

A chronic and incurable disorder biology essay

[Science](#), [Biology](#)



Diabetes mellitus is a chronic and incurable disorder existing in approximately 2.6 million diagnosed individuals in the United Kingdom and approximately 2.3 million are diagnosed with the type 2 diabetes. The first line management of type 2 diabetes in U. K. is with oral metformin therapy in suitable patients 1. Metformin is a biguanide oral antidiabetic drug with various proposed mechanisms of action 2. Metformin was first synthesized by Werner and Belly at Trinity College, Ireland, in 1922 and on basis of which, several experimental and clinical studies were performed. A French clinician Dr. Jean Sterne and his colleagues discovered metformin as an oral antidiabetic agent in 1950s 3. File: Metformin. svg*Structure of Metformin⁴The above structure represents Metformin (N-1, 1-dimethylbiguanide) which is structurally similar to phenformin. Out of the various proposed theories, the most common hypothesis for its mechanism of action is its inhibitory activity on hepatic glucose output. In addition to that, it has been proven that it also augments glucose oxidation, inhibits fatty acid oxidation leading to reduction in plasma glucose concentration, and also reduces rate of glucose absorption in intestines 4. Metformin also potentiates the insulin action at intracellular locus and decreases the glucose production from liver by gluconeogenesis and glycogenolysis. It increases the tissue uptake of glucose and reduces the gastro-intestinal absorption of carbohydrate. Metformin does not cause weight gain, hence is particularly useful in obese patients. It should be ideally used in conjunction with diet and physical exercise to reduce blood glucose level 1. Metformin is now considered as the first line therapy for people diagnosed with type 2 diabetes and this is supported by evidence based guidelines of UK National

Institute of Clinical Excellence. Initiating therapy with metformin has been proven to decrease the adverse effects associated with type 2 diabetes 5. It has also been found that it is effective in preventing the onset of diabetes in patients with impaired glucose tolerance and impaired fasting glucose 6.*Metformin structure was drawn with ChemDraw™ software. Analysis of numerous clinical trials data between the periods of 1966 to 2003 confirmed that metformin effectively inhibits hepatic glucose release and has shown to reduce glycosylated haemoglobin efficiently. Fasting blood glucose (FBG) was reduced with metformin only therapy in 10 placebo controlled studies, the FBG concentrations reduced by 2.0 mmol/L compared to placebo (95% CI, -2.4 to -1.7) and the HbA1c values decreased by 0.9 percentage points (95% CI, -1.1 to -0.7) 4 and 7. Microvascular and macrovascular diseases are responsible for most of the morbidity and mortality related to diabetes. Cardiovascular disease or stroke causes approximately 80% of those deaths in type 2 diabetes. Metformin therapy has an additional benefit as it leads to a significant risk reduction of macrovascular and microvascular disorders caused due to uncontrolled glycemic levels. It has also been shown to improve dyslipidemia and also reduces triglyceride levels 4. Metformin is available under many different brand names. Glucophage is the most common brand of metformin. Others include Actoplus Met, Apo-Metformin, Fortamet Extended release Tablets, Riomet, Glumetza, Obimet. Actoplus Met is a combination product of two different oral antidiabetic medicines metformin and pioglitazone. This includes prolonged release form of metformin with pioglitazone. Metformin helps to reduce the amount of glucose production in liver and pioglitazone targets insulin resistance 1.

Fortamet brand contains 1000mg metformin in extended release form. Riomet is the brand name of the metformin HCl oral solution; 5ml of oral solution contains 500mg Metformin. Glumetza is a prolonged release tablet formulation, while Obimet contains 500mg or 1000mg of metformin in tablet formulation. In a clinical study, it was found that the glycemic control achieved with a twice daily dosage of immediate release metformin formulation was same as the one achieved with a once daily dosage of extended release metformin formulation 8. This gives a considerable disadvantage to normal metformin formulations as increased dosage frequency will lead to lower adherence levels. It also proves to be suitable in patients where the gastrointestinal side effects cause a tolerability issue and a once daily regimen can increase the tolerability and thus the adherence. There are many drugs from different classes that are available for the treatment of type-2 diabetes. The different classes include biguanides, sulphonylurea, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, incretin mimetics and insulin. Metformin is the only available drug in the UK from biguanide class, since phenformin and buformin were withdrawn from the market because of death related to lactic acidosis. Lactic acidosis occurs very rarely with the use of metformin; about 0.0005% of cases can be observed with this complication while on treatment with metformin 1. Sulphonylureas include tolbutamide, chlorpropamide, glibenclamide, glipizide, gliclazide and glimepride. The drugs of this class decrease the blood sugar level by increasing the β -cell sensitivity to glucose, resulting in more insulin secretion from storage granules. It means these drugs have to rely on the ability of the pancreas and functioning of β -cell to

secret insulin. In case of metformin, it does not involve the stimulation of insulin secretion from pancreas; hence it also works when β -cells are not functioning appropriately. Unlike sulphonylureas, metformin does not cause hypoglycaemia and is not accompanied with weight gain ¹. Repaglinide and nateglinide are the drugs from meglitinides class. Research data shows that meglitinides have similar potency to metformin and may be useful when side effects from metformin are not tolerable. However, weight gain is associated with the use of meglitinides ⁹. Pioglitazone is the drug from thiazolidinediones class; clinical trials show that pioglitazone reduces the insulin resistance comparatively more than metformin ¹⁰ and ¹¹ and thiazolidinediones promotes peripheral glucose uptake ¹². Both drugs are well tolerated. However, edema is associated with the use of pioglitazone. Pioglitazone enhances the insulin sensitivity and stimulates glucose uptake and utilization in peripheral tissues. It can be used as an alternative to metformin for the first line treatment of type-2 diabetes ¹⁰. Sitagliptin comes under the category of dipeptidyl peptidase-4 inhibitor. Research analysis describes that treatment of type-2 diabetes with sitagliptin improves the measures of β -cell functions and is well tolerated as that with metformin ¹³ and ¹⁴. Also, a lower incidence of gastrointestinal side effects was observed with the use of sitagliptin ¹³. Clinical evidence shows that in type-2 diabetic patients, initial treatment with combination of metformin and sitagliptin provides substantial glycemic control ¹⁵. Clinical trials show that excellent glycemic control can be achieved with the use of insulin in the treatment of type-2 diabetes. However, weight gain and hypoglycemia are the most common side effects of insulin ¹⁶. In addition, insulin requires special device

for administration and specific storage condition. Also, patient has to be trained for the appropriate use of insulin device. Systematic review of oral medications for the treatment of type-2 diabetes shows that in comparison to newer and more expensive agents like thiazolidinediones, α -glucosidase inhibitors and meglitinides, metformin and second generation sulphonylureas have equal or greater effect on glycemic control 17. In addition, cost-effectiveness analysis shows that metformin is cost-saving and prolongs life expectancy when used as the first line treatment in overweight type-2 diabetic patients 18. However, metformin is highly associated with the adverse effects related to gastro-intestinal (GI) disturbances. A third of patients face these side effects, which include anorexia, nausea, abdominal discomfort and diarrhea 1. There is potential risk of vitamin B12 and folic acid deficiency in long term treatment with metformin. About 3%-11% patients complain of metallic taste. Lactic acidosis is the most clinically significant side effect, although the incidence of which is very low as previously mentioned. Hence, metformin is contraindicated in patients having compromised renal function, COPD and severe liver dysfunction due to the risk of lactic acidosis 4. Absolute oral bioavailability of metformin is 40% to 60%. Absorption occurs in upper intestine which is completed in 6 hours and the peak plasma concentration is reached in 2 to 3 hours. Metabolism of metformin is negligible and $t_{1/2}$ is reached within 2 to 6 hours 4. Several studies have exposed the role of metformin in different pathologies. United Kingdom Prospective Diabetic Study has detected its benefits in a large group of individuals. Metformin is also prescribed for the treatment of obesity and polycystic ovarian syndrome in unlicensed manner.

Metformin has shown positive role in lipid disorders. Previous experiments have revealed that metformin decreases cholesterol, plasma triglycerides, low density lipoproteins, platelet aggregation, C-reactive protein and body weight 2. Study shows that metformin is more potent than vitamin E for the treatment of non-alcoholic fatty liver disease. Metformin inhibits the accumulation of fat in liver by increasing the β -oxidation of free fatty acid and by decreasing their synthesis 2. Metformin also delays aging and is effective in aging related disorder. Experiments on lower animals have shown its efficacy as an anti-aging drug molecule. Several experimental studies have proved that there is a link between reduced cancer risk and use of metformin. Recently, research analysis discovered significant reduction in inflammatory cytokines like tumor necrosis factor- α , interleukin-1 β , interleukin-6, interleukin-18, MCP-1 and leptin in rats which were treated with metformin. This described that metformin can be used in the treatment of uveitis 2. From all the points which are discussed, it is clear that metformin is an extraordinarily useful drug molecule among many for the treatment of type-2 diabetes. Although one of the prominent reasons amongst patients that causes non-adherence towards metformin is the gastric side effects. If a transdermal formulation that avoids first pass metabolism is introduced, then it may not cause any of the gastric side effects and the patient adherence will further increase. Currently there are no such metformin products in the market other than those administered via oral route. Since metformin has a low bio-availability due to first pass metabolism, the dosage is high and frequent. Drugs with short half-life, which undergo first pass metabolism, which need frequent oral dosing and

associated with side effects and poor patient compliance are excellent candidates for transdermal delivery ²⁰. Hence if a transdermal patch is introduced, efficacy similar to oral delivery can be achieved with low and less frequent doses ²¹. The low dose reduces the risk of lactic acidosis even further. In a recent study done, a matrix type transdermal patch was developed and it showed promising results with a 95.89% drug release in 24 hours ²². Another study also showed a positive result of 96.92% drug release from the patch in 24 hours. It also confirmed absence of interaction between the drug and polymers of the patch ²³. These studies confirm that the development of a transdermal drug delivery for metformin is possible and can successfully increase adherence in patients who are sensitive to gastric side effects of oral metformin. However, a patch would have a disadvantage of cost when compared to an oral tablet. Another disadvantage depending on the materials used would be skin sensitivity issues. But if a patch with a controlled release profile lasting for at least few weeks is developed, then it has a greater potential in the current market. Another advantage would be a better controlled glycemic index compared to oral metformin therapy wherein patients might forget to take their tablets regularly. Since metformin caused diarrhea will decrease contact time of any drug to be absorbed via intestine, use of patches will offer better bioavailability profile for other oral medications, especially in patients with co-morbidities. Overall, metformin as an oral tablet is a successful therapy on its own or in combination with other agents for the management of type 2 diabetes. It has shown multiple benefits, it efficiently decreases HbA1c levels, triglyceride levels and reduces the risk of microvascular and

macrovascular diseases. Adverse effects of metformin are tolerable in most patients but a need to avoid the gastric side effects of oral metformin could be met by developing a transdermal patch.