Diabetes affects an estimated 285 million adults worldwide and causes approximately four million deaths each year. Management strategies in type 2 diabetes aim to achieve and maintain glycemic control to HbA1c levels of <6.5% or <7.0% to reduce the risk of complications. However, despite treatment with lifestyle changes and effective oral hypoglycemic monotherapy, the progressive decline in glucose control persists, eventually necessitating combination therapy for many patients. Research interest has turned to further assess the combination of linagliptin with metformin, the most commonly prescribed first-line treatment for diabetes, and considered to be the first choice in the management of type 2 diabetes. The dipeptidyl peptidase-4 (DPP-4) inhibitors are a promising class of drugs for the treatment of type 2 diabetes. Linagliptin is a novel, xanthine-based DPP-4 inhibitor which has a predominantly non-renal route of excretion. This potent and selective agent inhibits DPP-4 with an IC50 of ~nM and has a particularly long duration of action (>80% DPP-4 inhibition at 24-h postdose), both of which are factors that allow for convenient once-daily dosing. Metformin acts by improving insulin sensitivity and decreasing hepatic glucose production, so co-administration of linagliptin in individuals with inadequate glycemic control with metformin alone would be pharmacologically sound and intuitive because of the complementary mechanisms of action of these two agents. The effect of inhibiting DPP-4 is to increase exposure to GLP-1, resulting in the lowering of circulating glucose through enhanced insulin secretion and inhibition of glucagon secretion. This is believed to complement the suppression of hepatic glucose production and improved insulin sensitivity associated with metformin. Furthermore, the lack of clinically relevant pharmacokinetic interactions of these medications and their corresponding weight-neutral effects also support this combination. The objective of this study published in the journal Diabetes, Obesity and Metabolism was to investigate the efficacy and safety of linagliptin 5 mg vs. placebo administered for 24 weeks as add-on therapy to metformin in patients with type 2 diabetes having insufficient glycemic control. This 24-week, randomized, placebo-controlled, double-blind, parallel-group study was carried out in 82 centres in 10 countries. Patients with HbA1c levels of 7.0–10.0% on metformin and a maximum of one additional antidiabetes medication, which was discontinued at screening, continued on metformin ≥1500 mg/day for 6 weeks, including a placebo run-in period of 2 weeks, before being randomized to linagliptin 5 mg once daily (n = 524) or placebo (n = 177) add-on. The primary outcome was the change from baseline in HbA1c after 24 weeks of treatment, evaluated with an analysis of covariance (ANCOVA). The result of the study shows that Mean baseline HbA1c and fasting plasma glucose (FPG) were 8.1% and 9.4 mmol/l, respectively. Linagliptin showed significant reductions vs. placebo in adjusted mean changes from baseline of HbA1c (−0.49 vs. 0.15%), FPG (−0.59 vs. 0.58 mmol/l) and 2hPPG (−2.7 vs. 1.0 mmol/l); all P < 0.0001. Hypoglycemia was rare, occurring in three patients (0.6%) treated with linagliptin and five patients (2.8%) in the placebo group. Body weight did not change significantly from baseline in both groups (−0.5 kg placebo, −0.4 kg linagliptin). To summarize, linagliptin 5 mg once daily add-on therapy is an effective, well-tolerated and rational choice for patients with type 2 diabetes inadequately treated with metformin alone.
Results of a new study add to the evidence of an association between higher body mass index (BMI) and increased risk of cardio-metabolic diseases such as hypertension, coronary heart disease, type 2 diabetes, according to a study published by JAMA Cardiology. A connection between higher BMI and cardio-metabolic disease risk usually arise from observational studies that are unable to fully account for confounding by shared risk factors. Mendelian randomization (a method of analysis using genetic information) is an approach that partially overcomes these limitations. Using Mendelian randomization, the researchers conducted a study that included 119,859 participants in the UK Biobank (with medical, socio-demographic and genetic data) to examine the association between BMI and cardio-metabolic diseases and traits. Of the individuals in the study, 47 percent were men; average age was 57 years. The researchers found that higher BMI was associated with an increased risk of coronary heart disease, hypertension, and type 2 diabetes, as well as increased systolic and diastolic blood pressure. These associations were independent of age, sex, alcohol intake, and smoking history. The authors wrote that the results of this study have relevance for public health policies in many countries with increasing obesity levels. "Body mass index represents an important modifiable risk factor for ameliorating the risk of cardio-metabolic disease in the general population." A limitation of the study was that the sample lacked data on a complete range of potential mediators, such as lipid traits and glucose levels.

**Current Research**

**Higher BMI Linked with Increased Risk of High Blood Pressure, Heart Disease, Type 2 Diabetes**

The brain is the key in the regulation of appetite, body weight and metabolism. Specifically, there is a small group of hypothalamic neurons, called pro-opiomelanocortin (POMC) neurons, that detect and integrate signals that inform on the energy state of the organism and activate the appropriate physiological responses. These neurons are sensitive to fluctuations in nutrients such as glucose, fatty acids and amino acids. Proopiomelanocortin neurons are critical sensors of nutrient availability implicated in energy balance and glucose metabolism control. However, the precise mechanisms underlying nutrient sensing in POMC neurons remain incompletely understood. We show that mitochondrial dynamics mediated by Mitofusin 1 (MFN1) in POMC neurons couple nutrient sensing with systemic glucose metabolism. Mice lacking MFN1 in POMC neurons exhibited defective mitochondrial architecture remodeling and attenuated hypothalamic gene expression programs during the fast-to-fed transition. This loss of mitochondrial flexibility in POMC neurons bidirectionally altered glucose sensing, causing abnormal glucose homeostasis due to defective insulin secretion by pancreatic β cells. Fed mice lacking MFN1 in POMC neurons displayed enhanced hypothalamic mitochondrial oxygen flux and reactive oxygen species generation. Central delivery of antioxidants was able to normalize the phenotype. Collectively, our data posit MFN1-mediated mitochondrial dynamics in POMC neurons as an intrinsic nutrient-sensing mechanism and unveil an unrecognized link between this subset of neurons and insulin release. Now, a research project reveals the connection between POMC neurons at the hypothalamus and the release of insulin by the pancreas and describes new molecular mechanisms involved in this connection. The researchers publish the study in the journal Cell Metabolism. The POMC neurons detect changes in nutrient availability, but the molecular mechanisms involved are not known in detail. Also changes in the shape of mitochondria, a phenomenon known as mitochondrial dynamics, is a mechanism of energy adaptation in changing metabolic conditions, to adjust the needs of cells. To determine whether defects in the mitochondrial dynamics of this small nucleus of POMC neurons could cause alterations in metabolism, researchers removed a mitochondrial dynamics protein, Mitofusin 1, in these cells in mice. First, the scientists observed that these mice have defects in many organs levels and adaptation between the fasting state and after being fed. Second, they found that these defects lead to disturbances in the glucose metabolism that are caused by a lower secretion of insulin. "It was surprising to discover that these neurons are involved not only in the control of the intake, which was already known, but also in the control of the amount of insulin secreted by the β cells of the pancreas," explains the researcher. Scientists observed for the first time that this communication between the hypothalamus and the pancreas depends on the activity of the protein Mitofusin 1 and are starting to understand some molecular details of this connection. They describe that the alterations are due to a disproportionate, though transitory, increase in the production of radical oxygen species (ROS) in the hypothalamus. When the levels of ROS in the hypothalamus are restored in the laboratory, the pancreas starts to secrete the correct levels of insulin again. The researcher adds that "our results also suggest pathological implications of this animal model, since a diet rich in fats makes these mice more susceptible to developing diabetes." Insulin segregation is a major phenomenon in relation to diabetes. Type 2 diabetes patients, who represent the 85% of people with diabetes, have fewer β cells and less ability to secrete insulin in response to glucose. "Understanding the mechanisms involved in regulating insulin is important and therefore helps us to better understand the pathophysiology of diabetes," says the researcher, who emphasizes that "much research needs to be done to apply these findings, given that we are talking about neural mechanisms of complex intervention."
**Importance of Taking Diabetes Medications as Prescribed, Exercising and Managing Weight**

People with diabetes who took their medications at least 80% of the time and who exercised four or more times per week were at lower risk for poorly controlled blood sugar, according to a new study published in the American Journal of Pharmacy Benefits. The study also finds that people who were clinically obese were at higher risk for poorly controlled blood sugar. Poorly controlled blood sugar can lead to complications including kidney disease, retinal damage, heart disease, hospitalization and death, according to the American Diabetes Association (ADA). The ADA estimates that about 29 million Americans have diabetes, and according to the National Health and Nutrition Examination Survey, 21% of adults with diabetes have poorly controlled blood sugar. The study included nearly 20,000 patients. Many prior studies relied on asking patients if they took their medications, which is less reliable than patients’ medical records. "Our physicians can look at a patient’s electronic medical record and quickly see how often patients are refilling their diabetes, cholesterol and blood pressure medications. If patients are refilling medications when they’re supposed to, they’re also likely taking them when they’re supposed to,” said lead author. "During office visits we also ask patients if they are exercising and then enter this information into their medical record.” “It’s not that people are willfully not taking their medications, they just forget,” said the researcher. “There’s so much focus on new drugs and new technologies to improve diabetes care, but our study shows we could likely improve outcomes if we help patients do these three things: take their medications as prescribed, increase their exercise and manage their weight.” Researchers examined several lifestyle and demographic factors to determine which were most closely associated with poorly controlled blood sugar. They found that members who took their oral diabetes medications at least 80% of the time were 46% less likely to have poorly controlled blood sugar, compared to those who took their medications less than 80% of the time. Members who exercised four or more times a week were 25% less likely to have poorly controlled blood sugar, compared to members who exercised three or fewer times per week. Researchers also found that people who were clinically obese (a body mass index [BMI] of 30 or more) were 18% more likely to have poorly controlled blood sugar, compared to those who were not obese. African Americans and other racial and ethnic minorities were also more likely than non-Hispanic whites to have poorly controlled blood sugar. These differences remained even after adjusting for medication adherence and other lifestyle factors, according to the researchers.

**Efficacy and Safety of Voglibose in Patients of Type 2 Diabetes Mellitus Uncontrolled with Glimepiride and Metformin in Punjabi Population**

Diabetes mellitus is one of the most common non-communicable diseases globally. The prevalence of diabetes is steadily increasing worldwide, particularly in the developing countries like India. According to the study conducted by the Jalandhar diabetic society, the incidence of diabetes in urban Punjab is on the rise and the number of diabetics is increasing year by year. The predominant clinical form of DM is Type 2 DM which accounts for more than 90% of all cases. Its association with developing complications severely alters the quality of life and imposes an enormous burden on health care system. The key management goals in Type 2 DM are the relief of acute symptoms and prevention of long term complications, whilst avoiding hypoglycemia. The relationship between the degree of glycemic control and microvascular complications in Type 2 DM is well established. However, for prevention of macrovascular disease improving glycemic control is necessary but not sufficient. In some studies it was found that treating other risk factors like dyslipidemia and hypertension have been shown to be effective in reducing macrovascular disease. Dietary and lifestyle modifications form the mainstream of therapy for Type 2 DM. Pharmacological therapy is advocated when treatment goals are not achieved with dietary and lifestyle modifications. Several oral anti-hyperglycemic agents are available to optimize the management of Type 2 DM. Based on their mechanism of action, they are subdivided into agents that increase insulin secretion like sulfonylureas, meglitinides, GLP-1 agonists, DPP-4 inhibitors, reduce glucose production like biguanides, increase insulin sensitivity like thiazolidinediones and reduce carbohydrate absorption like α-glucosidase inhibitors. Voglibose is a competitive inhibitor of α-glucosidase enzyme present in brush border of small intestine. It inhibits the cleavage of complex carbohydrates into simple sugars and inhibit their absorption from small intestine. Although all the oral antidiabetic agents are reasonably effective as monotherapy in improving glycemic control but due to progressive nature of type 2 DM, monotherapy is often associated with inadequate control of glycemia and loss of efficacy over time. Combining agents with different modes of action produce additive effects on glycemic control, allows the use of submaximal doses of the agents, thereby decreasing the unwanted side effects and have complementary benefits on cardiovascular risk factors. Therefore, the present study was designed to study the effect of voglibose on glycemic and lipid profile as an add-on drug in patients with DM whose glycemic status was uncontrolled with glimepiride 2 mg BD and metformin 500 mg BD. This open study was conducted over a six months period. Thirty patients of type 2 DM of either sex in the age group of 30–75 years who were on maximum doses of glimepiride 2 mg BD and metformin 500 mg BD with FBG > 126 mg/dl and HbA1c between 7–10% were selected at random. They were given voglibose 0.2 mg TDS as add-on to triple drug. The effect of triple drug combination was then observed on various parameters i.e. FBG, PPG, HbA1c and lipid profile (Total cholesterol, TG, LDL, VLDL and HDL). At the end of 6 months it was observed that voglibose reduced FBG, PPG and HbA1c significantly (P < 0.001). The study found beneficial effect of voglibose on all the parameters of lipid profile (P < 0.01); but side effects like pain abdomen, headache, diarrhea, flatulence, sweating and hot flushes were also observed.
Efficacy of Metformin in Pregnant Obese Women: A Randomized Controlled Trial

Increasing evidence suggests obesity has its origins prior to birth. There is clear correlation between maternal obesity, high birth weight and offspring risk of obesity in later life. It is also clear that women who are obese during pregnancy are at greater risk of adverse outcomes, including gestational diabetes and stillbirth. The mechanism(s) by which obesity causes these problems is unknown, although hyperglycemia and insulin resistance are strongly implicated. This paper presents a protocol for a study to test the hypothesis that metformin will improve insulin sensitivity in obese pregnant women, thereby reducing the incidence of high birth weight babies and other pregnancy complications. The Efficacy of Metformin in Pregnant Obese Women, a Randomized controlled (EMPOWaR) trial is a double-masked randomized placebo-controlled trial to determine whether metformin given to obese (body mass index >30 kg/m²) pregnant women from 16 weeks’ gestation until delivery reduces the incidence of high birth weight babies. A secondary aim is to test the mechanism(s) of any effect. Obese women with a singleton pregnancy and normal glucose tolerance will be recruited prior to 16 weeks’ gestation and prescribed study medication, metformin or placebo, to be taken until delivery. Further study visits will occur at 28 and 36 weeks’ gestation for glucose tolerance testing and to record anthropometric measurements. Birth weight and other measurements will be recorded at time of delivery. Anthropometry of mother and baby will be performed at 3 months post-delivery. As of January 2014, 449 women had been randomized across the UK. This study finds metformin to be beneficial in reducing excess birth weight in obese pregnant women, it presents a potential future therapy where none currently exist. Metformin has been used for decades in pregnant women with no evidence of any teratogenic effects. There is no evidence from previous studies that metformin increases the incidence of babies with a low birth weight centile. Finally, metformin is a less expensive drug. Obesity and the associated maternal and fetal complications are a huge financial burden on health services. If metformin were found to be effective, its use could contribute to significant financial savings for health services.

Sitagliptin is Effective in Patients with Type 2 Diabetes and ESRD Receiving Dialysis

Diabetes is a leading cause of end-stage renal disease (ESRD). Hyperglycemia has been associated with increased mortality in patients with type 2 diabetes mellitus and ESRD. The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF–KDOQI) guidelines recommend standard hemoglobinA1c (HbA1c) targets for patients with type 2 diabetes mellitus and ESRD to potentially reduce the risk of other microvascular complications (neuropathy and retinopathy). However, treatment options available for these patients are limited due to safety and tolerability issues. Metformin, the most commonly used anti-hyperglycemic agent for type 2 diabetes mellitus, is excreted by renal route and is contraindicated in diabetic patients with ESRD. Of the sulfonylureas, only glipizide and gliptazide are recommended for use in patients with ESRD, but they are associated with an increased risk of hypoglycemia. Thiazolidinediones are associated with fluid retention and edema, which may limit their usefulness in patients with ESRD. Insulin is widely used in this patient population, but dosing needs to be monitored and adjusted to maintain good glycemic control while limiting the risk of hypoglycemia. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that improves glycemic control; it is well tolerated in individuals with type 2 diabetes mellitus, with an incidence of hypoglycemia similar to that of placebo when used alone or with other anti-hyperglycemic agents not associated with hypoglycemia. Sitagliptin is eliminated mostly through the kidneys, with ~80% of the oral dose excreted unchanged in urine. Based on the pharmacokinetics of sitagliptin, to achieve a plasma concentration of sitagliptin similar to that achieved with a once-daily 100-mg dose in patients with normal to mildly decreased kidney function, individuals with ESRD should receive one quarter of the usual clinical dose, or 25 mg daily. In a small placebo-controlled clinical trial, sitagliptin was well tolerated in patients with varying degrees of decreased kidney function, including a cohort of patients with ESRD on dialysis therapy. To further characterize the use of sitagliptin in patients with kidney disease, the present study evaluated the efficacy and safety of sitagliptin and glipizide monotherapy administered over 54 weeks in patients with type 2 diabetes mellitus and ESRD requiring dialysis. The efficacy and safety of sitagliptin and glipizide monotherapy in patients with type 2 diabetes and ESRD on dialysis therapy were assessed in this study. It was a 54-week, randomized, double-blind, parallel-arm study. From 31 clinical sites in 12 countries, 129 patients 30 years or older with type 2 diabetes and ESRD who were on dialysis therapy and had a HbA1c level of 7%-9% were randomly assigned 1:1 to treatment. Monotherapy with sitagliptin, 25 mg daily or glipizide (initiated with 2.5 mg daily and titrated up to a potential maximum dose of 10 mg twice daily or down to avoid hypoglycemia). Primary end points were 54-week change in HbA1c level from baseline and tolerability with sitagliptin. A secondary end point was the comparison of sitagliptin versus glipizide on the incidence of symptomatic hypoglycemia. Of 129 patients randomly assigned, 64 were in the sitagliptin group (mean baseline age, 61 years; HbA1c, 7.9%) and 65 were in the glipizide group (mean baseline age, 59 years; HbA1c, 7.8%). After 54 weeks, the least squares mean change from baseline in HbA1c level was -0.72% (95% CI, -0.95% to -0.48%) with sitagliptin and -0.87% (95% CI, -1.11% to -0.63%) with glipizide, for a difference of 0.15% (95% CI, -0.18% to 0.49%). The incidences of symptomatic hypoglycemia and severe hypoglycemia were 6.3% versus 10.8% (between-group difference, -4.8% [95% CI, -15.7% to 5.6%]) and 0% versus 7.7% (between-group difference, -7.8% [95% CI, -17.1% to -1.9%]) in the sitagliptin and glipizide groups, respectively. Higher incidences (ie, 95% CI around between-treatment difference excluded 0) of cellulitis and headache were found with sitagliptin compared to glipizide (6.3% vs 0%, respectively, for both). The study concludes that treatment with sitagliptin or glipizide monotherapy was effective and well tolerated over 54 weeks in patients with type 2 diabetes and ESRD who were receiving dialysis.