

“...obesity did not predict immediate up-grading, but rather long-term progression”

One key unanswered question is whether the link between obesity and prostate cancer progression is reversible. If an obese man diagnosed with prostate cancer loses weight, does he reduce his risk of disease progression? In animals, weight loss slows prostate cancer growth.⁸ Moreover, weight loss before prostate cancer diagnosis has been associated with a reduced risk of biochemical recurrence after diagnosis.⁹ Whether weight loss or other interventions targeting the obese milieu (such as increased physical activity or pharmaceutical agents) after diagnosis influences cancer outcomes remains unclear. Heart disease is the leading cause of death in men with prostate cancer;¹⁰ this is especially true among men with low-risk prostate cancer undergoing active surveillance where ‘progression’ is defined as a Gleason score ≥ 7 or ≥ 3 positive cores but risk of prostate-cancer-specific death is very low. Moreover, obesity has been linked to a poorer quality of life for patients with prostate cancer, including increased incidence of urinary problems such as incontinence and vitality.⁷ Thus, weight loss interventions among these men might have beneficial effects beyond reducing cancer progression, including improving cardiovascular health and quality of life.

The reasons behind the obesity-aggressive prostate cancer link are likely to be multifactorial.¹ Adipose tissue is an active endocrine organ that influences diverse physiological processes. Hormones, cytokines and other factors released by adipose tissue might act locally on prostate tissue or systemically by influencing tumour cells in circulation or by priming the site of metastasis. Circulating levels of insulin, free (bioavailable) insulin-like growth factor 1 (IGF-1), and lipids are altered in overweight patients compared with normal-weight individuals. Additionally, obesity is associated with chronic, low-grade inflammation that influences inflammatory cytokine levels and affects tissues in metabolic organs.¹ An understanding of the molecular basis of the link between obesity and prostate cancer progression will help to illuminate opportunities for secondary prevention or therapy by targeting the key tumour or systemic obesity pathways, and might also identify novel biomarkers that drive prostate cancer progression.

Given the unequivocal data linking weight loss and exercise with improved cardiovascular outcomes, and the increasingly strong data linking obesity with prostate cancer progression across nearly all disease stages, men with prostate cancer should be encouraged to exercise and lose weight (except in late-stage disease wherein cachexia sets in and, therefore, weight loss should be avoided). However, whether weight loss and exercise also lowers the risk of cancer progression remains to be determined.

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STONES

Guidelines reignite interest in medical treatment of stones

Hans-Göran Tiselius

New AUA guidelines on the management of patients with kidney stones are a welcome addition to a field that, over the past few decades, has been neglected by urologists. Despite some limitations, this document is an extremely important reminder of what we can—and should—offer our stone-forming patients.

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In the recently published AUA (American Urological Association) guidelines on the management of patients with kidney stones,¹ a number of straightforward recommendations are given with the aim of providing effective treatment to prevent recurrence for patients with stone formation in the urinary tract. This publication is a very welcome addition to a field that, over the past few decades, has been seriously neglected by urologists as well as other health-care professionals responsible for the care of these patients.

When modern techniques for stone removal (shockwave lithotripsy, percutaneous nephrolithotomy, ureteroscopy and retrograde intrarenal surgery) were introduced and developed during the 1980s, the enthusiasm for these new methods diverted interest away from biochemical and medical issues. Stone removal had become so easy, it was a common opinion that medical aspects did not require much attention.² The authors of these new guidelines state that there is an increased interest in medical issues; such a development would indeed

be nice, but I am not sure it is a true representation of the field. Medical treatment to prevent recurrence is, however, beneficial in several ways, both for the individual in terms of decreased suffering from new stones and complications associated with stone removal and for the health-care sector in terms of economical savings.³

The authors initially declare that these guidelines were written as a recommendation to practitioners and clinically active urologists and nephrologists. To convey this message to the medical profession is, of course, extremely important for the achievement of good outcomes, but it also requires a reasonable knowledge of the mechanisms of stone formation and how evaluation and treatment of affected patients should be designed. Obviously it is not possible to provide an extensive education in a guideline document, but if the principles presented in this document are adopted by the urologists and nephrologists responsible for the care of patients with urolithiasis, then the guidelines have served their purpose.

“Resuscitating the art of recurrence prevention in urinary stone disease is essential...”

24 h urine analysis for risk factors of stone formation has been established as a routine procedure for patients with recurrent stone formation, with residual stones or fragments, or those with stone compositions that suggest a high risk of recurrence (cystine, uric acid, infection and brushite stones). 24 h urine analysis is also recommended for children with stones and other patients who experienced stone formation early in life. The AUA panel's opinion is that two such samples should be collected and analysed. The handling of these samples is, however, of fundamental importance and it would probably have been of some additional help for the general practitioner to give some hint on the suitable preservatives to use, and to discuss the most common problems associated with urine collection and analysis. For example, urine is commonly collected during weekends when the risk situation might differ from that on other week days, and patients tend to drink more fluid than normal during the testing period. Loss of urine during the collection period is frequently encountered and, even with careful instructions, the period during which urine is collected might differ

from that prescribed. Without appropriate sample handling, 24 h urine analysis might be useless.

However, the guidelines continue with a series of valuable recommendations that provide an acceptable basis for recurrence prevention with dietary and possibly pharmacological treatment. Pharmacological intervention is reserved for those with severe disease. Although very few studies have critically analysed the effects of dietary and drinking advice, it can be assumed that such recommendations, in the long term, are hampered by a compliance that is markedly lower than for pharmacological agents, which is maximally around 50–60%. In view of this information, I agree completely that pharmacological treatment should be given to patients with severe disease, and to others who are motivated to prevent recurrence when stone formation continues despite dietary and drinking recommendations. In my own experience, it is very difficult to get a patient to accept the often demanding pharmacological treatment of cystinuria, and it would indeed be of interest to know how compliant the authors' patients are with the suggested protein-restricted diet. For patients with cystinuria, it would have been of value to include a warning against the common use of sodium bicarbonate, which increases the urinary excretion of cystine.

The advantages and disadvantages of calcium intake are a source of confusion to clinicians; the available literature is open to interpretation and might lead to inappropriate conclusions. Data demonstrating that a high calcium intake is associated with a reduced risk of stone formation is valid only up to a certain threshold and, therefore, I note with appreciation that an upper limit of 25–30 mmol of calcium (1,000–1,200 mg) is presented in the AUA guidelines.¹ Although there is a significantly increased risk of calcium oxalate stone formation in patients with a low intake of calcium, it is important to remember that an increased intake of calcium increases the risk of stone formation.

Many studies have shown that thiazides and potassium citrate are effective for recurrence prevention,^{4–6} but as the AUA guidelines also mention, few randomized studies have been performed, and those that have been published have relatively short follow-up periods. These shortcomings have been explained by a lack of interest from pharmaceutical companies, which is probably true to some extent, but we must also blame the urological profession for this lack of interest



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and progress. Nevertheless, so far it has been shown that thiazides and potassium citrate can counteract stone formation by lowering urinary calcium and by increasing citrate and pH, respectively. Moreover, potassium citrate increases inhibition of crystal growth and aggregation. For practical treatment of the recurrent stone former, the practitioner or clinician might be interested in the therapeutic doses that should be prescribed. For some reason, such data are only given for thiazides and not potassium citrate.

In a very interesting recommendation (number 16), it is suggested that thiazides or potassium citrate can be prescribed to recurrent stone formers even in the absence of knowledge of their urine composition or if their urine is without abnormalities. I fear that an unwanted consequence of this recommendation might be that clinicians with limited or no interest in biochemical issues will proceed directly to thiazide or potassium citrate treatment without undertaking urine analysis. Personally, I am strongly in favour of an adequate analysis of risk factors in urine; I believe the resulting information is mandatory both for dietary counselling and for selection of the most appropriate pharmacological agent, when needed.

Another doubtful recommendation is found under point 23, where it is suggested that “if patients remain free of stones for an extended period of time” treatment discontinuation should be considered, followed by new analysis of risk factors. Irrespective of how an “extended period” is defined, do the authors really believe in recurrence prevention? Freedom from recurrent stone formation should be the expected and desired outcome of the treatment and not a positive surprise. In my opinion, treatment to prevent recurrence should continue unless the basic risk-situation changes in a way that motivates urine analysis without medication.

I am also a little bit uncomfortable with the general recommendation to use aceto-hydroxamic acid (AHA) to treat selected patients with infection (struvite) stone disease. Given the serious adverse effects of AHA, which include alopecia, nervousness, nausea, vomiting, leg oedema and pain, I think that these patients should be managed only by those who have specific experience with this kind of treatment. An alternative in such cases might be percutaneous chemolytic treatment with Renacidin™ (United-Guardian, USA; hemiacidrin, a 10% solution containing citric acid, glucono-delta-lactone, magnesium hydroxycarbonate, magnesium citrate, and calcium carbonate and adjusted to a pH around 4) with or without simultaneous shockwave lithotripsy.^{7,8}

Aside from the few critical comments outlined above, it is important to emphasize that medical treatment of patients with stone disease is a very important, albeit difficult, task, partly complicated by our incomplete understanding of the mechanisms that lead to stone formation. These new guidelines are very useful and an extremely important reminder of what we can and should offer our stone-forming patients. Resuscitating the art of recurrence prevention in urinary stone disease is essential, and I strongly recommend that all urologists carefully read this document.

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MALE FACTOR INFERTILITY

Prediction models for assisted reproductive technology

Vitaly A. Kushnir and Norbert Gleicher

A new model that predicts *in vitro* fertilization outcomes is planned by the Society for Assisted Reproductive Technology based on US data. However, the proposed model ignores important variables and does not address the most important clinical outcome: the birth of a healthy baby to a healthy mother.

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Ideally, every medical treatment—including fertility treatments—should be predictable in outcome. Yet, the multifactorial nature of human disease, genetic factors, racial and ethnic differences and age considerations, among many other differentiating factors, have kept outcome prediction models wanting throughout medicine. Though commendable in its efforts, a recently published study by Luke *et al.*¹ on assisted reproductive technology (ART) provides a good example of this problem; in content and conclusions, this study demonstrates well the current limitations and dangers of exaggerating the prognostic accuracy of prediction models.

Having at their disposition the very large national database of the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) in the USA for the years 2004–2011, the investigators' intention was to build a predictive model for live and multiple births within the first three autologous egg cycles and a single-donor egg cycle. Uniquely, they used linked data by tracking patients who received care at different *in vitro* fertilization (IVF) centres across the USA. They announce in their manuscript that the model established in their study will be implemented on the SART website, “so that patients considering initiating a course of ART can input their data on the website to generate their expected outcomes.”

Though the authors note that they validated their data set against annual SART reports from various US clinics, we consider the invitation of the public to make use of their model premature and potentially misleading. In prematurely implementing this prediction model, SART would repeat their previous mistakes of agreeing to accumulate and report national ART outcomes under Congressional mandate (The Fertility Clinic Success Rate and Certification Act, 1992;

<http://www.cdc.gov/art/Policy.htm>) and, more recently, voluntarily doing so in the form of the SART CORS, after the Centers for Disease Control and Prevention (CDC) took over administration of the mandate (<http://www.cdc.gov/art>).

The shortcomings of these two existing national ART outcome-reporting systems were recently summarized by Williams *et al.*² and our group.³ We believe that current reporting by some ART centres is potentially misleading and that, sometimes, no reporting might be preferred.⁴ Analogies between shortcomings in national ART outcome reporting and the prediction model suggested by Luke *et al.*¹ seem obvious; during validation of the model, discrepancies were reported that largely related to over-reporting of so-called unexplained infertility and ‘other’ diagnoses. These diagnostic groups tend to include women who fail to be correctly diagnosed with low functional ovarian reserve (FOR).⁵

Inaccurate diagnoses reduce the usefulness of results. In addition to inaccurate diagnoses, the model is based on only seven variables: female patient age, BMI, history of prior full-term birth, number of diagnoses, specific diagnosis, oocyte



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