OP 9

Twelve-Week Efficacy and Tolerability of Sitagliptin, a Dipeptidyl Peptidase IV (DPP-IV) Inhibitor, in the Treatment of Type 2 Diabetes

Russell Scott*, Gary Herman, Jacqueline Yee,
Jayne De La Cruz, Ling Wu, Xun Chen, Mei Wu, Peter Stein

** Christchruch Hospital, Christchurch, New Zealand, Merck Research Laboratories, Rahway, NJ, USA*

Background and Aims. *Sitagliptin (MK-0431) is an oral, potent, and selective DPP-IV inhibitor currently under development for the treatment of type 2 diabetes.*

Materials and Methods. *In a randomized, double-blind, placebo-controlled, active-comparator, parallel group, dose-range finding study, sitagliptin was evaluated in patients with type 2 diabetes. After an initial diet/exercise phase and, for those on an antihyperglycemic agent, a drug wash off period, 743 patients aged 21-76 yrs who had A1C levels of 6.3 to 11.0% were randomized to one of 6 treatments: placebo; sitagliptin 5, 12.5, 25, or 50 mg b.i.d.; or glipizide 5 mg (up-titrated to 10, 15, and then to 20 mg/day) for a 12-wk treatment period.*

Results. *Mean baseline A1C levels ranged from 7.8-7.9% across treatment groups, with 20.8% of patients <7%. The efficacy analysis was based on a modified intention-to-treat population using an ANCOVA. At Week 12, treatment with all sitagliptin doses significantly reduced A1C compared to baseline with the largest reductions in the 50 mg b.i.d. group: the placebo-subtracted differences in A1C ranged from -0.4 to -0.8% in a dose-dependent manner for the sitagliptin treatment groups, and -1.0% with glipizide. At Week 12, placebo-subtracted A1C results did not appear to have reached a plateau in the active treatment groups. FPG increased by 0.44 mmol/L in the placebo group, and dose-dependently decreased by 0.04 to 1.01 mmol/L in the sitagliptin groups, and by 1.38 mmol/L in the glipizide group. A similar reduction was also observed for other glycemic endpoints including fructosamine and mean daily glucose. Treatment with sitagliptin was well tolerated and resulted in no significant weight change, whereas a 1.1 kg weight gain was observed in the glipizide group. Twenty-one patients (17.1%) in the glipizide group experienced one or more hypoglycemic events compared to 3 (2.4%) patients in the placebo group and 0, 5 (4.1%), 5 (4.1%), and 2 (1.6%) patients in the sitagliptin 5, 12.5, 25, 50 mg b.i.d. groups, respectively.*

Conclusion. *In this study, sitagliptin monotherapy was efficacious and generally well-tolerated in the treatment of patients with type 2 diabetes. The study is continuing with an active-controlled treatment phase to address the comparative efficacy, durability, ,-cell function, and safety with longer term treatment.*

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OP 10

Glibenclamide as Add-On Therapy to Insulin during Pregnancy in Women with Preexisting Type 2 Diabetes Mellitus

SP Pendsey, SS Pendsey, RR Sharma, SS Chalkhore

Diabetes Clinic & Research Centre, Nagpur, India

Background and Aims. *Type 2 diabetes mellitus is common in women contemplating pregnancy. Hyperglycaemia in them is exaggerated during pregnancy due to diabetogenic effect of pregnancy and inherent insulin resistance. Intensified insulin therapy is currently used for managing hyperglycaemia in pregnancy. It is sometimes difficult to achieve a desirable glycaemic control despite 4 or 5 insulin injections. Oral drugs are not recommended for concern of teratogenicity and neonatal hypoglycaemia. In the present study we used Glibenclamide as add - on to intensified insulin to achieve desirable glycaemic control.*

Materials and Methods. *We used glibenclamide in 22 pregnant women with pre existing type 2 diabetes, whose glycaemic control was unsatisfactory despite multiple insulin injections (3 to 5 per day) and whose total insulin dose was exceeding 1 unit/kg body weight. The dose of glibenclamide was titrated to achieve desirable plasma glucose values (FPG < 100mg% PPPG < 120mg%). Insulin doses were increased if maximum dose of glibenclamide did not achieve desired values. Glibenclamide was added after 24 weeks of gestation starting with 1.25 mg twice a day, increased to maximum 2.5mg b.i.d and stopped 24 hrs before delivery. Fasting (FPG) and Postprandial (PPPG) plasma glucose were measured every 15 days and home blood glucose monitoring continued. Glycosylated Haemoglobin A1c (GHbA1c) was estimated before starting glibenclamde and at every 6 weeks. The primary endpoint was achievement of the desired level of glycaemic control. Secondary endpoints included maternal and neonatal complications.*

Results. *The mean (+SD) pretreatment FPG, PPPG and GHbA1c were 119 + 18mg%, 151.2 + 21 mg% and 6.42 + 0.82% and before delivery were 88.16+11mg%($p<0.026$), 117+12mg%($p<0.020$) and 5.32+1.1%($p<0.5$). There were no episodes of severe maternal hypoglycaemia after glibenclamide. The mean birth weight was 3120 + 86grams; mean cord plasma glucose was 44.21+ 4.10mg% 3 babies required admission to neonatal units for observation. There were no congenital anomalies or serious neonatal complications.*

Conclusion. *Women with preexisting type 2 diabetes pose a challenge during pregnancy. It is difficult to achieve near normoglycaemia in 2nd and 3rd trimester despite intensified insulin therapy due to underlying insulin resistance. In all patients we noticed significant improvement in glycemic control after addition of glibenclamide. We found glibenclamide as effective adjuvant to insulin therapy and did not cause serious maternal or neonatal complications.*

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OP 11

Acarbose Prevents LDL Oxidation and Decreases Plasma PAI-1 Levels

Yuichi Shinoda*,
Ikuo Inoue**, Shigehiro Katayama**

Department of Biochemistry,Division of endocrinology and diabetes of Saitama Medical School, Japan*

Background and Aims. *We performed this study to determine whether and how acarbose affects, the fatty acid content in low-density lipoprotein (LDL) particles and thrombotic factors such as plasminogen activator inhibitor type-1 (PAI-1).*
Materials and Methods.*Forty patients with impaired glucose tolerance were randomized to acarbose (Acar group) or dietary therapy alone (Contol group) and followed for three months. CuSO4 initiated isolated LDL oxidation, and formation of conjugated dienes was continuously monitored spectrophotometrically at 234nm.*
Results.*Duration of the lag-phase of LDL in the Acar group was significantly longer than that in the Diet group. Moreover, duration of the lag phase of LDL after acarbose treatment was longer than that before acarbose treatment. The polyunsaturated fatty acid (omega-3) level in LDL was significantly increased and saturated fatty acids and triglyceride content in LDL were significantly decreased by acarbose treatment for three months. In addition to ameliorating susceptibility to LDL oxidation, acarbose treatment for three months significantly decreased the level of PAI-1. The present findings suggest that acarbose-induced amelioration of susceptibility to LDL oxidation, alteration of fatty acid content in LDL particles, and improvement of coagulation might be useful in preventing vascular complications in patients with diabetes.*
Conclusion. *The present findings suggest that acarbose-induced amelioration of susceptibility to LDL oxidation, alteration of fatty acid content in LDL particles, and improvement of coagulation might be useful in preventing vascular complications in patients with diabetes.*

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OP 12

Rosiglitazone Treatment Increases Plasma Adiponectin without Changing Plasma Level of Resistin in Patients with Type 2 Diabetes

Thongchai Pratipanawatr, Ratchanee Chotmongkol

Faculty of Medicine, Khon Kaen University, 40002, Thailand

Background and Aims. *Adiponectin and resistin are the members of adipocytokine. They are exclusively express in adipose tissue and may have an effect on insulin action. Rosiglitazone is one of a new class of anti-diabetic drugs, Thiazolidinedione which activate PPAR- receptor in adipocyte but improves insulin sensitivity in skeletal muscle. Alternating adipocytokine especially adiponectin and resistin, may be one of the possible mechanism of action Aims: To study effect of Rosiglitazone on insulin sensitivity, plasma adiponectin and plasma resistin*

Materials and Methods. *A group of 13 type 2 diabetics (7M/6F, 46 ± 2 years) from Srinagarind Hospital were enrolled voluntarily after giving informed consent – none was on any insulin-sensitivity altering medication. Before and after treatment (i.e. 4 months of 4 mg rosiglitazone•day-1), insulin sensitivity and total body composition were measured using the 120-minute euglycemic hyperinsulinemic clamp (40 mU•min-1•m-2 body surface area) and Dual Energy X-ray Absorbtiometry (DEXA), respectively. Plasma adiponectin and resistin were measured before and after the treatment. Data are presented as means ± SE. Before and after treatment results were compared using the paired t test.*

Results. *A group of 13 type 2 diabetics (7M/6F, 46 ± 2 years) from Srinagarind Hospital were enrolled voluntarily after giving informed consent – none Four months of rosiglitazone significantly improved glycemic control, HbA1c (8.6 ± 0.5 Before vs. 6.7 ± 0.3% After, $p < 0.05$) and whole body glucose uptake (3.9 ± 0.4 vs. 6.2 ± 0.7 mg•kg-1-FFM•min-1, $p < 0.05$). Rosiglitazone increased fat mass (19.1 ±1.5vs 20.2 ±1.6 kg, $p < 0.05$). Rosiglitazone increased plasma adiponectin (3.5±0.8 vs 8.2 ±1.6 mg.mL-1, $p<0.05$) but showed no effect on plasma resistin (10.6±1.8 vs 10.4±3.3 ng.mL-1, NS). Plasma adiponectin closely associate with whole body glucose uptake($r=0.7$, $p<0.05$). Plasma resistin showed no association with whole body glucose uptake.*

Conclusion. *Rosiglitazone treatment increased plasma adiponectin without changing in plasma resistin in type 2 diabetic patients. Plasma adiponectin also correlated well with whole body glucose uptake. These findings suggest that Rosiglitazone can regulate plasma level of adiponectin but can't alter plasma level of resistin. It may play a physiologic role in enhancing insulin sensitivity.*

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OP 13

Correlation between Changes of Blood Pressure with Insulin Resistance in Type 2 Diabetes Mellitus with 4 Weeks of Pioglitazone Therapy

Lukshmy Menik, Hettihewa, MBBS, PhD[1,2], KG. Imendra, BDS, PhD[3], TP Weerarathna, MBBS, MD[4]

Department of Pharmacology, Faculty of Medicine, University of Ruhuna, Galle, South, Sri Lanka

Background and Aims. *Objective: Present study examined the effects of 15 mg of pioglitazone (PIO) on changes in systolic, diastolic, pulse and mean blood pressures (SBP, DBP, PP and MAP respectively) in normotensive type 2 diabetes mellitus.*

Materials and Methods. *Materials and method: Total of 26 patients with type 2 diabetes mellitus (age 45 ± 3 years, BMI 24.3 ± 0.6 Kg/m2, fasting blood glucose 183 ± 6 mg/dL) who were already on 15 mg daily dose of pioglitazone for one month were recruited to this study. Pre treatment measurements were taken as their own controls to compare with post treatment measurements. They were examined for all basic clinical parameters including SBP, DBP, PP and MP. In addition to that fasting insulin, fasting blood sugar and lipid profiles were measured before and after the treatment with pioglitazone for one month.*

Results. *Results: There was a statistically significant reduction in SBP (123 ± 2 vs 118 ± 2 mmHg, $p < 0.05$), PP (41 ± 1 vs 37 ± 1mmHg, $p < 0.05$) and MAP (95 ± 1 vs 91 ± 1, $p < 0.05$) in PIO treated period. There was a reduction in DBP as well but the difference was not statistically significant (82 ± 2 vs 81 ± 1mmHg, $p > 0.05$). In contrary, there was no significant reduction in SBP or DBP during pretreatment period for 2 months (122 ± 2 vs 123 ± 3, 82 ± 2 vs 83 ± 1mmHg $p > 0.05$ respectively). There was a significant correlation between decline in SBP and DBP with respective baseline values in PIO treated period ($r = 0.76$, $p < 0.001$ and $r = 0.62$, $p < 0.001$ respectively). There was a parallel reduction of fasting blood sugar level after 4 weeks of PIO therapy (183 ± 2 vs 121 ± 3, $p < 0.001$). But there was no significant reduction in insulin resistance or lipid profiles during the first 4 weeks of therapy.*

Conclusion. *Conclusion: Pioglitazone treatment of type 2 diabetes mellitus patients had early effects on reduction of fasting blood glucose as well as systolic and mean blood pressures within first 4 weeks of therapy and not observed during pretreatment period in same group of patients. Results show that pharmacological effects of PIO on reducing blood pressure (BP) mainly affecting the systolic component. We suggest mechanism of BP lowering effect of pioglitazone may be independent from the mechanism causing insulin resistance as well as dyslipidaemia in normotensive diabetic patients.*

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OP 14

The Choice of Hypoglycaemic Agent rather than Glycaemic Control Improves Inflammation: A Randomized Trial Of Four Different Treatment Regimens In Poorly Controllled Type 2 Diabetes Mellitus Patients

SH Md Isa, N Idris Wan Nazaimoon, WMNA Kamarudin, BAK Khalid

National University of Malaysia, Kuala Lumpur, Malaysia

Background and Aims. *The importance of good glycaemic control has been clearly established in reducing long-term complications in type 2 diabetes. Inflammatory markers such as highly sensitive C-reactive protein (CRP) and vascular adhesion molecule-1 (VCAM) are recognized markers of future cardiovascular events. This study aimed to evaluate the efficacy of four different treatment regimens in reducing glycaemic parameters in poorly controlled type 2 diabetes patients and their effects on CRP and VCAM.*

Materials and Methods. *110 poorly controlled type 2 diabetes subjects (HbA1c e" 7.5% and d" 11%) on maximum doses of oral hypoglycaemic agents consisting of sulphonylurea, metformin +/- acarbose (with the exception of glimepiride, thiazolidinediones and insulin treatment) were randomized into four treatment groups: Group 1- continued their existing oral agents, group 2- glimepiride 3 mg and rosiglitazone 4 mg daily, Group 3- glimepiride 3 mg and bedtime NPH insulin adjusted according to fasting blood glucose and Group 4- multiple injections of insulin Actrapid and NPH insulin titrated according to fasting and premeal blood glucose levels. Subjects were reviewed every four weeks for up to 12 weeks where fasting plasma glucose (FPG), fructosamine, HbA1c, CRP and VCAM were measured.*

Results. *Subjects on multiple insulin injections had a significant decrease in FPG, fructosamine and HbA1c by -2.5±3.2 mmol/L ($p<0.005$), -84.0±77.7 mmol/L ($p<0.0005$) and -1.3±1.4% ($p<0.0005$) respectively. Subjects who continued their existing oral agents also showed a significant reduction in their FPG, fructosamine and HbA1c by -2.0±3.6 mmol/L ($p<0.05$), -67.0±72.5 mmol/L ($p<0.05$) and –0.6±1.3% ($p<0.05$) respectively However, there was no corresponding improvement in VCAM or CRP in either groups. Those who received glimepiride and rosiglitazone had a significant reduction in CRP by –2.8±3.6 mg/L ($p<0.05$) despite worsening of glycaemic control where fructosamine and HbA1c increased by 60.4±105.8 mmol/L ($p<0.05$) and 0.8±1.8% ($p<0.05$) respectively. Subjects receiving bedtime insulin plus glimepiride did not have any change in their glycaemic parameters. There was no change in VCAM levels in any of the treatment groups.*

Conclusion. *This study shows that improvement in glycaemic control does not necessarily result in improvement in inflammatory marker such as CRP. The type of treatment on the other hand, as in this study treatment regimen incorporating rosiglitazone improves CRP irrespective of glycaemic control.*

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OP 15

Effect of Glucomannan on Glucose and Lipid Metabolism in Elderly Type 2 Diabetic Subjects

Jee Hyun Kong, Chul Sik Kim, Jong Suk Park, Eun Kyung Jung[1], Hyang Mi Jang[1], Joung Soon Park[2], Chul Woo Ahn, Bong Soo Cha, Sung Ki[1] Lim, Kyung Rae Kim, Hyun Chul Lee

Division of Endocrinology and Metabolism, Department of Internal Medicine, Yonsei University, College of Medicine, [1]Department of Nursing, Yongdong Severance Hospital, [2]Department of Dietetics, Yongdong Severance Hospital, Seoul, Korea

Background and Aims. *Glucomannan is known to be effective in reducing glucose and lipid absorption from small intestine. In this study, we tried to investigate the relationship between glucomannan and glucose, lipid profile, and insulin resistance in the elderly type 2 diabetes patients.*

Materials and Methods. *We have taken 76 type 2 diabetes patinets with hypercholesterolemia, aged over 60 years old, who have visited our endocrine clinic of Yonsei University of Medical College and categorized them into two groups. The experimental group, which consisted of 39 subjects, received daily glucomannan, while the control group, which consisted of 37 patients, received daily placebo for 8 weeks. We have measured fasting glucose, 2hr post-prandial glucose at 0, 4, 8 weeks and HbA1C, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, insulin, c-peptide levels at 0, 8 weeks, and calculated HOMA score in order to determine insulin resistance.*

Results. *The following results were obtained. 1) 2hr postprandial glucose level was significantly reduced after taking glucomannan for 4 and 8 weeks, and fasting glucose level declined after taking glucomannan for 8 weeks. 2) Serum total cholesterol, triglyceride, LDL-cholesterol levels were significantly lowered after treatment. Serum HDL-cholesterol level had a tendency to increase in the experimental group, but was not statistically significant. 3) HbA1C was significantly decreased after taking glucomannan for 8 weeks. 4) HOMA-IR was reduced at 8 weeks, and HOMA-, showed a significant increase at 8 weeks. 5) Glucomannan did not have adverse effects on CBC, liver function, renal function, and electrolyte levels.*

Conclusion*. The above study results demonstrate that glucomannan is effective in improving glucose and lipid metabolism in elderly type 2 diabetes patients. Glucomannan enhances insulin resistance by lowering postprandial gluocse level and stimulating insulin secretion.*

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OP 16

Effects of A Traditional Medicine for Diabetes on Glucose Metabolism in Vitro

Subhadhcha Poonsatha, Tim Connor, Richard Fahey,
Gwyn Jones, Nicky Konstantopoulos, Ken Walder, Greg Collier

Metabolic Research Unit, School of Exercise and Nutrition Sciences, Deakin University, Waurn Ponds, Victoria, Australia

Background and Aims. *Traditional medicines (TM) represent a potential source of new leads for insulin resistance and type 2 diabetes therapeutic agents. We have previously shown that a TM used in the South Pacific improved the diabetic condition in Psammomys obesus, a polygenic model of obesity and type 2 diabetes. To determine how the TM extract has improved the diabetic condition in P. obesus, we have proceeded to investigate its effects on glucose metabolism in cellular model.*

Materials and Methods. *Differentiated 3T3-L1 adipocytes were treated with the TM extract (0.005–2% w/v) for 90 min in 14C-glucose incorporation into lipid (lipogenesis) assay or for 20 min in 14C-deoxyglucose uptake assay, and its effects were measured. Furthermore, as a key mechanism in glucose transport, translocation of GLUT4 to permeable membrane was measured by using HA-tagged GLUT4 translocation assay1 in 3T3-L1 adipocytes. In addition, effect of the TM extract on a rate-limiting enzyme in hepatic glucose production, PEPCK, was assessed using a dual luciferase promoter-reporter assay in rat FAO hepatomas. The FAO cells over-expressed both, the internal control, renilla luciferase under thymidine kinase promoter and the firefly luciferase under PEPCK promoter. These cells were then treated with dexamethasone and cAMP analogue (CPT-cAMP) to activate PEPCK. Co-treatments with the 0.5% TM extract were performed to measure effects on activated PEPCK. Data was statistically analysed by ANOVA to test for effects of the TM.*

Results. *In 3T3-L1 adipocytes, the TM extract caused dose-dependent increase in glucose incorporation into lipid by up to 55% ($p<0.05$; $n=2$), and glucose uptake by up to 80% ($p<0.05$; $n=3$) in the presence of 1 nM insulin. The TM extract (0.5% w/v) stimulated translocation of HA-GLUT4 to the PM by 35-70% ($n=3$) when compared to basal level of HA-GLUT4 at the PM. These results indicate that this TM increases glucose disposal in 3T3-L1 adipocytes, and support the previous in vivo findings of P. obesus using this TM. Moreover, the TM extract (0.5% w/v) also suppressed PEPCK promoter activity by 40% ($n=4$) when compared to the activation by dexamethasone and CPT-cAMP in the FAO cells.*

Conclusion. *Our results suggest that this TM possesses insulin-sensitising and insulin-mimetic activities. We are currently undertaking a chromatographic fractionation of the TM, and further studies will involve assessment for bioactivity in these fractions to identify effective components of this TM as potential source of novel compounds for treatment of type 2 diabetes. 1 Grovers R., et. al. Molecular Cell Biology. 2004, 24(14)6456*

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