

The Effect of *Opuntia* in Lowering Serum Glucose Among NIDDM Patients A Systematic Review – Preliminary Findings

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Background

The San Antonio Cochrane Center is one of nine centers of the international Cochrane Collaboration. The Collaboration is an organization that has as its primary mission the collection and systematic review of medical evidence in the treatment and prevention of disease and other health problems. The San Antonio Cochrane Center is an active participant in many of the activities of the Collaboration and, of particular interest to the issue at hand, participates with the Diabetes Collaborative Review Group and with the Alternative Medicine Field. The purpose of this review is to explore the effect of *Opuntia* (prickly pear cactus) in lower serum glucose levels among persons with Type II diabetes.

This interest in cactus and diabetes came about through involvement with other research centers which are actively engaged in diabetes research. The Mexican American Medical Treatment Research Center and the Texas Diabetes Institute, both in San Antonio, have conducted numerous research projects throughout South Texas. Extensive surveys of persons, primarily Mexican Americans, provided direct evidence of a widespread use of cactus and other herbal remedies for the treatment and/or control of diabetes. Through its networking activities, the San Antonio Cochrane Center received several reports of medical trials conducted by Drs. Frati Munari and Castaneda Andrade of Mexico regarding the beneficial effects of cactus when administered to persons with Type II diabetes and to healthy volunteers. This review of their literature is in response to an invitation by Dr. Peter Felker of Texas A&M University-Kingsville.

Methods

When conducting a systematic review of medical evidence, reviewers must consider factors of relevance and acceptability. Factors of relevance include those that are pertinent to the research question. Factors of acceptability are those that allow the statistical integration of the reported data. For this review, studies were considered relevant when the following factors were met: 1) study subjects were persons with Type II diabetes, 2) serum glucose was measured as an outcome and compared to either a control group or baseline values; and 3) the purpose of the study was to study the reduction effect of *Opuntia*. Relevant studies were considered acceptable when summary statistical data were reported in sufficient detail to allow the reviewers to conduct a meta-analysis. Meta-analysis is a collection of statistical techniques for quantitatively integrating summary statistics from independent studies; these techniques allow reviewers to obtain an overall summary estimate of effect for the combined studies.

Data

The reviewers had access to eight reports studying the effects of *Opuntia*. Several of these studies reported multiple serum glucose outcomes with each outcome reflecting either a different dose of *Opuntia* or a different preparation. Some of the studies with multiple outcomes were for

different sets of subjects while some were for the same subjects. The second slide reflects some of the study characteristics of four of the studies.

Most of the data in four of these studies were of NIDDM patients given a variety of *Opuntia* preparations usually in the dose of 500 g. One study examined healthy volunteers. These studies typically used a random-order design when multiple preparations or different doses were employed; these studies also had relatively small sample sizes. In each study, subjects were instructed not to modify their regular diet and those with Type II diabetes were taken off all diabetic medications during the course of the trial.

Descriptive Results

Figures 2 through 5 reflect the average reduction in serum glucose with 95% confidence intervals, as reported by the study authors. These reductions are reported at four times post ingestion: 30, 60, 120, and 180 minutes; a few of the reports reported levels at other times, e.g., 90 and 150 minutes, but these instances were too few to include in this review. Two key points to focus on are: 1) whether the large vertical bar (representing the average reduction) is to the left or right of the "0" reference line – the "0" reference line reflects no reduction; and 2) whether the 95% confidence bar overlaps "0", – when it overlaps "0", the observed reduction or increase is not statistically significant.

At 30 minutes post ingestion, four of the six (studies 1 and 3 did not report outcomes at this time increment) estimates show a reduction in serum glucose but all are statistically not significant. At 60 minutes post ingestion, all of the nine estimates are to the left of "0", indicating a reduction in serum glucose levels, and five of the nine are statistically significant. The most obvious feature at 60 minutes is an overall shift to the left of "0", which reflects a further reduction in serum glucose levels. At 120 minutes, the shift to the left of "0" is even more pronounced and now, only two of the nine estimates are statistically not significant. Finally, at 180 minutes, there is an even greater shift to the left of "0" and only one estimate remains statistically not significant.

The next step of this review was to conduct the meta-analysis. Two issues had to be dealt with before the analysis could proceed. First, because the research question focused on the effect of *Opuntia* on serum glucose levels among Type II diabetics, the fourth study, which examined healthy volunteers, had to be dropped from further analysis. Second, Study II had reported four sets of serum glucose outcomes for the same set of eight patients. In a meta-analysis, like any primary statistical data analysis, the data must be independent. Obviously, since the four sets of outcomes were of the same eight patients, these data were not independent. To include these for sets of outcome data in the meta-analysis, they were "meta-analytically" combined into a single estimate. The data which were then used for the final meta-analysis included: 1) Study I with 14 NIDDM patients; 2) Study II with a combined estimate of 8 NIDDM patients; 3) Study III with 16 NIDDM patients; and 4) Study IV with a different set of 6 NIDDM patients. These data were then combined into a statistic called an effect size.

Meta-Analytic Results

Figure 6 represents the distribution of effect sizes for serum glucose reduction. An effect size is simply a statistical measure of the magnitude of the effect observed. Effect sizes are preferred in systematic reviews because they are not influenced by the sample size of the study. Primary studies, such as those included in this review, typically report their results in terms of statistical

significance - and readers of studies typically have been taught to look for the status of statistical significance as if it were the "bottom line". Statistical significance, however, cannot answer conclusively the research question posed because statistical significance is a function of two factors: 1) the magnitude of effect observed (is there a small or large reduction in serum glucose); and 2) the sample size. A study could easily have a small, clinically insignificant effect and, if the sample size were large enough, this small difference could be statistically significant. On the other hand, a study with a large, clinically important effect could be statistically not significant if the sample size were too small. Meta-analysis, by incorporating effect sizes, avoids the problem of too small or too large sample sizes.

The meta-analysis clearly suggests a significant effect in reducing serum glucose as a result of *Opuntia*. The most impressive feature of Figure 6 is the increasing shift to the left of "0" or no effect. Also, because the four sets of confidence intervals do not overlap each other, each further reduction is significantly greater than that at the earlier measurement. The effects shown are large, given the normal distribution of effect sizes, which in most meta-analyses, tend to be less than 2.

Effect sizes, though ideal for meta-analyses, are difficult to visualize (even for statisticians). What is an effect size? This question is not as easy to answer as, for example, "What is a 5-unit reduction in serum glucose?". Effect sizes often need to be converted into a measure that is perhaps easier to visual and this has been done in Figure 7. The meta-analytic results are now represented as "the percentage of patients with a significant serum glucose reduction as compared to their baseline values" with 95% confidence intervals. At 30 minutes, 40 to 80% of patients in these studies had a significant reduction compared to their baseline values. At 60 minutes, almost all of the patients had a significant reduction and at 120 and 180 minutes, 100% of the patients had a significant reduction.

While perhaps a little easier to visualize, there is still the question of what is a significant reduction. This is a clinical question that one will find answered differently by different clinicians but reflecting on the original data reported by the authors, these reductions were in the range of 25 to 35 mg/dl serum glucose (at 180 minutes) – most physicians would consider this a clinically significant reduction.

Discussion – Implications and Limitations

This meta-analysis suggests *Opuntia* has a strong serum glucose reduction effect. Further review of these studies also indicate improvement in insulin levels, serum lipids, and body weight. These findings are further enforced by other studies which for example, demonstrate a slower rate of serum glucose increase among healthy volunteers receiving *Opuntia* and after being infused with 20% dextrose compared to a set of controls. Also, there are several animal physiological studies which report similar changes.

The findings of this systematic reviewer, however exciting, are preliminary at best. The review included few studies and those that were included had small sample sizes (even though meta-analysis avoids sample size issues related to statistical significance, it cannot circumvent issues of generalizability when sample sizes are small). Another limitation of this review is that the effect sizes were based on comparisons to baseline data. The ideal situation would have been to calculate effect sizes based on comparisons to a control group (most of the studies did incorporate a control group comparison but the summary data were not reported in sufficient detail to allow calculation of effect sizes). Finally, these studies were not randomized clinical

trials which are the gold standard for medical evidence.

Conclusions – What needs to be done next?

The initial step in continuing to explore these preliminary but exciting findings is to form an international collaborative research team. This will allow us to identify *all* of the relevant studies to include those which have not been published. Once all of the studies have been identified and retrieved, we will need to organize a team of reviewers to systematically abstract all of the relevant data to include the multitude of outcome measures, e.g., insulin, lipids, etc. When the data are missing in any report, we will need to contact the authors of the studies to attempt to retrieve the missing data. Once collected, the data will need to be coded and then subjected to more sophisticated meta-analytic techniques than that used for this preliminary examination to include multivariate meta-analytic statistical analogues. Once all of these steps have been successfully concluded, and only then, we can communicate our findings to the larger scientific community.

An additional goal should be to eventually conduct one or more large randomized clinical trials. These trials will need to be large to allow us to examine all of the potential confounding factors which could change the findings presented today. The trial(s) should also be international in scope. One of the critical factors in conducting such a trial, of course, will be funding and we should begin exploring opportunities immediately.

In closing, this review demonstrates there is much to be learned from traditional medical practices. Western medicine is based on knowledge from repeated observations of what works or doesn't work. Is this any different from knowledge represented by traditional medical practices which have emerged from cultures over hundreds of years of observation? Through the efforts of the Cochrane Collaboration, as well as others who employ scientific systematic review techniques to examine the evidence, we should be able to learn again what may already be known.

Cactus-Diabetes

Serum Glucose Reduction Meta-Analysis

- 14 NIDDM patients, 500g. grilled crude *Opuntia streptacantha* Lemaire stems
- 8 NIDDM patients, 500 g. *Opuntia ficus indica*: 1) entire broiled stems; 2) blended broiled stems; 3) blended crude stems; and 4) heated blended stems
- 16 NIDDM patients, 500 g. broiled *Opuntia streptacantha* Lemaire
- 6 NIDDM patients, 500 g. broiled *Opuntia streptacantha* Lemaire
- 8 Healthy volunteers: 1) 100 g.; and 2) 500 g. grilled *Opuntia streptacantha* Lemaire;
- All subjects instructed not to modify their regular diet and NIDDM patients taken off diabetic medications

Preliminary Findings

Figure 1

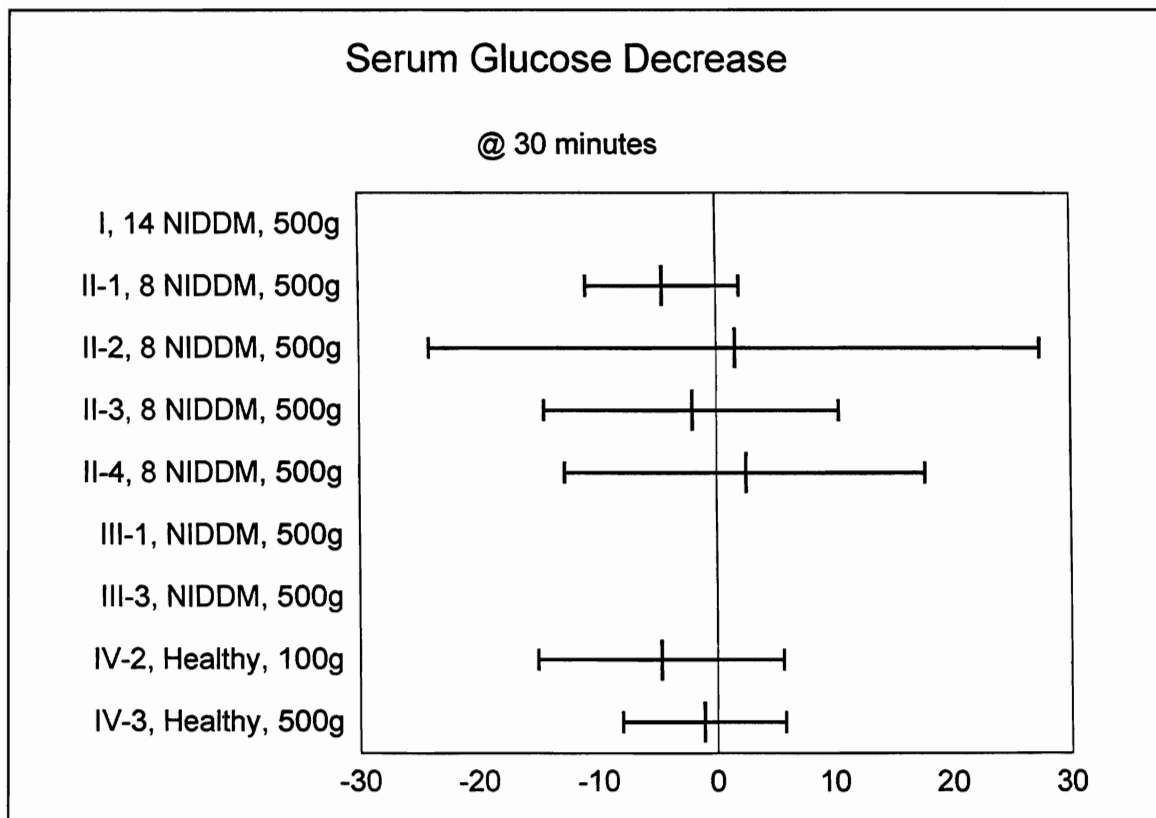


Figure 2

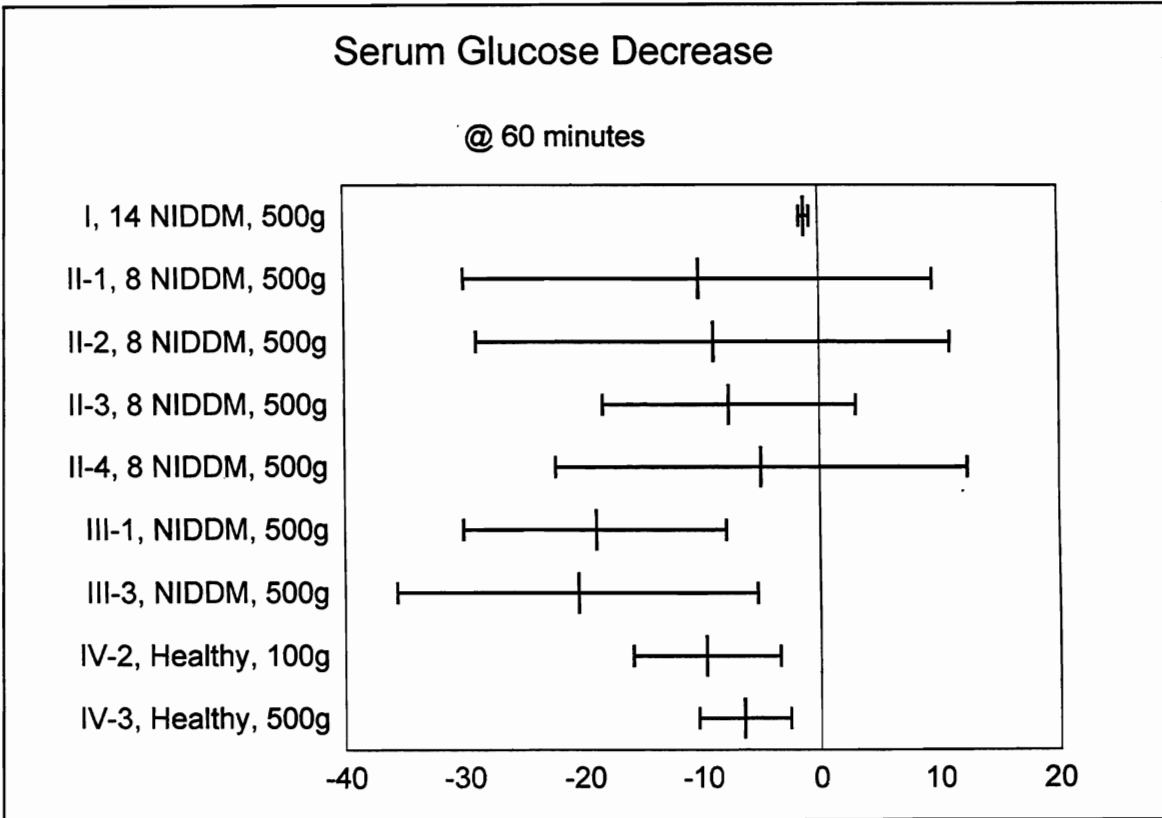


Figure 3

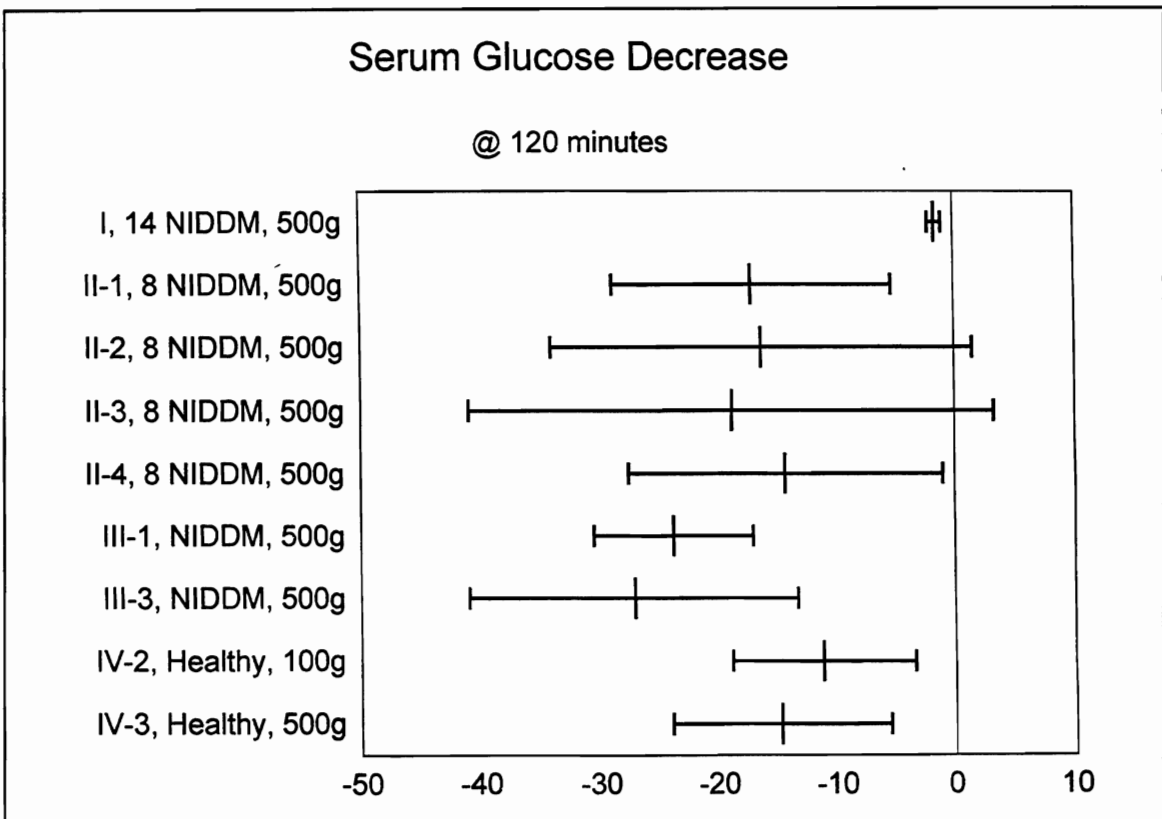


Figure 4

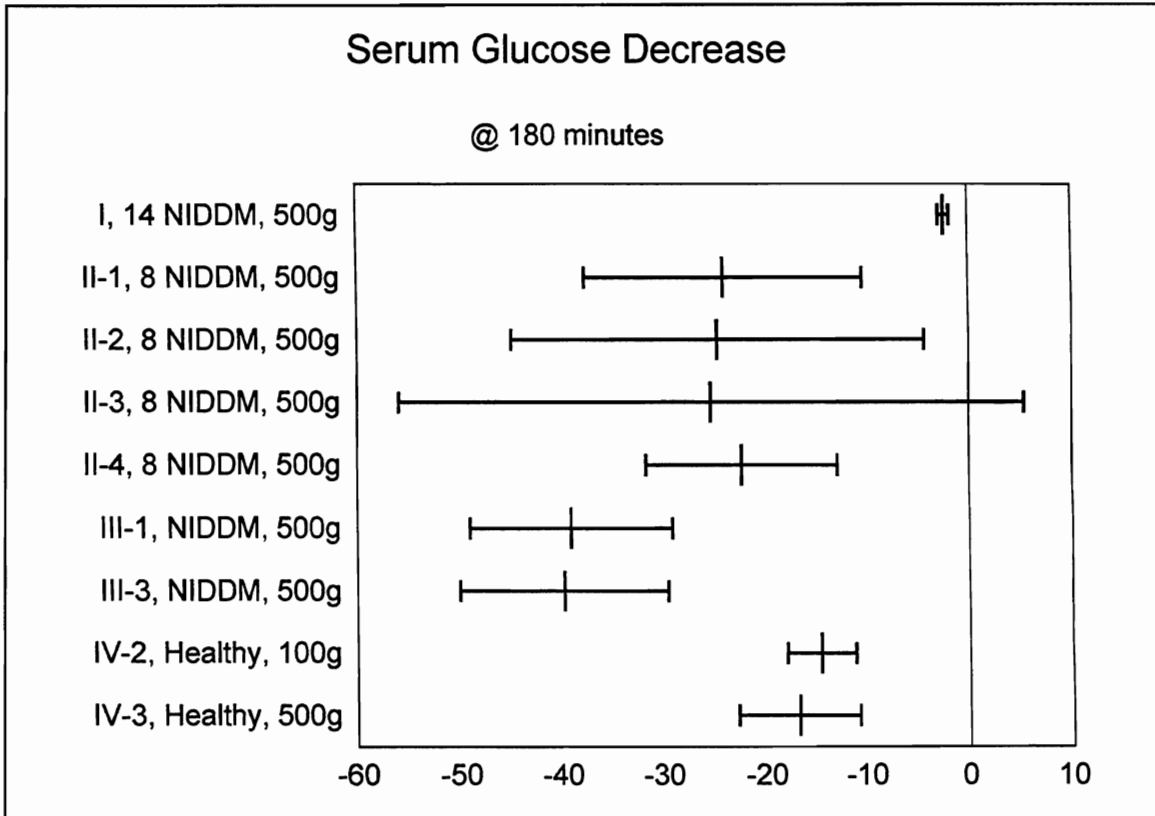


Figure 5

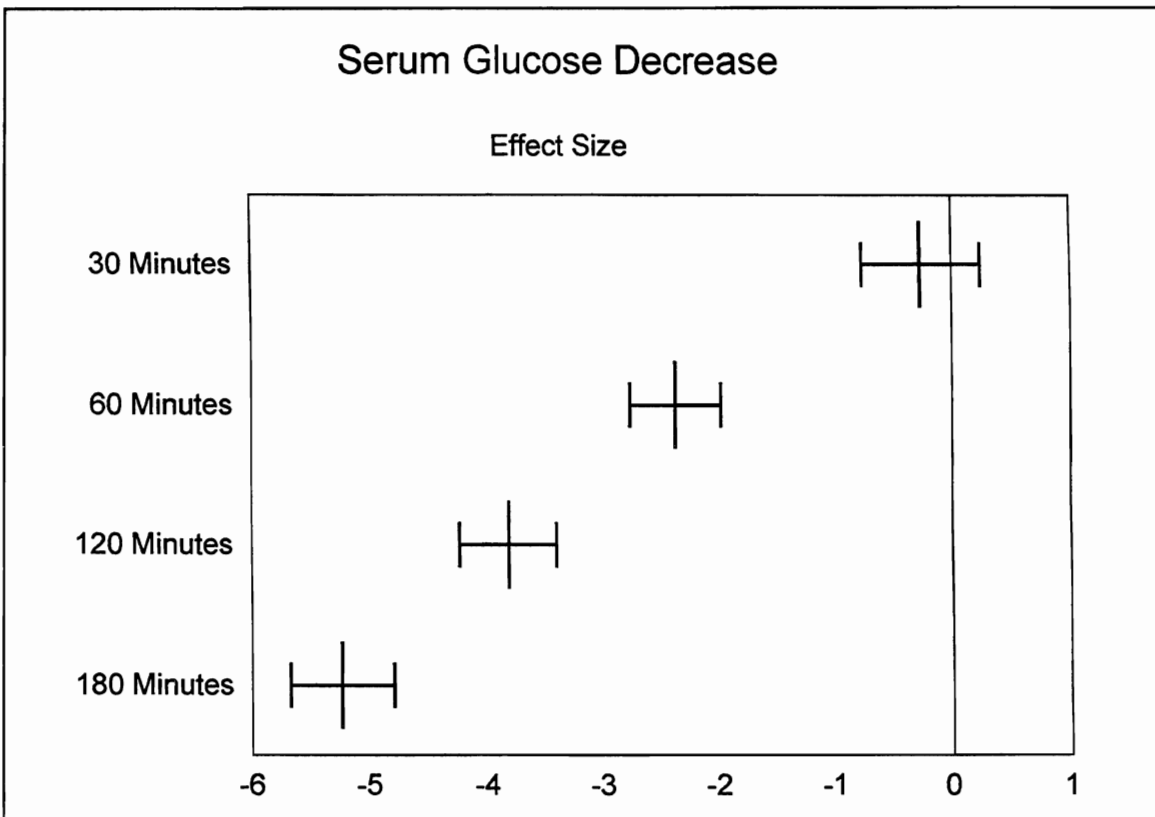


Figure 6

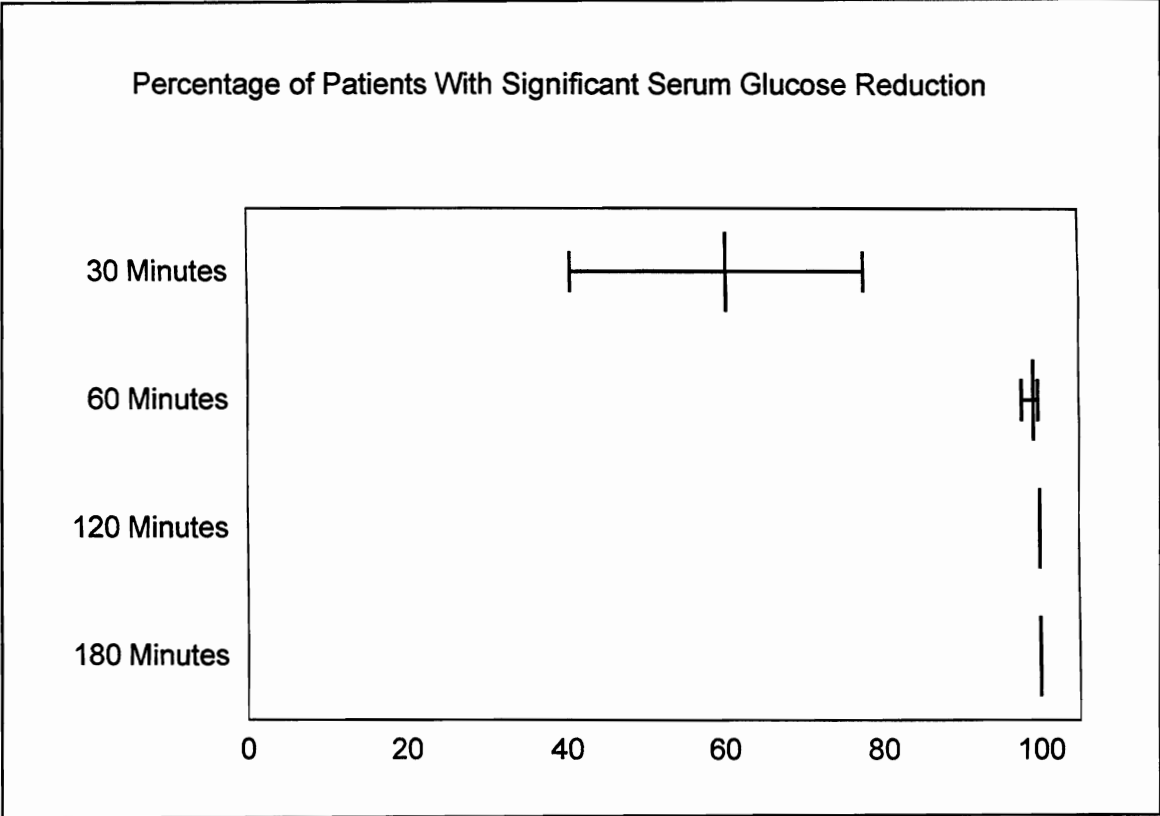


Figure 7