Managing Type 2 Diabetes in Patients Not Controlled on Metformin

a report by

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The incidence and prevalence of diabetes (and especially type 2 diabetes) are increasing worldwide. The World Health Organization (WHO) estimates that worldwide 171 million people suffered from diabetes in 2000, and predicts that by 2030 their number will increase to more than 300 million.[1] Due to the initially often silent course of the disease and thus late diagnosis, and also because of gross undertreatment of hyperglycaemia and additional cardiovascular risk factors, diabetes is a major cause of morbidity and mortality. Microvascular complications – such as retinopathy, neuropathy and nephropathy – and macrovascular disease cause human suffering, but are also a major burden to healthcare resources worldwide.

The ultimate goal of diabetes therapy is to prevent micro- and macrovascular disease in order to improve life expectancy and quality of life. The Diabetes Control and Complications Trial (DCCT)[2] and UK Prospective Diabetes Study (UKPDS)[3] demonstrated that lowering glycaemia, which can be measured as glycated haemoglobin (HbA_{1c}), leads to fewer microvascular complications – mainly retinopathy and nephropathy – in type 1 as well as type 2 diabetes, with the lowest risk being with HbA_{1c} values in the normal range. Glycaemia also plays a role in macrovascular disease, as demonstrated by studies such as the Epidemiology of Diabetes Interventions and Complications (EDIC) trial,[4] but the relationship is less pronounced, leaving even well-controlled diabetics at an increased cardiovascular risk[5] due to the contribution of other risk factors for macrovascular disease, such as hypertension, hypercoagulability and dyslipidaemia.

Despite major efforts to attract attention to the importance of glycaemic control, levels of HbA_{1c} remain problematic, especially in type 2 diabetic patients. Studies in different parts of the world show that HbA_{1c} levels in type 2 diabetic patients lie well above the target of 7%.[6,7] The international scientific endocrinological community realises that in order to get as many type 2 diabetic patients as possible to goal, earlier and more intensive treatment will be needed, and primary care physicians as well as diabetes educators will have to be mobilised in order to alter the fate of more type 2 diabetic patients. Due to the sheer numbers of patients, many different healthcare providers will be involved, and straightforward and clear treatment guidelines will have to be put forward.

This need led to the very valuable joint American Diabetes Association (ADA)–European Association for the Study of Diabetes (EASD) guidelines for the treatment of type 2 diabetes.[8] These guidelines provide strict advice for newly diagnosed type 2 patients: all should receive lifestyle advice on nutritional habits and exercise and, if possible, be started on metformin. This strong advice was based on the observation in UKPDS that metformin therapy (in overweight and obese patients) was efficient at lowering HbA_{1c} with less weight gain than with the other therapies (sulfonylureas (SUs) and insulin), but also affected overall mortality. Very often, however, metformin monotherapy will not be enough to control HbA_{1c}, especially not in the long term. Behind this decline of glucose control under metformin monotherapy lies the at present unstoppable decline in β-cell function that characterises type 2 diabetes. Therefore, additional steps are needed in most type 2 diabetes patients in order to maintain an HbA_{1c} below 7% and, for many, to ever get there in the first place. Here the guidelines give different options, describing pros and cons for each of them; however, they do not provide clear directions. In this article, the different glucose-lowering options available will be discussed and their place in the decision algorithm suggested.

Many Options

In the current guidelines, SUs, thiazolinediones or basal insulin are suggested as the next steps. However, these guidelines date from a time at which these were virtually the only options, whereas today several classes of medications are available for the treatment of type 2 diabetes, with three new groups becoming available in the last three years.[9] For most of the newer drugs we have little clinical experience and long-term safety studies are lacking; however, the mechanism of action behind them is interesting.

How to identify the right drug for the right patient? Here, the profile of the patient should be evaluated and compared with the profile of the available drugs in terms of efficacy at glucose lowering as well as in terms of safety, tolerability and cost. Moreover, some drugs have

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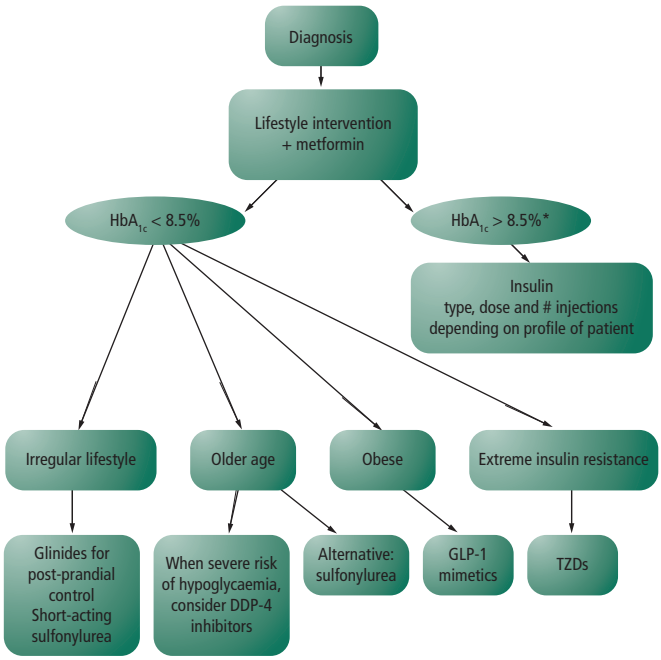
Figure 1: What if Metformin Is Not Enough?



** In case of very young age or pregnancy, insulin can be indicated at lower HbA_{1c} levels. DDP-4 = dipeptydil dipeptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; TZDs = thiazolinediones.*

pleiotropic effects that may be interesting in the avoidance of long-term diabetic complications.

One step is clear, however: when there is extreme hyperglycaemia, insulin should be initiated. Insulin is still the most potent of all glycaemia-lowering agents and has been demonstrated to be safe in the long run. However, the hassle of injecting insulin, the risk of hypoglycaemia, the weight gain and, in many type 2 diabetes patients, the fear of injecting have led to insulin being initiated too late and not being titrated or intensified properly. Therefore, many doctors and patients prefer oral antidiabetic drugs (OADs) as initial intensification steps after metformin.

At present, data are lacking on any differences of effects among the available OADs on long-term complications. A recent review could not find a difference in effectiveness of different classes of oral antidiabetic medication on all-cause mortality, cardiovascular mortality or morbidity, peripheral vascular disease, neuropathy or nephropathy of retinopathy.[10] This is consistent with the UKPDS study, which showed no difference in long-term complications with SUs, metformin or insulin. Glucagon-like peptide-1 (GLP-1) analogues and gliptines were not included because of the absence of large comparative randomised trials. The improvement of glycaemic control is similar for all oral agents in monotherapy, except for acarbose and repaglinide.

Sulfonylureas – Still a Good Choice

SUs as a group have been on the market for a long time and are relatively cheap. SUs have the advantage of being quite effective in blood glucose lowering, with an almost instant onset of the effect after start of therapy. Drops in HbA_{1c} of 1–2% can be expected as a mean, with the higher the baseline HbA_{1c}, the bigger the drop. Additive effects are seen when SUs are combined with metformin, and the different mechanisms of action of these two agents – 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. Suggestions that these drugs ultimately lead to faster β-cell failure (an observation already made in the 1970s) have not altered their popularity.

Because SUs have been used for so many years, their safety profile and side effects are well known. They increase insulin secretion by binding to a receptor (SUR) on the surface of the pancreatic β cell, resulting in a glucose-independent insulin release. Their mechanism of action also implicates that SU therapy will ultimately fail because of β-cell failure.

The main disadvantage of SUs is the risk of hypoglycaemia, which rises with advanced age, poor nutrition, alcohol consumption, liver or kidney disease and polypharmacy,[11] and is higher than with other oral medications.[10] This is a class effect, but differences between different products have been described.[12–14] Another class effect of SUs is that their use leads to weight gain, typically 1–4kg with stabilisation after about six months.[15] Here again, data are somewhat different between the products.[16,17]

SUs have a neutral effect on lipid profile or blood pressure and all current SUs – in contrast to the older products, where worrying reports on cardiovascular mortality abound – are neutral to the heart. Most SUs are renally cleared and dose adaptations will be needed in the case of renal insufficiency.

Therefore, it makes sense to choose SUs as the next step when metformin is not enough, but care should be taken in older patients because of the risk of hypoglycaemia.

Glinides – More Expensive

Glinides also stimulate β cells to secrete insulin, but their mechanism of action differs somewhat from that of the SUs.[15] They typically have short half-lifes, with rapid onset and short duration of action. Insulin release by glinides seems to be at least partly glucose-regulated. Literature on these drugs is scarce and in most countries only repaglinide is available.

Because of their short action profile as inducers of insulin secretion, they are the drug of choice to associate with metformin in cases of predominantly post-prandial hyperglycaemia in patients who have a limited rise in HbA_{1c}. Their potential to lower HbA_{1c} is slightly less than that of the SUs, with less effect on fasting glycaemia (lowering around 1%). A major advantage is the fact that they can be given directly at mealtimes and can be skipped when meals are skipped. Another asset is the lower risk of hypoglycaemia. When combined with metformin they appear to be weight-neutral.[15] As mentioned above, the number of studies is limited and no data on long-term diabetic complications are available. Theoretically, there could be an advantage in using short-acting insulin secreatagogues because patients are less exposed to pro-apoptotic stimuli and, as a result, have a longer preservation of their β-cell function. This has been shown *in vitro* but not *in vivo*.[18]

Glinides can be an alternative for and can even be preferred to SUs for people with an irregular lifestyle and a predominant problem of

post-prandial hyperglycaemia. However, they are more expensive than SUs.

α-glucosidase Inhibitors

These drugs have been around for many years and have an interesting mechanism of action: by competitively and reversibly inhibiting intestinal α-glucosidase, an intestinal brushborder enzyme responsible for cleavage of disaccharides, the inhibitors decrease the prandial uptake of carbohydrates, thus reducing post-prandial glucose excursions. The ideal patients for associating these drugs with metformin is again those with moderate post-prandial hyperglycaemia. Drops in HbA_{1c} of up to 1% can be expected. A major issue directly related to the mechanism of action is the intestinal side effects, such as bloating, diarrhoea and abdominal pain, limiting the use of these potentially valuable agents, especially since these side effects may aggravate any problems with metformin. α-glucosidase inhibitors should be taken with meals and it is important that patients have diets rich in complex carbohydrates and do not overconsume simple sugars.[15] Hypoglycaemia is not an issue with these agents and weight neutrality is present. Some studies report lowering of triglycerides, and intriguing data from the STOP-NIDDM[19] trial (NIDDM = non-insulin-dependent diabetes mellitus) point towards a potential cardioprotective effect; however, true studies on effects on diabetic complications are lacking.

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Acarbose and miglitol are available for use, but their popularity is limited for reasons of gastrointestinal discomfort and also cost. However, associating them with metformin in patients with post-prandial hyperglycaemia and moderately elevated HbA_{1c}, in combination with dietary measures, is an option.

Thiazolinediones – When Insulin Resistance Is the Whole Story

Two thiazolinediones are currently available: rosiglitazone and pioglitazone, which are specific ligands for the nuclear receptor proliferator-activated receptor-gamma (PPAR-γ), a master-switch in metabolism of cells. These agents are powerful enhancers of insulin sensitivity, thus stimulating glucose uptake in target tissues of insulin, but also affecting lipid and protein metabolism. Their main target is fat tissue, inducing differentiation of adipocytes into small but insulin-sensitive cells, but PPAR-γ receptors are present in cells throughout the body, including in β cells. The A Diabetes Outcome Progression Trial (ADOPT),[20] using rosiglitazone, demonstrated that when administered as monotherapy at an early stage of the disease it could prevent β-cell failure to a greater extent than metformin, but to an even greater extent than SUs. However, their main clinical effect is improving insulin sensitivity, with lower glucose and free fatty acid levels. The effects on β cells are seen only when intricate testing – e.g. looking for first-phase insulin release – is performed. Decreases of up to 2% in HbA_{1c} can be observed.

Long-term studies looking at effects on diabetic complications are lacking, but expectations of cardiovascular protection were high on the basis of the mechanism of action. A first large-scale trial, Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE),[21] failed to demonstrate striking effects, but more worrisome are the reports of increased myocardial infarction rates with rosiglitazone.[22] However, these effects are quite small and no definite conclusion can be reached. One cardiac side effect is clear for this class: due to fluid retention, a significant proportion of patients will develop oedema and congestive heart failure, with need for hospitalisation in some studies. Hypoglycaemia is rare, but weight gain is a major issue (3–6kg in the first year). This is a combined effect, with on the one hand fluid retention and on the other hand an increase in adipocytes, especially subcutaneously. An intriguing and until now unexplained observation is the increased risk of forearm and hand fractures in women.[20] Similar to their predecessor, troglitazone, liver problems have been described for rosi- and pioglitazone, but at a much lower level. However, hepatic function monitoring is still warranted.

At present, the patient who will benefit most from adding a glitazone to metformin is the one with an overwhelming problem of insulin resistance – typically, very obese patients who still have sufficient β-cell function and insulin stores. However, one should weigh the potentially beneficial effects of these drugs against their known side effects, such as weight gain and fluid retention, oedema and bone fractures in women, but also the worrisome issues of cardiovascular mortality. Therefore, many guidelines advise against initiating rosiglitazone, in particular in patients with a previous history of cardiovascular disease. Ongoing studies such as Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD)[23] will hopefully provide the necessary information to decide on the role of these agents in diabetic complications, and especially cardiovascular disease, and thus their fate.

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Exenatide and Liraglutide – A Brave New World

The re-discovery of the incretin system and its potential clinical usefulness led the pharmaceutical world to look for ways of administering GLP-1-like substances in a user-friendly way.[24] The presence of dipeptidyl dipeptidases (DPP) all over the body leads to a rapid degradation of the peptide. Two elegant solutions arose: the first to reach the market was exenatide, a homologue of GLP-1 found through searches in small molecule libraries to be present in the salivary glands of a reptile, the Gila monster. This homologue still

needs to be administered parenterally (in practice subcutaneously) but, by combining many similarities with the mother product and a resistance against degradation by dipeptidyl peptidase-4 (DPP-4), the main enzyme responsible for degrading GLP-1, twice-daily administration of exenatide is sufficient to reach therapeutic levels.[25]

GLP-1 and exenatide have been shown to stimulate insulin secretion by β cells and, interestingly, to suppress inappropriate glucagon secretion by α cells, a problem in type 2 diabetes. Interestingly, animal data and *in vitro* studies also show trophic effects on the β cell, thus opening a window of promise: drugs that may prevent β-cell failure in type 2 diabetes.

Another path aimed at exploiting the incretin system has been the development of agents that inhibit the action of the dipeptidyl peptidase-4 enzyme.

Glucose lowering is impressive, with drops of up to 2% being described, with the interesting additional feature of near absence of hypoglycaemic risk and a beneficial effect on weight (i.e. weight loss). This is a consequence in part of the major side effects of exenatide – nausea and vomiting, which occur in up to 57 and 17% of patients, respectively, due to slowing of gastric emptying – but weight loss is also observed independently of this side effect, probably due to central effects on appetite.[26] In some patients, pancreatitis can be triggered and, after prolonged administration, development of antibodies against the foreign peptide is observed. Interestingly, slow-release forms of exenatide have been developed, with a once-weekly administration producing similar effects on blood glucose to the short-acting form.

A second way to exploit the incretin system is the synthesis of a true analogue, liraglutide. By attaching a free fatty acid residue and altering amino acids in the peptide, albumin binding and thus slowed renal clearance is generated, as well as resistance to DPP-4 action. Liraglutide needs to be administered subcutaneously once daily and its efficacy and safety profiles are comparable to those of exenatide. Data on long-term effects are completely lacking and no studies have been performed studying their effect on diabetic complications.

Who benefits most from these new drugs? In principle, all patients with type 2 diabetes would benefit from an association of exenatide or liraglutide with metformin on the basis of their mechanism of action. In particular, the promise of β-cell preservation raises hopes. However, at present cost and the unknown long-term side effects are a worry. Moreover, many patients do not tolerate these drugs because of severe gastrointestinal side effects; others simply refuse to inject themselves.

Dipeptidyl Dipeptidase-4 Inhibitors – Great Expectations

Another path aimed at exploiting the incretin system has been the development of agents that inhibit the action of the DPP-4 enzyme. Several approaches have been taken and at present more than 10 products are under development or are already available, with the two pioneers being sitagliptin and vildagliptin. By inhibiting DDP-4, these products extend the life of the natural incretins.[27] They may also prolong the life of other neuropeptides that can play a role in glucose homeostasis, although it is currently accepted that GLP-1 is responsible for the main clinical effect.

The main advantage of this class of medications is that they can be taken orally and have an almost incredibly blank side effect profile: no weight gain, no gastrointestinal side effects and no hypoglycaemia are observed. In addition, they have a neutral effect on fasting lipids. Their glucose-lowering potential is good, but not striking (0.5–1% depending on starting value, with particularly good post-prandial effects). While long-term durability studies are still needed, vildagliptin has been shown to provide sustained HbA_{1c} production of ~1% after two years of monotherapy treatment.[28] Interestingly, and similarly to GLP-1, animal data also show trophic effects on the β cell, thus opening a window of promise: drugs that may prevent β-cell failure in type 2 diabetes.[29] Data regarding the effects on diabetic complications are lacking.

An interesting observation is the more than additive effects on glucose lowering when these drugs are combined with metformin. This is attributed to the fact that metformin itself raises GLP-1, thus allowing the DPP-4 inhibitors to have a greater effect.

Considering their very attractive side effect profile, the fact that they come in pill form and the fact that their use is supported by strong hypotheses, these DPP-4 inhibitors are to be considered the drugs of choice to be added to metformin: they lower glucose by stimulating β cells and inhibiting α cells (and thus especially affect post-prandial hyperglycaemia), and do not lead to weight gain or hypoglycaemia.

The main advantage of this class of medications is that they can be taken orally and have an almost incredibly blank side effect profile.

They should therefore be considered the combination of choice, even without long-term safety data, and especially in older patients.[30] The only hurdle to using these drugs, other than the absence of long-term data, is their cost.

Insulin – The Strongest Option and, Eventually, Everybody Will Need It

The progressive nature of the disease means that most patients with type 2 diabetes will eventually require insulin to achieve and maintain glycaemic control, due to both increased insulin resistance and, especially, diminished secretory capacity of the pancreatic β cells. How should the clinician decide which insulin to choose and when and how to add it?

Current ADA–ASD guidelines suggest adding one bedtime dose of long-acting insulin to oral agents when HbA_{1c} is above 8.5%. Basal insulin

added to existing OAD is an easy way to initiate insulin therapy in type 2 diabetic patients and achieves HbA_{1c} below 7% in many patients. A major hurdle with adding basal insulin to OAD is the occurrence of weight gain and, even more importantly, of (nocturnal) hypoglycaemia. The advent of insulin glargine and, more recently, detemir has revolutionised the concept of basal insulin therapy. Indeed, with the use of these analogues more patients can get to target, with fewer hypoglycaemic events[31] and, with detemir, less weight gain.[32]

However, basal insulin is not the perfect solution for every patient. In patients with normal fasting glycaemia whose main problem is post-prandial hyperglycaemia, the use of prandial insulins or of pre-mixes is more appropriate. Many studies exist that point to the advantages and disadvantages of the different regimens: the need for self-monitoring of glycaemia with prandial insulin, the increased weight gain with pre-mixes, the need for multiple daily injections, etc. The major message is that, based on the level of HbA_{1c}, the profile of glycaemias in the day and the needs and wishes of the individual patient, a choice can be made as to the mode of insulin initiation.

There is one common feature to all of these regimes: the need for titration and intensification. The evolution of β-cell function in type 2 diabetes will lead to the necessity of both prandial and basal insulin at the same time in all patients. Using insulin analogues will allow this intensification to eventually lead to a basal–bolus system, such as in type 1 patients. Basal–bolus regimes produce fewer side effects (hypoglycaemia, weight gain) and are also more comfortable for the patient. However, at present data on the effects of analogue insulins on long-term diabetes complications are lacking. The drop in HbA_{1c} that can be achieved by insulin regimens is limited only by the occurrence of hypoglycaemia. However, installing and intensifying insulin therapy is intricately linked to the installation of intensive diabetes education and the self-monitoring of blood glucose levels by patients.

Conclusion

The emerging new glucose-lowering agents provide us with new strategies to achieve better glucose control in patients with type 2 diabetes. The lack of prospective studies on hard end-points, i.e. the occurrence and progression of micro- and macrovascular complications, leaves us with surrogate end-points such as the lowering of HbA_{1c} and the action profile of the drugs to help the clinician decide on the choice of medication in individual patients. The cornerstone of our therapy of type 2 diabetic patients should remain patient education as to the character of the disease (explaining that type 2 diabetes is a progressive disease from the beginning takes away many misunderstandings regarding 'efficacy of treatment regimens'), motivation on lifestyle adjustments (physical activity and healthy food intake) and metformin. Based on the profile of the patient, the choice of OAD can be made: SUs when a rapid drop in HbA_{1c} is desired, glinides when a secretagogue for post-prandial control is needed, tiazolidinediones when insulin resistance is overwhelming, exenatide when weight is a major issue, DPP-4 inhibitors when a β-cell secretagogue is needed but hypoglycaemia is a major issue and, finally, insulin when hyperglycaemia is excessive or when combinations of OAD are not sufficient to control hyperglycaemia (see *Figure 1*). Importantly, controlling glycaemia is just one approach in type 2 diabetes – control of other cardiovascular risk factors, such as lipids and blood pressure, is imperative. ■

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