Efficacy Of Insulin Sensitizing Agents In Subjects With Metabolic Syndrome X And Impaired Glucose Tolerance After 6 Months Of Diet And Exercise Therapy

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A. Background

Impaired glucose tolerance (IGT) is a risk factor for developing diabetes and has increased mortality from athrosclerotic disease, particularly ishemic heart disease. Frequently, IGT manifests in the setting of central obesity, hypertension, and dyslipidemia, together known as metabolic syndrome X, conferring further risk for micro and macrovascular complications.

A few large, prospective, randomized trials demonstrated decreased progression from IGT to DM with intensive diet and exercise modifications. In an industrial province of China, after screening >1 10, 000 men and women, 530 patients with IGT were followed for six years. 67.7% of patients with IGT in the control group, only given handouts on diet and exercise, progressed to DM in 6 years while only 41-46% treated with diet counseling, exercise or both ultimately developed DM. [1] This study used the old WHO definition for DM of fasting glucose ~!140 mg/dl (7.8mmoUl) which has since been replaced with a lower cut off of fasting glucose >126mg/dl (7mmol/1) by the ADA.

Despite the old definition, the fasting glucose baseline mean plus one standard deviation in this study, was <126mg/dl suggesting that the rate of colliversion to DM would have been even higher with the new definition for diabetes.

The Malmö Prevention Tria1[2] followed 6389 men, 423 with impaired glucose tolerance, hypertension, obesity, hyperinsulinemia and hypertriglyceridemia for 12 years. The 288 with IGT assigned to a diet and exercise program had a similar all cause mortality rate to the 5577,Aith normoglycemia 6.2 (5.7-6.8) per 1000 person years vs. 6.5 (4.1-9.9). The 135 men with IGT randomized to routine treatment had a total mortality of 14.0 (8.7-21.4) which was statistically significant ($p<0.05$) compared to the diet and exercise group. Cardiovascular mortality accounted for the majority of the increase, rising from 3.6 (1.8-6.2) in the diet and exercise group to 7.3 (3.7-13. 1) in those with untreated IGT.

Despite initiating treatment, the diabetics had a dramatically increased mortality rate over the 12 years, 22.6 (9.2-22. 1), which further supports the quest to delay the progression to diabetes. This study also used the more liberal VfflO criteria for diabetes, but the baseline fasting glucose in the IGT group was 5.3±0.1 mmol/l = 95.4±1.8mg/dI, with impaired glucose tolerance tests.

Local data provided by the ICCR nutrition department, courtesy of Wahida Karmally, demonstrated a 5% weight loss over one year in 3 1% of subjects randomized to diet control with the assistance of a nutritionist and computer program compared to 15% of controls, only given a diet modification pamphlet.

Other studies have looked at using pharmacotherapy in patients with IGT to improve insulin resistance and glucose tolerance as a means to delay progression to diabetes.

Studies with metformin,[3] troglitazone,[4] and tolbutamide[5] have demonstrated improvements in insulin- resistance, glucose utilization, progression to diabetes as well as improvements in the associated findings with syndrome X including blood pressure, and lipid control. Data comparing these medications in preventing diabetes versus diet and exercise in patients with IGT is not available. As mentioned above, the criteria for diabetes was broadened to identify and treat those most at risk for the complications of diabetes in the early stages of the disease. It remains unclear if patents with impaired glucose tolerance and insulin resistance would also benefit from pharmacologic interventions.

Insulin resistance is hypothesized to be the primary metabolic derangement leading to the manifestations of syndrome X with dyslipidemia, hypertention, hypercoagulability, weight gain and ultimately diabetes.[6] Thus the introduction of thiazolidinediones (TZDs), that decrease insulin resistance and improve insulin stimulated glucose disposal by -30% was a welcomed addition to the fight against diabetes.[7]

> "Since treatment with the insulin-sensitizing TZI)s can improve most of the manifestations of syndrome X., this provides pharmacologic evidence that indulin resistance is the core abnormality in these patients."[8]

The initial TZD, troglitazone was removed from the market after its risk of liver toxicity was discovered. Rosiglitazone and pioglitazone have less experience in the literature, but do not have the liver toxicity. Another drug, metformin, lowers glucose by decreasing hepatic glucose production and enhances hepatic and peripjieral insulin sensitivity without effecting insulin secretion.[9] It also has positive effects on the manifestations of syndrome X by decreasing blood pressure, inducing weight loss, and improving lipids. Side effects of diarrhea, nausea and anorexia can limit its use in -6%, but lactic acidosis can be devastating with an incidence of 0.03 cases per 1000 patient years, limiting its use in patients with renal, liver or cardiac disease.

The ongoing Diabetes Prevention Program (DPP)[10] is a randomized clinical trial of >3,000 participants with impaired glucose tolerance and elevated fasting glucose designed to attempt to answer some of these questions. Three treatment groups: intensive diet and exercise, metformin or placebo with standard diet and exercise will be followed prospectively for 3.5-5 years with the primary end point of the development of diabetes. A fourth arm with troglitazone was discontinued after liver toxicity was discovered. Recruitment will close in 2002. While DPP will provide valuable information on the prevention of diabetes in patients with IGT comparing the efficacy of metformin with intensive diet and exercise. It will still leave a many questions unanswered.

Standard recommendations for treatment of isolated diabetes, obesity, hypertension, and dyslipidemia start with lifestyle changes of diet and exercise. Unfortunately, this is one of the most difficult treatment strategies for patients to succeed at, despite clear evidence for improvement in morbidity and mortality. Typically this trial lasts several months before starting drug therapy. Furthermore, despite initial weight loss, patients often regain the weight they have worked so hard to lose leading often leading to suboptimal control despite multiple medications.

It is unclear if weight loss plus an insulin sensitizing agent can have a further reduction in the metabolic derangements of syndrome X and ultimately delay the progression to diabetes and decrease its increased cardiovascular risk.

B. Hypothesis

In patients with Syndrome X (hyperlipidemia, hypertension, central obesity) with impaired glucose tolerance, does pharmacotherapy following six months of intensive diet and exercise therapy improve glucose tolerance and insulin resistance.

C. GOALS

1. Determine anticipated weight loss over six months with intensive diet and exercise counseling and its effect on glucose tolerance and insulin resistance.
2. Determine the efficacy of insulin sensitizing agents compared to diet and exercise.

This study aims to optimize the current treatment strategies known to decrease morbidity and mortality in patients with IGT and Syndrome X and then assess the potential benefits d additional pharmacotherapy with insulin sensitizing agents.

D. Methods: Conceptual and Operational Definitions

End points

a. Primary

- Glucose tolerance testing and insulin resistance.
- Oral Glucose Tolerance Test: standard, 3 hour, 75gin glucose dose after 3 days of 300gm carbohydrate diet preceding the test. Check glucose (finger stick mg/dl) every 30 minutes for 2 hours and then at end of test at 3 hours. IGT defigned if peak or 2 hour value >200, as per National diabetes data group classification. [11]
- Glucose-Clamp Study: At 40mU of insulin per square meter per minute. From this data, insulin-sensitivity index calculated and then correlated with calculated values of insulin basal resistance, using the homeostatic model assessment (HOMA
- Insulin resistance = fasting insulin x fasting glucose/22.5[12]

b. Secondary

Weight loss (kg), lipids: total cholesterol, triglycerides, LDL and HDL (after 12 hour fast) and blood pressure, and quality of life measures using the well validated SF-36 self-administered questionnaire. Progression to DM defined as fasting glucose >126mg/dI, non-fasting glucose >200mg/dI, HbAlc $\geq$ 6.5.

E. Study Design

Prospective, randomized, double-blinded controlled trial PROTOCOL: {See attached flow sheet}

After initial baseline data collection {see table) all participants undergo 32 weeks of optimization of medications for HTN, hyperlipidemia and obesity with aggressive diet and exercise therapy with a goal to loose >5% of body weight. Ideally each patient could tolerated an ACE-I and HMG-CoA reductase inhibitor. Other medications tolerated as needed. Re-test subjects after 32 weeks of diet and exercise and optimization of medication. If the insulin resistance measures and glucose tolerance test have normalized, the subjects are excluded from further randomization to avoid unnecessary exposure to risk of medication. Patients are stratified between those who lost greater than or equal to 5% of body weight and those who did not.

The remaining groups randomized to metformin 500mg PO BID, rosiglitazone 2mg PO BID or control. All groups continue intensive diet and exercise management to maintain a constant weight from what they achieved after 32 weeks over the next 12 weeks. Pt's followed for 12 weeks of therapy then final testing.

Baseline Data:	*Prospective Data:*
H&P:	Fasting glucose, OGTT insulin clamp study
Current medications	SF-36, fasting lipid profile
Allergies	
Comorbid illness	Follow *every 6 weeks:*
Family Hx of DK M and high cholesterol	Chem 7, liver function tests,
H/O gestational DM duration of HTN	blood pressure, heart rate
smoking status	weight, h ight

The aggressive diet and exercise program for the first 6 months with a goal to loose >5% of body weight, includes individual meal planning and education with dietitian, in addition to lifestyle modification and exercise program designed with individualized trainer. After initial meetings and program development over the first 2 weeks, patients continue with group sessions with a behavior

management specialist every two weeks for the first month and monthly for the remaining 5 months. Dietitians and trainers follow-up individually monthly. All visits and meetings after the first month separated by >I week to keep follow-up uniform.

After randomization, groups meet biweekly for the first month then monthly with the goal to maintain weight. Dietitians and trainers follow-up individually monthly.

a. Statistics

Compare before and after 32 weeks of diet and exercise:

1. Individual subject comparison with paired t-test of OGTT and clamp study, also t-test on BP, SF-36, lipids.
2. Same parameters compared between those who lost >5% body weight to those that did not, with an unpaired Mest.

After randomization:

Use ANCOVA to control for baseline variation in OGTT and glucose clamp results in the following three comparisons. Compare secondary outcomes of blood pressure control, lipids, SF-36 with a t-test. All groups analyzed by intention to treat.

1. Each treatment arm before and after therapy
2. Efficacy of drug after 5% weight loss compared to drug without weight loss.
3. Overall comparison of metformin vs. rosiglitazone vs. placebo.
4. Incidence of adverse outcomes and side effects after randomization.

Post HOC analysis to account for multiple tests on the data with Bonferoni correction.

b. Sample Size

POWER: Previous RCT with troglitazone lead to a ~40% improvement in glucose tolerance test point comparison and a similar decrease in plasma insulin levels.

Using an unpaired t -test: $n = I + 16 \{\text{std-devn/effect}\}^2$

Std-devn = 8 effect = 10 $n = 11.24 = 12$

Using a paired t-test: $n=2+8\{\text{std-devn/effect}\}^2$ $n = 7.12 = 8$

Metformin decreased fasting insulin and fasting glucose in IGT subjects. Unpaired t-testing required 5 subjects per group.

Diet and exercise modification is anticipated to produce a 5% reduction in weight in 6 months in -30% of participants. Of those who do loose >5% only a few are expected to normalize their glucose tolerance tests, estimate 20%.

Thus to have 12 patients per randomization group that have lost >5% (30% of initial enrollees), and anticipating normalization in 20% of the 30% (20% of 12 = 2.4) who do lose >5%, N = 25 + 12 + 3 = **40** enrolled per group.

F. Subjects

Recruited and screened from CPMC clinics, affiliated private offices, and local community for a goal of 50% women 50% minorities and 20% who are greater than 65 years old.

a. Inclusion Criteria

Subjects age 40-75 year old with hypertension, central obesity defined by waist to hip ratio (men >1, woman >0.8) and BMI >27, dyslipidemia (TG> 200 and HDL <3 5) with fasting blood sugar < I 26mg/dL, HbA I c <6.5.

b. Exclusion Criteria

Current treatment for diabetes or fasting glucose >126mg/dL, HbA I c 2: 6.5, allergy to metformin or rosiglitizion6 br history of liver toxicity with troglitizone, comorbid disease potentially requiring steroids, cancer, pregnancy, anticipated pregnancy, previous NH, chronic renal or liver disease or disease requiring chronic anticoagulation.

Consent obtained in native language within 3 weeks after meeting inclusion criteria. Subjects given 3 weeks to discuss protocol with family, personal physician and ask questions.

G. References

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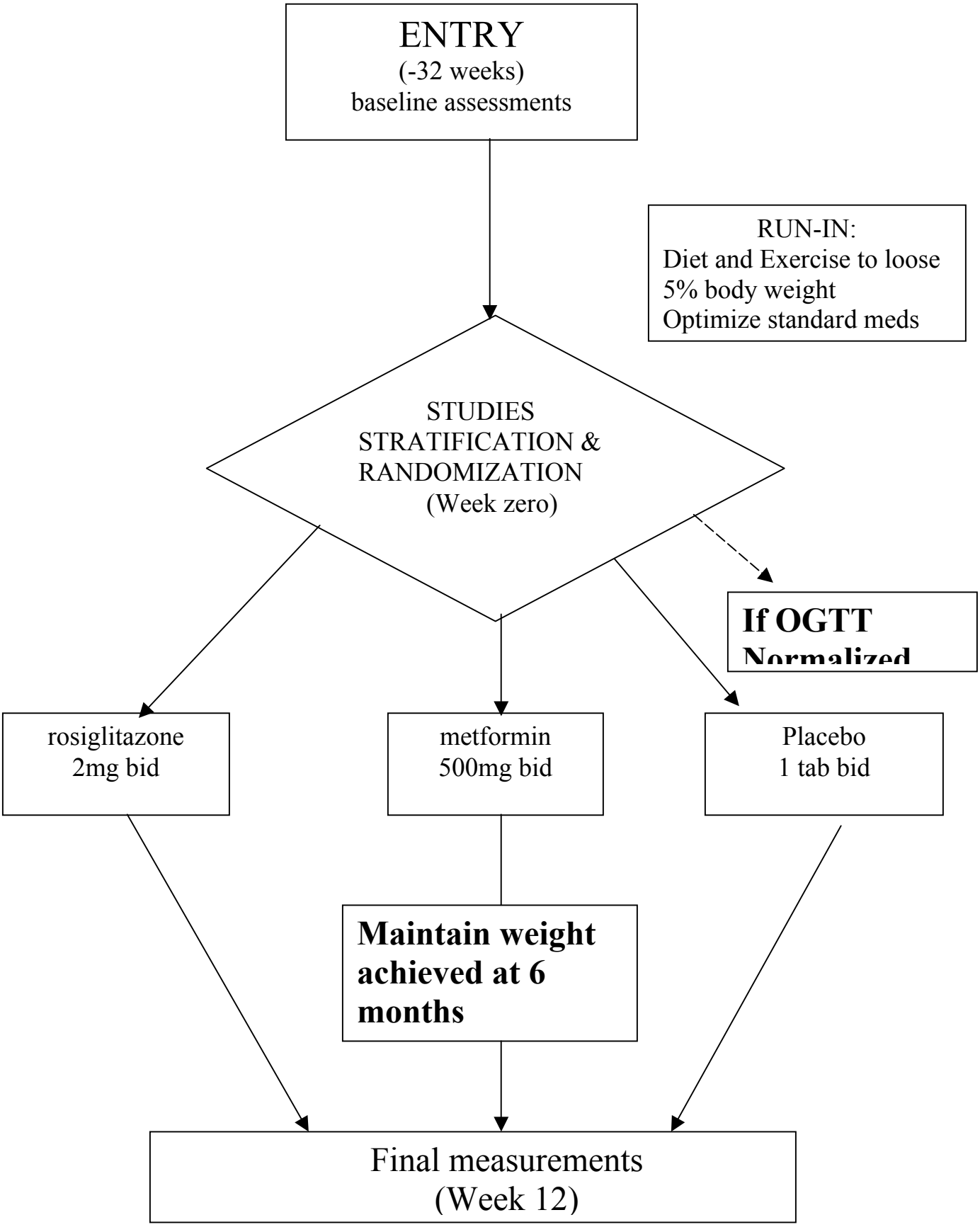
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(-32 weeks)
baseline assessments
RUN-IN:
Diet and Exercise to loose
5% body weight
Optimize standard meds
STUDIES
STRATIFICATION &
RANDOMIZATION
(Week zero)
If OGTT
Normalized
rosiglitazone
2mg bid
metformin
500mg bid
Placebo
1 tab bid
Maintain weight
achieved at 6
months
Final measurements
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