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ORIGINAL ARTICLE

IMPAIRED GLUCOSE TOLERANCE AND ROLE OF VOGLIBOSE: AN OBSERVATIONAL STUDY

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ABSTRACT: BACKGROUND: The increased prevalence of type 2 diabetes mellitus is a major concern for health providers. We therefore assessed whether voglibose, an α-glucosidase inhibitor, could prevent the development of type 2 diabetes in high-risk individuals with impaired glucose tolerance. **METHODS:** This study was an observational study comprising of voglibose and placebo in individuals with impaired glucose tolerance. 126 eligible patients were on the standard diet and taking regular exercise with impaired glucose tolerance were randomly assigned to oral voglibose 0.2 mg three times a day (n=66) or placebo (n=60) in this study. Treatment was continued until participants developed type 2 diabetes (primary endpoint) or normoglycaemia (Secondary endpoint). In the final analysis, 126 registered individuals fulfilled the inclusion criteria: 66 were randomly assigned to receive voglibose and 60 placebos (two participants in the placebo group did not take their medication and were excluded). The mean duration of treatment was 48·2 weeks (SD 36.2)—i.e, 45.1 weeks (34·6) for voglibose and 51·4 weeks (37.7) for placebo. Compliance with treatment was similarly high in the two treatment groups. In the analysis, we found that voglibose was better than placebo (p=0.0026) in individuals treated for an average of 48.2 weeks (SD 36.2). Patients treated with voglibose had a lower risk of progression to type 2 diabetes than did those on placebo. More people in the voglibose group achieved normoglycaemia than did those in the placebo group. **CONCLUSION:** Voglibose, in addition to lifestyle modification, can reduce the development of type 2 diabetes in high risk individuals with impaired glucose tolerance.

KEYWORDS: Voglibose; Alpha Glucosidase Inhibitors, Impaired Glucose Tolerance, Metformin.

INTRODUCTION: Metabolic disorders with a predisposition towards impaired glucose intolerance and ultimately leading to type 2 diabetes mellitus is the major health problem. Although type 2 diabetes has a genetic basis, evidence supports a key part played by modifiable behavioural risk factors such as obesity and physical inactivity. Disorders such as impaired glucose intolerance and metabolic syndrome seem to be intermediate stages between normal glucose tolerance and overt diabetes, and greatly increase the risk of type 2 diabetes and its attendant macroangiopathy. The International Diabetes Federation Taskforce on Prevention and Epidemiology convened a consensus workshop in Lisbon,(1) Portugal, and recommended a three-step approach-identification of those at risk, measurement of the risk, and appropriate intervention-to prevent or delay the development of type 2 diabetes. At the core of this strategy is lifestyle modification-ie, dietary control and increased exercise, but the International Diabetes Federation recognises that pharmacotherapy might be needed in some individuals who cannot maintain such behavioural changes.

The European DECODE study,(2) a meta-analysis of 13 prospective cohort studies, some in Asian individuals, reported that impaired glucose tolerance is a prognostic factor for both all-cause and cardiovascular death. Thus, impaired glucose tolerance not only increases the likelihood of

developing diabetes, but also exacerbates macrovascular pathological changes. Treatment strategies designed to slow or delay the progression of impaired glucose tolerance therefore have the potential to reduce cardiovascular morbidity and mortality, and some of the burden on health-care resources. Indeed, results of large, well designed trials have suggested that intensive diet and exercise programmes, and pharmacological intervention, help prevent or delay the development of diabetes in high-risk individuals with impaired glucose tolerance.[3]

Diabetes is a global problem, and its prevalence in Asia is predicted to increase substantially over the next 25 years. Studies specifically involving Asian people include the Da Qing study in China, the Indian Diabetes Prevention Programme, and a Japanese lifestyle intervention trial. Until now, no active drug intervention trial in Japanese individuals with impaired glucose tolerance has been reported.[4,5] We therefore investigated the effectiveness of voglibose, an α-glucosidase inhibitor that reduces diurnal insulin secretion, for prevention of the development of type 2 diabetes in Japanese patients with impaired glucose tolerance.[5]

METHODS:

STUDY DESIGN: This study was an observational study comprising of voglibose and placebo in individuals with impaired glucose tolerance. From October, 2012, we aimed to treat people until type 2 diabetes or normoglycaemia was diagnosed, or for at least 2 years.

PROCEDURE: We recruited individuals from all socio-economic status, mainly through assessment of high-risk populations, and in particular from first-degree relatives of patients with type 1 or 2 diabetes. We screened 540 men and women aged 30–70 years, with suspected impaired glucose tolerance for family history, blood pressure, body weight, body-mass index, routine blood chemistry (including lipid concentrations), fasting plasma glucose concentrations, and HbA_{1c}, and did an oral glucose (75 mg) tolerance test (OGTT) during a 4-week observation. Individuals were eligible, if they had a fasting plasma glucose concentration of less than 6.9 mmol/L, a 2 h plasma glucose concentration during OGTT (2hPG) of between 7.8 mmol/L and 11.0 mmol/L, HbA_{1c} less than 6.5%, and at least one of the following risk factors for type 2 diabetes: high normal blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg) or were being treated for hypertension; dyslipidaemia (concentrations of total cholesterol ≥5.7 mmol/L, triglyceride ≥1.7 mmol/L, or HDL cholesterol <1.04 mmol/L); obesity (body-mass index ≥25 kg/m^2); and a family history of diabetes (in a first-degree or second-degree relative). We excluded patients with diabetes or a disease likely to impair glucose tolerance. The patient who were fitting into the inclusion criteria were only 126.

After 4 weeks, eligible individuals were randomly allocated to voglibose 0.2 mg or an identical-looking placebo three times a day before meals. Randomisation was done with a stratified allocation procedure designed to balance the two treatment groups with respect to the number of risk factors (≤2 or ≥3), which were hypertension or high normal blood pressure, dyslipidaemia, obesity, a family history of diabetes, and a 2hPG greater than 9.4 mmol/L (a concentration associated with an increased risk of developing type 2 diabetes) to 11.0 mmol/L.

4–8 weeks before the start of treatment, each person was given advice about appropriate nutrition and exercise programmes (interview, survey of lifestyle, and individualised guidance on future lifestyle habits based on intensity of daily activity categories) and adherence to these was assessed at each visit. The primary endpoint was the development of type 2 diabetes, which was

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defined as an HbA_{1c} level of at least 6·5%, and, on two separate occasions, at least one of the following: a 2hPG of at least 11.1 mmol/L, fasting plasma glucose concentration of at least 7·0 mmol/L, or random plasma glucose concentration of at least 11.1 mmol/L. The secondary endpoint was the number of people who achieved normoglycaemia (ie, 2hPG <7.8 mmol/L and a fasting plasma glucose concentration <6.1 mmol/L). Once the primary or secondary endpoint was achieved, patients discontinued their medication (those who achieved normoglycaemia are being followed up until study completion, when their responses will be analysed).

Every 12 weeks, we measured the concentrations of fasting blood glucose, HbA_{1c}, and blood lipids (triglycerides, total cholesterol, HDL cholesterol, and free fatty acids), did clinical laboratory tests (chemistry, haematology, and urinalysis), measured blood pressure and body weight, did compliance checks (returned tablet counts), and questioned patients about adverse effects. We did an OGTT every 24 weeks. All blood and urinary analytical tests were done at a central laboratory with standard methods.

RESULTS: In the final analysis, 126 registered individuals fulfilled the inclusion criteria: 66 were randomly assigned to receive voglibose and 60 placebos (two participants in the placebo group did not take their medication and were excluded). The mean duration of treatment was 48.2 weeks (SD 36.2)-ie, 45.1 weeks (34.6) for voglibose and 51.4 weeks (37.7) for placebo. Compliance with treatment was similarly high in the two treatment groups.

In the analysis, we found that voglibose was better than placebo (p=0.0026) in individuals treated for an average of 48.2 weeks (SD 36.2). Patients treated with voglibose had a lower risk of progression to type 2 diabetes than did those on placebo. More people in the voglibose group achieved normoglycaemia than did those in the placebo group. Serious adverse events (all one each) in the voglibose group were cholecystitis, colonic polyp, rectal neoplasm, inguinal hernia, liver dysfunction, and subarachnoid haemorrhage, and in the placebo group were cerebral infarction and cholecystitis.

Manifestation	Voglibose	Placebo	p value
Gastrointestinal symptoms:			
Flatulence	11(17%)	4(7%)	<0.0001
Abdominal distension	8 (13%)	3(5%)	<0.0001
Diarrhoea	8(13%)	3(5%)	<00001
Abnormal bowel sounds	2(4%)	1(2%)	<0.0001

DISCUSSION: In our study, even though we reinforced diet and exercise programmes, individuals remained at risk of developing diabetes. Voglibose significantly reduced the risk of individuals with impaired glucose tolerance developing type 2 diabetes and significantly increased the proportion of people who achieved normoglycaemia compared with placebo. Thus, the clinically important benefits associated with voglibose were achieved in a short time, particularly in the high-risk group (≥3 risk factors). Similarly, in terms of achieving normoglycaemia, improvement in high-risk individuals was significant. These results are encouraging and emphasise the benefits of voglibose for people at increased risk of developing type 2 diabetes, and are in line with recommendations made at the International Diabetes Federation Taskforce on Prevention and Epidemiology consensus workshop convened in Lisbon.

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One of the potential benefits of a reduction in the progression of impaired glucose tolerance to type 2 diabetes might be a reduction in cardiovascular risk. However, a 20-year follow-up from the original Da Qing Diabetes Prevention Study[6,7] showed that, although lifestyle changes could produce a long-lasting reduction in the incidence of type 2 diabetes, the effect on cardiovascular events was at best modest.

In the past decade, several studies have drawn attention to the benefits of strict and individualised diet and exercise programmes in delaying the progression to type 2 diabetes. In these studies, lifestyle modification reduced the risk of type 2 diabetes by 42% over 6 years ($p<0.005$) in a Chinese cohort, by 58% over 4 years ($p<0.001$) in Finnish patients, and by 58% over 2.8 years in a US study. Lifestyle modification thus represents a mainstay of medical care for individuals with impaired glucose tolerance.[8,9] Pharmacological approaches have also been investigated as a means of delaying the onset of type 2 diabetes and drugs such as metformin, acarbose, orlistat, troglitazone, and rosiglitazone have all shown some ability to delay or prevent the progression of impaired glucose tolerance to type 2 diabetes.[9,10] For example, in the Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM),[11] the α-glucosidase inhibitor acarbose reduced the risk of progression to diabetes by 25% over 3·3 years compared with placebo. This result was achieved in people with impaired glucose tolerance that was given advice on diet and exercise. Similarly, the Diabetes Prevention Program Research Group reported[12] that metformin reduced the relative risk of people with impaired glucose tolerance developing diabetes by 31% over 2·8 years. Thus, current best practice indicates a primary role for diet and exercise programmes in the management of impaired glucose tolerance, with drug treatment reserved for those unable to achieve glycaemic control, at high risk of progression to type 2 diabetes, and unable to adequately exercise.

Defects in the action or secretion of insulin, or both, are the two main abnormalities leading to the development of type 2 diabetes, and any intervention that reduces insulin resistance or protects the pancreatic β cells could help to prevent or delay the progression of the disease. Results with voglibose show that it reduces diurnal insulin secretion through improvement of postprandial hyperglycaemia, and these changes should reduce the stress on overworked β cells.[13,16] In our study, 2hPG concentrations fluctuated at a lower level in the voglibose group than in the placebo group between 24 weeks and 96 weeks as indicated by lower HbA_{1c} levels during this period. Assessments beyond this time point are not meaningful because of the small numbers of patients.

Voglibose significantly improved glucose tolerance, in terms of delayed disease progression and in the number of patients who achieved normoglycaemia.[17] Thus, long-term prophylaxis with this α-glucosidase inhibitor in high-risk individuals with impaired glucose tolerance could provide a pharmacological option, along with lifestyle modification, to help reduce the burden of type 2 diabetes.

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