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# Current Approaches for the Treatment of Hyperglycaemia

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## ABSTRACT

Hyperglycemia can be a serious problem if untreated in time. Chronic hyperglycemia that persists even in fasting states is most commonly caused by diabetes mellitus, and in fact chronic hyperglycemia is the defining characteristic of the disease. Diabetes mellitus is the only non-infectious disease designated as an epidemic by the world health organization. This could have long lasting adverse effects on nation´s health and economic, especially for developing countries. the international diabetes federation(IDF) estimates the total number of people in India with diabetes to be around 50.8 million in 2010, rising to 87.0 million by 2030. The primary goal in the management of diabetes mellitus is the maintenance of blood glucose level. Therefore, there is an urgent need to develop novel therapeutic agents without the development and progression of complications or compromising on safety. The present review provides an approach for the safe and effective treatment of diabetes mellitus.

**Keyword:** Hyperglycemia, Hypoglycemic agents, PPARs

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# INTRODUCTION

Hyperglycemia (high blood sugar) is seen characteristically in diabetes mellitus. In diabetes, there is a deficiency of the function of insulin, the principal hormone that controls the blood levels of glucose, leading to persistent high levels of glucose in the blood, also known as hyperglycemia[1]. According to the National Institutes of Health **(**NIH), persistently high levels of glucose can lead to serious complications involving vital organs like the brain, heart, eyes and kidneys. Lifestyle modifications and, where necessary, medications are used to lower the blood levels of glucose in diabetic patients. The united kingdom prospective diabetes study(UKPDS), a long term study of diabetes, has shown that rigorous management of blood glucose levels(measured as glycosylated) and blood pressure substantially reduce the incidence of complications[2,3]. The current therapeutic strategies for diabetes are very limited, and involve insulin therapy and oral hypoglycemic agents such as sulphonylureas, biguanides and the thiazolidinediones. Combination therapy with one or more of these agents is now a viable option as target blood glucose levels become harder to maintain with monotherapy. While a wide variety of therapeutic approaches are now being examined for diabetes, these can generally be classified in one of the following categories[4-9].

**Various ways for the treatment of diabetes mellitus**

Timely initiation of insulin therapy, either as monotherapy or in combination with other agents, can establish good glycemic control in a majority of diabetic patients. A non-peptidyl fungal metabolite which have been shown to selectively activate the insulin receptor in vitro, and oral administration of this agent showed a 40% lowering of blood glucose when administered orally for 7 days. The mechanism of action of the agents likely involves intracellular activation of the insulin receptor tyrosine kinase(IRTK)[2-4].

**Agents which effect the secretion of insulin**

**Sulfonylureas (SUs)**:

It is remain a front line treatment for diabetic patient.SUs stimulate insulin release from pancreatic β-cells by a mechanism that involves blocking ATP-sensitive potassium channels. Common side effects of SU therapy include hypoglycemia, as their action may occur at times when insulin is not required, and weight gain. Prolonged treatment with SUs also exacerbates β-cell exhaustion through over-stimulation of insulin production.SU therapy is not effective when insulin receptor levels decline too far[6-9].

**Glucagon-like peptide-1(GLP-1):**

It is derived from the transcription product of the proglucagon gene. The major source of GLP-1 in the body is the intestinal L cell that secretes GLP-1 as a gut hormone and increases insulin secretion from the pancreas in a glucose-dependent manner. GLP-1 secretion by ileal L cells is dependent on the presence of nutrients in the lumen of the small intestine. The secretagogues (agents that cause or stimulate secretion) of this hormone include major nutrients like carbohydrate, protein and lipid. Now days DPP-4 inhibitors are play important role in glucose metabolism. It is responsible for the activation of incretins such as GLP-1. Long-term effects of DPP-4 inhibitors are nasopharyngitis (the common cold), headache, nausea, hypersensitivity and skin reactions, observed in clinical studies. Consistent with this FDA approval of Novartis' DPP-4 inhibitor vildagliptin was delayed because of skin lesions with blistering observed in nonhuman primate toxicology studies[6-9].

**Agents which effect the hepatic glucose production**

Excessive hepatic glucose production (HGP) is a significant contributor to diabetic hyperglycemia. Methods for the inhibition of HGP are becoming an important strategy for control of blood glucose levels.

**Biguanides:**

It can refer to a molecule, or to a class of drugs based upon this molecule. Biguanides can function as oral antihyperglycemic drugs used for diabetes mellitus. It interferes with several processes linked to HGP,lowering glucose production and resensitizing the liver to insulin. Precise molecular mechanism of action of the biguanides continue to be a subject of intense interest and has been reviewed extensively. The most important and serious side effect is lactic acidosis, therefore metformin is contraindicated in renal insufficiency. Renal functions should be assessed before starting metformin. Phenformin and buformin are more prone to cause acidosis than metformin; therefore they have been practically replaced by it. However, when metformin is combined with other drugs (combination therapy), hypoglycemia and other side effects are possible.new studies have described the effectiveness of combination therapy using metformin and other oral hypoglycemic agents for the maintenance of blood glucose levels[6-10]

**Agents which enhance the insulin action**

**Peroxisome proliferator activated receptors (PPARs)**:

PPARs are associated with diabetes and obesity, has recently been implicated in the transcriptional control of a wide variety of cellular processes. This is one of the most promising targets discovered as peroxisome proliferator activated receptors (PPAR) which are a superfamily belonging to the nuclear hormone receptors, which are ligand activated transcription

factors that play a key role in the regulation of the metabolism of lipids and carbohydrates. In addition, it has been discovered that PPAR's also play a key role in satiety induction and ingestion control and corporal fat modulation, as well as in the treatment and prevention of hyperglycemia and cardiovascular diseases such as rosiglitazone, pioglitazone and englitazone.

Investigation of the family of nuclear receptors PPAR-α,β and γ remains a highly active area of research in the diabetes field and was recently reviewed in annual reports in Medicinal Chemistry.most advanced are the PPAR-γ agonists balaglitazone 7(Dr. Reddy Lab/Novo Nordisk, Phase II) rivoglitazone 6 (Sankyo,Phase II), and R483(Roche/Chugai,Phase II). PPAR-γ agonists promote adipocyte differentiation and consequently cause weight as a side effect. In attempts to minimize this side effect, there is interest in developing dual acting PPAR-α, and γ co-activators which could be expected to simultaneously promote fatty acid oxidation and adipocyte differentiation. Tesaglitazar (Astra Zeneca) is in Phase III clinical development, and three other candidates with dual PPAR-α, and γ co-activators are in Phase II clinical development[11-31].

**Table 1: The tabular representation of hypoglycemic agents**

| S.No | Agent | Mechanism | Site of action | Way better than other | Adverse effects |
|---|---|---|---|---|---|
| 1 | Non-peptidyl fungal metabolite | Insulin receptor tyrosine kinas | Insulin receptor | Good glycemic control | Hypoglycaemia |
| 2 | Sulphonylureas | Blocking ATP-sensitive potassium channels | Pancreatic β-cells | Front line treatment for diabetic patient | Hypoglycemia, Weight gain |
| 3 | DPP-4 inhibitors | Activation of incretins such as GLP-1 | Lumen of the small intestine | Nutrients dependent action | Nasopharyngitis, Hypersensitivity |
| 4 | Bigunides | Resensitizing the liver to insulin | Liver | Does not cause hypoglycemia | Lactic acidosis |
| 5 | PPARs | Insulin sensitizers | Skeleton,fatty tissues | Does not cause hypoglycemia, Lactic acidosis | Not reported specific toxicity |
| 6 | Glucosidase inhibitors | Reduces intestinal glucose absorption | GI tract | Low risk | abdominal cramping, flatulence |
| 7 | SGLT inhibitors* | Renal re-absorption of glucose | Proximal tubule of kidney | Could be beneficial for obese patient | Electrolyte abnormalities |

*Safety and efficacy under clinical trial

**Agents which inhibits the glucose uptake**

Alpha-glucosidase inhibitors are "diabetes pills" but not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or sensitivity. These agents slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly, and can be matched more effectively by an impaired insulin response or sensitivity.

**Glucosidase inhibitors:**

Inhibition of intestinal α-glucosidases inhibits the breakdown of oligo and disaccharides from dietary complex carbohydrates and thus slows the absorption of glucose. Clnical data with acarbose has been reviewed and acarbose was shown to decrease $HbA_{1c}$ by 0.78% versus placebo[6-7].

**Sodium-glucose transporter (SGLT) inhibitors:**

Both intestinal absorption and renal re-absorption of glucose are mediated by SGLTs. Three isoforms, SGLT-1,SGLT-2 and SGLT-3, have been reported to date. The sodium-glucose co-transporter-2 (SGLT2) is a low-affinity transport system that is specifically expressed in the kidney and plays an important role in renal glucose reabsorption in the proximal tubule. Competitive inhibition of SGLT2 therefore represents an innovative therapeutic strategy for the treatment of hyperglycaemia and/or obesity in patients with type 1 or type 2 diabetes by enhancing glucose and energy loss through the urine. The preclinical and limited clinical data available to characterize the efficacy, safety and potential clinical utility of SGLT2 inhibitors in the management of diabetes[32].

## CONCLUSION

Diabetes mellitus has increased in incidence as lifestyles involving excessive calorie intake and lack of exercise have become more prevalent. The basic management of type 2 diabetes mellitus involves controlling the energy balance of the body by dietary means and by increasing exercise levels, and there is a lack of drugs that can be used to control energy balance in a negative direction. Thus, an hypoglycaemic agent that does this would represent a new approach to the treatment of diabetes mellitus.Treatment goals for hyperglycemia are to control the situation in a way that minimizes symptoms and help them to maintain normal blood glucose levels. Many new, exciting therapeutic strategies are being explored to treat diabetes. Among them PPAR modulators are now days consider first line therapy in diabetes, reason could be effective insulin

sensitizers along with better for diabetic associated problems and having minimum adverse effects.

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