

## Voglibose is Emerging as a Popular Drug for Management of Prediabetic in Indian Population

Prediabetes is a precursor of overt type 2 diabetes mellitus (DM); is associated with insulin resistance and an increased risk for cardiovascular disease. It is the 'grey area' between normal blood sugar and diabetic levels. Impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and elevated hemoglobin A1c



(HbA1c) are intermediate stages which precede prediabetes and all are precursors to overt type 2 DM. The World Health Organization (WHO) has defined prediabetes as a state of intermediate hyperglycemia using two specific parameters, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dL) and IGT defined as 2 hour plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 gm of oral glucose load or a combination of the two based on a 2 hour oral glucose tolerance test (OGTT). The American Diabetes Association (ADA), on the other hand has the same cut-off value for IGT (140-200 mg/dL) but has a lower cut-off value for IFG (100-125 mg/dL) and has additional HbA1c based criteria of a level of 5.7% to 6.4% for the definition of prediabetes. Though prediabetes does not require active management, apart from a strict control in diet and adequate exercise, this view has been challenged ever since voglibose has been approved for the management of prediabetes in Japan. A study published in the *Journal of Clinical and Diagnostic Research* suggests that voglibose is emerging as a popular alternative to metformin for the management of prediabetes in the Indian population. Metformin is the drug which is most often used in the initial therapy of DM, is also the drug which is also most often used in the management of prediabetes. This probably results from the fact that metformin reduces blood sugar levels only when its levels are raised and not otherwise. Alpha glucosidase inhibitors like voglibose was the most favored second line drug for management of prediabetes, after metformin. Here, it can be seen that the thiazolidinediones, which include pioglitazone, have been regarded as third line of management, and that the DPP-4 inhibitors were the fourth line of management. This probably is the result of the concern that the therapy of prediabetes with either these drug classes can lead to hypoglycemia, which is not a complication seen with therapy with either metformin or voglibose. Finally, most of the researchers agreed to the fact that the approval of voglibose for the management of prediabetes in Japan was very much relevant to Indian patients. In this regards, a survey was conducted amongst diabetologists, general practitioners and other specialists regarding their perceptions of the usage of various oral hypoglycemic agents (OHAs), especially the  $\alpha$ -glucosidase inhibitor, voglibose, in the management of prediabetes. A well-structured questionnaire was sent to 117 doctors across India (52 diabetes specialists, 45 general practitioners, and 20 specialists from other branches of medicine) to understand their views on the management of prediabetes, especially with regards to voglibose. The results show that there was an equivocal response to the question as to whether only diet and exercise were sufficient for the management of prediabetes. Most of the respondents used metformin for the management of prediabetes, while voglibose was the most favored second-line drug. Almost all the respondents agreed that the approval which voglibose got in Japan for the management of prediabetes was relevant in India as well. Among all the respondents 51.3% of all respondents had prescribed voglibose for prediabetes.

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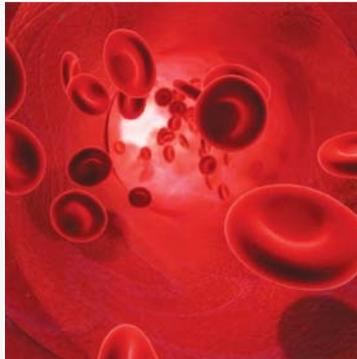
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## Diabetes Drug may also Offer Vascular Protection

Obesity and Type 2 diabetes are associated with vascular stiffening and the development of cardiovascular disease. Obese and diabetic premenopausal women are most at risk -- even more than men of the same age who have similar health issues. A study found that a diabetes medication offered protection against arterial stiffness in overweight female mice, a finding that may have future implications for disease prevention in humans. "The widespread overconsumption of a western diet high in fats and refined sugars is a contributing factor to the epidemic of obesity and diabetes around the world," said lead author of the study. "Our previous studies showed that young female mice consuming mostly western diet not only gained weight, but also exhibited arterial stiffening consistent with obese premenopausal women. Our current study sought to understand what effects, if any, the diabetes medication linagliptin had on preventing vascular stiffness." Linagliptin is a medication prescribed to lower blood glucose in patients with Type 2 diabetes. The medication blocks the enzyme dipeptidyl peptidase-4 (DPP-4). Previous studies have shown that the DPP-4 inhibitor also seemed to offer protection against vascular inflammation and oxidative stress -- conditions associated with arterial stiffening. The researcher team observed 34



female mice that were fed either a normal diet or a simulated western diet for four months. Another group of mice were fed a western diet containing a low dose of linagliptin. The team used an ultrasound system designed specifically for mice to evaluate stiffness of the aorta -- the main artery that supplies blood to the circulatory system. "The mice fed a western diet without receiving linagliptin gained weight and developed aortic stiffness," said the researcher. "However, a big surprise to us was an almost total prevention of aortic stiffening in the mice that were fed the western diet along with linagliptin, even though this group gained as much weight as the other mice." More research is needed to determine if linagliptin could be used as a therapeutic tool in the future to prevent aortic stiffening and the cardiovascular risks associated with obesity and diabetes. "Based on the results of our study, it is tempting to speculate that linagliptin could target arterial stiffness and reduce the risk of cardiovascular disease," said the researcher. "However, results from clinical trials already in progress will be needed to determine what, if any, future role linagliptin could play in the management of obesity-related cardiovascular disease."

## Linagliptin is Clinically Effective for Long-Term Use, Thirty-two Country Trial Suggests

An extended trial of a drug for people with type 2 diabetes has confirmed that the oral DPP-4 inhibitor linagliptin is a safe and effective means of lowering glucose levels for up to 102 weeks, either on its own or in combination with other selected oral anti-diabetic medication. The 32-country study, published in the *International Journal of Clinical Practice*, followed 2,121 individuals who had taken part in four previous 24-week randomized, double-blind, placebo controlled trials, in order to monitor them for a further 78 weeks. Those subjects who had previously received linagliptin (1,532) continued to do so and those who had received the placebo during the earlier trials (589) were also given the drug during the 78-week trial extension. The participants who took part in the extended trial came from 231 sites in 32 countries: Argentina, Austria, Belgium, Canada, China, Croatia, the Czech Republic, Finland, Germany, Greece, Hungary, India, Israel, Italy, Japan, Korea, Malaysia, Mexico, the Netherlands, New Zealand, the Philippines, Poland, Romania, Russia, Slovakia, Spain, Sweden, Taiwan, Thailand, Ukraine, the United Kingdom and the United States. "Initial 24-week trials showed that linagliptin, either on its own or with other glucose-lowering agents, was effective in improving glycemic control without weight gain or an independent increased risk of hypoglycemia," says co-author. Linagliptin was administered orally once a day in all cases, either on its own, or in combination with metformin or metformin plus a sulphonylurea or pioglitazone. Key findings of the extended study included: The study participants had an average age of 57.5 years, 75% were younger than 65 years, 51.8% were male and 52.5% had been diagnosed more than five years ago. The majority had a body mass index of less than 30 kg/m<sup>2</sup> (62.4%), a normal or mildly impaired kidney function (95.6%) and glycated hemoglobin (HbA1C) levels of less than 8% (71.2%). The mean baseline HbA1C and fasting plasma glucose levels were significantly lower in those



subjects who had received linagliptin rather than the placebo in the previous 24-week trials. Total 1,880 people (88.6%) completed the trial. The main reasons for discontinuing were adverse side effects (3.7%), refusal to continue medication (2.6%) and lack of therapeutic effect (1.1%). When linagliptin was taken on its own, the adverse side effects rate was lower at 78.8%, similar to those on linagliptin plus pioglitazone (76%). Most adverse side effects were mild or moderate and the incidence of severe adverse side effects was low at 3.8%, with 3.4% discontinuing the drug as a result. Overall, 14.3% of participants experienced drug-related adverse incidents. The investigators determined that 13.9% of participants experienced hypoglycemic events

and that about half of these (6.9%) were drug-related. The highest level of drug-related hypoglycemic events occurred in persons receiving metformin with a sulphonylurea (11%), with much lower rates for those receiving linagliptin plus metformin (2.1%), linagliptin on its own (0.5%) and linagliptin plus pioglitazone (0.2%). Serious adverse events were reported in 9.9% of the trial subjects, with eight deaths reported during the study period. However, these were not related to the drug. Long-term linagliptin use was not associated with a clinically relevant change in body weight, with individuals previously on the drug losing an average of 0.03kg and those previously on the placebo gaining an average of 0.47 kg. "This is the largest data set of long-term clinical evidence for linagliptin to date" concludes the researcher. "Findings from the 78-week open-label extension involving 2,121 people with type 2 diabetes demonstrate sustained glycemic control for up to 102 weeks treatment duration. They also provide evidence that supports the efficacy and tolerability profile seen in previously reported 24-week studies. Therefore this extension study shows that linagliptin is an effective and well tolerated therapy for the long-term management of type 2 diabetes."

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## Circulation Favors Placenta over Brain in Fetuses of Diabetic Mother

Blood flows preferentially to the placenta instead of the brain in fetuses of mothers with diabetes, reveals research presented at *EuroEcho-Imaging 2016*. The annual meeting of the European Association of Cardiovascular Imaging (EACVI), a registered branch of the European Society of Cardiology (ESC), was held on 7 to 10 December 2016 in Leipzig, Germany. "We know that maternal diabetes mellitus affects the fetal organs," said lead author. "Babies born to mothers with diabetes are sometimes bigger, especially if the diabetes is uncontrolled, and the placenta is larger. There is data to suggest that some other organs such as the pancreas and the kidneys in the fetus might be affected." Previous research identified subclinical changes in the heart muscle of fetuses of mothers with diabetes. In the current study the researcher investigated whether these fetuses had changes in blood circulation. This study included 14 fetuses of mothers with type 1 or 2 diabetes and 16 fetuses of mothers without diabetes (control group). Nine of the diabetic mothers used insulin, three took oral medications, and two used diet alone to control their glucose levels. The researchers used fetal Doppler echocardiography to measure blood flow to the brain, the left and right outflow tracts of the heart, the aorta, and the placenta. The data was plugged into a computerized model that mimics the fetal circulation. This research found that, compared to fetuses in the control group, in fetuses of diabetic mothers more blood flowed to the placenta and was diverted away from the brain.



Specifically, fetuses of diabetic mothers had lower placental resistance and compliance, lower blood flow to the arteries in the brain (measured from the cerebral artery radius), a reduced proportion of blood flow to the brain than the placenta and a lower cardiac output. The researcher said: "The computational model equivalent of the fetal circulation is an electrical circuit where there are resistances and compliances. It is easier for blood to flow to the placenta, and harder for blood to flow to the brain." The placenta in fetuses of diabetic mothers have changes in their blood vessels and are known to be large; therefore likely receive more blood supply. But she added that the lower proportion of blood supplying the brain is an interesting finding and could have

bigger implications. "The placenta gets taken away after a baby is born so it's no longer a part of the circulation," she said. "But it's possible that the reduced circulation to the brain in utero could affect the baby. We don't know enough about why this redistribution of blood flow occurs or the implications it might have. More research is needed to find out if this has any long-term impact on the health of the baby and whether anything can be done to prevent it." She concluded: "At the present time, I don't think any changes should be made in management of pregnant women with diabetes mellitus based on these findings. Standard obstetric recommendations for strict glucose control and healthy lifestyle should be continued."

## Proteins as an Early Warning System for Type 1 Diabetes?

Certain proteins in the blood of children can predict incipient type 1 diabetes, even before the first symptoms appear. A team of scientists reported these findings in the *Diabetologia* journal. The work was based on two large studies that are intended to explain the mechanisms behind the development of type 1 diabetes. The study participants are children who have a first-degree relative with type 1 diabetes and who consequently have an increased risk of developing the disease due to the familial predisposition. This autoimmune process does not develop from one day to the next, however: often the young patients go through longer asymptomatic preliminary stages that see the formation of the first antibodies against the child's own insulin-producing cells in the pancreas; the so-called autoantibodies. Biomarkers that indicate whether and when this is the case and how quickly the clinical symptoms will appear could significantly improve the treatment of patients at-risk. A team of scientists analyzed blood samples from 30 children with autoantibodies who had developed type 1 diabetes either very rapidly or with a very long delay. The researchers compared the data with data on children who displayed neither autoantibodies nor diabetes symptoms. In a second step with samples from another 140 children, the researchers confirmed the protein composition differences that they found in this



approach."Altogether, we were able to identify 41 peptides from 26 proteins that distinguish children with autoantibodies from those without," says the researcher. Striking in their evaluations: a large number of these proteins are associated with lipid metabolism. "Two peptides -- from the proteins apolipoprotein M and apolipoprotein C-IV -- were particularly conspicuous and were especially differently expressed in the two groups," he adds. In autoantibody-positive children, it was furthermore possible to reach a better estimate of the speed of the diabetes development using the peptide concentrations of three proteins (hepatocyte growth factor activator, complement factor H and ceruloplasmin) in combination with the age of the particular child. The researchers are

confident that the protein signatures they have discovered will be helpful as biomarkers for future diagnostics. "The progression of type 1 diabetes into a clinical disease takes place over a period of time that varies from individual to individual and that at this time is insufficiently predictable," explains the researcher. "The biomarkers that we have identified allow a more precise classification of this presymptomatic stage and they are relatively simple to acquire from blood samples."

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## Maternal B<sub>12</sub> Deficiency may Increase Child's Risk of Type-2 Diabetes

Vitamin B<sub>12</sub> deficiency may predispose children to metabolic disorders such as type-2 diabetes, according to research presented at the Society for Endocrinology's annual Conference in Brighton. These findings could lead to a review of current vitamin B<sub>12</sub> requirements for pregnant women, whether through an improved diet or supplements. Vitamin B<sub>12</sub> is naturally found in animal products, including fish, meat, poultry, eggs and milk, meaning deficiency is more likely in those following a vegan diet. Previous studies show that mothers with low B<sub>12</sub> levels had a higher BMI and were more likely to give birth to babies with low birth weight as well as high cholesterol levels. These children also had higher insulin resistance in childhood -- a risk factor for type-2 diabetes. In this study, a team of researchers hypothesized that the changes associated with B<sub>12</sub> deficiency may be the result of abnormal levels of leptin hormone. Leptin is produced by human body's fat cells and its levels rise in response to eating food. Whilst lean diets are associated with normal levels of leptin, obesity causes levels to rise and remain consistently higher than normal. This can eventually lead to leptin resistance, continued overeating, and an increased risk of insulin resistance, which leads to type-2 diabetes. Scientists and doctors therefore see leptin as



providing an effective 'marker' for body fat. The researchers found that babies born to mothers with B<sub>12</sub> deficiency had higher than normal leptin levels. This suggests that maternal B<sub>12</sub> deficiency can adversely program the leptin gene, changing the levels at which the hormone is produced whilst the fetus grows. "The nutritional environment provided by the mother can permanently program the baby's health," said senior author of the study. "We know that children born to under or over nourished mothers are at an increased risk of health problems such as type-2 diabetes, and we also see that maternal B<sub>12</sub> deficiency may affect fat metabolism and contribute to this risk. This is why we decided to investigate leptin, the fat cell hormone." The next steps in the study will be to determine the details of how and why the leptin increase is seen in babies born to mothers with low B<sub>12</sub>. "The leptin can increase for two reasons," said the researcher. "Either low B<sub>12</sub> drives fat accumulation in the fetus, and this leads to increased leptin, or the low B<sub>12</sub> actually causes chemical changes in the placental genes that produce leptin, making more of the hormone. As B<sub>12</sub> is involved in methylation reactions in the body which can affect whether genes are turned on and off, we suspect it may be the latter" --he concluded.

## Regular Intake of Sugary Beverages, but not Diet Soda, is Associated with Prediabetes

Adult Americans who regularly consumed sugar-sweetened beverages had a 46 % higher risk of developing prediabetes compared to low- or non-consumers over a 14-year period, according to a new epidemiological analysis led by scientists at the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University. Higher sugar-sweetened beverage intake was also associated with increased insulin resistance, a risk factor for type 2 diabetes. No associations between diet soda consumption and risk of prediabetes or increased insulin resistance were found. However, the research team notes that previous studies on associations between diet soda and risk of type 2 diabetes have produced mixed results, and further studies are needed to reveal the long-term health impact of artificially sweetened drinks. The findings were published in the *Journal of Nutrition*. "Although our study cannot establish causality, our results suggest that high sugar-sweetened beverage intake increases the chances of developing early warning signs for type 2 diabetes. If lifestyle changes are not made, individuals with prediabetes are on the trajectory to developing diabetes," said senior study author. "Our findings support recommendations to limit sugar-sweetened beverage intake, which can be achieved by replacing sugary beverages with healthier alternatives such as water or unsweetened coffee or tea," added the researcher. "This is a simple dietary modification that could be of substantial health benefit to people who consume sugary drinks daily and who are at increased risk of diabetes." In the current study, the researcher analyzed longitudinal data on 1,685 middle-aged adults over a period of 14 years, obtained from the Framingham Heart Study's Offspring cohort -- a National Heart, Lung, and Blood Institute-funded program that has monitored multiple generations for lifestyle and clinical characteristics that contribute to cardiovascular disease. Selected participants did not have diabetes or prediabetes



during an initial baseline examination, and they self-reported their long-term sugar-sweetened beverage and diet soda consumption habits through food frequency questionnaires. Sugar-sweetened beverages were defined as colas and other carbonated beverages, and non-carbonated fruit drinks such as lemonade and fruit punch. Fruit juice was not included in the sugar-sweetened beverage category. The team found those who drank the highest amounts of sugar-sweetened beverages -- a median of six 12 fluid ounce servings a week -- had a significantly greater risk of developing prediabetes compared to low- or non-consumers, after adjusting for factors such as age, sex and BMI. The highest consumers of sugar-sweetened beverages had roughly 8 % higher insulin resistance scores, compared to low- or non-consumers after follow-up at seven years. Even after accounting for change in weight and other aspects of diet, the relationships between sugar-sweetened beverages and these metabolic risk factors for diabetes persisted. Diet soda intake -- defined as low-calorie cola or other carbonated low-calorie beverages -- had no statistical associations with risk for either prediabetes or insulin resistance. However, previous research on the relationship between diet soda and type 2 diabetes has been mixed, and it is still unclear whether any observed associations are due to direct or indirect factors. More research is needed to determine whether there are real health risks with long-term diet soda consumption, said the study author. A significant body of research has found associations between regular consumption of sugar-sweetened beverages and increased risk of type 2 diabetes. The new findings now provide evidence of an association with the major predictor of type 2 diabetes. If diagnosed early, prediabetes is reversible through lifestyle changes such as diet and exercise.



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