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Insulin therapy in renal disease

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Diabetes mellitus (DM) is the main cause of end-stage renal disease (ESRD). Conversely, chronic renal failure (CRF) is also associated with diverse alterations in carbohydrate and insulin metabolism. CRF-induced metabolic disorders should be borne in mind when treating diabetic patients, to ensure the introduction of adequate therapy adjustments that are in line with the onset of renal function decline. Moreover, several specific therapies employed in CRF may also influence pharmacological therapy of DM in uraemic patients. Adequate glycaemic control has also been associated with a reduction in the onset and progression of diabetic nephropathy as well as in the morbidity and mortality in uraemic diabetic patients during dialysis. Intensive insulin therapy can notably improve glycemic control and it should be considered part of the management of insulin-treated CRF diabetic patients. Insulin analogues have been recently evaluated in CRF diabetic patients, with encouraging results. In this study, we review the more relevant aspects related to insulin therapy in diabetic patients with different degrees of renal failure and in patients with ESRD, both in conservative therapy and dialysis.

Keywords: chronic renal failure, diabetes, dialysis, insulin, insulin analogues, kidney, renal failure
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Introduction

Diabetes mellitus (DM) is the leading cause of chronic renal failure (CRF) and dialysis therapy [1]. Numerous drugs with different action mechanisms may serve to reduce both acute and chronic diabetic complications as well as to improve the quality of life in diabetic patients [2,3]. In patients with altered renal function, therapeutic possibilities are limited because of reduction in glomerular filtration rate (GFR) that is accompanied by accumulation of some oral agents and/or their metabolites [4,5].

Relationships between the kidney and carbohydrate metabolism have been recognized for many years. The kidney acts on insulin metabolism and, at the same time, is one of its target organs [6–9]. CRF is associated to multiple alterations in the carbohydrate and insulin metabolism that should be taken into account when treating diabetic patients with altered renal function [9–11]. Specific therapeutic needs (oral agents or insulin) will be determined based on the degree of insulin resistance (IR) or insulin deficiency of CRF diabetic patients [12]. On the other hand, carbohydrate and insulin metabolism alterations affect renal function. Chronic hyperglycaemia contributes to the development and progression of diabetic nephropathy through flow and pressure changes at the glomerular level [13,14]. IR and hyperinsulinaemia, as related to metabolic syndrome (MS), may also compromise renal function because of their association with DM and hypertension [15]. This study offers a review of the more relevant findings related to insulin therapy in diabetic patients in their various phases of diabetic nephropathy, from microalbuminuria through end-stage renal disease, whether

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on conservative management or on dialysis therapy, and finally, post-transplant diabetes mellitus (PTDM).

Insulin and the Kidney

Renal Metabolism of Insulin

Insulin, a 51-amino acid peptide hormone with a molecular weight of approximately 6000 Da, is synthesized by pancreatic islet beta cells and codified by a gene located in the short arm of chromosome 11 [16]. Half-life ($t_{1/2}$) of insulin is short (~3–5 min), and it is not bound to plasma proteins. Under fasting conditions, insulin secretion is continuous with a secretion rate of approximately 0.5–1 unit/h. Insulin secretion increases 3–10 times with food ingestion, putting the total daily insulin secretion at about 18–32 units [17,18].

Approximately 40–50% of the endogenous insulin produced by the pancreas is metabolized by the liver in its first pass, whereas 30–80% of systemic insulin is metabolized particularly in the kidney [6,7,9]. The kidney is, therefore, the main organ responsible for metabolizing exogenous insulin administered to diabetic patients (figure 1). About 65% of insulin that reaches the kidney is filtered in the glomerulus and is, subsequently, metabolized in the proximal tubular cells. About 35% of insulin diffuses from postglomerular peritubular vessels to the contraluminal cell membrane of the proximal tubular cell, where it is also degraded. Less than 1% of filtered insulin appears in the urine [8,9,19,20].

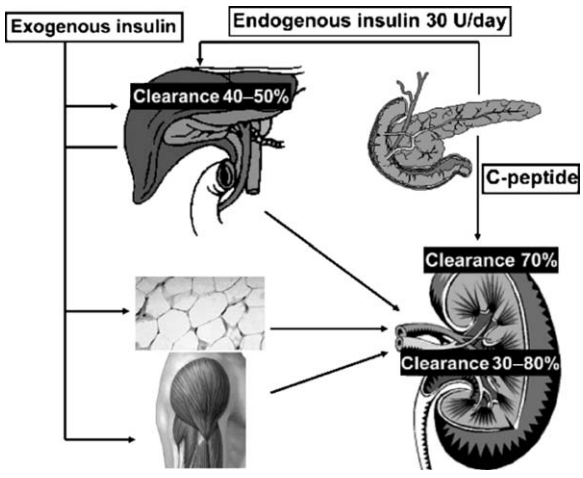

Fig. 1 Schematic representation of the metabolic clearance of insulin and C-peptide. The major site of endogenous insulin degradation is the liver. The kidney plays a greater role in the degradation of C-peptide and exogenous insulin.

Unlike insulin, C-peptide is not metabolized during its first pass through the liver and, approximately 70% of its plasma clearance is performed in the kidney [21] (figure 1). For that reason, serum concentration of C-peptide reflects pancreatic liberation of endogenous insulin in subjects with normal renal function [22].

Effects of Insulin on the Kidney

Insulin acts on the kidney by binding with receptors located in proximal tubular cells at both luminal and contraluminal levels [23,24]. Insulin increases sodium tubular reabsorption after stimulating Na/K-ATPase [25]. This effect might in part explain the insulin oedema occasionally associated with insulin therapy [26]. Insulin also increases glucose and phosphate reabsorption at tubular level [27]. These effects seem to be mediated by the stimulation of insulin receptors located in the contraluminal cell membrane of the proximal tubular cells [9]. Besides, insulin increments by 10% in the renal blood flow by means of its vasodilatador action. This haemodynamic effect of insulin is at least partially dependent on nitric oxide synthesis at endothelial cell level [28,29]. Recently, it has been demonstrated that human podocytes are insulin responsive with insulin-induced glucose uptake mediated through glucose transporter 4 (GLUT4) and GLUT1. This response is specific to the podocyte in the filtrations barrier of the glomerulus. This finding might be related to the development of microalbuminuria in insulin deficiency (type 1 diabetes) or in IR (type 2 diabetes and MS) situations [30].

Effect of CRF on Carbohydrate Metabolism

CRF is associated with several disorders in insulin metabolism, some of which have been documented for over 30 years [9–11,31–33]. Alterations in secretion, action and renal clearance of insulin are among these. Such alterations may be expressed as normoglycaemia in combination with hyperinsulinaemia and elevation of plasma C-peptide concentration, hypoglycaemia, fasting hyperglycaemia or glucose intolerance.

Both secretion and action of insulin are altered in CRF [10,31,32,34]. When insulin secretion compensates IR, normoglycaemia is maintained at the expense of hyperinsulinaemia. However, when insulin secretion is normal or slightly reduced, impaired basal glucose or glucose intolerance can develop. A relationship between uraemia-associated calcium and phosphate metabolism changes and alterations in carbohydrate metabolism has also been reported [32]. Both secondary hyperparathyroidism and vitamin D deficiency associated with CRF

reduce the insulin-secreting capacity of pancreatic beta cells. Medical or surgical control of hyperparathyroidism as well as therapy with 1,25-dihydroxyvitamin D serve to improve glucose tolerance and insulin secretion in CRF patients [31,32].

Uraemia-associated IR is a long-known metabolic alteration [35,36]. This particular IR begins in non-diabetic patients when GFR is less than 50 ml/min [37]. Insulin sensitivity can decrease by as much as 60% in uraemic patients in predialysis [38].

The mechanism for IR in CRF might be related to alterations in oxidative and non-oxidative pathways of the carbohydrate metabolism induced by uraemic toxins, as the number of insulin receptors, insulin affinity for its receptor, beta subunit phosphorylation, kinase activation and glucose transporter expression are normal [32,34,39–41]. Other factors that can influence uraemia-associated IR are some specific alterations in plasma levels of adipocytokines (tumour necrosis factor-α, resistin, leptin and adiponectin) and more indirect mechanisms, such as anaemia, metabolic acidosis and secondary hyperparathyroidism [33].

As renal failure progresses, insulin clearance also decreases. This reduction in insulin clearance is, initially, compensated with an increment in insulin uptake by proximal tubular cells [9]. When GFR is less than 20 ml/min, insulin clearance is markedly reduced. Furthermore, insulin catabolism in other tissues, such as liver or muscle, also decreases during uraemia. All these facts contribute to increase insulin $t_{1/2}$ [32]. The reduction in insulin clearance and catabolism is associated with more persistent metabolic effects, which increase the risk of severe and symptomatic hypoglycaemia, particularly in those diabetic patients in whom insulin doses have not been decreased [42,43]. The reduction in insulin requirements from the onset of overt nephropathy (proteinuria >0.5 g/24 h and creatinine clearance >80 ml/min) through to the final stage of renal disease (creatinine clearance <10 ml/min) was similar in type 1 (~40%) and type 2 (~50%) diabetic patients and was not affected by the residual insulin secretion in subjects with type 2 diabetes [44]. Other factors that contribute to decreasing exogenous insulin requirements in CRF diabetic patients are the reduction of renal gluconeogenesis, uraemia-induced anorexia and weight loss [20]. As a consequence of these alterations in the insulin metabolism, For these reasons The American College of Physicians recommends decreasing insulin doses by ~25% of insulin dose when GFR is 50-10 ml/min and by ~50% when GFR is less than 10 ml/min [12].

Dialysis therapy improves uraemia-associated IR [45,46]. Insulin sensitivity was completely normalized in 10 uraemic non-diabetic patients and markedly improved in another 10 patients after 5 and 10 weeks of haemodialysis (HD) respectively [45,46]. Although, initially, it was thought that intraperitoneal glucose overload might reduce insulin sensitivity in patients on peritoneal dialysis (PD), there have recently been reports about normalized or improved IR in uraemic non-diabetic patients, just a few weeks after initiating PD [38,45].

Effects of Carbohydrate Metabolism Disorders on Renal Function

Alterations in the carbohydrate metabolism, particularly chronic hyperglycaemia, also affect renal function. Nowadays, diabetic nephropathy constitutes the most common cause of CRF [1]. The increase in both glomerular flow (hyperperfusion) and pressure (hypertension) and renal hypertrophy are the first alterations associated with chronic hyperglycaemia in diabetic nephropathy [13,14]. This glomerular capillary hypertension observed in DM would appear to be a consequence of the deficiency of insulin action as strict glycaemic control reduces both renal haemodynamic response and kidney size [47–49].

Several mediators serve to maintain glomerular hyperfiltration associated with renal damage. Some of them are gluconeogenic amino acids, advanced glycated end products (AGEs), vascular endothelial growth factor, transforming growth factor-beta, growth hormone and insulin-like growth factor type-1 (IGF-1) [50–54]. It has been recently reported that insulin lispro, a rapid-acting insulin analogue with structural homology with IGF-1, prevented glomerular hyperfiltration and offset the renal effects of meal-associated hyperglycaemia in type 2 diabetic patients with overt nephropathy (serum creatinine <2.0 mg/dl and persistent macroalbuminuria ≥200 μg/min). The mechanism of this action might be related to IGF-1 antagonism [55].

IR is present in the majority of patients with MS [56]. Other disorders associated to MS are central obesity, hypertension, glucose intolerance or type 2 diabetes, atherogenic lipid profile (low HDL cholesterol and high triglyceride levels), hyperuricaemia, hypercoagulability state (elevation of plasma fibrinogen and plasminogen activator inhibitor) and microalbuminuria. Both MS and IR are risk factors in developing renal disease because of their association with type 2 diabetes and hypertension [15]. In this setting, the use of insulin sensitizer drugs, such as glitazones, which have shown favourable effects on the modulation of IR, hypertension, hyperlipaemia and inflammation, might be useful in the prevention

and treatment of MS-associated renal derangements [5,15].

Benefits of Glycaemic Control

The beneficial effect of intensive glycaemic control on the onset and progression of renal involvement in precocious phases of diabetic nephropathy has been demonstrated both for type 1 [57] and for type 2 [58] diabetes. However, little information regarding its effect on renal function and morbidity and mortality in diabetic patients with advanced renal insufficiency on conservative or dialysis therapy has been reported. Some isolated studies have shown that adequate glycaemic control in diabetic predialysis CRF patients can reduce morbidity and mortality in the first years following the start of dialysis [59–64]. Likewise, certain clinical advantages to intensive glycaemic control in diabetic patients following kidney transplantation have also been reported [65,66].

Given the benefits of intensive glycaemic control in diabetic CRF patients, an adequate management of hyperglycaemia is nowadays recommended in obtaining a better therapeutic efficacy. Intensive glycaemic control with multiple insulin doses has proven effective in reducing chronic diabetic complications [57,67]. Finally, the recent introduction of insulin analogues, whose main objective is to stimulate physiologic insulin secretion, has opened new therapeutic possibilities in diabetic CRF patients. Although only a few studies have evaluated the clinical efficacy and safety profile of insulin analogues in CRF patients, preliminary results appear hopeful.

Glycaemic Control in Diabetics with Renal Disease

Chronic hyperglycaemia plays a significant role in the development of diabetic nephropathy through its effect on proteins, on AGEs production and on the activation of numerous cell mediators [52,53,68]. Hence, glycaemic control in diabetic patients is fundamental in preserving renal function, in avoiding the development and progression of diabetic nephropathy, in reducing cardiovascular complications and those secondary to diabetes and in decreasing the mortality rate in CRF patients, both in predialysis and dialysis, as well as in patients with PTDM (table 1) [57–61,63,64,66,67].

Diabetic Nephropathy

Adequate glycaemic control diminished haemodynamic response and kidney size in the initial phases of diabetes [47–49]. In addition, it prevented or delayed diabetic nephropathy, both in type 1 and type 2 diabetes [57,58,67,69–73]. Long-term results of the main studies performed in type 1 and 2 diabetes patients showed that adequate objectives for prevention of onset and progression of diabetic nephropathy were glycated haemoglobin (HbA1c) $\leq$7.0%, fasting blood glucose concentrations 80–120 mg/dl and 2-h postprandial blood glucose concentrations $\leq$140–180 mg/dl [57,58,67,71,73–75].

Predialysis

No randomized studies on glycaemic control in diabetic patients with advanced CRF exist. However, it has been reported that good glycaemic control in the predialysis state is essential in improving long-term prognosis in diabetic patients on dialysis. Good glycaemic control before dialysis was closely correlated with morbidity (cardiovascular disease, diabetic complications and malnutrition) and with mortality in dialysis patients in both HD [61–64] and PD [59,60]. It is for that reason that the same glycaemic control objectives are, today, recommended in diabetics with normal renal function. The higher risk of hypoglycaemia because of the reduction in insulin clearance as GFR declines is to be taken into account in the management of these predialysis patients [44]. It would be advisable to obtain predialysis HbA1c levels <7.5% to improve the long-term outcome during the dialysis period [61,64].

Table 1 Proposed glycaemic control parameters for diabetic patients with renal disease

		Fasting blood glucose		Two hours postprandial blood glucose	
	Glycated haemoglobin (%)	mg/dl	mmol/l	mg/dl	mmol/l
Diabetic nephropathy	<6.5	80–120	4.4–6.7	<140	<7.8
Predialysis (CrC < 10 ml/min)	<7.5	100–120	5.6–6.7	<140–160	<7.8–8.9
Dialysis	<7.5–8.0	100–140	5.6–7.8	<200	<11.1
Renal transplantation	<6.5	80–120	4.4–6.7	<140	<7.8

CrC, creatinine clearance

Dialysis

Diabetic patients on dialysis also show a higher morbidity and mortality than non-diabetic dialysis patients [76–78]. Cardiovascular disease is the main cause of mortality in CRF diabetic patients [77]. The degree of glycaemic control correlates with morbidity and mortality in dialysis diabetic patients. Good glycaemic control for the first 6 months after starting HD predicted long-term survival for type 2 diabetics, and poor glycaemic control was associated with increased morbidity from vascular and diabetic complications, malnutrition and shortened survival [79].

Several factors can negatively influence glycaemic control in diabetic dialysis patients. These include uraemia-associated anorexia, poor and irregular food intake, insulin metabolism disorders (IR and reduced insulin clearance), inadequate gastrointestinal glucose absorption, multiple drug therapy and dialysis-dependent factors. At the beginning of PD, peritoneal transcapillary ultrafiltration capacity is lower in diabetics than in non-diabetics. For that reason, diabetic patients require higher dialysate glucose concentrations, which could potentially worsen glycaemic control [32]. On the other hand, although HD does not seem to have a significant effect on long-term glycaemic control in type 2 diabetic patients, the incidence of hypoglycaemia tended to be higher than in predialysis state [80].

At present, HbA1c is the best laboratory parameter in estimating glycaemic control in diabetic dialysis patients [81]. One recommended objective is to maintain HbA1c $<$7.5–8.0%, fasting blood glucose concentrations $<$140 mg/dl and 2-h postprandial blood glucose concentrations $<$200 mg/dl [82]. Besides, it is advisable to avoid hypoglycaemic events because of associated co-morbidity and the possibility of hypoglycaemia awareness [32]. More recently, it has been reported that continuous glucose monitoring systems and more biocompatible and non–glucose-containing dialysis fluids may be useful in improving glycaemic control in PD patients [83]. An intensive diabetes education programme has shown its clinical efficacy with regards to improving patient outcome and quality of life in diabetic dialysis patients [84].

Renal Transplantation

The presence of DM prior to renal transplantation is associated with early acute coronary syndrome and associated mortality in kidney transplant recipients [85]. The development of PTDM is also associated with a reduced graft and recipient survival [65,66]. Furthermore, the prevalence of PTDM is more elevated than diabetes, in the population at large [86].

Clinical risk factors for PTDM in renal transplant recipients are IR, old age, increased body mass index, smoking and virus C infection at the time of transplant [87–89]. HbA1c is a more sensitive index than fasting blood glucose in detecting subclinical PTDM. It is for that reason that its use has been recommended as a screening test for PTDM [90]. Adequate glycaemic control can help decrease the elevated mortality rate and negative influence on graft and recipient survival rates [66].

Insulin Therapy in Patients with CRF

Intensive insulin therapy (multiple daily injections or continuous subcutaneous insulin infusion) in diabetics with normal renal function has shown to be more effective than conventional insulin therapy (once- or twice-daily injections) in protecting renal function. Several studies have proven the efficacy of intensive insulin therapy in delaying the onset and progression of diabetic nephropathy, both in type 1 [57,70] and type 2 [67,71] diabetic patients.

Intensive insulin therapy was more effective as regards glycaemic control (HbA1c 7.2 vs. 9.1%) than conventional insulin therapy in 1441 type 1 diabetics treated for an average treatment period of 6.5 years. Moreover, it was associated with a 39% reduction in microalbuminuria risk ($>$40 mg/day) (primary prevention) and a 54% reduction in progression to macroalbuminuria ($>$300 mg/day) (secondary intervention) [57]. Long-term effects of intensive insulin therapy have also been favourable. The reduction in the risk of progressive nephropathy resulting from intensive therapy in type 1 diabetics persisted for at least 4 years, despite increased hyperglycaemia (HbA1c increase from 7.2 to 7.9%). The risk of new microalbuminuria (primary prevention) and macroalbuminuria (secondary intervention) was reduced by 53 and 86% respectively [91]. These findings suggest that type 1 diabetics should be treated with intensive therapy as early as possible and for a long term with the aim of improving glycaemic control and reducing the risk of renal involvement.

Type 2 diabetics also benefit from intensive insulin therapy. In a 6-year study, performed on 110 non-obese Japanese patients with type 2 diabetes, intensive insulin therapy was associated with a smaller percentage of patients with new onset diabetic nephropathy or with progression to macroalbuminuria than those treated with conventional insulin therapy, both in primary prevention (7.7 vs. 28%) and in secondary intervention (11.5 vs. 32%) [71]. After 8 years of intensive insulin therapy,

such differences were not only maintained but also increased [67]. During this period, intensive insulin therapy was associated with better glycaemic control than conventional insulin therapy (HbA1c 7.2 vs. 9.4%).

Among the main limitations of intensive insulin therapy are hypoglycaemia and weight gain. Frequent capillary glucose monitoring, a daily food intake schedule and adequate adherence to diet, particularly as regards carbohydrate ingestion, are the most important measures in avoiding hypoglycaemic events. The effect of insulin therapy on weight gain is important mainly in type 2 diabetics in whom obesity is prevalent. In these patients, intensive insulin therapy might increase the degree of obesity and, therefore, blood pressure [92].

Little data exist regarding insulin therapy in diabetic patients with advanced degrees of renal insufficiency. It may be considered that if intensive insulin therapy can help to improve glycaemic control, this therapeutic regimen might also be more efficacious than conservative insulin therapy in uraemic diabetic patients.

Ideal insulin therapies in diabetic patients with advanced CRF are difficult to establish given the lack of pharmacokinetic studies for the various types of insulin in patients with different degrees of renal insufficiency and the absence of therapeutic guidelines that define insulin adjustments based on GFR [43,93]. As regards type of insulin, whereas some authors recommend avoiding intermediate- and long-acting insulins in CRF diabetics, others are active proponents [20,32]. The absence of comparative studies does little to support their usage, as does the little information available on clinical consequences for the different types of insulin in uraemic diabetic patients.

Insulin Therapy in HD

In HD patients, insulin requirements are reduced in probable relationship with an improvement in IR associated to dialytic procedure [94]. It has been reported that 1 year after HD initiation, approximately one-third of insulin-treated type 2 diabetic patients did not need insulin, whereas less than 20% of diabetics treated with oral agents were insulin dependent [61]. On the other hand, long-term chronic HD does not seem to affect glycaemic control [95]. Neither HbA1c nor fasting blood glucose were modified after 12 months of HD in a group of 20 insulin-treated type 2 diabetic patients. However, hypoglycaemic events tended to be higher than in the predialysis period. Moreover, the residual diuresis decrement during the first year on HD is associated with a significant reduction of insulin requirements. In fact, patients with residual diuresis <500 ml/day showed a reduction in insulin needs by about 29%, whereas no changes were reported in patients with higher residual diuresis [95]. These data suggest that the reduction in insulin requirements in HD patients seem to be related to a decrease both in IR associated with dialysis and in insulin clearance because of loss of renal function.

Adequate glycaemic control in HD diabetic patients is feasible using two doses of intermediate-acting insulin and adding one preprandial dose of rapid-acting insulin as needed [32]. Finally, HD solutions with high glucose concentration have shown to be useful in preventing hypoglycaemic events during the HD session, without significant effects on HbA1c [95].

Insulin Therapy in PD

Initiation of PD improves IR and is accompanied by a decrease in insulin requirements. This reduction is more pronounced when insulin is instilled into the empty abdominal cavity than when it is subcutaneously administered [96]. Conversely, continuous glucose absorption from the peritoneum may impair glycaemic control. In order to reduce hyperglycaemia induced by glucose absorption from the dialysis fluid, the use of non–glucose-containing dialysis fluids – such as those with icodextrin or amino acids – has been proposed [97,98].

Intraperitoneal insulin administration is a more physiological alternative than the subcutaneous route because insulin absorption from parietal peritoneum and its subsequent portal venous delivery mimic endogenous insulin secretion without affecting dialysis efficacy [96,99–101]. Insulin requirements increase two- or threefold when insulin is intraperitoneally administered along with the dialysis fluid despite hyperinsulinaemia decreases [100,102–104]. Reasons for this higher exogenous insulin need are glucose absorption from peritoneum, delayed insulin absorption consequential to dilution by the fluid, insulin adsorption to the plastic surface of the dialysis solution delivery systems and insulin elimination in the non-absorbed effluent. These inconveniences may, in part, be avoided by administering insulin directly into the empty abdominal cavity. Nevertheless, a more elaborate manipulation is required [96,105].

Although some studies have reported better glycaemic control with intraperitoneal rather than subcutaneous insulin administration [96,106,107], this has not been systematically confirmed [104,108–111]. Moreover, increased costs are associated to the need for higher insulin doses in intraperitoneal administration.

Although intraperitoneal insulin avoids injections and is associated with lower hyperinsulinaemia than subcutaneous insulin, the higher doses of insulin are associated to some unfavourable effects on lipid control [107,110,111], risk of peritonitis [104,112] and fibroblastic proliferation [113], as well as the development of specific complications such as hepatic subcapsular steatonecrosis [114–118] and malignant omentum syndrome [117].

These untoward effects have limited the use of intraperitoneal insulin (table 2) and suggest that switching from the subcutaneous to intraperitoneal route of insulin administration is not recommended where patients are well controlled with the former system.

Insulin Analogues in Renal Insufficiency

Several new human insulin-derived molecules have been developed in recent years with the aim of improving glycaemic control in diabetic patients. The rationale for insulin analogues is based on structural changes in the insulin molecule to take advantage of the analogue's new pharmacokinetic properties, reproducing both basal (long-acting insulin analogues) and prandial (rapid-acting insulin analogues) insulin secretion more physiologically in response to glucose [118].

Rapid-acting insulin analogues are insulin lispro (LysB28-, ProB29-human insulin), insulin aspart (AspB28-human insulin) and insulin glulisine (GluB29-, LysB3-human insulin). Each of these molecules is produced by recombinant DNA technology. These structural changes in the molecule of human insulin reduce the insulin monomers tendency to self-associate. They confer a more rapid absorption and onset of action, higher maximum serum insulin concentrations and shorter action durations than for the same doses of regular human insulin [119–121].

Two long-acting insulin analogues are available: insulin glargine (21A-Gly-30Ba-l-Arg-. 30Bb-l-Arg-human insulin) (HOE 901) and insulin detemir [LysB29(Nε-tetradecanoyl) des(B30) human insulin] [122,123]. Structural changes introduced in these insulin molecules give rise to insulin analogues with more delayed absorption and receptor binding capacity [124–126].

Clinical efficacy and safety profile of insulin analogues are not clearly defined in CRF. As a result of fears of potentially carcinogenic and proliferative effects, most studies with analogues to date have excluded diabetic patients with advanced diabetic complications [127]. Therefore, there is little information regarding the use of these analogues in CRF patients, so far. Most of the reported studies are case reports or small series of patients reported in medical meetings, in abstract form. However, pharmacologic properties of the insulin analogues make these drugs interesting in managing diabetic patients with CRF, simply because they could reduce glycaemic excursions and the risk of hypoglycaemia, thus improving glycaemic control (table 3).

The first diabetic patient with CRF on dialysis treated with intensive insulin lispro therapy was reported in 1999. Adequate glycaemic control with improved quality of life had been achieved [128]. The pharmacokinetics and pharmacodynamics of insulin lispro was evaluated in eight diabetic patients (two type 1 and six type 2) on HD [129,130]. In this study, insulin lispro showed a more rapid absorption (maximum peak 30 vs. 51 min) and a shorter absorption $t_{1/2}$ than regular human insulin (12 vs. 32 min). Moreover, maximum insulin concentration (Cmax) was higher with insulin lispro than with regular human insulin (146 vs. 88 μU/ml). Finally, serum glucose level decreased in the first 20 min after insulin lispro administration, whereas it occurred in the first 40 min when regular human insulin was used [129,130].

Rave *et al.* [131] were the first to prove that insulinaemia (maximum peak and serum insulin concentrations

Table 2 Arguments in favour and against the utilization of intraperitoneal insulin in peritoneal dialysis patients

Pros	Cons
More physiologic absorption	Higher cost
Continuous insulin infusion	High insulin requirement
Avoids injections	Insulin losses in the non-absorbed effluent
Higher levels of 25-hydroxyvitamin D	Lipid effects
Lower hyperinsulinaemia	Specific dialysis complications

Table 3 Potential advantages and disadvantages of using insulin analogues in end-stage renal disease

Advantages	Disadvantages
Reduced hypoglycaemic events	Higher cost than human insulin
Better glycaemic control in basal–bolus regimen	Fewer safety profile data
Greater mealtime flexibility	Absence of clinical studies
Lower postprandial hyperglycaemia	Fewer clinical efficacy data
Greater convenience for the patient	Increased risk of hypoglycaemia if meal ingestion is low (anorexia) or absorption (gastroparesis) is delayed
Lower hyperinsulinaemia	
More rapid recovery from hypoglycaemic symptoms	

during 8 h after subcutaneous administration of 0.2 U/kg of insulin lispro or regular human insulin) was higher in type 1 diabetic patients with overt nephropathy (proteinuria >0.5 g/day and/or serum creatinine >1.5 mg/dl) than in non-nephropathic patients. Although insulin levels were higher in patients with overt diabetic nephropathy, the metabolic response to regular insulin – although not to insulin lispro – was reduced. This finding would indicate that a higher dose of regular human insulin with the consequent higher risk of hypoglycaemia would be necessary in achieving the same metabolic effect in patients with overt diabetic nephropathy. This study also showed that insulin analogues maintained their pharmacokinetic and pharmacodynamic properties in CRF patients. This finding might help to improve glycaemic control and avoid hypoglycaemia in these patients [131].

The pharmacokinetics of insulin aspart has been studied in type 1 diabetic patients with and without CRF [132]. Six type 1 diabetic patients with normal renal function were compared with 12 diabetic patients with mild/severe CRF in conservative therapy. The pharmacokinetics of subcutaneous insulin aspart (0.1 U/kg) administration was similar for both groups of patients. Absorption and clearance of insulin aspart was not altered by CRF. Moreover, there was no correlation between CRF severity and insulin Cmax, area under curve (AUC) for insulin and time taken in reaching peak plasma concentration [132].

Long-acting insulin analogues have recently been evaluated in uraemic patients on HD. Pscherer *et al.* [133] reported the results of a retrospective clinical study performed on 20 diabetic (4 type 1 and 16 type 2) patients with CRF on HD (time on dialysis approximately 43 months) treated with insulin glargine. Glycaemic control and the incidence of hypoglycaemia were analyzed. Nineteen patients had previously been treated with human insulin (conventional or intensive insulin therapy) and one patient with oral agents. All patients were changed to insulin glargine and those patients on conservative insulin therapy were treated with intensive insulin therapy. Insulin glargine doses were individualized and therapy duration was approximately 9 months. With this therapeutic regimen, HbA1c was reduced 0.9% ($p < 0.01$), severe hypoglycaemic events were not reported and dry weight increased approximately 1.5 kg [133]. The use of insulin glargine was also safe and effective in improving glycaemic control in severe type 2 diabetic patients with renal failure [134].

More recently, the case of a 62-year-old woman with type 2 diabetes on HD for 8 years treated with intensive insulin therapy was reported (four doses, three prandial doses of regular insulin and 1 dose of Neutral Protamine Hagedorn [NPH] at bedtime). During her hospitalization, her treatment was switched to insulin analogues (three prandial doses of insulin lispro and one dose of insulin glargine at bedtime). This therapeutic regimen provided better glycaemic control with absence of hypoglycaemic events for 1 year after discharge [135].

Pharmacokinetic properties (Cmax, AUC and $t_{1/2}$) of insulin detemir were similar in diabetic patients with different degrees of CRF (conservative therapy and dialysis) than in healthy subjects. There was no correlation between creatinine clearance and any of the pharmacokinetic variables. Elimination of insulin detemir during HD was negligible [136]. To date, there are no clinical studies available that evaluate insulin detemir in patients with renal disease.

Conclusions

Glycaemic control in CRF diabetic patients can be difficult to obtain because of multiple factors intrinsic to diabetes, renal insufficiency and concomitant therapy (pharmacological, dialytic and immunosuppressive therapy). IR and hyperinsulinaemia can impair the capacity to reach satisfactory target blood glucose levels. Intensive insulin therapy is an adequate option for improving glycaemic control in CRF, although it might increase the risk of hypoglycaemic events. In the few studies reported until now, the use of insulin analogues in CRF patients has been associated with potential advantages and benefits with regard to glycaemic control, yet without any significant elevation in hypoglycaemic event frequency. Whether pharmacokinetic properties of insulin analogues can be used for improving glycaemic control and reducing hypoglycaemia in CRF patients remains to be determined. Consequently, it is both convenient and recommendable that studies be conducted on a larger number of diabetic patients with various degrees of renal insufficiency and with different therapeutic modalities, in order to establish the therapeutic role of new insulin analogues in uraemic patients.

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