Recent advances in pharmacotherapy for Type-2 diabetes: a review (Part 1)

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The global incidence of Type-2 diabetes is on the rise and the public health and resource implications of the disease will be very enormous. The therapeutic armamentarium has been very much static up to the last decade of the last century when more several agents were developed and marketed. New oral agents followed the footsteps of the sulphonylureas and biguanides, and agents like the alpha-glucosidase inhibitors, meglitinides, thiazolidinediones and incretin-based therapeutic agents have added a new dimension to the management of the disease and more options for the increasing number of patients. Other novel agents are still in development. Furthermore, advances in scientific research and clinical practice and patient's care have shed the light on the importance of the holistic approach for management of these patients, and the need to address the devastating complications and the best way of achieving this. This paper is the first part of a series of reviews that is aimed at surfing the current developments in pharmacotherapy of Type-2 diabetes.

Keywords: Diabetes mellitus, Type-2 diabetes, Sudan, Sulphonylurea, metformin, meglitinides, Thiazolidinedione, Alpha glucosidase inhibitors.

Introduction

The prevalence of Type-2 diabetes globally has been exponentially rising in the last few decades and there are predictions for more rise in the near future to rates akin to epidemic proportions\(^1,2\). The main burden of such huge increase in the prevalence will mostly fall on the developing countries\(^3,4\). Middle Eastern countries in particular have witnessed explosion in diabetes and obesity rates\(^5,6\), and there are some preliminary epidemiological studies from Sudan which point to similar trends\(^7,8\). Diabetes is increasingly known as a leading cause of chronic kidney disease in Sudanese patients\(^9\). The mechanisms behind such rise...
in prevalence is postulated to be due to changes in lifestyle, less physical activities, concomitant upsurge of obesity and the global changes in dietary habits with more consumption of high fat, high refined carbohydrate and low fibre diets. Added to this, diabetes is a complex disease, with potential for devastating complications which result in major morbidities and mortalities. Furthermore, Type-2 diabetes commonly clusters with other major morbid conditions including hypertension, obesity, dyslipidemia (which have been collectively described as metabolic syndrome, or syndrome X) as well as atherosclerotic vascular disease.

Type-2 diabetes is a progressive disease, characterized by both insulin resistance and gradual decline of pancreatic beta-cell function. Disease progression is usually associated with worsening hyperglycaemia, which is attributed to insulin deficiency caused by dysfunction and eventually failure or loss of pancreatic beta cell function. This worsening hyperglycaemia, in turn, leads to an increased risk of development of microvascular as well as macrovascular complication, such as retinopathy, nephropathy, neuropathy, and atherosclerosis, including cardiovascular disease, stroke and peripheral vascular diseases. Thus the goal of treatment in patients with Type-2 diabetes is effective and appropriate blood glucose control in order to prevent microvascular as well as macrovascular complications commonly associated with chronic hyperglycaemia. Thus the main objective in the management of (Type-2 diabetes mellitus) T2DM is to achieve blood glucose levels as close to normal as possible\(^{(10)}\). Maintaining blood glucose control as close to normal as possible in people with T2DM has been demonstrated to have powerful beneficial effects in reducing or slowing the progression of diabetes specific complications, such as eye, kidney and nerve complications\(^{(10)}\). However, the role of intensive blood glucose control on macrovascular diseases and cardiovascular outcome is currently under active investigations.

The traditional approach in management of Type-2 diabetes is the initial introduction of dietary modification, exercise and lifestyle intervention. When these non-pharmacological modalities prove inadequate in controlling the patient’s hyperglycaemia, pharmacologic intervention is indicated, in the form of oral anti-diabetic agents, insulin or both. The oral agents used to treat diabetes are diverse and involve several classes. However, these drugs can largely be classified into two groups based on their pharmacodynamics and their effect or lack of effect on insulin secretion and action. The first group of agents includes insulin secretagogues or oral hypoglycaemic agents, such as sulphonylureas and meglitinides, which stimulate pancreatic insulin secretion. The other group of agents is the anti-hyperglycaemic agents, such as biguanides, and thiazolidinedione which improve insulin sensitivity. The latter group of anti-hyperglycaemic agents also includes α-glucosidase inhibitors, which inhibit intestinal glucose absorption. At the present time there is no sufficient evidence to support a recommendation of one anti-diabetic agent over others with regard to effects on the late diabetes complications. The selection of specific anti-diabetic agents is predicted on their effectiveness in lowering blood glucose, extraglycaemic effects that may reduce late diabetes complications, safety profile, tolerability and expense. It is apparent that the positive effect of intervention on the late diabetes complications is predominantly related to the blood glucose lowering effect rather than
any other specific attributes of the intervention or the agent. The UK Prospective Diabetes Study (UKPDS) compared three classes of glucose lowering agents, sulphonylurea, metformin and insulin, but was unable to demonstrate clear superiority of any one drug over the others with regard to diabetes microvascular complications\textsuperscript{(10)}. The exception to that is metformin, which is alone among all anti-diabetic medications to show beneficial macrovascular outcome and cardiovascular protective effect\textsuperscript{(11,12)}, and these findings have not been demonstrated with any other agent and for this reason, metformin is recommended as the first line anti-diabetic agent in T2DM in all the current national and international guidelines and policies. In the last two decades, the therapeutic armamentarium for Type-2 diabetes has witnessed significant revolution with several agents launched or under development. Further, new technologies have added a new dimension to the way we manage these patients. Furthermore; clinical and basic research has added more insights to the ways we should manage them. This is translated in continuous dynamics in changing guidelines for management of these patients\textsuperscript{(13)}. Recent large scale studies have shed the light on other aspects surrounding the quest for normoglycaemia. The discussion of these studies is beyond the scope of this review which will focus primarily on advances in the field of pharmacotherapy of Type-2 diabetes. Further reviews that deal with the new agents in pharmacotherapy of Type-2 diabetes as well as the latest advances in insulin therapy for Type-2 diabetes will be presented in this journal in the near future.

**The Pharmacotherapy of Type-2 diabetes**

Type-2 diabetes as an ancient disease did not have any specific treatment in the pre-insulin era. Following discovery of insulin by Banting and Best and its pharmacological use in 1922, insulin thereafter was used for management of all patients with diabetes who could afford to obtain it. The discovery of insulin had been followed by discovery and production of various type of oral anti-diabetic agent, with different mode of action, pharmacokinetic and pharmadynamics. These agents are expanding and include biguanide, sulphonylurea, thiazolidinediones, gliptins and others. The use of these anti-diabetic agents is usually guided by traditional stepwise pathways and guidance for treating T2DM. These stepwise pathways mostly start with lifestyle modifications and continuing with one or more oral anti-diabetic agents, which usually lead to an extended period of avoidable hyperglycaemia

**A. Sulphonylureas (SUs)**

These agents were the first of oral hypoglycaemic agents (OHA) to be available to treat ‘maturity onset diabetes’ (as Type-2 diabetes used to be called then), following the clinical use of insulin in 1920s. The use of SUs was started in 1955 when the first generation agents became available. SUs stimulate the release of insulin through a direct effect on Beta cells of the pancreas, via their specific Sulphonylurea Receptor-1 (SUR1) on the B cells, which are closely associated with another cell receptor, Kir-2. Stimulation of this complex, leads to inhibition of the K-ATPase dependent efflux from the cell, with increase depolarization of the beta cells culminating in opening of the calcium channels, intracellular calcium flux and the augmentation of the first phase of insulin release from its granules. SU also has some effect on the second phase of insulin release which begins 10 min after the first phase with more insulin granules been formed and moved into the surface. The first generation
agents of SUs are chlorpropamide and tolbutamide, however chlorpropamide is now rarely available and is not commonly prescribed at present due largely to the risk of severe, prolonged and very rarely fatal hypoglycaemia. Tolbutamide, is the second drug of the first generation SUs and is possibly one of the commonest used SUs in developing world. Second generation SUs are the most widely used among the SUs, and these include glibenclamide (Glyburide), gliclizide, glipizide. There are marked differences in the absorption, metabolism and elimination kinetics of these various SUs. In addition, several factors influence the absorption and bioavailability of these SUs, notably the time of ingestion in relation to meal, blood glucose levels and type of formulation.

The first generation SUs, chlorpropamide, has a relatively long half-life, with 24-48 hours duration of action, and thus can be given once daily. Its long half life makes it less popular in those prone to hypoglycaemia particularly the elderly. Tolbutamide is short acting with 6–10 h half life, has the potential advantage of being metabolised by the liver and not excreted in the urine, hence can be use in early renal impairment. The so called second generation SUs, glibenclamide, gliclazide, glipizide, gliquidone, have shorter plasma half life compared to chlorpropamide, and have generally been given twice daily, although there is growing evidence that this is unnecessary.

Glibenclamide (Glyburide in USA), gliclazide, together with glipizide are intermediate acting, have variable degree of metabolism and variable route of excretion. Glibenclamide, for instance is metabolized by the liver to active metabolites and those are primarily excreted by the kidneys, hence the high risk of severe hypoglycaemia with renal impairment and in the elderly(14). The same might be true for the modified release form of gliclazide (Diamicron MR) which is intermediate to long acting and despite that its metabolites are inactive like the parent compound but it should not be used in patients with renal impairment as per risk of severe hypoglycaemia. Other agents in this group are glimepride and gliquidone.

In term of efficacy, SUs monotherapy is as effective as metformin and can result in 1.5% reduction in HbA1c, and typically the onset of glucose lowering effect of SU is relatively rapid compared with metformin and thiazolidinedione (glitazone, TZD), however SUs are less effective in maintaining effective blood glucose control or glycaemic targets compared to metformin and TZD(15). SUs are generally well tolerated but hypoglycaemia and weight gain are notable side effects. However, hypoglycaemia can be prolonged and life threatening, but such episodes are uncommon. Severe episodes are relatively more frequent in the elderly, and long acting agents, chlorpromide and glibenclamide are associated with greater risk of hypoglycaemia than other second generation SUs(16).

There is little evidence to suggest that one SU is more effective than the other. Most studies comparing the clinical efficacy of second generation SUs have reported that glibenclamide, glipizide and gliclazide are equipotent. Although the blood glucose lowering effect of these drugs is not different, there is variability in the timing of the effect. These observations include the lower fasting blood glucose with glibenclamide compared to glipizide and better postprandial blood glucose with glipizide(17).

The main use of SUs agents as been shown in UKPDS(10) continues to be primarily as first line for non-obese newly diagnosed patients who failed to respond to non-
pharmacological measures. Its place also is an adjunct to metformin for overweight and obese patients who do not achieve the target blood glucose control or target HbA1c. SUs could be combined with other agents including alpha-glucosidase inhibitors, TZD as well as insulin.

**B. Biguanide**

Historically, biguanides were extracted from the plant Galega Officinalis (Goat rue; or French lilac), and were widely used to treat diabetes for decades in Europe. However, their scientific formulations, metformin and phenformin did not become available for clinical use until 1958. Phenformin was withdrawn from the clinical use because of its high risk of causing lactic acidosis, a risk 10 times that associated with metformin. Metformin has remained in use in Europe and many other countries, and has been approved for use in USA in 1994, and is currently the most widely used agent to treat Type-2 diabetes. Metformin absorption is incomplete, with 20%-30% found in the faeces, and has negligible protein binding properties (hence low rate of drug interaction), and is excreted unchanged in the urine (cimitidine interferes with its excretion). It has a half life of 6 hours and it reaches peak of action in 1-2 hours. Its main mode of action is by decreasing the rate of hepatic glucose production, inhibiting gluconeogenesis and glycogenolysis, and decreasing intestinal glucose absorption. To a lesser extent, metformin can also enhance glycogenesis. It also enhances insulin-mediated glucose uptake by peripheral tissues and has a lipid lowering effect (mainly triglycerides). It also improves fibrinolysis and decreases PAI.

Metformin reduces plasma glucose concentration by an average of 25%, with somewhat better effect on postprandial than on fasting glucose levels. In clinical practice, metformin is expected to lower fasting plasma glucose level by approximately 2.0 mmol/l and HbA1c by about 1%[18]. Diabetes Prevention Program Research and other reports demonstrated that Metformin therapy can reduce the risk of developing diabetes, but not as much as those in the lifestyle intervention group. These reports demonstrated that treatment of high-risk subjects with metformin results in modest or minimal weight loss and favorable changes in insulin sensitivity, which contribute to a reduction in the risk of diabetes as well as improvement in fasting blood glucose levels[19]. Metformin has been widely used as an effective glucose lowering agent, and its benefit in improving glycaemic control and reducing the risk of microvascular as well as macrovascular complications has clearly been shown in the UKPDS. In the UKPDS, intensive glucose control with metformin[10,11] appeared to reduce the risk of diabetes-related end points in overweight patients and was associated with less weight gain and fewer hypoglycemic attacks than insulin. In addition to its use in Type-2 diabetes, metformin has also been studied as an adjunctive therapy in overweight patients with Type-1 diabetes. Recent reports confirmed that addition of metformin to insulin therapy in Type-1 diabetes can improve blood glucose control and reduce the total daily insulin doses[20, 21]. Metformin provides a new option for the management of children and adolescents with type 2 diabetes. While initial studies with metformin in children and adolescents have been favourable, more research is needed to establish the efficacy and safety of long-term use in the pediatric population[22]. The main side effects of metformin is GI-related (less so with the slow release preparation, Glucophage SR®), and it rarely causes lactic acidosis, especially in patients with moderate to severe renal impairment, hence
it should not be used in patients with eGFR <30 ml/min. Chronic use may lead to vitamin B12 deficiency in susceptible patients. An important practical aspect of its use is that it should be stopped 48 hours before any IV contrast agent is used in radiological investigations (very high risk of contrast-induced nephropathy).

Metformin therapy is generally recommended as the initial pharmacological therapy in people with Type-2 diabetes, in the absence of specific contraindications; however, metformin therapy should always be initiated concurrently with continuous and ongoing lifestyle intervention and nutritional therapy. The current national and international guidelines recommend that metformin therapy should be initiated concurrently with lifestyle intervention at diagnosis, or when target blood glucose control has not been achieved with lifestyle intervention alone \(^{(13)} \). It is the preferred mode of therapy for overweight and obese patients with Type-2 diabetes who failed to respond to non-pharmacological management. It is also very useful in combination with SUs (e.g Glucovance®, (metformin, glibenclamide)) \(^{(10)} \), and in combined formulation with thiazolidinediones (Avandamet®), insulin and with the new incretin-based agents (e.g sitagliptin: Januvia (Janumet®)).

**C. Alpha glucosidase inhibitors**

These agents were introduced into clinical practice in the early 1990s, and they are widely used in West Europe, especially in Germany. The first of this group is acarbose (Glucobay®), follows by miglitol and voglibose. These agents act through competitive inhibition of the enzyme α-glucosidase at the small intestinal brush borders that is responsible for digesting disaccharides into monosaccharides. This helps to reduce primarily the postprandial surge of glucose. Thus acarbose works principally to lower postprandial blood glucose level, and after a carbohydrate meal, acarbose lowers the postprandial rise in blood glucose by approximately 20%, or 2.75 to 3.30 mmol/L, depending on the dose, and the type of carbohydrate ingested. There is a greater effect on postprandial hyperglycaemia after ingestion of starch than of sucrose \(^{(23)} \). Several clinical trials confirmed that acarbose monotherapy significantly lowers fasting blood glucose (p< 0.02) by 1.1 to 1.3 mmol/L, or approximately 10 to 15%, in patients with Type-2 diabetes. The mechanism for this effect is secondary to the lowering of postprandial hyperglycaemia \(^{(24)} \). As a result of improving postprandial as well as fasting glycaemia, acarbose reliably reduces HbA1c. However, the initial improvement in blood glucose with acarbose tends to be modest, but with long-term use efficacy steadily improves. Benefits are more pronounced after 3 months and are maintained over several years without evidence of decreased effect or treatment failure. The UK Prospective Diabetes Study, for example, demonstrated that in 309 patients with Type-2 diabetes the hypoglycaemic and HbA1c-lowering effect of acarbose, when used in combination therapy, was highly significant (p < 0.001) and sustained for at least 3 years \(^{(25,26)} \). Acarbose treatment is weight neutral, and there has been no detectable effect of acarbose on energy or nutrient intake, and patients ‘eating habits’ are not markedly changed \(^{(27)} \). Acarbose has been shown to improve insulin resistance in patients with T2DM as well as those with IGT. The mechanism by which acarbose increases insulin sensitivity is probably based on lowering fasting and postprandial hyperglycaemia and decreasing glucose toxicity. In addition, a decrease in post-challenge hyperinsulinaemia is considered
by some authorities to contribute to insulin sensitivity. Other investigators have reported improvements in insulin sensitivity following a rise of the incretin hormone, GLP-1, and the 'priming' effect it induces. These agents are not absorbed, and generally have to be used as an adjunct therapy with other agents. Their main side effect is GI related, mainly abdominal distension, flatulence, borborygmi, loose bowel motion or severe diarrhoea which could limit their use. It has been shown that, these agents are not effective as monotherapy and they should be used as an adjunct to other available agents.

D. Meglitinides (Postprandial glucose regulator)
The origin of this group of oral hypoglycaemic drugs (OHA) came from their first agent, meglitinide which was discovered in the early 1980 to be a non-sulphonyl portion of glibenclamide molecule. Two agents so far are available for clinical use, repaglinide (Novo-Norm, Novo-Nordisk®) and netaglinide (Starlix, Novartis®). These agents bind to the SUR1 receptor on the pancreatic β-cell and produce a non-sustained release of insulin in the first phase and to a lesser degree of the second phase insulin secretion. They are short acting, metabolised exclusively by the liver and their inactive metabolites are excreted in the bile (repaglinide) and the urine (netaglinide). They are effective in reducing the postprandial glucose excursion (hence, the name postprandial glucose regulator), and are not useful in reducing fasting hyperglycaemia hence, they should generally be combined with other anti-diabetic agents, mainly metformin. They should be administered immediately before meals. They are as effective as metformin and SUs in improving blood glucose control, decreasing HbA1c by up to 1.5%. Nateglinide is somewhat less effective than repaglinide in improving blood glucose levels and control. Their main side effect is hypoglycaemia, though meglitinides-induced hypoglycaemic episodes are less compared with the sulphonylurea agents, and their shorter duration of action and rapid onset will provide flexibility in their use in patients with busy life-style. However, the risk of weight gain is similar to that of SU. They also interact with erythromycin, rifampicin and antifungal agents which can interfere with their renal excretion. They could be useful in patients who have a very busy professional life and also they are attractive to be used for fasting patients during Ramadan.

E. Thiazolidinediones (Glitazones)
Thiazolidinediones (TZD) or glitazone group of drugs have been marketed in the late 1990s when the first of this group troglitazone was launched in 1998, and rosiglitazone and pioglitazone followed suit later. Troglitazone was withdrawn from the market few months after its launch as it can result in fatal hepatic failure. These drugs are peroxisome proliferator activator receptor gamma (PPARγ) modulators, act through binding to the PPARγ nuclear receptor, which results in its activation and subsequent initiation of a cascade of cellular pathways that control carbohydrate and lipid metabolism. Their main action culminates in improvement of insulin resistance, a prime feature of Type-2 diabetes. TZD agents also exert some effects on the lipoprotein subfractions with differential effects and have either beneficial or neutral effect on the atherogenic lipid profile. Rosiglitazone mainly raise low density lipoprotein (LDL) cholesterol, and pioglitazone lower triglycerides and increase high density lipoprotein (HDL) cholesterol. There is a recent evidence to suggest that rosiglitazone modifies HDL structure and modifies HDL-
Apo AI synthesis and catabolic rates\(^{31}\), which has been postulated to be anti-atherogenic. PPAR gamma agonists have also been shown to have a favourable effect on \(\beta\)-cells of the pancreas by preserving its cell mass and inhibiting apoptosis\(^{32}\) and this has been tested in the clinical setting in prevention of development of Type-2 diabetes in susceptible subjects. Troglitazone was used in women with previous history of gestational diabetes and it showed promise in prevention of development of diabetes in these groups of patients\(^{33}\). Recently, rosiglitazone have been shown to have similar effect in adult patients with Latent Autoimmune Diabetes of Adults (LADA)\(^{34}\). The mechanism of such protection has been proposed to be mediated via their direct anti-apoptotic actions at the level of beta cells, increase insulin secretory capacity, and improve peripheral insulin action. Glitazones also have other favourable effects, including improvement of microalbuminuria by rosiglitazone\(^{35}\), improve endothelial dysfunction and arterial elasticity\(^{36}\), have anti-atherogenic properties in animal models\(^{37}\) and have favourable effects on fibrinolysis via reducing PAI-1 and increasing tissue-type plasminogen activator (tPA).

Rosiglitazone is metabolized into weakly active metabolites which are excreted primarily in the urine (70%), and pioglitazone is metabolised into active metabolites which are mainly excreted via the bile. Their main side effects are primarily related to weight gain and fluid retention which can precipitate heart failure in susceptible patients\(^{38}\). The use of rosiglitazone has recently been surrounded by intense controversy relating to increased risk of myocardial infarction and vascular events. Several meta-analyses have suggested a 30-40% increase in the risk of myocardial infarction with rosiglitazone. However, this had led to significant reduction in the use of the drug\(^{39,40}\). On the other hand, pioglitazone have been proposed to have a tendency to improve vascular outcomes\(^{41}\). The Prospective Pioglitazone Clinical Trial in macrovascular events (PROactive) demonstrated no adverse outcome with pioglitazone therapy compared with placebo on primary CVD outcome after 3 years of follow up, however, pioglitazone was found to be associated with 16% reduction in death, myocardial infarction, and stroke; a controversial secondary end points reported to have marginal statistical significance\(^{42}\). Thus pioglitazone not only doesn't seem to have the adverse effects on cardiovascular complications that were seen with the other drug of this class, rosiglitazone, but in fact has a beneficial, protective effect in reducing the complications of death, heart attack, and stroke among diabetic patients. Much heat was added to the controversy when published reports suggested some adverse effects on bones in postmenopausal women\(^{43}\). A recently reported randomised prospective study, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD), has demonstrated that cardiovascular outcome and risk of rosiglitazone is not different from that of the comparators, metformin and sulphonylurea\(^{44}\), however, the study has shown increased risk of heart failure and bone fractures with rosiglitazone.

The controversy continues and the uncertainties continue to loom over the continuing use of these agents\(^{45}\), but so far the drugs have remain in the market, as they seem to be of benefit to significant proportion of patients.
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References


