
UNIVERSITY OF NORTH TEXAS
HEALTH SCIENCE CENTER AT FORT WORTH
1970

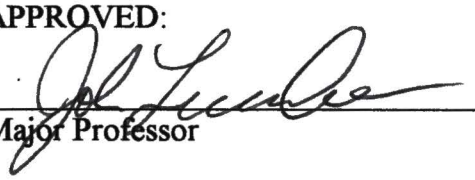
Garcia, Anna R., Meta-analysis: Effects of Opuntia species. Master of Public Health (Epidemiology), May, 2000, 73 pp., 10 tables, 10 figures, references, 62 titles.

The Mexican American population is more susceptible to diabetes mellitus due to a number of risk factors. The earliest recorded treatments for diabetes mellitus involved the use of natural plants. *Opuntia* species are any member of the genus *Opuntia* of the Cactus family and who are native to the Western Hemisphere. In order to determine the efficacy of *Opuntia* species as a hypoglycemic agent in non-insulin dependent diabetics, a meta-analysis was conducted to analyze the identified studies. In addition, insulin and the presence of a dose-response relationship upon ingestion of *Opuntia* were investigated. A statistically significant reduction in serum glucose was found after the ingestion of 500 grams of *Opuntia* species. Additional studies are needed to determine the mechanism of hypoglycemic action and to further investigate the properties of *Opuntia* species.

META-ANALYSIS: EFFECTS OF *Opuntia* SPECIES

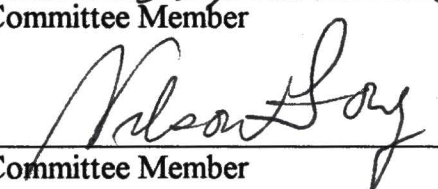
Anna R. Garcia, B.S.

APPROVED:

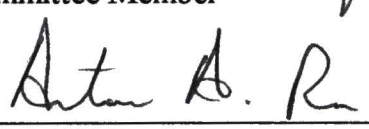


Major Professor

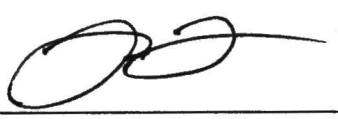
Committee Member



Committee Member



Track Director



Dean, School of Public Health

META-ANALYSIS: EFFECTS OF *Opuntia* SPECIES

THESIS

Presented to the School of Public Health

University of North Texas

Health Science Center at Fort Worth

For the Degree of

Master of Public Health

By

Anna R. Garcia, B.S.

Fort Worth, Texas

May 2000

ACKNOWLEDGMENTS

I would like to thank each of my committee members, Dr. Licciardone, Dr. Ramirez, and Dr. Fong for their guidance and support of my thesis as well as their flexibility. I wish to especially thank Dr. Ramirez for guiding me towards this project and continuing to work with me while in San Antonio.

I would also like to thank my parents who have supported my decisions and have inspired me to reach my goals. Lastly, I wish to thank Jason for his amazing amount of patience and his continuing support.

TABLE OF CONTENTS

CHAPTER		
I.	INTRODUCTION	1
II.	LITERATURE REVIEW	4
	Diabetes Mellitus	4
	Alternative Medicine	12
	Opuntia species	14
	Meta-analysis	21
III.	METHODS	24
IV.	RESULTS	29
V.	DISCUSSION	42
APPENDIX		47
A.	IDENTIFIED STUDIES	48
B.	MICROSOFT EXCEL WORKSHEET: GLUCOSE	51
C.	MICROSOFT EXCEL WORKSHEET: INSULIN	54
D.	GALBRAITH PLOTS	57
E.	META-ANALYSIS REGRESSION	63
REFERENCES		66

CHAPTER I

INTRODUCTION

The World Health Organization estimates there are currently 154 million individuals with diabetes mellitus in the world (1999). The rising prevalence of diabetes mellitus is of concern to the American Diabetes Association as it is the seventh leading cause of death in the United States and the sixth leading cause of death by disease status (1999). Treatment of diabetes mellitus consists of dietary guidelines, weight loss and hypoglycemic agents. Hypoglycemic agents include oral treatments and injectible insulin. Based on a cohort study of a large health maintenance organization, Hayward et al. (1997) determined insulin use was not effective in achieving tight glycemic control. Glycemic control is an important protective factor for complications in individuals with non-insulin dependent diabetes mellitus. The Texas Diabetes Council recently amended the algorithm for treatment of patients with non-insulin dependent diabetes mellitus in recognition of tight glycemic control as an important factor in the reducing complications (Davidson, 1999).

Mexican Americans constitute the largest and most rapidly growing ethnic minority in the United States. It is estimated that in the year 2005, the Hispanic population in America will surpass non-Hispanic African Americans to become the nation's largest minority group (U.S. Census Bureau, 1999). The prevalence of non-

insulin dependent diabetes mellitus has been examined by researchers and studies confirm the Mexican American population is more susceptible to diabetes mellitus due to a number of risk factors (Haffner, 1998; Hanis, Hewett-Emmett, Bertin & Schull, 1991; Harris et al., 1999).

The earliest recorded treatments for diabetes mellitus involved the use of natural plant therapies. Prior to the development of insulin in 1922, the most commonly used treatments involved dietary measures including traditional medicines derived from plants (Swanston-Flatt, Flatt, Day & Bailey, 1991). Only one plant, *Galega officinalis*, has led to the development of a treatment for non-insulin dependent diabetes mellitus. Loyoza (1994) suggests that many countries are seeking assistance in identifying additional ethnobotanical treatments and envisions a future increase in the use of alternative treatments.

Opuntia species are any member of the genus *Opuntia* of the Cactus family who are native to the Western Hemisphere (Britannica Online, 1999). *Opuntia* species have been used for many years by the indigenous people of Mexico as a food source for both humans and animals. A recent study by Noel, Pugh, Larme and March (1997) documented the use of alternative treatments used for non-insulin dependent diabetes mellitus in South Texas. Of the users of alternative treatments, the consumption of *Opuntia* species for diabetes mellitus constituted over half of the users. Numerous studies have been performed on humans and animals to study the effects of ingestion of *Opuntia* species, particularly the hypoglycemic effect (Ibanez-Camacho, Meckez-

Loyoza, & Mellado-Campos, 1983; Meckez-Loyoza & Ibanez-Camacho, 1989; Meckez-Loyoza & Roman-Ramos, 1986; Appendix A).

The purpose of this thesis is to investigate the efficacy of *Opuntia* species as a hypoglycemic agent in non-insulin dependent diabetes mellitus patients. The meta-analysis indicates if there is a statistically significant reduction in the level of serum glucose based on the number of grams consumed and the time points analyzed. This thesis may provide clarification for individuals seeking alternative therapies as adjuncts for the treatment of non-insulin dependent diabetes mellitus and provide direction as to the effectiveness of one unconventional therapy for diabetes mellitus.

Through Microsoft Excel and STATA, I analyzed the relevant data utilizing meta-analysis techniques. The main study questions involved in the meta-analysis of relevant literature were: What is the overall effect of ingestion of *Opuntia* species on serum glucose and insulin? And does a dose-related relationship exist with the ingestion of *Opuntia* species?

CHAPTER II

LITERATURE REVIEW

Section I: Diabetes mellitus

Diabetes mellitus may be defined as a "chronic disorder of carbohydrate metabolism characterized by hyperglycemia and glycosuria and resulting from inadequate production or utilization of insulin" (Taber's Cyclopedic Medical Dictionary, 1993). Symptoms of diabetes mellitus include: frequent urination, unusual thirst and weight loss, and extreme fatigue, hunger and irritability. Diabetes mellitus may be classified into two major types: Type I and Type II. Type I, or insulin-dependent diabetes mellitus (IDDM) is characterized by an inadequate insulin production by the beta cells of the pancreatic islets and has been referred to as juvenile-onset or brittle diabetes (Martini & Welch, 1998). Glucose is the most important carbohydrate in body metabolism and is not able to be transported in the absence of insulin. Type II, or non-insulin-dependent diabetes mellitus (NIDDM) results from near normal or normal insulin levels but an inability of peripheral tissues to respond due to reduced sensitivity. The presence of NIDDM is found in 90 to 95% of persons with diabetes mellitus (American Diabetes Association, 1999).

Epidemiological studies have enumerated risk factors for NIDDM and include age, socioeconomic, ethnicity, family history, and behavioral factors. The San Antonio Heart Study found that there is an inverse relationship between socioeconomic status and the prevalence of NIDDM (Haffner, 1998). The familial nature of diabetes mellitus is well known. In a Finnish study, an association between NIDDM and a mutation in the glycogen synthase gene on chromosome 19 has been reported (Groop, 1993). A 22-year follow-up of NHANES I showed the age-adjusted mortality rate was higher among persons with cardiovascular disease and diabetes mellitus. This may be explained by the high number and high levels of risk factors in persons with diabetes. These risk factors include elevated fasting plasma glucose, blood pressure, cholesterol, and triglycerides as well as obesity and cigarette smoking (Haffner). A number of studies have illustrated the importance of obesity in relation to NIDDM. In the NHANES II, NIDDM was approximately three times more common among overweight individuals (Manson, 1996). In the Nurses' Health Study, moderately overweight women, based on body mass index, had ten times the risk of developing NIDDM when compared to leaner women. Insulin insensitivity and impaired glucose tolerance have recently been examined as possible risk factors and may be important predictors for the development of NIDDM. A five-year study conducted on the Pima Indians found a relationship between the development of NIDDM and impaired glucose tolerance (Haffner). This study also found a relationship between the development of NIDDM and fasting insulin concentration.

Ethnicity and genetics play a large role in the prevalence of NIDDM. When compared to Hispanics and Native Americans, African Americans are the least susceptible to NIDDM. NHANES III conducted in 1988-1994 determined the prevalence of NIDDM in African Americans to be 12.5% and among non-Hispanic whites to be 7.2%. Hispanics are 2.5 times more likely to have NIDDM than non-Hispanic whites and Native Americans show a fivefold increase in risk (Harris et al., 1998). The prevalence of undiagnosed diabetes also varies according to ethnicity, as determined by NHANES III. Using the criteria of fasting plasma glucose greater than 140 mg/dl, the prevalence of undiagnosed diabetes among non-Hispanic whites was 6.1%, 6.7% among African Americans, and 9.9% among Mexican Americans (Harris et al.).

According to the American Diabetes Association (ADA), diabetes prevalence increases with age, with half of all cases occurring in persons above the age of 55. The World Health Organization estimates there are currently 154 million individuals with diabetes in the world. By the year 2025, the number of individuals with diabetes mellitus in the world is expected to increase to 299 million. The rising prevalence of diabetes mellitus is an important consideration as it is the seventh leading cause of death in the United States and the sixth leading cause of death by disease status (ADA). According to the American Diabetes Association, 15.7 million Americans have diabetes mellitus. Although a large percentage of these persons have been diagnosed by a health care professional, it is estimated that 5.4 million Americans are not aware they have diabetes mellitus (ADA). The increased incidence of NIDDM in developed countries has led to

the labeling of diabetes by some researchers as a disease of affluence. According to the Texas Diabetes Fact Sheet (1998), 1.6 million people in Texas have diabetes mellitus. Of these 12.1% of Texans, it is estimated that there are 680,000 people who have undiagnosed diabetes in Texas.

Treatment for individuals with NIDDM consists of dietary guidelines, exercise and weight loss which may elevate insulin production. Forms of hypoglycemic agents including insulin injections may also be required if weight loss fails to control serum glucose concentrations. Oral hypoglycemic agents available include sulfonylureas, biguanides and alpha-carbose inhibitors (Deglin & Vallerand, 1999). Hypoglycemic agents such as sulfonylurea act by stimulating the release of insulin from the pancreas and increasing sensitivity to insulin at receptor sites. Alpha-carbose inhibitors lower glucose by inhibiting the enzyme alpha-glucosidase which results in a delayed glucose absorption. Oral hypoglycemic use has been associated with side effects and decreased effectiveness over time (Deglin & Vallerand).

The complications of diabetes mellitus are numerous and devastating. The macrovascular complications include ischemic heart disease, stroke, and vascular disease. Microvascular complications include blindness due to diabetic retinopathy, end-stage renal disease due to diabetic nephropathy, and neuropathy. Microvascular complications are the result of the progression of abnormalities in small blood vessels over many years. NIDDM effects the vascular system and common problems include increased susceptibility to infections and ischemia which may lead to amputation.

The level of blood glucose is an important risk factor for complications in NIDDM patients. Hayward et al. conducted a cohort study to examine the effectiveness and complication rates of improving glycemic control in a large health maintenance organization. It was determined that insulin users had more laboratory tests performed, had more outpatient visits per year, and approximately 300 more fingersticks for home glucose testing per year when compared to sulfonylurea users. Based on the cohort study conducted, Hayward et al. determined insulin use was not effective in achieving tight glycemic control. Preliminary data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) suggests that poor glucose control leads to a decreasing quality of life and poor glucose control may be partially due to the limitations in treatment options (Klein & Klein, 1998). This study did not determine whether the decreased quality of life is due to the presence of NIDDM or the complications of NIDDM. Cerveny, Leder and Weart (1998) reviewed the findings of the Diabetes Control and Complications Trial (DCCT). The results of the DCCT have shown that intensive glucose control prevents and slows the progression of microvascular and neuropathic complications in type I diabetics. Cerveny, Leder and Weart conclude that glucose control should be initiated in type II diabetics in order to reduce long-term complications. Testa and Simonson (1998) examined short-term quality of life and the economic benefits of improved glycemic control in NIDDM patients. The researchers found favorable health economic outcomes and quality of life which included higher retained employment, less absenteeism, and fewer restricted-activity days.

Recently, the Texas Diabetes Council has amended the algorithm for treatment of patients with NIDDM as a result of the American Diabetes Association revising criteria for standards of treatment and due to results from the U.K. Prospective Diabetes Study (UKPDS). The UKPDS Group examined the effects of intensive glucose control, a sulfonylurea or insulin, on the risk of microvascular and macrovascular complications associated with NIDDM. The UKPDS Group (1998) found substantial decreases in the risk of microvascular complications but no effect in the risk of macrovascular complications. The new guidelines from the Texas Diabetes Council recognize the importance of tighter glycemic control and glycosylated hemoglobin for the prevention of complications associated with NIDDM (Davidson, 1999).

NIDDM in Mexican Americans

Based on the Current Population Survey, the U.S. Census Bureau estimates there were nearly 32 million Hispanics in the United States as of March 1999. Hispanic persons are individuals of Spanish decent in the United States and generally may be classified into three major Hispanic groups: Mexican American, Puerto Rican and Cuban. Nearly two-thirds (63%) of all Hispanics may be classified as Mexican American (U.S. Census Bureau, 1999). Characteristics of the Mexican American population in the United States include lower educational attainment rates and greater rates of poverty. The Hispanic population of the United States is a young population, with a median age of 26.5 years, nine years younger than the median age for the U.S. population as a whole.

It is projected that by the year 2005, the nation's Hispanic population will surpass non-Hispanic African Americans to become the nation's largest minority group (U.S. Census Bureau).

The prevalence of NIDDM in Hispanics and Mexican Americans has been examined and may vary according to geographic region. The Centers for Disease Control and Prevention (CDC) analyzed data from the Behavioral Risk Factor Surveillance System (BRFSS) from 1994 through 1997 to assess the prevalence of diabetes in Hispanics. The CDC found that the prevalence of diabetes among Hispanic adults varied by geographic location, with the highest prevalence found in the West and Southwest areas of the United States. After controlling for age, sex, education, and geographic location, Hispanics remained 1.8 times more likely to have diabetes than non-Hispanic white adults with a 95% confidence interval of 1.6 to 1.9 (Morbidity and Mortality Weekly Report, 1999). According to the American Diabetes Association, 1.2 million Mexican Americans, or nearly 11% have diabetes. Of Mexican Americans between the ages of 45 and 74, the prevalence of diabetes rises to 24% (ADA). The NHANES III, completed in 1994, determined the prevalence of diagnosed and undiagnosed diabetes was highest among Mexican Americans. A study in the early 1980's examined the prevalence rate of NIDDM in Starr County (Hanis et al., 1983). The statewide distribution of diabetes deaths for 1970 to 1981 was illustrated and indicates the counties with the highest diabetes-specific mortality rate are located in the lower Rio Grande Valley of South Texas. The prevalence rate of diabetes in Starr

County varied from 6% in persons under the age of 45 to 19% in persons 45 and older. Hanis et al. determined that one-half of the population in Starr County above the age of 35 is affected by diabetes either by having the disease or being a first-degree relative of a diabetic.

A number of studies have examined the risk factors present in Mexican Americans. Hanis, Hewett-Emmett, Bertin and Schull (1991) examined the genetic ancestry of Mexican Americans. The group estimated the contribution of ancestral populations to the modern gene pool utilizing genetic information. According to their estimate, 61.2% of the modern gene pool is estimated to be Spanish derived in Mexican Americans. Native American ancestry and African also contribute to the gene pool, with 31% and 8% respectively. The Pima Indians of Arizona have the highest reported prevalence of obesity and NIDDM (Ravussin et al., 1994). Stern et al. (1991) identified the three alleles of the insulin-receptor gene, one of which was labeled C-allele. Stern et al. determined the allelic frequency of the C-allele in Pima Indians (34%), which was double the frequency found in Mexican Americans. These findings strengthen the argument for commonality in the causation of diabetes in both Mexican Americans and Native Americans.

In the Insulin Resistance Atherosclerosis Study, ethnic groups were examined for the role of insulin sensitivity and obesity (Haffner, 1998). The results of this study suggest that Mexican Americans may be more insulin resistant than non-Hispanic whites. Mexican Americans have a higher prevalence of obesity when compared to non-Hispanic whites. A recent study was conducted to determine the racial and ethnic differences in

glycemic control of patients with NIDDM (Harris et al., 1999). Data from the NHANES III was utilized as well as measurements of fasting plasma glucose and glycosylated hemoglobin. Glycosylated hemoglobin (HbA1) indicates the long term glucose regulation in NIDDM patients. The data indicated that both Mexican American men and African-American women had the highest rates of glycosylated hemoglobin when compared to non-Hispanic whites.

Section II: Alternative Medicine

Complementary and alternative medicine (CAM) covers a broad range of healing philosophies and therapies. According to the National Institutes of Health, National Center for Complementary and Alternative Medicine (1999), CAM is generally defined as those treatments and practices not taught widely in medical schools, not generally used in hospitals and not usually reimbursed by medical insurance companies. A study by Eisenburg et al. (1993) examined unconventional therapies in a national telephone survey. The findings indicate that unconventional therapy use is generally confined to treatment adjuncts, rather than replacements and subjects are more likely to use unconventional medicine for chronic, as opposed to acute conditions. Ernst, Resch and White (1995) conducted a meta-analysis to measure physicians' perception about complementary or unconventional medicine. Ernst et al. found that on average, physicians perceive complementary medicine as moderately effective (46%) and when compared by age, determined younger physicians tended to be more receptive to utilizing complementary medicine.

Ethnobotanical Approach

The earliest recorded treatments for diabetes mellitus involved the use of plants. The *Ebers Papyrus* was written in 552 B.C., and was a collection of drugs and prophylactics derived from plants, animals and minerals (Oubre, Carlson & Reaven, 1997). The *Ebers Papyrus* described a clinical condition which resembles diabetes. Bailey and Day (1989) describe traditional plant medicines used as treatments in diabetics and state there are more than 400 different plants and extracts that have been described as beneficial for NIDDM. Documented biological activity in plants has led to a number of chemically isolated compounds: alkaloids, glycosides, peptidoglycans, guanidine, steroids, terpenoids and inorganic ions (Oubre et al.). Only one recognized medicinal plant, *Galega officinalis*, used historically as a treatment for NIDDM, has led to the development of metformin, a drug for the treatment of NIDDM. Many countries are now seeking assistance in identifying safe and effective herbal remedies and new evidence supports the future increase in use of herbal remedies (Loyoza, 1994).

Mexican Americans and Alternative Treatments

The most common form of folk medicine practiced by Mexican Americans in the southwestern United States is curanderismo. A curandera, or healer presides over a ritual that incorporates religion and the use of herbs or plants. Chesney et al. (1980) conducted interviews of Mexican American families to determine the utilization of folk medicine and conventional care in Galveston, Texas. The researchers concluded that a large percentage of patients sought both folk medicine remedies and conventional care. Nearly

68% of the families surveyed by Chesney et al. utilized folk medicine for their most recent illness. Other studies have examined the use of alternative treatments for NIDDM. A recent study by Noel, Pugh, Larme and Marsh (1997) indicated that 49% of individuals living in South Texas use alternative treatments to treat NIDDM. Health care providers should be aware of the effects of folk medicine remedies since Mexican Americans may use both systems of health care simultaneously (Winkleman, 1989). Chesney et al. found the sample group had strong ties to Mexico and folk medicine was integrated into the Mexican American families and communities even if they had assimilated into the American culture.

Several studies have illustrated the importance of health care provider awareness of alternative treatments in the Mexican American population (Chesney et al.; Fishman et al., 1993; Winkelman). Often, nondisclosure of alternative treatments is a result of health care provider negativity or lack of awareness (Chesney et al.). Cultural beliefs may affect acceptance of health care, compliance and treatment outcomes (Fishman et al.). The health care provider's ethical obligation to the patient is to discuss alternative treatments, even if they are considered alternative medicine (Sugarman & Burk, 1998). The goal is to guide the patient towards the best medical decision for effective treatment. More research is needed in the area of alternative treatment in order to have clear guidelines for the health care practitioner (Sugarman & Burk).

Section III: *Opuntia* species

Opuntia species is known by different names: prickly pear cactus in English and nopal in Spanish. *Opuntia* species are any member of the genus *Opuntia* of flat-stemmed spiny cacti of the family Cactaceae, and are native to the Western Hemisphere (Encyclopedia Britannica Online, 2000). The total number of species of *Opuntia* is estimated to be 258, however only 110 different species have been well identified (Munoz de Chavez, Chavez, Valles & Roldan, 1995). The prickly pear cactus is composed of three parts: the leaves of the plant, known as cactus pads, leaves or cladodes; the prickly pear or fruit; and the flowers of the prickly pear. Some of the uses of the cactus pads include: food source for humans and animals; fuel source for fire; as a glue for adobe bricks; as medicine; and to support the growth of an insect. Prickly pear cactus has been used a supplement for animal feed for goat, sheep and cattle not only in times of drought, but as a regular component. Nopal is a distinctive host of the cochineal insect, which reproduces in the fleshy cactus pads. It was found in pre-Hispanic times that the insect, when harvested and cooked, produces a brilliant red color. The dye is currently used to dye military jackets, such as the queen of England's personal guards and persian rugs (Munoz de Chavez et al.). The prickly pear itself may be eaten raw after peeled and the prickly pear flower is used in the preparation of foods.

The *Opuntia* species has served as an excellent fruit and vegetable source for the indigenous people of Mexico. The average nutrient content of *Opuntia* species per 100 grams is shown in Table 1. Expressed as retinol in Table 1, the amount of β-carotene and

Table 1. Average nutritional values of 100 grams of edible cladodes and the prickly pear of *Opuntia* species.

Nutrients	Nopal (cladodes)	Prickly pear
Edible portion, %	0.78	0.55
Water content, %	90.1	91.0
Fiber, g	3.5	0.2
Energy, kcal	27	31
Carbohydrates, g	5.6	8.1
Proteins total, g	1.7	0.6
Lipids total, g	0.3	0.1
Cholesterol, mg	0.0	0.0
Calcium, mg	93	49
Iron, mg	1.6	2.6
Magnesium, mg	-	85
Sodium, mg	2	5
Potassium, mg	166	220
Retinol, eq, μg	260	5
Ascorbic acid, mg	8	22
Thiamin, mg	0.03	0.02
Riboflavin, mg	0.06	0.02
Niacin, mg	0.3	0.20

Note. Adapted from "The nopal: a plant of manifold qualities" by M. Munoz de Chavez, A. Chaves, V. Valles and J.A. Roldan, 1995, Plants in Human Nutrition, 77, p.120.

calcium contributed by the cladodes is significant. The amino acid content of the cladodes also contains significant quantities of lysine, methionine, theonine and tryptophan (Munoz de Chavez et al.). Fiber contained in *Opuntia* species is both soluble and insoluble. The soluble fiber may be classified into the following groups: mucilages, pectin, gums and hemicellulose. Insoluble fiber in the nopal is composed of cellulose, lignin and hemicellulose. In the Nutrient Evaluation Database for Mexican American Food, prepared by the American Diabetes Association (1994), *Opuntia* species is listed under carbohydrates as a recommended vegetable. For one-half cup of nopales, the grams per serving are 75 grams for cooked nopal. The polyunsaturated and monounsaturated fatty acid content for one-half cup of nopal is .01 and .02 grams respectively (ADA, 1994).

Various studies have been conducted to determine the effects of *Opunia* species on animals. In a study by Ibanez-Camacho, Meckez-Loyoza and Mellado-Campos (1983), an extract of the stems of *Opuntia streptacantha* reduced basal concentrations of glucose in alloxan-induced diabetic rabbits, but not in healthy rodents. Meckez-Loyoza and Ibanez-Camacho (1989) conducted experiments on normal rabbits to find if there was a seasonal variation in the hypoglycemic effect of *Opuntia streptocantha*. Throughout the ten months of extraction, there was a consistent effect in the hypoglycemic properties of *Opuntia streptocantha*. Trejo-Gonzalez, Gabriel-Ortiz, Puebla-Perez, Huizar-Contreras, Munguia-Mazariegos, Mejia-Arreguin and Calva (1996) examined the effects of *Opuntia fulginosa* on diabetic and non-diabetic rats which resulted in a significant reduction in the final body weights and a hypoglycemic action. Fernandez, Trejo and

McNamara (1990, 1993) have examined the effects of *Opuntia* species on cholesterol levels in guinea pigs. Guinea pigs fed a hypercholesterolemic diet were found to have reduced low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol levels and may be due to increased expression of hepatic apo B and apo E receptors (Fernandez, Lin, Trejo & McNamara, 1992).

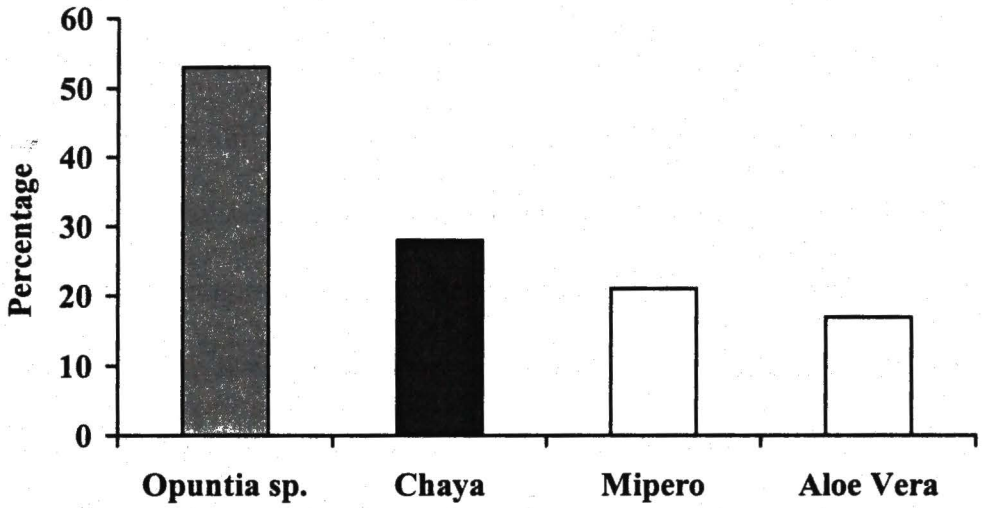
Opuntia streptacantha has been described in a review of natural plants as potential treatments for NIDDM patients in the Journal of Ethnopharmacology and Diabetes Care (Ivorra, Paya & Villar, 1989; Bailey & Day, 1989). Numerous studies have been conducted by Frati et al. on the hypoglycemic effect on NIDDM patients in Mexico (Appendix A). Meckez-Loyoza and Roman-Ramos (1986) studied the hypoglycemic effect of *Opuntia streptacantha* sap on a diabetic patient who was receiving sulfonamides. The subject's serum glucose and insulin levels decreased following the intake of *Opuntia* and the researchers suggested that sap from *Opuntia* may be used as a complementary source of treatment in NIDDM patients.

Noel et al. conducted a study to document the different types of alternative treatments used for NIDDM in South Texas. A total of 61 plant treatments were reported and the four most commonly reported were the *Opuntia* species, chaya, mispera and aloe vera as shown in Figure 1. Of the individuals using alternative treatments, the consumption of *Opuntia* species for NIDDM constitutes over half of the users. According to Munoz de Chavez et al., the consumption of *Opuntia* species by families in

Mexico has been underreported. The underreported consumption of *Opuntia* species may have been due to the "fact that many people are ashamed to admit they eat nopal as it is traditionally consumed by the poor and therefore has low prestige" (Munoz de Chavez et al., 1995, p. 130).

Although the effects of *Opuntia* species are well documented, the mechanism of effect remains unknown. Frati-Munari, Gordillo, Altamirano, and Ariza (1988) suggest the hypoglycemic effect may be due to an improvement of glucose cellular utilization due to an increased sensitivity to insulin. Munoz de Chavez et al. cite a study conducted at the National Nutrition Institute which suggests the hypoglycemic effect of *Opuntia* species may be due to a mechanical effect of gastric distension and the release of an enterohormone. Thorburn, Brand and Truswell (1987) compared the digestibility and metabolic responses of western foods with traditional staples of the Australian Aborigines and Pacific islanders. Their findings were consistent with the hypothesis that traditional bushfoods are slowly digested and absorbed and may have once been a protective factor against NIDDM.

Figure 1. The four most commonly reported traditional plant treatments among NIDDM Mexican Americans in South Texas.



Note. From "The use of traditional plant medicines for non-insulin dependent diabetes mellitus in South Texas" by P.H. Noel, J.A. Pugh, A.C. Larme, and G. Marsh, 1997, Phytotherapy Research, 11, p. 514.

Section IV: Meta-Analysis

Meta-analysis may be defined as the "statistical analysis of a collection of analysis results from individual studies for the purpose of integrating findings" (Cooper, Handbook of Research Synthesis, 1994). In order to evaluate and plan new studies, researchers and health care practitioners need to utilize the current medical research. Meta-analysis provides a more structured and quantitative approach to reviewing literature when compared to the traditional narrative review (L'Abbe, Detsky & O'Rourke, 1987). A well conducted meta-analysis provides a more precise picture of the treatment effect and may explain heterogeneity between the results of individual studies (Egger, Smith & Phillips, 1997). The validity of the results of meta-analysis is dependent upon accurately reported information in published articles and illustrates the need for standardization and comprehensive reporting (L'Abbe et al.). The main objective of meta-analysis is to provide one conclusion based on many studies as to the effect of a certain treatment or medical intervention. Many benefits and limitations of meta-analysis research exist and must be acknowledged here.

The benefits of meta-analysis include improving the power of small studies and the ability to detect sources of diversity among studies. Meta-analysis brings together studies of the same outcome and as a result the power to detect differences grows larger

and uncertainty about the magnitude of effect becomes smaller (Ioannidis & Lau, 1999). Another benefit is the ability of meta-analysis to quantitatively define the effect and provide guidance for health care professionals that may be faced with contradicting and numerous studies.

The limitations of meta-analysis include not being able to affect the quality of studies analyzed and when the quality of data and potential for bias is ignored. Meta-analysis has not gained wide spread acceptance as a research tool, in part due to the lack of a generally accepted strategy for performing meta-analyses (Fagard, Staessen & Thijs, 1996). A potential problem with meta-analysis is publication bias. Publication bias may affect the outcome of a meta-analysis as a result of utilizing only published studies which may systematically differ from unpublished studies. Publication bias may be adequately detected after a meta-analysis is completed using a funnel plot which graphs effect estimates against sample sizes (Egger, Smith, Schneider & Minder, 1997). Publication bias may be reduced by searching for unpublished studies and reviewing the references of published studies. Easterbrook, Berlin, Gopaloan and Matthews (1991) investigated publication bias in clinical research through a retrospective survey. The researchers found that of the unpublished studies, 55% had null results (OR = 1), 29% had statistically significant results (OR = 2.32; CI = 1.25-4.28) and 15% had non-significant

results (OR = .61; CI = .23-1.59). After conducting logistic regression, they found a statistically significant study result was a predictor for publication with an odds ratio of 2.32 (95% CI = 1.25-4.28) when adjusted for study design, funding source, sample size and principal investigator rating of importance of study. Company sponsored trials were significantly less likely to be published or presented, with an odds ratio of .17 (CI = .05 to .53.)

Other types of bias may exist in meta-analysis and include "Tower of Babel bias" and "reverse publication bias" (Ioannidis & Lau, 1999, p.462). Research may suffer from the "Tower of Babel bias" when the data are generated in foreign, non-English speaking countries and appear in prominent English-language journals when they are statistically significant (Ioannidis & Lau). When the data is not statistically significant from non-English speaking countries, it appears in non-English journals. "Reverse publication bias" results from the publication of only significant results in non-English language journals.

CHAPTER III

METHODS

The main study questions involved in the meta-analysis of relevant articles were: What is the overall effect of ingestion of *Opuntia* species on blood glucose and insulin?; and does a dose-related relationship exist in the effects of *Opuntia* species?

Several sources were utilized to gather the relevant information. The literature reviewed was found through MEDLINE, the Texas Agricultural Extension Service and the World Wide Web. The MEDLINE database search was conducted using the following MeSH subject headings: diabetes mellitus, non-insulin dependent diabetes mellitus, hypoglycemic agents, alternative medicine, ethnobotany, medicinal plants, meta-analysis and the scientific name *Opuntia* species. Documents not available at the University of North Texas Health Science Center Library were obtained through interlibrary loan. Other articles obtained were collected by reviewing the references of relevant documents found in the MEDLINE search. I contacted several Extension Agents to obtain information on the use of *Opuntia* species as fodder and as a food source for diabetic patients. The World Wide Web was used to obtain relevant information from Encyclopedia Britannica Online and the National Institutes of Health

National Center for Complementary and Alternative Medicine. The World Wide Web was used to obtain statistics from the American Diabetes Association, Centers for Disease Control and Prevention, United States Census Bureau, Texas Department of Health and the World Health Organization.

Analysis

I used techniques of meta-analysis to compare the findings of 14 studies on *Opuntia* species. Data on serum glucose and insulin was extracted from each of the studies. The data collected from each study included type of study design, number of subjects, dose of *Opuntia* species, times of ingestion, and type of preparation of *Opuntia* species. In addition, means and standard deviations or standard errors were extracted for each time point from the text, tables or graphs.

The formula used for calculating effect size was based on Hedges *g* and was the difference between the post-test means of the experimental and control groups divided by the pooled standard deviation. For the studies involving pre-test and post-test design, the effect size was the difference between the follow-up and baseline measurements divided by the pooled standard deviation: $g_i = \frac{\overline{x}_{\Delta t} - \overline{x}_{\Delta c}}{S\,pooled}$. Where x is the mean of the treatment and control groups and where s_{pooled} is the pooled standard deviation:

$$Spooled = \sqrt{\frac{(n_t-1)\,s_{\Delta t}{}^2 + (n_c-1)\,s_{\Delta c}{}^2}{n_t+n_c-2}}.$$

A final adjustment of the effect size, standardized effect size, was made to correct for overestimation of effect sizes due to small sample size. The formula for the standardized

effect size, *d*, is equal to a correction factor multiplied by the effect size: $d_i = c_i g_i$. The correction factor used for a treatment versus a control group and for the pre-test and post-test design were:

$$c_i = 1 - \frac{3}{4(n_{\Delta t} + n_{\Delta c} - 2) - 1} \qquad c_i = 1 - \frac{3}{4(n-1) - 1}$$

If the correction factor was near one, a large enough sample was used in the study and there would be no small sample bias (Mulrow & Oxman, 1997). The variance for each g was calculated as: $$Var(g) = \frac{n_{\Delta t} + n_{\Delta c}}{n_{\Delta t} n_{\Delta c}} + \frac{g_i^2}{2(n_{\Delta t} + n_{\Delta c})}.$$

In the pre-test and post-test study design, the variance was calculated as:

$$Var(g) = \frac{n_{\Delta b} + n_{\Delta f}}{n_{\Delta b} n_{\Delta f}} + \frac{g_i^2}{2(n-1)}.$$

The standard error of g was calculated as the square root of the variance of g for both types of studies: $se(g) = \sqrt{Var(g)}$. For each time point, the 95% confidence interval was calculated as well as the weight. The weight was calculated as the inverse of the variance for the study's effect size measure: $w = \frac{1}{Var(g)}$.

The above equations were entered into a Microsoft Excel worksheet and each study was analyzed. At each time point, the effect size, standardized effect size and standard error of the effect size were placed into a second worksheet (Appendix B: Glucose; Appendix C: Insulin). The average effect size, standard deviation and 95% confidence intervals were determined for each time point. In a third Excel worksheet, adjusted standardized effect sizes were calculated as the difference between the

standardized effect size at follow-up and the standardized effect size at baseline: $d_{adj} = d_f - d_b$. The preferred data in the third Excel worksheet consisted of frequently reported time points, dosages and effect sizes for each time point. I chose to analyze the most frequently measured time points which were: 60, 120 and 180 minutes. In studies with more than one treatment group, I chose the most frequently reported dosage, 100, 300 or 500 grams. One study examined the effects of differing species of *Opuntia* and I chose the most common reported species, *Opuntia streptacantha* as the species for the purposes of this meta-analysis. The preferred data was then analyzed utilizing the statistical program STATA.

Description of studies

The outcome of interest in the 17 collected studies (Appendix A) was the effect of human ingestion of *Opuntia* species on serum glucose and insulin. The most common type of *Opuntia* species studied was *Opuntia streptacantha*, however several studies, reference numbers 9, 11 and 15 examined the effects of ingestion of *Opuntia ficus-indica*. Glucose data reported as means and standard deviations or standard errors were sufficient in 15 of the original 17 studies. Data from the latest study on the effects of *Opuntia* species, conducted by Rayburn, Martinez, Escobedo, Wright and Farias (1998), contained insufficient data for this meta-analysis. Insulin was studied as an outcome and data was sufficient in 4 of the original studies. One of the 15 studies was excluded due to the lack of serum glucose or insulin as measured outcomes.

The remaining studies involving serum glucose ranged in years from 1983 to 1992. All of the studies were conducted in Mexico and involve consumption of either 100, 300 or 500 grams of *Opuntia* species. One study, reference number 17, examined the effects of *Opuntia* at 500 and 1000 grams post-ingestion. A majority of the studies measured the effects of *Opuntia* species at 60, 120 and 180 minutes post-ingestion. Six studies examined the effects of *Opuntia* species at additional time points at 30, 90, 150, 240 or 360 minutes post-ingestion. The preparation of *Opuntia* species is generally broiled or grilled, although two studies examined the post-ingestion effects of dehydrated extract contained in capsules. Reference number 10 examined the effects of *Opuntia* species in supernatant, precipitant, and homogenate forms and reference number 11 examined the effects of *Opuntia* species in crude, broiled and heated blended forms.

CHAPTER IV

RESULTS

Results of this meta-analysis are reported as effect sizes. Effect sizes may be translated as the standard deviation lower or above the average serum glucose at baseline. Effect sizes may also be transformed into the equivalent reduction or addition of serum glucose in milligrams per deciliter. In the results of meta-analysis, effect sizes may be reported as the random or fixed effect size. The random effect size is a more conservative estimate of the effect size than the fixed effect and is based on the random effects model which assumes other factors can influence the underlying true effect. The fixed effects model assumes that all studies included in the meta-analysis are measuring the same population effect. Due to the conservative nature of the random effect size and based on the results of the Galbraith plots (Appendix D), I chose to report the random effect size as the best estimate of the effect size as opposed to reporting the fixed effect size.

A significant reduction of serum glucose was not found at 100 grams of ingestion at 60, 120 or 180 minutes. The combined effect size for five studies at 100 grams and 1 hour post ingestion was .520, which suggests an initial rise in the level of serum glucose however the p value was not statistically significant at .06 (Table 2, Figure 2). The test for statistical homogeneity illustrates that different studies may represent different

underlying populations of effect sizes. The test for heterogeneity was not significant in the five studies of 100 grams of *Opuntia* at 1 hour post-ingestion. The Q statistic was less than .1 and therefore the effect sizes are not substantially different from the other studies. For 2 and 3 hours post-ingestion, the combined effect size was -.515 and -.529 with non-significant p values (Table 3, Figure 3; Table 4, Figure 4). The test for heterogeneity was significant in the 2 and 3 hour measurements which suggests that one of the effect sizes is substantially different from the other effect sizes.

No significant reduction in serum glucose was found in the analysis of the three studies on the ingestion of 300 grams of *Opuntia* species at 60, 120 and 180 minutes. The reported effect size of 300 grams at 1, 2 and 3 hours post ingestion was -.011, .108, and .166 and is shown in Figures 5, 6, 7. The p values corresponding to the effect sizes were .978, .783 and .574 respectively (Tables 5, 6 and 7). The test for heterogeneity was significant in the 1 and 2 hours time points and not significant in the post-ingestion of *Opuntia* species at 3 hours.

The results of the analysis on the ingestion of 500 grams of *Opuntia* species indicate a statistically significant reduction in serum glucose at 60, 120 and 180 minutes. The effect size for the analysis of 500 grams at 1, 2 and 3 hours post-ingestion was -.807, -1.45 and -1.472 (Figures 8, 9 and 10). The p values for the corresponding time points were less than .0001 and are found in Tables 8, 9, and 10. The test for heterogeneity was significant at all time points indicating one of the effect sizes was substantially different from the other effect sizes.

Table 2. Effect sizes, pooled and by study for serum glucose, 100 grams, 1 hour post-ingestion.

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z value	Asymptotic p value	No. of Studies
Fixed	0.520	-0.023	1.064	1.878	0.060	5
Random	0.520	-0.023	1.064	1.878	0.060	

Test for heterogeneity: Q= 0.984 on 4 degrees of freedom (p= 0.912)
Moment-based estimate of between studies variance = 0.000

Study	Weights Fixed	Weights Random	Study Est.	95% CI Lower	95% CI Upper
2 (83)	2.28	2.28	0.94	-0.36	2.24
3 (84)	1.90	1.90	0.58	-0.84	2.00
4 (86)	1.36	1.36	0.15	-1.52	1.83
7a (88)	3.51	3.51	0.67	-0.37	1.72
8a (89)	3.96	3.96	0.24	-0.74	1.23

Figure 2. Forest Plot of study number and year vs. effect size of serum glucose, 100 grams, 1 hour post-ingestion.

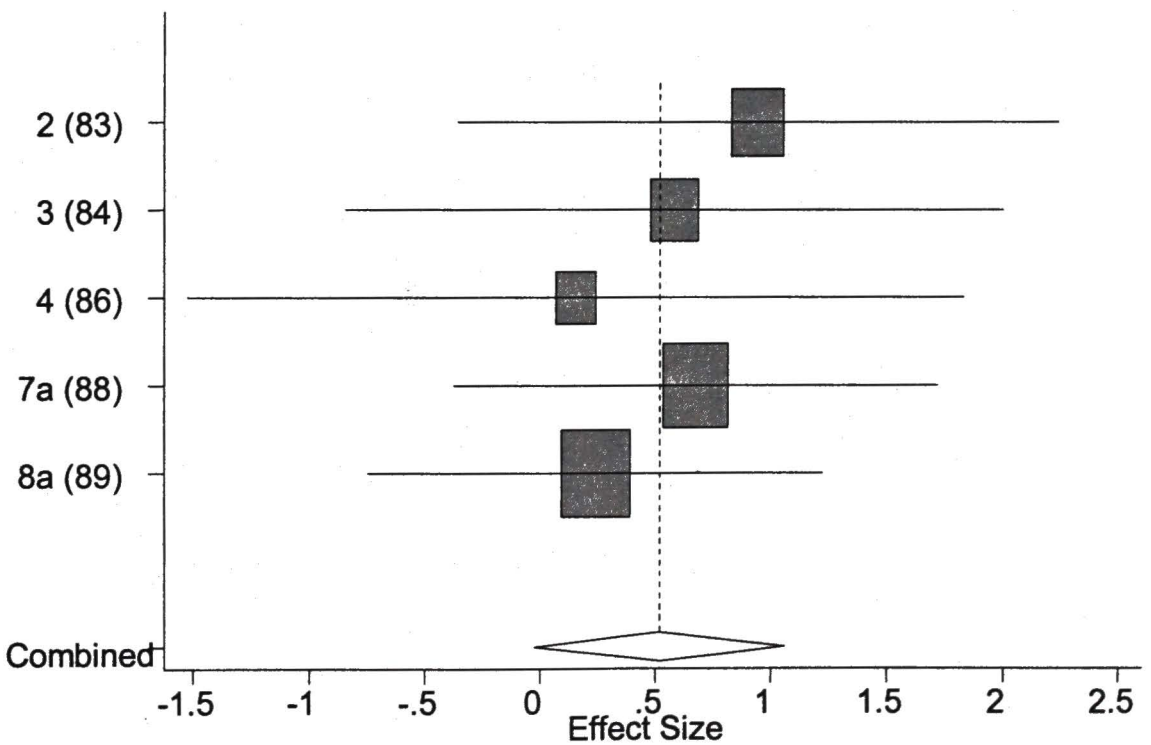


Table 3. Effect sizes, pooled and by study for serum glucose, 100 grams, 2 hours post-ingestion.

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z value	Asymptotic p value	No. of Studies
Fixed	-0.714	-1.314	-0.144	-2.333	0.020	5
Random	-0.515	-1.508	0.477	-1.017	0.309	

Test for heterogeneity: Q= 10.478 on 4 degrees of freedom (p= 0.033)
Moment-based estimate of between studies variance = 0.781

Study	Weights Fixed	Weights Random	Study Est.	95% CI Lower	95% CI Upper
2 (83)	1.75	0.74	0.44	-1.04	1.93
3 (84)	1.42	0.67	0.06	-1.59	1.70
4 (86)	1.50	0.69	0.65	-0.95	2.25
7a (88)	3.00	0.90	-1.71	-2.84	-0.58
8a (89)	3.02	0.90	-1.43	-2.56	-0.30

Figure 3. Forest plot of study number and year vs. effect size of serum glucose, 100 grams, 2 hours post-ingestion.

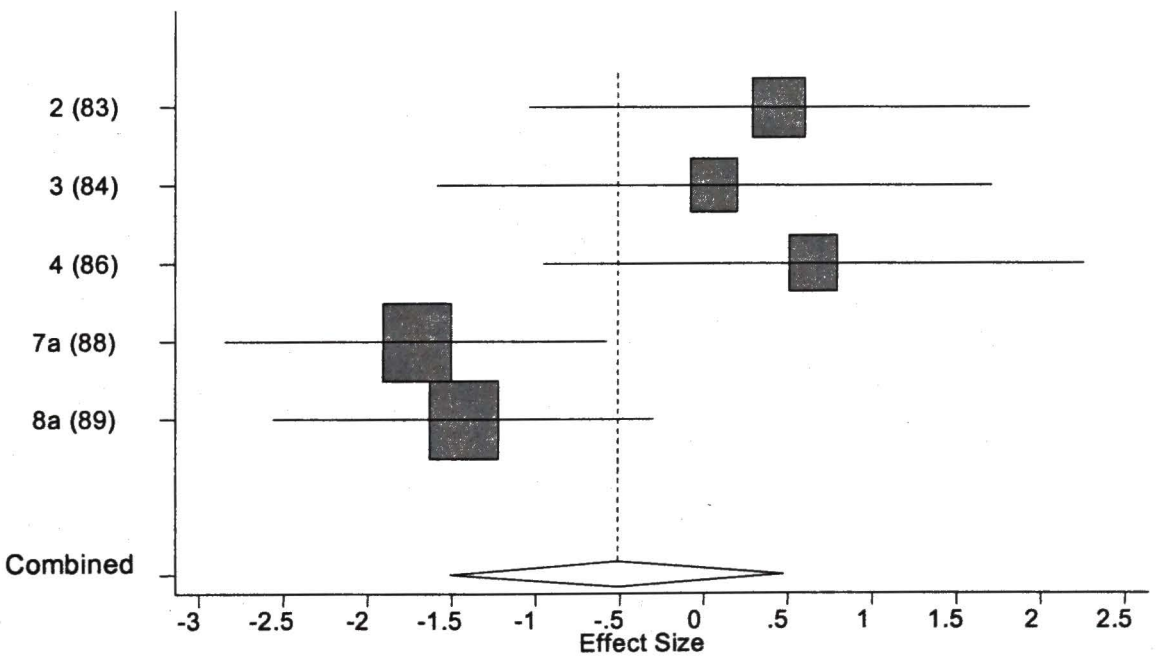


Table 4. Effect sizes, pooled and by study number for serum glucose, 100 grams, 3 hours post-ingestion.

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z value	Asymptotic p value	No. of Studies
Fixed	-0.663	-1.300	-0.025	-2.037	0.042	5
Random	-0.529	-1.725	0.668	-0.866	0.387	

Test for heterogeneity: Q= 12.208 on 4 degrees of freedom (p= 0.016)
Moment-based estimate of between studies variance = 1.197

Study	Weights Fixed	Weights Random	Study Est.	95% CI Lower	95% CI Upper
2 (83)	1.02	0.46	-0.33	-2.27	1.60
3 (84)	0.77	0.40	-0.72	-2.96	1.51
4 (86)	1.31	0.51	1.43	-0.28	3.14
7a (88)	2.46	0.62	-2.24	-3.49	-0.99
8a (89)	3.88	0.69	-0.44	-1.44	0.55

Figure 4. Forest plot of study number and year vs. effect size for serum glucose, 100 grams, 3 hours post-ingestion.

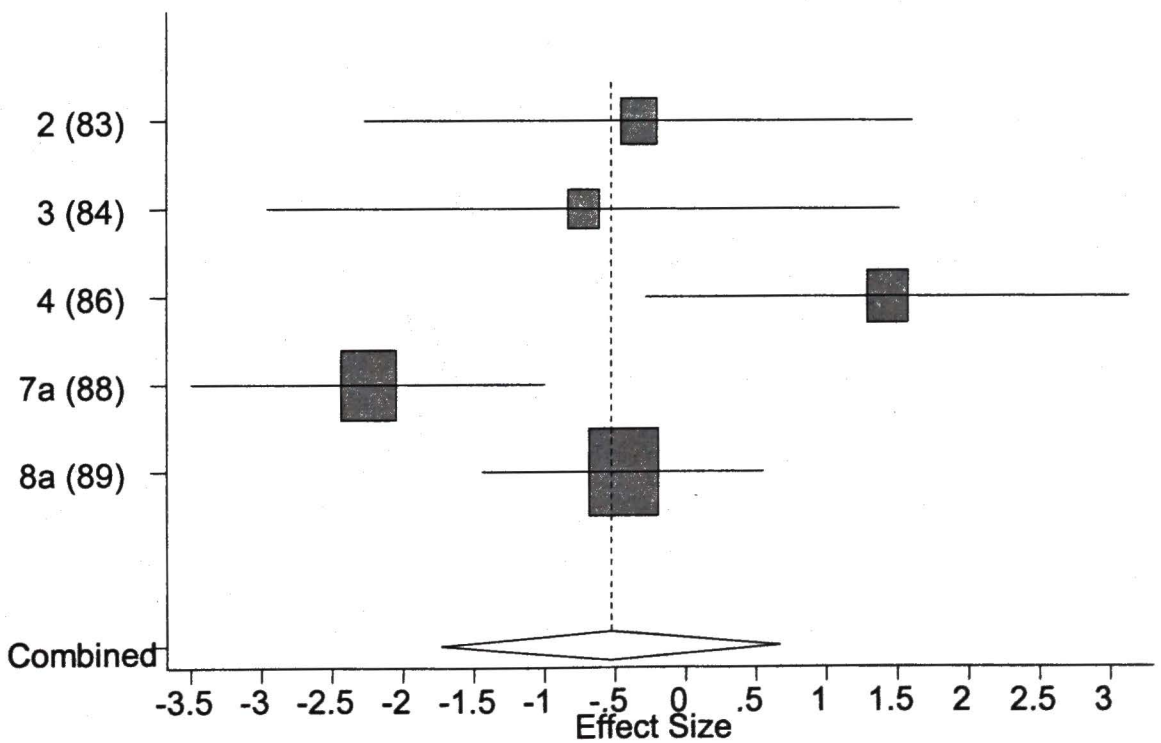


Table 5. Effect sizes, pooled and by study number for serum glucose, 300 grams, 1 hour post-ingestion.

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z value	Asymptotic p value	No. of Studies
Fixed	-0.044	-0.610	0.522	-0.153	0.878	3
Random	-0.011	-0.753	0.732	0.028	0.978	

Test for heterogeneity: Q= 3.376 on 2 degrees of freedom (p= 0.185)
Moment-based estimate of between studies variance = 0.176

Study	Weights Fixed	Weights Random	Study Est.	95% CI Lower	95% CI Upper
8b (89)	3.99	2.35	-0.49	-1.47	0.50
9 (89)	2.99	1.96	0.86	-0.28	1.99
15 (92)	5.00	2.66	-0.23	-1.11	0.65

Figure 5. Forest plot of study number and year vs. effect size for serum glucose, 300 grams, 1 hour post-ingestion.

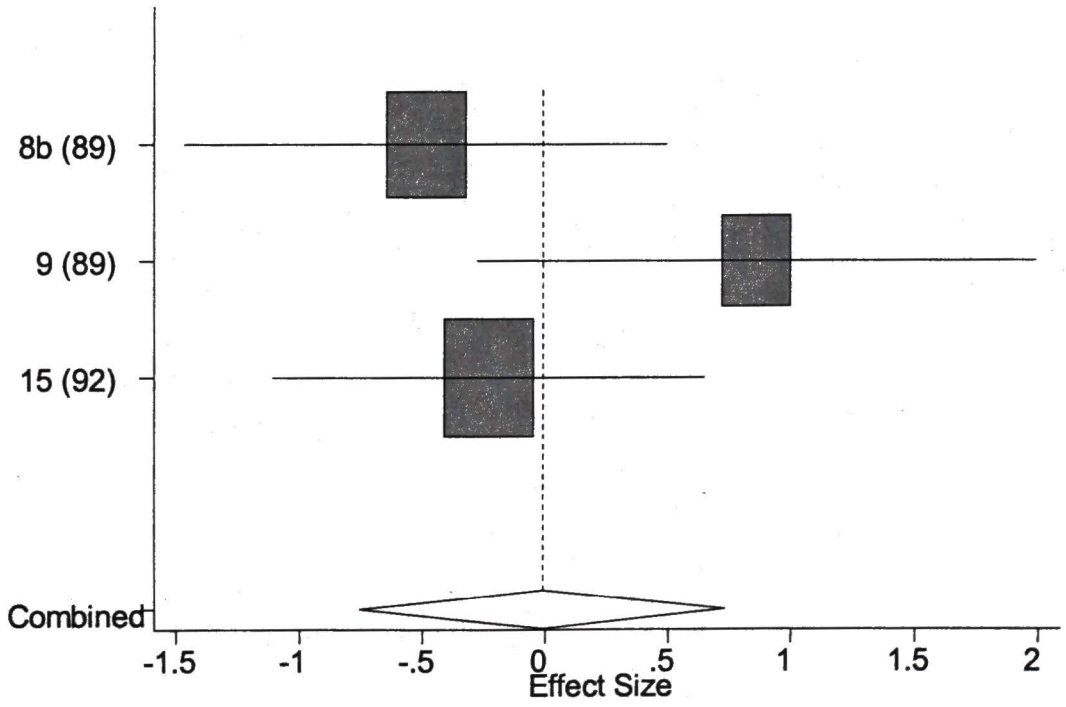


Table 6. Effect sizes, pooled and by study number for serum glucose, 300 grams, 2 hours post-ingestion.

Method	Pooled Est	95% CI Lower	Upper	Asymptotic z value	p value	No. of Studies
Fixed	0.093	-0.475	0.662	0.322	0.747	3
Random	0.108	0.-0.565	0.781	0.315	0.753	

Test for heterogeneity: Q= 2.768 on 2 degrees of freedom (p= 0.251)
Moment-based estimate of between studies variance = 0.099

Study	Weights Fixed	Random	Study Est.	95% CI Lower	Upper
8b (89)	3.99	2.86	-0.44	-1.42	0.54
9 (89)	2.99	2.31	0.83	-0.30	1.97
15 (92)	5.00	3.31	0.07	-0.81	0.96

Figure 6. Forest plot of study number and year vs. effect size for serum glucose, 300 grams, 2 hours post-ingestion.

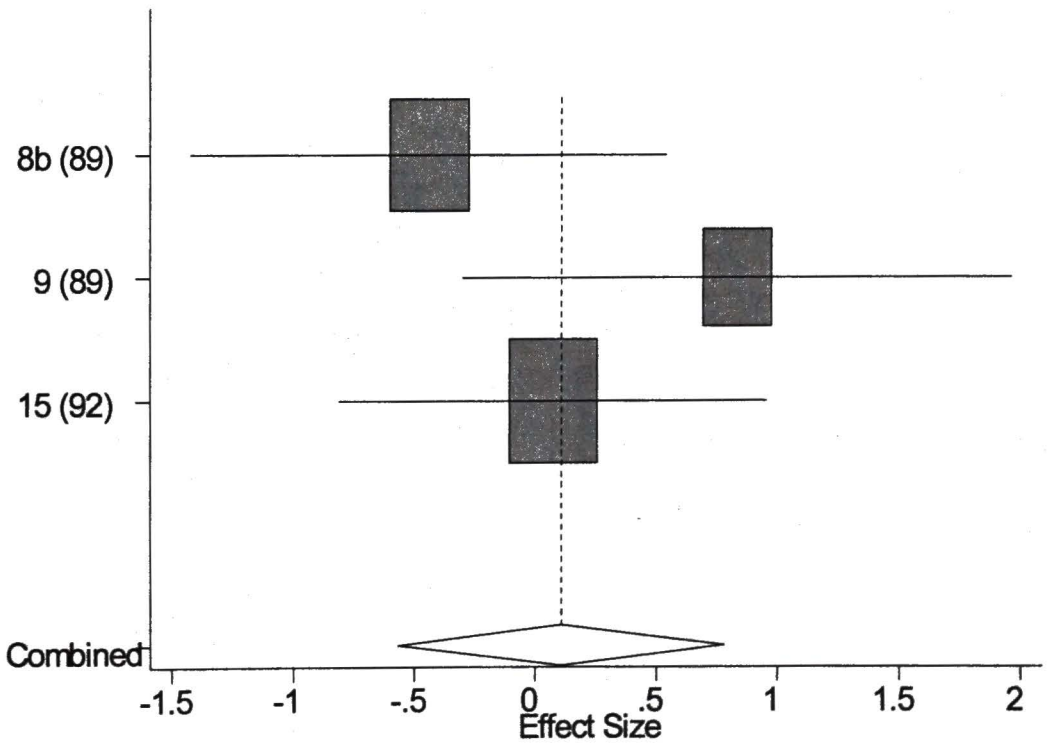


Table 7. Effect sizes, pooled and by study number for serum glucose, 300 grams, 3 hours post-ingestion.

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z value	Asymptotic p value	No. of Studies
Fixed	0.166	-0.414	0.747	0.562	0.574	3
Random	0.166	-0.414	0.747	0.562	0.574	

Test for heterogeneity: Q= 0.344 on 2 degrees of freedom (p= 0.842)
Moment-based estimate of between studies variance = 0.000

Study	Weights Fixed	Weights Random	Study Est.	95% CI Lower	95% CI Upper
8b (89)	3.84	3.84	-0.08	-1.08	0.92
9 (89)	2.78	2.78	0.29	-0.88	1.47
15 (92)	4.78	4.78	0.29	-0.61	1.18

Figure 7. Forest plot of study number and year vs. effect size for serum glucose, 300 grams, 3 hours post-ingestion.

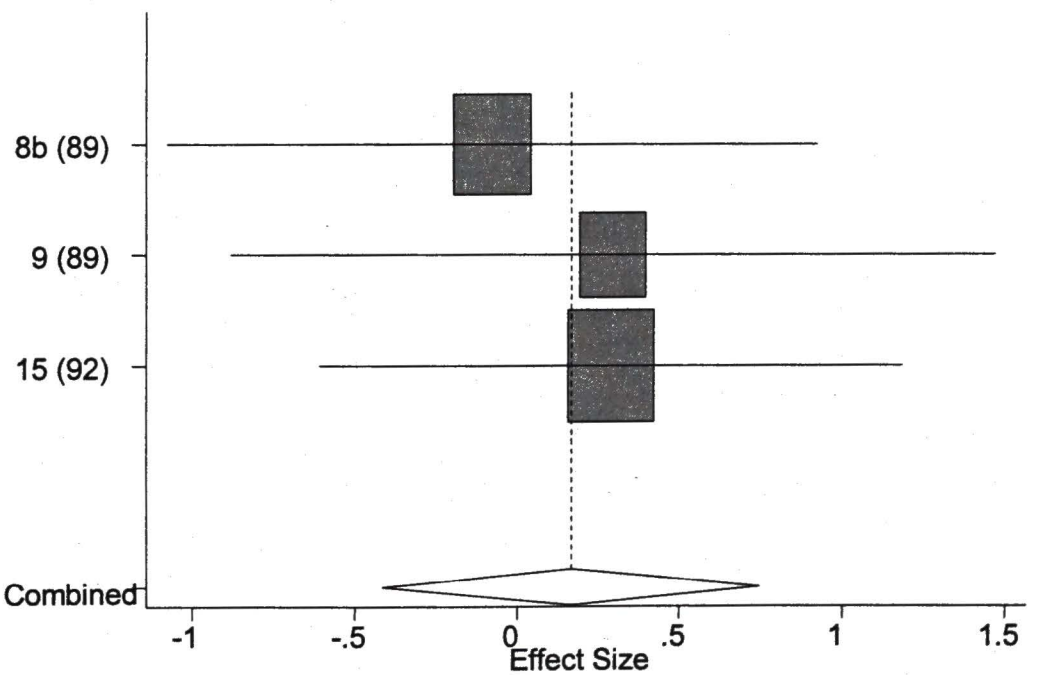


Table 8. Effect sizes, pooled and by study number for serum glucose, 500 grams, 1 hour post-ingestion.

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z value	Asymptotic p value	No. of Studies
Fixed	-0.803	-1.146	-0.461	-4.598	0.000	8
Random	-0.807	-1.180	-0.435	-4.246	0.000	

Test for heterogeneity: Q= 8.199 on 7 degrees of freedom (p= 0.315)
Moment-based estimate of between studies variance = 0.042

Study	Weights Fixed	Weights Random	Study Est.	95% CI Lower	95% CI Upper
6 (88)	4.81	3.99	-1.39	-2.28	-0.50
7b (88)	3.69	3.19	-0.55	-1.57	0.47
8c (89)	3.34	2.92	-1.60	-2.66	-0.51
10 (89)	3.19	2.81	-0.81	-1.91	0.29
11 (90)	3.38	2.96	-0.98	-2.05	0.08
13 (90)	3.41	2.98	-0.88	-1.94	0.18
14 (91)	7.00	5.40	-0.59	-1.33	0.15
16 (89)	3.97	3.40	0.18	-0.81	1.16

Figure 8. Forest plot of study number and year vs. effect size for serum glucose, 500 grams, 1 hour post-ingestion.

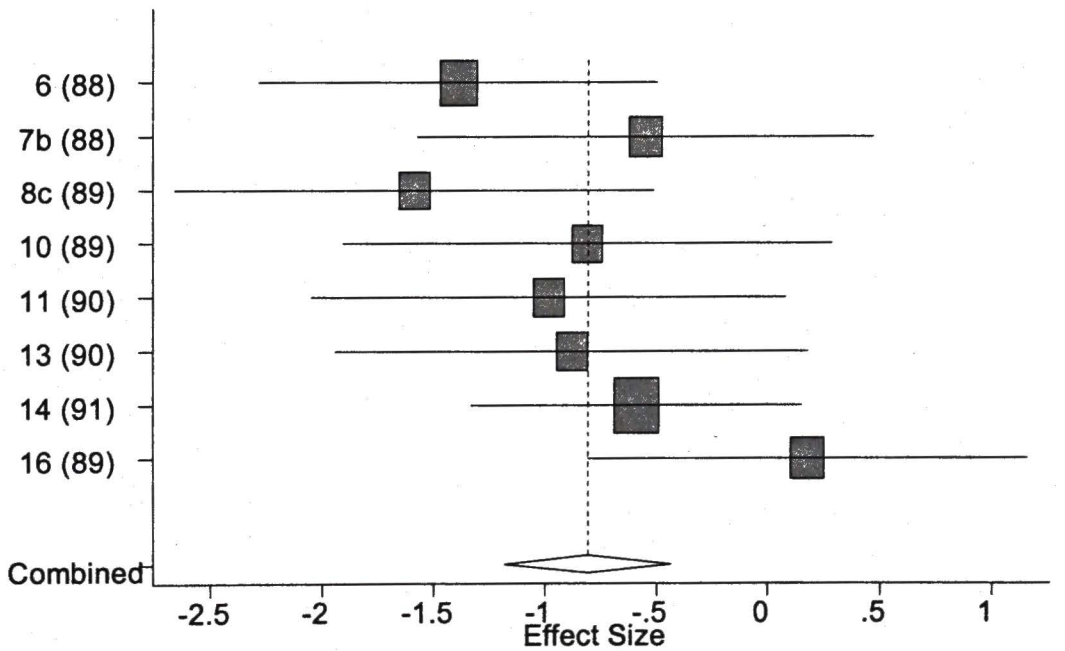


Table 9. Effect sizes, pooled and by study number for serum glucose, 500 grams, 2 hours post-ingestion.

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z value	Asymptotic p value	No. of Studies
Fixed	-1.204	-1.563	-0.845	-6.569	0.000	9
Random	-1.450	-2.134	-0.766	-4.155	0.000	

Test for heterogeneity: Q= 27.436 on 8 degrees of freedom (p= 0.001)
Moment-based estimate of between studies variance = 0.752

Study	Weights Fixed	Weights Random	Study Est.	95% CI Lower	95% CI Upper
6 (88)	3.45	0.96	-2.35	-3.41	-1.29
7b (88)	2.86	0.91	-1.40	-2.56	-0.24
8c (89)	3.30	0.95	-1.62	-2.70	-0.54
10 (89)	1.05	0.59	-3.75	-5.67	-1.84
11 (90)	2.40	0.86	-1.95	-3.21	-0.69
13 (90)	2.68	0.89	-1.84	-3.04	-0.64
14 (91)	6.66	1.11	0.02	-0.74	0.78
16 (89)	3.40	0.96	-1.06	-2.12	0.01
17a (91)	3.97	1.00	-0.35	-1.33	0.63

Figure 9. Forest plot of study number and year vs. effect size for serum glucose, 500 grams, 2 hours post-ingestion.

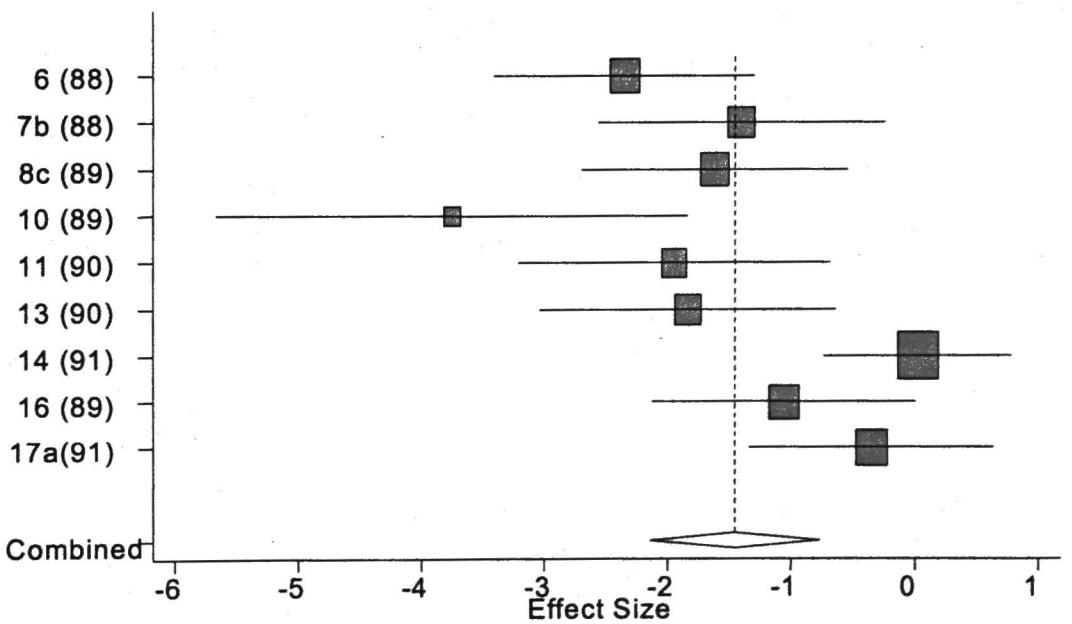


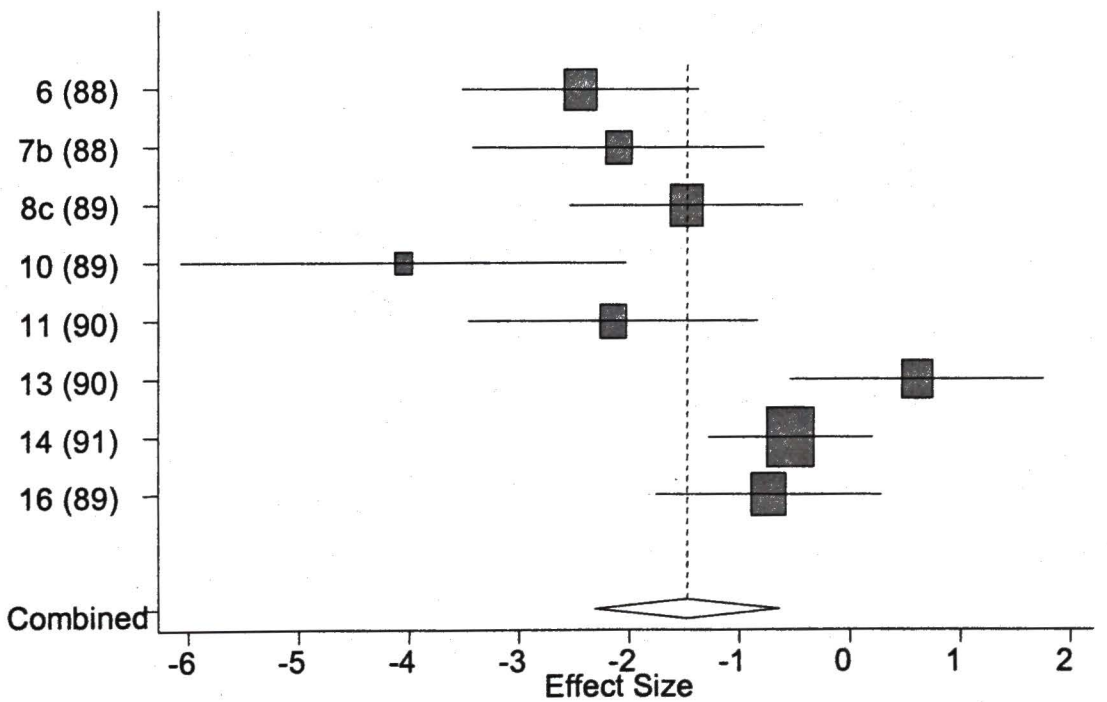
Table 10. Effect sizes, pooled and by study number for serum glucose, 500 grams, 3 hours post-ingestion.

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z value	Asymptotic p value	No. of Studies
Fixed	-1.210	-1.597	-0.824	-6.139	0.000	8
Random	-1.472	-2.306	-0.637	-3.455	0.001	

Test for heterogeneity: Q= 30.235 on 7 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance = 1.073

Study	Weights Fixed	Weights Random	Study Est.	95% CI Lower	95% CI Upper
6 (88)	3.33	0.73	-2.45	-3.52	-1.37
7b (88)	2.19	0.65	-2.10	-3.43	-0.77
8c (89)	3.44	0.73	-1.48	-2.54	-0.43
10 (89)	0.94	0.47	-4.05	-6.07	-2.03
11 (90)	2.22	0.66	-2.15	-3.46	-0.83
13 (90)	2.92	0.71	0.61	-0.54	1.75
14 (91)	7.00	0.82	-0.54	-1.28	0.20
16 (89)	3.68	0.74	-0.74	-1.76	0.28

Figure 10. Forest plot of study number and year vs. effect size for serum glucose, 500 grams, 3 hours post-ingestion.



In order to determine if there was a dose-response in the reduction of serum glucose, a meta-analysis regression was carried out. With the 1, 2, and 3 hour effect size as dependent variables and both baseline effect size and dosage as independent variables, there was insufficient evidence to suggest a dose-related response (Appendix E). The regression results of the effects of insulin were not statistically significant, with each of the confidence intervals including zero. A dose-related response appears to be present based on the effect sizes found at 100 and 500 grams and there were only three studies analyzed at 300 grams, therefore a separate regression was conducted removing the effects sizes at 300 grams post-ingestion. When excluding the studies which examine 300 grams post-ingestion of *Opuntia* species, there was not a statistical significant dose response. The data are insufficient to conclude anything about a dose-response relationship, but this aspect needs to be investigated.

The Galbraith plots are a visual representation of the outliers in the meta-analysis and are found in Appendix D. In the 100 grams, 3 hours post-ingestion Galbraith plot, reference study numbers 4 and 7 were identified as outliers. A possible explanation for study number 4 being an outlier may be a result of the reported control group means, which readily fluctuate. After reviewing the study, I could not identify possible reasons for study number 7 to be identified as an outlier. In the Galbraith plot of 500 grams at both 2 and 3 hours post-ingestion, study 10 is identified as an outlier. Study numbers 14 and 15 were also identified as outliers in the post-ingestion of 500 grams of *Opuntia* species. I chose to report the random effect effects estimate in my results due to the number of outliers as it was not feasible to eliminate the outliers in this analysis.

In order to determine the milligram per deciliter reduction in serum glucose at 500 grams post-ingestion, I utilized the average standard deviation found in the preliminary research of Ramirez and Aguilar. No measures of statistical tests probability were available for the preliminary data. Based on the calculation of average standard deviation and the effect size, the average serum glucose reduction found at 500 grams and 3 hours post-ingestion was 56.5 mg/dl.

CHAPTER V

DISCUSSION

Limitations

As mentioned in Chapter II, publication bias is a main source of bias in meta-analysis. To counteract publication bias, I reviewed the references of published articles in order to obtain unpublished studies. No unpublished studies on the effects of *Opuntia* species were found in my review of the literature or by reviewing the references of published articles. Other methods of obtaining unpublished studies, such as speaking with the primary researchers, were not feasible for this thesis and therefore were not carried out. A Begg's funnel plot was conducted to examine the possibility of publication bias in this meta-analysis. The results of the funnel plot test were not conclusive as to the detection of publication bias due to the small number of studies analyzed. The small number of studies analyzed may also serve as a limitation for the application of the results of this meta-analysis. This meta-analysis is not subject to "Tower of Babel" or "reverse publication" bias due to the source of the published studies consisting of only research conducted in Mexico (Ioannidis & Lau, 1999, p. 462).

The quality of data in the published studies is a potential source of bias in the meta-analysis. In general, the data reported means and standard deviations or standard error of the mean as outcomes measured. In some instances, data was abstracted from

graphs included in the publication and may be a source of error. Study design may be another source of error and may affect the quality of data reported. Generally, the analyzed studies consisted of a small sample size with the same subjects involved in the treatment and control group. The ideal study design for the purpose of this meta-analysis would involve a large sample size, randomization and double-blinding. In addition, although the primary author, A. C. Frati-Munari, was involved in the majority of the studies, the study designs and methodology varied greatly.

The findings of this meta-analysis are consistent with the preliminary research conducted by Ramirez and Aguilar (1996). The previous research also found a significant reduction in serum glucose upon ingestion of 500 grams of *Opuntia* species with an effect size of .95 and an average serum glucose reduction of 36.5. Measures of statistical probability for their results were not obtained. My meta-analysis differed from Ramirez and Aguilar's previous work in that I used a more conservative approach in calculating effect sizes by controlling for baseline measurements and utilizing an updated review of the literature. Although I used more conservative statistical methods than this previous meta-analysis, my results show an increased reduction in serum glucose levels.

The findings of this meta-analysis do not support the conclusion reached by Rayburn et al. (1998). Rayburn et al. conducted a study in El Paso, Texas and tested *Opuntia lasiacantha*, *Opuntia velutina* and *Opuntia macrocentra* versus a zucchini squash and a water group. Rayburn et al. found a reduction in the water treatment group which contradicts earlier findings of a constant glucose level in other studies (Appendix A: Study numbers 6, 7, 11, 14 and 16). Rayburn found ingestion of *Opuntia* species did

not decrease glucose concentrations more than zucchini squash or the water group. Rayburn et al. has concerns over the use of an appropriate comparison group "one with a falling a.m. baseline rather than a constant one" in the work of Frati et al (Rayburn et al, 1998, p. 74). Rayburn et al. believe that the statistically insignificant results may be due to the use of differing species of *Opuntia* when compared to past studies but believes the results should still be consistent with earlier findings. The existence of past studies which contradict my results confirms that further research is necessary to examine the effects of *Opuntia* species.

Recommendations

Due to the rising prevalence of diabetes mellitus in the world, alternative treatments for non-insulin dependent diabetes mellitus (NIDDM) in underdeveloped countries must be considered as viable options for the future. More research is needed to determine and isolate the active components of *Opuntia* species. The importance of developing inexpensive treatments for NIDDM patients can not be understated. In 1992, as determined by the American Diabetes Association, the estimated direct cost of treating diabetes mellitus for the United States was 45.2 billion dollars (Jonsson, 1998). Loyoza (1994) has mentioned evidence which supports the future increase in the use of herbal remedies. If an active component of *Opuntia* species can be isolated, a great likelihood exists that the active component will lead to the development of an affordable drug for NIDDM patients due to the natural abundance of *Opuntia* species in Texas and Mexico.

The increasing prevalence of NIDDM is of concern to the rapidly growing Mexican American population, who have been found to be more susceptible to risk

factors of NIDDM and developing NIDDM. The increased frequency of alternative treatments used for treatment of NIDDM has been associated with the Mexican American population (Noel et al.). Even after assimilating into an American culture, Mexican Americans have been found to be users of folk medicine (Chesney et al., 1980). More studies must be conducted to determine the long term effects of ingestion of *Opuntia* species in the Mexican American population as well as an investigation of side effects associated with it's use.

Health care providers must be aware that cultural beliefs have been associated with compliance rates, acceptance of health care and treatment outcomes (Fishman et al., 1993). In addition to cultural awareness, health care providers must acknowledge that patients may be utilizing more than one type of health care system, such as folk medicine and conventional care (Chesney et al, 1980; Winkleman, 1989). Guidelines concerning alternative treatments are necessary for the health care practitioner in order to guide patients to the best course of action (Sugarman & Burk, 1998).

Glycemic control is essential in patients with NIDDM. Several studies have examined the relationship between improved glycemic control and the reduction in complications. The Texas Diabetes Council revised their algorithm for the treatment of NIDDM patients due to the recognition of tight glycemic control as effective in reducing complications associated with diabetes mellitus. Upon the identification of an active ingredient in the *Opuntia* species, *Opuntia* can serve as a potential hypoglycemic agent that may be used as an adjunct to conventional treatment.

The effect sizes calculated at 100 and 500 grams suggest a dose response in the ingestion of *Opuntia* species. However, the regression analysis results illustrate the results are non-significant. This may be due to an artifact of the data analyzed, as the 3 studies investigated at 300 grams post-ingestion show an increase in the effect size. The average serum glucose reduction found at 500 grams and 3 hours post-ingestion was 56.5mg/dl. When compared to the average basal glucose value of 167mg/dl, a 56.5mg/dl reduction results in a normal glucose level of 110.5mg/dl. Although the findings of this meta-analysis show a statistically significant reduction in serum glucose, it is important to note the practicality of ingestion of 500 grams of *Opuntia* species to induce a hypoglycemic effect. The 500 grams of *Opuntia* species translates into 1.03 pounds per serving which may not be feasible on a daily basis. No studies to date have examined the long term effects of ingestion of *Opuntia* species on glucose levels. Future studies are needed to clarify whether the hypoglycemic effect of *Opuntia* species is due to an acute response or can be maintained through the regular ingestion of *Opuntia* species. A number of studies have examined the effects of *Opuntia* species on cholesterol levels, insulin and weight in animal subjects. Further human studies are needed to investigate additional properties of Opuntia species. Additional studies on the hypoglycemic effect of *Opuntia* species are necessary to provide strength to the conclusion of a significant hypoglycemic effect of *Opuntia* species and to determine the mechanism of effect.

APPENDIX

APPENDIX A

IDENTIFIED STUDIES

Study No.	
1	Frati-Munari, A.C., Fernandez-Harp, J.A., De la Riva, H., Ariza-Andraca, R., & Carmen-Torres, C. (1983). Effects of nopal on serum lipids, glycemia and body weight. Archivos de Investigacion Medica, 14, 117-125.
2	Frati-Munari, A.C., Fernandez-Harp, J.A., Banales-Ham, M., & Ariza-Andraca, C.R. (1983). Decreased blood glucose and insulin by nopal. Archivos de Investigacion Medica, 14, 269-274.
3	Fernandez-Harp, J.A., Frati-Munari, A.C., Chavez-Negrete, A., Hermenegilde, B., De la Riva , P., & Gomez, G.M. (1984). Estudios hormonales en la accion del nopal sobre la prueba de tolerancia a la glucosa: Informe preliminar. Revista Medica, Instituto Mexicano del Seguro Social, 22, 387-390.
4	Frati-Munari, A.C., Medina-Beltran, G.R., Chavez-Negrete, A., Banales-Ham, M., De la Riva Pinal, H. (1986). Efecto de diferentes especies de nopal en la prueba de tolerancia a la glucosa. Medicina Interna de Mexico, 2, 24-26.
5	Frati-Munari, A.C., Yever-Garces, A., Islas-Andrade, S., Ariza-Andraca, C.R., & Chavez-Negrete, A. (1987). Studies on the mechanism of the hypoglycemic effect of nopal. Archivos de Investigacion Media, 18, 7-12.
6	Frati-Munari, A.C., Gordillo, B.E., Altamirano, P. & Ariza, C.R. (1988). Hypoglycemic effect of Opuntia streptacantha Lemaire in NIDDM. Diabetes Care, 11, 63-66
7	Frati-Munari, A.C., Lazaro, J.L., Altamirano-B, P., Banales-Ham, M., Andrade, S., & Arisa-Andraca, C. R. (1988). The effect of different doses of prickly-pear cactus on the glucose tolerance test in healthy individuals. Archivos de Investigacion Medica, 19, 143-147.
8	Frati-Munari, A.C., Valle-Martinez, L.M.D., Ariza-Andraca, C.R., Islas-Andrade, S., & Chavez-Negrete, A. (1989). Hypoglycemic effect of different doses of nopal in patients with type II diabetes mellitus. Archivos de Investigacion Medica, 20, 197-201.
9	Frati-Munari, A.C., Leon, C.D., Ariza-Andraca, R., Banales-Ham, M., Lopez Ledesma, R., & Lozoya, X. (1989). Influence of a dehydrated extract of the nopal of glycemia. Archivos de Investigacion Medica, 20, 211-216.

Study No.	
10	Frati-Munari, A.C., Altamirano-B., E., Rodriguez-Barcenas, N., Ariza-Andraca, R., & & Lopez-Ledesma, R. (1989). Hypoglycemic effect of *Opuntia streptacantha* lemaire: research with crude extracts. Archivos de Investigacion Medica, 20, 321-325.
11	Frati, A.C., Jimenez, E., Ariza, R. (1990). Hypoglycemic effect of *Opuntia ficus* in Non Insulin-dependent Diabetes Mellitus Patients. Phytotherapy Research, 4, 195-197.
12	Frati, A.C., Gordillo, B.E., Altamirano, P., Ariza, C.R., Cortes-Franco, R., Chavez-Negrete, A. (1990). Acute Hypoglycemic Effect of *Opuntia streptacantha* Lemaire in NIDDM. Diabetes Care, 13, 455-456.
13	Frati-Munari, A.C., Licona-Quesada, R., Ariza-Andraca, C.R., Lopez-Ledesma, R., & Chavez-Negrete, A. (1990). The action of *Opuntia streptacantha* on healthy subjects with induced hyperglycemia. Archivos de Investigacion Medica, 21, 99-102.
14	Frati-Munari, A.C., Gordillo, B.E., Altamirano, P., Ariza, C.R., Cortes-Franco, R., Chavez-Negrete, A., & Islas-Andrade, S. (1991). Influence of nopal intake upon fasting glycemia in type II diabetics and healthy subjects. Archivos de Investigacion Medica, 22, 51-56
15	Frati-Munari, A.C., Vera-Lastra, O. & Ariza-Andraca, C.R. (1992) Evaluacion de capsulas de nopal en diabetes melitus. Gaceta Medica de Mexico, 128, 431-436.
16	Frati-Munari, A.C., Gil, U.R., Ariza-Andraca, C.R., Andrade, S.I., & Lopez-Ledesma, R. (1989). Duration of hypoglycemic action of *streptacantha* Lemaire. Archivos de Investigacion Medica, 20, 297-300.
17	Frati-Munari, A.C., Diaz, N., Altamirano, P., Ariza, R., & Lopez-Ledesma, R. (1991) The effect of two sequential doses of *Opuntia streptacantha* upon glycemia. Archivos de Investigacion Medica, 22, 333-336.

APPENDIX B

MICROSOFT EXCEL WORKSHEET: GLUCOSE

ref#	year	dose	comparison groups	d_T0	se_T0	d_60	se_60	d_120	se_120	d_180	se_180
1	1983		no glucose info.								
2	1983	100g	pre/post gp 1 and 2	-1.386	0.881	-0.445	0.662	-0.943	0.757	-1.720	0.988
3	1984	100g	pre/post; gp 1 and 2	-0.8658	0.858	-0.2861	0.725	-0.809	0.84	-1.59	1.14
4	1986	100g	1 vs 4 strepthacantha	-0.736	0.8789	-0.582	0.856	-0.088	0.8174	0.693	0.8721
5	1987		missing data								
6	1988	500g	1 vs 2, nopal vs water	-0.036	0.4031	-1.425	0.4561	-2.386	0.5385	-2.482	0.5483
7a	1988	100g	1 vs 2	0.267	0.5028	-0.94	0.5341	-1.442	0.5771	-1.977	0.6374
7b	1988	500g	1 vs 3	-0.178	0.5013	-0.728	0.5208	-1.582	0.5916	-2.278	0.6762
8a	1989	100 g	1 vs 2	0.002	0.5	0.243	0.5024	-1.429	0.5758	-0.441	0.5077
8b	1989	300 g	1 vs 3	0.582	0.5134	0.097	0.5004	0.144	0.5008	0.505	0.5101
8c	1989	500 g	1 vs 4	0.472	0.5088	-1.114	0.5474	-1.147	0.5501	-1.01	0.5392
9	1989	10g (300 g)	1 vs 2	-0.97	0.6233	-0.114	0.578	-0.136	0.5783	-0.676	0.6001
10	1989	500g	4 vs 5 water vs broiled	-0.449	0.508	-1.26	0.56	-4.2	0.977	-4.5	1.03
11	1990	500g	5 vs 1 entire broiled stem	-0.088	0.5	-1.071	0.544	-2.038	0.645	-2.236	0.671
12	1990	500g	missing data								
13	1990	500g	1 vs 2	0.484	0.5449	-0.395	0.5414	-1.355	0.6107	1.089	0.5849
14	1991	500g	1 vs 2 healthy; data missing NIDDM	0.571	0.3867	-0.019	0.378	0.595	0.3874	0.032	0.378
15	1992	10g (330 g)	1 vs 2	0.257	0.4493	0.027	0.4472	0.345	0.4509	0.569	0.4572
16	1989	500g	1 vs 2	0.014	0.5	0.192	0.502	-1.043	0.542	-0.723	0.521
17a	1991	500g	1 vs 2, 1 dose of nopal	0.13	0.501			-0.221	0.502		
17b	1991	1000g	1 vs 3, 2 doses of nopal	-1.86	0.623			-1.041	0.542		
			average	-0.21		-0.49		-1.04		-1.05	
			standard deviation	0.70		0.55		1.14		1.48	
			number of effect sizes	18		16		18		16	
			lower 95% CI	-0.56		-0.78		-1.61		-1.84	
			upper 95% CI	0.14		-0.20		-0.48		-0.26	

d_30	se_30	d_90	se_90	d_150	se_150	d_240	se_240	d_300	se_300	d_360	se_360
-0.605	0.5144	-1.441	0.577	-1.034	0.5411						
-0.147	0.5009	-0.713	0.5199	-1.739	0.6089						
-2.46	0.703										
-1.666	0.601										
-0.169	0.5358	0.904	0.5697	-0.056	0.5347						
						-1.291	-1.305			-1.416	0.575
						-0.823	0.526			-0.899	0.531
						-1.424	0.575			-1.412	0.574
-1.01		-0.42		-0.94		-1.18				-1.24	
1.02		1.20		0.85		0.32				0.30	
5		3		3		3				3	
-2.27		-3.40		-3.04		-1.96				-1.98	
0.26		2.56		1.16		-0.40				-0.50	

APPENDIX C

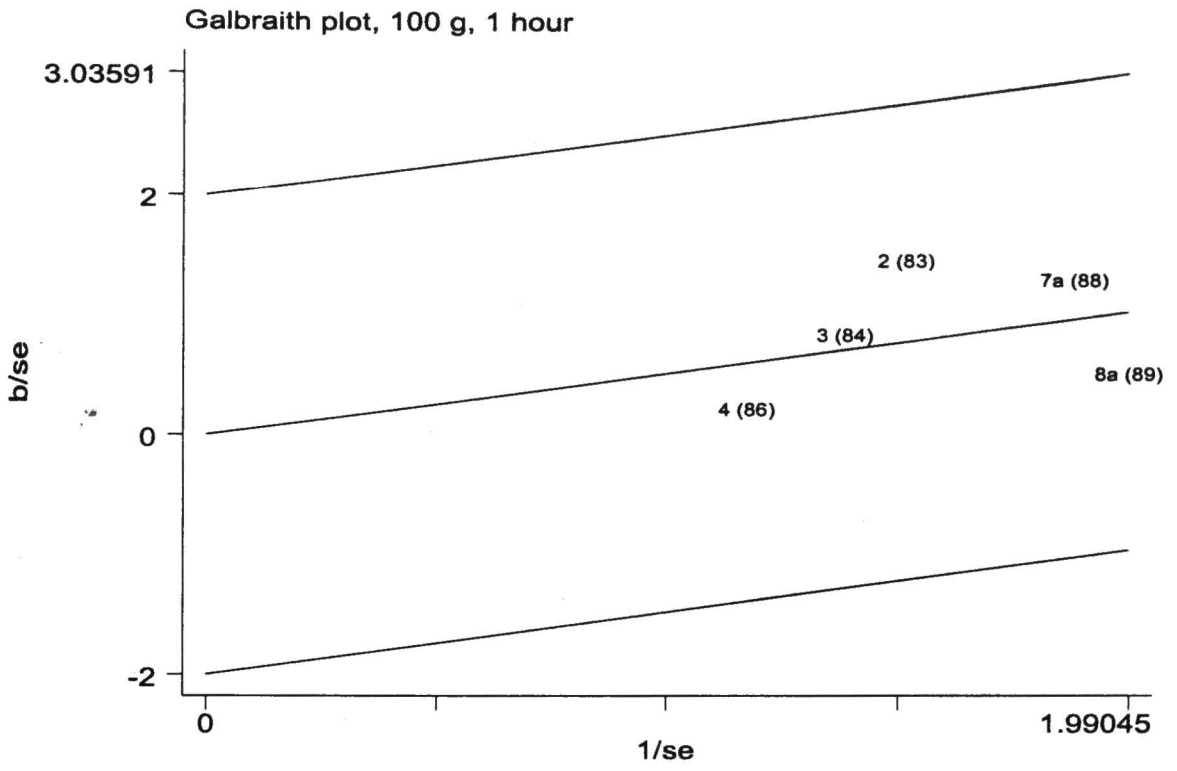
MICROSOFT EXCEL WORKSHEET: INSULIN

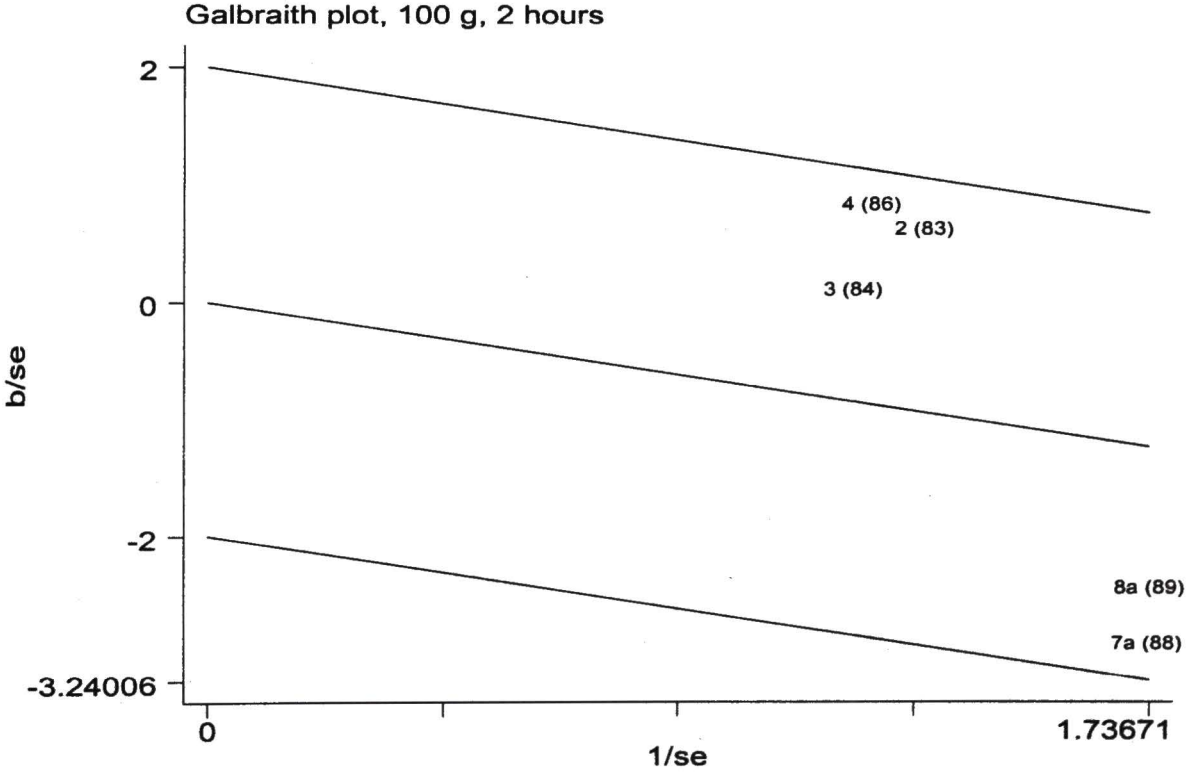
ref#	year	dose	comp gps	d_T0	se_T0	d_60	se_60	d_120	se_120	d_180
1	1983									
2	1983	100g	pre/post; gp 1; gp 2	-1.490	0.913	-1.407	0.887	-1.727	0.991	-1.264
3	1984	100g	pre/post; gp1; gp 2	-1.450	1.080	-1.120	0.945	-1.350	1.040	-1.000
4	1986									
5	1987									
6	1988	500g	1 vs 3c; 3 vs 3c	-0.277	0.4809	-3.678	0.7701	-3.106	0.6989	-1.828
7a	1988	100g	1 vs 2	-0.012	0.6325	-0.242	0.636	-0.251	0.6363	-0.04
7b	1988	500 g	1 vs 3	-0.063	0.6327	-1.378	0.7385	-0.84	0.9738	0
8	1989									
9	1989									
10	1989									
11	1990									
12	1990									
13	1990									
14	1991									
15	1992									
			Average	-0.66		-1.57		-1.45		-0.83
			Standard deviation	0.75		1.27		1.08		0.79
			No. of effect sizes	5		5		5		5
			Lower 95% CI	-1.59		-3.14		-2.79		-1.81
			Upper 95% CI	0.27		0.01		-0.12		0.16

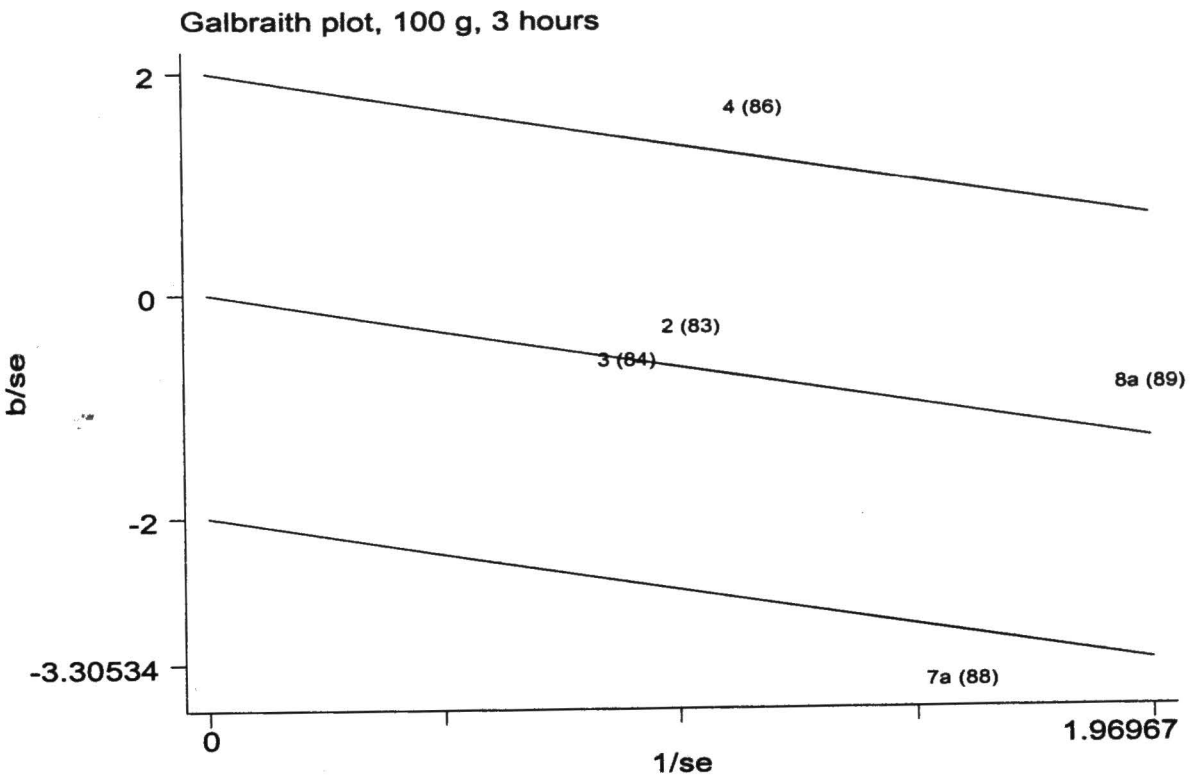
se_180	d_30	se_30	d_90	se_90	d_150	se_150	d_T0	se_T0	d_60	se_60
0.844										
0.903										
0.5648							-0.439	0.5871	-3.495	1.0247
0.6326	-0.251	0.6363	-0.104	0.6331	-0.212	0.6352				
0.6325	-1.139	0.7067	-0.86	0.6757	-0.399	0.642				
	-0.70		-0.48		-0.31		-0.44		-3.50	
	0.63		0.53		0.13					
	2		2		2		1		1	
	-6.34		-5.28		-1.49					
	4.95		4.32		0.88					

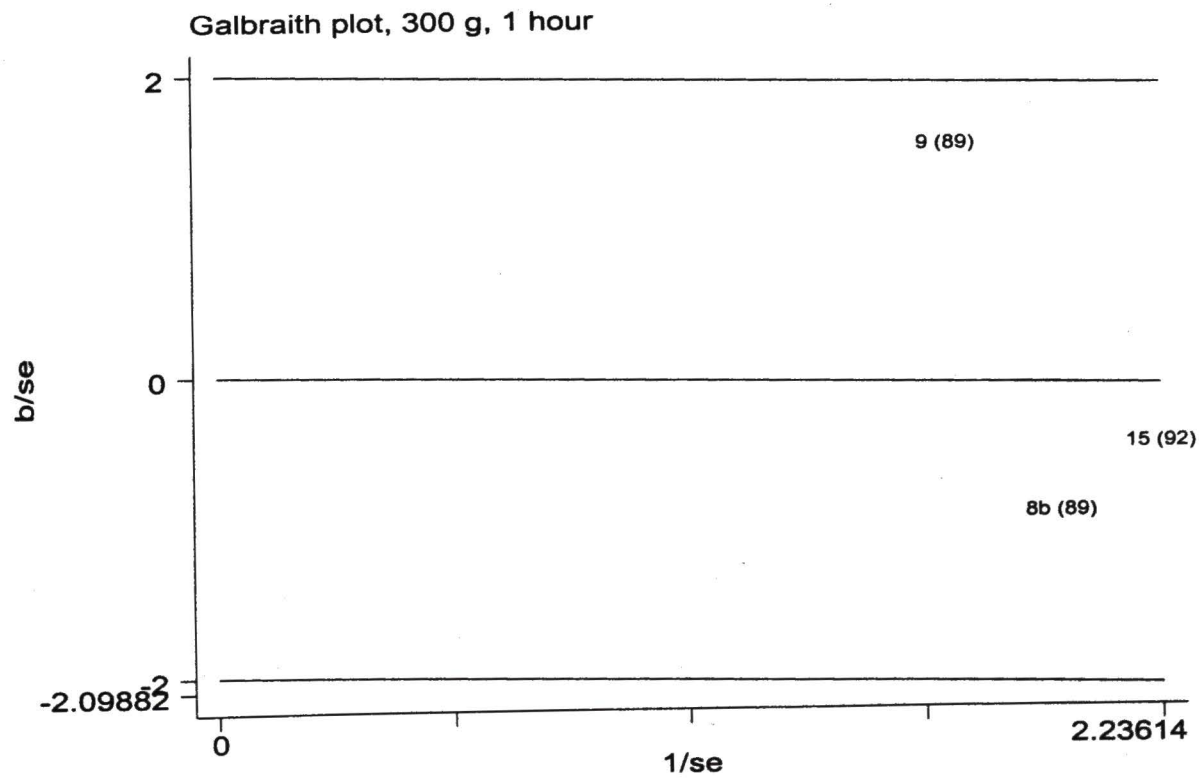
APPENDIX D

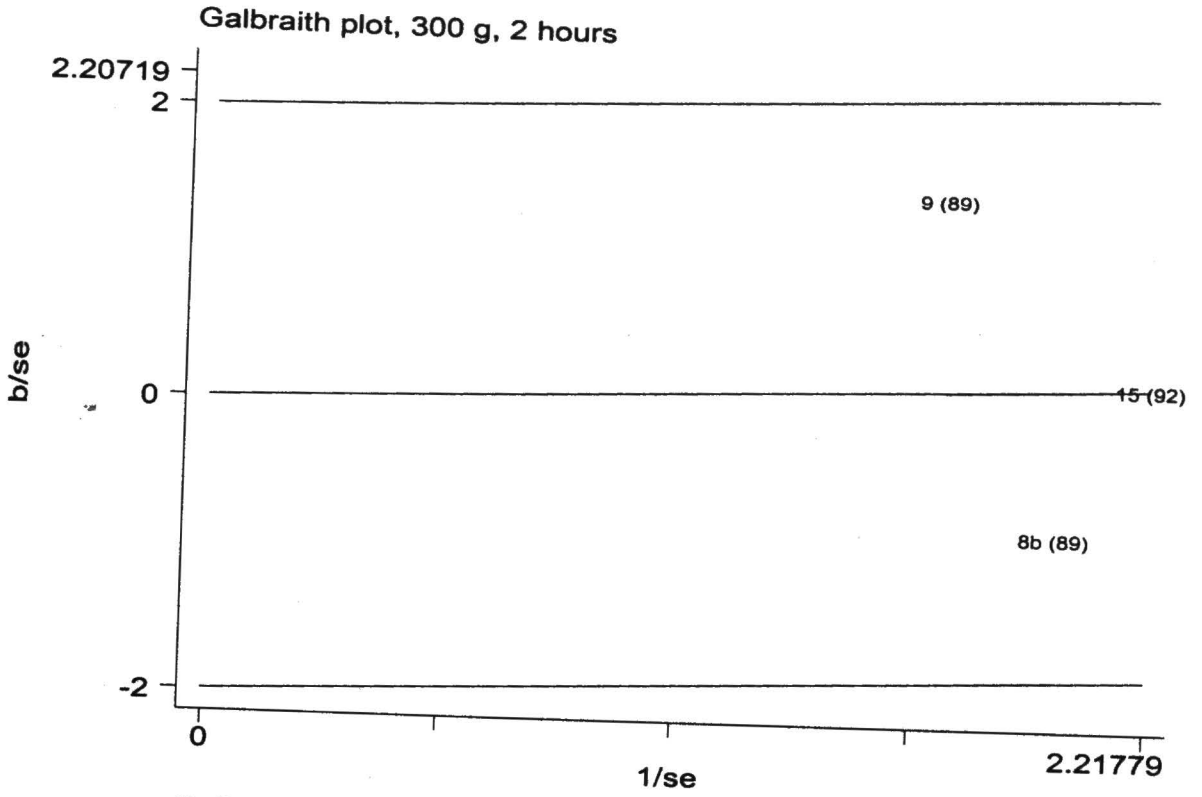
GALBRAITH PLOT

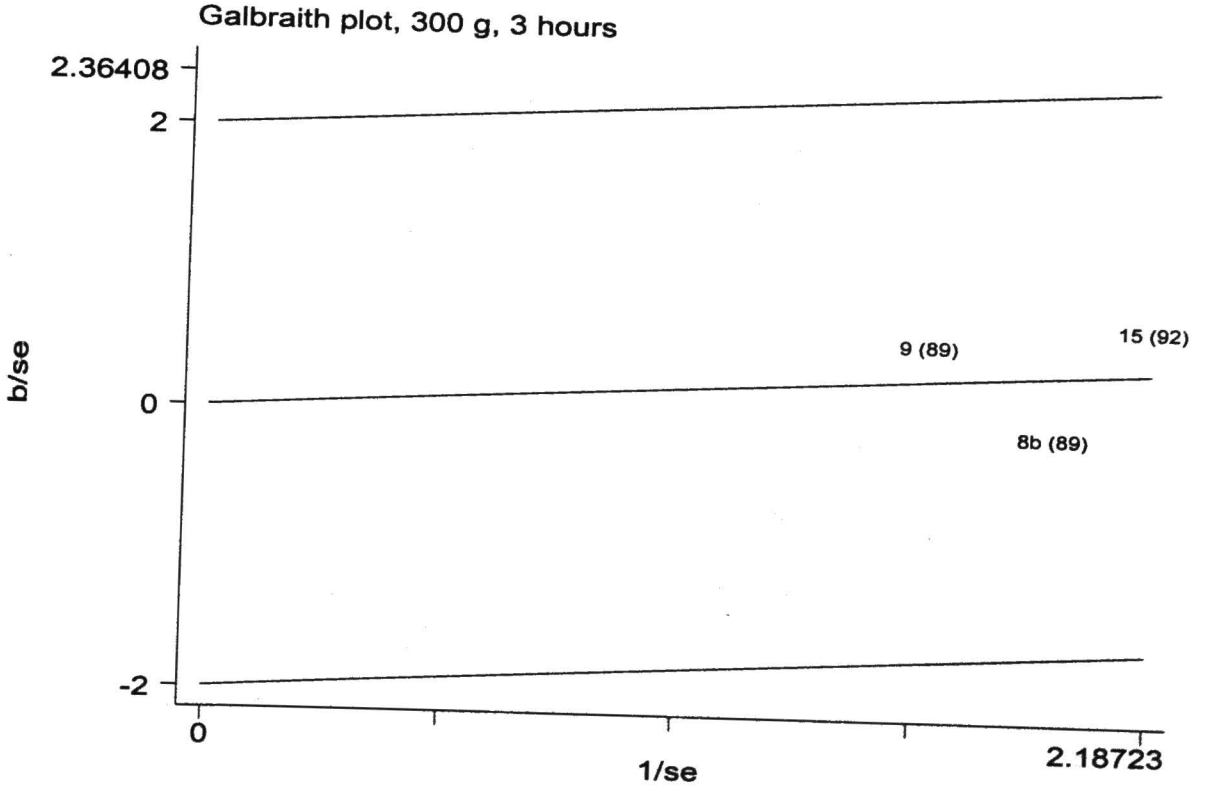

Galbraith plot, 100 g, 1 hour
3.03591
2
0
-2
b/se
2 (83)
7a (88)
3 (84)
8a (89)
4 (86)
0
1.99045
1/se

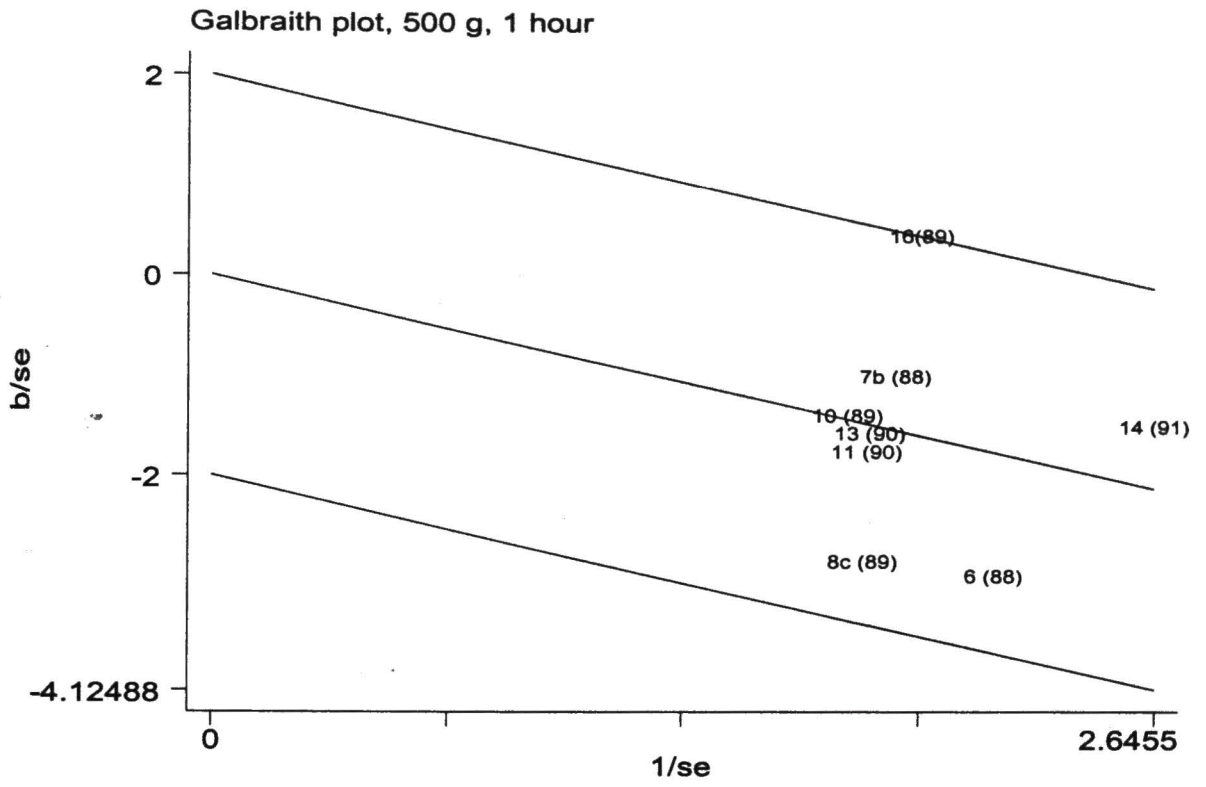

Galbraith plot, 100 g, 2 hours
2
0
-2
-3.24006
b/se
4 (86)
2 (83)
3 (84)
8a (89)
7a (88)
0
1.73671
1/se

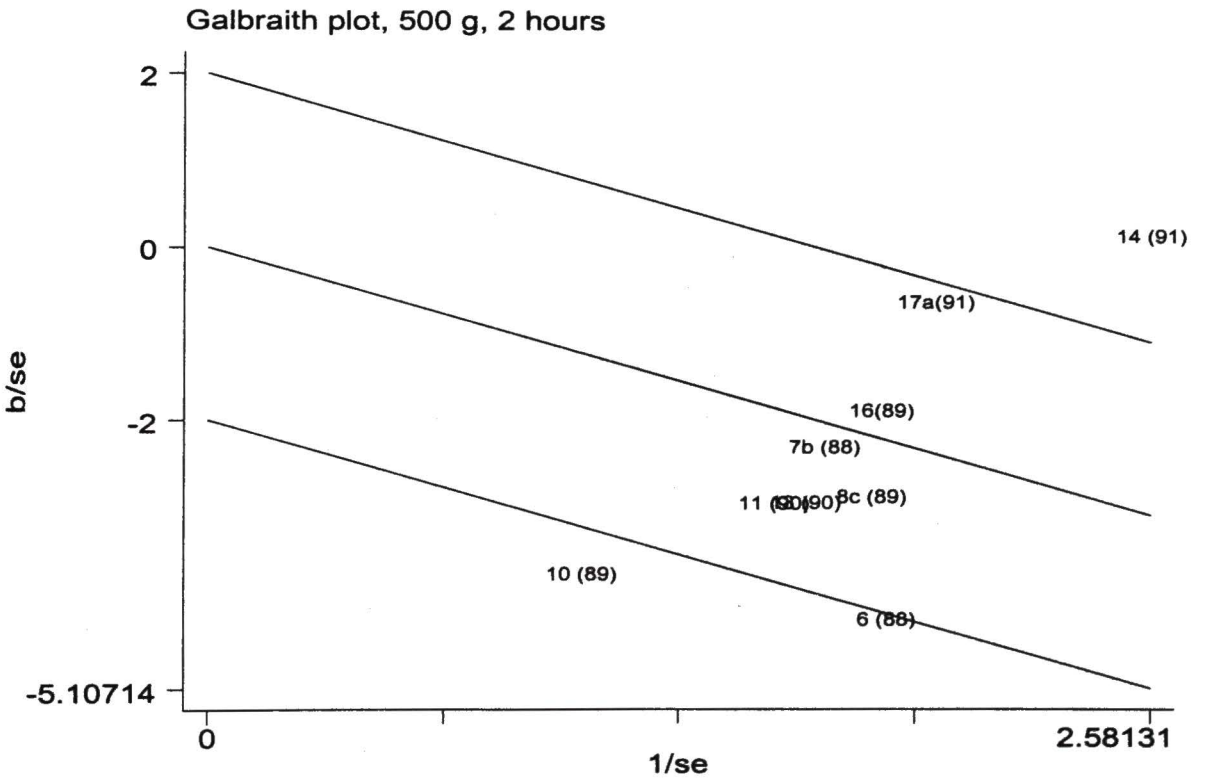

Galbraith plot, 100 g, 3 hours
2
0
-2
-3.30534
b/se
4 (86)
2 (83)
3 (84)
8a (89)
7a (88)
0
1.96967
1/se

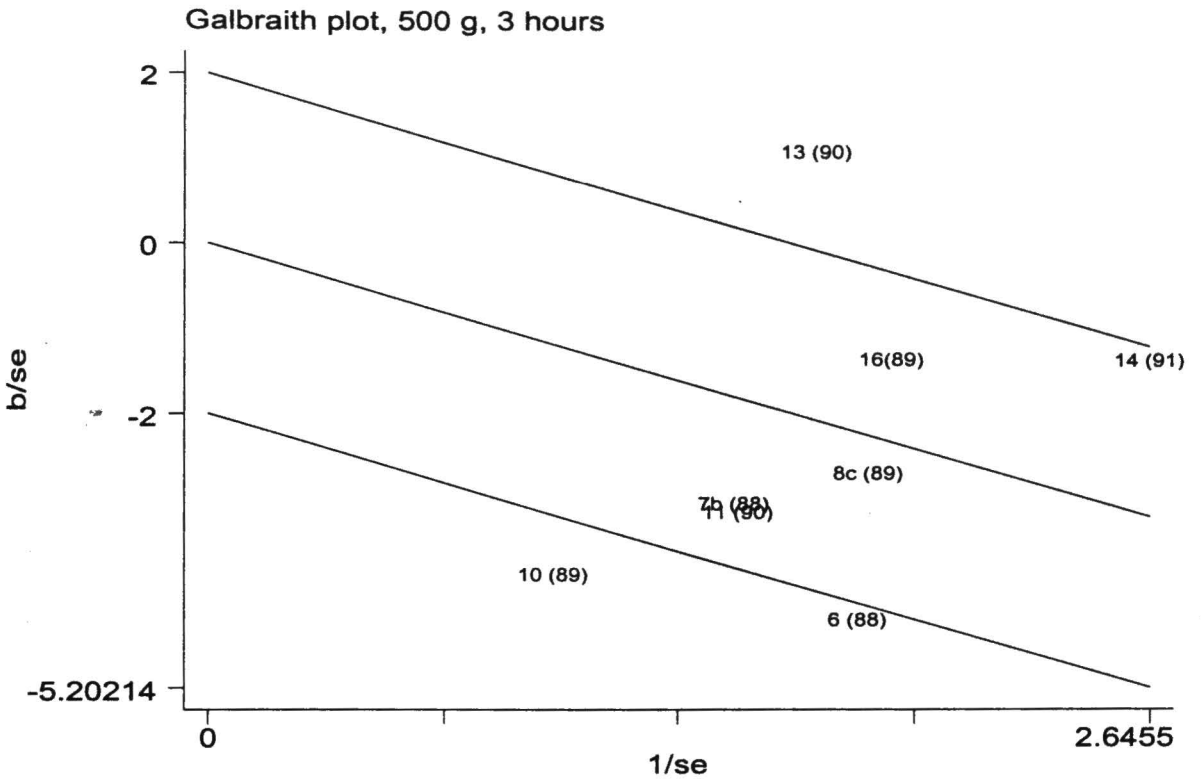

Galbraith plot, 300 g, 1 hour
2
0
-2
-2.09882
b/se
9 (89)
15 (92)
8b (89)
0
2.23614
1/se


Galbraith plot, 300 g, 2 hours
2.20719
2
0
-2
b/se
9 (89)
15 (92)
8b (89)
0
1/se
2.21779


Galbraith plot, 300 g, 3 hours
2.36408
2
0
-2
b/se
9 (89)
15 (92)
8b (89)
0
1/se
2.18723


Galbraith plot, 500 g, 1 hour
2
0
-2
-4.12488
b/se
0
2.6455
1/se
16(89)
7b (88)
10 (89)
13 (90)
11 (90)
14 (91)
8c (89)
6 (88)


Galbraith plot, 500 g, 2 hours
2
0
-2
-5.10714
b/se
0
2.58131
1/se
14 (91)
17a(91)
16(89)
7b (88)
8c (89)
10 (89)
6 (88)


Galbraith plot, 500 g, 3 hours
2
0
-2
-5.20214
b/se
13 (90)
16(89)
14 (91)
8c (89)
7b (88)
11 (90)
10 (89)
6 (88)
0
2.6455
1/se

APPENDIX E

META-ANALYSIS REGRESSION

Meta-regression, dependent variable = 1 hour effect size, independent variables = baseline effect size and dosage

Meta-analysis regression — No of studies = 16

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
dose3	-.0014075	.000977	-1.441	0.150	-.0033224	.0005075
d_t0	.3211931	.3028694	1.061	0.289	-.27242	.9148062
_cons	.0572723	.3888176	0.147	0.883	-.7047962	.8193408

Meta-regression, dependent variable = 2 hour effect size, independent variables = baseline effect size and dosage

Meta-analysis regression — No of studies = 18

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
dose3	-.0006319	.001156	-0.547	0.585	-.0028975	.0016337
d_t0	.1841888	.379457	0.485	0.627	-.5595333	.9279108
_cons	-.6789036	.5193479	-1.307	0.191	-1.696807	.3389995

Meta-regression, dependent variable = 3 hour effect size, independent variables = baseline effect size and dosage

Meta-analysis regression — No of studies = 16

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
dose3	-.0031415	.0021151	-1.485	0.137	-.007287	.001004
d_t0	1.291676	.6501544	1.987	0.047	.017397	2.565955
_cons	.2409263	.825446	0.292	0.770	-1.376918	1.858771

Insulin results

Meta-regression, dependent variable = 1 hour effect size, independent variables = baseline effect size and dosage

Meta-analysis regression — No of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
dose3	-.0056618	.0029824	-1.898	0.058	-.0115072	.0001836
d_t0	.863532	.9033134	0.956	0.339	-.9069298	2.63399
_cons	.4707749	1.260275	0.374	0.709	-1.999319	2.940869

Meta-regression, dependent variable = 2 hour effect size, independent variables = baseline effect size and dosage

Meta-analysis regression — No of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
dose3	-.0047205	.0026148	-1.805	0.071	-.0098454	.0004044
d_t0	1.029677	.817325	1.260	0.208	-.5722502	2.631605
_cons	.3418802	1.076274	0.318	0.751	-1.767577	2.451338

Meta-regression, dependent variable = 3 hour effect size, independent variables = baseline effect size and dosage

Meta-analysis regression — No of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
dose3	-.0022524	.0025753	-0.875	0.382	-.0073	.0027951
d_t0	.9031328	.8143527	1.109	0.267	-.6929692	2.499235
_cons	.3242656	1.13181	0.287	0.774	-1.89404	2.542571

References

American Diabetes Association. (1995). Exchange lists for Meal Planning, Appendix 4: Nutrient Evaluation Database for Mexican American food practices, customs, and holidays. Alexandria, Virginia. pp. 20-30.

American Diabetes Association. (1999). Diabetes Facts and Figures. American Diabetes Association [On-line]. Available: http://www.diabetes.org/ada/facts.asp

Bailey, C. J., & Day, C. (1989). Traditional plant medicines as treatments for diabetes. Diabetes Care, 12, 553-564.

Centers for Disease Control and Prevention, Epidemiology and Statisitics Branch. (1999, January 15). Self-reported prevalence of diabetes among Hispanics in the United States, 1994-1997. Morbidity and Mortality Weekly Report.

Cerveny, J. D., Leder, R. D., & Weart, C. W. (1998). Issues surrounding tight glycemic control in people with type 2 diabetes mellitus. Annals of Pharmacotherapy, 32 (9), 896-905.

Chesney, A. P., Thompson, B. L., Guevara, A., Vela, A., & Schotistaedt, M. F. (1980). Mexican-American folk medicine: Implications for the family physician. The Journal of Family Practice, 11, 567-574.

Cooper, H., & Hedges, L. (Eds.) (1994). The Handbook of Research Synthesis. New York: Russel Sage Foundation.

Davidson, J. (1999). Revised standards for the treatment of type 2 diabetes in Texas. Diabetes Care, 22, 1219.

Deglin, J. H., & Vallerand, A. H. (1999). Davis's drug guide for nurses. (6th ed). Philadelphia: F. A. Davis Co.

Egger, M., Smith, G.D., & Phillips, A.N. (1997). Meta-analysis: Principles and procedures. British Medical Journal, 315, 1533-1537.

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. British Medical Journal, 315, 629-634.

Eisenburg, D. M., Kessler, R. C., Foster, C., Norlock, F. E., Calkins, D. R., & Delbanco, T. L. (1993). Unconventional medicine in the United States: prevalence, costs, and patterns of use. New England Journal of Medicine, 328, 246-252.

Encyclopedia Britannica Online. (2000). Prickly pear cactus. [On-line]. Available: http://search.eb.com/bol/topic?eu=62910&sctn=1

Ernst, E., Resch, K. L., & White, A. R. Complementary Medicine: What physicians think of it: a meta-analysis. Archivals of Internal Medicine, 155, 2405-2408.

Fagard, R. H., Staessen, J. A., & Thijs, L. (1996). Advantages and disadvantages of the meta-analysis approach. Journal of Hypertension, 14, (Suppl. 1), 9-12.

Fernandez, M. L., Lin, E. C. K., Trejo, A., & McNamara, D. (1992). Prickly pear pectin reverses low density lipoprotein receptor suppression induced by a hypercholesterolemic diet in guinea pigs. Journal of Nutrition, 122, 2330-2339.

Fernandez, M. L., Lin, E. C. K., Trejo, A., & McNamara, D. (1993). Prickly pear pectin alters hepatic cholesterol metabolism without affecting cholesterol absorption in guinea pigs fed a hypercholestrolemic diet. Journal of Nutrition, 33, 817-823.

Fernandez, M. L., Trejo, A., & McNamara, D. (1990). Pectin isolated from prickly pear modifies low density lipoprotein metabolism in cholesterol-fed guinea pigs. Journal of Nutrition, 120, 1238-1290.

Fishman, B. M., Bobo, L., Kosub, K., & Womeodu, R. J. (1993). Cultural issues serving the minority populations: emphasis on the Mexican Americans and African Americans. The American Journal of the Medical Sciences, 306, 160-166.

Haffner, S. M. (1998). Epidemiology of type 2 diabetes: risk factors. Diabetes Care, 21, (Suppl. 3), 3-5.

Haffner, S. M., Mitchell, B. D., Stern, M. P., & Hazuda, H. (1991). Macrovascular complications in Mexican Americans with type II diabetes. Diabetes Care, 14, 665-670.

Hanis, C. L., Ferrell, R. E., Barton, S. A., Aguilar, L., Garza-Ibarra, A., Tulloch, B. R., Garcia, C., A., & Schull, W. J. (1983). Diabetes among Mexican Americans in Starr County, Texas. American Journal of Epidemiology, 118, 659-671.

Hanis, C. L., Hewett-Emmett, D., Bertin, T. K., Schull, W. J. (1991). Origins of U.S. Hispanics. Diabetes Care, 14, 618-626.

Harris, M. I. (1998). Diabetes in America: Epidemiology and scope of the problem. Diabetes Care, 21, (Suppl. 3), 11-14.

Harris, M. I., Eastman, R. C., Cowie, C. C., Flegal, K. M., & Eberhardt, M. S. (1999). Racial and ethnic differences in glycemic control of adults with type 2 diabetes. Diabetes Care, 22, 403-408.

Harris, M. I., Flegal, K. M., Cowie, C. C., Eberhardt, M. S, Goldstein, D. E., Little, R. R., Wiedmeyer, H. M., & Byrd-Holt, D. D. (1998). Prevalence of diabetes, impaired fasting glucose and impaired glucose tolerance in U. S. Adults. Diabetes Care, 21, 518-524.

Hayward, R. A., Manning, W. J., Kaplan, S. H., Wagner, E. H., & Greenfield, S. (1997). Starting insuline therapy in patients with type 2 diabetes. Journal of the American Medical Association, 278, 1663-1669.

Ibanez-Camacho, R., Meckes-Lozoya, M., & Mellado-Campos, V. (1983). The hypoglycemic effect of *Opuntia* cactus. Archivos de Investigacion Medica, 10, 223-230.

Ioannidis, J. P. & Lau, J. (1999). Pooling Research Results: Benefits and Limitations of Meta-Analysis. Joint Commission on Quality Improvement, 25 (9), 462-469.

Ivorra, M.D., Paya, M., & Villar, A. (1989). A review of natural products and plants as potential antidiabetic drugs. Journal of Ethnopharmacology, 27, 243-275.

Jonsson, B. (1998). The economic impact of diabetes. Diabetes Care, 21, (Suppl. 3), 7-10.

Klein, R., & Klein, B. E. K. (1998). Relation of glycemic control to diabetic complications and health outcomes. Diabetes Care, 21, (Suppl. 3), 39-43.

L'Abbe, K. A., Detsky, A. S., & O'Rourke, K. (1987). Meta-Analysis in Clinical Research. Annals of Internal Medicine, 107, 224-233.

Loyoza, X. (1994). Two decades of Mexican ethnobotany and research in plant drugs. Mexican Ethnobotany, 185, 130-140.

Manson, J. E., Ridker, P. M., Gaziano, J. M., & Hennekens, C. H. (Eds.). (1996). Prevention of Myocardial Infarction. New York: Oxford University Press.

Marsh, W. W., & Hentges, K. (1988). Mexican folk remedies and conventional medical care. American Family Physician, 37, 257-262.

Martini, F. H., & Welch, K. (1998). Applications Manual: Fundamentals of Anatomy & Physiology. (4th ed.). New Jersey: Prentice Hall.

Meckes-Lozoya, M., & Ibanez-Camacho, R. (1989). Hypoglycaemic activity of *Opuntia streptacantha* throughout its annual cycle. American Journal of Chinese Medicine, 27, 221-224.

Meckes-Lozoya, M., & Roman-Ramos, R. (1986). *Opuntia streptacantha*: A coadjutor in the treatment of diabetes mellitus. American Journal of Chinese Medicine, 14, 116-118.

Mulrow, C. D., & Oxman, A. (Eds.). (1997). Cochrane Collaboration Handbook. In: The Cochrane Library. The Cochrane Collaboration. Oxford: 1997, Issue 4.

Munoz de Chavez, M., Chavez, A., Valles, V., & Roldan, J. A. (1995). The Nopal: a plant of manifold qualities. World Review of Nutritional Diets, 77, 109-134.

National Institutes of Health, National Center for Complementary and Alternative Medicine. (1999). Frequently Asked Questions. [On-line]. Available: http://nccam.nih.gov/nccam/fcp/faq

Noel, P. H., Pugh, J. A., Larme, A. C., & Marsh, G. (1997). The use of traditional plant medicines for non-insulin dependent diabetes mellitus in south Texas. Phytotherapy Research, 11, 512-517.

Oubre, A.Y., Carlson, T.J., King, S.R., & Reaven, G.M. (1997). From plant to patient: an ethnomedical approach to the identification of new drugs for the treatment of NIDDM. Diabetologica, 40, 614-617.

Ramirez, G., & Aguilar, C. (1995, September). The effect of Opuntia in lowering serum glucose among NIDDM. A systematic review-preliminary findings. Paper presented at the first annual conferences, Professional Association for Cactus Development, San Antonio, Texas.

Ravussin, E., Valencia, M. E., Esparza, J., Bennett, P. H., & Schulz, L. O. (1994). Effects of a traditional lifestyle on obesity in Pima Indians. Diabetes Care, 17, 1067-1074.

Rayburn, K., Martinez, R., Escobedo, M., Wright, F., & Farias, M. (1998). Glycemic Effects of various species of Nopal in type 2 diabetes mellitus. Texas Journal of Rural Health, 16, 68-76.

Stern, M. P., Knapp, J. A., Hazuda, H. P. Haffner, S. M., Patterson, & J. K., Mitchell, B. D. (1991). Genetic and environmental determinants of type II diabetes in Mexican Americans. Diabetes Care, 14, 649-653.

Sugarman, J., & Burk, L. (1998). Physicians' ethical obligations regarding alternative medicine. Journal of the American Medical Association, 280, 1623-1626.

Swanston-Flatt, S. K., Flatt, P. R., Day, C., & Bailey, C. J. (1991). Traditional dietary adjuncts for the treatment of diabetes mellitus. Proceedings of the Nutritional Society, 50, 641-651.

Testa, M. A., & Simonson, D. A. (1998). Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus. Journal of the American Medical Association, 280, 1490-1496.

Texas Department of Health (1998). Texas Diabetes Council: Texas Diabetes Fact Sheet 1998. [On-line]. Available: http://www.tdh.state.tx.us/diabetes/factshee.html

Thomas, C. L. (Ed.). (1993). Taber's Cyclopedic Dictionary (17th ed.). Philadelphia: F. A. Davis Company.

Thorburn, A. W., Brand, J. C., & Truswell, A. S. (1987) Slowly digested and absorbed carbohydrate in traditional bushfoods: a protective factor against diabetes? American Journal of Clinical Nutrition, 45, 98-106.

Trejo-Gonzalez, A., Gabriel-Ortiz, G., Puebla-Perez, A. M., Huizar-Contreras, M. D., Munguia-Mazariegos, M. R., Mejia-Arreguin, S., & Calva, E. (1996). A purified extract from prickly pear cactus controls experimentally induced diabetes in rats. Journal of Ethnopharmacology, 55, 27-33.

U.K. Prospective Diabetes Study Group (1998). Intensive blood glucose with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet, 352, 837-851.

United States Census Bureau (1999, March). Current Population Reports: The Hispanic Population in the United States. [On-line]. Available: http://www.census.gov

United States Census Bureau (1998, September). Census Bureau Facts for Features. [On-line]. Available: http://www.census.gov/Press-Release/cb98-ff.11.html

Urdaneta, M. L, & Krehbiel, R. (1989). Cultural heterogeneity of Mexican Americans and its implications for the treatment of diabetes mellitus type II. Medical Anthropology, 11, 269-282.

Vijan, S., Hofer, T. P., & Hayward, R. A. (1997). Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Annals of Internal Medicine, 127, 788-794.

Winkelman, M. (1989). Ethnobotanical treatments of diabetes in Baja California Norte. Medical Anthropology, 11, 255-268.

World Health Organization, Diabetes Programme. (2000, March). Diabetes database. [On-line]. Available: http://www.who.int/ncd/dia/database2.html