Challenges in the Management of Hyperglycaemia in Type 2 Diabetes

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The ultimate goal of diabetes therapy is to prevent micro- and macrovascular complications in order to improve life expectancy and quality of life. The Diabetes Control and Complications Trial (DCCT) [1] and United Kingdom Prospective Diabetes Study (UKPDS) [2] studies demonstrated that lowering glycaemia (measured as HbA1c) leads to less microvascular complications in type 1 as well as type 2 diabetes. An important new insight is the existence of a 'glycaemic metabolic memory'. In both DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) and UKPDS follow-up studies [3, 4], it was demonstrated that the level of glucose control in the early years of disease impacts dramatically on the development of later complications. In both studies, patients with tighter glycaemic control during the study developed less micro- and macrovascular complications more than 10 years after discontinuation of the study. These observations emphasize the need to control glycaemia as tight as possible and as early in the disease process as possible.

Despite major efforts to attract attention to the importance of glycaemic control, levels of HbA1c, especially in type 2 diabetic patients remain problematic. Studies in different parts of the world show that HbA1c levels in type 2 patients lay well above the target of 7%. The international scientific community realized that in order to get as many type 2 diabetic patients as possible to goal, earlier and more intensive treatment will be needed. Due to the sheer numbers of patients, many different healthcare providers will have to be involved, and straightforward and clear treatment guidelines will have to be put forward. This need lead to the joint American Diabetes Association (ADA) – European Association for the Study of Diabetes (EASD) guidelines for the treatment of type 2 diabetes [5].

The right therapy in the right patient

In all patients with type 2 diabetes, lifestyle advice on nutritional habits and exercise should be part of the therapy. The main focus should be on healthy, balanced diets, aimed at maintaining normal weight and avoiding overweight. In overweight patients, realistic weight loss should be achieved, as studies indicate that moderate weight losses (10%) have dramatic effects on glucose levels and even progression to type 2 diabetes [6]. Similar conclusions can be made for exercise, where sustained exercise (walking, swimming, cycling) for limited amounts of time (30 minutes per day) has spectacular effects on one of the pathogenic pillars of type 2 diabetes: insulin resistance. These lifestyle interventions should be maintained throughout the life of type 2 diabetic patients, as they not only positively affect glucose levels, but also have beneficial effects on other cardiovascular risk factors, such as blood pressure and lipids. HbA1c drops of 1-2% may be expected and lifestyle measures are cheap and have no long term side effect.

The ADA-EASD guidelines recommend that next to lifestyle advice, metformin should be started in all newly-diagnosed type 2 diabetic patients, if no contraindications exist. This advice is based on the observation in the UKPDS [7] that metformin therapy (in overweight and obese patients) was efficient in lowering HbA1c with less weight gain compared to other therapies (sulfonylurea and insulin), and also led to significant improvements in cardiovascular outcomes and overall mortality. The glucose-lowering effect of metformin is mainly due to decreased hepatic glucose output and to a lesser extent, enhanced peripheral glucose uptake in muscle. Metformin monotherapy lowers A1c levels by approximately 1.5% [8]. Important advantages of metformin therapy are that it does not cause hypoglycaemia, its low cost and the presence of long-term safety data. Gastrointestinal adverse effects (abdominal discomfort, anorexia, nausea or diarrhea) are common but these effects can be minimized by gradual up-titration and concomitant administration with meals. The most dreaded adverse effect is lactic acidosis, although its rate is almost similar in patients with type 2 diabetes not taking metformin, leading to a plea to loosen the contraindications profile of this useful drug

[9]. At present, renal dysfunction with a glomerular filtration rate < 30ml/min and severe cardiac dysfunction (NYHA 3 and 4) are considered major contraindications.

Often however metformin will not be enough to control HbA1c, particularly in the long term. Behind this decline of glucose control under metformin monotherapy lies the—at present—unstoppable decline in beta cell function that characterizes type 2 diabetes. Additional steps are needed to maintain HbA1c below 7% in most type 2 patients and for many, to even get there. Here the guidelines offer different options. A choice is offered between sulfonylurea (SU), thiazolinediones or basal insulin as next steps. The less validated therapies that have only recently become available, and where data on long term efficacy and safety are lacking, are considered alternative options.

SU as a group have been available for a long time and are relatively cheap. They are quite effective in blood glucose lowering, with an instant onset of effect. HbA1c lowering of 1-2% can be expected, with the higher the HbA1c the greater effect [10]. Additive effects are seen when combined with metformin and their different mechanism of action (the one stimulating insulin secretion, the other increasing insulin sensitivity) make them the obvious couple in the dual disease that is type 2 diabetes. The success story of this combination can be seen in many countries where this combination is the standard treatment in type 2 diabetes. Due to their long-standing availability, their safety profile and side effects are well known. They increase insulin secretion by binding to a receptor (SUR) on the surface of pancreatic beta cells that result in a glucose-independent insulin release. Their mechanism of action also implicates that eventually SU therapy will fail because of beta cell failure. Their main disadvantage is the risk for hypoglycaemia, which rises with advancing age, poor nutrition, alcohol consumption, liver or kidney disease and polypharmacy. Another class effect of SU is weight gain. SU have a neutral effect on lipid profile or blood pressure and newer SU, in contrast to older products where there were worrying reports on cardiovascular mortality, are neutral to the heart [11]. Most SU are cleared via the kidney and dose adaptations are needed in renal insufficiency.

Glinides also stimulate insulin secretion via the SUR, but their effect is more rapid with a shorter duration of action. They may associate with metformin in case of predominantly postprandial hyperglycaemia. Their potential to lower HbA1c is slightly less than for SU (lowering around 0.5-1%), with less effect on fasting glycaemia [10]. A major advantage is that they can be given directly at mealtimes and can be skipped when meals are skipped. Another asset is the lower risk of hypoglycaemia. The number of studies available on these drugs is limited and no data on long term diabetes complications are available.

Acarbose and miglitol are available for use, but their popularity is limited for reasons of gastrointestinal discomfort and also cost. An option is to associate them with metformin in patients with postprandial hyperglycemia and moderately elevated HbA1c, and in combination with dietary measures. Drops in HbA1c of 0.5-0.8% can be expected. They do not cause hypoglycaemia and they are weight neutral [12].

Two thiazolinediones (TZDs) are available: rosiglitazone and pioglitazone, specific ligands for the nuclear receptor proliferator-activated receptor gamma (PPARγ), a master switch in metabolism. They are powerful enhancers of insulin sensitivity thus stimulating glucose uptake in target tissues of insulin, but also affecting lipid and protein metabolism. TZDs appear to have protective effects on the beta cell, with data from the 'A Diabetes Outcome Progression' (ADOPT) trial [13] showing more durable effects on glycaemic control with monotherapy of rosiglitazone, particularly when compared to SU. Decreases up to 2% in HbA1c were observed. Hypoglycaemia was rare, but weight gain was a major issue (3-6 kg in the first year). This was a combined effect of fluid retention and an increase of subcutaneous fat. An intriguing, and until recently unexplained, observation was the increased risk of forearm and hand fractures in women. Further, as liver problems have been described, hepatic function monitoring is warranted. Large

scale long term studies looking at effects on diabetes complications are scarce. A first large-scale trial, the Prospective PioglitAzone Clinical (PROACTIVE) trial [14], failed to demonstrate striking cardiovascular protection, but more worrisome were reports on increased myocardial infarction rates for rosiglitazone [15]. One cardiac side effect is clear: due to fluid retention, a significant proportion of patients will develop congestive heart failure, and in some studies, there was even need for hospitalization [16]. Due to these issues, many instances including the recent ADA-EASD consensus statement [5] advise against using TZDs, especially rosiglitazone, in patients with a previous history of cardiovascular disease.

Newer options based on incretin action

GLP-1 mimetics bind to GLP-1 receptors on pancreatic beta cells, but have a longer half-life because dipeptidyl peptidase-4 (DPP-4) enzymes can not degrade the homologue or analogue peptides as rapidly as natural GLP-1. The first developed GLP-1-agonist is exendin-4 (exenatide). It is administered subcutaneously twice daily, with slow-release forms of exenatide with a once weekly administration being developed. Lowering of HbA1c levels by 0.5-1% may be expected, mainly by lowering postprandial blood glucose levels. The higher the baseline level, the greater the magnitude of HbA1c reduction. Hypoglycaemia occurs rarely and only in patients receiving SU in combination with exenatide. Another important advantage is the progressive weight loss (up to 5 kg over 6 months), some of which may be a result of gastrointestinal side effects. These gastrointestinal adverse effects are dose-dependent, with 30-45% of patients experiencing nausea, vomiting or less frequently diarrhoea [17]. Some reports have suggested a risk for pancreatitis with exenatide, but it is unclear at this time whether the relationship is causal. Up to 67% of patients develop antibodies to exenatide which may become an issue in long term use. Claims on prevention of functional beta cell decline are based only on *in vitro* and animal data. A major issue is cost and the lack of data on long-term effectiveness and safety. Analogues of GLP-1 are being developed (e.g. liraglutide, taspoglutide), some sharing and even exceeding the beneficial effects of exenatide [18].

A different path aimed at exploiting the incretin system has been the development of agents that inhibit the action of the DPP-4 enzyme, with two pioneers, sitagliptine and vildagliptine. By inhibiting DDP-4, these products expand the life of natural incretins. These products are taken orally and very few side effects (mostly an increase in upper respiratory infections) have been reported until now. Neither weight gain, nor gastrointestinal side effects, nor hypoglycaemia were observed. The glucose lowering potential is comparable to other oral agents (0.5-1.5% depending on starting value) [19]. Long term studies on durability of glucose lowering effects or diabetes complications are lacking. The major hurdle in using these drugs, next to absence of long term data, is their cost.

Insulin in type 2 diabetes

Due to the progressive nature of the disease, most patients with type 2 diabetes will eventually require insulin to achieve and maintain glycaemic control. Current ADA-EASD guidelines [5] suggest adding one bedtime dose of long-acting insulin to oral agents (OAD) when HbA1c is not on target. Basal insulin added to existing OAD is an easy way to initiate insulin therapy in type 2 diabetic patients and achieves HbA1c below 7% in many patients. An important hurdle to adding basal insulin to OAD is the occurrence of weight gain and even more importantly, (nocturnal) hypoglycaemia. The advent of insulin glargine, and more recently detemir, has revolutionized the concept of basal insulin therapy. Indeed, more patients can reach the target using these analogues, and with fewer hypoglycaemic events, and for detemir, with less weight gain [20]. Basal insulin is however not the perfect solution for every patient. In patients with a normal fasting glycaemia, but with mainly a problem of postprandial hyperglycaemia, the use of prandial insulins or premixes is more appropriate.

A common feature exists for all insulins: the need for titration and intensification. However, the hassle of injecting insulin, the hypoglycaemia risk, the weight gain and the fear of injecting in many type 2 patients have lead to insulin being initiated too late and not being titrated or intensified properly. Using insulin analogues will allow intensification to occur with fewer side effects (hypoglycaemia, weight gain) and, especially, more comfort. At present, however, data on the effects of analogue insulins on long term diabetes complications are lacking. The drop in HbA1c that can be achieved by insulin regimens is only limited by the occurrence of hypoglycaemia. Installing and intensifying insulin therapy is intricately linked to intensive diabetes education and self-monitoring of blood glucose levels by the patients.

Conclusion

The therapeutic cornerstone in type 2 diabetic patients should remain patient education, which should focus on the character of the disease (explaining that type 2 diabetes is a progressive disease from the beginning takes away many misunderstandings on 'efficacy of treatment regimens') and motivating patients to make lifestyle adjustments (physical activity and healthy food intake). The motivation of all healthcare workers to persist with these interventions should be strengthened by the insight that lifestyle measures not only affect glucose levels, but are essential for interfering with one of the pathogenic bases for type 2 diabetes, insulin resistance. Moreover, the impact of lifestyle measures on other cardiovascular risk factors, such as blood pressure, lipids and weight, is equally important for the quality of life of the patient. Cheap and efficacious, metformin remains the first choice OAD to be initiated. Advice on the second step in OAD is harder. The lack of prospective studies on hard endpoints, being the occurrence and progression of micro- and macrovascular complications, leaves us with surrogate endpoints, such as HbA1c lowering and the drug action profile, to decide on the choice of medication in the individual patient. Based on the profile of the patient, a choice in second OAD can be made: SU when a rapid drop in HbA1c is desired, glinides when a secretagogue for postprandial control is needed, and TZDs when insulin resistance is overwhelming. The emerging new glucose lowering agents exploiting the incretin concept offer interesting alternatives. How does one choose between GLP-1 mimetics and DPP-4 inhibitors? Mimetics may be preferred when weight is a major issue, DPP-4 inhibitors when an oral beta cell secretagogue is needed, but hypoglycaemia is a major issue. Finally, insulin may be the second step after (or together with) metformin when hyperglycaemia is excessive. It is still the necessary step for all patients when combinations of OAD are not sufficient to control hyperglycaemia. Importantly, early and sustained glycaemic control is important and glucose control should be embedded in a multifactorial approach, as controlling glycaemia is just one part of type 2 diabetes therapy, where control of other cardiovascular risk factors, such as lipids and blood pressure, is imperative.

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