would obviously be of paramount importance. In the study by Liu et al. [9], hypovolaemia was identified in only 20% of patients, but identifying hypovolaemia retrospectively is difficult so this number may not be accurate. In the clinical situation, assessing ongoing fluid needs and responsiveness is complex as physicians balance the risks of fluid overload with those of hypovolaemia. Second, should vasopressors be used to restore baseline blood pressure or limit the risks of hypotension? This is a controversial area but there is no good evidence that liberal use of vasopressors decreases the incidence of acute renal failure. Finally, what level of arterial pressure should be chosen as the target? Finding one value that could be applicable to all patients would be difficult, perhaps such a value should be related to the patient’s own baseline blood pressure value which may be unknown.

Clearly, even if relative hypotension does participate in the development of acute renal failure, focusing primarily on arterial blood pressure as a target may be rather limited. Rather than providing a new goal, these observations by Liu et al. [9] are more a message supporting the importance of early, rapid and complete resuscitation in all patients.

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(See related article by Y. L. Liu et al. Changes in blood pressure before the development of nosocomial acute kidney injury. Nephrol Dial Transplant 2009; 24: 504–511.)

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Which hypoglycaemic agents to use in type 2 diabetic subjects with CKD and how?*

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DCCT [1], UKPDS [2,3] and Kumamoto studies [4] clearly indicate that good glycaemic control can reduce the risk of nephropathy in subjects with both type 1 and type 2 diabetes. Furthermore, the recent ADVANCE trial confirmed that much tighter glycaemic control (mean HbA1c = 6.5%) is beneficial for nephropathy in subjects with type 2 diabetes [5]. In order to achieve tight glycaemic control, we would like to try to describe which hypoglycaemic agents to use in type 2 diabetic subjects with CKD and how, in this comment.

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Type 2 diabetic subjects with CKD stage 1 or 2

There is no limitation to use any hypoglycaemic agent in this stage of subjects. However, from UKPDS, it was suggested to start with metformin for obese subjects and sulfonylureas for non-obese subjects [2,3]. This concept was used in Steno-2 trials for type 2 diabetic subjects with microalbuminuria [6]. In 2006, a consensus algorism for the initiation and adjustment of the treatment with hypoglycaemic agents was proposed from ADA and EASD [7]. This algorism recommended to use metformin with life-style intervention first and to add basal insulin (most effective), sulfonylurea (least expensive) or glitazones (no hypoglycaemia), if HbA1c values still exceeded 7.0%. However, after this algorism was developed, concerns about increased risk of myocardial infarction with the use of rosiglitazone were raised [8] and other medications such as glinides, α-glucosidase inhibitors, GLP-1 analogues and DPP4 inhibitors were not included owing to less glucose-lowering effectiveness, limited clinical data and/or relative expense [9]. Meanwhile, the ADOPT study, which examined the glycaemic durability of monotherapy, was published [10]. The results indicate that monotherapy failure was more frequent in glyburide than metformin or rosiglitazone. However, the cardiovascular event was less frequent in the glyburide group. Thus, the authors stated that the potential risks and benefits, the profile of adverse events and the costs of the drugs should all be considered [10]. In the case of insulin, ADA recommended to initiate that at the time of diagnosis for individuals presenting with weight loss or other severe hyperglycaemic symptoms or signs [9].

Type 2 diabetes is recently considered as a progressive disorder. The UKPDS [11] and ADOPT [10] studies indicate progressive loss of β-cell function during the study periods. An autopsy study also clearly indicates that β-cell volume was decreased and apoptosis of β-cells was increased in type 2 diabetic subjects [12]. Therefore, in the next decade, it is necessary to develop the method not only to achieve good glycaemic control but also to preserve β-cell function by inhibiting the apoptosis or inducing regeneration.

Type 2 diabetic subjects with CKD stages 3–5

The beneficial effect of tight glycaemic control itself on diabetic nephropathy in CKD stages 3–5 has unfortunately not been established yet. However, if blood pressure was controlled, good glycaemic control was shown to be associated with reduced GFR decline [13]. Furthermore, glycaemic control is generally considered to be important in the prevention of other diabetic complications, such as retinopathy, neuropathy or macroangiopathy. Indeed, even in diabetic subjects on maintenance haemodialysis, poor glycaemic control was shown to be associated with increased risk of mortality [14,15]. Therefore, it is important to keep good glycaemic control in diabetic subjects with CKD stages 3–5.

In diabetic subjects with CKD, there are several factors that influence the glycaemic status and/or insulin action. First, insulin resistance will appear in a relatively early stage of CKD and increase the risk of hyperglycaemia. In contrast, renal gluconeogenesis is impaired and the clearance of insulin and other hypoglycaemic agents is delayed, thus increasing the risk of hypoglycaemia [16]. The latter will make a serious problem.

We have a large emergency unit in Asahikawa Red Cross Hospital. During the last one and a half years, 57 cases were with consciousness disturbance due to severe hyperglycaemia in a total of 6276 emergency cases (0.9%). Forty-eight cases were drug-induced hypoglycaemia (3 with type 1 diabetes and 45 with type 2 diabetes), 60.4% of which occurred in subjects older than 70. Twenty-five cases were insulin-induced hypoglycaemia and 23 cases were due to sulfonylurea. In elderly subjects (>70), sulfonylurea-induced hypoglycaemia occurred in more than 60%. Initial levels of serum creatinine were available in 34 cases. As shown in Figure 1, in elderly subjects (>70), hypoglycaemia occurred more frequently (>60%) in subjects with CKD stages 3–5. Therefore, we should be very careful in treating elderly diabetic subjects with CKD stages 3–5.

How to use hypoglycaemic agents in type 2 diabetic subjects with CKD stages 3–5 is briefly described below. However, it should be noticed that the pharmacokinetics of each agent was examined in a small group of subjects and there is a substantial individual variation in the half-life of each agent. Moreover, the long-term data examining the safety of hypoglycaemic agents in diabetic subjects with CKD stages 3–5 are not available.

Insulin secretagogues

Sulfonylureas. First-generation sulfonylureas are rarely used and should be avoided in subjects with CKD stages 3–5. Among second-generation sulfonylureas, glibenclamide (glyburide) undergoes oxidation by the liver to three major metabolites. One of them (4-hydroxy-glibenclamide) has ∼15% of the potency of glibenclamide itself and excreted in the urine [17]. Thus, the risk of hypoglycaemia is increased in subjects with reduced renal function. Glipizide and gliclazide are metabolized by the liver to several inactive metabolites and thus generally considered to be used in subjects with reduced renal function [18]. Glimepiride,
one of the agents frequently used worldwide, is metabolized in the liver to two metabolites, one of which is weakly active and excreted in the urine, thus increasing the risk of hypoglycaemia in subjects with reduced renal function [16].

**Glinides.** Glinides are the insulin secretagogues with a short half-life and duration of action. They have modest glycaemic efficacy and a relatively low risk of hypoglycaemia. A small amount of nateglinide is excreted in the urine, and its active metabolite is also excreted in the urine [16,18]. Thus, in the advanced stage of CKD, nateglinide has an increased risk of hypoglycaemia. Other glinides, rapaglinide and mitiglinide, are considered to be used in subjects with CKD.

**Incretin-based insulin secretagogues.** These include GLP-1 receptor agonists and DPP-4 inhibitors. Since these are a new class of agents, long-term safety in subjects with CKD has not been determined. However, exenatide, one of GLP-1 receptor agonists, is cleared by the kidney and its use in subjects with advanced CKD is not recommended or tolerated [16]. Sitagliptin, one of DPP-4 inhibitors, is excreted in the urine and thus reduced doses are recommended in subjects with CKD stages 3–5 [19].

**Insulin sensitizer**

**Biguanides.** The most common side effect is gastrointestinal disturbance, and it is well known that metformin can cause lactic acidosis. Since metformin is excreted unchanged in the urine, it is accumulated with the reduction of renal function. Thus, the use of metformin is considered to be contraindicated in subjects with CKD stages 3–5.

**Thiazolidinediones.** The data of pharmacokinetics of thiazolidinediones, rosiglitazone and pioglitazone, indicate that they can be used without dose adjustment in subjects with CKD [20,21]. However, fluid retention is one of the side effects of thiazolidinediones. Therefore, these agents need to be carefully used in subjects with CKD.

**α-Glucosidase inhibitors**

Acarbose and voglibose are essentially not absorbed, while almost 50% of miglitol are absorbed. Although they act in the intestine, the use of α-glucosidase inhibitors in subjects with advanced CKD is generally not recommended [16,18].

**Insulin**

The use of insulin, human or analogue, is recommended in diabetic subjects with CKD stages 3–5. However, the dose of insulin needs to be reduced in the advanced stage of CKD, because exogenously administered insulin is mainly eliminated by the kidney. The American College of Physicians recommended a 25% decrease in doses of insulin when GFR decreased to between 50 and 10 mL/min, and a 50% decrease when GFR decreased to <10 mL/min [22,23]. Self-monitoring of blood glucose (SMBG) will help make this adjustment. The target HbA1c will be <7.0% in this group of subjects, because the recent report indicates that HbA1c levels >7.3% at the baseline significantly increase the risk of death in diabetic subjects under haemodialysis [24].

**How to evaluate the status of glycaemic control in subjects with ESRD**

HbA1c values are generally used to evaluate glycaemic control all over the world. However, in subjects with ESRD, there are some problems. Recent reports indicate that HbA1c levels underestimate glycaemic control in diabetic subjects with haemodialysis due to renal anaemia and the use of erythropoietin [25,26]. Since the levels of glycated albumin are not affected by these factors, glycated albumin might be a better marker of glycaemic control in diabetic subjects under haemodialysis with renal anaemia treated with erythropoietin [25,26]. Indeed, better survival in subjects with low glycated albumin has recently been reported [27].

**Conclusion**

In type 2 diabetic subjects with the early stage of CKD, all hypoglycaemic agents can be applicable. However, in subjects with the advanced stage of CKD, some of the drugs are contraindicated and others need to be used with caution in a reduced dose because of the increased risk of hypoglycaemia. In that case, switching to insulin with SMBG will be recommended. The dose of insulin needs to be reduced in the advanced stage of CKD.

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**References**


Association of oral calcitriol with improved survival in non-dialysed and dialysed patients with CKD

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Introduction

A large body of evidence suggests that vitamin D has health benefits beyond its central role in calcium-phosphorus homeostasis, regulation of PTH and formation and maintenance of bone [1]. Activated vitamin D binds to the vitamin D receptor (VDR) and influences diverse genetic responses in many tissues. This is because VDR is expressed not only in the classical target organs (bone, parathyroid glands, kidneys and intestine) but also in other non-classical targets including arteries, heart, immune system, endocrine organs and even the nervous system [1]. Vitamin D can inhibit various aspects of inflammation, which have been established as a key pathogenic mechanism in atherosclerosis: Vitamin D through VDR activation increases the Th2 cell population of lymphocytes [2]. Th2 lymphocytes are antiatherogenic through their production


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