The crucial role of tubulotoxic chemicals in renal failure

U Ravnskov*

Abstract

Introduction
Glomerulonephritis (GN) is an innocent disease as long as renal function is normal. To prevent or to treat serious GN it is therefore necessary to know what causes renal failure. For many years, the interest has been focused on various immunological reactions, either between foreign antigens that arrive into the glomeruli after having reacted with circulating antibodies and complement; or between autologous anti-kidney antibodies and various kidney cells or membranes. In addition severe proteinuria has been considered noxious for the tubular cells. However, there are a host of contradictory observations. This review discusses the crucial role of tubulotoxic chemicals in renal failure.

Discussion

The author has referenced some of his own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in the studies.

The role of the immunological processes

If the immunological reactions in the glomeruli are the cause of renal failure, directly or indirectly, there should exist an association between the number of glomerular immune complexes (ICs) or the degree of glomerular damage, and renal function, but it is not so. Greater amount of glomerular ICs are often seen in sheep, steers, guinea pigs, horses, mice and rabbits with normal renal function and normal urine. Patients with malignancies, alcoholic liver disease and essential hypertension may have such deposits as well, although their renal function and their urine are normal.

A single injection of a foreign antigen into experimental animals results in the production of circulating and glomerular ICs, but unless the animals are injected with Freund's adjuvant (FA) as well, or unless the foreign antigen is injected repeatedly, no renal damage is seen apart from mild and transient proteinuria. In accordance, most cases of human GN following an acute infection may heal without permanent damage of the kidneys, but renal failure may be seen in patients with chronic infections, or if the patients are exposed to tubulotoxic chemicals.

Experimental GN can also be produced in rats by autologous anti-brush border or anti-podocyte antibodies, either by immunisation with rat kidney cells (active Heymann nephritis), or by injecting rabbit anti-rat brush border antibodies into rats (passive Heymann nephritis). These models are used as an argument for the idea that serious GN is caused by immunologic mechanisms.

However, without FA autologous anti-kidney antibodies do not produce more than mild and transient proteinuria. In passive Heymann nephritis injected heterologous rabbit antibodies bind to the glomerulus immediately, but no harm is produced until a few days later, when the autologous anti-rabbit Ig antibodies lead to complex formation in situ. However, this model cannot be used as an argument for an immunologic mechanism, as the presence of heterologous antibodies is most unlikely in human GN.
Similar objections are relevant as regards experimental anti-glomerular-basement (GBM) nephritis. GN is produced by injecting heterologous or homologous anti-GBM antibodies, but without FA no renal damage is seen. The innocence of anti-GBM antibodies in human GN also appears from the fact that they can be found in the circulation of animals and human beings with normal renal function and in kidneys transplanted to patients with terminal anti-GBM nephritis without causing any harm.

**The missing link**

Obviously immunologic reactions in the kidney do not produce renal failure by themselves. In most animal experiments, the crucial factor is FA, a mixture of mycobacteria emulsified with mannidemonooate in hydrocarbon oil. There is general agreement that the role of FA is to enhance the immunological reactions, which is partly true, because many hydrocarbons interfere in an unpredictably and unfortunate way with the immune system. However, there is much evidence that the chemical factors alone are able to produce renal failure, both in animal and human GN.

Several authors have demonstrated that an injection of FA without antigen causes typical signs of GN in experimental animals including proteinuria and tubulointerstitial damage. The changes are less severe compared with experiments that include immunisation, but much worse using immunisation alone. Most patients with post-streptococcal GN (PGN) recover with no sequels. Exceptions are seen in epidemics in oil producing areas such as South Trinidad and Maracaibo in Venezuela. Here, epidemics of PGN are not only frequent, but PGN often progresses to renal failure.

Exposure to toxic compounds may be the trigger in many cases, but if the exposure is accidental and of short duration, the GN may heal without sequels. In a study of 15 patients with acute PGN, 6 of them had been exposed to hydrocarbons between the infection and the acute onset of the PGN, and 4 had been exposed in their occupation for several years. At follow-up those who were no longer exposed had regained normal renal function, whereas three of the four who still were exposed, had proteinuria and a decreased glomerular filtration rate (GFR). A few of 15 age- and sex-matched controls, who had been infected with nephritogenic streptococci without developing GN, had insignificant exposure only and unrelated to the streptococcal infection.

There is much evidence that tubular damage plays an important role in the development of renal failure in GN, both in animals and in man. Mercury, gold, lithium, silicon, penicillamine, selenium and most hydrocarbons are tubulotoxic, and numerous reports and experiments have documented that they may produce serious GN as well. Immunologic processes may participate, because these chemicals also disturb the immune system.

**Hydrocarbons**

The most common and the best-studied factor is hydrocarbon exposure. Several case reports have been published, and serious interest in the subject was raised, when Zimmerman et al. published a case–control study of patients with terminal renal failure and controls without renal disease matched for age and gender. They found that almost all patients with GN had been exposed to toxic substances, mainly hydrocarbons, but only a few of the controls. Since then 20 case–control studies of patients with GN and healthy control individuals or patients with various non-renal diseases have been published. With one exception, these studies have shown that the degree of hydrocarbon exposure of patients with acute or early chronic GN was the same compared with the controls; whereas patients with chronic and in particular terminal renal failure were significantly more exposed.

The exception was a nationwide, population-based case–control study of 926 patients with renal failure, 222 of whom had GN, and 998 control subjects matched for age and gender. In that study, no difference was found with regard to the degree of renal failure between exposed and unexposed patients, including those with GN. The authors, therefore, claimed that organic solvents have no adverse effect on the development of renal failure.

The study had several biases, however. Statisticians, who were not blinded to the patient’s case–control status, interviewed the subjects; occupational hygienists were only involved, if the patient reported exposure to solvents. A kidney biopsy specimen was available in only 61% of the patients. Diagnoses of underlying renal disease were based on routine clinical evaluation, and as the study included patients from all the hospitals in the country, some of the diagnoses must have been made by non-nephrologists. The most serious bias was the exclusion of patients who had died before the interview, patients who were too ill to be interviewed and patients who had received a kidney transplant, because all other studies have shown that exposure is most pronounced in patients with terminal renal failure.

A strong argument for hydrocarbons being the cause of renal failure in GN is that renal function improves if the exposure is discontinued. In one study, 50 patients were followed for 7–8 years. Nine of 26 were heavily exposed, but none of 24 moderately or rarely exposed had end-stage renal disease at follow-up. In another study, 68 patients were followed up for 5 years; 21/29 among those, whose disease had progressed, had been exposed to hydrocarbons, but

---

**Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)**

**FOR CITATION PURPOSES:** Ravnskov U. The crucial role of tubulotoxic chemicals in renal failure. OA Nephrology 2013 Aug 01;1(2):14.
The mechanism
Tubular damage in human GN is seen as a result of decreased renal blood flow due to obstruction of the glomerular capillaries. However, several authors have measured the renal blood flow in acute GN, and there has been a general agreement that it is unchanged or reduced only to a small extent, even in patients with renal failure.

The role of glomerular damage is also contradicted by the findings in focal glomerular sclerosis (FGS). This GN type is almost always associated with tubulointerstitial damage. As obstruction of a juxtamedullary, but not of a cortical glomerulus results in the formation of a vasa recta connecting vas afferent with vas efferent, tubular damage in FGS should be confined to the cortex, which it is not. That the primary event is tubular damage is more likely, because FGS is seen in many non-glomerular renal diseases with tubulointerstitial damage.

In accordance a highly significant correlation has been found in chronic GN between GFR and the extent of tubular damage, but a much weaker correlation, if any at all with the degree of glomerular damage. The crucial role of tubular damage is supported by the finding that patients with GN and decreased GFR have tubular proteinuria correlated with the degree of renal failure. A large number of clinical and experimental observations have also shown that even pronounced MGN may appear without proteinuria or renal failure. Also, in spite of severe glomerular changes in patients with diabetic nephropathy or renal amyloidosis, no elevation of serum creatine is seen in the absence of tubulointerstitial damage.

It is a common view that the tubular cells are damaged by severe proteinuria. However, the GN type with the most pronounced proteinuria is minimal change nephropathy, and patients with this disease most often have a normal GFR without tubular proteinuria or other signs of tubular damage, even after many years.

The crucial role of the tubulointerstitial changes is also illustrated by a meta-analysis of nephritis caused by treatment with non-steroidal anti-inflammatory drugs (NSAID). In 97 case reports of NSAID-nephropathy, six different types of GN were reported. Treatment time was strongly associated with the diagnoses; the mean time of those with acute tubulointerstitial nephritis was 1.7 months; for those with minimal change, it was 8.2 months and for those with membranous GN, it was 39 months. Treatment time was strongly associated with the number of glomerular IC, but inversely associated with GFR and the degree of interstitial damage.

A probable mechanism behind renal failure is that tubular degeneration and cortical interstitial fibrosis, the usual findings after exposure to tubulotoxic chemicals, lead to post-glomerular capillary resistance. The decline of the glomerular blood flow may further glomerular trapping of circulating macromolecules which explain, why the tubular changes in the animal experiments and in NSAID-nephropathy appear before the glomerular immune deposits. In accordance, both GFR and tubulointerstitial damage in patients with GN are associated with degree of hydrocarbon exposure.

If exposure to tubulotoxic chemicals may cause renal failure in patients with GN, such exposure should have a similar effect in other renal diseases as well, and this is also what has been observed. In a case-control study of 272 men and women with chronic renal failure (CRF) of all types and 272 controls matched for age, sex, and region of residence, significantly increased risks of CRF were found for exposure to lead, chromium, tin, mercury, welding fumes, silicon-containing compounds, oxygenated hydrocarbons and grain dust, which contains high proportions of chronic renal failure.

Experimental evidence
That GN can be produced by chemicals alone without immunisation has been demonstrated in at least 29 experiments on rats, mice and guinea pigs exposed to xylene, bromoform, dibromochloromethane, trichloroethylene, diacetil-benzidine, dinitorchlorobenzene, white spirit, carbon tetrachloride, trimethylpentane, petrol, maleic vinyl ether anhydride, 4'-fluoromethylbenzanthrene, styrene or mixed organic solvents. Most types of GN have been produced including proliferative and focal segmental proliferative GN, extra capillary GN, anti-GBM and anti-TBM nephritis, IgA nephritis, minimal change nephropathy and focal and segmental sclerosis. Tubular damage was noted in all experiments; renal function was measured at different times during or after the exposure, the tubular changes were observed immediately, whereas the glomerular deposition of IC and complement appeared late in the course.

amounts of silicon. The frequencies of various occupational exposures were especially high among patients with diabetic nephropathy. The latter is in support of a previous study by Yaqoob et al., who found a higher level of hydrocarbon exposure in patients with incipient and in particular those in those with overt diabetic nephropathy compared with diabetic patients with normal renal function.

Immunosuppressive treatment

The standard treatment of GN is the use of immunosuppressive drugs. Most trials have compared various types of such drugs. There are only a few randomised, controlled trials where immunosuppression has been compared with placebo, and several of them have failed. Most important is that possible exposure to nephrotoxic chemicals has not been investigated in any trial. It is therefore impossible to know, whether improvement is due to the drugs used or to cessation of the patient’s exposure.

Conclusion

There is much evidence that renal failure in most cases of GN is caused by exposure to tubulotoxic chemicals and that such exposure may be deleterious in other kidney diseases as well. Several studies of GN associated with hydrocarbon exposure have reported improvement of renal function after cessation of the exposure. It is reasonable to assume that improvement may be achieved also by cessation of exposure to other tubulotoxic chemicals and in other kidney diseases. It should therefore be mandatory to ask all the patients with renal failure about possible toxic exposure and to suggest cessation of such exposure. Experienced occupational hygienists should perform the interviews because many doctors are unfamiliar with the working conditions of their patients and many patients are unaware of their exposure.

References

24. Ravnskov U. Glomerular, tubular and interstitial nephritis associated with non-steroidal antiinflammatory drugs,