26 do sexo feminino, com o diagnóstico de angiomiolipoma renal foram estudados. Destes, 23 apresentavam comprometimento renal unilateral (85%) e, das 4 pacientes com lesão bilateral (15%), três tinham associação com a esclerose tuberosa (10%).

Resultados: Tratamento cirúrgico foi instituído em 3 pacientes com lesão renal bilateral e num caso com acentuado comprometimento renal, unilateral. Os demais encontram-se em seguimento, cujo período mediano é de 38 meses.

Conclusão: tumores com tamanho superior a 4 cm, sintomáticos ou associados à esclerose tuberosa devem ser tratados cirurgicamente. Nos tumores menores de 4 cm, a observação clínica periódica está indicada.

Comentário Editorial

Os angiomiolipomas ou hamartomas renais são tumores benignos, ocorrendo ao redor de 3%, podendo manifestar-se de duas formas: isolada ou associada à esclerose tuberosa. A forma isolada é, geralmente, unilateral, de pequeno tamanho e assintomática. Quando associada à esclerose tuberosa, geralmente é bilateral e multifocal. A associação com a esclerose tuberosa ocorre entre 40 a 80% dos casos. Em 10% pode ocorrer sangramento intenso, acompanhado de choque hipovolêmico.

A presença de gordura no interior de um nódulo renal, apesar de não patognomônica, virtualmente conduz ao diagnóstico de angiomiolipoma. Por isso, o método radiológico ideal para caracterizar o angiomiolipoma é a tomografia computadorizada, que apresenta acurácia de 95%.

No presente estudo a maioria dos casos era unilateral (85%) e assintomáticos, tamanho mediano de 2.3 cm x 2.0 cm. O padrão de crescimento tumoral permaneceu inalterado em 20 pacientes, e em 3 houve crescimento médio de 1.2 cm, durante 38 meses de acompanhamento. Todos os casos de comprometimento bilateral eram sintomáticos, com manifestação dolorosa abdominal intensa, e choque hemorrágico, associados à esclerose tuberosa (75%).

Dessa forma, os dados sugerem que quando o tumor é bilateral, e principalmente quando associado à esclerose tuberosa, as complicações são maiores e necessitam tratamento cirúrgico precoce.

A crioablação por laparoscopia ou terapia por radiofreqüência, permitindo a enucleação de pequenas lesões renais com segurança, poderão vir a ser o tratamento de eleição desses tumores em condições clínicas favoráveis.

Dr. Osamu Ikari

Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng/ml or less

Carvalhal G F, Smith DS, Mager DE, Ramos C, Catalona W
J Urol, 161: 835-839, 2000

Toque retal para detectar Ca de próstata com PSA igual ou menor que 4 ng/ml

Objetivo: Avaliar os índices de detecção do Ca de próstata em indivíduos com alterações no toque retal (TR), diante de PSA 4ng/ml ou inferior, como também, determinar o estádio e o grau dos tumores evidenciados.

Material e Métodos: Em programa de rastreamento interessando 22.513 voluntários, foram levantados dados de PSA e TR a cada 6 meses. A biópsia (BX) foi recomendada na presença de alterações. O subgrupo de 2.703 homens, brancos e negros, todos com PSA até 4ng/ml ou inferior, mas com TR suspeito foram submetidos a BX.

Resultados: Em 70% das biópsias realizadas não foram encontradas diferenças quanto à idade, raça ou nível do PSA. BXs positivas (13%) foram correlacionadas com a idade, raça e PSA ($p < 0.003$). O valor preditivo positivo do TR suspeito foi 5%, 14% e 30% em homens com PSA entre 0-1.0; 1.1-2.5 e 2.6-4.0 ng/ml, respectivamente. Todos os tumores eram localizados clinicamente. Em 72% dos casos estadiados cirurgicamente, 82% foram órgãos confinados e 78%, moderadamente diferenciados.

Conclusões: O valor preditivo positivo do TR suspeito foi importante em homens com PSA baixo. A maioria dos tumores detectados era clinicamente significativos e potencialmente curáveis.

Comentário Editorial

Mais recentemente tem-se concluído que o rastreamento do câncer da próstata contribui para a redução das taxas de mortalidade específica por doença (1). A melhor estratégia para a implementação destes programas de rastreamento, no entanto, ainda não está bem definida. Estudo europeu concluiu que o toque retal teria um valor preditivo muito baixo para a detecção de câncer e que pouco acrescentaria à dosagem simples dos níveis de PSA (2).

O presente trabalho se reveste de grande importância, pois ao estudar as taxas de detecção de câncer prostático, em pacientes com toque retal suspeito, demonstra que o valor preditivo positivo (VPP) do mesmo não é desprezível (VPP geral = 13%; VPP para PSA entre 2.6/4.0 ng/ml = 30%). Considerado a raça, o estudo revela que entre os Afro-americanos o VPP do toque retal é ainda maior (VPP para PSA entre 2.6 e 4.0 ng/ml = 50%; sendo a raça negra um determinante positivo para a detecção do câncer da próstata através do toque retal [$p = 0.003$]).

Talvez o achado mais significativo do estudo seja o de que a maioria dos canceres detectada exclusivamente pelo toque retal mostrou-se confinados ao órgão, sendo potencialmente curáveis pela cirurgia radical. Tais dados, inegavelmente, reforçam a necessidade de continuarmos a realizar o toque retal na população, no intuito de detectar e tratar precocemente as neoplasias malignas da próstata.

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Dr. Aloysio Floriano de Toledo

UROLOGICAL NEUROLOGY AND FEMALE UROLOGY

Bladder stretch alters urinary heparin-binding epidermal growth factor and antiproliferative factor in patients with interstitial cystitis

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J Urol, 163: 1440-1444, 2000

Distensão vesical altera o fator de crescimento heparina-epitelial e o fator anti-proliferativo na urina de pacientes com cistite intersticial

Objetivo: Verificar se o estiramento provocado pela hidrodistensão altera a atividade do fator anti-proliferativo ou a produção de fator de crescimento epidérmico capaz de ligar heparina (HB-EGF – Heparin-Binding Epidermal Growth Factor), previamente relatados como alterados em pacientes com cistite intersticial.

Material e Métodos: 15 pacientes (13 mulheres e 2 homens) e 13 controles (mulheres pareadas por idade) colheram urina imediatamente antes, 2 a 4 horas após e 2 semanas após hidrodistensão vesical a 80 cm H₂O, repetida 3 vezes, sob analgesia. O HB-EGF foi mensurado com ELISA e o fator anti-proliferativo foi mensurado pela captação de 3H-timidina por células uroteliais normais.

Resultados: A hidrodistensão levou a um acréscimo do HB-EGF urinário na direção dos valores dos controles ($P = 0.003$, 2 horas após, porém $P = 0.67$, 2 semanas após) e reduziu a atividade do fator anti-proliferativo tanto após 2 horas ($P = 0.0000004$) quanto após 2 semanas ($P = 0.04$), com relação aos controles.

Conclusões: A hidrodistensão vesical foi capaz de aumentar o HB-EGF urinário e reduzir a atividade antiproliferativa dos pacientes com cistite intersticial com relação aos controles, isto dando suporte ao possível papel desses fatores na fisiopatologia da cistite intersticial.

Comentário Editorial

Qualquer estudo acerca de cistite intersticial (CI) já começa com um viés, pois desconhecemos em grande parte a fisiopatologia e o diagnóstico da cistite intersticial. Dessa maneira, como assegurar que os pacientes, realmente, tenham cistite intersticial. Talvez isso explique o baixo impacto na melhoria da qualidade de vida, a longo prazo, quando utilizados tratamentos, como agora proposto (2).

Pelo exposto, são necessários marcadores para a doença, que seriam superiores aos escores ou ao teste do potássio, de baixa especificidade (3). Além de fornecer alguma informação fisiopatológica, os autores nos apresentam alterações de peptídios urinários que podem eventualmente tornar a CI uma doença de diagnóstico e tratamento menos empíricos.

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Variations in strategy for the treatment of urethral obstruction after a pubovaginal sling procedure

Amudsen CL, Guralnick ML, Webster GD
J Urol, 164: 434-437, 2000

Estratégias de tratamento de obstrução uretral após sling pubouretral

Objetivo: Avaliar o sucesso de diversas técnicas para o tratamento da obstrução após cirurgia de sling pubouretral.

Materiais e Métodos: 32 mulheres tratadas com sling (vários materiais), referidas por possível obstrução infravesical, foram avaliadas por história clínica, exame físico, diário miccional, cistoscopia e video-urodinâmica. A correção da obstrução foi realizada sempre por via transvaginal e a técnica utilizada levou em conta o material do sling, erosão uretral, incontinência urinária ou outra enfermidade uretral. O resultado foi avaliado através de questionários de qualidade de vida, diário miccional e questionário uroginecológico.

Resultados: 30/32 (93.7%) mulheres tinham urge-incontinência, 20/32 (60.5%) faziam cateterismo intermitente limpo, 6/32 (18.7%) estavam com sonda de demora e 3/32 (9%) e também tinham queixa de IUE. Após a incisão do sling 29/32 (93.5%) obtiveram micção eficiente em uma semana, 20 tiveram os sintomas de urge-incontinência solucionados, mas 3 desenvolveram IUE. O total de 27 mulheres (84%) informou que a continência estava muito melhor que antes do primeiro sling.

Conclusões: A uretrolise pode não ser apropriada para o tratamento de todos os casos de obstrução após cirurgia de sling. A utilização de várias técnicas, levando-se em conta o material do sling, e a presença de doença uretral associada, permitem alcançar sucesso na maioria dos casos.

Comentário Editorial

Os autores adotaram uma abordagem cirúrgica passo-a-passo (dissecção, isolamento e seção do sling na linha média, dissecção lateral, dissecção circumferencial da uretra, uretrolise completa) até que o objetivo intra-operatório (correção da angulação sagital e micção com credé com a bexiga cheia) fosse alcançado. Dois pontos chamam a atenção: slings de fáscia autóloga foram associados a uma maior fibrose periuretral e necessitaram de maior dissecção; todos os casos de erosão uretral (3 casos) estavam associados a slings sintéticos, sendo que em 2 destes casos além do desbridamento e fechamento da uretra foi interposto um retalho de Martius. Causa alguma estranheza que 5 casos com persistência de obstrução tenham sido incluídos nesta casuística. Os autores relatam sucesso de 84%, mas melhor seria se todas as pacientes, e não apenas aquelas com incontinência recidivada, fossem submetidas à avaliação urodinâmica, para que dados objetivos da desobstrução fossem obtidos (ainda não temos parâmetros definitivos de obstrução infravesical em mulheres (1-3). Ficam 2 lições: a complicação mais frequente do sling pubovaginal, a obstrução, pode ser tratada de forma eficiente com uma abordagem cirúrgica racional e escalonada; a incontinência após este tipo de tratamento geralmente não é pior que a inicialmente referida (apenas uma paciente solicitou tratamento adicional: injeção de colágeno).

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The urethrodetrusor facilitative reflex in women: results of urethral perfusion studies

Bump RC

Am J Obstet Gynecol, 182: 794-804, 2000

Reflexo uretrodetrusor facilitatório em mulheres: resultados de estudo de perfusão uretral

Objetivo: Descrever os efeitos da perfusão uretral sobre a atividade detrusora em mulheres com incontinência urinária (de esforço, urge-incontinência ou mista) e/ou prolapsos genitais.

Métodos: Em 63 pacientes foram mensuradas a pressão vesical, abdominal e uretral com instilação de fluido na uretra. O estudo foi considerado positivo se a perfusão uretral provocasse contração detrusora.

Resultados: Em 9 (14%) das mulheres o estudo foi positivo. O estudo foi positivo em 53% (9/17) das mulheres com instabilidade detectada na cistometria sem perfusão e em nenhuma com bexiga instável. Mulheres com incontinência mista tinham maior probabilidade de terem o teste positivo que as que não tinham incontinência mista (57% versus 10%, P = 0.006).

Conclusões: Positividade no teste de perfusão uretral foi mais comum em mulheres com instabilidade, mas não discriminou nenhuma paciente a mais que a cistometria convencional. A associação da positividade do teste com incontinência mista parece ser mais associada a perda de inibição central que à estimulação uretral.

Comentário Editorial

Este estudo foi planejado para responder uma questão importante do ponto de vista prático. Definir quais são as mulheres com incontinência mista a ser primeiramente operadas (porque a instabilidade é causada pela perda de urina e estimulação uretral) ou tratadas clinicamente (sem instabilidade com perfusão uretral e instabilidade na cistometria provocativa convencional). O teste foi positivo em uma parcela significativa das pacientes, todavia não discriminatório. Uma explicação possível é a pequena casuística com grande heterogeneidade diagnóstica. No seguimento dessas pacientes, apenas duas optaram pelo tratamento cirúrgico (colágeno periuretral). Todas as demais pacientes com instabilidade foram tratadas clinicamente (medicações ou tratamento comportamental) com bom resultado. Embora o estudo seja preliminar, o dogma de estimulação uretral per se gerando instabilidade detrusora deve ser questionado, principalmente pelo seu pequeno suporte na literatura.

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RECONSTRUCTIVE SURGERY

The Monti procedure: applications and complications

Monti PR, de Carvalho JR, Arap S

Urology, 55: 616-621, 2000

A técnica de Monti: indicações e complicações

Em 1980, Mitrofanoff conseguiu restabelecer a continência urinária com sucesso, implantando em bexigas neurogênicas, tubos confeccionados com intestino delgado. Desde o início, a dificuldade era a escolha do conduto eferente, a ser cateterizado.

O apêndice cecal é a estrutura ideal a ser usada como conduto eferente, entretanto, nem sempre é disponível. Assim, quando o apêndice não é disponível, qualquer outro substituto não oferece os mesmos resultados. Além disso, é praticamente impossível prever no pré-operatório, a possibilidade de utilização do apêndice na reconstrução urinária.

Quanto ao aspecto técnico, deve-se utilizar segmentos muito curtos, de preferência único. O comprimento do tubo é determinado pela espessura da parede abdominal, medida através de uma agulha introduzida no local previsto para o estoma.

O processo de Monti, reproduzindo o conceito de Mitrofanoff, é a principal característica dessa técnica, obtendo a continência urinária em 90% dos casos.

A técnica é sempre recomendada quando o apêndice não está disponível.

Comentário Editorial

A técnica de Monti, pela simplicidade e efetividade, representa uma das grandes contribuições para o tratamento da incontinência urinária, quando indicado o princípio de Mitrofanoff.

Como tudo que é simples e efetivo, sua utilização é altamente recomendada.

Dependendo da extensão a ser substituída, pode-se usar um único ou duplo segmento intestinal, sempre com excelente resultado.

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