The implications of metabolic acidosis in intensive care unit patients

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Metabolic acidosis is often overlooked in the intensive care setting because the dangers associated with this metabolic derangement are simply not appreciated. The repercussions that stem from a lack of appreciation of these factors can lead to significant morbidity. Metabolic acidosis is detected by finding a low concentration of the plasma bicarbonate or blood pH. Often, respiratory compensation or a superimposed metabolic alkalosis masks the severity of an underlying metabolic acidosis.

The normal adult generates approximately 1 meq/kg of acid each day mainly stemming from metabolism of protein in the diet. Under normal circumstances, there is sufficient renal reserve to excrete this acid load by generating ammonium or through the excretion of titratable acids. However, an increase in the acid load or a diminution in the renal reserve compromises the ability of the kidney to maintain neutral acid/base balance. Thus, separately or together, an increase in the amount of protein ingested or amino acids infused, sepsis causing protein breakdown, the emergence of diarrhoea or the loss of renal function with ageing or with acute renal failure lead to accumulation of acid. Homeostasis can be maintained but only at the expense of maladaptive responses including bone demineralization and muscle wasting. Both responses are common in the elderly and in intensive care unit patients.

Acidosis and protein metabolism

Regardless of the amount of protein ingested, a normal adult synthesizes and degrades about 4 g protein/kg/d during processes of cellular metabolism [1]. However, when the diet is restricted, the normal adult can activate several mechanisms to conserve nitrogen balance. With a modest dietary protein restriction, essential amino acid oxidation decreases, and as dietary restriction becomes more severe, protein degradation decreases [2]. With very severe protein restriction, it becomes impossible to maintain neutral nitrogen balance and protein losses result in loss of lean body mass.

Regarding the first adaptation, a reduction in amino acid oxidation, the response has been documented in studies of branched-chain amino acids (BCAA—leucine, isoleucine and valine). BCAA play an important role in protein metabolism, for they constitute 18% of muscle protein. Degradation of BCAAs requires various enzymes, but the most important and rate-limiting enzyme is branched chain ketoacid dehydrogenase enzyme (BCKAD). The second adaptation, a reduction in the degradation of protein, is activated when dietary protein falls below the minimum daily requirement.

With metabolic acidosis, both animal [3] and human [4] studies have shown that accelerated amino acid and protein degradation results in negative nitrogen balance and loss of muscle mass. Moreover, albumin synthesis is inhibited by acidosis [5]. The mechanism for these responses involve several enzymes. First, BCKAD enzyme activity is stimulated. The maximal activity \( V_{\text{max}} \) of the enzyme is increased without a change in the Km [6], and England et al. [7] showed that in metabolic acidosis, a greater fraction of the BCKAD is present in the activated, dephosphorylated form. There also appears to be an increase in production of the enzyme as measured by increases in the abundance of mRNAs encoding subunits of the enzyme. Quantification of cellular enzyme levels suggest that increased production of the enzyme is offset by accelerated degradation of BCKAD. Wang et al. [8] recently used cultured cells that do not express the glucocorticoid receptor to show that the changes in BCKAD activity to acidification require glucocorticoids.

Metabolic acidosis also stimulates one of the four known pathways for degradation of cellular protein, namely the ATP-ubiquitin-proteasome pathway [1]. In this pathway, proteins destined for catabolism are joined to a heat-shock protein known as ubiquitin, in an ATP-dependent reaction. The ubiquitin-labelled protein is then recognized by a multi-protein complex, the proteasome, which degrades the substrate protein and releases the ubiquitin. The increase in muscle protein degradation in response to metabolic acidosis is blocked by inhibiting the activity of the ATP-dependent pathway, while inhibition of other cellular degradative pathways (lysosomal, calcium activated or non-ATP-dependent pathways) has little or no effect.
on muscle protein degradation. Again, there is a requirement for glucocorticoids. Price et al. [9] showed that in the presence of metabolic acidosis, there is an increase in gene activity as measured by higher levels of mRNA for ubiquitin and subunits of the proteasome in muscle. In the absence of glucocorticoids or acidosis, an increase in mRNAs did not occur, but with both signals, mRNA levels rose sharply. Bailey and colleagues [10] proved that acidosis does increase transcription of genes encoding ubiquitin and subunit of the proteasome. It is important to note that even modest degrees of metabolic acidosis stimulate activity of this pathway and can lead to progressive loss of lean body mass. Signal transduction pathways eliciting these responses are complex, but available evidence suggests that glucocorticoids are involved. For example, when acidosis was induced in adrenalectomized rats with or without added glucocorticoids, muscle proteolysis increased only in the presence of both glucocorticoids and acidosis [11]. In the absence of either factor, increased muscle catabolism did not occur. Another endogenous hormone that appears to have an important role in regulating muscle protein catabolism and the ubiquitin-proteasome pathway is insulin [12].

Loss of lean body mass also occurs in a variety of other disease states (AIDS, chronic renal failure, cancer), and loss of lean body mass is a predictor of the risk of death in acutely and chronically ill patients. Consequently, physicians should address not only the nutrient intake of their patients but identify specific factors causing malnutrition such as metabolic acidosis. It is important to emphasize that acidosis also blocks the benefits of other strategies used to improve nutritional status. For example, growth hormone or IGF-1 has been used to promote positive nitrogen balance in the hospitalized patient, particularly the critically ill. However, the IGF-1 response to growth hormone is blunted significantly by metabolic acidosis [13]. Thus, the intended benefit of this therapy would be lost in the presence of metabolic acidosis.

**Acidosis and bone metabolism**

Besides its deleterious effects on protein metabolism, metabolic acidosis exerts ill effects on bone. First, metabolic acidosis leads to bone demineralization. This can occur directly through physicochemical bone dissolution with release of bicarbonate, sodium, potassium and calcium [14] or indirectly through a direct stimulation of osteoclast activity and concurrent inhibition of osteoblast activity [15]. Besides removing bone alkali, metabolic acidosis inhibits renal calcium reabsorption by the kidney, resulting in calciuria. The net effect is loss of calcium from bone. For the bed-bound patient, immobilization will compound the tendency towards osteopaenia. What is worse, hypercalcaemia may be masked by a low serum albumin, and the changes in mental status, nausea, vomiting and inanition will be unrecognized. These factors retard efforts to mobilize the patient, worsen the patient’s condition and result in complications. Ultimately, the patient’s hospitalization is prolonged.

**Acidosis and haemodynamic regulation**

Besides muscle and bone, there is abundant evidence that metabolic acidosis exerts a pernicious effect on hemodynamics. With metabolic acidosis, myocardial function declines and venoconstriction occurs [16], and the effects of hypoxaemia are potentiated [17]. Pulmonary artery pressure as well as medial wall thickness increase while the number of arterioles to alveoli decreases. Hypoxia-induced venoconstriction results, and more blood is returned to an already compromised heart. Watson et al. [18] noted a decrease in amplitude and activation of sodium current generated by ventricular myocytes cultured in acidified media. They concluded that metabolic acidosis could predispose to ventricular arrhythmias.

**Therapeutic considerations**

What about increasing dietary protein to overcome the loss of lean body mass in ICU patients? In the elderly [19] and in those with compromised renal function, an increase in dietary protein could overwhelm the kidney’s ability to excrete acid generated from metabolism of the amino acids. In this case the accumulation of hydrogen ions (and other waste products) would unleash counterproductive maladaptive responses, resulting in loss of lean body mass and osteopaenia.

To what degree should the metabolic acidosis be corrected? Available evidence suggests that the serum bicarbonate should be in the normal range in order to maintain neutral calcium and nitrogen balance. Preminger et al. [20] followed nine patients with incomplete distal renal tubular acidosis for a period of 8 months while they were given potassium citrate. Not only was calcium balance improved, but there also was a significant increase in the fractional intestinal calcium absorption. Reza Albarran et al. [21] showed that bone mineral density in hypokalemic distal renal tubular acidosis improved significantly when metabolic acidosis is fully corrected with potassium citrate. Metabolic acidosis does not need to be severe to cause negative calcium balance. In a study 18 postmenopausal women who were in negative calcium balance, addition of potassium bicarbonate to the diet decreased urinary calcium excretion and improved net calcium balance [22]. Even the rise in urinary calcium excretion stimulated by an increase dietary protein intake is reversed by the administration of potassium bicarbonate [23]. Thus, it appears that excessive dietary protein intake or a lower protein intake in patients with decreased renal reserve (e.g. as occurs with ageing) is
associated with negative calcium balance and osteoporosis.

Nitrogen balance is also improved in patients with kidney disease when their metabolic acidosis is corrected. Graham and colleagues [24,25] demonstrated that rates of protein degradation decrease markedly when alkali is given to bring the serum bicarbonate into the normal range. This occurred regardless of the type of dialysis (peritoneal or haemodialysis) used. Stein et al. [26] showed that these short term results have important long-term ramifications. An increase in the alkali content of the peritoneal dialysate by raising the acetate only 5 mM during a year-long clinical trial resulted in a significant weight gain, improved indices of muscle mass, higher serum albumin levels and lower serum urea levels. Thus, the key to proper nutrition in the ill patient hinges on appropriate attention to the correction of underlying acidosis.

In summary, the metabolic derangements that occur with metabolic acidosis are not widely recognized. Metabolic acidosis stimulates the degradation of essential amino acids and proteins. There is up-regulation of the ATP-dependent, ubiquitin-proteasome pathway as well as specific enzymes such as the branched-chain ketoacid dehydrogenase that degrade essential amino acids. Glucocorticoids are necessary but not sufficient in these responses. Factors such as growth hormone that could promote positive nitrogen balance are ineffective in the presence of metabolic acidosis. Besides muscle, there is bone loss as the body neutralizes excess acid by buffering from bone. This maladaptive response results in bone demineralization, osteopenia, and fractures can eventually occur.

The physician must monitor the patient’s acid-base status and appreciate that even ‘minor’ degrees of metabolic acidosis are deleterious. The physician should also appreciate that increasing dietary protein can be counterproductive, especially in the elderly and in those patients with compromised renal function. Lastly, bicarbonate should be employed to eliminate acidosis.

References

Susceptibility genes for end-organ damage. New strategies to understand diabetic and hypertensive nephropathy

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Introduction

The recent development of new methods in genetics has made it possible to obtain remarkable insights into the molecular and genetic mechanisms of various diseases. In the field of nephrology, the identification of genes responsible for polycystic kidney disease or X-chromosomal Alport’s syndrome mark the beginning of this new genetic approach to increase our understanding of these inherited disorders [1–3]. While it is obvious that these rare diseases with mendelian mode of inheritance are caused by gene defects, there is now overwhelming evidence from epidemiological as well as animal studies that multiple genes and environmental factors play an important role in the development of the most common forms of end-stage renal disease (ESRD) such as hypertensive and diabetic nephropathy. The identification of genes responsible for these diseases will be important for two reasons. First, the identification of genes will lead to new diagnostic tests for early detection which may lead to improved therapeutic intervention, and second this will increase the understanding of the disease process, therefore, facilitating the discovery of new treatment strategies. We delineate the most recent efforts to determine genes responsible for diabetic and hypertensive end-organ damage of the kidney and describe the various approaches to identify the genes for this multifactorial disease.

Genetic epidemiology of diabetic and hypertensive ESRD

Diabetes mellitus and hypertension affect hundreds of millions of people worldwide and are responsible for increased morbidity and mortality. However, these diseases do not directly increase morbidity and mortality, but rather progress into life-threatening end-organ damage like end-stage renal disease, myocardial infarction, or stroke. Interestingly, patients with the same apparent underlying risk factors may develop different or no complications. Moreover, there are marked differences in the risk of ESRD in various ethnic populations [4,5]. There is striking evidence from epidemiological studies that inherited factors are responsible for the ethnic differences and, furthermore, influence the risk and determine the pattern of end-organ damage. Genetic epidemiological studies recently analysed familial clustering of ESRD to determine the genetic risk in relatives. For example, in siblings who are concordant for insulin dependent diabetes, the cumulative risk of developing persistent proteinuria is 71.5% for a second sibling if the first sib has already developed proteinuria. In comparison, the risk for proteinuria is only 25.4% if the first sibling has not developed renal complications, suggesting a major genetic effect [6]. Using a logistic regression analysis in sib-pairs both with diabetes mellitus, Seaquist et al. could demonstrate that nephropathy in one sib is the only factor significantly predictive for the renal status of the other sib [7]. Most recently, it has been shown that the offspring of diabetic patients with nephropathy show, albeit in a non-pathological range, increased baseline and postexercise urinary albumin levels compared to offspring from diabetic patients without nephropathy [8].

Genetic factors or susceptibility genes are also likely to be responsible for differences in the sensitivity of the kidney to injury in certain ethnic groups. For example, the increased risk of hypertensive and diabetic nephropathy in African-Americans cannot be totally explained by a greater prevalence of the underlying disease or the differences in therapy [4,5]. In African-Americans, the risk of developing ESRD is increased ninefold in the presence of a first-degree relative, and increased fivefold in the presence of either a first or second degree relative [9]. In Pima-Indians, who inherit an increased genetic risk for diabetes, the susceptibility to diabetes-associated nephropathy is different from the presence of non-insulin dependent diabetes mellitus (NIDDM) suggesting that a separate risk factor must be segregating within this population [10].

Although these epidemiological data from studies in humans implicate an independent genetic risk factor for hypertensive and diabetic ESRD, valuable insights
were obtained studying an animal model of hypertensive nephropathy.

**The role of animal models for gene identification**

**Localizing susceptibility genes for hypertensive ESRD**

To overcome the limitations which are inherent in the search for genes in humans, inbred animal models, in particular rats strains, were developed to study multifactorial diseases like hypertension, diabetes and renal failure. Inbred rats and mice are powerful tools to localize disease genes and to study their function for multiple reasons. For example, by selecting for a particular disease and brother-sister mating over multiple generations, genetically identical rates were established which are enriched for genes responsible for the selected disease. Using these genetic animal models in a controlled setting, it is now possible, both to control for environmental factors and to produce the necessary number of progeny, therefore, increasing the power for a statistical analysis to localize responsible genes.

So far, the most compelling evidence for the existence of renal disease susceptibility genes comes from a rat model. The fawn-hooded hypertensive rat (FHH/EUR) is a genetically hypertensive strain which develops chronic renal failure with an early onset. The renal impairments of these rats are characterized by glomerular hypertension, proteinuria, reduced urinary kalikrein activity levels, and glomerular sclerosis. Performing a total genome scan and linkage analysis to localize genes responsible for blood pressure regulation and renal damage in a backcross between FHH rats and a normotensive control strain (ACI), two genes, Rf-1 and Rf-2, were determined contributing substantially to renal damage in this animal model [11]. Interestingly, Rf-1, which explains 44% of the genetic component of the renal impairment, acts through a mechanism which is independent of blood pressure. Although the second distinct locus, Rf-2, maps closely to a locus responsible for blood pressure, the results from the statistical analysis suggest that this renal damage gene is different from the gene influencing blood pressure.

**Identify genes and gene function: congenic strains**

While the localization of susceptibility genes for renal damage could demonstrate their importance in the pathogenesis, the ultimate goal will be to identify these genes and to analyse their function, in particular with respect to their interaction with the underlying risk factors for kidney damage. In the animal model, a powerful approach to identify genes and study their function is to transfer chromosomes or chromosomal segments containing genes influencing a disease or phenotype of interest from a disease strain onto a control strain, resulting in consomic or congenic animals, respectively. By selective breeding of animals, it is possible for example to transfer a small segment containing a renal failure locus onto normal control animals, resulting in a strain which, compared to the progenitor strain, differs only in the selected region of interest. Transferring various segments of different size not only allows to closely localize a gene, but also gives the opportunity to study a particular gene effect in the absence of influences due to the genetic background. Furthermore, crossing animals which are congenic for different disease loci, for example a renal failure susceptibility locus and loci responsible for diabetes or hypertension, will be a powerful tool to study gene-gene interactions.

While studies are now underway using the above described methods to identify renal failure genes in animals, great attention is focused to translate the insights from animal models in order to identify the homologous genes in humans.

**From the animal model to human**

The constantly increasing knowledge of nucleotide sequence and map position of genes, both in animals and humans, results in valuable insights illustrating how data from animal studies may be translated to humans. Not only the nucleotide sequence of various genes is conserved between different species and humans, but the gene order is also conserved throughout the evolution of mammalian species, although some chromosomal rearrangements have occurred. Using this information of conserved gene order among mammalian species (synteny), it is possible to test homologous ‘positional candidate’ loci from an animal model in human populations.

Various approaches exist in humans to determine whether a gene or genomic region influences a particular disease or phenotype [12]. Traditional methods of linkage analysis have used families with multiple affected members to calculate the likelihood of linkage between a genetic marker and a disease. Another approach to determine whether a gene is linked to a disease uses affected sib or relative pairs. Briefly, if a marker or gene is linked to a disease, one might expect that the affected members share a particular allele more frequently in comparison to the expected frequency, under the assumption that the gene is not linked [13]. Most recently, using this approach, linkage of end-stage renal disease in African-Americans to candidate genes for different growth factors and the interleukin-1 beta receptor antagonist gene could be excluded [14]. Another approach to test a particular gene uses association studies which compare gene frequencies between affected patients and a non-affected control group. While this type of study design depends most critically on the selected control group, there is evidence that a polymorphism of the angiotensin-converting enzyme gene is associated with increased urinary albumin excretion in NIDDM [15].

**Conclusion**

Given the knowledge gained from animal and human studies, major efforts are now underway to identify the genes responsible for the susceptibility to diabetic and.
Individual kidney function in atherosclerotic nephropathy

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Radionuclear measurement of individual kidney functions

The central paradox of atherosclerotic renal-artery stenosis is that unlike most other forms of renal disease the process and our interventions are asymmetrical, but we measure outcome in terms of overall, bilateral renal function. In this issue of Nephrology Dialysis Transplantation we report some preliminary results attempting to use a simple measure of individual kidney function in these patients. We have chosen two routinely used nuclear medicine tests of differential function and overall clearance. For estimation of differential function 99mTc-Technetium...
dimercaptosuccinic acid scintigraphy scan ($^{99m}$Tc-DMSA scan) scintigraphy was used. It offers advantages over alternative nuclear medicine procedures that might be used because of the high uptake and fixation to cortical tissue. This allows for high count studies, which reduce statistical errors and increases precision compared to dynamic techniques with other agents. In addition, by taking anterior and posterior images a geometrical mean of counts may be obtained, which compensates for the kidneys lying at different depths from the surface, a problem leading to errors in dynamic scintigraphic techniques. For estimation of overall renal function the single-injection $^{51}$chromium ethylenediaminetetraacetic acid glomerular filtration rate ($^{51}$Cr-EDTA GFR) method was used, as it is accurate and precise, correlating with inulin techniques [1]. In addition it is widely available to most departments of Nuclear Medicine and is convenient for routine use.

**Kidney size, an adequate surrogate marker for functional recovery?**

Previously, nephrologists have used renal size as a surrogate marker for individual function in renal disease. If a kidney is 6 cm in length on ultrasound then it is unlikely to have significant function. However, the converse has also been presumed—that a 10-cm kidney has good function. The data reported in this journal show that routine ultrasound does not closely correlate with individual kidney function as measured by $^{99m}$Tc-DMSA scan and $^{51}$Cr-EDTA clearance in kidneys with stenosed renal arteries, angioplastied renal arteries, or even normal renal arteries but atherosclerotic aortic disease. No special attempts were made to evaluate renal size, but the routine estimations available to the nephrologists at our institution were used. This finding is in keeping with the practice reported by Dr Novick at the Cleveland Clinic, where intraoperative biopsies are performed to determine the potential for revascularization, irrespective of renal size [2]. The data also demonstrate that in the presence of renal-artery occlusion, function is poor irrespective of renal length. This may not be surprising but has not previously been demonstrated for individual kidneys.

**Paradoxically better function in the stenosed kidney**

Paradoxically, the data show that renal function may be better in the kidney with atherosclerotic renal-artery stenosis than in the contralateral kidney without renal-artery stenosis. This does raise the possibility that the stenosed kidney may be protected from the hypertensive and atheroembolic disease experienced by the kidney with a normal renal artery. These findings have a number of potential implications.

**The decision to intervene**

The decision to intervene by angioplasty or surgery in a kidney with atherosclerotic renal-artery stenosis should be based on measurement of its individual function. The data show that in half the cases examined more function was coming form the kidney with a stenosed renal artery. An illustration is presented by a recent patient had unilateral severe atheromatous renal-artery stenosis with a normal contralateral renal artery. Each kidney had a filtration rate of 6 ml/min. It is not surprising that the patient had presented with a doubling of her creatinine on an ACEI! This illustrates that when we have a quantitative measure of individual renal function we may be able to predict the consequence to overall renal function of progression to occlusion of a stenosed renal artery. Progression to occlusion is symptomless [3] but its likelihood is related to the severity of the stenosis [4]. In the case quoted where the patient had 6 ml/min of function from each kidney, then she would be dialysis independent with both kidneys functioning, that is with a clearance of 12 ml/min. However, she would be dialysis dependent if the stenosed kidney occluded and all function in that kidney were lost. A decision on intervention in this case would be based on the likelihood of progression to occlusion and the importance of the kidney with renal-artery stenosis to overall renal function.

**Renal injury by mechanisms other than stenosis**

The data show that in atherosclerotic nephropathy there is an underlying renal dysfunction separate from the damage caused by the alteration in renal blood flow. There may in fact be a worse decline in renal function in kidneys of patients with atheromatosus disease but normal renal arteries, as illustrated by the paired kidney data. This is also supported by our report on patients with sole functioning kidneys where progressive renal function occurred even after technically successful renal angioplasty or stenting [5]. These processes may not cause a parallel decline in renal size and function as in many other forms of renal disease. As previously discussed this has been recognized in major centres performing significant numbers of renal revascularizations where renal histology has been used as the determinant for recoverable renal function [2]. The presumption has previously been that the only process causing renal damage was as a result of ischaeamic nephropathy [6]. This is supported by extensive animal data from the time of Goldblatt et al. [7] onwards, where severe alterations in renal blood flow have caused renal fibrosis and atrophy. However, it is not difficult to imagine the other pathological processes involved in atherosclerotic nephropathy, in addition to ischaemic changes which may not cause severe and immediate atrophy. It is well known that aortic atherosclerotic disease in associated with renal atheroembolic disease and that this is a common renal biopsy finding in patients over the age of 65 years [8]. The importance of this process in atherosclerotic nephropathy has been difficult to determine as the diagnosis cannot be made without finding a cholesterol cleft on histology [9].

The patchy nature of the disease would be compatible with a process where size and function may become dissociated. Certainly the postmortem data, where multiple sections can be made, support a much more
frequent involvement of the kidneys in atherosclerotic aortic disease. In fact the data from 1957 [10] showed that there was a very high incidence of this pathology in association with an atheromatous aorta with or without surgery. If hypertension, as a consequence of or in parallel with the renal-artery stenosis, is present then hypertensive glomerulosclerosis can be invoked as another cause of renal damage separate form any decline in renal blood flow.

In addition to this, Thadhani et al. [11] have suggested a high prevalence of focal glomerulosclerosis in older patients with atherosclerotic renal-artery stenosis. In many ways an analogy can be drawn from SLE, where we recognize many different renal histological features, some of which warrant very different forms of treatment from others. The same can be applied to atherosclerotic nephropathy, where the changes may be due to ischaemia, atheroemboli, hypertensive nephrosclerosis, or focal segmental glomerulosclerosis, or any combination of these. However, only the ischaemic changes dependent on decreased renal blood flow will be improved by renal revascularization. We should recognize a number of features as compatible with atherosclerotic nephropathy just as we do in lupus nephritis.

Points to remember in managing the patient with atherosclerotic renal-artery stenosis

The management of atherosclerotic nephropathy must include prevention of renal-artery occlusion by whatever means possible. In assessment of a patient for intervention then, the two critical features will be: (i) what the overall renal function will be if the stenosed kidney progresses to occlusion, and (ii) what is the likelihood of progression to occlusion? However, after the relief of the stenosis progressive renal dysfunction in the absence of restenosis caused by the other processes in atherosclerotic nephropathy may occur. The challenge for the future is twofold. The first challenge is to prevent progression of a tight renal artery to occlusion in patients where the kidney provides a important renal function. The second is to prevent the gradual decline in renal function in atherosclerotic nephropathy not due to alterations in renal blood flow. As in lupus nephritis, in the future we may be able to tailor treatment in individual patients to their specific manifestation atherosclerotic nephropathy.

References


Choices of long-term immunosuppression in renal transplantation: balancing the benefits and risks

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Introduction

Early after renal transplantation an intensive immuno-suppressive regimen is necessary, because the graft appears to be especially sensitive to the rejection response of the recipient during this phase. Cyclosporin A (CsA), and more recently tacrolimus, have become cornerstones in our initial immunosuppressive protocols, which usually contain steroids as well. The risks of immunosuppressive treatment are far from negligible, and therefore it is important to decide how to proceed when a stable graft function has been achieved.

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after 3–6 months. The ideal immunosuppressive agent has yet to be discovered. Several new and promising drugs such as mycophenolate mofetil are currently being tested. However, we will have to wait several years before their long-term effectiveness becomes clear. For current decisions about long-term treatment we have therefore to rely on the existing experience with the older, established drugs, especially prednisone (Pred), azathioprine (Aza), and CsA. With regard to these three drugs there are several options for long-term immunosuppression. The treatment of choice must provide an optimal balance between effectiveness and quality of life on one hand, and side-effects and costs on the other.

**Triple drug therapy vs double therapy with CsA and Pred**

Triple drug therapy seems the most safe approach with regard to effectiveness, and this regimen is therefore used as long-term therapy in many transplant centres. However, since it combines the toxic effects of three drugs it needs to be established that it is more effective than one of the other therapeutic options, especially CsA–Pred. Kunz and Neumayer [1] have performed a meta-analysis and identified five relevant controlled trials in which triple therapy with Aza dosages of 1–2 mg/kg/day (in a total of 454 patients) was compared to treatment with double therapy (CsA–Pred, in 453 patients). Rates of acute rejection were not different. There was a trend to less graft failure with triple therapy (odds ratio 0.82), but this difference was not significant. Because of the relatively low number of patients the meta-analysis had insufficient power to detect differences in graft survival of less than 20%. Thus, a definitive answer awaits further trials and longer follow-up.

**Strategies to circumvent the long-term side-effects of CsA or Pred**

Of the three classic drugs, CsA and Pred are most feared for their side-effects. Of all side-effects of CsA, nephrotoxicity is the most important and chronic CsA nephropathy has been associated with end-stage renal disease in non-renal transplant patients. The lack of improvement in long-term kidney graft survival after the introduction of CsA, has further strengthened the suspicion that the histopathological lesions observed after chronic treatment with CsA are clinically relevant. Both CsA and Pred are implicated in the pathogenesis of post-transplant hypertension and hyperlipidaemia which is of particular clinical relevance since cardiovascular diseases are a major cause of morbidity and premature mortality in the population concerned. Therefore strategies that allow the discontinuation of one of these drugs deserve strong consideration. Three of such treatment options will be discussed with regard to their effectiveness and side effect profile: Pred-Aza, CsA monotherapy, and CsA–Aza.

**Effectiveness**

Soon after the introduction of CsA reports began to appear on attempts to circumvent chronic nephrotoxicity of CsA by conversion from treatment with triple therapy or CsA–Pred to Pred–Aza at 3–6 months after transplantation. A meta-analysis of 10 randomized trials showed an increased incidence of rejection in the 407 patients in whom CsA was withdrawn as compared to 384 patients who continued on CsA [2]. Despite this, there were no significant differences in patient or graft survival rates at a mean follow-up of 26 months after transplantation, and this held true also for each individual trial. In our own centre, conversion from CsA–Pred to Pred–Aza has been especially effective in living-related transplantsations with HLA-identical, MLC-negative donors. In 35 recipients treated in this way, graft failure due to rejection occurred only once.

The results of steroid withdrawal have been reviewed in a meta-analysis comprising 592 control patients on steroids and 681 patients in whom steroids were withdrawn or completely avoided [3]. Similar to the aforementioned results with conversion to Pred–Aza there was an increased incidence of acute rejection, but no influence on patient or graft survival. Follow-up periods ranged from 6 months to 5 years. There is some reason for caution here, since the largest trial with the longest follow-up showed a significantly decreased graft survival rate in the CsA monotherapy group that became apparent only after 5 years [4]. In selected patients on triple therapy, steroid withdrawal resulting in CsA-Aza therapy could be carried out without the occurrence of any rejection episode [5].

The overall experience with long-term treatment with CsA–Aza is limited. A retrospective analysis from a large database by Opelz [6] suggested that 5-year graft survival was superior to those obtained with triple-drug therapy, CsA–Pred, or Pred–Aza. However, these data suffer from the usual biases of all retrospective analyses, the most important being the selection bias. Preliminary results from a prospective study comparing CsA–Pred with CsA–Aza from 6 months after transplantation, performed in our centre, show that conversion form CsA–Pred to CsA–Aza is a safe procedure associated with a risk of acute rejection of less than 5%.

**Side-effects**

Conversion from CsA–Pred to Pred–Aza is followed by a sustained improvement in graft function and a reduction in blood pressure. Withdrawal of steroids from triple therapy or from the combination CsA–Pred leads also to blood-pressure reduction, but on the other hand to a slight increase of serum creatinine [5,7]. The individual contributions of CsA and Pred
to the disturbance of lipid metabolism are not clear. To clarify this issue we have conducted a study comparing CsA monotherapy with Pred–Aza from 3 months after transplantation. Treatment with CsA without steroids was associated with lower high-density lipoprotein cholesterol levels and higher values for serum triglycerides and lipoprotein (a) [8]. We concluded that with respect to risk for hyperlipidaemia, Pred–Aza seemed more preferable than CsA monotherapy. In addition our data contradicted the general belief that withdrawal of steroids in CsA-treated patients improves the serum lipid and lipoprotein profile. Since bone loss takes place mainly during the first 6 months of treatment with steroids, it remains to be established whether subsequent steroid withdrawal has any clinically relevant advantages in this respect. Likewise, the effect of steroid withdrawal on the incidence of osteonecrosis is not clear. Although prospective comparisons of the incidence of malignancies with different regimens are lacking, it seems logical that a treatment providing the lowest amount of immunosuppression would be the most attractive in this regard.

High costs may be regarded as a special sort of undesirable side-effect. It has been shown that the savings on drug expenditure achieved by conversion from CsA–Pred to Pred–Aza are only partly set aside by the costs related to treatment of rejection episodes after conversion [7,9]. Conversion to Pred–Aza therefore appears to be the most cost-effective regimen.

An emerging concept in the evaluation of different treatment regimens, taking into account both efficacy and side-effects, is to measure the health-related quality of life. This particularly applies to the present subject since the primary goal of renal transplantation is to improve the quality of life of the patients with end-stage renal disease. We have shown that the withdrawal of steroids, if successfully completed, may increase the degree of psychosocial well-being [10].

Conclusions

In an attempt to translate the above-mentioned results into some recommendations for daily practice, several statements can be made. We believe that there is no compelling reason to use triple therapy for maintenance treatment. Furthermore discontinuation of either CsA or Pred after a stable engraftment has been reached during treatment with the combination of CsA and Pred, appears to be safe with regard to medium-term graft survival. However, the occurrence of rejections after both conversion of CsA to Aza and withdrawal of steroids, may negatively influence graft survival rates after still longer follow-up. Compared to CsA monotherapy, Aza–Pred has the advantages of better graft function, more favourable serum lipid and lipoprotein levels, and lower costs. Currently the only outcome in favour of CsA monotherapy is the indication of a higher degree of psychosocial well-being.

In summary, CsA–Pred and Pred–Aza are at present our most favoured maintenance protocols. Immunological characteristics and risk factors for long-term complications in the patient concerned, may guide the choice between these two regimens. Pred–Aza should be used universally as maintenance therapy in HLA-identical living-related transplants. When there is an urgent need to withdraw the maintenance dose of Pred in CsA–Pred treated patients, e.g. in case of severe osteoporosis, replacement of Pred by Aza may prove to be the preferable strategy.

The introduction of new immunosuppressive drugs has expanded the number of available maintenance treatment protocols. Cost-effectiveness and quality of life should be important parameters to evaluate the chronic treatment with these drugs in ongoing and future studies.

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