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Sitagliptin + Glimepiride + Metformin: Monograph

Overview of current trends related to type 2 diabetes

Introduction

Diabetes is defined by the World Health Organisation (WHO) as "a metabolic disorder of multiple aetiologies characterized by chronic hyperglycaemia with disturbance of carbohydrate, fat, and protein metabolism due to defects in insulin secretion or insulin action".[1]

Type 2 Diabetes (T2D) is the most common and clinically significant metabolic disorder which has become a global pandemic and a significant health burden worldwide in recent decades.[1] There is relative insulin deficiency due to pancreatic β-cell dysfunction and insulin resistance in target organs.[2] Type 2 diabetics are more likely to suffer short- and long-term complications, which often lead to their premature death.[3]

Diabetes mellitus: A growing burden

It was estimated that 90% diabetes patients are diagnosed with type 2 the majority of the remaining 10% of patients have type 1 diabetes (T1D)[1]

Diabetes affects more than 537 million individuals across the globe and is one of the leading causes of death worldwide.[4] **Figure 1**

Globally, the number of people with diabetes was estimated to be 285, 366, 382, 415 and 425 million in the years 2009, 2011, 2013, 2015 and 2017.[1]

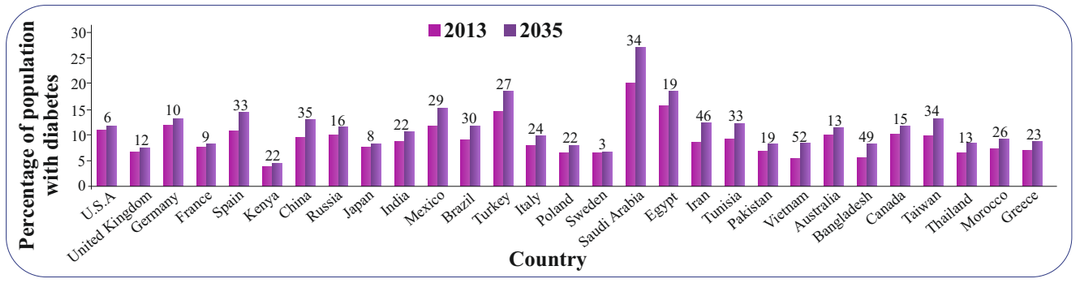


Figure 1: The varying estimated prevalence of T2D in 2013 and projections for 2035, between ages 20–79 years.[1]

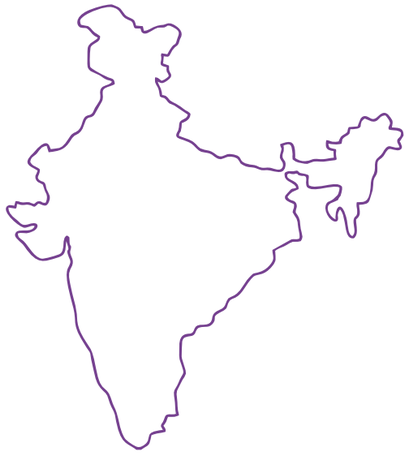
Indian scenario from International Diabetes Federation (IDF)-2021 10th edition

In India, the burden of diabetes has been increasing steadily since 1990 and has been increasing at a faster pace from the year 2000.[6]

The largest nationally representative survey on diabetes and prediabetes was undertaken in India by the Indian Council of Medical Research (ICMR), and included data of individuals aged 20 years and older drawn from urban and rural areas of 31 states, union territories, and the National Capital Territory of India.[6] (Table 1)

The overall weighted prevalence of diabetes by OGTT was 11·4%

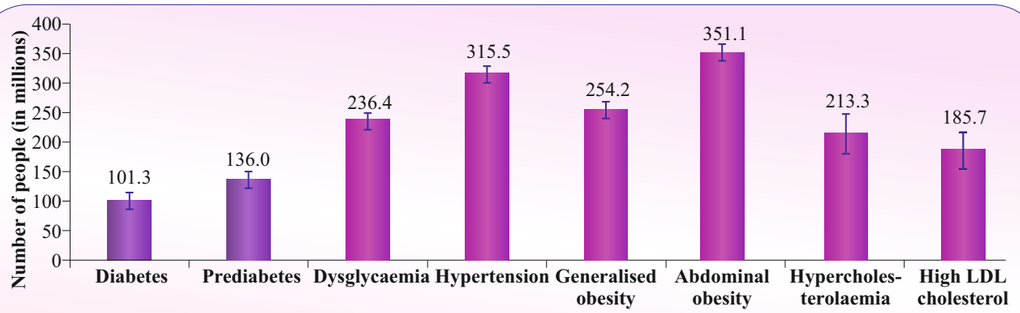
Significantly higher prevalence in urban compared with rural areas (urban areas 16·4% vs rural areas 8·9% ($p<0·0001$).



- Accounts for 1 in 7 of all adults living with diabetes worldwide[5]
- Ranks 2nd amongst the highest number of people with undiagnosed diabetes[5]
- Ranks 3rd amongst the highest annual number of deaths from diabetes[5]

Significantly higher prevalence in among males compared with females **(males 12·1% vs females 10·7% (p<0.0001).**

Table 1: Weighted prevalence of diabetes and prediabetes in 31 states/Union territory of India - the ICMR INDIAB Study.[6]



	Projections (in millions)	95% CI
Diabetes	101·3	90·7-111·1
Prediabetes	136·0	123·5-147·5
Dysglycaemia	236·4	222·2-251·5
Hypertension	315·5	300·4-331·5

	Projections (in millions)	95% CI
Generalised obesity	254·2	239·1-269·3
Abdominal obesity	351·1	335·1-367·9
Hypercholesterolaemia	213·3	179·5-247·1
High LDL cholesterol	185·7	153·8-217·7

Projections for metabolic disease prevalence in india

India has the 2nd largest number **(101.3 Million)** of people with diabetes in the world[4,6]

1/4th achieve glycaemic targets, and even less achieve blood pressure control targets[4]

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Pathophysiology of diabetes

The two major metabolic abnormalities, insulin resistance and insulin deficiency, contribute to hyperglycaemia and result from both genetic and environmental factors. Type 2 diabetic individuals are also characterised by reduced β-cell mass likely due to increased cellular apoptosis.[7] **Figure 2**

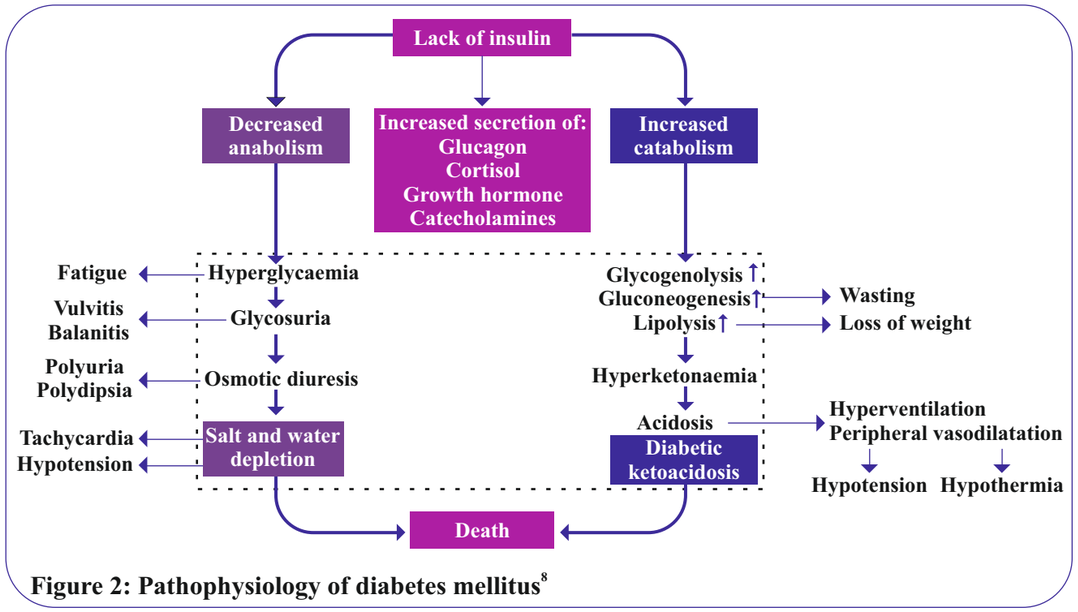


Figure 2: Pathophysiology of diabetes mellitus[8]

The pathophysiological mechanisms include:[9]

- Reduced insulin secretion from pancreatic β cells
- Increased glucagon secretion from pancreatic α cells
- Increased hepatic glucose production
- Neurotransmitter dysfunction and insulin resistance in the brain

- Increased lipolysis
- Increased renal glucose reabsorption
- Reduced incretin effect in the small intestine
- Reduced glucose uptake in peripheral tissues such as skeletal muscle, liver and adipose tissue

Hyperglycemia alone can impair pancreatic β-cell function and contributes to impaired insulin secretion.[10]

A vicious cycle of hyperglycemia leading to an impaired metabolic state[10]

β-cell dysfunction occurs quite early and rapidly in Asian Indians[11]

Due to the progressive decline in β-cell function, oral anti-diabetic drugs (OADs) can lose efficacy with prolonged use and a progression from monotherapy to combination (dual or triple) therapies may be necessary[11]

Asian Indian phenotype has been associated with high levels of abdominal fat and insulin resistance even at low levels of body mass index (BMI), which is thought to be a factor for their increased tendency to develop type 2 diabetes.[11]

Type 2 diabetes in Asian Indians appears to have a slightly different pathophysiology, with severe insulin deficiency.[11]

Asian Indian population with type 2 diabetes are classified into **four phenotype** clusters with important implications for prognosis and management.[11]

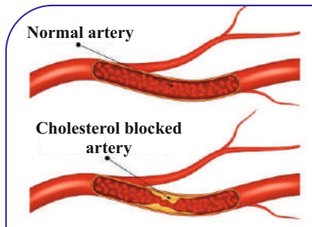
- **CIRDD:** Combined Insulin Resistant and Deficient Diabetes
- **IROD:** Insulin Resistant Obese Diabetes
- **MARD:** Mild Age-Related Diabetes
- **SIDD:** Severe Insulin Deficient Diabetes.

Novel subgroups with certain unique phenotypic and biochemical characteristics[11]

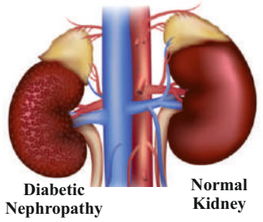
Persistent suboptimal glycaemic control is invariably associated with the onset and progression of acute and chronic diabetic complications in diabetic patients[12]

Complications associated with diabetes in Indian population

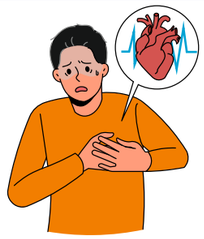
The complications related to diabetes account for most of the morbidity and mortality associated with this disorder:[13-16]

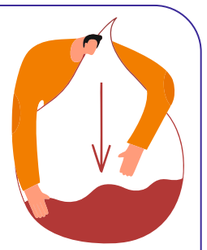


Atherosclerosis



Kidney (Diabetic nephropathy)


Heart failure


Hypoglycaemia

Diabetic nephropathy:[12]

In India, diabetic nephropathy ranged from 0.9% to 62.3%. It is the main cause of end-stage renal disease (ESRD) and it is projected that 20% T2DM patients reach ESRD during their lifetime. **Table 4**

- Poor glycaemic control
- Long duration of diabetes
- Systolic blood pressure

Main risk factors for nephropathy

Increasing prevalence of diabetes in India and increased burden of undiagnosed diabetes leads to irreversible **long-term vascular complications**[12]

Table 2: Chronic complication of diabetes mellitus in India

Type of complication	Study population	Prevalence percentage	Author
Diabetic Retinopathy	1414	4.8%	Raman et al 2012
	1500	5.1%	Sosale et al 2016
	4600	6.1%	Sosale et al 2014
	306	15.36%	Manoj Kumar et al 2016
	1715	17.6%	Pradeepa et al 2008
	1414	18.0%	Raman et al 2009
	5130	21.7%	Salil et al 2016
Diabetic Nephropathy	1500	0.9%	Sosale et al 2016
	4600	1.06%	Sosale et al 2014
	306	5.56%	Manoj Kumar et al 2016
	390	12.1%	Akila et al 2020
	200	13%	Ravindran et al 2020
	1629	26.1%	Pradeepa et al 2008
	1716	26.9%	Unnikrish-n et al 2007
	365	34.4%	Hussain et al 2019
	6175	62.3%	Dash et al 2018
Diabetic Neuropathy	1414	10.5%	Raman et al 2012
	4600	13.15%	Sosale et al 2014
	1500	13.2%	Sosale et al 2016
	1401	18.84%	Rani et al 2010
	306	20.26%	Manoj Kumar et al 2016
	390	44.9%	Akila et al 2020

Hypoglycaemia

- In diabetic patients, hypoglycaemia is the biggest obstacle to tight glycaemic control.[14]
- ~96% reported any one symptom of hypoglycaemia.[14]
- Severe or recurrent hypoglycaemic episodes can lead to significant psychosocial dysfunction and lower quality of life.[14]

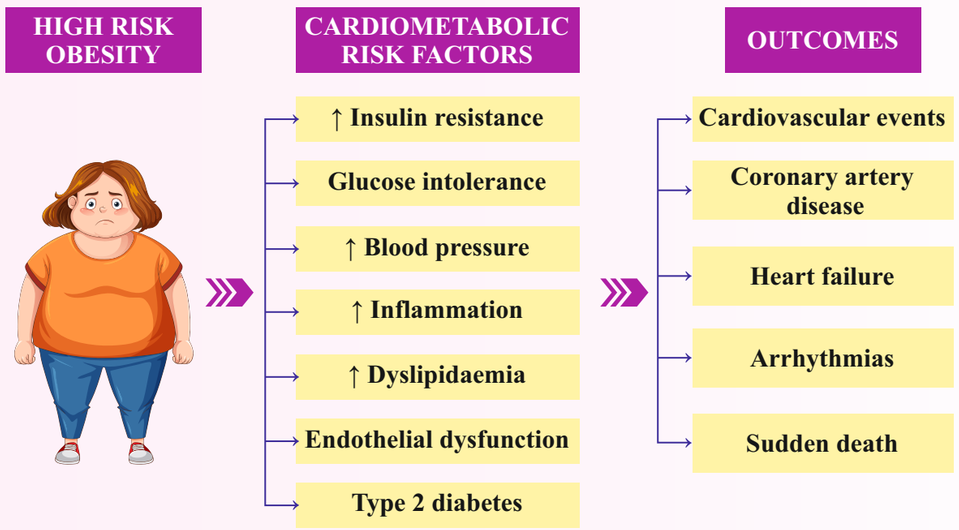
Heart failure

- Patients with diabetes have an increased risk of developing heart failure (HF).[15]
- Diabetes mellitus is 4X more likely to cause HF in patients (25% of chronic heart failure patients and up to 40% of acute heart failure patients) than in non-diabetics.[15]

Cardiovascular disease is a common cause of death and morbidity in T2DM patients.[16]

Sharma A et al. reported that endothelial dysfunction, enhanced coagulation, and increased oxidative stress are frequently present in T2DM patients which further contributes to the development of cardiovascular diseases. Thus, elevated cardiovascular risk factors put patients with T2DM at greater risk for chronic heart failure, stroke, revascularization, myocardial infarction, and other disorders of the cardiovascular system.[16]

Figure 3: Relationships between high-risk obesity, intermediate cardiometabolic risk factors, and cardiovascular outcomes (obesity phenotypes, diabetes, and cardiovascular diseases).[16]



Patients with diabetes are at increased risk for cardiac events due to cardiovascular (CV) risk factors like obesity, hypertension, and dyslipidaemia.[17]

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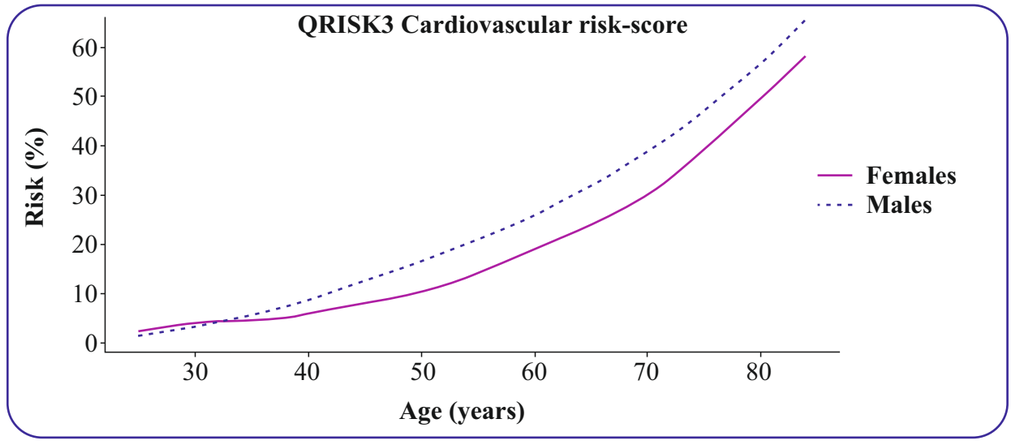
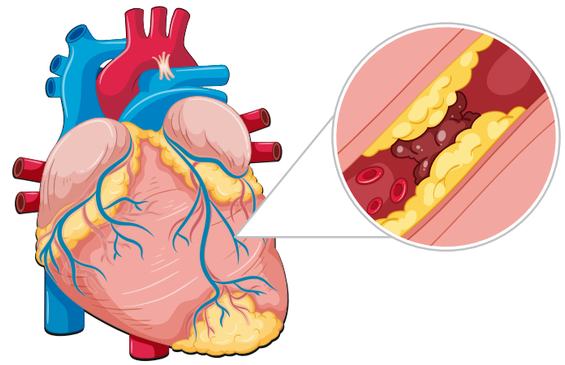
Cardiovascular disease[18]

- The most common CV risk factor was a low HDL value according to LAI criteria with, 68% of all subjects appeared to have at least one lipid abnormality.
- Smokers had 7% higher CV risk than non-smokers and hypertensives almost 5% higher risk than normotensives.
- Most patients with T2DM are at very high risk of fatal CV events and males were at higher risk than females. **Figure 4**
- Atherosclerotic cardiovascular disease remains the principal cause of death and disability among patients with diabetes mellitus, especially in those with type 2 diabetes mellitus in whom it typically occurs 14.6 years earlier, with greater severity, and with more diffuse distribution than in individuals without diabetes mellitus.[19]

Figure 4: CV risk based on QRISK3 chart related to age and separated for sex[18]



Appropriate and intensive management of CV risk factors is important in young people at risk of diabetes as well as in young people recently diagnosed with type 2 diabetes mellitus (T2DM)[18]



The (ICMR)-India Diabetes (INDIAB) study present the control of cardiometabolic risk factors among those with self-reported diabetes[4]

- Poor achievement of glycaemic targets despite widespread use of anti-diabetic drugs suggests a lack of timely escalation of treatment, which could be due to insufficient monitoring and follow-up.
- A number of individuals with diabetes across India have markedly elevated LDL cholesterol and are at high risk for adverse cardiovascular outcomes.
- Patients have average BMI of 25.6 kg/m^2 and HbA1c level of 8.1%.
- State-wise assessment revealed that the highest mean HbA1c levels were found in Punjab, Bihar, Chandigarh, Haryana, and Karnataka.

Achievement of treatment targets and adoption of healthy behaviours remains suboptimal in India[4]

There is an urgent need to improve awareness regarding healthy diet and importance of physical activity among the Indian population[4]

Current therapeutic approaches in management of T2DM

- The physiology and treatment of diabetes are complex and need multiple interventions for successful disease management as follows:[20,21]
- First-line therapy depends on comorbidities, patient-centred therapy factors, as well as management needs and usually includes metformin and comprehensive lifestyle changes.[21]

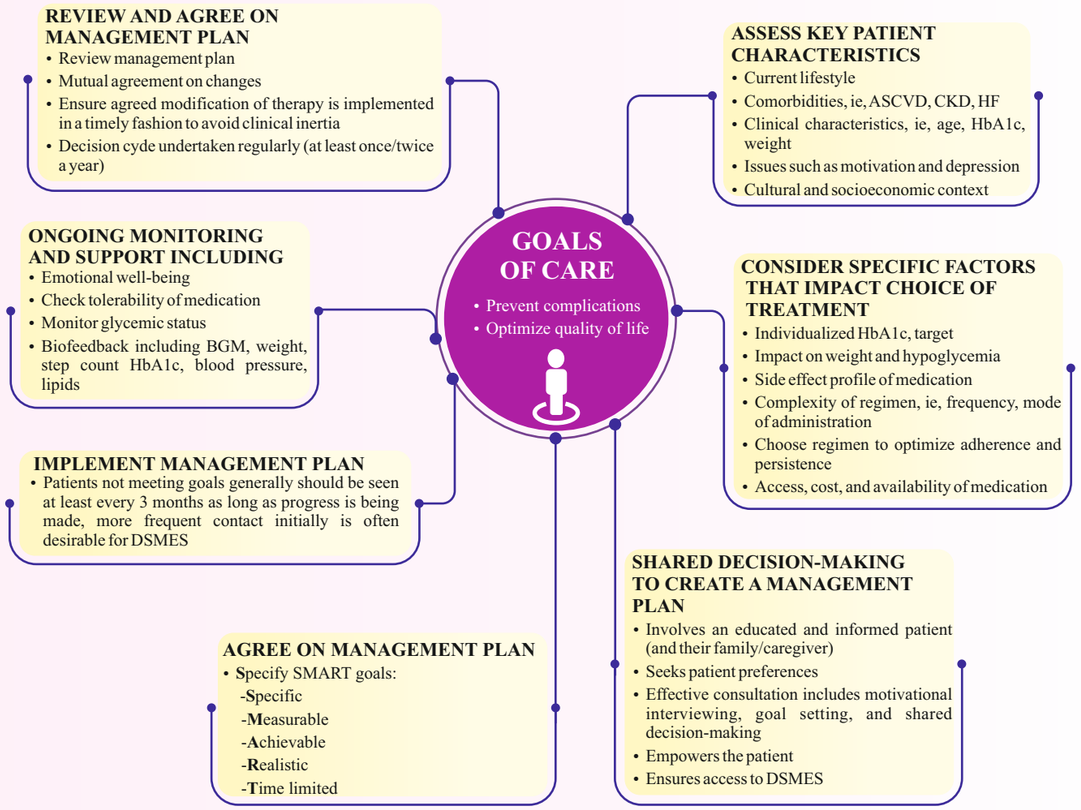
Non-pharmacological measures: Diet, physical activity, and behavioral therapy

Pharmacological measures: Glucose-lowering medications

ADA 2022 guideline recommendation on Patient-Centred Care Goals[16]

- In adults with overweight/obesity at high risk of type 2 diabetes, care goals should include.
  - Weight loss or prevention of weight gain
  - Minimizing progression of hyperglycaemia
  - Attention to CV risk and associated comorbidities
- A successful medical evaluation depends on beneficial interactions between the patient and the care team.
- The use of person-centred, strength based, empowering language that is respectful and free of stigma in diabetes care and education can help to inform and motivate people.
- The person with diabetes, family or support people, and health care team should together formulate the management plan, which includes lifestyle management, to improve disease outcomes and well-being.

DECISION CYCLE FOR PATIENT-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD - Atherosclerotic Cardiovascular Disease
CKD - Chronic Kidney Disease
HF- Heart Failure
DSMES - Diabetes Self-Management Education and Support
BGM - Blood Glucose Monitoring

Figure 5: Decision cycle for patient-centred glycaemic management in type 2 diabetes.

The goals of treatment for diabetes are to prevent or delay complications and optimize quality of life[16]

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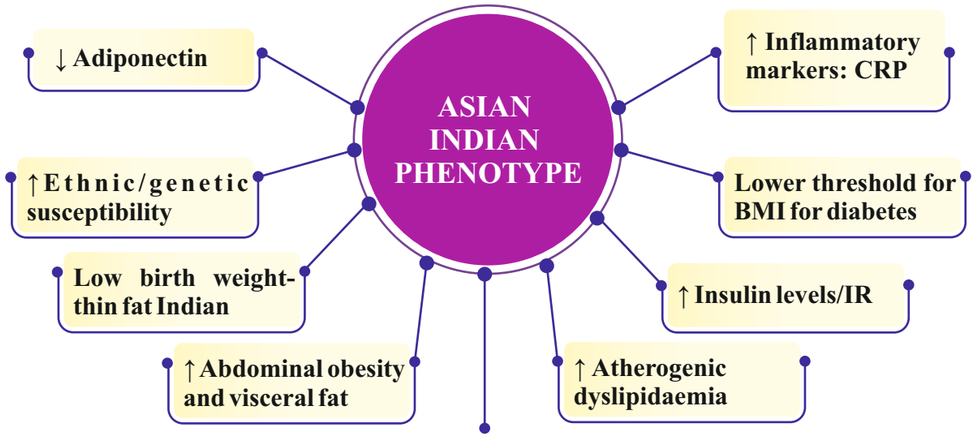
Challenges in treatment management of T2DM in Indian patients

Challenges in India include variable diet pattern, habits, poor compliance, poor treatment adherence, clinical inertia, and late diagnosis with comorbidities.[22]

Asian Indians exhibit a peculiar collection of abnormalities that makes them more prone to diabetes and insulin resistance than Caucasians of similar BMI, due to their excess body fat, visceral fat, and insulin resistance.[23] **Figure 6**

Figure 6A: The Asian Indian phenotype[23]



CRP: C-reactive protein; IR: Insulin resistance; CVD: Cardiovascular disease; BMI: Body mass index

Metabolic derangements in type 2 diabetes

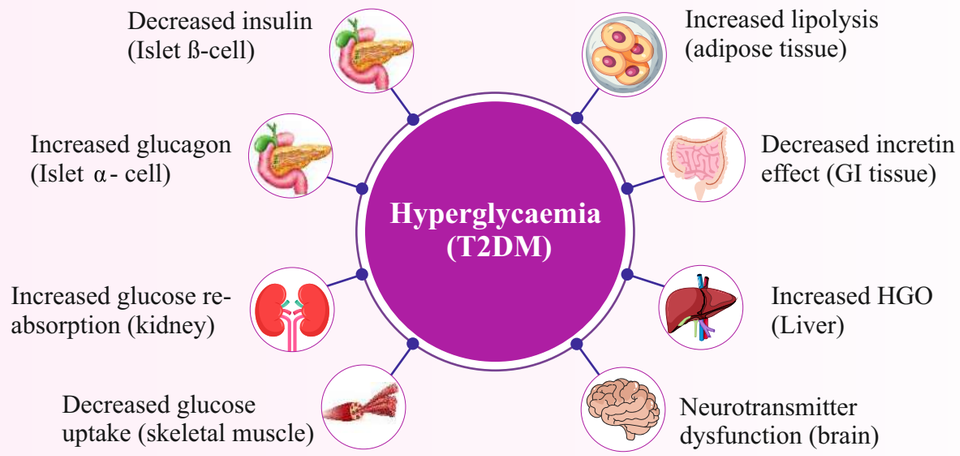


Figure 6B: Eight metabolic derangements in type 2 diabetes[24]

Gl: Gastrointestinal HGO: Hepatic glucose output

Unmet needs and scope in management of T2DM

- T2DM remains uncontrolled in 67% of Indian patients.[24]
- Patient remains uncontrolled with an average HbA1c of 8.2%.[23]
- Treatment with traditional oral antihyperglycaemic agents necessitates use of insulin for increased blood glucose control.[25]
- Further, glucotoxicity and lipotoxicity of these drugs cause malfunction of the pancreatic β-cells due to apoptosis.[25]
- Indian patients already have a decline in β-cells and management of DM in such cases with traditional agents (sulfonylureas) eventually leads to uncontrolled DM.[26]
- Thus, oral antihyperglycaemic agents that can control blood glucose levels by glucose-stimulated insulin secretion (GSIS) and preserve the function of pancreatic β-cells are needed.[25]
- Multiple pathophysiological mechanisms of hyperglycaemia must be addressed in a combination approach to ensure glycaemic control.[24]
- Need for additional treatments that provide both glycaemic and non-glycaemic benefits, especially since the control of diabetic comorbidities is less than optimal in most patients.[24]
- It is essential to reduce the occurrence of hypoglycaemia or weight gain, as recurrent distressing side effects of traditional antidiabetic agents reduces the morale of not only the patient but also the treating physician.[24]
- An oral treatment option that not only meets all of the pressing needs but additionally improves the compliance of patients is required.[24]

There is a need for evaluating health outcomes of diabetes medication and delivery systems that can improve adherence and HbA1c control[27]

An overview on DPP-4 inhibitors

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are oral agents which can be used safely in elderly patients. The drugs are highly effective for the treatment of T2DM in the elderly, as they control basal and postprandial hyperglycaemia, and are easy to tolerate, with low risk of hypoglycaemia, and without significant drug interactions, or weight gain.[28] **(Figure 7)**

Sitagliptin was the first agent introduced in 2006. The most widely used substances are sitagliptin, linagliptin, vildagliptin, saxagliptin, and alogliptin. Anagliptin, gemigliptin, teneligliptin, and evogliptin are used in Asian countries.[29,30] DPP-4 inhibitors are implemented into the treatment algorithms of type 2 diabetes mellitus in many national and international guidelines.[29] **(Figure 8)**

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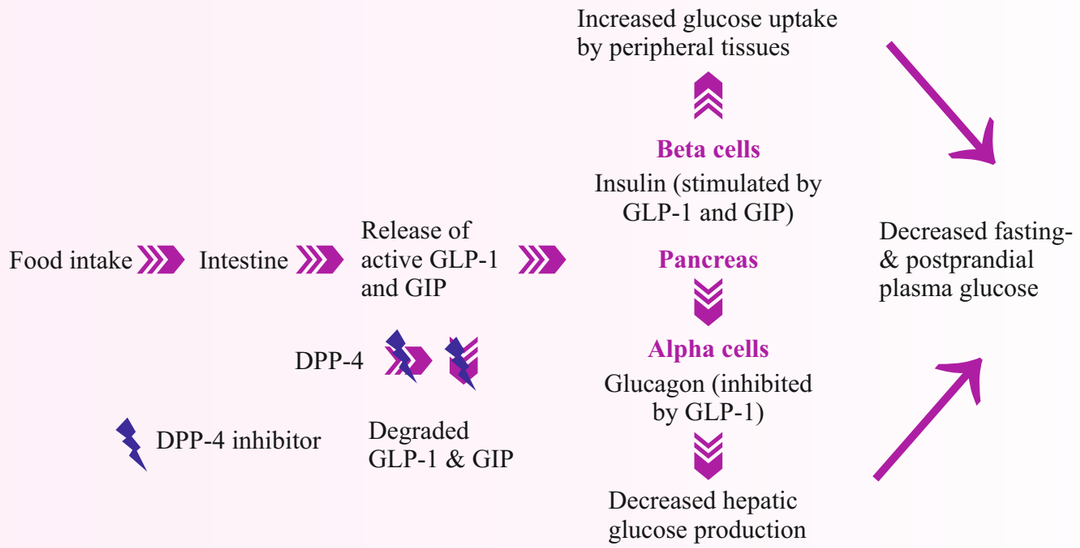
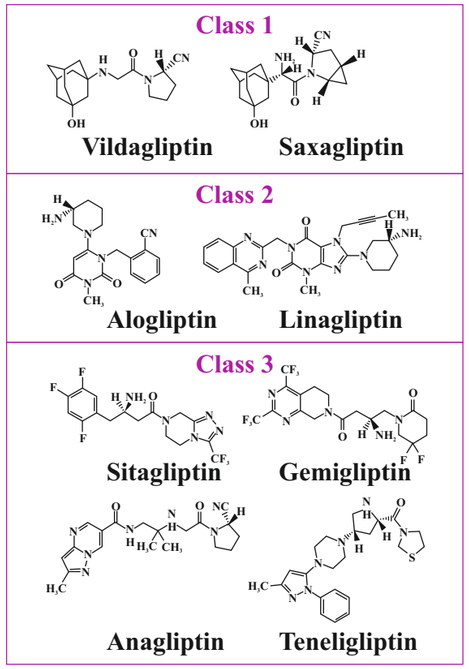
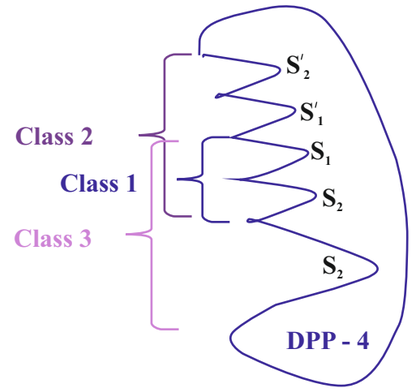
Figure 7: Physiology of the post-prandial regulation of glucose homoeostasis by the incretin system and the action of DPP-4 inhibitors.[29]



GLP-1: Glucagon-like peptide-1; GIP: Gastric inhibitory polypeptide

Figure 8: Classes of DPP-4 inhibitors with the various commonly used DPP-4 inhibitors (left side) and the binding domains of the various classes to specific areas of the DPP-4 molecule (right side) according to Tomovic et al. and Nabeno et al.[29]





The various DPP-4 inhibitors do not form a homogenous class of molecules, and they show different interactions with the active site of the enzyme molecule.[29]

DPP-4 inhibitors and their clinical characteristics[29]

The DPP-4 inhibitors available demonstrate a high efficacy in inhibiting DPP-4, and under clinical conditions DPP-4 is inhibited by >80-90%. GLP-1 plasma concentrations are induced postprandial by this inhibition and glucose-dependent insulin secretion is stimulated and glucagon secretion is inhibited. The DPP-4 inhibitors have good bioavailability and their pharmacodynamics and pharmacokinetics are suitable for clinically sufficient DPP-4 inhibition by once-daily administration. DPP-4 inhibitors are capable of lowering HbA1c by ~0.5% - 1%. The reduction in HbA1c relative to placebo was greater in the Indian subpopulations because the mean HbA1c increased from baseline in placebo-treated patients in India. Compared with placebo, the LS-mean (95% CI) reductions in HbA1c with sitagliptin treatment were -1.4% (-1.7% to -1.0%) in India. The most important and common indication for DPP-4 inhibitors is their add-on use in patients who are not sufficiently controlled on metformin monotherapy. Fixed dose combinations of DPP-4 inhibitors with metformin are available and may safely be used in patients on this treatment combination. DPP-4 inhibitors can be administered in patients with impaired kidney function due to the good safety and tolerability.

Pharmacokinetic and pharmacodynamic properties of DPP-4 inhibitors

Dipeptidyl peptidase-4 inhibitor (DPP-4i) represent a heterogeneous class of small molecules with differences in chemistry, in pharmacokinetic characteristics as absorption, distribution, metabolism, and excretion routes and in pharmacodynamic characteristics as potency and selectivity of DPP-4 inhibition.[31] **(Table 3)**

Table 3: Main pharmacokinetic and pharmacodynamic properties of DPP-4 inhibitors[31]

	Sitagliptin	Vildagliptin	Saxagliptin	Alogliptin	Linagliptin
Daily recommended dose	100 mg	100 mg	5 mg	25 mg	5 mg
Pharmacokinetic properties					
Oral bioavailability	87%	85%	75%	70%	30%
Volume distribution	198 l	71 l	151 l	300 l	368-918 l
Fraction bound to proteins	38%	9.3%	<10%	20%	70%
Half-life ($T_{1/2}$)	8-14 h	2-3 h	2.2-3.8 h	12.4-21.4 h	120-184 h
Kidney excretion	87%	85%	75%	76%	5%
Liver excretion	13%	4.5%	22%	13%	85%
Proportion excreted unchanged	79%	23%	24%	95%	-90%
Substrate for CYP3A4/5	Low	No	Yes	No	No
Active metabolites	ND	No	Yes	ND	ND
Inactive metabolites	ND	Yes	No	ND	ND
Pharmacodynamic properties					
In vitro DPP-4 inhibition (IC50)	19 nM	62 nM	50 nM	24 nM	1 nM
Selectivity for DPP-4 versus DPP-8/DPP-9	> 2,600	< 100	< 100	> 14,000	> 10,000

- Sitagliptin has a higher selectivity for DPP-4 than for the other enzymes of the same family (e.g., FAP, DPP-8, and DPP-9).
- The oral bioavailability of sitagliptin is the highest among all the gliptins.
- Sitagliptin is a "competitive enzyme inhibitor" which inhibits the enzyme in a dose dependent manner and has immediate dissociation.

Sitagliptin: A comprehensive overview

Introduction[32]

The DPP4-inhibitor sitagliptin has been approved in more than 130 countries globally as monotherapy and in combination with other anti-hyperglycaemic drugs for the treatment of adult patients with T2DM.

Extensive clinical experience over the last 10 years in clinical trials as well as real-world settings has firmly established the glycaemic efficacy of oral sitagliptin.

Pharmacodynamic properties[31]

Sitagliptin exhibits potent, highly selective inhibition of DPP-4 with inhibitory concentration (IC_{50}) values for DPP-8 and DPP-9 >2600-fold greater.

A single dose or multiple doses of sitagliptin 50-600 mg/day significantly decreased the activity of DPP-4 and increased GLP-1 and gastric inhibitory polypeptide (GIP) levels postprandial, for both patients with T2DM and non-diabetic obese individuals.

Pharmacokinetic properties[31]

Oral sitagliptin is rapidly absorbed after a single 100 mg dose, with peak plasma concentrations attained 1-4 h post-dose. The area under the plasma concentration-time curve (AUC) from time zero to infinity increased in a dose-proportional manner with single doses of sitagliptin 25-400 mg. The absolute bioavailability of sitagliptin is 87% and its oral absorption is not affected by food. ~80% of an administered dose eliminated as unchanged drug in the urine.

In vitro studies indicate that CYP3A4 and, to a lesser extent, CYP2C8 are involved in the limited hepatic metabolism of sitagliptin. The apparent terminal elimination half-life of sitagliptin is 12.4 h and renal clearance is ~350 mL/min.

Dosage adjustments are required in patients with moderate and severe renal impairment since plasma AUC levels increased approximately 2 to 4-folds. However, no dosage adjustments are required in patients with mild renal impairment.

Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin and is considered unlikely to cause interactions with other drugs that utilize these pathways. Sitagliptin is not associated with clinically meaningful changes in the pharmacokinetic properties of metformin, sulfonylureas, simvastatin, warfarin, or oral contraceptives. Similarly, coadministration of metformin or ciclosporin with sitagliptin did not markedly alter the pharmacokinetics of sitagliptin.

The therapeutic benefit of sitagliptin as monotherapy or as a combination shows significant improvement in achieving glycaemic control[33]

Clinical benefits of sitagliptin

The clinical benefits of sitagliptin are as follows

- Convenient once-daily regimen and low potential for drug–drug interactions[34]
- Improves glycaemic control as monotherapy or combination with antihyperglycaemic drugs[34]
- Does not increase or reduce the rate of 4-point MACE and 3-point MACE outcomes after a median of 3 years' follow-up[34]
- Generally well tolerated, with low risk of hypoglycaemia[34]
- Neutral effects on bodyweight[34]
- No dose adjustment is required on the basis of age, gender, race or body mass index[28]
- No dosage adjustments are necessary in patients with mild renal impairment[36]
- Reduces proteinuria, ameliorates renal function, and produces anti- inflammatory effect in early-stage diabetic nephropathy[35]
- Improves serum gamma-glutamyl transpeptidase in non-alcoholic fatty liver disease (NAFLD)[37]
- Shows pleiotropic impacts towards cardiovascular system either with or without diabetes[38]

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Clinical evidence on safety and efficacy of sitagliptin

Effect of sitagliptin in glycaemic control[39]

Study objective

The study aimed to evaluate the benefits of sitagliptin in patients with T2DM.

Study design

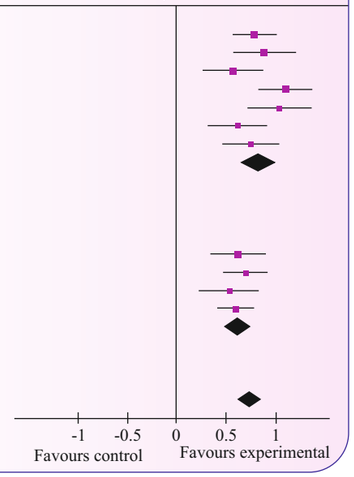
Meta-analysis of randomised clinical trials (18 trials) evaluating efficacy of sitagliptin therapy in management of type 2 diabetes mellitus.

Findings of the study

Significant reduction in HbA1c with sitagliptin as compared to placebo (MD = 0.74, 95% CI 0.63 to 0.85) **(Figure 9)**

Figure 9: Mean difference in change in haemoglobin A1C (HbA1c) percentage value for sitagliptin vs. placebo in adults with type 2 diabetes.[39]

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV. Fixed, 95% CI
1.1.1 sitagliptin vs placebo								
Aschner 2006	0.62	1.13	229	-0.17	1.28	244	11.1%	0.79 [0.57, 1.01]
Goldstein 2007	0.69	1.39	175	-0.2	1.41	165	7.9%	0.89 [0.59, 1.19]
Hanefeld 2007	0.4	1.11	106	-0.17	1.11	107	7.9%	0.57 [0.27, 0.87]
Mohan 2009	0.7	1.28	339	-0.4	1.51	169	9.1%	1.10 [0.83, 1,37]
Nonaka 2008	0.64	1.02	75	-0.4	1.05	75	6.9%	1.04 [0.71, 1.37]
Raz 2006	0.46	1.11	193	-0.16	1.29	103	81%	0.62 [0.33, 0.91]
Scott 2007	0.49	1.07	121	-0.26	1.22	121	8.2%	0.75 [0,46, 1.04]
Subtotal (95% CI)			**1238**			**984**	**59.3%**	**0.82 [0.68, 0.97]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 10.96$, df = 6 (P = 0.09) ; $I^2 = 45\%$								
Test for overall effect: Z=11.21 (P < 0.00001)								
1.1.2 sitagliptin + active control vs placebo+ active control								
Charbonnel 2006	0.7	0.08	453	0.08	1.98	224	8.7%	0.62 [0.35, 0.89]
Rosenstock 2006	0.88	0.95	163	0.18	1.08	174	11.2%	0.70 [0.48, 0.92]
Scott 2008	0.74	1.02	91	0.21	1.07	88	7.7%	0.53 [0.22, 0.84]
Vilsboll 2010	0.6	1.04	305	0	1.22	312	13.1%	0.60 [0.42, 0,78]
Subtotal (95% CI)			**1012**			**798**	**40.7%**	**0.62 [0.51, 0.74]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.90$, df = 3 (P = 0.83) ; $I^2 = 0\%$								
Test for overall effect: Z = 10.65 (P < 0.00001)								
Total (95% CI)			**2250**			**1782**	**100%**	**0.74 [0.63, 0.85]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 18.26$, df = 10 (P=0.05); $I^2 = 45\%$								
Test for overall effect: Z= 13.55 (P < 0.00001)								



- Significant reduction in fasting plasma glucose (FPG) with sitagliptin compared to placebo (MD = 1.20, 95% CI 1.03 to 1.38). (Figure 17)
- Sitagliptin significantly improved the homeostasis model assessment of β-cell (HOMA-β index) (MD = -10.84, 95% CI -14.07 to -7.80) compared to placebo. (Figure 18)
- No significant difference was observed between the sitagliptin and active treatments in incidence of hypoglycaemia adverse experiences (Relative risk [RR]= 0.38, 95% CI 0.14 to 1.08) or serious adverse experiences (RR = 1.15, 95% CI 0.83 to 1.65).

Figure 10: Mean difference in change in fasting plasma glucose (mmol/L) for sitagliptin vs. placebo in adults with type 2 diabetes.[39]

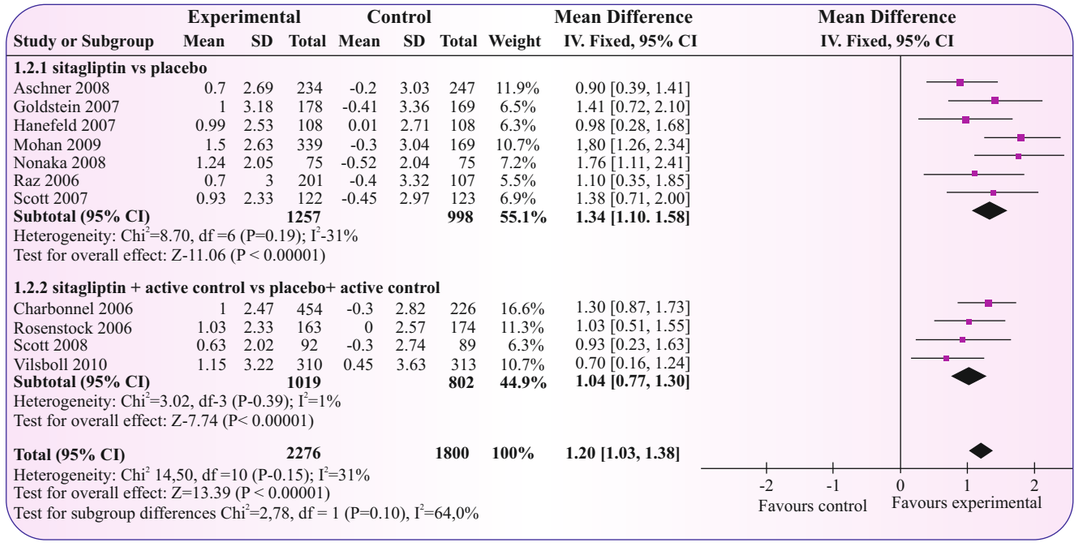
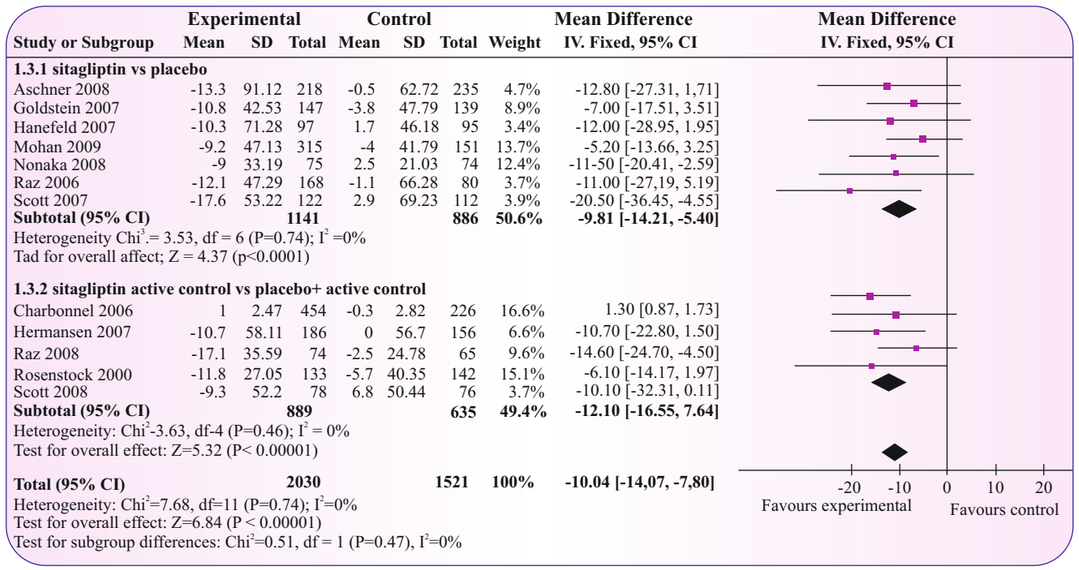


Figure 11: Mean difference in change in HOMA-β for sitagliptin vs. placebo in adults with type 2 diabetes.[39]



Effect of sitagliptin in atherosclerosis[40]

Atherosclerosis associated with diabetes may be caused by hypercoagulability, hyperaggregability of platelets, as well as an increase in platelet-activation markers.

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Study objective

Study by Omoto S et al. assessed the effects of sitagliptin on the circulating levels of soluble receptor for advanced glycation end products (sRAGEs), monocyte chemoattractant protein-1 (MCP-1), selectins, and adiponectin in patients with type 2 diabetes.

Study design and methodology

The study enrolled 72 non-diabetic and 113 diabetic patients and were assigned for sitagliptin monotherapy if their diet/exercise therapy had continued unchanged for 3 months.

Levels of soluble P-selectin (sP-selectin), soluble E-selectin (sE-selectin), soluble vascular cell adhesion molecule-1 (sVCAM-1), MCP-1, sRAGEs, and adiponectin were assessed after 3 and 6 months of treatment.

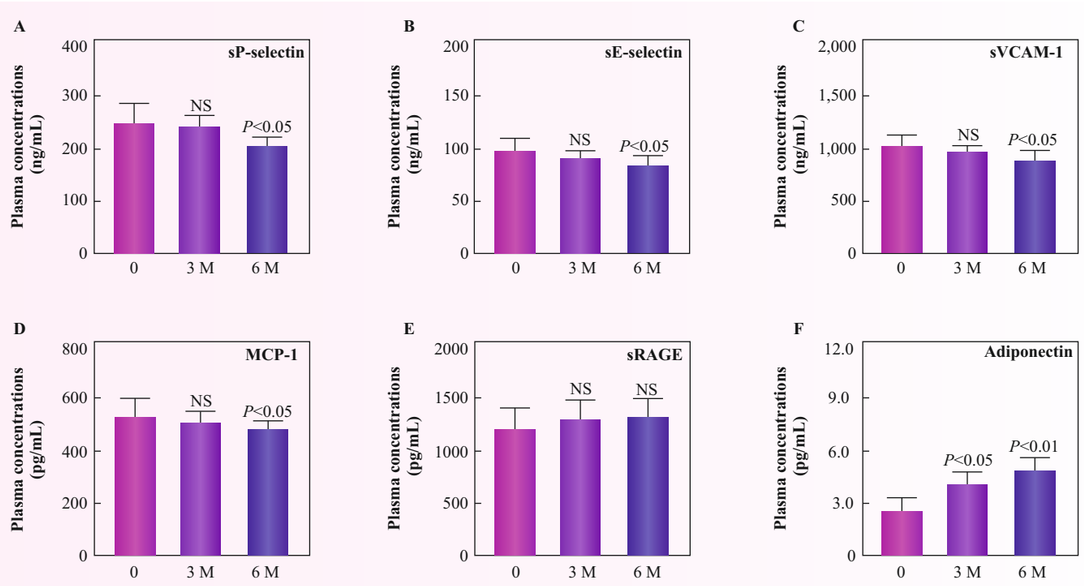
Findings

Sitagliptin therapy at 3 and 6 months significantly reduced plasma levels of sP-selectin, sE-selectin, sVCAM-1, and MCP-1 relative to baseline, while significantly increasing adiponectin levels. **(Figure 12)**

Reductions in sP-selectin, sE-selectin, sVCAM-1, and MCP-1 during sitagliptin therapy were significantly greater in responders, defined as patients with a significant increase in adiponectin levels, than in non-responders.

Responders showed a significant increase in the plasma concentration of sRAGEs.

Figure 12: Plasma concentrations of sP-selectin (A), sE-selectin (B), sVCAM-1(C), MCP-1(D), sRAGE (E), and adiponectin (F) before and after sitagliptin treatment in diabetic patients.



In type 2 diabetics, sitagliptin has an adiponectin-dependent anti-atherothrombotic effect that may be beneficial for primary prevention of atherothrombosis.[40]

Effect of sitagliptin in elderly population[41]

Study objective

The study by Hsieh C et al. demonstrated the durability of sitagliptin and evaluated changes in clinical chronic complications following 48 months of monotherapy with sitagliptin in elderly diabetic patients with type 2 diabetes (T2DM).

Study design and methodology

The study enrolled 76 drug-naive patients (40 women and 36 men) with T2DM who received 25-100 mg of sitagliptin therapy.

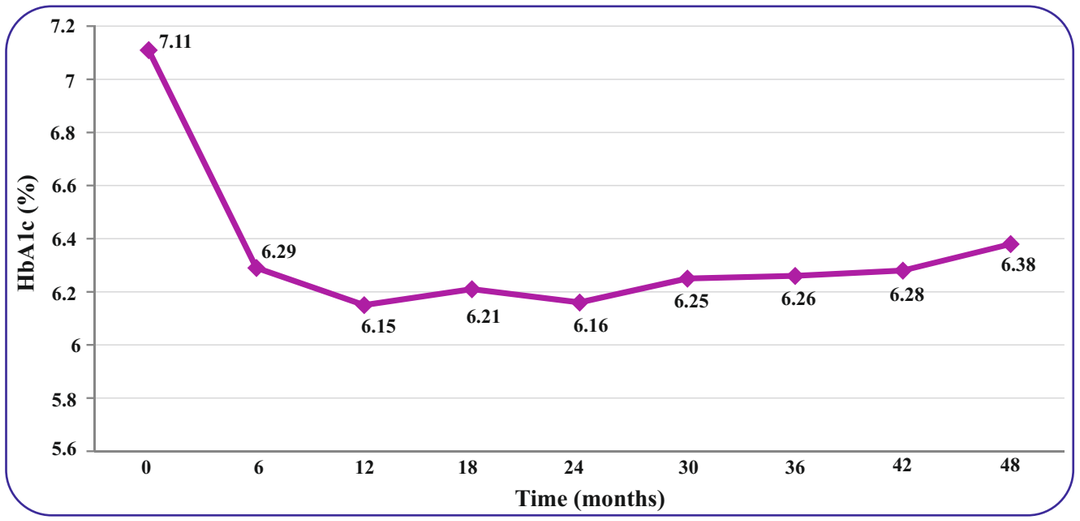
The fasting plasma glucose and glycated haemoglobin (HbA1c) was measured every 3-6 months.

Findings

The change in HbA1c was significantly reduced after 6 months of therapy (7.1% +/- 0.8% to 6.3% +/- 0.2%). **(Figure 13)**

No significant changes were reported in FPG, creatinine, serum total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, body mass index, and microvascular complications.

Figure 13: Change in the HbA1c levels from baseline at 6-month intervals



Sitagliptin has a durable effect and stabilizes microvascular complication progression in elderly patients

Effect of sitagliptin in renal outcome[42]

Study objective

The study by Mori H et al. aimed to determine effect of sitagliptin on microalbuminuria in patients with type 2 diabetes mellitus.

Study design and methodology

The study enrolled 85 patients with type 2 diabetes and were randomised to sitagliptin 50 mg or other oral glucose-lowering agents.

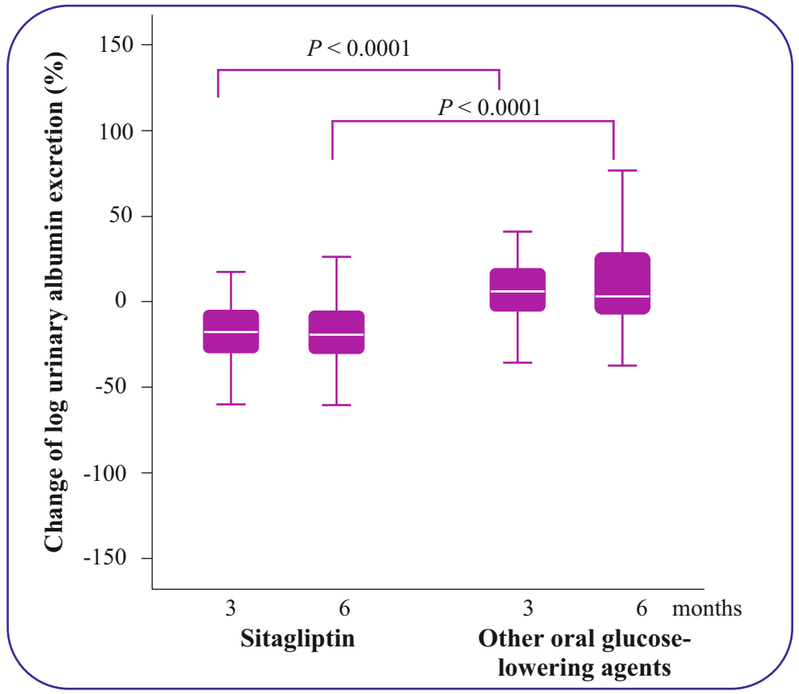
The primary outcome was changes in urinary albumin excretion at 6 months.

Findings

Significant and comparable reduction in HbA1c and fasting plasma glucose were found in both groups.

Sitagliptin significantly reduced urinary albumin excretion within 6 months, especially in patients with high urinary albumin at baseline. **(Figure 14)**

Figure 14: Mean percentage change in log urinary albumin excretion.



The study concluded that sitagliptin improved albuminuria, in addition to improving glucose level in patients with T2DM

Hypoglycaemia in Type 2 diabetes treated with Sitagliptin monotherapy[43]

Study objective

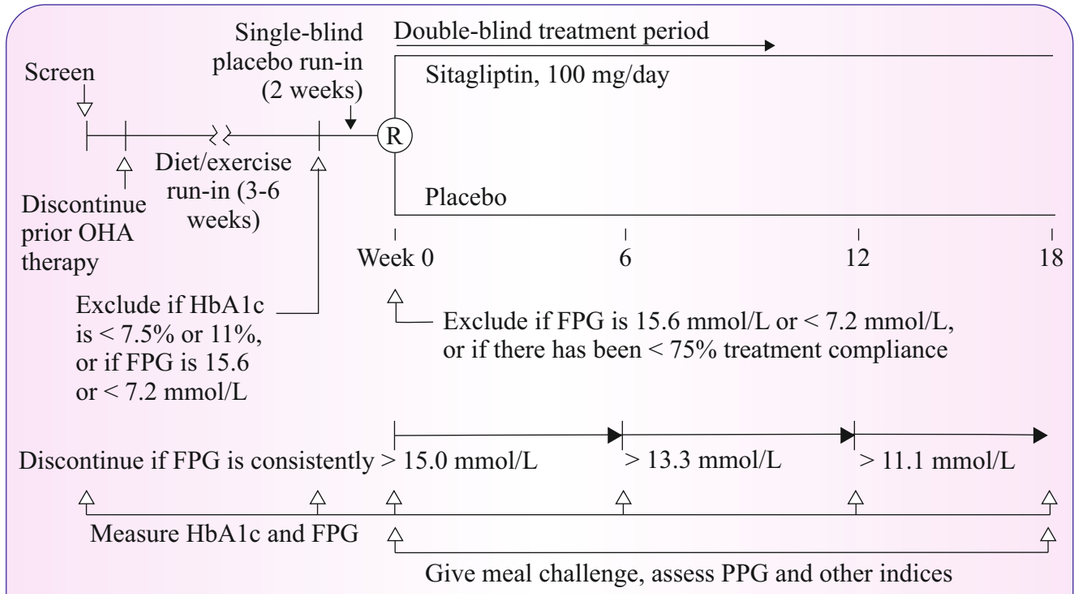
The study by Mohan V et al. evaluated the efficacy and safety of sitagliptin monotherapy in patients with type 2 diabetes inadequately controlled on diet and exercise.

Study design and methodology

A randomised, placebo-controlled, double-blind, 18-week trial, enrolled 530 patients with HbA1c ≥7.5% and ≤11.0% (mean baseline 8.7%).

Patients were assigned to receive sitagliptin 100 mg once daily or placebo. **(Figure 15)**

Figure 15: Study design



FPG: Fasting plasma glucose; PPG: Post prandial glucose; HbA1c: Glycated haemoglobin; OHA: Oral hypoglycaemic agents

Findings

No hypoglycaemic events were reported in patients receiving sitagliptin 100 mg. (Table 4)

Sitagliptin significantly ($p < 0.001$) reduced mean HbA1c (-1.0%), fasting plasma glucose (-1.7 mmol/L), and 2-h postprandial glucose (-3.1 mmol/L).

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Table 4: Summary of clinical adverse events (AEs).

	Placebo (n = 178)	Sitagliptin (n = 352)
Number (%) of patients with one or more		
Clinical AE	27 (15.2%)	82 (23.3%)
Drug-related clinical AE	3 (1.7%)	10 (2.8%)
Serious clinical AE	2 (1.1%)	6 (1.7%)
Serious, drug-related clinical AE	1 (0.6%)	1 (0.3%)
Number (%) of patients who		
Discontinued due to an AE	2 (1.1%)	5 (1.4%)
Discontinued due to a drug-related AE	1 (0.6%)	2 (0.6%)
Discontinued due to a serious AE	2 (1.1%)	3 (0.9%)
Discontinued due to a serious, drug-related AE	1 (0.6%)	1 (0.3%)
Died	0	1 (0.3%)
Number (%) of patients who had		
Hypoglycemia	0	0
Any gastrointestinal AE	1 (0.6%)	18 (5.1%)
Prespecified selected gastrointestinal AEs		
Abdominal pain	0	3 (0.9%)
Nausea	0	0
Vomiting	0	0
Diarrhea	0	0

Sitagliptin 100 mg once daily was associated with low gastrointestinal adverse events and no reported hypoglycaemic events

Effect of sitagliptin on body weight[44]

Study objective

Hussain M et al. evaluated effect of sitagliptin on blood sugar, body weight, blood pressure, and serum lipid profile in type 2 diabetic patients.

Study design and methodology

The 12 weeks, open label, observational study enrolled 78 patients with diabetes and poor glycaemic control.

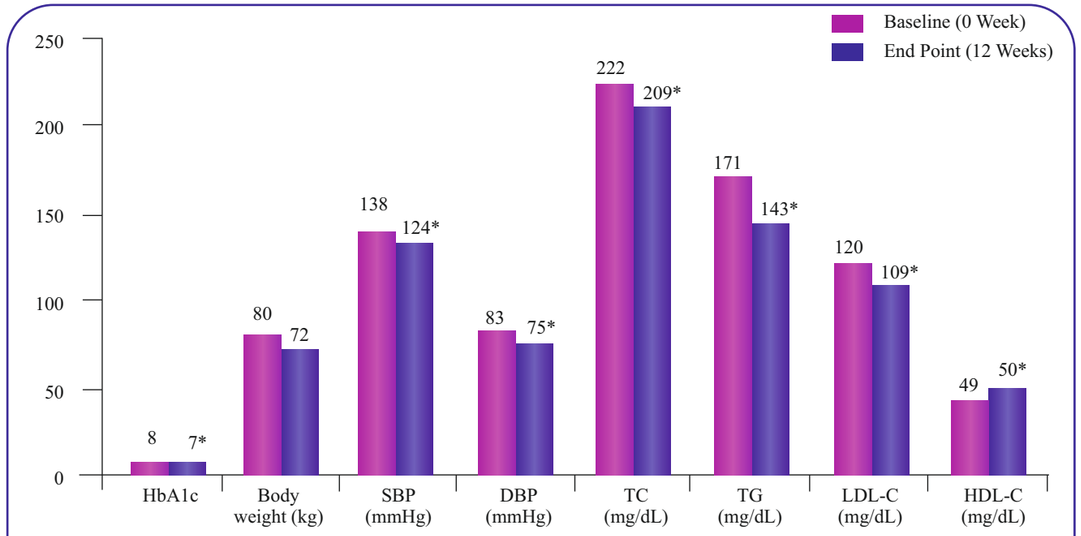
Patients were assigned to receive sitagliptin 50 mg twice daily for 12 weeks.

Findings

Sitagliptin showed significant reduction in body weight from 80.21 kg +/- 7.156 at baseline to 71.74 kg +/- 6.567 at 12 weeks ($p<0.05$). (Figure 23)

Sitagliptin showed significant reduction in HbA1c from 8.184% +/- 0.467 at baseline to 7.0200% +/- 0.459 at 12 weeks ($p<0.05$). Significant reduction was reported in Blood pressure at 12 weeks (Figure 23) Serum level of cholesterol.

Figure 16: Clinical and biochemical parameters of patients



*p<0.05. HbA1c: Haemoglobin A1c; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol

Use of sitagliptin improves not only blood glucose control, but also weight, blood pressure, and lipid profile in type 2 diabetic hyperlipidaemia patients.

CV safety with sitagliptin

TECOS trial[45]

Study objective

McGuire DK et al. assessed the association of sitagliptin use with hospitalization for HF (hHF) and related outcomes.

Study design and methodology

TECOS was a randomised, placebo- controlled clinical trial from 673 sites in 38 countries.

The study enrolled 14,671 patients with T2DM and atherosclerotic vascular disease

Assigned (1:1)

Sitagliptin 100 mg daily | **Placebo**

Median follow-up was 2.9 years

Findings

Among patients with type 2 diabetes and established cardiovascular disease, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events.

Sitagliptin use in high-risk T2DM patients does not alter hHF risk

Sitagliptin treatment for type 2 diabetes is effective and well tolerated

Sitagliptin offers a novel therapeutic approach for the treatment of type 2 diabetes

TECOS: Trial evaluating cardiovascular outcomes with sitagliptin; HF: Heart failure; CV: Cardiovascular

Due to a progressive decline in β-cell function, oral antidiabetic agents lose efficacy with prolonged use and a progression from monotherapy to combination (dual or triple) therapies may be necessary[46]

The role of Sulfonylureas (SUs) in treatment management of T2DM

Sulfonylureas (SUs) are widely used in the management of T2DM as insulin secretagogues and are named for their common core configuration. They are classified as first- and second generation SUs. First-generation SUs include long-acting chlorpropamide, tolbutamide, tolazamide, and acetohexamide. Substitutions at either end of the compound result in pharmacologic and pharmacokinetic differences among SUs.[47]

Second-generation SUs include glyburide (glibenclamide), glipizide, gliquidone, and glimepiride, which vary in duration of action. Glimepiride and glyburide are longer-acting agents than glipizide. Glimepiride is the newest second-generation SU and is sometimes classified as a third-generation SU because it has larger substitutions than other second-generation SUs. The United States Food and Drug Administration (FDA) approved glimepiride in 1995 for the treatment of T2DM as monotherapy as well as in combination with metformin or insulin.[47]

Glimepiride: Overview

Pharmacokinetic properties of glimepiride[48]

Absorption	Completely absorbed after oral administration within 1 hour of administration; significant absorption occurs: plasma protein binding is 99.4% and volume of distribution is 8.8 L. Accumulation does not occur after multiple doses.
Metabolism	The drug is primarily metabolized in the liver by CYP2C9 to the active M_1 (hydroxyl) metabolite and then to inactive M_2 (carboxy) metabolite.
Excretion	The main route of excretion is through kidneys. A total of 60% of the metabolites are excreted in urine (predominantly M_1) and remainder in feces (predominantly M_2).

Mechanism of action[49]

Glimepiride is an insulin secretagogue and, like other sulfonylureas, is only effective in patients with residual pancreatic beta-cell activity. They act at ATP-dependent potassium channels on the cell membrane of pancreatic beta cells, causing iatrogenic depolarization by preventing potassium from exiting the cell. The depolarization activates voltage-dependent calcium channels on the cell membrane, leading to a rise in intracellular calcium and subsequent exocytosis of insulin into the bloodstream. Insulin then acts on cell membrane receptors triggering GLUT-4 expression and the movement of glucose into the cell, lowering blood glucose levels. Additionally, research has shown that glimepiride interacts with Epac3, a nucleotide exchanger that mediates the exocytosis of insulin granules.

Clinical efficacy

Glimepiride as monotherapy:

To assess the efficacy of glimepiride in T2DM, Goldberg et al randomized 304 patients to receive either placebo or one of the three doses (1, 4, or 8 mg) of glimepiride during a 14-week study period. All glimepiride regimens significantly reduced FPG, PPG, and HbA1c values ($P < 0.001$) compared to placebo by the end of the study period. Median changes in FPG levels were 43, 70, and 74 mg/dL at glimepiride doses of 1, 4, and 8 mg, respectively. HbA1c levels were lowered by 1.2%, 1.8%, and 1.9%, and the corresponding decreases in PPG were 63, 92, and 94 mg/dL, respectively. The 4- and 8-mg doses of glimepiride were more effective than the 1-mg dose; however, the 4-mg dose provided a nearly maximal antihyperglycemic effect.[50]

Another multicenter, randomized, placebo-controlled clinical trial by Schade et al studied glimepiride (1–8 mg) titrated over 10 weeks compared with placebo in T2DM subjects who were not controlled by diet alone. In this study, glimepiride lowered FPG by 46 mg/dL, PPG by 72 mg/dL, and HbA1c by 1.4% more than the placebo ($P < 0.001$). Good glycemic control (HbA1c < 7.2%) was achieved in 69% of glimepiride subjects compared to 32% of controls. C-peptide levels and non-fasting insulin levels were also increased in the study subjects.[51]

Glimepiride monotherapy reduced both FPG and PPG levels more than placebo and once daily administration is equivalent to twice daily dosing. Studies also suggest that glimepiride controls blood glucose level throughout the day through its effect on stimulating insulin release, which appears to be greater 2 h after meals than under fasting conditions. These findings suggest that glimepiride enhances insulin and C-peptide secretion under physiologic conditions.[48]

In a study involving 372 patients with poorly controlled T2DM, glimepiride was added to metformin monotherapy. Study subjects were divided into three groups: metformin group, glimepiride group, metformin plus glimepiride group. In this study, a combination of glimepiride and metformin was shown to be more effective for controlling blood glucose levels compared to the use of either drug alone.[52]

Combination treatment was significantly more effective in controlling HbA1c (% change $+0.07 \pm 1.20$ for metformin, $+0.27 \pm 1.10$ for glimepiride, -0.74 ± 0.96 for combination treatment, $P < 0.001$). No significant difference was observed between metformin or glimepiride monotherapy with respect to change in HbA1c or fasting blood glucose; however, glimepiride was significantly more effective than metformin in reducing postprandial blood glucose. Episodes of symptomatic hypoglycemia was also higher in the combination group than in either monotherapy group ($P = 0.039$).[52]

Comparison with other sulfonylureas

Glimepiride has been compared to other SUs, including glibenclamide, glipizide, and gliclazide in several clinical trials.

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Glimepiride 1–8 mg/day was found to be as effective as glibenclamide 1.26–20 mg/day in lowering FPG, PPG, and HbA1c. Dills et al evaluated the efficacy of glimepiride (≤16 mg) and glyburide (≤20 mg) as monotherapy in 577 patients with T2DM. There was no significant glycemic difference between FPG, PPG, or HbA1c in both study groups after the 1-year treatment period. However, the incidence of hypoglycemia was lower with glimepiride (1.7%) than with glibenclamide (5.0%) ($P < 0.015$).[53]

Another multicenter, prospective, double-blind study comparing glimepiride (1 mg daily, n = 524) and glibenclamide (2.5 mg daily, n = 520) by Draeger et al showed similar results.[54] Glimepiride provided equal glycemic control compared to glyburide, with mean FPG and HbA1c of 174 mg/dL and 8.4% for glimepiride and 168 mg/dL and 8.3% for glibenclamide. Additionally, in this study, glimepiride caused fewer hypoglycemic symptoms compared to glibenclamide. Glimepiride was associated with significantly smaller increases in fasting insulin ($P = 0.04$) and C-peptide ($P = 0.03$) concentrations than glyburide. In this trial, 11% of glimepiride-treated patients experienced 105 hypoglycemic episodes, and 14% of the glibenclamide treated patients experienced 150 such episodes.[55]

Schernthaner et al compared once daily gliclazide MR and glimepiride in patients with T2DM.[56] In this double-blind, 27-week parallel group study, 845 subjects were randomized to either gliclazide modified release (MR) 30–120 mg daily or glimepiride 1–16 mg daily as monotherapy or in combination with their current treatment (metformin or α glucosidase inhibitor). Efficacy was evaluated based on HbA1c and safety by hypoglycemic episodes using the European Agency definition. HbA1c decreased similarly in both groups from 8.4% to 7.2% in patients on gliclazide MR and from 8.2% to 7.2% in patients receiving glimepiride. The study concluded that glimepiride is as effective as gliclazide MR either as monotherapy or in combination therapy; however, the safety of gliclazide MR was significantly better in terms of hypoglycemic episodes compared with glimepiride.

Combination of glimepiride with dipeptidyl peptidase-4 inhibitors[57-62]

Recently, several new classes of hypoglycemic agents have been introduced, including glucagon like peptide-1 and dipeptidyl peptidase-4 (DDP-4) inhibitors. These agents improved glycemic control in T2DM patients either as monotherapy or in combination with SU, metformin, thiazolidinedione, or insulin. Glimepiride can be used in combination with metformin and DDP-4 inhibitors if glycemic control is not achieved with a single or with two agents. Studies have reported an equal efficacy for glimepiride plus metformin vs vildagliptin/sitagliptin plus metformin in terms of HbA1c reduction.

Although DDP-4 induces less weight gain and hypoglycemia compared to glimepiride, further long-term follow-up studies are needed to determine their safety and efficacy.

Advantages of glimepiride compared to other SUs[48]

Hypoglycemia and weight gain are two important disadvantages of SU therapy; however, the unique properties of glimepiride may provide advantages over other currently available insulin secretagogues.

Glimepiride is generally well-tolerated, and its safety has been reviewed in various randomized clinical studies involving more than 5000 patients. Data from these clinical trials indicate that the overall incidences of adverse events associated with glimepiride are generally lower compared with other SUs.

Hypoglycemia

Severe hypoglycemia is a potentially life-threatening condition and is typically associated with SUs; however, glimepiride differs from older agents in this class, as it is associated with equivalent metabolic control and lower stimulation of insulin secretion.

In a prospective analysis, frequency of severe hypoglycemia with glimepiride was compared with glibenclamide in T2DM patients.[63] In this 4-year population-based study, blood glucose levels of all

30,768 patients who attended the emergency department of the region's central hospital were determined to identify severe hypoglycemia, which was defined as blood glucose level of <2.8 mmol/L or a requirement for intravenous glucose or glucagon injection.

The results showed that although glimepiride was prescribed more frequently than glibenclamide (6976 vs 6789 persons-years), glimepiride induced fewer episodes of hypoglycemia compared to glibenclamide (6 vs 38 episodes). The study concluded that in routine clinical practice, glimepiride is associated with fewer episodes of severe hypoglycemia; the risk can be minimized if individual targets are determined before prescribing this medicine. Glimepiride has been shown to induce a statistically significant decrease in C-peptide and insulin levels compared with glibenclamide, which may explain the reduction of hypoglycemia during and after physical exercise;[54] however, the risk of hypoglycemia is increased with concomitant use of other antihyperglycemic agents. Similarly, advanced age, renal, hepatic, and/or cardiovascular comorbidities may increase hypoglycemia risk; this drug should be used with caution in these patients.[65]

Weight gain[48]

Most patients with T2DM are overweight. In these patients, weight reduction results in considerable improvements in their clinical and metabolic profiles, including HbA1c. Weight gain is considered a disadvantage of SUs, thiazolidinediones, and insulin; however, studies suggest that glimepiride has a weight-neutral effect on patients with T2DM.

Several observational cohort studies have shown considerable weight loss with glimepiride. In one study, an average weight loss of 3 kg was reported after 1–5 years of glimepiride, while in another study, treatment with glimepiride resulted in weight loss of up to 2.2 kg within 8 weeks.

The effects of glimepiride or glibencalmide treatment on body weight in patients with T2DM were observed over a 12-month period in a retrospective observational cohort study. In this study, mean weight loss and reduction in body mass index from baseline to the end of the study period were greater with glimepiride compared to glibenclamide ([-2.01 ± 4.01 kg/-0.7 ± 1.4 kg/m^2] vs [-0.58 ± 3.7 kg/-0.2 ± 1.3 kg/m^2]; $P < 0.001$). The study concluded that initial treatment of T2DM with glimepiride was associated with a significantly greater decrease in body weight and body mass index than treatment with glibenclamide, while providing equivalent glycemic control.

Weight gain associated with therapies for managing T2DM is an important consideration in clinical practice and a major limitation in achieving good glycemic control. Glimepiride differs from other agents in this class in that it is associated with equivalent metabolic control with weight-neutral effects on patients with T2DM.

Glimepiride CV safety

Sulfonylureas, including glimepiride, have demonstrated glycemic efficacy, microvascular benefit, and even potential long-term mortality benefit.[66] While these medications are still recommended in World Health Organization guidelines ahead of newer glucose-lowering medications, the American Diabetes Association–European Association for the Study of Diabetes consensus report recommends sulfonylureas when cost is the primary consideration in medication selection. Despite their long clinical experience and very low cost, the less favoured status of sulfonylureas is due mainly to adverse effects of weight gain and risk for hypoglycemia, as well as long-standing uncertainty regarding their cardiovascular safety.[67]

Rosenstock et al for the CAROLINA[68] Investigators included 6033 adults with type 2 diabetes, with atherosclerotic cardiovascular disease or multiple cardiovascular risk factors, aged 70 years and older, or with evidence of microvascular complications. Participants were randomly assigned to linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, 5 mg daily (n = 3023), or the sulfonylurea glimepiride, 1-4 mg

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daily (n = 3010). The maximum glimepiride dose of 8 mg daily was not part of the protocol.

As in the other CVOTs, non-study diabetes medications could be intensified or added to maintain glycemic control in both groups. The enrolled population had a mean age of 64 years, with median diabetes duration of 6.3 years and mean glycated hemoglobin level of 7.2%. At baseline, 59% were treated with metformin monotherapy and 42% had established vascular disease. After a median follow-up of 6.3 years, the rate of major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, was 11.8% in the linagliptin group and 12% in the glimepiride group (hazard ratio, 0.98 [95% CI, 0.84-1.14]; P < .001 for noninferiority, P = .76 for superiority), with the hazard ratio consistent across all subgroups, including participants with established vascular disease and those aged 70 years and older. There was also no difference in all-cause death, cardiovascular death, or hospitalization for heart failure.

Unsurprisingly, the incidence of any hypoglycemia was nearly 5-fold higher in the glimepiride group than in the linagliptin group (11.1 vs 2.3 events per 100 participant years). Rates of severe hypoglycemia were low: 0.45 per 100 patient-years in the glimepiride group and 0.07 per 100 participant-years in the linagliptin group; hospitalization for hypoglycaemia was 0.18 vs 0.01 per 100 participant-years (P < .001 for all comparisons). At the end of the trial, weight was 1.54 kg higher in the glimepiride group. Over the course of follow-up, 49.3% of participants in the linagliptin group required additional glucose-lowering medication compared with 47.1% of participants in the glimepiride group, with shorter time to intensification required in the linagliptin group. Rates of study drug discontinuation were similar between intervention groups.

Glimepiride in special situations[48]

Glimepiride appears to be well-tolerated in patients with T2DM, including the elderly. However, it should be used cautiously in elderly, debilitated or malnourished patients. Although it can be used in renal insufficiency, patients should be monitored for signs and symptoms of hypoglycemia and lower doses of glimepiride should be used in these situations.

An overview on Metformin

Introduction

- The discovery of metformin began with the synthesis of galegine-like compounds derived from Gallega officinalis, a plant traditionally employed in Europe as a drug for diabetes treatment for centuries[69].
- In 1950, Stern et al. discovered the clinical usefulness of metformin while working in Paris. They observed its glucose lowering capacity and that metformin toxicity also displayed a wide safety margin[69].
- Metformin acts primarily at the liver by reducing glucose output and, secondarily, by augmenting glucose uptake in the peripheral tissues, chiefly muscle.
- These effects are mediated by the activation of an upstream kinase, liver kinase B1 (LKB-1), which in turn regulates the downstream kinase adenosine monophosphatase co-activator, transducer of regulated CREB protein 2 (TORC2), resulting in its inactivation which consequently downregulates transcriptional events that promote synthesis of gluconeogenic enzymes.[70]
- Inhibition of mitochondrial respiration has also been proposed to contribute to the reduction of gluconeogenesis since it reduces the energy supply required for this process[71].

- Metformin's efficacy, safety profile, cardiovascular and metabolic effects, and its ability to be associated with other antidiabetic agents makes this drug the first glucose lowering agent of choice when treating patients with type 2 diabetes mellitus (TDM2).

Metformin: pharmacokinetic[69]

- Oral bioavailability 50-60%
- Lacks dose proportionality with increasing doses: decreased absorption at higher doses
- Food decreases extent and slightly delays absorption
- Poorly protein bound
- Does not undergo hepatic metabolism
- Excreted unchanged in urine: 90% of absorbed drug excreted within first 24 hrs.
- Plasma half-life 6.2 hr.

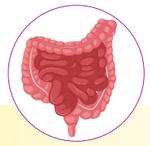
Metformin: proposed mechanisms of action

Liver

↓ hepatic glucose output

Peripheral tissues

↑ peripheral glucose uptake by muscle and adipose tissues



Gut

↓ intestinal glucose absorption

↓ appetite

Adipose tissue

↓ FFAs

↓ IR

Clinical benefits of Metformin[72]

Metformin in the management of adult diabetic patients

- Current guidelines recommend early initiation of metformin as a first-line drug for monotherapy and combination therapy for patients with T2DM.
- This recommendation is based primarily on metformin's glucose-lowering effects, relatively low cost, and generally low level of side effects, including the absence of weight gain.[73]
- Metformin's first-line position was strengthened by the United Kingdom Prospective Diabetes Study (UKPDS) observation that the metformin-treated group had risk reductions of 32% (p = 0.002) for any diabetes-related endpoint, 42% for diabetes-related death (p = 0.017), and 36% for all-cause mortality (p = 0.011) compared with the control group.
- The UKPDS demonstrated that metformin is as effective as sulfonylurea in controlling blood glucose levels of obese patients with type 2 diabetes mellitus.[74]
- Metformin has been also been shown to be effective in normal weight patients.[75]

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Metformin effects on vasculo-protection

Study	Design	Duration	Key findings
UKPDS 33	Prospective	10 yr	Significant reduction in all-cause mortality, diabetes related mortality, and any end-point related to diabetes.
Sgambato et al.	Retrospective	3 yr	Trend towards reduction in angina symptoms (p=0.051). Significant lower re-infarction rates.
Johnson et al.	Retrospective	9 yr	Reduction of all-cause mortality and of cardiovascular mortality
Kao et al.	Prospective	2 yr	Significant risk reduction for any clinical event, myocardial infarction and all-cause mortality
Jadhav et al.	Prospective	8 weeks	Improved maximal ST depression, Duke score, and chest pain incidence
Kooy et al.	Prospective	4, 3 yr	Reduction of the risk of developing macrovascular disease

Need for fixed dose combination in management of T2DM

- Among Indian Patients with diabetes, mean HbA1c is 8.9% (Diabcare India Study – 2011) & 2/3rd are NOT at target HbA1c (ICMR-INDIAB Study)[76,77]
- With diabetes, there is a progressive loss of β-cell function, many patients eventually require multiple agents with differing MOAs to achieve target HbA1c levels[78,79]
- With over 30% of patients taking 3-4 tablets/day, pill burden results in poor treatment adherence, which in turn leads to inadequate glycemic control[80-83]
- Progressive decline of A1C resumes within 6 months after an SU is added to metformin, and increasing SU dose further can increase the chances of side-effects (like hypoglycaemia).[84]
- Dual therapy (Met + SU1/SGLT2i + Met) with mean baseline HbA1c of 8-8.9% has shown <22% are able to achieve target HbA1c < 7%[85]
- High pill burden and complex treatment regimens reduces adherence
- FDCs improve patient compliance, glycaemic control and have potential to decrease risk of complications
- In a meta-analysis involving data from 70,573 patients, use of FDCs with oral anti diabetic agents was associated with lower HbA1c and higher medication possession ratio compared to co-administered dual therapy use in type II DM[87]
- Each 10% increase in OAD medication adherence was associated with a 0.1% HbA1c reduction3 (p = 0.0004)[88]
- In a study of oral antidiabetics, it was observed that compliance reduced with increased frequency of administration - 79% for OD vs 65% for BID vs 38% for TID regimens[89]

Fixed dose combination of Sitagliptin + Glimepiride + Metformin – Rationale

Parameter	Metformin	Glimepiride	Sitagliptin	Comments
Efficacy (HbA1c, reduction)	0.9 -1.3%	1.0-1.2%	0.6-0.8%	**FDC can show improved efficacy**
Mechanism of action	Reduction of hepatic glucose output	Stimulation of insulin secretion from beta cells	Increase GLP-1, improving glucose-induced insulin secretion and reduction of glucagon	**Complementary mechanisms of action of 3 drugs**
Dosing	1000 mg ER OD	1/2 mg OD	100 mg OD	**PK parameters matching and conducive to OD dosing**
Weight reduction	Weight neutral/loss	Less weight gain compared to other SU	Weight Neutral	**Weight neutral benefits offered by sitagliptin and metformin**
Hypoglycemia	-	+	-	**Minimal risk from Sita and metformin**
CV outcome data	UKPDS: Proven cardiovascular safety	Glimepiride shown to have a non-inferior risk compared to placebo for 3-point MACE, all-cause mortality, CV & non-CV death. (indirect comparison from Carolina & Carmelina)[90]	TECOS: Proven cardiovascular safety	**CV & renal safety will make the FDC beneficial to diabetics with comorbidities**

Addition of Sitagliptin to glimepiride & metformin in patients offers better glycaemic control, additional benefit of weight neutrality with less risk of hypoglycaemia along with proven CV and renal safety

- Metformin can reduce insulin resistance and glimepiride can increase insulin secretion through stimulation of pancreatic beta cells, thus addressing multiple pathophysiological issues in type 2 diabetes

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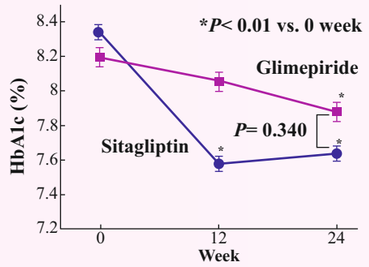
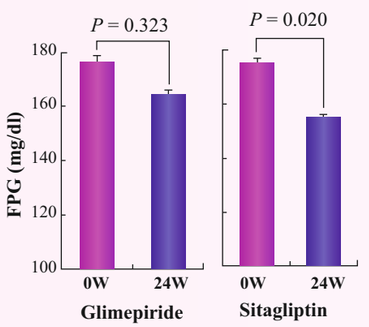
- Addition of Sitagliptin provides a complementary mechanism for glucose induced insulin secretion leading to improved diabetes control
- Sitagliptin exhibits known synergism with Metformin through several mechanism
- Sitagliptin when added to lower dose of glimepiride has shown to improve glycemic control with no increased risk of hypoglycemia
- Addition of Sitagliptin is expected to preserve the β-cell function as seen through studies evaluating Proinsulin/Insulin ratio (lower PI/I ratio)[91]

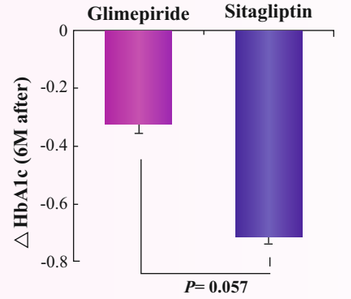
Protection of Pancreatic Beta cells Study: High dose Glimepiride vs 'Low dose Glimepiride + Sitagliptin'[91]

Efficacy in Treatment Arms

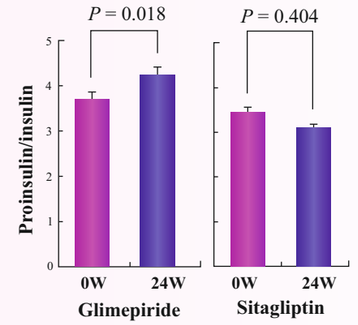


a Fasting plasma glucose





b Proinsulin/insulin



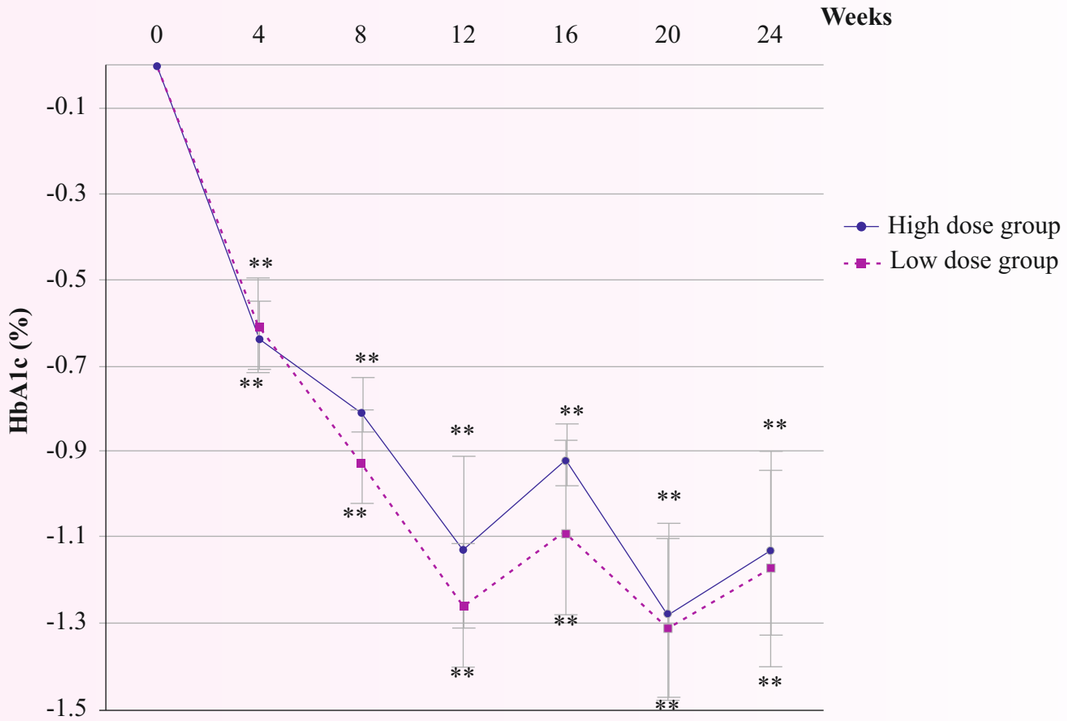
- **Significant higher reduction in HbA1c at 12 weeks** with Sita + Glime vs Glime high dose
- **Near significant reduction in 6 month HbA1c** with Sita plus Glime vs High dose Glime
- **Target fasting plasma glucose -** achieved in **36.7% of Sitagliptin group vs 16.7% in high dose glimepiride** group
- Glimepiride high dose group → **Higher Pro-insulin/Insulin ratio** indicating towards Beta cell **dysfunction**
- Low dose Glimepiride plus Sitagliptin **preserves Beta cell function (lowered PI/I)**
- **Hypoglycaemia was mild and comparable in both arms (1 patient in glimepiride and 2 patients in Sita arm)**

Dose reduction in Glimepiride reduces hypoglycemia risk – when Sitagliptin is added to Glimepiride

Study: Sitagliptin plus baseline low dose Glimepiride vs baseline only high dose Glimepiride[92]

Efficacy

Figure 17: Degrees of HbA1c reduction are shown. A statistical analysis was performed by the Wilcoxson rank sum, test paired t-test P<0.01 vs. 0 week



Safety

- None of the patients showed even mild hypoglycemic symptoms, such as palpitation, sweating, or unusual feelings of hunger, at each visit
- Body weight remained unchanged in both groups during the study period

In patients with baseline glimepiride 2-3 mg/day or 4 - 6mg/day - Sitagliptin plus use of low dose glimepiride (dose reduction) results in significant and comparable reduction in HbA1c (-1.1 to -1.2%) in both treatment arms

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Clinical evidence on combination of Sitagliptin and Glimepiride and Metformin

Phase III study of the Sitagliptin + Glimepiride + Metformin FDC in India – Study by Sun Pharma

Assessing effectiveness and safety of triple drug combination of Sitagliptin + Glimepiride + Metformin in type 2 diabetes patients

Objective:

Efficacy and safety of FDC of Sitagliptin, Metformin and Glimepiride Tablets (50 mg/1000 mg/1 mg) and (50 mg/1000 mg/2 mg) given BID in comparison to Co-administration of Metformin 1000 mg and Glimepiride 2 mg BID in patients with T2DM

Method:

Phase III, Multi-centric, Randomized, Comparative, active controlled, double blind, double dummy clinical trial

N=392

Patients on Glimepiride 4 mg and Metformin ≥ 1500 mg for at least 10 weeks with HbA1c between >8 to <11% were included

Randomization

Test Group (N=190)
Sitagliptin 50 mg+Metformin 1000 mg+ Glimepiride 1mg BID

Comparator Group (N=202)
Metformin 1000 mg + Glimepiride 2 mg BID

Up-titrated

If HbA1C ≥8% at week 16
FDC of Sitagliptin 50 mg+ Metformin 1000 mg + Glimepiride 2 mg BID

Double-blind period (16 weeks)

Open-label period

- End of study (EOS) for test group: 28 weeks; EOS for comparator group: 16 weeks

Outcomes Evaluated:

Primary outcome

- Mean change in HbA1c from baseline to week16

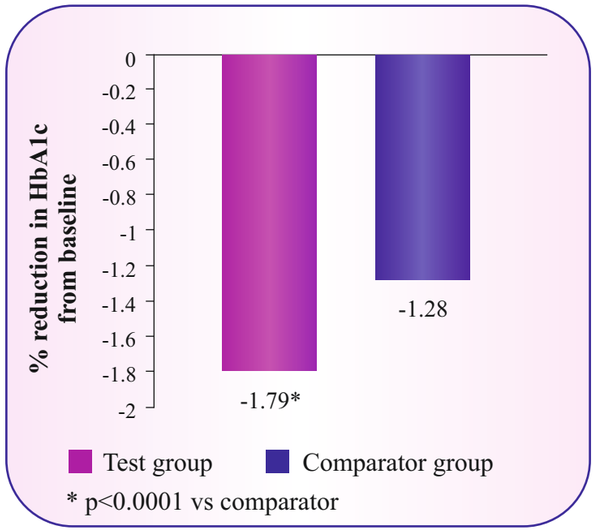
Secondary outcomes

- **Mean change in**
  - HbA1c from baseline at the end of week 28
  - Postprandial blood glucose (PPBG) from baseline to end of weeks 12, 16, 24 and 28
  - Fasting blood glucose (FBG) from baseline to end of weeks 12, 16, 24 and 28
- **Number of patients**
  - Achieving HbA1c < 7.0% at weeks 12, 16 and 28
  - Requiring hypoglycemia management
- **Safety assessment includes treatment emergent adverse events (TEAEs) assessment during the study**

Results:

Efficacy results:

Compared to the comparator group, the test group showed significant reduction in HbA1c at week 16 ($p < 0.0001$)



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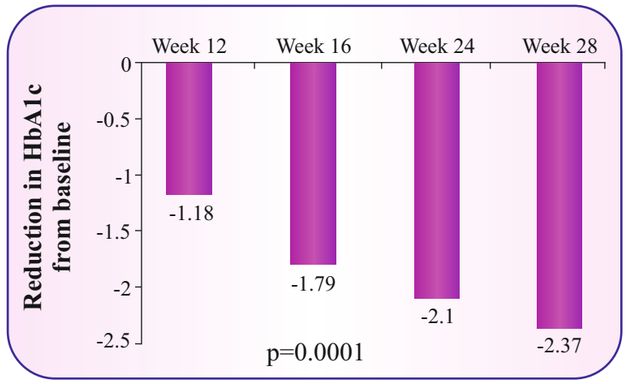


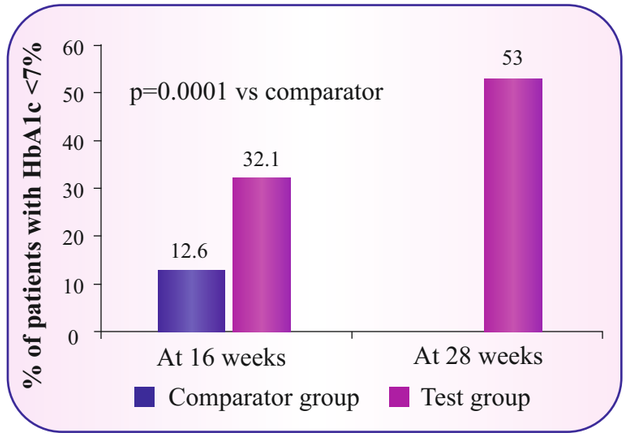
Sustained reductions in HbA1c over a period of 28 weeks with with FDC of Sitagliptin, Metformin and Glimepiride (50 mg / 1000 mg / 1 mg)

Mean change in HbA1c (%) from baseline to 28 weeks

With FDC of Sitagliptin 50 mg, Metformin 1000 mg and Glimepiride 1 mg, a significant reduction in FBG and PPBG from baseline to 12, 16, 24 and 28 was reported.

Table: Change in glycemic parameters from baseline

	Week 12	Week 16	Week 24	Week 28
Change in FBG	-32.6	-41.4	-48.4	-53.6
Change in PPBG	-41.8	-56.7	-72.8	-78.6



Compared to the comparator group, the test group depicted significantly greater number of patients achieving HbA1c target of <7%

Safety results:

No serious adverse events (SAEs) were reported

No patient required hypoglycaemia management during the study period.

Conclusion:

The triple drug combination of Sitagliptin, Metformin, and Glimepiride was well-tolerated and outperformed the co-administration of Metformin and Glimepiride in reducing HbA1c levels by week 16.

Stepdown approach on Glimepiride dose[93]

2007

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin

K. Hermansen, M. Kipnes, E. Luo, D. Farurik, H. Khatami and P. Stein, for Sitagliptin Study 035 Group

First published: 26 June 2007| https://doi.org/10.1111/j.1463-1326.2007/00744x | Citations: 382

See online appendix for list of Sitagliptin Study 035 investigators.

Efficacy: After 24 weeks, in the subset of patients on glimepiride plus metformin, sitagliptin reduced HbA1c by 0.89% relative to placebo, compared with a reduction of 0.57% in the subset of patients on glimepiride alone.

Beta cell: The addition of sitagliptin increased homeostasis model assessment β, a marker of β-cell function, by 12% ($p<0.05$) relative to placebo.

Hypoglycemia: Higher incidence of hypoglycaemia AEs (12 vs. 2%, respectively) in the sitagliptin group compared with the placebo group.

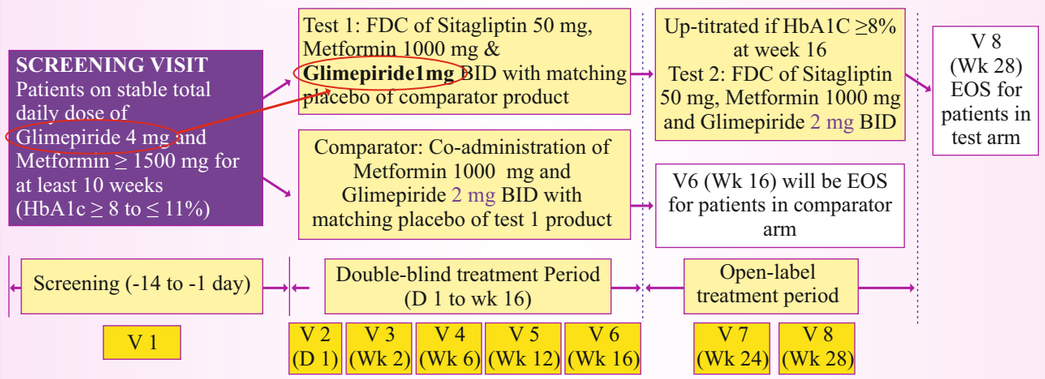
No dose de-escalation done, 441 patients received dose of glimepiride >4mg/day

VS

2023

Dose de-escalation strategy

Study Design



Step down Approach on Glimepiride dose

BID: Twice daily; D: Day; DSMB: Data safety monitoring board; EOS: End of study; FDC: Fixed dose combination; HbA1c: Glycosylated hemoglobin; V: Visit; Wk: Week

Statistically significant reduction in HbA1c with Test product in comparison with Comparator product demonstrating Superior efficacy-with lower dose of Glimepiride (-1.79% vs 1.28%)

No statistically significant increase in hypoglycemic events

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Summary

Type 2 diabetes mellitus (T2DM) is the most common and clinically significant metabolic disorder in India. It is progressive in nature and is characterized by the "Ominous octet" of eight factors that contribute to its pathophysiology. It is also associated with higher risks for myocardial infarction, stroke, diabetic kidney disease, microvascular events, and mortality.

Most Indian patients have uncontrolled diabetes (69%), as indicated by their inability to achieve the target level of HbA1c. Moreover, the achievement of treatment targets with traditional oral antihyperglycaemic agents and the adoption of healthy behaviour remains suboptimal in India. Further, the Asian Indian phenotype has unique characteristics that make it more susceptible to cardiometabolic risk.

Therapy with traditional oral antihyperglycaemic agents is associated with a progressive decline in β-cell function. Thus, there is an increased need for compliance and the use of combination therapy to achieve the treatment targets. Further, it is imperative that the newer agents address the maximum number of pathophysiological factors of T2DM.

Dipeptidyl peptidase-4 (DPP-4) inhibitors, Sulfonylureas and Metformin are highly effective in the management of T2DM. The rational fixed dose combination of SU, DPP4i and Metformin exhibits a synergistic effect resulting in improved glycaemic control, reduced insulin resistance, and improved beta cell function. The combination of these drugs addresses 6 out of 8 pathophysiological factors of metabolic derangement. Further, the combination results in improved compliance.

These drugs in combination with glimepiride at low dose are very efficacious in glycemic control and are less likely to cause hypoglycaemia. More importantly, studies have clearly demonstrated the cardiovascular safety of all three drugs. Therefore, the association of Sitagliptin, Glimepiride and Metformin is an attractive option to achieve optimal blood glucose control in T2DM, considering all these factors.

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