Metformin: Old Wine in New Bottle - *Evolving Technology and Therapy in Diabetes*

Shashank R Joshi

**Abstract**

Metformin is the most common prescribed oral antidiabetic drug in the world. It shall continue to maintain its position despite of several other classes of oral agents have been recently introduced both as initial therapy and in combination with these newer drugs for prevention and treatment of type 2 diabetes mellitus (DM). The current review focuses on novel mechanism of action, efficacy, toxicity, administration of newer metformin formulation and technology of metformin. Metformin is a hepato-selective insulin sensitizer. It has beneficial properties of metformin including weight loss, lipid reduction and modulator of endothelial function. It is an atherostatic agent and also improves ovarian function in some insulin-resistant women. It does not cause hyperinsulinaemia or hypoglycaemia. Metformin is effective as monotherapy and, in combination with both insulin secretagogues and thiazolidinediones (TZDs) and may obviate the need for insulin treatment. Several fixed-dose combination pills containing metformin and other agents are available. Metformin remains a safe and effective agent for the therapy of patients with type 2 DM. It is still in most circumstances the agent of choice for first line initial therapy of the typical obese patient with type 2 DM and mild to moderate hyperglycaemia. With the current sustained release (XL) formulation of metformin, metformin therapy has now upgraded itself from the Gold Standard to Platinum. These unique XL bioequivalent metformin preparations will become the platinum standards in modern diabetes management.

**HISTORY**

Guanidine was recognized as the active glucose-lowering constituent of French lilac (Gallega officinalis), which had been employed in continental Europe as a traditional remedy for DM for centuries. The use of guanidine and guanidine derivatives (Phenformin, Buformin, Metformin) as therapeutic agents for diabetes mellitus (DM) dates from the early 1900s. Phenformin (phenylethylbiguanide), the first biguanide, was introduced in the late 1950s, but due to its association with lactic acidosis was withdrawn from across the globe in the late 1970s, in India only recently. Metformin is substantially different from phenformin structurally, the latter possessing a phenyl-ethyl ring on a guanidine side chain, thus rendering it less polar and more lipid soluble. In clinical use, it appears that secondary failure to metformin therapy occurs with approximately the same frequency (about 5–10% per year) as to sulfonylureas, which is likely to reflect the progressive nature of type 2 DM. Trials show that metformin monotherapy in patients with type 2 DM reduces fasting plasma glucose by 50-70 mg%, (3–4 mmol/l) and glycosylated haemoglobin A1c (HbA1c) by 1.5–2%. While metformin was not licensed for use in the US until 1995, it remained in widespread use throughout Canada, Europe and much of the world including India for the period from 1978 through 1995. In India, Metformin was available since 1980s as traditional agent (Glyciphage) and since last 5 years several newer sustained release formulations have also become available (like Glyciphage SR, Metaday, etc).

**MECHANISM OF ACTION OF METFORMIN**

Despite decades of clinical use, the molecular mechanisms by which metformin acts still have not been definitively determined and many more mechanisms will be elucidated. Unlike secretagogues, metformin has no effect on plasma insulin concentration increase, and due to reduction in glucotoxicity it has an indirect effect on beta cell secretory function (marginal, secondary effect). When administered to non-diabetic subjects, metformin reduces fasting plasma glucose by 50-70 mg%, (3–4 mmol/l) and glycosylated haemoglobin A1c (HbA1c) by 1.5–2%. While metformin was not licensed for use in the US until 1995, it remained in widespread use throughout Canada, Europe and much of the world including India for the period from 1978 through 1995. In India, Metformin was available since 1980s as traditional agent (Glyciphage) and since last 5 years several newer sustained release formulations have also become available (like Glyciphage SR, Metaday, etc).

Hepato-Selective Effect: The principal glucoregulatory actions of metformin occur primarily at the liver to reduce glucose output and secondarily at the peripheral tissues (muscle, adipose tissue) to augment glucose uptake. Metformin has shown a reduction in...
fasting hepatic glucose by inhibiting gluconeogenesis. A variety of possible mechanisms has been now demonstrated, including phosphorylation of the insulin receptor and insulin receptor substrate-2, inhibition of key enzymes in the gluconeogenic pathway (e.g. phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase and glucose-6-phosphatase) and activation of pyruvate kinase. Reduction in hepatic uptake of gluconeogenic substrates (lactate and alanine), possibly by depolarization of the hepatocyte membrane, has also been postulated. Studies have also demonstrated inhibition of mitochondrial respiration by metformin, which may reduce the energy supply required to execute gluconeogenesis.

**Muscle Effect**: Metformin augments peripheral insulin-mediated glucose uptake, chiefly into muscle. Metformin therapy may restore the activity of enzyme systems involved in the intracellular insulin-signalling cascade. Enhanced muscle uptake of insulin, increased insulin receptor tyrosine kinase activity, as well as increased glucose transporter-4 translocation and transport activity may account for improved peripheral glucose utilization in response to metformin. As expected, augmented glucose uptake is achieved by an increase in glucose transport across the cell membrane, although the precise cellular action of metformin remains to be elucidated.

**AMPK Activator**: Recently, metformin it has been observed stimulates adenosine monophosphate-activated protein kinase (AMPK). AMPK inhibits hepatic glucose production, stimulates muscle glucose uptake and suppresses lipogenesis, making it potentially an ideal mediator of metformin’s action. A recent report, however, demonstrated AMPK activation by Glitazone as well as by metformin, raising the possibility that AMPK activation is a non-specific consequence of insulin sensitization.

**Other Effects**: In addition to its actions on glucose metabolism, several other metabolic effects have been ascribed to metformin (Table 1), of which a number are beneficial to the cardiovascular risk profile.

**Weight**: Best documented and least controversial of these is its effect on body weight. Most studies have reported either modest weight reduction in patients taking metformin, or stability of weight, in contrast to the weight gain often observed in patients taking sulfonylurea, thiazolidinedione (TZD) or insulin therapy. However in absence of insulin resistance or diabetes it cannot be used as an weight loss agent. Its anorectic property also contributes to weight loss.

**Lipids**: Several studies have reported a beneficial effect on lipid parameters, including a lowering of total cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides. An increase in plasma high-density lipoprotein (HDL) concentrations has also been reported, although others have found no alteration in this fraction. The observed increase in HDL-cholesterol may be predominantly related to an increase in the HDL-2 subfraction. A few reports have also found no alteration in any lipid parameter with metformin therapy.

**Blood Pressure**: A number of reports have documented a reduction in blood pressure during therapy with metformin, either in systolic or diastolic pressure alone, or in both phases. It has been suggested that lowering of blood pressure may be consequent upon the attendant weight reduction associated with administration of metformin; however, significant reductions in blood pressure have been observed in studies where no change of weight was reported to occur. Overall, metformin has no effect or possibly (in isolated studies cited above) a small effect on blood pressure. However, a lack of effect of metformin on blood pressure has been reported with equal frequency.

**Endothelial Modulator**: Additional possibly beneficial effects of metformin include improvement in endothelium-dependent vasodilatation, a reduction in fibrinogen levels and increased activity of the fibrinolytic system, as well as diminished platelet aggregation and plasminogen activator inhibitor-1 activity. Reductions in both fasting and postprandial insulin concentrations have been reported. Metformin therapy is also associated with reduced levels of C-reactive protein. All of the above factors may have contributed to the fact that metformin use in obese subjects with type 2 DM in the UK Prospective Diabetes Study (UKPDS) study was associated with a reduction in stroke, all-cause mortality and total DM endpoints compared to insulin or sulfonylurea, despite a similar degree of improvement in glycaemia. In the Diabetes Prevention Program (DPP), the use of metformin (850

<table>
<thead>
<tr>
<th>Table 1: Benefits of Metformin</th>
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<tr>
<td>Glucose: Improved glycaemic control (F 50-70 mg%, HbA 1c 1.5-2%)</td>
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<tr>
<td>Lipids: Reduced triglycerides, reduced total cholesterol, reduced LDL-cholesterol, increased HDL-cholesterol</td>
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<tr>
<td>Weight Loss: Weight reduction</td>
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<tr>
<td>No Hypoglycaemia: Low incidence of hypoglycaemia or reduced serum insulin</td>
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<tr>
<td>Blood Pressure: Blood pressure reduction</td>
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<tr>
<td>Atherostatic: Increased fibrinolytic activity (reduced PAI-1 levels), reduced platelet aggregation, reduced fibrinogen levels</td>
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<tr>
<td>Endothelial Modulator: Improved vascular relaxation, rescued C-reactive protein</td>
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<tr>
<td>Ovulation: Increased ovulation in PCOS</td>
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<tr>
<td>GDM, Pregnancy: Reduced gestational DM in PCOS Reduced first trimester pregnancy loss in PCOS</td>
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mg twice daily) in subjects with impaired glucose tolerance reduced the incidence of type 2 DM by 31% (from 11% per year to 7.8% per year); this protection was most effective in younger, more obese subjects. Subjects over 60 years of age or with body mass index less than 30 kg/m² did not benefit from metformin.64

Heart Failure: Recently in a new study suggests that the diabetes drug metformin, may improve survival and clinical outcome in diabetic patients with heart failure, even though US FDA labeling recommends against using the drug in these patients. “Stable heart failure and diabetes I think can be safely treated with metformin,” Said Johnson et al of the University of Alberta in Edmonton & his team in the October 2005 issue of Diabetes Care.63 Warnings against using metformin are based on past experience with phenformin — a similar drug that was taken off the market in the 1970s after being linked to hundreds of cases of lactic acidosis, a potentially life-threatening build-up of lactic acid in the blood that can damage vital organs. However, there is a scarcity of information metformin to this side effect, and recent studies suggest metformin may actually be more effective than so-called sulfonylurea drugs in reducing death from cardiac causes. According to Johnson et al, as many as 10 to 15 percent of diabetic patients with heart failure are prescribed metformin despite the labeling, largely due to the scarcity of other treatment options. To investigate whether contraindications are warranted, the researchers identified 12,272 new users of oral antidiabetic drugs, 1833 of whom developed heart failure, and classified them based on the type of drug they were taking. Compared to treatment with a sulfonylurea, treatment with metformin was associated with reduced hospitalization and death among patients with heart failure, the team reports in the October issue of Diabetes Care. One third of patients on metformin died, compared with 52 percent of patients on sulfonylureas only. Seventy-seven percent of patients on metformin died or were hospitalized, compared with 85 percent of patients on sulfonylurea alone. Given that this is a comparative study, Johnson notes, it’s not possible to say whether metformin improved outcomes or sulfonylureas worsened them.

Pregnancy: Metformin has recently used to treat pregnant women with type 2 diabetes or gestational diabetes, although several studies suggest this is safe.66–69 One small study suggested that metformin use in pregnancy increased rates of preeclampsia and perinatal mortality,70 however, because metformin was preferentially used in obese women, among whom rates of preeclampsia and perinatal mortality are known to be higher,71 the results are most likely related to characteristics of the treated women, rather than metformin itself.

PCOS/NASH: Recently, beneficial effects of metformin on reducing androgen levels and restoring ovulation in women with polycystic ovary syndrome (PCOS) have been published.55,72,73 In addition, preliminary studies of metformin use during pregnancy in PCOS have shown normalization of the often high rates of gestational DM and first trimester fetal loss in these women.74–76 Given the importance of insulin resistance as a predictor of diabetes, hypertension and coronary artery disease, metformin is increasingly prescribed to insulin-resistant women with PCOS.77 Studies on NASH are ongoing.

ADVERSE EFFECTS OF CONVENTIONAL METFORMIN THERAPY

These are summarized in Table 2. The most widely publicized adverse effect of biguanide therapy is lactic acidosis.4–6 This is due to stimulatory action of biguanides on non-oxidative glucose metabolism, which results in accelerated conversion of pyruvate to both lactate and acetyl CoA.78 In settings of increased lactate production or reduced lactate clearance, like hepatic or renal dysfunction (including acute renal failure related to administration of radiocontrast dye) or other illness causing tissue hypoxia, especially cardiac or respiratory dysfunction, this action of the biguanides may provoke lactic acidosis, which has a high mortality.79 However, the incidence of lactic acidosis is clearly much greater with phenformin than with metformin, being about 10–15 times higher,4,80–83 and metformin causes little or no rise in plasma lactate levels.11,12,15,40 In addition, data on the incidence of lactic acidosis in diabetic patients not receiving biguanide therapy are lacking. The overall incidence of lactic acidosis with metformin has been estimated at one case per 30 000 patient-years.4,84 MALA Study: The MALA (Metformin Associated Lactic Acidosis) study showed that except elderly and with renal insufficiency (creatinine above >3mg%) it was safe.

The most frequently encountered adverse effects of metformin therapy are gastrointestinal namely, abdominal discomfort, anorexia or diarrhoea initially affects about one-fifth of patients (4% to 5%).75,76 Fortunately, these effects are minimized when administered with meals and with gradual dosage titration,15 and generally necessitate discontinuation of the drug in less than 5% of patients.15,47,56,79,82 Hypoglycaemia is very uncommon with metformin monotherapy11,47 but has been reported in combination regimens,12,59,61 presumably as a function of potentiation.

| Table 2: Conventional metformin adverse effects |
|-----------------|-----------------|
| Common          | Metallic taste  |
|                 | Gastrointestinal (diarrhoea, abdominal discomfort and anorexia) |
| Rare, remote    | Lactic acidosis |
|                 | Reduced serum B12 levels,11,85 |
|                 | Megaloblastic anaemia,86 |
|                 | Leucocytoclastic vasculitis87 |
|                 | Cholestatic jaundice88 |
by metformin of the other therapeutic agent or agents.

**Drug Interaction:** Clinically significant drug interactions involving metformin are rare. The α-glucosidase inhibitor acarbose has been reported to cause a significant reduction in bioavailability and peak plasma levels of metformin when co-administered, however, this did not prevent improvement in HbA1c by 0.65% when acarbose was added to the treatment of patients inadequately controlled on diet plus metformin. Cimetidine reduces renal clearance of metformin.

**Contraindications**

Contraindications are shown in table 3.

Table 3: Contraindications to the use of metformin

| 1. Renal disease* |
| 2. Use of intravenous radiocontrast |
| 3. Any condition predisposing to tissue hypoxia |
| 4. Hepatic disease |
| 5. High alcohol intake |
| 6. Acute or severe cardiac or respiratory dysfunction |
| 7. Severely ill or unstable hospitalized patients (any cause) |
| 8. Patients about to undergo surgery |
| 9. Previous history of lactic acidosis |
| 10. Gastrointestinal disorders causing vomiting or diarrhoea |
| 11. History of allergic reaction to metformin |

*Creatinine >135 mmol/l in men or >110 mmol/l in women; verify normal renal function by calculating creatinine clearance in older patients.

**METFORMIN: THE NEED FOR SUSTAINED RELEASE (XL) FORMULATIONS**

Metformin is usually marketed in the form of its hydrochloride salt. Metformin hydrochloride has intrinsically poor permeability in the lower portion of the gastrointestinal tract leading to absorption almost exclusively in the upper part of the gastrointestinal tract. Its oral bioavailability is in the range of 40 to 60% decreasing with increasing dosage, which suggests some kind of saturable absorption process, or permeability/transit time limited absorption. It also has a very high water solubility (>300 mg/ml at 25°C). This can lead to difficulty in controlling the release of drug that occurs from oral controlled delivery systems. The burst of highly water soluble drug is released from oral controlled delivery systems at the initial rapid release of drug that occurs from oral controlled delivery systems. The burst of highly water soluble drug is released from oral controlled delivery systems at the initial rapid release of drug that occurs from oral controlled delivery systems.

In a controlled release dosage form, the formulator tries to reduce the rate of dissolution by, for example, embedding the drug in a polymeric matrix or surrounding it with a polymeric barrier membrane through which drug must diffuse to be released for absorption. To reduce the rate of release of drug from the dosage form to an appropriate level consistent with the blood level profile desired for a drug possessing very high water solubility, very large amounts of polymer would be required for the matrix or barrier membrane. If the total daily dose of drug to be delivered is of the order of only a few milligrams this may be feasible, but many drugs having the solubility properties described require total daily doses of the order of many hundreds of milligrams. Whilst it is possible to create oral controlled release dosage forms for such products by use of large amounts of polymer, an unacceptably large dosage form may result.

A further problem with highly water soluble drugs formulated into a controlled release dosage form is that a significant and variable “burst” of drug can occur from these systems. The burst of highly water soluble drug is the initial rapid release of drug that occurs from oral...
controlled release dosage forms when first contacting fluid, such as gastric fluids, prior to release controlling mechanisms of the dosage form establishing themselves and a stable release rate being provided. Hydration of any polymer matrix used to formulate the dosage form is a pre-requisite of establishing a stable release rate. Thus, a readily hydrating polymer is required to establish the desired stable release rate. However, if the polymer used is slow to hydrate, then an undesirable variable burst can occur.

Studies by Vidon strongly suggest that there is permeability limited absorption of metformin. Drug will transit down the small intestine following dissolution from an ingested dosage form and, if absorption rate is slow, it is possible that drug can reach regions of poor permeability before absorption of a given dose is complete. In such a case, increasing the given dose may be predicted to result in a reduction in the percentage of administered dose absorbed.

Conventional extended release formulations have been demonstrated to invariably compromise the availability of metformin. This is probably because the dosage form carries a significant proportion of the drug content remaining to be released, as the dosage form is carried to regions of the gastrointestinal tract with very poor permeability to the drug. To reduce dosing frequency, the rate of release from the dosage form must be such as to extend effective plasma levels, but the potential for effective delivery at this rate is compromised by the combined influences of the significant reduction in permeability to the drug in passing from the proximal small intestine down to the colon and the limited residence time in the regions of the gastrointestinal tract where the drug is well absorbed. That transit time down the “useful” region of the gastrointestinal tract is only likely to be of the order of a few hours.

Maintained or even improved bioavailability from an extended release dosage form that releases metformin at a rate likely to provide the desired plasma levels of drug for an extended time period might, however, be possible from a dosage form that has extended residence time in the upper gastrointestinal tract, resisting mechanisms that promote normal transit time for solid materials. That this principle might work in practice was demonstrated in an in-house study where metformin was co-administered with propantheline, an agent that reduces gastrointestinal motility. Compared with giving metformin alone, the combination provided an increased AUC, a delayed t\(_{\text{max}}\) and an extended time period over which therapeutically beneficial plasma levels of drug were maintained.

Giving a drug such as metformin for the treatment of diabetes with a further drug, such as propantheline, not used for the treatment of diabetes and where the sole intent of using the second agent is to achieve extended residence time in the upper GI tract, has many disadvantages although it is likely to allow effective extended delivery of metformin to an optimal absorption site. The co-administered drug may have other undesirable pharmacological effects or side effects deleterious to the patients well being and detract from the improved quality of life offered by the treatment for their diabetes. Furthermore, it may be difficult or impossible to appropriately co-formulate the two agents due to chemical compatibility issues or solubility differences, the latter preventing the required release rate of agent influencing residence time in the upper GI tract. Thus, the patient could be required to take separate, multiple medications to achieve the desired effect. The timing of taking the two medications would be critical to effective delivery of the drug with the limited window of absorption and many patients may thus fail to take their medication correctly resulting in ineffective treatment of their diabetes.

It would be desirable to provide a dosage form that inherently has the property of extended gastric residence, possessing some resistance to the pattern of waves of motility present in the gastrointestinal tract that serve to propel material through it. There have been many attempts to provide for this, with varying degrees of success.

Technologies employed in formulation of controlled release metformin XL none tablets are Wax Matrix, Monolithic devices Gastro retentive Systems: Swellable Matrix devices (soluble & insoluble), and GITS –Laser Based Technology. The wax matrix system has wax granules and beads with coating with hot melt, hard gelatin capsules filled with waxes and change in drug property like polymorphism/recrystallization. The channelizing agents concentration is critical for proper release pH may alter the release pattern of drug. Ghost matrix which passes through feasces. These are not recommended for tropical countries like India though few Indian preparation exist like Glycomet SR where the wax melt can get erratic. The monolithic devices are monolithic systems viz. the bio active agent is incorporated in the polymer phase either in dissolved or in dispersed form. Release is achieved by simple diffusion through the polymer. This is the most common of the devices for controlling the release of drugs, they are relatively easy to fabricate, and there is no danger of an accidental high dosage that caused result from the rupture of the membrane of a reservoir device. The gastroretentives (GRT, GRDF) are based on gastric emptying is naturally phenomenon and can be modified for the sake of drug delivery. The retention in gastric medium can be achieved by modifying drug delivery systems. These are swellable matrix tablets activated by water and drug release control depending on the interactions between water, polymer and drug. The presence of water decreases the glassy-rubbery temperature (glass transition temperature) giving rise to the transformation of glassy polymer in gel phase. These
are mucoadhesive involving alginic acid, sodium CMC, sodium alginate, polycarbophil, polyacrylic acids and need adequate quantity of media required to float the tablets like metaday. These can be packaged as very small size pills. The SR technology is an hydrophilic matrix systems like HPMC based which is GRAS excipient in USA a swellable and erodable matrix and pH independent.

The different drug delivery systems are:
(1) Floating or buoyant systems

These are designed to have a low density and thus should float on gastric contents after administration until the system either disintegrates or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying.

(2) Bioadhesive systems

These are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer.

(3) Swelling and expanding systems

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (for example, less than approximately 23 mm long and less than 11 mm wide for an oval or capsule-shaped tablet). On ingestion they rapidly swell or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree.

The distinct advantages of Metformin XL are it reduces the number of daily doses and increases patient compliance. Metformin XL, being a modified release preparation can also avoid “dose-loading”. This commonly occurs with conventional oral formulations when large doses are given which may cause sudden release and absorption of a large amount of drug. Metformin XL is released in smaller doses in upper part of the small intestine, and hence ensures increased bioavailability and decreased side effects. In contrast, conventional Metformin has less bioavailability since its absorption decreases as it passes through the lower part of small intestine. Conventional Metformin has an oral bioavailability of 40 to 60 % and gastrointestinal absorption is apparently complete within 6 hours of ingestion. Plasma t ½ is 2 to 6 hours. Hence it has to be given 2 to 3 times a day, whereas Metformin XL being a controlled release “gastro-retentive” formulation, is released in small quantities in upper part of small intestine where the drug is better absorbed and has a prolonged duration of action (24 hours). Metformin XL- the absorption is more dependable and complete as the drug is released gradually mainly in the upper part of small intestine, whereas in Metformin plain the absorption is erratic as Metformin is also absorbed in the latter part of small intestine where absorption is erratic and “non-dependable”. Since Metformin XL is released slowly, side effects like flatulence, abdominal discomfort, diarrhoea and lactic acidosis are less unlike plain Metformin. An inverse relationship was observed between the dose ingested and relative absorption with therapeutic doses ranging from 0.5 to 1.5 gms suggesting the involvement of an active, saturable absorption process. Thus an extended release formulation of Metformin can not only optimizes the daily requirement of Metformin, but can also reduce the need of a higher dose. The bioequivalence study as per US FDA are required to be compared with Glucophage and Metaday (Fig. 1) while the plain and ‘XL’ comparisons are made in Fig. 2 and Fig. 3.

Metformin XL is a modified release gastro-retentive formulation. By virtue of its gastro-retentive property it releases Metformin gradually in small amounts, which is well absorbed in the upper part of the small intestine and duodenum. Metformin incorporated into the gastro-retentive formulation is released slowly over a prolonged period of 24 hours; hence given once a day. Other then release technology which improves availability of active drug, what is important is also size of the tablet. Currently there are some brands that are large in size making it difficult for the patient to swallow while the newer ones like Metaday™, the size of the tablet is very small making it the more patient friendly.

METFORMIN MONOTHERAPY IN CLINICAL PRACTICE: WHEN TO START?

In head-to-head clinical trials, metformin and TZD
monotherapy as oral agent naive subjects achieved comparable benefits in glycaemic control and hepatic glucose uptake, both improved indices of peripheral insulin sensitivity, consistent with their differing mechanism of action. But in these trials, metformin use was associated with weight loss while the TZDs were associated with mild weight gain or stable weight. Another factor to consider in choosing a TZD vs. metformin is the need to regularly monitor liver-function tests. The majority of patients with type 2 DM are >190% of ideal body weight and exhibit a fasting glucose less than 250 mg% (14 mmol/l) when drug therapy is initiated, and metformin is currently the drug of choice for this group, for considerations of efficacy, cost, frequency of monitoring for adverse effects, and associated beneficial metabolic actions; if not contraindicated. If a patient is to receive radiocontrast dye, metformin should be discontinued prior to the procedure and not restarted until laboratory evidence of normal renal function is obtained 48 h late, often N-acetyl cysteine may co-administered.

It is important to initiate metformin therapy slowly, as this may markedly improve patient acceptability and minimize gastrointestinal side effects. A dose–response study showed that 2000 mg daily is the most effective dose of metformin (HbA1c lowered 2% compared to placebo), best given as 1000 mg with breakfast and dinner to facilitate compliance with therapy. The current XL formulations of 500 mg, 1000 mg have obviated this need with better bioequivalence.

For this reason, sulfonylureas be administered with metformin when immediate high-dose oral agent therapy is required in symptomatic patients with marked hyperglycaemia. Additionally, in this setting, avoidance of sulfonylurea-induced hypoglycaemia is a less immediate concern, and the short-term potential for metabolic decompensation to hyperosmolar non-ketotic syndrome is greater.

**PLACE OF METFORMIN IN COMBINATION THERAPY**

**With Sulfonylurea (SU):** Hitherto, when employed as part of a combined therapeutic regimen, metformin has been most frequently used in combination with sulfonylureas. In patients already on maximal sulfonylurea dosage in whom glycaemic control remains unsatisfactory, metformin therapy can be initiated in the same manner as for monotherapy. Dosage titration should be gradual, because the tendency of sulfonylureas to cause hypoglycaemia may re-emerge when metformin is added. Combination of metformin with sulfonylureas does not generally result in weight gain. Conversely, sulfonylureas may be added when glycaemic control is suboptimal with metformin alone. Most patients remain on maximal dosage of sulfonylurea when metformin is added, or vice versa. The ideal time to add is when 50 mg% of the pharmacological does not combined metformin and repaglinide therapy has been shown to produce superior glycaemic control to monotherapy with metformin or repaglinide in subjects with poorly controlled type 2 DM (1.4% HbA1c vs. no significant change on monotherapy). An open-label, randomized, multicentre trial found significantly greater reductions in HbA1c and fasting glucose with repaglinide plus metformin (1.28% and 2.2 mmol/l) than with nateglinide plus metformin (0.67% and 1.2 mmol/l). Combination therapy may allow a number of patients to avoid the need to switch from oral agent to insulin therapy.

**With TZD:** Because metformin’s insulin-sensitizing effect occurs mainly at the liver, combination with TZDs, which mainly sensitize muscle to insulin-mediated glucose uptake, is a rational therapeutic strategy. The

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**Table 4 : Currently available formulations containing metformin**

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<thead>
<tr>
<th>Formulation</th>
<th>Available Doses</th>
<th>Comments</th>
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<tr>
<td>Metformin (plain; Glyciphage; oral solution : Riomet)</td>
<td>500 mg, 850 mg, 1000 mg; oral solution: 500 m/5 ml</td>
<td>Start 250-500 mg po qd or 850 mg po bid, increase by 500 mg/day q 1-2 week. Maximum 3000 mg/day</td>
</tr>
<tr>
<td>Metformin XL (Metaday 1000, Glyciphage SR, Biogomet SR, Di beta SR, Riomet OD etc)</td>
<td>500 mg, 1000 mg</td>
<td>Start 500 mg qpm, increase by 500 mg/day q week. Maximum 2000 mg/day</td>
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FPG, fasting plasma glucose; po, by mouth; qd, every day; bid, twice a day; q, every, qpm, every evening.

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first study to address this showed that metformin and the TZD troglitazone had an additive effect on glycaemic control in subjects with type 2 DM;\textsuperscript{102} however, troglitazone is no longer available. More recently, patients poorly controlled on metformin monotherapy were randomized to metformin plus placebo or metformin plus pioglitazone 30 mg daily; patients in the latter group attained greater reduction in fasting plasma glucose 40 mg\% (2.1 mmol/l) and HbA1c levels (0.83\%), as well as greater improvements in triglycerides (18.2\%) and HDL-cholesterol (8.7\%).\textsuperscript{103} Several randomized, placebo-controlled, double-blind trials of the addition of glitazone to the regimen of patients poorly controlled on metformin monotherapy consistently demonstrated improved glycaemic control on the combination therapy (0.7–1.2\% reduction in HbA1c), as well as improvements in insulin sensitivity and beta-cell function.\textsuperscript{50,104,105} Thus, combined treatment of patients poorly controlled on metformin in subjects failing sulfonylurea therapy and compared addition of pioglitazone to addition of metformin and TZD therapy is a safe and efficacious method of improving glycaemic control, without hyperinsulinaemia or significant hypoglycaemia. As monotherapy metformin is associated with weight loss and TZDs with weight gain, in combination, no change or slight weight gain (3 kg) was observed in clinical trials. Nevertheless, some experts favour a combination of insulin sensitizer plus insulin secretagogue to address both the fundamental metabolic defects present in type 2 DM.\textsuperscript{106}

Since last decade, preparations of metformin in fixed-dose combination with glibenclamide, gliclazide, glimepiride, pioglitazone and rosiglitazone have become available in the India. While compliance may be expected to be greater with a combination preparation, flexibility of dosing the individual components is necessarily limited. Metformin can be used in combination with insulin, in which case, metformin has an ‘insulin-sparing’ effect, permitting about a 15–25\% reduction in total daily insulin dosage.\textsuperscript{56,107,108} This property is of particular usefulness in patients on large doses of insulin, whose insulin dosage may otherwise exceed the capacity of a single syringe, necessitating a second injection at a given time. There is experimental evidence to suggest that such a reduction in insulin dosage may attenuate possible atherogenic effects of high circulating insulin concentrations.\textsuperscript{109}

The question of which insulin sensitizer (metformin or TZD) to add to patients failing sulfonylurea therapy has been addressed in many clinical trials. One trial randomized patients failing sulfonylurea therapy to 4 mg rosiglitazone or 1 g metformin and found comparable HbA\textsubscript{c} lowering of approximately 1\%.\textsuperscript{110} Two trials have compared addition of pioglitazone to addition of metformin in subjects failing sulfonylurea therapy and also found comparable effects on HbA\textsubscript{c} (1.20 to 1.36\%).\textsuperscript{111,112} The longer trial (1 year) demonstrated improvements in triglycerides, HDL-cholesterol and urinary albumin-to-creatinine ratio with pioglitazone and decreased LDL-cholesterol with metformin.\textsuperscript{111} More such studies, using currently available TZDs, are needed to address which class of insulin sensitizer, if any, is preferable in combination therapy with sulfonylureas. In terms of addition to patients failing insulin therapy, in one study, troglitazone addition resulted in better glycaemic control and lower triglyceride levels while metformin addition resulted in less weight gain (0.5 vs. 4.4 kg) and less hypoglycaemia.\textsuperscript{113} This emphasizes the need to individualize therapy according to each patient’s needs.

**Conclusions**

Metformin has been an ideal therapeutic option available for the patient with type 2 DM. In monotherapy, metformin will often achieve a significant reduction in glycaemia, with ancillary benefits of weight reduction and improvement in the lipid profile, and possibly secondary markers of atherogenesis and endothelial function; without hypoglycaemia. In combination therapy, it has an important place in obviating the need for insulin therapy in patients inadequately controlled on insulin secretagogues or TZDs alone and, in selected patients, may be used in combination with insulin for its ‘insulin-sparing’ properties. When used appropriately and with gradual upward adjustment of dosage, adverse effects of metformin are rarely troublesome, nor are they dangerous. Patient compliance with metformin has increased with the availability of long acting preparations. Moreover GI side effects associated with regular metformin therapy is also reduced significantly with metformin long acting preparations. Small size and improved release technology has evolved the therapy of metformin. Thus, despite the appearance of several new oral agents in recent years, metformin still is used as a therapeutic agent of first choice for monotherapy of the typical overweight patient with type 2 DM and low risk of metabolic acidosis who exhibits mild to moderate hyperglycaemia, and as adjunctive therapy for patients poorly controlled on sulfonylureas or TZDs. Newer sustained release formulation like ‘XL’ technology have obviated the need for GE side effects and better bioequivalence. With the current sustained release (XL) formulation of metformin, metformin therapy has now upgraded itself from the Gold Standard to Platinum. These unique XL bioequivalent metformin preparations will become the platinum standards in modern diabetes management.

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