Invited Comment

Hyperglycaemia in diabetes: impact on nephropathy and cardiac risk

Ole Torffvit

Department of Medicine, University Hospital of Lund, Sweden

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Introduction

In the past there has been much discussion whether improved control of hyperglycaemia translates into better cardiovascular and renal outcomes. Today this has been proven both for type 1 diabetes in the DCCT (Diabetes Control and Complications Trial) [1] as well as for type 2 diabetes by the Kumamoto trial [2] and UK-PDS study (United Kingdom Prospective Diabetes Study), respectively [3]. It has also become clear, however, that important though hyperglycaemic control is, it is absolutely necessary to use an integrated approach controlling the entire spectrum of risk factors such as hypertension, smoking, dyslipidaemia, etc. [4].

The urgency of intervention is illustrated by our own 10 year observational study: mortality was 14% in type 1 and 33% in type 2 diabetic patients with microalbuminuria; it was even higher, i.e. 38% for type 1 and 73% for type 2 diabetic patients with macroalbuminuria [5]. In our cohort coronary bypass surgery in diabetic patients with angina pectoris reduced mortality from 67 to 17% [6], illustrating that not only primary prevention but secondary intervention is called for as well.

Integrated treatment approach

If patients are empowered to participate in their own treatment adopting a multifactorial approach, substantial reduction of cardiovascular events and of the progression of renal disease can be achieved as illustrated by the experience of Gaede [4,7]. For instance Sawicki reported that self-adjusted blood pressure therapy for 5 years reduced the risk for death or need of dialysis from 41 to 11%; the risk of progression of renal disease decreased from 59 to 27% [8]. Rachmani [9] found that patient participation in the treatment for 4 years reduced the number of cardiovascular events from 55 to 36%. In this study, the decrease in glomerular filtration rate diminished from 3.5 to 2.25 ml/min/year. A most impressive reduction of both cardiovascular and microvascular events by > 50% in type 2 diabetic patients receiving intensified multifactorial treatment compared with treatment in accordance with national guidelines only, has recently been reported by Gaede et al. [4,7].

Metabolic control and progression of renal disease

Poor metabolic control is associated with the development [10] of diabetic nephropathy. In observational studies, an effect on progression of nephropathy in either type 1 [11] or type 2 diabetes [10,12] is either not demonstrable or very minor [13]. Consequently the major role of metabolic control is the prevention of diabetic nephropathy. It is particularly post-prandial blood glucose elevation, but not HbA1c, which is correlated to the decline in GFR in type 2 diabetic patients [14]. The importance of metabolic control, despite the above negative results of observational studies [10–13], is illustrated by targeted intervention studies. Renal biopsies documented that intensified glycaemic control retards [15,16] and pancreas transplantation even reverses the lesions of diabetic glomerulosclerosis in type 1 diabetic patients [17]. In contrast to observational studies, more recent clinical intervention studies also showed that improved control of glycaemia indeed decreases the decline in GFR [18].

Apart from the renal effects of glycaemic control, the nephrologist has also to consider that intensified treatment reduces cardiovascular mortality as well (see below).
**Improved glycaemic control: the role of intensified traditional insulin treatment**

Intensified insulin treatment delays the onset and slows the progression of nephropathy in type 1 diabetic patients [1]. The UK-PDS study showed that in type 2 diabetic patients intensified insulin treatment decrease the risk of microvascular, but not the risk of macrovascular disease [3]. Nevertheless, the Kumamoto trial clearly documented that intensified insulin treatment with reversal of elevated postprandial glucose concentrations delayed the onset and the progression of diabetic nephropathy even in type 2 diabetic patients [2]. We believe that it is not sufficient to correct only fasting hyperglycaemia or HbA1c concentrations (or both). Rather, in addition, correction of post-prandial hyperglycaemia is necessary if one wishes to reduce the incidence of cardiovascular disease in type 2 diabetic patients.

The experience of Bonora [19] shows that only strict control of both preprandial and postprandial hyperglycaemia was able to reduce the frequency of cardiovascular events in type 2 diabetic patients.

This new recognition of the importance of postprandial hyperglycaemia is not surprising in view of the observations [20,21] that despite normal fasting blood glucose concentrations increased 2h blood glucose concentrations after an oral glucose tolerance test were associated with excess cardiovascular mortality. This is particularly relevant in type 2 diabetes: it is characterized by a lack of the first phase insulin response and an overshooting compensatory second phase response [22]. The late hyperinsulinaemia is presumably the result of an inadequate early beta cell response and not (at least not only) the result of insulin resistance [23]. The net result is that the beta cell response to glucose is sluggish and delayed when a blood glucose concentration is either rising or falling [24]. These abnormalities, i.e. impaired early insulin response and late hyperinsulinaemia precede the onset of overt type 2 diabetes and are independent predictors of type 2 diabetes [25–27]. This observation is also important to explain the fact that cardiovascular mortality is excessive in patients with impaired glucose tolerance who are not yet frankly diabetic [21].

**How to prevent hyperinsulinaemia and restore the early rise of plasma insulin?**

The above paradigm predicts that the development of insulin resistance is a defence mechanism against the late postprandial hyperinsulinaemia, so to speak to prevent deleterious hypoglycaemia. Recently, the fast acting insulin analogue Lispro has permitted to prevent postprandial hyperglycaemia and late hyperinsulinaemia [28]. With glinides, i.e. insulin secretagogues one can restore the early phase of insulin secretion after an oral glucose load and the glycaemic response can be almost normalized [29]. This observation illustrates that it is the early insulin response rather than insulin resistance, which is mainly responsible for postprandial hyperglycaemia.

For the nephrologist it is not without interest that glomerular hyperfiltration is induced by hyperglycaemia via activation of the renin–angiotensin system [30]. Ruggenenti et al. [31] showed that this effect on glomerular hyperfiltration is fully prevented by Lispro. One further advantage of Lispro is that the pharmacodynamic and pharmacokinetic properties in type 1 diabetic patients are favourable; in contrast to the reduced response to regular insulin in patients with overt diabetic nephropathy, the response to Lispro is maintained [32].

**Glycaemic control: new insulin types**

When oral glycaemic agents fail, the results are poorer if one adds long acting insulin at nighttime compared with a mixture of Lispro and long acting insulin [33]. Against what was mentioned above it comes as no surprise that Lispro is far better to control the postprandial glucose concentration than regular insulin in either type 1 [34] and type 2 diabetic patients [35,36]—and this with the added benefit of a lesser risk of hypoglycaemia. In the patients of the DCCT study [37], treatment with Lispro resulted in a further decline of HbA1c [37]. Lispro treatment also caused a reduction of albuminuria in patients with type 2 diabetes [38]. The new direct acting insulin Aspart has similar effects [39,40].

We have experience with both. Lispro as well as Aspart proved to be extremely powerful tools as illustrated by the case shown in Figure 1. A 60-year-old patient with diabetes type 2 and all diabetic complications showed the effects of changing the insulin regimen from regular insulin to Lispro or Aspart. This was illustrated in Figure 1. A 60-year-old patient with diabetes type 2 and all diabetic complications showed the effects of changing the insulin regimen from regular insulin to Lispro or Aspart.

![Fig. 1. The effect of changing from regular to direct acting insulin in a 60-year type 2 diabetic patient with all diabetic complications. Humalog, lispro; insulinatard, NPH insulin.](image-url)
man with type 2 diabetes since 15 years was treated with a beta-blocker, ACE inhibitor and diuretic. He received a mixture of regular and long acting insulin. He had albuminuria and an increased serum creatinine concentration of 150 μmol/l. When he was switched to Lispro without changing the insulin dose HbA1c concentrations and blood pressure levels decreased as did body weight and albuminuria. There was no other change in treatment. This case is representative for many observations that HbA1c may decrease during treatment with Lispro even if patients had failed on conventional treatment. Lower concentrations of HbA1c are achieved compared with patients on regular insulin, as illustrated by Figure 2.

Oral hypoglycaemic agents, e.g. sulfonylureas and metformin

There is no doubt that oral hypoglycaemic agents are useful, but there are new considerations about non-classical actions, both positive and negative.

Sulfonylureas inhibit ATP-sensitive K channels and prevent ischaemic pre-conditioning [41,42]. Ischaemic pre-conditioning is important for cardiac protection in patients with ischaemic heart disease. In contrast to sulfonylamides such as glibenclamid, pre-conditioning is preserved if patients are treated with glimepiride [41] or insulin [42].

At least according to in vitro experiments, glimepiride inhibits platelet aggregation strongly by a factor of 2 compared with glibenclamid. It is at least as effective as acetylsalicylic acid [43]. Glimepiride may also prevent the development of atherosclerosis, as at least in experimental studies it inhibited endothelial cell-mediated LDL oxidation [44].

The potentially adverse effect of sulfonylurea compounds may explain why the UK-PDS study was not able to demonstrate a reduction of macrovascular disease [3]. A long-term study comparing coronary angioplasty and coronary bypass surgery noted that the outcome after angioplasty was worse in patients treated with sulfonylurea compounds [45]. In a population-based observational study Olsson [46] noted that cardiovascular mortality was higher in patients treated with a combination of sulfonylurea and metformin than in patients treated with sulfonylurea alone [46].

These observations illustrate that there is a need for new drugs. In the past few years, new drugs have been introduced, which are devoid of these side effects, e.g. repaglinid, nateglinid and glitazones. In-depth discussion is beyond the scope of this brief comment, but the interested reader is referred to several recent reviews [47–49].

It is also of note that the greatest threat in the diabetic patient, i.e. cardiovascular disease, is effectively ameliorated by insulin treatment. In type 2 diabetic patients with myocardial infarction, insulin treatment reduced the 3-year mortality by 51% [50]. This may be due, at least in part, to the fact that insulin has anti-inflammatory and anti-atherogenic actions [51]. It also restores, at least in part, endothelial cell function [52] and increases hyperaemic myocardial blood flow [53]. It is uncertain whether there is a specific beneficial effect of insulin, or whether these positive results reflect better glycaemic control, but these extremely impressive outcomes [50] make it imperative that normoglycaemia by administration of insulin is achieved in all diabetic patients with symptomatic coronary heart disease.

Conclusions and recommendations

New data suggest the importance of reducing post-prandial blood glucose concentration. To this end one should use either direct acting insulin release tablets (i.e. glinides) or better short acting insulin analogues.

Secondly, beyond glycaemic control multifactorial and interdisciplinary treatment yields substantial reduction of the risk of cardiovascular complications and reduction of the risk of progression of renal disease. The lesson to be learned from such observations [4,7–9] is obvious and is illustrated by our observation that over 4 years cardiovascular death (myocardial infarction, heart failure, stroke) in our patients with type 2 diabetes and albuminuria was lowered from 46% to 23% with the above strategy.

Conflict of interest statement. None declared.

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