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Decreased Lymphocyte 5'-Nucleotidase Activity in NIDDM Patients Treated with Gliclazide

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Conflicting results exist on the causative role of adenosine in insulin resistance. Recent studies have demonstrated that a decreased adenosine production or action could play a causative role in insulin resistance. In contrast, some earlier studies have shown that removing of adenosine or blocking its action increases insulin sensitivity. 5'-Nucleotidase is likely to play a key role in the regulation of the local concentration of adenosine, which is a powerful vasodilator and also behaves as an immunosuppressor and an anti-inflammatory agent. Glibenclamide, a sulfonylurea drug, was previously found to inhibits in vitro production of adenosine and 5'-nucleotidase activity of cardiac muscle. The aim of this study was to assess the effect of gliclazide, another sufonylurea drug, on lymphocyte ecto-5'-nucleotidase of NIDDM patients.

We have studied expression of lymphocyte ecto-5'-nucleotidase in patients with NIDDM treated for two months with gliclazide (80 mg b.i.d.). Twelve patients, 8 males and 4 females, age 45 to 69, participated in the study. Petreatment 5'-nucleotidase activity was 1.49 nmol/min/10^6 lymphocytes, and was not different from the level in 10 healthy controls. After two months of gliclazide treatment suface 5'-nucleotidase activity significantly decreased by 47, 39 and 37 percent in unstimulated, and Con A- or PMA-stimulated lymphocytes, respectively. Another lymphocyte ectoenzyme, aminopeptidase N (APN), was also studied, however, gliclazide treatment did not significantly changed ecto-APN of both, unstimulated and Con A- or PMA-stimulated lymphocytes. Glucoregulation was improved after gliclazide treatment, as mean glucose level was found decreased from 9.6 to 7.8 mmol/L. However, there was no correlation between lymphocyte ectoenzymes and pre- or post-treatment fasting glucose levels.

These results suggest that gliclazide treatment inhibits the activity of lymphocyte ecto-5'-nucleotidase and presumably decreases concentration of adenosine at the cell surface. Decrease of 5'-nucleotidase activity and attenuation of adenosine production may be a factor in the pathogenesis of tissue injury associated with sulfonylurea's treatment. This study cannot answer about the role of adenosine in insulin resistance of NIDDM patients. The effect of gliclazide treatment on 5'-nucleotidase and adenosine concentration of striated muscle and adipocytes could possibly reveal the role of these in insulin resistance, and the mechanism of gliclazide action.

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Suppertime 70/30 Insulin and Sulfonylurea Combination Therapy for Japanese Type 2 Diabetic Patients

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Several studies have demonstrated the efficacy of a combination therapy of insulin and sulfonylurea (SU) in type II diabetics with secondary failure to SU. The purpose of this study was to compare suppertime 70/30 insulin, bedtime intermediate-acting insulin (combination therapy) and insulin monotherapy by measuring the glycemic control levels and other personal data. Forty-five patients with insufficient glycemic control on maximal doses of SU alone (mean age: 65.4±1.8 years.; duration of diabetes: 11.8±1.3 years.; body mass index (BMI): 20.9±0.8 kg/m^2; mean±SE) were allocated treatments using computed randomization. Group A (suppertime 70/30 insulin, n=15), group B (bedtime intermediate-acting insulin, n=15) and group C (morning intermediate-acting insulin, monotherapy, n=15). Group A and B were administered their usual dose of SU and were each given additional medicines. Insulin was given as a single injection and initial dosage was 6 U/day for the first 2 weeks in group A and B and 10 U/day in group C. Fasting blood samples were collected at 0, 2, 4, 12, and 24 weeks. Fasting plasma glucose levels were significantly improved in all groups. In group A and C especially HbA1c levels were improved more than group B. CPR and lipids levels did not change. BMI levels did not change significantly in group A or B, but increased at 24 weeks in group C. The daily insulin doses were increased at week 2 in group C, with a trend towards a further increase thereafter (22.5±4.7 U/day) and the need to inject twice a day. In conclusion, these findings suggest that the suppertime 70/30 insulin plus SU therapy is safe and is as effective as insulin alone in improving glycemic control levels. On the other hand, a combination therapy might be of importance in lowering the hyperinsulinemia which causes atherosclerosis. We recommend a combination of suppertime 70/30 insulin and SU in patients with insufficient glycemic control on maximal doses of SU alone before the switch to insulin monotherapy, because this method restores glycemic control more rapidly and with lower doses of insulin.

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The Efficacy and Safety of Amaryl as Compared to Placebo in Mexican-Americans with Type 2 Diabetes Inadequately Controlled by Exercise and Diet Alone

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Purpose: Type 2 diabetes is a prevalent disease among Hispanic Americans. We studied the efficacy and safety of glimepiride (G), a long acting sulfonylurea, as compared to placebo (P) in Mexican-Americans with type 2 diabetes inadequately controlled by exercise and diet alone. **Methods**: This double blind, placebo controlled, randomized (2:1, G:P), parallel design study was conducted at 7 primary care sites in California. 70 adult Mexican-American patients with type 2 diabetes inadequately controlled with exercise and diet alone for at least 3 months were randomized to G (n=48) or P (n=22). Patients had not received any antidiabetic medication within 3 months of study entry. Following randomization, patients entered a 2 week titration period. During the titration period patients initially received 1 mg daily and were titrated to 2 mg then 4 mg daily based on a target FBG of $\leq$ 120 mg/dL. Following titration, patients entered a 12 week maintenance period. All statistical analysis are intent to treat performed at a two-sided 0.05 significance level. **Results**: From baseline to endpoint, mean HbA1c (%) ± S.D. decreased from 10.1 ± 1.8 to 7.8 ± 1.5 for G and 10.6 ± 2.4 to 9.9 ± 2.8 for P [adjusted mean treatment difference ± S.E.: -1.8 ± 0.4, p=0.0001]. Mean FPG (mg/dL) ± S.D. decreased from 222 ± 72 to 176 ± 62 for G and increased from 206 ± 73 to 213 ± 93 for P [-47 ± 17, p=0.0073]. 69% of patients randomized to G experienced an excellent response (HbA1c of <7% or at least a 20% decrease from baseline) compared to 28% of patients randomized to P. 41 (85%) and 15 (68%) of the patients treated with G and P, respectively, completed the study successfully. The majority of the patients who dropped out were lost to follow-up [6 (13%) G and 4 (18%) P]. Treatment related adverse events were similar across both treatment groups. Headache was the most common reported treatment related adverse event for both G and P. **Conclusions**: G is safe and effective for the treatment of inadequately controlled type 2 diabetes in Mexican-Americans providing statistically significant reductions in HbA1c and FPG with a safety profile similar to placebo.