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Effects of Sitagliptin on 24-H Glycemic Changes in Indian Patientswith Type 2 Diabetes Assessed Using Continuous Glucose Monitoring

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Abstract:
Diabetes mellitus is one of the the most common, oldest and non communicable chronic disease in India.Diabetes is a serious, costly and heterogeneous metabolic disorder which ischaracterized by chronically elevated blood glucose levels (BGLs) and an inability to maintain BGL homeostasis. According to Indian council of medical research (ICMR, section 1,2005) diabetes is defined as a metabolic cum vascular syndrome of multiple etiologies factorise by hyperglycemia with disturbance of carbohydrate, protein and fat metabolism resulting from insulin deficiency or resistance to insulin or both.According to American diabetes association (ADA) diabetes is is defined as a group of metabolic diseases characterized by inappropriate hyperglycemia resulting from defects in insulin secretion, insulin action or both.

I. INTRODUCTION

Diabetes happens when your body isn't able to take up sugar (glucose) into its cells and use itfor energy. This results in a buildup of extra sugar in your bloodstream .Poorly controlled diabetes can lead to serious consequences, causing damage to a wide range of your body's organs and tissues including your heart, kidneys, eyes and nerves. The process of digestion includes breaking down the food you eat into various different nutrient sources. When you eat carbohydrates (for example, bread, rice, pasta), your body breaks this down into sugar (glucose). When glucose is in your bloodstream, it needs help – a "key" – to get into its final destination where it's used, which is inside your body's cells (cells make up your body's tissues and organs). This help or "key" is **INSULIN**.

Insulin is a hormone made by your pancreas, an organ located behind your stomach. Yourpancreas releases insulin into your bloodstream.

If you have diabetes:

Your pancreas doesn't make any insulin or enough insulin.

Your pancreas makes insulin but your body's cells don't respond to it and can't use itas it normally should.

If glucose can't get into your body's cells, it stays in your bloodstream and your bloodglucose level rises.

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Table No. 1 Chart of Normal Blood Sugar Levels for Diabetic Adults

Age	Blood Sugar Level After Fasting (FBS Range)	Normal Sugar Level Before Meal (Food)	Sugar Level After 1 to 2 Hours of Eating Food	Blood Sugar Level at Bedtime
20+ years Age	70 to 100 mg/dL	70 to 130 mg/dL	Less than180 mg/dL	100 to 140 mg/dL
Pregnant women	70 to 89 mg/dL	89 mg/dL	Below 120 mg/dL	100 to 140 mg/dL

Type of Diabetes

TYPE -1

This type is an autoimmune disease, meaning your body attacks itself. In this case, the insulin-producing cells in your pancreas are destroyed. Up to 10% of people who have diabetes have Type 1. It's usually diagnosed in children and young adults (but can develop at any age). It was once better known as "juvenile" diabetes. People with Type 1 diabetes need to take insulin every day. This is why it is also called insulin-dependent diabetes.

TYPE-2

With this type, your body either doesn't make enough insulin or your body's cells don't respond normally to the insulin. This is the most common type of diabetes. Up to 95% of people with diabetes have Type 2. It usually occurs in middle-aged and older people.
Other common names for Type 2 include adult-onset diabetes and insulin-resistantdiabetes.
GESTATIONAL DIABETES

This type develops in some women during their pregnancy. Gestational diabetes usually goes away after pregnancy. However, if you have gestational diabetes you'reat higher risk of developing Type 2 diabetes later on in life.
Classification of Antidiabetic drugs

1Biguanidese:METFORMIN
Thiazolidinediones: Pioglitazone, Rosiglitazone
Sulfonylureas: a. First generation Chlorpropamide,Tolbutamide
b.Second generation- Glimepiride,
Meglitinides: Repaglinide, Nateglinide
Glucagon-like peptide-1 receptor agonists: Exenatide,Liraglutide,Albiglutide

Dipeptidyl peptidase-4 inhibitors : Sitagliptin ,Saxagliptin ,Linagliptin
Sodium-glucose cotransporter 2 inhibitors: Dapagliflozin ,Empagliflozin
Alpha-glucosidase inhibitors: Acarbose,Miglitol

Causes of Type 2 Diabetes

Insulin is a hormone made by your pancreas that acts like a key to let blood sugar into the cells in your body for use as energy. If you have type 2 diabetes, cells don't respond normally to insulin; this is called insulin resistance Your pancreas makes more insulin to try to get cellsto respond. Eventually your pancreas can't keep up, and your blood sugar rises, setting the stage for prediabetes and type 2 diabetes. High blood sugar is damaging to the body and can cause other serious health problems, such as heart disease, vision loss, and kidney disease .

Symptoms of Type 2 Diabetes

These type of patients usually experience symptoms of acutehyperglycemia which include frequent urination that is polyuria, polydipsia (they might become thirsty all the time), polyphagia (experience is more hunger), weight loss, blurred vision, fatigue, headache and poor wound healing. Long term complications of diabetes include retinopathywith the potential loss of vision, nephropathy leading to renal failure, peripheral neuropathy with risk of foot ulcers, amputations and charcot joints and autonomic neuropathy causinggastrointestinal, genitourinary and

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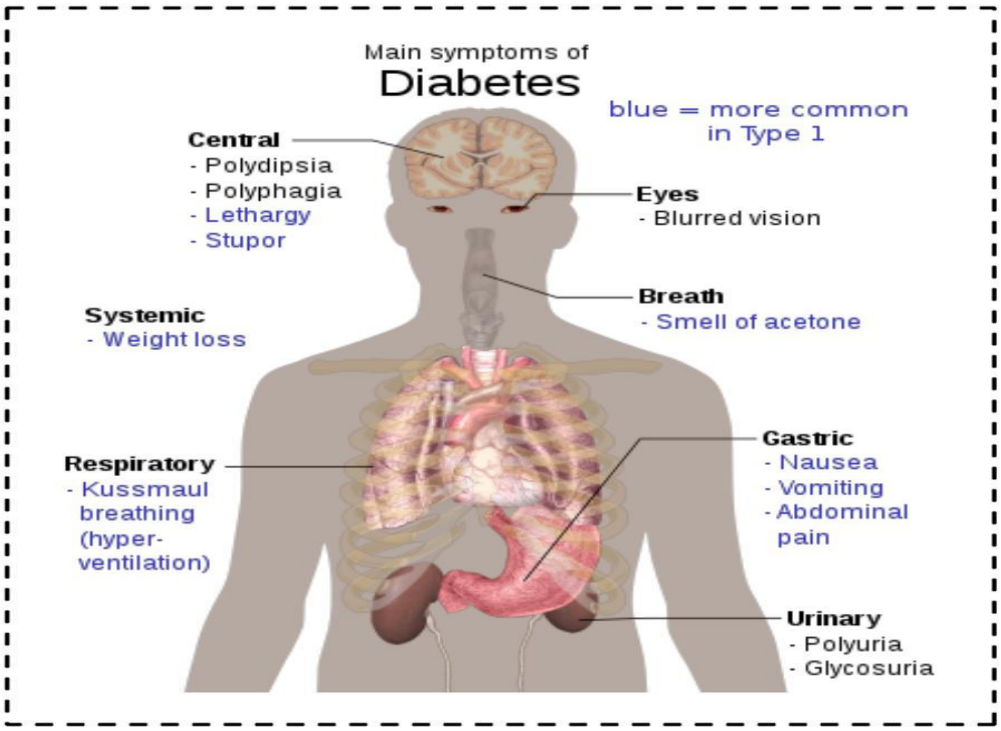
cardiovascular systems and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral atrial and cerebrovascular disease, hypertension and abnormality of lipoprotein metabolism are often found in people with diabetes. (shown in fig)



Diabetes has grown to become one of largest public health challenges globally, affecting 25.8 million in the United States and 382 million worldwide; and this number is expected to grow to more than 592 million by 2045.

Indians get diabetes much earlier i.e. at an average of 35 years. About 25-30 million Indians suffer from diabetes, almost half of which are aware of the disease. However, urban population has a much higher incidence of diabetes than rural counterparts. People leading sedentary life style and consuming high cholesterol diet, who are generally obese or with a family history of diabetes are more prone to diabetes. Till date medical science cannot claim that it knows all that needs to be known about this disease, including the management. This is the main reason for the persistent interested all over the world to explore alternative remedies from the so called “Alternative system” of medicine. Treatment of diabetes has been attempted with different indigenous plant and polyherbal formulations. Many herbal products have been describe for the care of diabetes mellitus in ancient literature of Ayurveda in India.

Treatment of diabetes need constant monitoring of blood glucose level, regulating it through modified dietary sugar intake, physical exercise and insulin therapy (subcutaneous administration) to attain normogly.Therefore the current standard of care for type 1 and advanced type 2 diabetes involves daily subcutaneous insulin injections, and frequent finger pricks to draw blood for the measurement of BGLs.Additionally, periodic measurement of blood glucose may not detect large fluctuations in BGLs which occur between points of measurement. Therefore, systems which improve blood glucose monitoring, or “close the loop” between glucose measurement and insulin delivery, are highly desirable.In order to optimize different routes of insulin therapy, novel drug delivery systems have been suggested, and alternative routes of administration have been investigated. One such method used for the advancement of medicine is nanotechnology. Nanotechnology involves the use of particles within 1–100 nm. It is the size of these particles, as

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well as their large surface to volume ratio, that has increased interest in their application for molecular therapeutic targeting. The use of nanoparticles (NPs) allows for improved bioavailability, controlled release, and targeted drug delivery (TDD). To date, the advancement of nanomedicine has focused on the safe, effective, and accurate delivery of drugs foran array of pathological conditions

Treatment

The treatment goals of diabetes are to prevent complications and inhibit their progression by controlling the glycemic level at a level similar to that in healthy people. Hemoglobin A1c (HbA1c) has been used as a surrogate marker of glycemic control or a surrogate end point in several large-scale clinical studies. However, the DECODE study1 and the STOP-NIDDM study2 showed that patients with postprandial hyperglycemia had a higher risk of cardiovascular events, even when their fasting glucose levels were the same as those in patients without hyperglycemia. These studies also showed that it is difficult to monitor glycemic control with HbA1c only because HbA1c is a marker of the average glycemic level. Based on these findings, the International Diabetes Federation announced the Guidelines for Management of Post meal Glucose in 2007.3 .These guidelines indicated the importance of management of postprandial hyperglycemia, which cannot be evaluated with HbA1c only and proposed a new method of continuous glucose monitoring (CGM) to evaluate postprandial glucose level.

In CGM, the average glucose level is measured at an interval of 1–5min. This allows monitoring of postprandial glycemic changes, which have previously been partially monitored by conventional self-monitoring of blood glucose (SMBG). In CGM, the pattern of glycemic changes can be visualized; the 24-h glycemic fluctuation range (the time for which the glucose level is greater than or less than a certain level) can be obtained; and asymptomatic hypoglycemia, which cannot be determined by conventional methods, can be analyzed using software. These advances have improved glucose management by facilitating control of the glucose level with smaller 24-h glycemic fluctuation and less swing at the same HbA1c value.

Sitagliptin is a dipeptidyl peptidase (DPP)-4 inhibitor that enhances the activity of incretins, which then promote insulin secretion in a glucose-dependent manner, and inhibits glucagon secretion. A comparative clinical study with an alpha glucosidase inhibitor showed that sitagliptin significantly improved the glucose level at 2 h after meal, the fasting blood glucose level, and HbA1c.8 However, each of these parameters was measured at a single time point, and the effects of sitagliptin on 24-h glycemic changes in Indian patients are still unclear. Therefore, in this study, we examined the effects of sitagliptin on 24-h glycemic changes using CGM in single administration or concomitant administration with another oral hypoglycemic drug.

Research into the role of gut hormones in the regulation of pancreatic beta-cell function has led to new targets in the management of type-2 diabetes. It is known that eating food leads to the release of multiple hormones that regulate gut motility, the secretion of gastric and pancreatic enzymes, the contraction of the gallbladder, and the absorption of various nutrients. Several hormones facilitate the process of glucose removal by stimulating the release of insulin from the pancreas. The two main hormones involved in this endocrine signaling from the gut are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).

Secretion of GLP-1 occurs from the enteroendocrine L cells of the distal small intestine, whereas GIP is mainly secreted from the K cells in the proximal small intestine.[4] In the early 1900s, research involving the treatment of glycosuria with the administration of intestinal extracts first supported the in-cretin (Intestinal secretion of Insulin) effect that is mediated by these hormones. The incretin effect refers to the greater amount of insulin secretion noted with giving oral glucose versus a comparable intravenous (IV) dosage, suggesting that oral ingestion stimulates pancreatic beta cells and the regulation of glucose. This effect is reduced in patients with type-2 diabetes and is thought to be related to decreased insulinotropic action of GIP but not GLP-1. In addition, continuous infusions of GLP-1 increase insulin secretion in patients with type-2 diabetes; however, higher doses of GIP have not been shown to do the same. These attributes of GLP-1 make it an opportune target for the management of type-2 diabetes.

The role of GLP-1 in lowering blood glucose levels occurs via several mechanisms in addition to insulin secretion, including a reduction in glucagon concentrations, a delay of gastric emptying, and potential induction of satiety. GLP-1

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may also play a role in the proliferation of beta cells and the decrease in beta-cell apoptosis. Circulating levels of GLP-1 are low in the fasting state and rise quickly after meals; these circulating levels also decrease rapidly (half-life, less than 2 minutes) because of inactivation by the proteolytic enzyme, DPP-4. DPP-4 inhibitors, such as sitagliptin and saxagliptin, slow the inactivation and degradation of GLP-1, offering the newest FDA-approved treatment approaches for type-2 diabetes.

Sitagliptin and saxagliptin have been studied in the treatment of type-2 diabetes as monotherapy and in conjunction with other antidiabetic medications. In placebo-controlled trials, these agents, when used as monotherapy, decreased HbA1c values by 0.6% to 0.9% and were not associated with fluctuations in weight or alterations in lipids; they were associated with an incidence of hypoglycemia similar to that of placebo.

Sitagliptin in combination with a sulfonylurea or insulin has been associated with additive hypoglycemic effects.9 Saxagliptin, in combination with insulin, has not been studied; hypoglycemia is more common when saxagliptin is combined with a sulfonylurea as well.7 No clinical trials to date have assessed the efficacy of sitagliptin or saxagliptin at reducing macrovascular complications associated with type-2 diabetes.

Sitagliptin has been evaluated for use in combination with other agents for type-2 diabetes, including metformin, pioglitazone, rosiglitazone (Avandia, GlaxoSmithKline), glimepiride (Amaryl, Sanofi-Aventis), and insulin.

Sitagliptin/metformin.
Charbonnel et al. conducted a 24-week, randomized, double-blind, placebo-controlled trial to assess the addition of sitagliptin 100 mg/day to metformin therapy for patients with mild-to-moderate hyperglycemia (mean baseline HbA_{1c}, 8%).In this study, sitagliptin was associated with the following significant reductions:
HbA_{1c}: least-squares change in mean HbA_{1c} from baseline, −0.65% for sitagliptin vs. −0.02% for placebo ($P < 0.001$)
fasting plasma glucose (FPG): least-squares mean change from baseline, −16.2 mg/dL for sitagliptin vs. 9 mg/dL for placebo ($P < 0.001$)
postprandial plasma glucose (PPG) at two hours: least-squares mean change from baseline, −61.3 mg/dL for sitagliptin vs. −10.8 mg/dL for placebo ($P < 0.001$)

Sitagliptin/pioglitazone. A second 24-week, multicenter, randomized, double-blind, placebo-controlled trial was conducted in which sitagliptin was added to pioglitazone therapy. Significant reductions were achieved as follows:
HbA_{1c}:
○ adjusted mean change from baseline, −0.85% for sitagliptin/pioglitazone; −0.15% for placebo/pioglita-zone; and adjusted mean difference from placebo/pioglitazone, −0.70%; 95% confidence interval [CI], −0.85 to −0.54 ($P < 0.001$)
FPG:
○ adjusted mean change from baseline, −16.7 mg/dL for sitagliptin/pioglitazone; 1 mg/dL for placebo/pioglitazone; and adjusted mean difference from placebo/pioglitazone, −17.7 mg/dL; 95% CI, −24.3 to −11 ($P < 0.001$)

Using Continuous Glucose Monitoring in Clinical Practice

Continuous glucose monitoring (CGM) systems are more than just glucose monitors. Recent CGM systems have moved beyond mere blood glucose monitoring (BGM) by providing both real-time and predictive glycemic data. The robust data garnered from CGM can also be used Increased frequency of glucose monitoring is associated with decreased hypoglycemia and increased glycemic time in range (TIR), which correlates with improved A1C. Moreover, glucose patterns captured via CGM data analysis can highlight areas in need of treatment intervention (e.g., to prevent hypoglycemia, improve glycemic control at specific times of day, and increase overall TIR). As is well known, the A1C test provides an indication of average glycemic control over the previous 2–3 months. However, it does not capture glycemic variability; thus, individuals who have the same A1C may have vastly different glucose ranges. CGM can be a good option for patients with inconsistent or confounding glycemic control, who desire engagement in their own disease management, or whose treatment plan puts them in danger of hypoglycemia.

Health care providers (HCPs) can implement two different modalities of CGM. They may prescribe a personal CGM device, which a patient can use either co tinuously or intermittently, or they may purchase for their practices . Professional CGM systems that canbe

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sent home with a patient for a brief period of time for diagnostic purposes. The Medtronic iPro2 and the FreeStyle Libre Pro are professional CGM systems for which data are blindedto the patient. The data are uploaded in the HCP's office for retrospective review with the patient. The Dexcom G6 professional CGM system can be prescribed in blinded and unblinded modes. HCPs may use the unblinded option to help patients increase their awareness of their own glucose levels and make real-time treatment decisions.

The data collected by these devices and either down- loaded in the clinic or transmitted remotely allow for visualization of a patient's true glycemic picture and the effects of current interventional treatments. CGM data also give HCPs insight into patients' behaviors and glycemic patterns and may reveal previously undetected issues such as hypoglycemia. Retrospective review of CGM data can reveal therapeutic impacts on glucose management, aid in making treatment decisions, and provide opportunities for education.

Professional CGM systems have been used clinically to measure the effects of variables over an intermittent or specific time interval, such as 3 days or 2 weeks. More specifically, such CGM has been used to evaluate the effects of various interventions, behaviors, and therapies, including the effects of foods or various types of exercise and medication titration.

The abundance of data gathered via CGM can be reviewed and interpreted through the ambulatory glucose profile (AGP) report, a standardized CGM report that provides a graphical and quantitative display of glycemic activity. The AGP visually displays the dynamics of glycemic activity, including periods of hypoglycemia, glycemic excursions (both high and low), TIR, and recurring glucose patterns, all of which are meaningful metrics for guiding comprehensive diabetes management.

From the patient perspective, CGM offers the benefit of real-time glycemic monitoring with glucose trend in- formation indicated by directional arrows. These trend arrows are a visual display of the direction of glycemic activity (i.e., whether the current glucose level is rising, stable, or decreasing). The visual display of CGM data allows patients to view their glycemic activity and monitor the effects of different types of food, timing of meals, activity levels, stress, and illness. This opportunity facilitates increased patient engagement with diabetes management. Having glucose data readily available is also relevant for loved ones and caregivers of people with diabetes, allowing them to better assist in care and offering them peace of mind with regard to hypoglycemia and hyperglycemia.

Integrating CGM into clinical practice can be challenging for several reasons. Common issues reported include data overload, increased clinic staff time, and the need for HCP education on data interpretation. Orienting practice staff to the use of CGM technology and down- loading reports to a standalone computer and printer that are separate from restrictive administrative firewalls can streamline analysis of CGM data.

Although there can be some barriers to CGM use, there is also strong evidence for its utility in patients with either type 1 or type 2 diabetes and with either personal or professional CGM systems. Patient benefits include improvement in A1C, reductions in hypoglycemia and glycemic variability, and greater treatment satisfaction and improved sense of mental well-being.

One solution to overcoming barriers is intermittent use, of personal or professional CGM, from every other week to perhaps every 6 months, followed by office review of the AGP report . This option permits an overview of the glycemic picture at important intervals, such as during lifestyle intervention or after medication changes. In addition, reviewing the AGP report with a patient offers an HCP the opportunity for patient education and a means of encouraging communication and shared decision-making.

DPP-4 inhibitors increase the activity of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, which are endogenous incretin hormones that regulate glucose-dependent insulin and glucagon secretion, and this effect improves hyperglycemia. Thus, whereas sulfonylurea's and glinide drugs decrease the glucose level through a direct action on insulin secretion with closing of KATP channels of pancreatic b cells, the effect of a DPP-4 inhibitor such as sitagliptin depends on the blood glucose level itself. In this study, the average 24-h blood glucose level was decreased by sitagliptin, and this effect was mainly due to improvement of

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postprandial hyperglycemia. The glycemic changes after administration of sulfonylurea drugs to patients with type 2 diabetes suggest that these drugs decrease the average 24-h glucose level, based on the HbA1c value, but do not decrease the range of glycemic fluctuation, as well as decrease postprandial hyperglycemia and the fasting glucose level to a similar extent. Administration of sitagliptin alone and concomitant administration with a sulfonylurea drug decreased the average glucose level and improved glycemic fluctuation. Thus, sitagliptin appears to be a more appropriate drug for improvement of postprandial hyperglycemia and is also likely to improve glucose spikes, which cannot be monitored using HbA1c only, and prevent macrovascular complications. In this study, we found a significant decrease in the time period of hyperglycemia (blood glucose level >180 mg/dL), but the period of hypoglycemia did not increase and actually showed a tendency to decrease. Vildagliptin, another DPP-4 inhibitor, has been found to significantly increase the level of glucagon in blood in a hypoglycemia clamp study. Incretin hormones have various bioactivities other than a direct increase in insulin secretion via receptors on the pancreatic b cell membrane. Expression of a glucagon-like peptide-1 receptor has been shown in the central nervous system, and a preclinical study showed that glucagon-like peptide-1 signals in the central nervous system control glucose uptake and production in the peripheral tissues. Therefore, sitagliptin may also maintain homeostasis of blood glucose via the central nervous system through increased activity of incretin, in addition to having a direct action in pancreatic b cells. The extent of the decrease in the average blood glucose level induced by sitagliptin was correlated with the average glucose level before administration. This indicates that patients with a higher glucose level before administration of sitagliptin are likely to have a greater decrease in the glucose level. These data confirm the results with sitagliptin, which have shown that the decrease in the glucose level is greater in patients with a higher HbA1c level before administration The findings also support the evaluation of drug efficacy with CGM because they show that changes in the average 24-h glucose level are related to changes in HbA1c. The MAGE level before sitagliptin administration was also correlated with the decrease in MAGE after administration, which suggests that larger glycemic fluctuation may result in a greater effect of sitagliptin in maintaining the homeostasis of blood glucose.

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