Progression of Treatment Strategies in Type 2 Diabetes

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Abstract

There is a global pandemic of diabetes and the progression of disease and long-term complications impose a major health burden. The older diabetes treatments improve glycemic control but have minimal effect on disease progression and long-term cardiovascular complications. Additionally, comorbid hypertension, hyperlipidemia and smoking significantly contribute to morbidity and mortality. Lifestyle changes remain the cornerstone of management, particularly as a large number of people with diabetes are obese and take little physical activity. Structured education interventions, dietary advice and exercise programs form the basis of changes that are necessary. Current guidelines for the management of type 2 diabetes suggest a glycated hemoglobin (HbA_{1c}) treatment goal of 6.5–7.0% (48–53mmol/mol). The first-line pharmacological treatment is metformin. Second-line treatment strategies are varied and the subject for debate; generally, guidelines allow the clinician much flexibility. Until the past few years, drug therapy with metformin, sulfonylureas and thiazolidinediones, followed by treatment with insulin, has been the norm, but adverse events of hypoglycemia and weight gain have limited their effectiveness. There are now a number of new agents available with differing mechanisms of action. The glucagon-like peptide-1 receptor agonists have shown effective glycemic control and may preserve beta-cell function. Recently, a once-weekly parenteral incretin mimetic was shown to be more effective than daily insulin. Dipeptidyl peptidase-4 inhibitor agents are orally administered, as effective as metformin and not associated with hypoglycemia or weight gain. Human amylin analogs are effective agents when combined with insulin therapy. Long-term studies are not yet available for these new agents, but their effect on beta-cell function preservation in animal models leads to the hope that progression of diabetes may be delayed. Initiation of more intensive treatment at an earlier stage may be associated with reduced complications, but possibly at the expense of more adverse events.

Keywords

Type 2 diabetes, metformin, insulin, incretin, dipeptidyl peptidase-4 inhibitors, amylin

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There is currently a global pandemic of obesity and diabetes. Worldwide, the number of people with diabetes is estimated to be 285 million and is projected to reach 438 million in 2030.[1] Approximately 10% of the US adult population have diabetes.[2] Type 2 diabetes results in considerable morbidity and mortality, primarily the result of the development of microvascular disease (retinopathy, nephropathy and neuropathy) and macrovascular disease (cardiovascular, cerebrovascular and peripheral vascular disease) complications. The increasing prevalence of type 2 diabetes is imposing a huge clinical and economic burden on medical institutions and will continue to do so for the foreseeable future. Most currently available guidelines for the treatment of hyperglycemia in people with type 2 diabetes suggest lifestyle changes followed by the use of metformin or a combination of both. Should this initial regimen fail, there is uncertainty and variation of opinion as to what are the most effective second-line treatment strategies. The introduction of newer pharmacological agents, such as glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, has complicated the situation further. In addition, the lack of comparative and long-term studies of these agents in people with type 2 diabetes hinders clinicians' ability to determine the most appropriate place for these new agents in management strategies.

This review discusses current glycemic management strategies and their shortcomings. It details the introduction of newer agents and their proposed place in the treatment of type 2 diabetes.

Natural History of the Disease and Current Therapy

Type 2 diabetes is a chronic and progressive condition. Despite adequate control of hyperglycemia, there is a progressive failure of

insulin secretion. Medication inevitably needs to be increased over time to meet treatment goals and patients will ultimately require additional drugs or insulin therapy.

The UK Prospective Diabetes Study (UKPDS) followed patients with newly diagnosed type 2 diabetes over a 15-year period.[3] Sulfonylureas and metformin treatment resulted in an initial decline in glycated hemoglobin (HbA_{1c}) levels followed by a gradual increase, which was associated with a decline in beta-cell function. Similarly, in the ADOPT (A Diabetes Outcome Progression Trial) study, metformin and sulfonylurea treatment led to an initial improvement in glycemic control followed by a progressive increase in HbA_{1c}.[4] Metformin produced a more sustained reduction of HbA_{1c} than sulfonylurea treatment but thiazolidinediones (TZDs) produced the most durable glycemic control. This is believed to reflect both the direct and indirect protective effects of TZDs on beta-cell function.[5,6] This longer duration of action, however, came at the expense of significant weight gain.

Although currently available medications are effective in managing the symptoms of hyperglycemia, they do not normalize glucose metabolism nor completely eliminate the risk of long-term complications, which remain the major concern for physicians and patients alike. The UKPDS study showed that more intensive treatment with a sulfonylurea or insulin resulted in a 12% reduction (p=0.029) in any diabetes-related end-point and a significant reduction of 25% (p=0.0099) in the risk of microvascular disease compared with conventional therapy.[3] There were also clinically relevant post-trial risk reductions emerging over time for myocardial infarction (15%, p=0.01) and death from any cause (13%, p=0.007).[7] The adverse events of hypoglycemia and weight gain were, however, more frequently observed compared with conventional therapy.

Lifestyle Management of Type 2 Diabetes

Modification of lifestyle is an important factor in the management of type 2 diabetes. Proper management of smoking, physical inactivity and inappropriate diet are essential for improved glycemic control and the prevention of macrovascular disease.[8] Long-term microvascular complications may also be adversely affected by smoking.[9] International guidelines all emphasize the importance of lifestyle changes and collectively state that people with newly-diagnosed type 2 diabetes should be assessed by a dietician and given advice on an appropriate diet. It is also recommended that patients are offered interventions to encourage smoking cessation and that patients with comorbid depression are appropriately managed.

In addition to the above, patients require education on self-management, increased physical activity, smoking cessation and regular monitoring, with specific goals to improve adherence. Structured education programs are associated with improved psychological well-being, reduced anxiety and overall improvement in quality of life,[10,11] but show modest effects on HbA_{1c} improvement, usually in the range of 0.3–1.0% (3–11mmol/mol).[12] For patients with type 2 diabetes, a meta-analysis of 22 studies demonstrated a mean weight loss of 3.1% (1.7kg or 3.7lbs) from baseline body weight with lifestyle intervention.[13] Supervised exercise programs lasting from eight weeks to one year are effective for improving glycemic control and cardiovascular risk factors in people with type 2 diabetes.[14] These programs have been shown to decrease HbA_{1c} levels by 0.6% (7mmol/mol; p<0.05).[14]

Established Therapies for Type 2 Diabetes

Metformin is now established as the first-line therapy for type 2 diabetes. Its precise mechanism of action remains unclear, but its foremost effect is to reduce hepatic glucose output. Clinical trials have shown typical reductions in HbA_{1c} of approximately 1.5% (17mmol/mol).[15,16] It is usually well tolerated and the most common adverse events are typically gastrointestinal in nature. Hypoglycemia is uncommon when compared with other oral hypoglycemic agents but metformin may cause the rare but potential side effect of lactic acidosis. Metformin treatment is usually associated with weight stability or modest weight loss. The UKPDS study demonstrated a beneficial effect of long-term metformin treatment on macro- and microvascular complications, as well as all-cause mortality, albeit in a small subgroup.[3]

Sulfonylureas enhance insulin secretion and are similar in efficacy to metformin, lowering HbA_{1c} levels by 1–2% (11–22mmol/mol).[16,17] Their major disadvantage is an increased risk of hypoglycemia, which can be prolonged and life-threatening, particularly in the elderly. Furthermore, weight gain of approximately 2kg (4.4lbs) is common following the initiation of sulfonylurea therapy. Glycemic control appears to be less durable than TZD or metformin monotherapy[4] and there are concerns about the effect of sulfonylureas on ischemic preconditioning.[18]

TZDs increase the sensitivity of muscle, fat and liver to endogenous and exogenous insulin ('insulin sensitizers') and typically lower HbA_{1c} levels by approximately 1% (11mmol/mol).[19] They are effective in reducing hepatic steatosis and have a particular role in the treatment of people with diabetes and non-alcoholic fatty liver disease. The most common adverse events with TZDs are weight gain and fluid retention, which may precipitate overt heart failure. Several recent meta-analyses have suggested that the TZD rosiglitazone is associated with an increase in the incidence of myocardial infarction[20–23] and its safety is currently being reviewed by the US Food and Drug Administration (FDA). In Europe, the European Medicines Agency suspended the marketing authorization for rosiglitazone in September 2010. It appears that pioglitazone is not associated with increased atherosclerotic vascular events and may actually reduce mortality from cardiovascular disease.[5] Both drugs are associated with an increased risk of fracture, particularly in women.

Insulin remains the most effective hypoglycemic treatment for people with type 2 diabetes but is associated with weight gain and hypoglycemia and must be given by injection. More recently introduced insulin analogs with a longer duration of action reduce the risk of hypoglycemia compared with conventional insulin.[24]

Treatment of Patients with Impaired Glucose Tolerance or Impaired Fasting Glycemia

The aim of treating patients with impaired glucose tolerance (IGT) or impaired fasting glycemia (IFG) is to delay the onset of type 2 diabetes and therefore reduce the risk of long-term complications. Several studies from China, Finland, India and the US have demonstrated the effectiveness of lifestyle interventions, which are recommended as

the treatment of choice in this group of people.[25] The US Diabetes Prevention Program also showed that metformin reduced the development of diabetes but it is unclear whether this has an additive effect to lifestyle modification.[26] Similarly, rosiglitazone, pioglitazone and acarbose have been shown to delay the onset of diabetes.[27–30] With more evidence and a trend towards earlier intervention, it is probable that more people with IGT will be pharmacologically treated, particularly those with high risk factors for diabetes. At present, however, the American Diabetes Association (ADA) recommends that only metformin be considered as drug therapy for individuals with IFG/IGT. It was also recommended that metformin be limited to individuals <60 years of age with a BMI ≥35kg/m^2 and with associated risk factors for diabetes, such as family history in first-degree relatives, elevated triglycerides, low HDL-cholesterol and hypertension.[25]

Recent Advances in Type 2 Diabetes Therapy

Over the past decade, accumulating evidence has reaffirmed that beta-cell failure and decreased insulin secretion, in addition to insulin resistance, are important factors that lead to the development of type 2 diabetes.[31,32] They also occur much earlier in the natural history than originally thought.[31,32] Other pathogenic mechanisms include abnormalities in the adipocyte, leading to insulin resistance. Reduced incretin secretion from the gut and sensitivity to their actions have been observed in people with diabetes.[33] In addition, increased glucagon secretion from alpha cells, enhanced glucose reabsorption in the kidney and central nervous system, and insulin resistance resulting from neurotransmitter dysfunction may all contribute to the development of type 2 diabetes.[33] This increased understanding of the broader pathophysiology of type 2 diabetes has led to the development of new targeted agents that inhibit these underlying disease processes.

New Antihyperglycemic Therapies

Glucagon-like Peptide-1-based Therapies

GLP-1 is one of the key incretin gut hormones and is secreted by the L cells of the small intestine. GLP-1 is released after food intake and acts as a secondary control of blood glucose by stimulating insulin secretion in a glucose-dependent manner.[34] GLP-1 also inhibits glucagon secretion[35] and, as evident from animal studies, may increase beta-cell mass.[36] In addition, GLP-1 induces satiety and may regulate body weight.[37] Endogenous GLP-1 is broken down by the enzyme DPP-4, limiting its therapeutic application. Two approaches have been adopted to overcome this: first, GLP-1 receptor agonists that mimic endogenous GLP-1 activity but are resistant to breakdown by the DPP-4 enzyme, resulting in more prolonged action, have been developed. Two examples of GLP-1 receptor agonists in use are parenteral exenatide and liraglutide. Second, oral inhibitors of DPP-4 have been developed that prolong the action of endogenous GLP-1 by preventing its breakdown.

Glucagon-like Peptide-1 Receptor Agonists

The first GLP-1 receptor agonist to be approved for human clinical use was exenatide. The efficacy and safety of exenatide (twice-daily subcutaneous injections of 5 or 10µg) as add-on therapy to metformin, sulfonylurea, or sulfonylurea plus metformin in patients with type 2 diabetes, was demonstrated in three pivotal, 30-week clinical studies.[38–40] Compared with placebo, exenatide demonstrated significant reductions of HbA_{1c} (0.5–1%; 5.5–11mmol/mol), fasting and post-prandial glucose. In an open-label extension of the three studies, three-year sustained effects on HbA_{1c} were demonstrated with respect to baseline.[41] Similar to exenatide, liraglutide treatment resulted in significant reductions of HbA_{1c} levels (both as monotherapy and in combination with one or two antidiabetic therapies),[42–46] but this agent has a more favorable pharmacokinetic profile, making it suitable for once-daily dosing.[47]

Many of these studies were examined in two meta-analyses of randomized clinical trials evaluating GLP-1 receptor agonists in type 2 diabetes. These analyses confirmed the effectiveness of GLP-1 receptor agonists in reducing HbA_{1c}.[48,49] The magnitude of the reduction in HbA_{1c} with GLP-1-based therapies was dependent on the baseline HbA_{1c}, with greater reductions being seen in groups of participants with higher baseline HbA_{1c}.[48] GLP-1 receptor agonists have also been shown to have a similar efficacy to once- or twice-daily insulin.[48] A further important effect of GLP-1 receptor agonists is weight loss, which ranged from 1.6 to 3.1kg in patients participating in these studies despite improved glycemic control.[49] This is a distinct advantage over treatment with sulphonylureas and TZDs, and many patients prefer GLP-1 receptor agonists to these older oral treatments, despite requiring injection, because of the weight loss.

Of particular interest, a randomized, head-to-head comparison study of 26-weeks' duration suggested that liraglutide (1.8mg daily) was marginally more efficacious than exenatide 10µg twice daily (mean reduction in HbA_{1c} levels of 1.12 versus 0.79% [12 versus 8mmol/mol]; p<0.0001) when added to oral glucose-lowering agents.[50] Liraglutide reduced mean fasting plasma glucose more than exenatide, but post-prandial glucose increments were reduced more by exenatide than by liraglutide after breakfast and dinner. Reductions in body weight were similar in the two groups (~3kg).

Overall, GLP-1 receptor agonists have been shown to be well tolerated, with nausea and vomiting the most frequently observed adverse events. These adverse events are dose-dependent and decline over time.[39,40,51] Severe hypoglycemia was rare and occurred only when sulphonylureas were co-administered.[49] There was a high incidence of development of antibodies to exenatide (up to 67% of patients) during the initial 30 weeks of treatment.[48] Some data suggest that liraglutide appears to have a lower immunogenicity than exenatide.[42–46] However, a retrospective analysis found that in patients who developed antibodies to exenatide, the titers peaked early in treatment and declined thereafter, and were not predictive of safety and efficacy.[52] A pooled analysis of four phase III studies of liraglutide found the prevalence of anti-liraglutide antibodies was <10%, although it should be noted that serum samples were taken off drug treatment.[53]

Pancreatitis has been reported in patients who were treated with exenatide during post-marketing surveillance[54] and in several participants of the liraglutide clinical trial program.[42] At this point, no causal relationship between pancreatitis and GLP-1–based therapy has been shown. A retrospective, cohort study showed that patients with type 2 diabetes may have nearly a three-fold greater risk of acute pancreatitis compared with patients without diabetes.[55] Furthermore, a recent claims-based active drug safety surveillance system showed the

risk of acute pancreatitis in patients treated with exenatide was similar to that of patients treated with metformin or glyburide.[56] Understanding the potential relationship between diabetes therapies, the disease setting and pancreatic inflammation is of considerable clinical importance. Finally, in carcinogenicity studies with liraglutide C cell tumors were observed in the thyroid tissue of mice and rats,[57] although this does not appear to be clinically relevant as it has not been observed in clinical trials.

There is some evidence that GLP-1 receptor agonists may improve beta-cell function[4] and maintain long-term glycemic control.[41,58] In one study, adjunctive exenatide treatment for at least 3.5 years resulted in sustained glycemic control and reduced cardiovascular risk.[41] However, this study was open-label and not placebo-controlled. The GLP-1 receptor agonists appear to improve cardiovascular risk factors (blood pressure, lipid profile and, coagulation defects) as well as have direct beneficial effects on the myocardium.[59]

Currently, there are no long-term outcome studies but the effects on glycemic control, weight, and beta-cell function are promising. However, further trials are needed to prove conclusively that these treatments will reduce long-term complications.

Both exenatide and liraglutide were approved for use in the US in 2005 and 2010, respectively, as a second- or third-line agent for obese adults with type 2 diabetes who are not optimally treated with metformin and/or sulphonylureas. The low incidence of hypoglycemia, good tolerability profile, and the positive effect on weight and satiety suggests that GLP-1 receptor agonists may also be suitable as a first-line agent in the future for metformin-intolerant individuals.

There are several other GLP-1 receptor agonists in development. A once-weekly long-acting release formulation of exenatide has been shown to be more effective than the standard twice-daily administration.[60] The marketing authorization application for this once-weekly version of exenatide was recently (October 2010) deferred by the FDA pending more information on the safety and efficacy of this formulation, including additional studies to assess the potential effects on QT prolongation.

Albiglutide, taspoglutide, and lixisenatide are agents currently under investigation. Once-weekly taspoglutide and once-daily lixisenatide have been shown to improve glycemic control significantly in subjects with type 2 diabetes on metformin in randomized, placebo-controlled trials.[61,62] Albiglutide reduced fasting plasma glucose and 24-hour glucose concentrations relative to placebo in subjects with type 2 diabetes in a single-blind dose-escalation study.[63] Late-stage trials of taspoglutide have been delayed because of hypersensitivity problems observed in trial subjects, including skin reactions and digestive symptoms, but albiglutide and lixisenatide are currently undergoing phase III clinical evaluation in people with type 2 diabetes.

Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors are oral agents that inhibit the activity of the DPP-4 enzyme and prolong the actions of endogenous GLP-1. In randomized placebo-controlled studies, the DPP-4 inhibitors sitagliptin, vildagliptin and saxagliptin were shown to be effective at lowering HbA_{1c} levels by 0.6%–0.7% (7–8mmol/mol).[64–67] DPP-4 inhibitors have been assessed as monotherapy or in combination with metformin, sulfonylurea or TZDs and one study assessed sitagliptin in a triple-therapy regimen.[68]

The addition of a DPP-4 inhibitor to metformin therapy resulted in a markedly lower incidence of hypoglycemia when compared with sulfonylurea treatment.[69,70] Furthermore, sitagliptin and vildagliptin were shown to have a minimal effect on weight following treatment of at least 24 weeks' duration.[48,64] The drugs are well tolerated, with mild nausea being the most common side-effect.

The first oral DPP-4 inhibitor, sitagliptin, was approved by the FDA in 2006 for use as monotherapy or in combination with metformin or TZDs. Saxagliptin was subsequently approved by the FDA in 2009 and vildagliptin was approved in Europe in 2008. A potential advantage of DPP-4 inhibitors is that they are orally active compared with the subcutaneously-administered GLP-1 receptor agonists. At present, DPP-4 inhibitors are usually reserved for second-line therapy because of the lack of long-term follow-up data. If these agents are proven to be effective at reducing disease progression as well as long-term complications, they could be incorporated into management strategies as first-line therapies. Further DPP-4 inhibitors are in development, with alogliptin and linagliptin being the most advanced.[71,72]

Human Amylin Analogs (Pramlintide Acetate)

Pramlintide is a synthetic human analog of amylin, a small peptide that is almost exclusively secreted from pancreatic beta-cells. Pramlintide administered by subcutaneous injection slows gastric emptying, inhibits glucagon production and decreases post-prandial glucose excursions.[73] Two studies have shown that the addition of pramlintide to insulin treatment for type 2 diabetes resulted in reduced post-prandial hyperglycemia and a reduction of HbA_{1c} levels of 0.7–1% (8–11mmol/mol), without evidence of weight gain.[74,75] The main adverse events were gastrointestinal in origin, particularly nausea, although this abated with time on therapy. Currently, pramlintide is approved for use in the US as adjunctive therapy with regular insulin or rapid-acting insulin analogs.

Bromocriptine

Bromocriptine is an ergot alkaloid dopamine D_2 receptor agonist that has been used extensively in the past to treat hyperprolactinemia, galactorrhea and parkinsonism. A new, quick-release formulation has recently been approved in the US for the treatment of type 2 diabetes. Bromocriptine-QR (administered once-daily, in the morning) appears to act centrally to the reset circadian rhythms of hypothalamic dopamine and serotonin and to improve insulin resistance and other metabolic abnormalities.[76] Clinical studies show that bromocriptine-QR lowers HbA_{1c} by 0.6–1.2% (7–13mmol/mol), either as monotherapy or in combination with other antidiabetes medications.[76] Apart from nausea, the drug is well tolerated.

The Role of New Anti-hyperglycemic Therapies in Type 2 Diabetes Management

The availability of these new agents offers the potential to enhance the effectiveness of therapeutic regimens for type 2 diabetes. Current

Table 1: American Association of Clinical Endocrinologists Algorithm for Dual and Triple Therapy Regimens for Glycemic Control[78]

Dual Therapy Regimens			Triple Therapy Regimens				
Baseline HbA_{1c} 6.5%–7.5%							
Metformin	+	GLP-1 agonist or DPP-4 inhibitor	Metformin	+	GLP-1 agonist or DPP-4 inhibitor	+	TZD
		TZD					
		glinide or sulphonylurea					
TZD*	+	GLP-1 agonist or DPP-4 inhibitor					glinide or sulphonylurea
Metformin	+	colesevelam					
		AGI					
Baseline HbA_{1c} 7.6%–9.0%							
Metformin	+	GLP-1 agonist or DPP-4 inhibitor	Metformin	+	GLP-1 agonist or DPP-4 inhibitor	+	TZD
		TZD			GLP-1 agonist or DPP-4 inhibitor	+	sulphonylurea
		glinide or sulphonylurea			TZD		
Baseline HbA_{1c} >9.0%†							
Metformin	+	GLP-1 agonist or DPP-4 inhibitor	Metformin	+	GLP-1 agonist or DPP-4 inhibitor	+	sulphonylurea
		TZD			TZD		
					GLP-1 agonist or DPP-4 inhibitor		TZD

**When metformin is contraindicated*
†Dual therapy or triple therapy may be sufficient in asymptomatic patients; if the patient is symptomatic then insulin therapy should be initiated.
HbA_{1c} = glycated hemoglobin; GLP-1 = glucagon-like peptide-1; TZD = thiazolidinedione; DPP-4 = dipeptidyl peptidase-4; AGI = alpha-glucosidase inhibitor.

guidelines recommend (see next section) their use as adjuvant therapy, which is a sensible proposal as they have different mechanisms of action to metformin and therefore could act in an additive or possibly even in a synergistic way. They should not replace metformin as first-line drug therapy as they do not have an established long-term tolerability profile and have not yet been proven beneficial in the reduction of type 2 diabetes progression or long-term complications. As more evidence becomes available over the next few years, with more comparative data between agents and also between drug combinations, a reassessment of the current treatment strategies for restoration of glycemic control will be essential.

Current Guidelines and Recommendations

The American Diabetes Association

The ADA published its annual guidelines in January 2010 and covered management strategies for all aspects and complications of type 2 diabetes.[77] It included specific goals set for different groups, including hospitalized, pregnant, young and elderly patients.[77] Screening, diagnosis and the importance of multidisciplinary teams were discussed. It was recommended that screening for the long-term complications of nephropathy, retinopathy, neuropathy, dyslipidemia, hypertension and coronary heart disease be performed at an early stage and regularly thereafter. For optimal control of hyperglycemia and a reduction in the long-term complications of diabetes, the recommended target HbA_{1c} is <7% (53mmol/mol). This guideline did not specifically discuss therapeutic options, but metformin is the advised first-line drug of choice for the majority of patients.

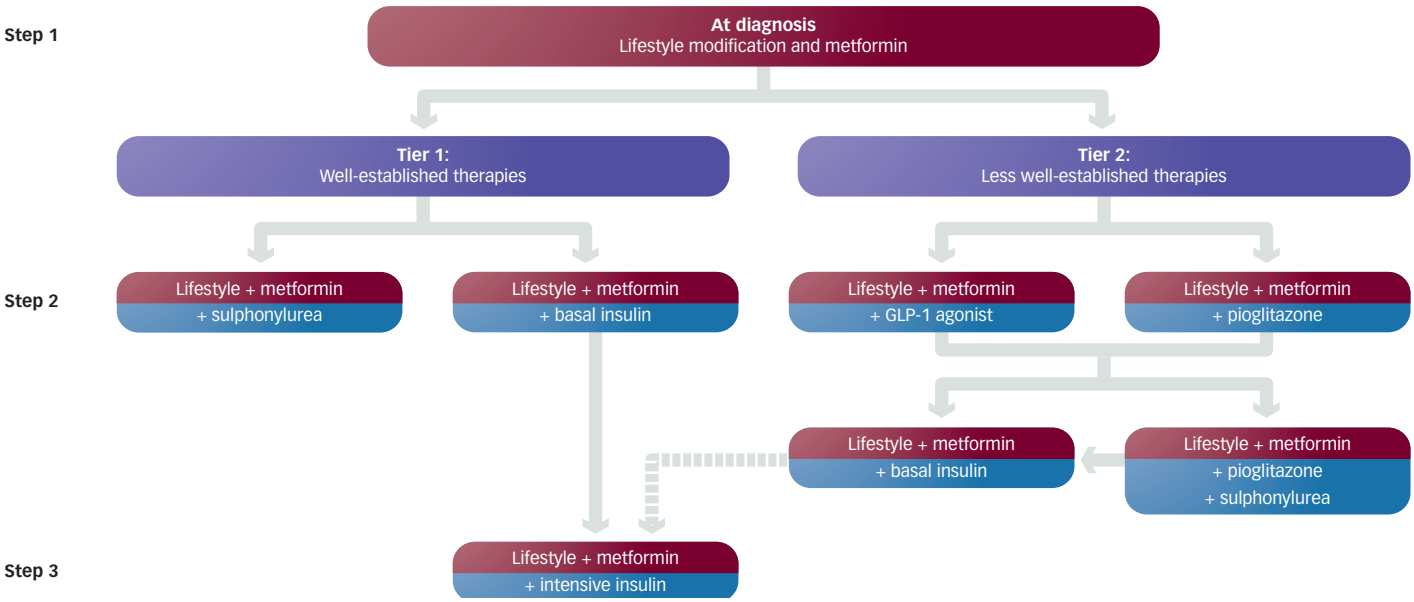
The American Association of Clinical Endocrinologists

The American Association of Clinical Endocrinologists (AACE) formulated an algorithm for glycemic control in people with type 2 diabetes in October 2009, as newer agents and the results of important clinical studies had become available.[78] The group stated that an HbA_{1c} of ≤6.5% (47mmol/mol) is recommended as the primary goal, but this goal must be customized for the individual patient. Appropriate therapy is stratified according to the HbA_{1c} level. For levels <7.5% (58mmol/mol), monotherapy with metformin is advised because of its proven efficacy and tolerability profile, advancing to dual or triple therapy if monotherapy proves unsuccessful. Dual or triple therapy is recommended for patients with higher HbA_{1c} levels, each regimen including metformin as the cornerstone of therapy (see *Table 1*).

The National Institute for Clinical Excellence in England and Wales

National Institute for Health and Clinical Excellence (NICE) published guidelines in May 2008[79] and issued an addendum on new pharmacological agents in June 2009.[80] NICE recommends metformin for patients with HbA_{1c} levels greater than or equal to 6.5% (47mmol/mol). A stepwise increase in treatment is advised for those patients with persistent or increasing levels of HbA_{1c}. A sulfonylurea may be considered as a first-line therapy in certain individuals, such as those who do not tolerate metformin or for whom a rapid response to therapy is required because of hyperglycemic symptoms. For second-line therapy, the addition of sulfonylurea to metformin is recommended when blood glucose control remains or becomes inadequate. A TZD may be added to metformin instead of a sulfonylurea where the person's job or other issues make the risk of hypoglycemia with sulfonylureas particularly significant. In addition, a TZD may be combined with a sulfonylurea when metformin is not tolerated. GLP-1 receptor agonists are considered only for select individuals, such as those with inadequate blood glucose control with conventional oral agents and with specific problems of a psychological, biochemical or physical nature arising from

Figure 1: American Diabetes Association/European Association for the Study of Diabetes Consensus Algorithm for the Management of Type 2 Diabetes



GLP-1 = glucagon-like peptide-1. Adapted from Nathan et al.[81]

high body weight. Insulin therapy may be initiated when other measures no longer achieve adequate blood glucose control.

The NICE addendum recommended the addition of a DPP-4 inhibitor or a TZD to metformin as second-line therapy as well as sulfonylureas. Recommended third-line therapy consisted of a combination of these three agents or the addition of a GLP-1 receptor agonist to metformin and a sulfonylurea when the level HbA_{1c} remains below 7.5% (59mmol/mol).

American Diabetes Association/European Association for the Study of Diabetes Consensus Algorithm

An algorithm for the treatment of type 2 diabetes was jointly published by a group of EASD and ADA members in 2009 (see *Figure 1*).[81] This consensus group advocated both lifestyle changes and commencement of metformin therapy at diagnosis, with a target HbA_{1c} of <7% (53mmol/mol). Should this combination not maintain HbA_{1c} levels <7%, then the established treatment would be the introduction of basal insulin or a sulfonylurea. The insulin regimen should then be intensified if the control of diabetes remains suboptimal. A second algorithm involving less well-established treatments was proposed for selected clinical settings, such as in patients for whom hypoglycemia is particularly undesirable (for example, in patients who have hazardous jobs). In these patients the addition of exenatide or pioglitazone to metformin may be considered, with addition of a sulfonylurea reserved for more resistant cases.

The above guidelines for the treatment of type 2 diabetes are generally broad and allow individual clinicians considerable flexibility in their treatment choices. The common theme is that lifestyle changes and metformin are the first-line treatment strategy for the majority of patients. With the progression of disease, however, different strategies are adopted by different clinicians. There is debate as to which is the best second-line therapy and how best to add or change medications, as well as when insulin should be introduced.[82]

The Future of Diabetes Management

There are several novel classes of drugs under development for the treatment of type 2 diabetes, suggesting that the choice of treatment will become more complicated in the future. The class of drugs that is nearest to introduction is sodium-glucose transporter (SGLT) inhibitors. SGLT-2 inhibitors, such as dapagliflozin, block the reabsorption of glucose from the renal filtrate, leading to an increase in glycosuria.

A phase III, randomized, placebo-controlled trial of dapagliflozin including 546 adults with type 2 diabetes and inadequate glycemic control with metformin was carried out. Dapagliflozin was shown to reduce HbA_{1c} (mean reduction from baseline of 0.84% [9mmol/mol]; p<0.0001) with 10mg dapagliflozin without any causing any weight gain.[83] The most important side-effect recognized to date is an increase in genitourinary infections, such as candidiasis.

There might be an increasing role for bariatric surgery, given the relationship between obesity and type 2 diabetes, particularly as lifestyle interventions and drug therapy are associated with only a modest degree of weight loss. In a large non-randomized study, morbidly obese patients underwent gastric surgery.[84] After two years there was weight gain of 0.1% in the control group compared with a weight loss of 23.4% in the surgical group (p<0.001). After 10 years, weight gain of 1.6% was noted in the control group, whereas a weight loss of 16.1% was maintained in the surgical group (p<0.001). A meta-analysis of clinical trials assessing bariatric surgery demonstrated that this approach completely resolved type 2 diabetes in >75% of

patients and that this remission lasted at least two years.[85] Bariatric surgery, however, is usually reserved for morbidly obese patients (>35kg/m^2), although glycemic control has been demonstrated in non-obese patients using this treatment approach.[86]

Summary and Conclusions

The morbidity associated with long-term microvascular, neuropathic and renal complications of type 2 diabetes can be reduced by improved glycemic control. Current management strategies do not normalize glucose metabolism and people with type 2 diabetes continue to suffer disease progression and long-term complications. The comorbid diseases of hypertension and hyperlipidemia also need to be aggressively controlled to prevent macrovascular disease. New classes of medications and numerous combinations have been demonstrated to improve glycemic control. Their long-term effects on preservation of beta-cells and prevention of micro- and macrovascular complications, however, remain to be determined. Research that is still ongoing has provided a better understanding of the pathophysiology of type 2 diabetes. With the introduction of newer classes of medications, a more targeted, early and aggressive treatment strategy may be appropriate. Clinicians need to balance aggressive therapy with the risk of adverse events, such as hypoglycemia, and different regimens will be required for different patients. With data becoming available in the next few years, an almost continual appraisal of guidelines and algorithms will be necessary. ■

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