Insulin Therapy to Improve BMI in Cystic Fibrosis Related Diabetes Without Fasting Hyperglycemia: Results of the CFRDT Trial

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

Clinical Trials Number: NCT00072904; www.clinicaltrials.gov

Submitted 25 March 2009 and accepted 24 June 2009.

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Objective: Cystic fibrosis related diabetes (CFRD) without fasting hyperglycemia (FH-) is not associated with microvascular or macrovascular complications, leading to controversy about the need for treatment. The CFRD Therapy Trial (CFRDT) sought to determine whether diabetes therapy improves body mass index (BMI) in these patients.

Research Design and Methods: A 3-arm multi-center randomized trial compared 1 year of therapy with pre-meal insulin aspart, repaglinide, or oral placebo in CF subjects with abnormal glucose tolerance.

Results: One hundred adult patients were enrolled. Eighty-one completed the study including 61 with CFRD FH- and 20 with severely impaired glucose tolerance (IGT). During the year before therapy, BMI declined in all groups. Amongst CFRD FH-, insulin-treated patients lost 0.30±0.21 BMI units the year before therapy; after one year of insulin therapy, this pattern reversed and they gained 0.39±21 BMI units (p=0.02). No significant change in the rate of BMI decline was seen in placebo-treated patients (p=0.45). Repaglinide-treated patients had an initial significant BMI gain (0.53±0.19 BMI units, p=0.01) but this effect was not sustained. After 6 months of therapy they lost weight so that by 12 months there was no difference in the rate of BMI change during the study year compared to the year before (p=0.33). Amongst IGT patients, neither insulin nor repaglinide affected the rate of BMI decline. No significant differences were seen in the rate of lung function decline or the number of hospitalizations in any group.

Conclusions: Insulin therapy safely reversed chronic weight loss in patients with CFRD FH-.
Approximately 30,000 persons with CF live in the US. With steady advances in medical care, average life expectancy is now about 38 years. Diabetes due to insulin insufficiency is the most common co-morbidity in this population, occurring in 40-50% of adult CF patients (1). Approximately 15% have diabetes with fasting hyperglycemia (CFRD FH+) and require insulin therapy to prevent classic diabetes symptoms and microvascular complications. The 25% of adult CF patients who have diabetes without fasting hyperglycemia (CFRD FH-) pose a greater clinical dilemma. During a standard oral glucose tolerance test (OGTT) they have normal fasting glucose levels but their two hour glucose is ≥200 mg/dl (11.1 mmol/L). It has been argued that patients with CFRD FH- do not require diabetes therapy since they are asymptomatic, have relatively normal glucose levels when measured at home by self-monitoring of blood glucose (SMBG), and minimal hemoglobin A1c elevation (2). Unlike the general diabetes population, they do not appear to be at risk for microvascular or macrovascular complications (3). However, it has also been argued that while the metabolic complications of intermittent post-prandial hyperglycemia may not be severe in these patients, the nutritional consequences of insulin deficiency may be life-threatening (4).

Survival in CF is intimately connected to nutritional status; underweight and protein catabolism are associated with poor pulmonary function and death. Insulin is a potent anabolic hormone, and insulin insufficient CF patients have increased protein and fat breakdown (4-6). Pulmonary function decline is also related to the severity of insulin insufficiency (7). Thus, insulin insufficiency may increase morbidity and mortality by contributing to loss of weight and lean body mass. We hypothesized that insulin therapy would reverse nutritional deterioration in these patients.

The addition of an insulin regimen is a significant treatment burden for patients whose lives involve complex and time-consuming medical cares, and prescription of such a regimen requires clear evidence of benefit. The question of whether CFRD FH-patients should receive diabetes therapy was given the highest research priority by a national consensus conference on CFRD (2). The Cystic Fibrosis Related Diabetes Therapy Trial (CFRDT) was undertaken to determine whether pre-meal therapy with either rapid-acting insulin or the oral insulin secretagogue repaglinide would improve body mass index (BMI) in this population.

**RESEARCH DESIGN AND METHODS**

**Subjects:** Fourteen CF Centers in the US, Canada and Great Britain participated (see Appendix A in the online appendix at [http://diabetescare.diabetesjournals.org](http://diabetescare.diabetesjournals.org)). The University of Minnesota (UM) was the Coordinating Center, and the Data Management Center was located at the University of Massachusetts, Amherst. Participating centers routinely performed annual OGTT screening. Fasting subjects were given 1.75grams/kg (maximum 75gr) of an oral glucose solution and glucose levels were measured over two hours. OGTTs were performed during stable baseline health.

CF patients were recruited who had CFRD FH- (fasting plasma glucose <126 mg/dl/7.0 mmol/L and 2-hour glucose ≥200 mg/dl/11.1 mmol/L) or severe IGT (glucose level ≥200 mg/dl/11.1 mmol/L during the OGTT and 2-hour glucose level 180-199 mg/dl/10.0-11.1 mmol/L). Additional eligibility criteria included completion of linear growth, weight stable within 5% during the previous 3 months, and no evidence of acute infection in the previous 2 months. Exclusion criteria included fasting
hyperglycemia in the previous year, oral or intravenous glucocorticoid therapy in the previous 6 months, liver dysfunction, and pregnancy. Block randomization, using a pseudo-random number generator and stratified by center, was used to ensure a more even distribution of treatments over time and across sites in the study. One third of patients per block were assigned to each treatment arm. IRB approval was obtained at the Coordinating Center and at each center; informed consent was obtained from all subjects.

**Treatment Protocol:** Patients were randomly assigned to receive insulin aspart 0.5 units per 15 grams dietary carbohydrate, repaglinide 2.0mg orally, or oral placebo three times a day before meals. The oral agents were double-blinded; there was no injectable placebo due to ethical concerns. Study coordinators contacted patients weekly. If subjects experienced hypoglycemia, additional education was provided to ensure sufficient carbohydrate intake. If dietary measures were insufficient to prevent post-prandial hypoglycemia, the medication dose was reduced. Persistent post-prandial hyperglycemia led to a dosage increase. Subjects were followed for 1 year and seen by the study team quarterly. Insulin vials and pill bottles were returned quarterly for medication adherence monitoring.

Ongoing diabetes education was provided. Dietary recommendations were the same as for all CF patients including consumption of a high-calorie diet with 3 meals and at least 3 snacks per day with no restriction on total daily carbohydrate intake. Patients were taught carbohydrate counting and instructed to consume a minimum of 60 grams carbohydrate with each meal to reduce the risk of hypoglycemia. Those receiving rapid-acting insulin were taught to match the insulin dose to the carbohydrate content of the meal at a dose of 0.5 units per 15 grams carbohydrate.

Patients with CFRD FH- are at risk for permanent progression to CFRD FH+. This was a planned stopping point because it required patients switch to basal-bolus insulin therapy. However, CF patients can develop transient fasting hyperglycemia during acute illness. Patients were withdrawn from the study only if they developed acute illness-associated fasting hyperglycemia which persisted for more than 1 month, at which point a chronic change in their diabetes condition was considered to have occurred. In addition, patients were withdrawn if they required systemic glucocorticoids for more than 1 month because of the effect of these drugs on BMI.

**Study Endpoint Measurement:** All patients were followed at accredited CF centers with standardized procedures for quarterly measurement of clinical outcomes including BMI and pulmonary function. BMI was chosen as the primary study endpoint because it is well-correlated with survival in CF (8-10). BMI and lung function parameters measured 12 months prior to study entry were obtained from chart review. During the study they were prospectively measured quarterly. Additional measures obtained at baseline and 12 months included DXA for body composition, the NIH prognostic score (a measure of overall clinical health) (11; 12), a validated CF quality of life (CFQOL) survey (13), 3-day dietary histories, HbA1c (measured centrally at UM) and fasting and 90 minutes post-main meal capillary glucose levels obtained at home by SMBG.

**Data Analysis:** Summary statistics were constructed at each measurement occasion with the use of means, standard deviations, medians, and interquartile ranges for continuous factors and frequencies and percentages for categorical factors. Chi-square or Fisher’s Exact tests were used to evaluate association of treatment arm and baseline OGTT status with patient baseline characteristics, study completion and
treatment adherence for each categorical factor; analysis of variance models were used to evaluate differences for continuous-scale factors. To assess treatment effects a series of analysis of covariance models for change from baseline in BMI, FVC and FEV1 were evaluated for each measurement occasion, adjusting for patient baseline characteristics, adherence and prior year change. Initial models included all subjects with data available at each measurement occasion. Final models were stratified by OGTT class (FH- or IGT) at baseline and include the 81 patients who completed the full study year. Additional models evaluate the change from baseline to 1 year in fat free mass, NIH score, CFQOL, and HbA1c.

RESULTS

Study Enrollment, Drop-Outs and Adherence: One hundred patients were enrolled, 74 with CFRD FH- and 26 with severe IGT. Nineteen dropped out or were stopped early; the study was completed by 77% of IGT and 82% of CFRD FH- subjects (p=0.57). There was no difference by treatment group in the percentage of patients dropping out/stopping early (p=0.87) (Online-Only Appendix B). Among all participants, 8 chose to quit, including 5 (13%) on insulin and 3 (5%) on oral therapy (p=0.25). Five patients were stopped early because they developed permanent FH, including 2 (5%) on insulin, 3 (10%) on placebo, and none on repaglinide (p=0.27). Six additional patients (1 insulin, 5 oral) discontinued the study for other medical reasons, including chronic steroids (1 insulin, 1 repaglinide), pregnancy (1 repaglinide), rash attributed by the patient to medication (placebo), and chronic hospitalization, too ill to take medication (2 repaglinide) (p=0.12 for association of reason for discontinuation with treatment). Reasons for drop-out are shown in Online-Only Appendix C.

Study drug adherence was similar amongst the study arms. Compliance data was available at ~75% of study visits. Patients were deemed compliant if they used 90% or more of the expected drug. Approximately 25% of those with adherence data were deemed noncompliant. This is similar to reported adherence to medication regimens in adults with CF (14). There was no difference in adherence between CFRD FH- and IGT (p=0.91) and no difference by treatment arm (p=0.91).

Baseline Characteristics: There were no significant differences in baseline characteristics between patients who completed the study and those who stopped early, with the exception of CFQOL. Those who stopped early were lower for eating disturbance (p<0.05) and social/marginalization scales (p<0.05).

Baseline characteristics of the 81 study completers are presented in Table 1. Patients in the placebo group appeared slightly healthier at baseline, with somewhat higher BMI and better pulmonary function, but these did not achieve statistical significance. Age, baseline BMI and BMI change during the preceding year, baseline lung function and change during the preceding year, body composition and CFQOL did not differ between CFRD FH- and IGT. However, a greater proportion of IGT were male (75% vs 49%, p=0.04). As expected, HbA1c was lower in the IGT group (5.5±0.4 vs 6.1±0.6%, p=0.0002).

Treatment Effect on Body Composition: Change in BMI the year before study participation was compared to change during the study year (Table 2). The previous year, all groups showed a decline in BMI with no significant difference among treatment groups in the loss (Figure). Insulin-treated patients with CFRD FH- lost an average of 0.30±0.21 BMI units in the year prior to therapy (about 2.5 pounds in women, 3 pounds in men). After one year of study...
participation, those who received pre-meal rapid-acting insulin reversed this chronic downward clinical course and gained 0.39±21 BMI units (p=0.02, Figure). Weight gain distribution was about 80% fat and 20% fat free mass. No significant difference in the rate of BMI loss relative to the prior year was seen in placebo-treated CFRD FH- patients (p=0.45). Patients who received repaglinide had an initial significant gain in BMI of 0.53±0.19 within the first 6 months of therapy (p=0.01). This effect, however, was not sustained. After 6 months they lost weight so that by the end of 12 months there was no difference in the rate of BMI change during the study year compared to the year before (p=0.33). Adjustment for baseline BMI, weight, or gender did not influence these conclusions. Changes in body composition were not related to dietary intake; there was no significant difference in daily calorie consumption from baseline to 12 months in any treatment group and no differences between the groups. The absolute change in BMI during the study year did not differ significantly between CFRD FH-groups: insulin vs placebo p=0.36, repaglinide vs placebo p=0.95, insulin vs repaglinide p=0.35.

Among IGT patients, neither the insulin nor the repaglinide treated groups showed a significant difference in the rate of BMI decline during the study year compared to the previous year. A significant improvement was seen in the placebo group (p=0.02). The absolute change in BMI during the study year was significantly worse for repaglinide treated IGT patients: p=0.34 insulin vs placebo, p=0.03 repaglinide vs placebo, p=0.18 insulin vs repaglinide.

**Treatment Effect on Clinical Status:** HbA1c levels did not significantly change in any group. After 1 year of therapy there was no difference in fasting glucose between treatment groups, and no difference from baseline. Post-prandial glucose, however, was somewhat lower in those on insulin therapy, although this did not achieve statistical significance. For CFRD FH-, the 90 minute post-prandial glucose was 116±4 mg/dl (6.4±0.2 mmol/L) in the insulin group, 138±12 mg/dl (7.7±0.7 mmol/L) in the placebo group, and 131±7 mg/dl (7.3±0.4 mmol/L) in the repaglinide group (p=0.06 insulin vs placebo; p=0.81 repaglinide vs placebo). Amongst those with IGT the 90 minute post-prandial glucose was 114±3 mg/dl (6.3±0.2 mmol/L) in the insulin group, 122±4 mg/dl (6.8±0.2 mmol/L) in the placebo group, and 131±9 mg/dl (7.3±0.5 mmol/L) in the repaglinide group (p=0.20 insulin vs placebo, p=0.81 repaglinide vs placebo, p=0.03 insulin vs repaglinide).

While there appeared to be a trend towards less decline in FVC in all of the CFRD FH- study arms and less decline in FEV1 in the insulin and repaglinide arms, these changes were not statistically significant (Table 2). There were no differences in the number of episodes of acute illness during the study year by treatment arm or OGTT class. NIH and CFQOL scores did not differ between groups at baseline or over the treatment year in any group.

**Adverse Events:** No serious adverse events related to study medication occurred. In the first 3 months, significantly more patients on active medication compared to placebo reported mild hypoglycemic events: insulin-16%, repaglinide-23%, placebo-none, p<0.04. In most cases these resolved with patient education. After the first 3 months there were no significant differences between groups in the frequency of hypoglycemia, and there were some episodes of mild hypoglycemia reported by patients receiving placebo. Of 30 subjects who completed the study on insulin, persistent post-prandial glucose abnormalities led to an increased dose in 4 patients (13%) and a decreased dose in 2 (7%). Of 26 subjects who completed the study on repaglinide, persistent post-prandial glucose abnormalities led to an increased dose
in 3 patients (12%) and a decreased dose in 4 (15%).

CONCLUSIONS

It has been hypothesized that insulin insufficiency compromises health and survival in CF by producing a catabolic state with associated weight loss and reduced lean body mass (4). Previous reports have suggested that weight and/or pulmonary function might improve following institution of insulin therapy, but none of these were randomized controlled trials and most had mixed populations of CFRD patients with and without FH (15-20). In the current placebo-controlled multi-center trial, insulin replacement therapy significantly reversed the trajectory of chronic weight loss in CFRD FH-.

No significant changes were seen in the annual rate of decline in FEV1 or FVC or the number of acute illnesses, and there were no changes from baseline in NIH-scores. This is not surprising given that an earlier study required four years of observation before significant trends in lung function could be documented between subjects with normal, impaired and diabetic glucose tolerance (7). CF patients die from chronic inflammatory lung disease, and ultimately lung function is the most important endpoint. However, body weight is strongly related to CF lung function and survival (8-10).

In the current study, insulin treated patients stopped losing weight and gained both fat and lean body mass. This appeared to be mediated primarily via the anabolic rather than the glucose homeostatic effect of insulin since it was accomplished without a significant change in HbA1c or blood glucose levels. Although total caloric intake did not differ between groups and all patients received the same education with regards to carbohydrate counting, we can not exclude the possibility that patients on insulin therapy were more attentive to carbohydrate intake since they were matching it to insulin dose and since patients on insulin were not blinded.

Repaglinide had a transient effect on weight gain in CFRD FH-. It was chosen for this study because sulfonylureas had previously been anecdotally associated with hypoglycemia in CFRD. In pilot studies, pre-meal treatment with either insulin or 1mg repaglinide improved glucose and insulin excursion during a standardized liquid mixed meal, but insulin had a significantly greater effect (21). In the current study, the initial benefits of 2mg repaglinide were not sustained, since after 6 months the rate of weight loss was similar to pre-treatment values and early gains were lost. There was not a measureable change in medication adherence to explain this. Concerns have been raised in other conditions of reduced beta-cell mass that agents that stimulate insulin secretion may ultimately wear out stressed beta-cells. In one study, a year of insulin therapy improved endogenous insulin secretion in subjects with early type 2 diabetes, while patients who received one year of sulfonylurea therapy had a decline in beta-cell function (22). The proposed mechanism was “resting” versus “exhausting” the cells. Prolonged excessive stimulation with sulfonylureas has been shown to induce beta-cell apoptosis in cultured human islets (23). Paradoxically, repaglinide therapy had a negative effect on weight in IGT. Thus, use of this agent in CF patients with IGT cannot be recommended at present.

Insulin therapy is not easy. Although the number of drop-outs was similar between treatment groups, patients receiving insulin injections were more likely to choose to quit, whereas in the other groups drop-out was more likely due to a medical problem which disqualified the patient from further study participation. However, the majority of subjects in all three groups completed the study, adherence with study drug was similar between the oral and injection treatment arms,
and there was no difference in CFQOL between treatment groups. During the study, patients were told that it was not known whether diabetes therapy would have a positive health impact. Adherence may be easier when there is a proven benefit.

Is pre-meal rapid-acting insulin the best regimen for patients with CFRD FH-? It was chosen for this trial based on evidence that metabolic defects in CF are most pronounced in the post-prandial state (4; 5; 23), and because of theoretical concerns that bedtime NPH insulin might result in hypoglycemia in these patients with normal fasting glucose levels. At the time the study began, the newer basal insulin analogs were not yet widely available. Recently, small pilot studies have suggested that low-dose insulin glargine may improve weight or pulmonary function in CF patients with abnormal glucose tolerance without causing significant hypoglycemia (19; 20). Further work needs to be done to compare and/or combine basal and pre-meal insulin regimens in this population.

No apparent clinical improvement was seen with treatment of CF patients with severe IGT, although for reasons that are not clear, BMI improved in placebo-treated patients. These data need to be interpreted with caution. Glucose tolerance abnormalities in CF represent a spectrum. We originally believed that IGT and CFRD FH- subjects were metabolically similar enough that their results could be pooled, but their responses to treatment proved to be different. There was greater variability in the IGT group compared to CFRD FH-, along with fewer participants; we would have needed a greater number of subjects with IGT to derive any definitive conclusions about the effect of treatment. Furthermore, there were significantly more males in the IGT group. This may be an important difference since prognosis is worse in women with CFRD (24). The present data demonstrate that studies exploring carbohydrate metabolism in CF should separately consider subjects with CFRD from those with IGT, and that further research is needed to determine the most appropriate treatment of IGT.

In the CFRDT trial, insulin therapy safely reversed chronic weight loss in patients with CFRD FH-. Insulin may be successful in breaking the cycle of protein catabolism, weight loss, and pulmonary function decline because of its anabolic effects. A significant percentage of the adult CF patient population could benefit from this therapy, with a substantial impact on morbidity and mortality.

**ACKNOWLEDGMENTS**

This project was supported by NIH-R01-DK58356 (Moran), NIH-M01-RR-00400 (GCRC), and a grant from the Cystic Fibrosis Foundation.

**Disclosures:** Study drug and blood glucose testing supplies were generously donated by Novo Nordisk Inc. (Princeton, NJ) and Lifescan (Johnson & Johnson, Milpitas, CA), respectively.

**Figure Legend**

Figure 1. BMI 12 months before and 6 and 12 months after treatment with insulin (red), placebo (blue) or repaglinide (black) in A. 61 subjects with CFRD FH- and B. 20 subjects with IGT. Mean ± S.E.M. P values are for study year (0-12 months) compared to previous year (-12-0 months) within each group.
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Table 1. Baseline characteristics of the 81 subjects who completed the CFRDT Trial. Data for the CFRD FH- and IGT total cohorts are presented as mean ± SD; data by treatment group as mean ± SEM.

|                     | CFRD FH- | IGT       |
|---------------------|----------|-----------|
|                     | Total Cohort | Insulin | Repaglinide | Placebo | Total Cohort | Insulin | Repaglinide | Placebo |
| Number              | 61        | 23       | 22          | 16      | 20          | 7       | 4           | 9       |
| N, (% Female)       | 31 (51%)* | 12 (52%) | 11 (50%)    | 9 (50%) | 5 (25%)     | 3 (43%) | 0 (0%)      | 2 (22%) |
| Age, years          | 28 ± 9    | 29 ± 2   | 26 ± 2      | 28 ± 3  | 28 ± 7      | 27 ± 2  | 29 ± 5      | 28 ± 2  |
| BMI kg/m2           | 21.3 ± 2.9| 20.6 ± 0.6| 21.3 ± 0.7  | 22.2 ± 0.6| 22.0 ± 2.7 | 20.7 ± 0.7| 22.9 ± 1.7 | 22.5 ± 0.9|
| % Fat free mass     | 79 ± 9    | 79 ± 2   | 80 ± 2      | 77 ± 2  | 80 ± 8      | 81 ± 3  | 79 ± 5      | 80 ± 3  |
| FVC %predicted      | 90 ± 22   | 87 ± 4   | 90 ± 6      | 94 ± 4  | 88 ± 17     | 79 ± 7  | 82 ± 10     | 98 ± 4  |
| FEV1 %predicted     | 70 ± 25   | 63 ± 5   | 71 ± 6      | 78 ± 5  | 69 ± 21     | 61 ± 7  | 61 ± 13     | 78 ± 6  |
| NIH score           | 83 ± 13   | 80 ± 3   | 84 ± 3      | 88 ± 3  | 82 ± 14     | 79 ± 6  | 74 ± 9      | 89 ± 2  |
| HbA1c (%)           | 6.1 ± 0.6*| 6.2 ± (0.1)| 6.2 ± 0.1  | 6.0 ± 0.1| 5.5 ± 0.4   | 5.5 ± 0.3| 5.6 ± 0.1   | 5.5 ± 0.1|

There were no significant differences across treatment groups for CFRD FH- or IGT
* =Total Cohort CFRD FH- vs IGT, p<0.05

Table 2. Comparison of the change in BMI (kg/m²) and lung function (% predicted) the year before and after 1 year of study participation. Data are presented as mean ± SEM.

|                     | CFRD FH- (n=61) | IGT (n=20) |
|---------------------|-----------------|------------|
|                     | Insulin | Repaglinide | Placebo | Insulin | Repaglinide | Placebo |
| BMI -12 months to Baseline | -0.30 ± 0.21 | -0.14 ± 0.21 | -0.29 ± 0.25 | -0.60 ± 0.30 | -0.08 ± 0.40 | -0.66 ± 0.27 |
| BMI Baseline to +12 months | 0.39 ± 0.21 | 0.15 ± 0.21 | 0.45 | 0.02 | 0.33 | 0.45 |
| p-value             | 0.02     | 0.33       | 0.45  | 0.02     | 0.33       | 0.45  |
| FVC -12 months to Baseline | -5.8 ± 2.0 | -5.5 ± 2.1 | -4.3 ± 2.5 | 2.0 ± 4.2 | -3.4 ± 5.6 | -2.8 ± 3.7 |
| FVC Baseline to +12 months | -0.5 ± 2.0 | -2.1 ± 2.1 | -1.1 ± 2.5 | -10.3 ± 4.2 | -3.1 ± 5.6 | -5.1 ± 3.7 |
| p-value             | 0.21     | 0.25       | 0.37  | 0.05     | 0.96       | 0.6   |
| FEV1 -12 months to Baseline | -5.7 ± 2.2 | -6.5 ± 2.2 | -0.5 ± 2.7 | 0.6 ± 5.6 | -2.5 ± 7.4 | 2.8 ± 4.9 |
| FEV1 Baseline to +12 months | -1.8 ± 2.2 | -1.3 ± 2.2 | -3.0 ± 2.7 | 12.1 ± 5.6 | -4.9 ± 7.4 | -11.5 ± 4.9 |
| p-value             | 0.21     | 0.10       | 0.51  | 0.12     | 0.82       | 0.05  |
Results of the CFRDT Trial

A. CFRD FH-

B. IGT

Time, Months

P=0.02  P=0.45  P=0.33  P=0.43  P=0.02  P=0.28