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Editorial Board of *World Journal of Transplantation*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjt@wjgnet.com
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Jin-Lei Wang, Director
World Journal of Transplantation
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjt@wjgnet.com
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EDITORIAL

Ischaemic/reperfusion injury: Role of infliximab

Atul Bagul

Atul Bagul, Transplant Division, III Department, University of Leicester, Leicester-UK and University Hospitals of Leicester, Leicester LE5 4PW, United Kingdom
Author contributions: Bagul A solely contributed to this paper.
Correspondence to: Atul Bagul, MBBS, MRCS, MD, FRCS, NIHR Lecturer, Transplant Division, III Department, University of Leicester, Leicester-UK and University Hospitals of Leicester, Leicester LE5 4PW, United Kingdom. atulbagul@yahoo.com
Telephone: +44-11-62584601 Fax: +44-11-62490064
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Abstract

Ischaemia/reperfusion (I/R) injury is an underlying complex interrelated patho-physiological process which effects the outcome of many clinical situations, in particular transplantation. Tumor necrosis factor (TNF)-α is a pleiotropic inflammatory cytokine; a trimeric protein encoded within the major histocompatibility complex which plays a pivotal role in this disease process. This review is based at looking into an update, particularly the new insights in the mechanisms of action of TNF antagonist such as infliximab. Infliximab may thus play a dual role in the field of transplantation where it might not only down regulate the I/R injury, it may also have a beneficial role in the reduction of acute rejection.

Key words: Infliximab; Ischaemia/reperfusion injury; Tumor necrosis factor-α

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BACKGROUND

Transplantation, in particular renal is the best modality for treating end stage disease[1]. Due to a lack of suitable organs for transplantation from traditional sources[1], there is a renewed interest into other alternatives such as live donors, extended criteria donors (ECD) and donation after cardiac death donors (DCD) (non-heart beating donors[2]). The long term function and survival of DCD's are comparable to heart beating donors, hence making the ongoing research and development important[3,4]. Though results are encouraging, delayed graft function (DGF) and primary non function are a significant problem as a consequence of prolonged warm ischaemic insult during renal organ retrievals[4-8]. DGF leads to significant service related burdens such as prolonged haemodialysis and psychological impact on the patient[9]. Early graft injury in addition is associated with an increase in acute rejection (AR) and chronic allograft nephropathy[10,11]. The underlying pathophysiology of early graft injury is thought to be a complex interrelated sequence of events called ischaemic/reperfusion (I/R) injury. This review is aimed to assess and construct a concise evidence based literature document about the possible role of infliximab and its effects on I/R injury and use in transplantation, particularly ECD and DCD's.

SEARCH STRATEGY

MEDLINE (PubMed - 1966-2010), The Cochrane Central Register of Controlled Trials, EMBASE (1974-2009) the Database of Abstracts of Reviews of Effects, Health Technology Assessment Database and by attended relevant meetings, hand searched pertinent journals to identify relevant studies of all randomizes trials, meta analysis and case series. The search strategy included: (1) ischaemia reperfusion injury; (2) infliximab; (3) cytokines in I/R injury; and (4) tumor necrosis factor (TNF). No other search restrictions were applied and all related reference articles were reviewed.

I/R INJURY

I/R injury involves ATP breakdown product accumulation in an ischaemic environment, which following reperfusion are converted to xanthine and superoxide anion by xanthine oxidase, an isoform of xanthine dehydrogenase. The conversion of dehyrogenase to oxide is under the influence of a calcium dependent protease which is activated by ischaemia[12,13]. This commences a cascade of free radical formation, causing direct injury to lipids, proteins, DNA and initiating pro-inflammatory, apoptotic and complement pathways[12]. Depletion of ATP in this process leads to cell membrane instability *via* the incapacitated sodium/potassium (Na^+/K^+) pump[14] and thereby intracellular calcium accumulation which inhibits mitochondrial function and acts as a secondary messenger in apoptotic pathways[15].

Apoptosis, a morphological form of programmed cell death has dual role in renal injury. On one hand it serves as a healing mechanism related to the resolution of inflammation[16-18], while on the other hand it leads to accelerated apoptosis causing cell deletion and graft injury[16,19-22]. Although different signals initiate apoptosis, the patho-physiological process of apoptosis is surprisingly similar even in different cell types, suggesting that the final stage of apoptotic death is highly conserved[16,23]. Two phases of the apoptosis process have been described[23] The initiation phase involves death factors/death receptors or mitochondrial dysfunction. Death receptors are members of TNF super-family from which the TNF-α, TNF receptor 1 (TNF-R1) and Fas CD95/APO-1 play major roles.

The ischaemic proximal tubule epithelial cells generate a number of mediators that potentiate the tubule-interstitial inflammatory response. These include TNF-α, interleukin (IL)-1, IL-α, IL-β, IL-6 which are pivotal factors in IRI process for native and transplanted kidneys. TNF is a homotrimeric cytokine produced by numerous cell types including monocytes and macrophages that play an important role in pathogenesis of the inflammatory response. TNF-α and other cytokines expression can be regulated at different levels. The two principal mechanisms identified are a transcriptional and a post-transcriptional regulation triggered by different transcription factors and signalling cascades activated by a variety of stimuli ranging from cell damaging physical factors to mitogens and cytokines.

Upon activation by their cognate ligands, TNF-α, Fas and TNF-R1 recruit an intracellular death complex consisting of adapter proteins and procaspases. The death complex then activates apical caspases, mainly caspase-8, which subsequently activates downstream effector caspases; caspase-3. In the alternative initiation pathway, cellular stress triggers release of cytochrome c to bind Apaf-1, which in turn activates caspase-9. Here onwards both the pathways converge because caspase-9 also activates effector caspases. Caspases (14 different members) are a class of proteases contributing to cell injury and execution of the death programme[24-26]. As all pro-forms of caspases contain both recognition and cleavage sites implying their activation occurs either autocatalytically or by other capases. Thus Caspase-3 activation is by two major pathways, either mediated by death receptors (caspase-8) or by mitochondria (caspase-9)[27,28] during the execution phase of apoptosis dismantle the cells by sequential activation and cleavage of key proteins. Caspase-3 is major execution enzyme acting upstream of DNA fragmentation[27-29] and can also be activated *via* endoplasmic reticulum pathways (caspase-12)[30]. Previous studies demonstrate the increase of caspases in I/R injury in various organs[31,32].

The pathophysiology of I/R injury has been investigated by a large number of *in vivo* and *in vitro* studies. Methods described to attenuate this process include removal and inhibition of leucocytes, inhibition of classical and alternative complement pathways, inhibition of platelets, down regulation of endothelial cell adhesion molecules, inhibition of cytokines (TNF and IL-1)[33-35], inhibition of free radical forming enzymes, free radical chelation and antiapoptic agents[32,36-39]. Post ischaemia protection is possible because genes are up regulated after ischaemia, allowing a window of opportunity for intervention[39]. Gene transfer technology, with RNA interference, allows specific silencing of genes by delivering highly homologus RNA into the cell[40].

ROLE OF TNF-α IN I/R INJURY

TNF-α is a central regulator of inflammation, and thus TNF-α antagonists may be effective in treating inflammatory disorders of which TNF-α plays an important pathogenetic role[41]. TNF-α is a pleiotropic inflammatory cytokine; a trimeric protein encoded within the major histocompatibility complex. It is evident that this mediator is the prototypic member of a gene superfamily that regulates essential biologic functions such as immune response, cell proliferation, survival, differentiation and apoptosis[41]. These biological activities include beneficial effects in immune response against several pathogens and in organogenesis of lymphoid structures as well as host damaging effects in sepsis, cachexia, autoimmune and inflammatory diseases[42].

TNF-α is primarily produced by immune cells such as monocytes and macrophages, but other cell types are also capable of releasing this cytokine, including acinar cells. It is initially synthesized as a 26 kDa cell surface associated molecule anchored by an N-terminal hydrophobic domain. This membrane-bound form of TNF-α possesses biological activity. A specific matrix metalloproteinase protein, called TNF-converting enzyme, cleaves the 26 kDa form into a soluble 17 kDa form[41] which self-assembles in non covalent bound homotrimers[43], an important feature for the cross-linking and the activation of TNF receptors.

TNF-α and its specific receptors TNFR1/TNFR2 are the major members of a gene superfamily of ligand and receptors that regulates essential biologic functions.

Receptor activation by TNF family ligands causes recruitment of various adaptor proteins with subsequent activation of downstream signalling pathways. TNFR superfamily can be classified in three major groups according to specific intracellular sequences and to signalling adaptors recruited. The first group include receptors, such as TNFR1 (p55 or 55-kDa TNFR), Fas, where they share a highly conserved sequence of about 80 amino acids in the cytoplasmic region called the death domain. Activation of these receptors leads to homotypic interactions with adaptor proteins containing death domains such as Fas-associated death domain (FADD) and TNFR-associated death domain (TRADD). The latter signalling pathway requires an interaction between TRADD and FADD, which in turn interact with caspase-8. Though Recruitment of TRADD can also trigger downstream events related to inflammation through further adaptor proteins including TNF receptor associated factors, receptor interacting protein and mitogen activated kinase-activating death domain[41].

A strong link has been established between TNF-α production and oxidative stress during the IRI process[33,34]. Thus inflammatory mediators such as the cytokine, TNF-α is thought to have a central role in the pathophysiology of renal injury[44]. TNF-α is consistently up-regulated in response to renal ischaemic injury, induced by the activation of p38 mitogen-activated protein kinase *via* enhanced tyrosine phosphorylation[33,34,45,46]. It is also known to induce other mediators of inflammation and tissue injury such as IL-1, IL-2, interferon-γ, adhesion molecules (ICAM-1, VCAM-1) which exacerbate the injury process[47]. Activation of TNF-α may induce apoptosis, cell death as well as inflammation[41]. TNF-α is implicated in the pathogenesis of different renal diseases and can promote renal dysfunction by direct cytotoxicity, vasoconstriction, and inflammatory cells recruitment[33,48-50]. Up-regulation of mRNA and protein levels of TNF occurs at a whole-organ level within minutes to hours of the onset of I/ R Injury[33]. To date FR167653, an inhibitor of TNF-α has been shown to improve effects of warm ischaemia in a porcine model[35].

INFLIXIMAB

Infliximab is one of 3 licensed TNF antagonists. Infliximab is a chimeric antibody with a mouse variable fragment (Fv) and human antibody with immunoglobulin G1 (IgG1) and k constant regions[41,51,52], which neutralizes the biological activity of TNF by binding to the soluble and trans-membrane forms of TNF and inhibits the binding of TNF with its receptors. The structure of Infliximab is similar to that of naturally occurring antibodies[41]. Though Infliximab's mechanism of action is not completely understood. This chimaeric monoclonal antibody, composed of a complement fixing 'human' IgG1 constant region (75%) and a murine derived antigen-binding variable region (25%), binds soluble TNF; however, its action is thought to depend in part on its ability to bind precursor cell-surface TNF, perhaps leading to monocyte apoptosis[41]. Two pivotal trials demonstrated the efficacy of infliximab in patients with Crohn's disease (FDA approved)[53-55].

Infliximab has been shown to inhibit functional TNF-α activity in a variety of *in vitro* bioassays using human fibroblasts, endothelial cells, neutrophils, lymphocytes, and epithelial cells[56]. *In vivo*, infliximab is indicated for the treatment of rheumatologic, gastrointestinal, dermatologic, and chronic ocular diseases[51,57]. The role of infliximab has been shown to improve I/R injury in spinal injury models[51,58] and cardiac injury models[59,60]. Guven *et al*[51] demonstrated that the use of infliximab significantly reduced vascular proliferation, oedema and neuron loss following I/R injury and concluded that the agent may protect the spinal cord against injury in a rabbit I/R model. Niemann *et al*[59] in a porcine ventricular fibrillation cardiac arrest model showed that infliximab significantly blocked TNF-α levels at 30 min after cardiac arrest and these animals showed a significantly greater mean arterial pressure and stroke volume which was sustained throughout 3-h post resuscitation period.

Porcine TNF shares a similar structure with that of human and murine TNF and exhibits cytotoxicity to target indicator cells (PK and L929)[61] at similar concentrations[62]. Porcine TNF-α cytotoxic activity can be totally neutralized with anti-human TNF monoclonal antibody[59,63]. Porcine TNF-α receptors likewise share a structure similar to that of humans, and mice and human soluble TNF-α receptors bind porcine TNF-α[64]. Considering these characteristics, binding to and neutralization of porcine TNF-α by Infliximab would be expected and has been successfully used to improve cardiac dysfunction in a porcine model[59].

Although it is generally safe, serious complications can ensue. In addition to occasional hypersensitivity and infusion reactions, a number of deaths have been reported as a result of tuberculosis or sepsis[65]. The complication may simply be due to effective immune modulation rather than the specific drug. Infliximab has been associated with hypersensitivity reactions that include urticaria, dyspnoea and hypotension, and usually occur within 2 h of infusion. Serum sickness-like reactions were observed in some Crohn's disease patients 3 to 12 d after therapy was reinitiated following an extended period without infliximab. Fever, rash, headache, sore throat, myalgia, polyarthralgias, hand and facial oedema and dysphagia were also associated with a marked increase in antibodies to infliximab[58,66,67].

However, the effects of infliximab in reducing renal ischaemic injury have not been clearly determined and this manipulating agent may have a potential role in DCD, ECD kidney transplantation. To date, Cau *et al*[35] has shown that the use of an agent FR167653, a potent inhibitor of TNF-α and IL-1β reduces the early and long term effects of WI in the their porcine ischaemic model. This effect was particularly marked against fibrosis and inflammation, which would contribute to deterioration

of renal function. Bagul *et al*[68] have shown preliminary results of Infliximab are promising where this agent significantly improved kidney perfusion, oxygen delivery and reduced TNF-α levels in an *ex-vivo* model of renal transplantation and concluded that further investigation to assess infliximab's potential to ameliorate I/R injury in renal transplantation is warranted.

In addition to this Infliximab may play a role to reduce AR as not only it may reduce DGF which has a direct link to AR[10,11], it is a potent TNF antagonist where TNF-α in itself is a Th1-type cytokine (IL-2, interferon-γ, TNF-α) which mediates cellular response[69-72]. Importantly Th1-type cytokines may down regulate Th2-type cytokines (IL-4, IL-5, IL-10) which mediate the humoral response[72]. There is a body of evidence which show cytokines are involved in allograft rejection, where Th1-type cytokines are believed to be associated with rejection while Th2 cytokines with tolerance[73,74].

CONCLUSION

The new insights into the mechanisms of action of TNF antagonist such as Infliximab need to be studied further and coupling this with the drug's safety profile, pharmacokinetics and immunogenicity; the drug may have dual role in transplantation benefiting not only from I/R injury but also AR.

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OBSERVATION

Walter Guillermo Douthat, MD, PhD, Professor, *Series Editor*

New options for the management of hyperparathyroidism after renal transplantation

Walter Guillermo Douthat, Carlos Raul Chiurchiu, Pablo Ulises Massari

Walter Guillermo Douthat, Carlos Raul Chiurchiu, Pablo Ulises Massari, Bone and Mineral Metabolism Section, Renal Service, Hospital Privado, Centro Médico de Córdoba, 5016 Córdoba, Argentina
Walter Guillermo Douthat, Carlos Raul Chiurchiu, Pablo Ulises Massari, Postgraduate School of Nephrology, Catholic University of Córdoba, Fundación Nefrológica de Córdoba, 5016 Córdoba, Argentina
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Correspondence to: Walter Guillermo Douthat, MD, PhD, Professor of Nephrology, Chief of Bone and Mineral Section, Renal Service, Hospital Privado, Centro Médico de Córdoba, Naciones Unidas 346, 5016 Córdoba,
Argentina. wdouthat@hospitalprivadosa.com.ar
Telephone: +54-351-4688230 Fax: +54-351-4688844
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Abstract

The persistence and severity of hyperparathyroidism (HPT) post-renal transplantation is relatively frequent and primarily associated with the timing and its magnitude in the pre-transplant period and with the presence of parathyroid adenomas. HPT after renal transplantation is clinically manifested with hypercalcemia, hypophosphatemia, bone pain, fractures, and in more serious cases with cardiovascular calcifications that affect the survival. The primary clinical objective for patients with secondary HPT after renal transplantation is to obtain a level of parathyroid hormone (PTH) adequate to the renal transplanted function and to normalize levels of calcium, phosphorus and vitamin D. In many cases during this period, the development of hypercalcemia and/or hypophosphatemia makes it necessary to take different therapeutic measures. The use of vitamin D or its analogues has been extrapolated from the management of pre-transplant HPT obtaining variable outcomes, although its use is limited by its capacity to produce hypercalcemia. Calcimimetics are drugs that have proven be effective in reducing PTH levels in patients with HPT on dialysis and has been effective in reducing up to 50% PTH levels in moderate to severe HPT in post-renal transplantation.When HPT persists after renal transplantation and does not respond to medical treatment, invasive management by percutaneous ethanol injection therapy of parathyroid glands or parathyroidectomy should be considered. The emergence of new methods for the management of HPT expands the availability of therapeutic tools for transplant patients.

Key words: Hyperparathyroidism; Renal osteodystrophy; Renal transplantation; Percutaneous ethanol injection therapy; Parathyroidectomy; Percutaneous ethanol injection therapy

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INTRODUCTION

As the number of kidney transplants grows and the

survival of patients who have received a kidney graft improves, new challenges in managing their long-term complications appear. Disorders of bone and mineral metabolism are common in these patients, causing high morbidity and affecting the quality of life in transplant recipients.

The type and severity of bone lesions in the renal transplant recipients are determined by factors such as pre-transplant bone disease, renal graft function, effect of immunosuppressive agents on the bone, menopause, age, and comorbidities, such as diabetes, among the most important ones[1,2].

The progressive loss of kidney function leads to the gradual development of bone and mineral metabolism disorders, and bone disease is almost universally present in all patients with less than 60 mL/min of glomerular filtration rate. The pathophysiology of bone disorders is complex, predominantly related to increased bone turnover as it occurs in secondary hyperparathyroidism (HPT) or with low bone turnover, as seen in osteomalacia and adynamic bone disease. These patients have reduced bone strength, and increasing the risk of fractures in presence of renal osteodystrophy, with a prevalence of hip fractures four times compared to the general population[3].

INFLUENCE OF PARATHYROID FUNCTION BEFORE RENAL TRANSPLANTATION

Secondary HPT and its complications are frequently found in chronic kidney disease (CKD), especially in patients with dialysis therapy[4,5]. Data obtained in Latin America from bone biopsies show that about half of them present osteitis fibrosa due to secondary HPT[6]. Similar findings were shown in a prevalent hemodialysis population[6], but they differ from those found in some European countries, where low levels of parathyroid hormone (PTH) prevail over secondary HPT[7,8].

The development of secondary HPT is related to the presence of hyperphosphatemia, low levels of vitamin D, hypocalcemia, time on dialysis, parathyroid gland size and the presence of parathyroid adenomas[6,9]. If secondary HPT is not prevented or treated early during the period of dialysis, the patient will receive a renal transplantation having a disorder in the parathyroid function that is difficult to revert.

A high number of patients who receive renal grafts present altered calcium-phosphate metabolism and abnormal levels of PTH. Data from our own center on levels of markers of mineral metabolism in 365 patients at the time of renal transplantation, showed that 58% had intact PTH levels > 250 pg/mL, 12.4% had hypercalcemia and 27.9% presented severely elevated levels of serum phosphorus (Figure 1). The mean level of intact PTH was 518.5 ± 520.4 pg/mL, serum calcium of 9.2 ± 1.3 mg/dL and phosphorus 5.6 ± 2.0 mg/dL. These data highlight the prevalence of secondary HPT with hyperphosphatemia at the time of renal transplantation and match with the finding of patients undergoing bone biopsy[6].

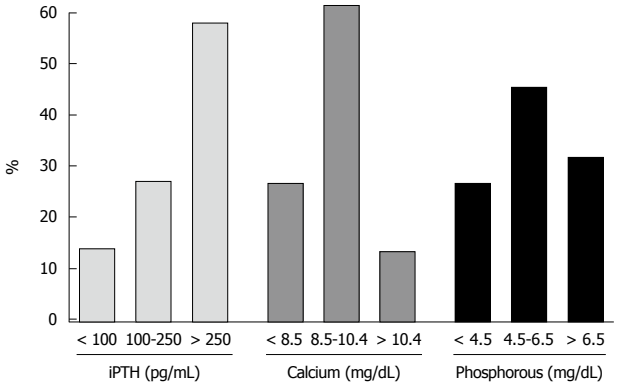

Figure 1 Markers of mineral metabolism immediately before renal transplantation. Data from Hospital Privado Centro-Médico de Córdoba.

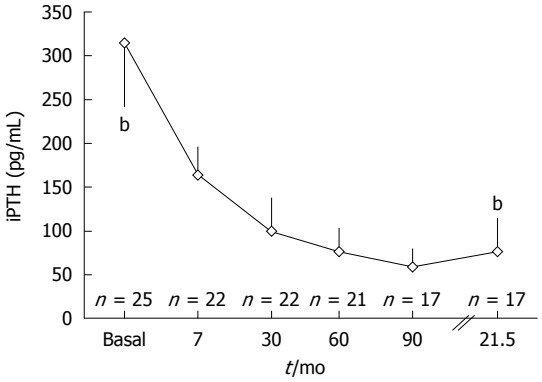

Figure 2 Changes in iPTH levels in post-renal transplantation. Data from Hospital Privado-Centro Médico de Córdoba. [b]$P < 0.001$.

PERSISTENT SECONDARY HPT AFTER RENAL TRANSPLANTATION

A successful renal transplantation normalise most of the endocrine and metabolic imbalances since the beginning of recovery of renal function[1]. Thus, with renal function the capacity to produce 1-25 dihydroxyvitamin D is recovered, phosphate levels are corrected due to the improvement of renal tubular function and the levels of serum calcium are normalized. The consequence of these changes is the spontaneous decrease in PTH levels in most patients[10]. In our experience, intact PTH levels showed a significant decrease from a mean value of 353 pg/mL to 77 pg/mL in an average time of 2 years from transplantation (Figure 2). However, in 56% of registered cases, intact PTH levels remained high at the end of follow-up, 32% had hypercalcemia and 28% had hypophosphatemia. According to Bertoni *et al*[11], serum PTH levels remain above 100 pg/mL in one-third of the patients at 6 mo of a functioning kidney transplant while in 20% of cases PTH levels remain abnormally high at 5 years of transplantation. Our data are consistent with those published by Heaf *et al*[12] where 50% of patients

achieved spontaneous recovery of PTH levels 1 year after transplantation, while 21% remained with high levels 15 years after successful kidney transplant.

The persistence and severity of HPT in post-renal transplantation is primarily associated with its duration and magnitude in the pre-transplant period and with the presence of parathyroid adenomas[1,2]. Although the pathophysiology of persistent HPT after transplantation is not fully elucidated, it is likely related to the presence of parathyroid adenomas in the pre-transplant phase, whose cells have low density of calcitriol receptors (Vitamin D receptors, or VDR), calcium-sensing receptor in the plasma membrane and receptors for phosphatonin FGF23 (FGFR)[13-15]. Thus, proliferating cells in the adenomatous tissue do not respond to circulating calcitriol, calcium or FGF23[15].

HPT after renal transplantation is clinically manifested with hypercalcemia, hypophosphatemia, bone pain, fractures, and in more serious cases with cardiovascular calcifications that determine the survival of patients with CKD.

MANAGEMENT OF BONE DISEASE AFTER TRANSPLANTATION

Although advances in the management of transplantation have improved its outcomes, still exist a high morbidity rate that affects the survival of the graft and the patient, and that is mainly related to cardiovascular disease, rejections, infections, cancer and bone disease[16].

Overall, there is little consensus about how to manage post-transplant osteodystrophy and how long it should be waited for an adequate renal function that influences on the correction of the deviations of bone and mineral metabolism from the stage of dialysis. Therapeutic options at this stage include optimizing the dosage of immunosuppressive drugs, particularly corticosteroids, calcium or vitamin D supplements, hormone replacement, correction of hypophosphatemia and the use of bisphosphonates[16,17].

The recommendations for this population indicate that all transplant patients should be assessed and eventually treated for their bone disease due to its high prevalence and the implications on morbidity and mortality rates in this population. This includes measures to improve skeletal health such as promoting mobilization, controlling excessive alcohol intake or smoking and correcting levels of gonadotropic hormones and negative balance of calcium and vitamin D[18]. KDIGO guidelines on the management of bone disease in patients with CKD recommend for post-renal transplantation, periodic measurement of serum calcium, phosphorus, vitamin D and PTH levels with a frequency that will vary according to the severity of bone disease and function of the transplanted kidney[17]. In patients with renal function grades 1 to 5, it is advisable to measure levels of 25-OH vitamin D and correct them by implementing similar measures to those of the general population, if deficiency or insufficiency were detected (< 10 *vs* 10-30 ng/mL respectively).

Perhaps one of the conditions that more questions arise when deciding the type and length of therapy is the correction of persistent secondary HPT after renal transplantation and the presence of hypercalcemia.

MEDICAL MANAGEMENT OF HPT AFTER RENAL TRANSPLANTATION

The primary clinical objective for patients with secondary HPT after renal transplantation is to obtain a level of PTH adequate to the graft function and to normalize levels of calcium, phosphorus and vitamin D. It is a common practice to follow an expectant course with regard to serum PTH levels until adequate renal function, allowing the normalization of calcemia, phosphatemia and increasing the production of calcitriol to control HPT.

In many cases during this period, the development of hypercalcemia and/or hypophosphatemia makes it necessary to take different therapeutic measures. The use of vitamin D or its analogues has been extrapolated from the management of pre-transplant HPT to the period after renal graft obtaining variable outcomes. The use of calcitriol allowed the decrease of PTH levels in normocalcemic recipients with post-transplant HPT[19] although its use is limited by its capacity to produce hypercalcemia similarly to the pre-transplant period[20]. For the presence of persistent post-transplant HPT with low 25-hydroxyvitamin D levels, even with normal 1-25 dihydroxyvitamin D levels, the use of nutritional supplements of vitamin D may be an adequate therapy to restore the levels of 25-hydroxyvitamin D[21]. However, despite the many studies of vitamin D or its analogues, the presence of autonomous parathyroid adenomas with decreased calcitriol, FGF23 or calcium-sensing receptor expression makes it unlikely to obtain a successful outcome and many post-transplant HPT becomes refractory to the medical treatment.

Calcimimetics are drugs that have proven effective in reducing PTH levels in patients with HPT on dialysis through modulating the activity of the calcium sensing receptor (CaR) on the plasma membrane of parathyroid cells[22]. Cinacalcet has been effective in reducing up to 50% PTH levels in moderate to severe HPT in post-renal transplantation[23,24]. In addition to the effective decrease of PTH levels, Cinacalcet could control two of the major problems of post-transplant HPT such as, hypercalcemia and hypophosphatemia[25]. As it also happens in the treatment with Cinacalcet in the HPT of patients on dialysis, might produce hypocalcemia[25] and PTH may return to pre-treatment levels after discontinuation of this drug, especially in patients with persistent adenomas or tertiary HPT.

Other treatments such as bisphosphonates or calcitonin have proven efficacy in controlling some of the disorders of HPT such as loss of bone mass or hypocalcemia but without effects on PTH levels[26,27].

When HPT persists after renal transplantation and does not respond to medical treatment, invasive management by percutaneous ethanol injection therapy (PEIT) of parathyroid glands or parathyroidectomy should be considered.

INDICATIONS FOR PARATHYROIDECTOMY IN POST-RENAL TRANSPLANTATION

The decision to perform a parathyroidectomy in a patient with a functioning renal transplant is rare and is usually taken when HPT leads to mineral disorders that cannot be controlled with medication. The prevalence of this interventons in post-renal transplantation ranges from 0.6% to 5.6%[28]. The indications tend to come from a combination of clinical, imaging and laboratory abnormalities, as the presence of hypercalcemia and/or severe hypophosphatemia, calciphylaxis, progressive vascular calcification, symptomatic and severe bone disease and spontaneous fractures. A retrospective study of 90 renal transplant patients who underwent parathyroidectomy determined the factors that significantly influenced on the decision to perform surgery were the highest pre-transplant PTH levels, female sex and hypercalcemia[28]. Parathyroidectomy resulted in decreased levels of PTH and calcium, increased serum phosphate and improving blood pressure and serum lipids[29,30].

Some studies have associated post-transplant parathyroidectomy with subsequent decreasing renal function[30,31], but this effect could not be confirmed in subsequent studies[28]. While this finding not had a definitive explanation so far, some researchers link it to specific effects of surgery and anaesthesia rather than changes related to parathyroid function[32]. The surgery-related risks and the potential development of low-turnover bone disease indicate the need for further assessments to determine risks and benefits of surgery or to postpone surgical treatment.

MANAGEMENT OF HPT AFTER RENAL TRANSPLANTATION BY USING PEIT

An alternative for these patients is to use PEIT into parathyroid adenomas with 95% ethanol solution[32,33]. This technique is indicated for patients with elevated PTH levels (300 to 1500 pg/mL), recurrent post-parathyroidectomy HPT[34], clinical contraindication to parathyroid surgery, and with 1 or 2 nodular parathyroid glands are observed by ultrasonography[32,33,35].

PEIT of the parathyroid gland is a low-risk technique that requires the use of a needle with small side holes to inject 95% ethanol solution into parathyroid nodules under ultrasonographic guidance with local anaesthesia in an outpatient basis[35].

We have recently showed that patients with persistent post-transplant HPT can be successfully managed by using PEIT[36]. These represent the first published data on the use of PEIT in post-renal transplantation.

Intact PTH levels decreased an average of 36.5% ± 9.5% in patients who underwent PEIT (286.9 ± 107.2 to 154.6 ± 42.2 pg/mL), with a marked long-term improvement of calcemia and phosphatemia without major complications after PEIT[36] (Figure 3). Although this was a small series of patients, PEIT has proved to be a safe and useful method to manage HPT after transplantation and avoid expensive and risky surgeries such as parathyroidectomy.

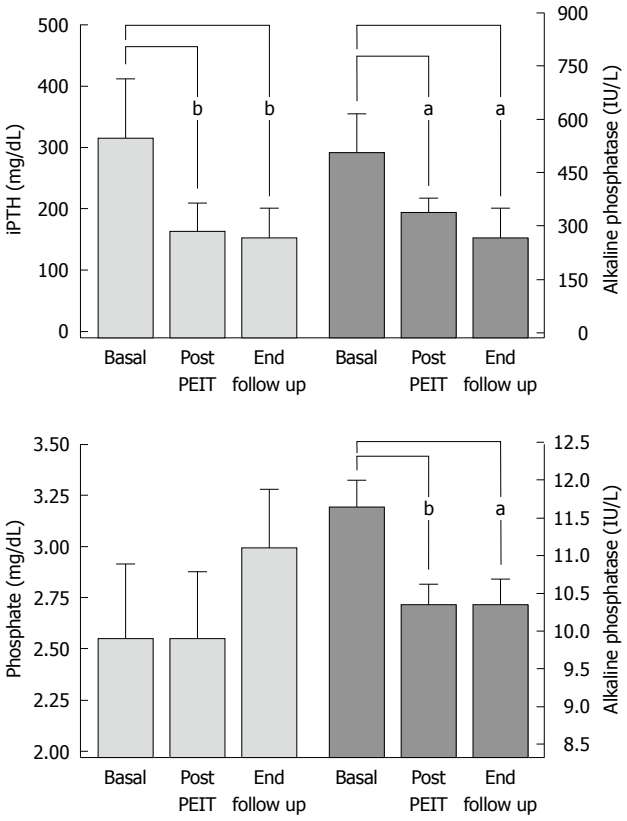

Figure 3 Markers of mineral metabolism before and after percutaneous ethanol injection therapy of parathyroid gland in renal transplant patients with hyperparathyroidism at Hospital Privado, Córdoba, Argentina. PEIT: Percutaneous ethanol injection therapy. $^{a}P < 0.05$, $^{b}P < 0.01$.

CONCLUSION

The high prevalence of bone diseases in post-transplantation of solid organs, especially osteoporosis and secondary HPT, should promote a more rigorous emphasis on early diagnosis and management of these conditions. At present, more data are required on the effect of immunosuppressive drugs on bone health and the use of antiresorptive agents in transplantation in order to prevent or treat bone mass defects. The emergence of new methods for the management of HPT such as PEIT of the parathyroid gland expands the availability of therapeutic tools for transplant patients.

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World J Transplant 2012 June 24; 2(3): I
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Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Transplantation*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

Andrea De Gottardi, MD, PhD, Assistant Professor, Clinic of Visceral Surgery and Medicine, Hepatology, Freiburgstrasse, CH-3010 Berne, Inselspital, Switzerland

Yu-Fan Cheng, MD, Department of Radiology, Chang Gung Memorial Hospital Kaohsiung Medical Center, 123, TA Pei Road, Niao Sung Hsiang, Kaohsiung Hsien 833, Taiwan, China

Sarah Anne Hosgood, Miss, BSc, Department of Infection, Immunity and Inflammation, Transplant Group, Leicester General Hospital, University of Leicester, LE5 4PW, United Kingdom

Ahad Eshraghian, MD, Department of Internal medicine, Namazi hospital, Shiraz University of medical science, Shiraz, 71345-1377, Iran

Frank JMF Dor, MD, PhD, Division of Transplant Surgery, Department of Surgery, Erasmus MC Rotterdam, room H-811, PO BOX 2040, 3000 CA Rotterdam, The Netherlands

Olivier Detry, MD, PhD, Associate Professor, Department of Abdominal Surgery and Transplantation, University of Liège, CHU Liège, Sart Tilman B35, B4000 Liège, Wallonia, Belgium

Andres Beiras-Fernandez, MD, PhD, Department of Cardiac Surgery, University Hospital Munich, Marchioninistraße 15, 81377 Munich, Germany

Ilka FSF Boin, MD, PhD, Associate Professor, Director of Unit of Liver Transplantation, HC, Unicamp, Surgery Department, Faculty of Medical Sciences, State University of Campinas, Av. Carlos Chagas, 420, Postal Code 13983-000, Campinas, SP, Brazil

Costas Fourtounas, MD, PhD, Associate Professor, Department of Nephrology, Patras University Hospital, Rio-Patras 26500, Greece

Wenda Gao, PhD, Assistant Professor, Department of Medicine, Transplant Institute, Beth Israel Deaconess Med Ctr, SL-427, Harvard Medical School, Boston, MA 02215, United States

Mehdi Hamadani, MD, Assistant Professor of Medicine, Hematology, Oncology, West Virginia University, PO Box 9162, 1 Medical Center Drive, Morgantown, WV 26506, United States

Kuzhuvelil B Harikumar, Post Doctoral Associate, Department of Biochemistry, Virginia Commonwealth University, 1101 East Marshall St, Richmond VA 23298, United States

Walid Mohamed El Moghazy, MD, PhD, Department of Hepatobiliary, Pancreas and Transplant Surgery, Kyoto University Hospital, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto city, Kyoto, 606-8507, Japan

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Events Calendar 2012

January 29 - 31, 2012
2nd Joint AIDPIT and EPITA Winter Symposium & 31st AIDPIT Workshop
Innsbruck, Austria

February 1 - 5, 2012
2012 BMT Tandem Meetings
American Society for Blood and Marrow Transplantation
Manchester Grand Hyatt,
San Diego, CA, United States

February 22 - 24, 2012
British Transplantation Society 15th Annual Congress
Glasgow, Scotland

February 23 - 25, 2012
2012 Canadian Society of Transplantation Annual Scientific Conference
Fairmont Château Frontenac,
Québec, Canada

March 8 - 10, 2012
3rd International Conference on Transplantomics and Biomarkers in Organ Transplantation
La Jolla/San Diego,
CA, United States

April 18 - 21, 2012
The International Society for Heart and Lung Transplantation (ISHLT), 32nd Annual Meeting and Scientific Sessions
Prague, Czech Republic

April 25 - 27, 2012
United Network for Organ Sharing's 20th Annual Transplant Management Forum
Wyndham Rio Mar Beach Resort,
Puerto Rico

June 2 - 6, 2012
2012 American Transplant Congress
John B. Hynes Convention Center,
Boston, MA, United States

July 15 - 19, 2011
24th International Congress of the Transplantation Society
Berlin, Germany

September 13 - 15, 2012
ELITA - LICAGE LIVER MEETING and 4th ELITA Split-Liver Course
Ghent, Belgium

September 29 - 30, 2012
Advances in nephrology, dialysis, Kidney Transplantation
Odessa, Ukraine

October 5 - 7, 2012
V Congress of Transplantologists
Kharkiv, Ukraine

October 5 - 7, 2012
2012 European Organ Donation Congress, 24th ETCO-EDC
Dubrovnik, Croatia
October 12 - 14, 2012
ESOT and AST Joint Meeting - Transformational therapies and diagnostics in transplantation
Nice, France

November 2 - 4, 2012
5th ELPAT Invitational Working Groups Meeting
Sicily, Italy

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GENERAL INFORMATION

World Journal of Transplantation (*World J Transplant*, *WJT*, online ISSN 2220-3230, DOI: 10.5500) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 100 experts in transplantation from 29 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

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WJT aims to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of transplantation. *WJT* covers topics concerning organ and tissue donation and preservation; tissue injury, repair, inflammation, and aging; immune recognition, regulation, effector mechanisms, and opportunities for induction of tolerance, thoracic transplantation (heart, lung), abdominal transplantation (kidney, liver, pancreas, islets), transplantation of tissues, cell therapy and islet transplantation, clinical transplantation, experimental transplantation, immunobiology and genomics, xenotransplantation, and transplantation-related traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of transplantation-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

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The columns in the issues of *WJT* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in transplantation; (8) Brief Articles: To briefly report the novel and innovative findings in transplantation; (9) Case Report: To report a rare or typical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJT*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of transplantation; and (12) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in transplantation.

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Editor-in-Chief

Maurizio Salvadori, MD, Professor, Renal Unit, Careggi University Hospital, Viale Pieraccini 18, Florence 50139, Italy

Editorial Office
World Journal of Transplantation
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjt@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381891
Fax: +86-10-85381893

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There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

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Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/2220-3230/g_info_20100725072755.htm.

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Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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