Urol Res (2006) 34: 118–121
DOI 10.1007/s00240-005-0022-4

ARTICLE

Norbert Laube · Michael Pullmann

The use of risk indices: do they predict recurrence? Yes, they (at least some) do

Accepted: 2 November 2005 / Published online: 6 January 2006

Abstract A suitable and advisedly used risk index is an effective tool for improving prevention, therapy monitoring and classification of almost unmanageable amounts of analysis data and diagnoses. In contrast to statistically founded indices, causality-based risk indices can provide a fundamental insight into the mechanisms of the underlying pathology. However, understanding of stone formation as the result of many linked and often non-linear individual processes must be further improved. Only in this way can risk indices be optimized or better ones be developed. We are confident that, with consistent research efforts, science will be able to predict recurrence of stone formation more accurately within the next couple of years.

Keywords Risk index · Stone formation · Causality · Predictive ability

Introduction

Risk indices: placebos for physicians and hospital statisticians or meaningful tools for the medical practice? This is an exciting question and we are delighted to define our positive viewpoint.

As scientists in the area of medicine who are personally involved in the development of risk indices, we strongly believe in their potential.

N. Laube (✉)
Division of Experimental Urology, Department of Urology,
University of Bonn, Sigmund-Freud-Straße 25,
53105 Bonn, Germany
E-mail: norbert.laube@ukb.uni-bonn.de
Tel.: +49-228-2879106
Fax: +49-228-2876344

M. Pullmann
Geodynamics and Physics of the Lithosphere,
University of Bonn, Bonn, Germany

Classifying risk

In our daily life, risk has several aspects. While personal risk is in most cases problematic to specify, statistical risk can be calculated with sufficient precision for a (homogenous) group of individuals. But what is risk itself?

In the common language use, the term ''risk'' is used in different contexts [1]. Hence, its meaning differs considerably. In the general medical context, ''risk'' describes a state ranging from ''speculation'' to ''danger''.

In the scientific context, risk has at least two components: the probability of occurrence and the magnitude of event to arise. For example in the view of an insurance, the risk of an earthquake occurring in Los Angeles due to the San-Andreas fault can be described as the product of the probability of occurrence and the damage caused by it.

In order to rate and to manage risk it is useful to classify it. One way of gaining a measure for risk is to define a risk index.

An index can be regarded as a calculable quantity, which can be ranged in a scale of risk. By specifying a risk index, we can classify the risk according to all other risks within the scale. Therefore, researchers have created a process of objectifying risk by the means of introducing a measurement for it.

Introductory example

Since we have not yet accomplished a definite prediction of an individual risk of recurrence, doubts regarding the usefulness of such indices—backed by ''negative examples from the daily clinical routine''—can arise quickly. However, we believe that suitable indices, properly applied, should be used more often for the benefit of patients.

The principal necessity of indices for compressed depiction of a complex disease pattern is undisputed:

For example, what does the following urinalysis of a CaOx stone patient tell us? V 1.46 l/12 h; pH 5.91; Na 40 mmol/l; K 17 mmol/l; Ca 2.28 mmol/l; Mg 1.48 mmol/l; NH_4 14.4 mmol/l; Cl 41 mmol/l; PO_4 8.9 mmol/l; SO_4 5.1 mmol/l; creatinine 3.25 mmol/l; uric acid 0.86 mmol/l; oxalic acid 0.098 mmol/l; citric acid 0.878 mmol/l.

Does this patient have a metabolic problem? Is the patient at a high risk of stone formation? Are the concentration values ''good'' or ''bad''? How much time do you have in your daily clinical routine for detailed interpretation of individual data? A crystallization risk index can be of help here. The BONN-Risk-Index of this sample is 4.9/l; thus, this urine reflects a ''very high'' crystallization risk [2]. With this figure, the patient can be classified simply and rapidly.

Prediction

First, a short introduction about predictions: predictions have assumed a major role in our everyday life: weather forecasts influence our weekly schedules, and traffic hold-up warnings influence our choice of itinerary. How many people are spellbound followers of share price developments and are prepared to risk a considerable amount of their fortune dabbling on the stock exchange?

In the area of medicine, for example, Kaplan–Meyer survival curves influence choice of therapy. In most departments, risk indices are used to register ''conspicuous'' patients and to identify ''problematic'' cases early on enabling quality assurance and quality management of an applied therapy. The necessity of quality assurance in medicine and the wish for predictability and prognosis of treatment results are in direct contrast to the impossibility of registering all pathological processes in a real patient.

Impact and influence of ''predictions'' on our life differ. But what is a ''prediction''? Everyone of us has a different concept. This is probably the case because, in order to fulfil the prediction, different fundamentals are consulted ranging from application of generally accepted physical laws to purely subjective ''intuition''. Three types of prediction can be distinguished:

1. Prediction with a very high probability of occurrence. Normally, this is made based on definite mathematical–physical laws (prognosis). The laws are almost universally known, and the parameters can be determined with very high accuracy. Observed aberrations of the model from nature are used to improve the model. These predictions include, for example, calculation of a planet constellation at a specific point in time.
2. Prediction according to, in most cases, a highly simplified model is adapted as much as possible to reality as an abstract representation of a complex process. This is also mostly based on purely mathematical–physical laws and simplification methods. The number of relevant event parameters is considerably higher than the number of model parameters and often they are not even known. In part, causality and its interactions are weak, further increasing the non-specificity of prediction. These models are often only valid for a restricted set of parameters, i.e. only ''special cases'' can be reflected with sufficient accuracy. The probability of occurrence of a predicted event is, therefore, lower than in the first type of prediction. A classic example for this type of prediction is the weather forecast. This is based on physical measurement data from which arguable predictions are made with the help of simulated physical models. However, chaotic and incalculable components do not allow exact calculation of the weather processes. Many medical diagnoses (''risk indices'', ''scores'') are further examples of this type of prediction.
3. In contrast to scientific prognoses are assertions which are characterized as ''predictions'', but which have no consistent or definitely proven method. Often, there is no clear causal structure, but only statistical correlation. Occasionally, these predictions are based on long-term experience and thus may be surprisingly accurate. A good example are weather proverbs. Astrological assumptions as well as religious prophecies lack all causality while attempting to interpret obscure patterns.

Models and its boundary conditions

The sensitivity of an index and thus the quality of the model behind this prediction depend on the quality of observation and the resulting model, which is by definition always a simplification of reality. A model is false or unrealistic because:

1. It fails to adequately consider the complexity and variability of the boundary conditions,
2. Its assumptions are weak due to the fact that the results are too strongly dependent on parameters and boundary conditions which cannot be quantified with sufficient accuracy,
3. Its input parameters were incorrectly assessed, or
4. Incorrect input parameters were used.In the area of medicine, almost every phenomenon is characterized by parameters and boundary conditions, which, in many cases, are temporally variable and which are at least as influential as physico-chemical processes in pathogenesis. Multi-causal stone formation is the result of a long chain of individual, linked events, of which each on its own was initially implausible. Areas with a strong historical component, and medicine is one of them, use the strong influence of boundary conditions on development to reconstruct history from the presence.

The model as basis of prediction combines empirical/epidemiological process observation with abstract mathematical–physical concepts of explanation. There-

fore, comprehensive interdisciplinary research is required to continuously improve existing model approaches and to increase their accuracy of prediction. While in other fields of science, such as physics, chemistry and geosciences, model-based research is no longer inconceivable, in medicine and certainly in stone research, we are only beginning to advance from a phase of primary observation.

Causality versus statistical correlation

The goal in developing stone formation risk indices is exact predictability of crystallization. To reach this goal, long-cherished one-dimensional, static explanation patterns (search for a substance "X") must be abandoned. For example, despite the fact that we know for certain that a high oxalate concentration in urine is one definite risk factor of calcium oxalate stone formation, studies are still carried out to confirm this fact. Increased mean intake of oxalic acid rich foodstuffs will inevitably result in a raised oxalic acid excretion in urine and thus an increase in the crystallization potential of calcium oxalate. For the physician, knowledge of the (bioavailable) oxalate contents of few but important foodstuffs is sufficient for choice of therapy. Oxalate contents commonly detected in "white pepper" only marginally influence search for causes of stone formation and are almost irrelevant for the determination of the crystallization risk in a patient.

Obviously, these investigations can provide important details for certain problems. However, in general, they fail to offer any insight into stone formation as a symptom of complex interconnected sub-processes since they divert from the overview. Their value is often a purely academic one. Nobody would board a plane if it would only be able to land according to the same statistical probability which correlates an increased oxalic acid concentration in urine with stone formation.

The group of "one-dimensional" risk parameters also includes figures using single urinary parameter assessment or simple combinations of parameters.

A variety of such approaches were developed to estimate the risk of urinary stone formation [3–6, 15]. These are, for example, the calcium/citrate index according to Parks and Coe [7] as well as the ion-activity product indices for different stone types [6, 8].

Here, values from many individual measurements form the basis for calculation of, in part, multi-dimensional regression degree equations, whose formulas do not reflect physical–chemical laws (e.g. in the AP(CaOx-)-index unit [$mmol/h^{1.51}/l^{1.03}$]). They only demonstrate statistical relationships with no definite medical relevance.

Process-oriented approach

In order to develop time-dependent and hence dynamic models, the linear principle of sequencing of (possible) causes of stone formation must be abandoned in favour of a process-oriented approach. The "urinary depletion model", for example, attempts to consider the multi-dimensional and dynamic nature of stone formation by application of the law of mass conservation to the specific requirements of urinary stone formation [9, 10].

Birdwell Finlayson took a decisive step in this direction around 28 years ago. His development of the mathematical EQUIL model [11, 12] was a milestone in understanding stone formation as a result of a physico-chemical process. For the first time, taking into account a larger number of urine components potentially involved in the process, a risk index was calculated iteratively by systematic interaction of these components within the framework of existing boundary conditions. With this model's clear formulation, stone formation research stepped onto virgin soil.

Ashby and Gyory [13] embarked on a similar complex strategy of risk evaluation when developing the computer program SEQUIL.

Limits to these (computational) approaches include an overly complex pathological reality as well as the economic costs of analysis in order to obtain a more realistic scenario.

Risk indices that consider the overall effect of all urine components offer a possible solution to the aforementioned dilemma. Generalized efficacy tests are stone crystallization models in native urine samples without individual analysis of urine components. These strategies of analysis not only circumvent any unknown reaction mechanisms in their actual interaction, they also avoid the problem of more or less restricted analytical access to the individual urine components.

With unspecific consideration of all urine components in their native quantity proportions, a controlled crystallization process is triggered in the urine sample to determine the index [2]. Despite limited analytical effort high significance may be reached, even with a very fragmentary knowledge of sub-processes of stone formation and their interaction.

Advantages of risk indices

With application of a suitable risk index patients who, over a longer period of time, have repeatedly been excreting high-risk urine [14] will inevitably present a higher risk of recurrence than healthy individuals. Exact prediction of an actual reoccurrence in the strictest sense is not possible due to the real complexity of stone formation. However, a good risk index is a reliable simplification of the complexity of the pathogenetic scenario and successfully provides sufficient differential indicators for a variety of treatment options enabling reasonable grading of the continuing extent of diagnosis.

Therapy-optimizing considerations and possible treatment changes may be carried out promptly by the physician during therapy, since therapy is only effective when individually adapted to the medical reality of the

patient. In combination with active input from the patient, the index-based crystallization risk can be reduced. This in turn can motivate the patient to higher compliance as he/she can ''measure'' and monitor success of his/her input so far. A thus improved therapy concept will inevitably result in a decreased rate of recurrence.

Counter-arguments

One of the most common arguments against the significance of risk indices is their (sometimes) ''insufficient'' medical verification. That is correct, but does it invalidate their ability to predict the incidence of a process in general? No, because most verification methods of ''quality'' are statistical ones, like, e.g. the double-blind test. These test methods are only mandatory for statistic-based indices, but not necessarily for causality-ruled ones. However, ethic restrictions must be considered when immediately requiring so-called evidence-based ''proof''. Is a non-initiation of therapeutic measures in a patient who repeatedly reflects increased risk markers justifiable, only in order to observe the development of his/her state of health: will the patient form stones or not? Only in case of further stone formation, is the index ''good'' as its predictability has then been proven. However, nobody, when affected by an increased stone risk, wants to be treated as a test animal.

Nevertheless, science demands for objective control methods and the verification of insight-based models is generally preferable.

Some scientist may argue that the validity of applied models is neither obvious nor proven, and therefore, risk indices based on such a model are at least uncertain. This argument has some interesting aspects.

On the one hand, it points out that process-oriented models derived from fundamental scientific laws must be checked by experimental evidence. Otherwise, improper use of concepts, assumptions, or boundary conditions will result in invalid models. But proof of causality-ruled models cannot be achieved by another ''white pepper experiment''. Such a model's validity can be proven by conservative test of the made assumptions and careful consideration of the conclusions drawn. In many cases—the more the model is governed by application of physico-chemical processes [e.g. 3, 8]—such a validation can be performed with high accuracy, under standardized boundary conditions, and with low clinical efforts.

On the other hand, the aforementioned argument demonstrates a widespread misunderstanding. Risk indices are only indicators; they do not provide a specific conclusion. They must be interpreted by a physician familiar with the limits of the model concerned.

References

1. Kirkpatrick B (ed) (1987) Roget' thesaurus of English words and phrases. Harlow, Longman
2. Laube N, Hergarten S, Hoppe B, Schmidt M, Hesse A (2004) Determination of the calcium oxalate crystallization risk from urine samples—the BONN-Risk-Index in comparison to other risk formulas. J Urol 172:355–359
3. Ogawa Y, Hatano T (1996) Risk factors in urinary calcium oxalate stone formation and their relation to urinary calcium oxalate supersaturation. Int J Urol 3:356–360
4. Robertson WG, Peacock M, Marshall RW, Marshall DH, Nordin BEC (1976) Saturation-inhibition index as a measure of the risk of calcium oxalate formation in the urinary tract. N Engl J Med 294:249–252
5. Robertson WG, Peacock M, Heyburn PJ, Marshall DH, Clark PB (1978) Risk factors in calcium stone disease of the urinary tract. Br J Urol 50:449–454
6. Tiselius HG (1997) Risk formulas in calcium oxalate urolithiasis. World J Urol 15:176–185
7. Parks JH, Coe FL (1986) A urinary calcium–citrate index for the evaluation of nephrolithiasis. Kidney Int 30:85–90
8. Tiselius HG (2001) Possibilities for preventing recurrent calcium stone formation: principles for the metabolic evaluation of patients with calcium stone disease. BJU Int 88:158–168
9. Laube N, Pullmann M, Hergarten S, Hesse A (2003) Influence of urinary stones on the composition of a 24-hour urine sample. Clin Chem 49:281–285
10. Pullmann N, Hergarten S, Laube N (2004) The influence of a variable differential function on the stone growth-related urinary depletion effect. Clin Chem 50:1675–1678
11. Finlayson B (1978) Physicochemical aspects of urolithiasis. Kidney Int 13:344–360
12. Werness PG, Brown CM, Smith LH, Finlayson B (1985) EQUIL 2: a basic computer program for the calculation of urinary supersaturation. J Urol 134:1242–1244
13. Ashby R, Gyory AZ (1997) A thermodynamic equilibrium model for calcium salt urolithiasis: clinical application. Exp Nephrol 5:246–252
14. Parks JH, Goldfisher E, Asplin JR, Coe FL (2002) A single 24-hour urine collection is inadequate for the medical evaluation of nephrolithiasis. J Urol 167:1607–1612
15. Robertson WG (2003) A risk factor model of stone formation. Front Biosci 8:1330–1338