ACUPUNCTURE FOR TREATMENT OF OBESITY AND INSULIN RESISTANCE

By

ANGELA WU

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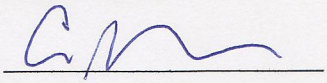

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Department of Physiology

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Abstract

Obesity is a serious problem in our modern society that is associated with many economic and social burdens. Complications related to obesity such as cardiovascular disease and type 2 diabetes are leading causes of death in the United States, and also carry heavy medical costs. A state of obesity is often accompanied by a state of insulin resistance that can eventually lead to type 2 diabetes. If the prevalence of obesity or insulin resistance can be reduced, the progression to type 2 diabetes may be slowed or reversed. There are many drugs that treat those two conditions, but they all have potential adverse side effects. Acupuncture, a popular technique used in traditional Chinese medicine that inserts sharp needles to adjust the flow of Qi within the body, has been suggested as a viable and inexpensive alternative treatment for obesity and insulin resistance, and is rarely linked to adverse events. While promising, existing studies on the efficacy of acupuncture in treating obesity and insulin resistance are inconclusive and often poorly designed. This thesis will examine the background of acupuncture and etiology of obesity and type 2 diabetes, and propose a study design to confirm the effectiveness of acupuncture as a treatment.

Background

Epidemiology of Obesity and Prevalence in the US

Obesity, defined by the World Health Organization (WHO) as "abnormal or excessive fat accumulation that presents a risk to health", has become an increasing problem in our modern society and associated with many economic and social costs (36). The most common method of diagnosing and measuring obesity is through the use of Body Mass Index (BMI), calculated from the subject's weight and height, as an estimate of body fat. The NIH determines that a BMI score for adults between 25.0 and 29.9 is considered overweight, above 30.0 is obese, and above 40.0 is extremely obese (23). The BMI assessment for children is organized differently because they are still growing and maturing. They are measured with BMI-for-age percentile which takes into account growth charts of their age and sex, and compares them to other children of the same age (23). Although BMI is a common measurement tool, it has drawbacks because it does not differentiate between muscle weight and fat weight, so athletes with large amounts of muscle mass could have a BMI score falsely indicating obesity. Another method of determining overweight and obesity is measuring waist circumference, as it is an indicator of health risks that accompany an excess of abdominal and waist fat. The International Diabetes Federation considers a waist circumference of greater than 80 centimeters in women and greater than 94 centimeters in men to indicate obesity in Europids. For people of Asian origin, the cutoff is greater than 80 centimeters and 90 centimeters for women and men, respectively (50). The US, however, follows the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) statement of 2001 that considers greater than 88 centimeters in women and 102 centimeters in men to represent abdominal obesity, regardless of ethnicity (50). Another common

measurement of obesity is waist-to-hip ratios. The WHO recommends values greater than 0.85 to indicate obesity in women, and greater than 0.9 in men (39).

The prevalence of obesity among the world's adult population has almost doubled since 1980, up to 10%, and the incidence of childhood obesity increased 60% since 1990. Over 40 million children under the age of five were overweight in 2011, and over 1.4 billion adults aged 20 years and older were overweight, with nearly 500 million of those adults considered obese (37). In the US, more than one-third of the adult population are obese and this number has been projected to reach 42% by 2030 (39). This actually still represents a slowing in the progression of the obesity epidemic, which was once predicted to reach 51% of the US population by 2030 (21).

Overweight and obesity are leading risk factors for global deaths, and were found to be responsible for more deaths worldwide than underweight (37). The top seven leading causes of death in the US in 2010 were heart disease, cancer, chronic lower respiratory disease, stroke, accidents, Alzheimer's disease, and diabetes (26). Besides unintentional injuries from accidents, obesity is a potential contributing factor to all other causes of death. According to the WHO, overweight and obesity can be associated with the development of ~44% of cases of diabetes, 23% of ischemic heart disease, and between 7% and 41% of certain cancer burdens (26). Increased fat mass is associated with increased blood pressure and levels of low-density lipoprotein, cholesterol, and triglycerides in the blood (39). This in turn increases the risk for heart disease and atherosclerosis of blood vessels, leading to stroke and cardiac arrest. The connection between obesity and cancer is less direct because cancer is affected by many factors, but studies have shown that obesity can contribute to the development of certain cancer types such as endometrial, prostate, and renal cancer (43). Lung function can be physically impaired

by the accumulation of visceral fat lowering the flexibility of the chest wall, and the metabolic function of the alveoli can be impeded through an increase in inflammatory cytokines released in the obese state (47). Obesity has even been associated with a 42% higher risk for Alzheimer's disease (8).

Most importantly, obesity strongly influences the etiology of Type 2 diabetes. The increased amount of fat cells, especially abdominal adiposity, in obesity affects many processes in the body. Adipocytes secrete a variety of hormones called adipokines and substances that promote inflammation, which can reduce the body's sensitivity to insulin and negatively affect the way the body metabolizes fats and carbohydrates (39). Obesity and abdominal adiposity are also key factors in the Metabolic Syndrome, a group of cardiovascular and metabolic disease risk factors that include hypertension, dyslipidemia, and high blood sugar due to insulin resistance (38).

With the prevalence of many chronic diseases that are perpetuated by obesity, this trend also translates into a high economic burden on society as these diseases require expensive treatment over a long period of time. A 2010 study estimated that US-wide annual cost of excess medical spending attributable to obesity is $86-$147 billion, and obese individuals may have 36%-100% higher medical costs relative to normal weight individuals. Childhood obesity is also creating $14.3 billion in direct medical costs annually (20). There is immense concern over the high US health-care costs, which constitute 17.7% of our GDP, higher than any other industrialized country in the world (19). Considering the additional medical costs accrued by diseases related to obesity, attempts to reduce overall healthcare spending in the US needs to emphasize the reduction of the US obese population. Beyond these direct costs, there are additional indirect costs, defined as "resources forgone as a result of a health condition". Obese

individuals may have higher absenteeism, long-term disability, premature death rates, and higher life insurance premiums than non-obese workers (39). Research also shows that the extra weight carried by obese people results in excess fuel being used during transportation amounting to billions of dollars (20). From both an economic and health standpoint, obesity is a significantly detrimental condition that necessitates action and treatment.

Type 2 Diabetes Mellitus Background

Diabetes is a disease hallmarked by hyperglycemia due to a complex cluster of metabolic dysfunctions. The four clinical categories of diabetes include type 1 diabetes mellitus, type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and other specific types of diabetes (4). Type 1 diabetes mellitus is characterized by total destruction of pancreatic β-cells, and thus complete insulin deficiency. T2DM manifests as insulin secretory defects coupled with insulin resistance, defined as a reduced response of tissues to the actions of insulin (15). GDM occurs during pregnancy when elevated blood glucose levels may develop, but is usually transient and generally resolves after birth. However, it can increase risk for developing T2DM when improperly controlled (4). T2DM is the most prevalent of these categories, associated with 90-95% of diagnosed diabetes cases (2). The 2011 National Diabetes Fact Sheet estimated that 18.8 million diagnosed and 7 million undiagnosed people in the United States, 8.3% of the population, have diabetes (34). New cases are diagnosed every year, and 79 million people have pre-diabetes, an intermediate group with elevated glucose levels below the diagnosis criteria for diabetes (see below) (34).

Common risk factors for T2DM include increasing age, obesity (especially visceral abdominal adiposity), sedentary lifestyle, hypertension, dyslipidemia, prior diagnosis of GDM,

genetic predisposition, family history of diabetes, and certain racial/ethnic groups (2). From a 2007-2009 national survey and Indian Health Services information on patients ages 20 and older, 14.2% of Native-American Indians and Alaskan natives, 12.6% of non-Hispanic blacks, 11.8% of Hispanics, 8.4% of Asian Americans, and 7.1% of non-Hispanic whites had diagnosed diabetes (34). This data clearly indicates certain ethnic groups are at a higher risk for diabetes.

The condition of diabetes carries further risk for microvascular and macrovascular diseases. Microvascular complications include retinopathy, nephropathy, and neuropathy, which lead to blindness, end-stage renal disease, and limb amputations (45). Macrovascular complications include cardiovascular diseases such as stroke and ischemic heart disease (45). Altogether, the American Diabetes Association (ADA) estimated the total economic burden of diagnosed diabetes in the US in 2012 to be $245 billion. This estimate showed a 41% increase from the 2007 estimate of $174 billion, and costs associated with diabetes will continue to rise with the upward trend of diabetes prevalence and diagnosis (3).

Many techniques exist for the diagnosis of diabetes, and generally involve measuring blood glucose to make inferences about insulin sensitivity. The hyperinsulinemic-euglycemic clamp is the gold standard for measuring insulin sensitivity in research settings (31). The procedure requires overnight fasting of the participant and then intravenous infusion of insulin, raising circulating levels of insulin and glucose to maintain the euglycemic state. Blood glucose levels are maintained as steady as possible, and plasma glucose is measured in regular intervals. This information is used to determine the glucose disposal rate. Low glucose disposal rates characterize an individual with insulin resistance (31). However, this procedure is difficult to implement in clinical practice and studies of large populations due to the cost and complicated experimental setup.

Current common diagnostic measures recommended by the ADA are the glycated hemoglobin test (HbA1c), fasting plasma glucose (FPG), and oral glucose tolerance test (OGTT) (4). The HbA1c test reflects average blood glucose over the past 2-3 months (A1c level ≥ 6.5% is diagnostic), and is more convenient than other tests because no fasting is required (16). However, it has greater cost, may vary with race/ethnicity and certain blood abnormalities (anemia, hemoglobin variation, hemolysis), requires a certified lab setting which is not widely available, and has questionable precision. This latter issue has led the WHO to reject it as an appropriate diagnostic test (4, 14). FPG is a measure of glucose levels after fasting for at least 8 hours before the test (FPG ≥ 126 mg/dL is diagnostic), and is the main diagnostic test favored by the ADA (4, 16). The OGTT measures glucose levels before and after ingestion of a sugary drink (two-hour PG ≥ 200mg/dL is diagnostic) (16). The WHO highly recommends the OGTT as a supplementary diagnostic tool alongside the FPG despite greater cost and inconvenience, because studies found that FPG alone failed to diagnose 30% of diabetes cases (14). The two tests can diagnose diabetes in individuals who may have developed the disease due to different factors such as abnormal liver glucose production, skeletal muscle insulin resistance, and beta cell dysfunction (14). A combination of tests would provide the greatest accuracy in diagnosing diabetes, but at a higher cost.

Development and Pathogenesis of T2DM

The progression to T2DM is an accumulation of metabolic disorders, and can result from chronic insulin resistance creating hyperglycemia and impaired β-cell function, or inherent β-cell dysfunction with elevated insulin secretion leading to insulin resistance (44). Weir's multistage model of diabetes development describes an initial period of insulin resistance and compensatory insulin secretion, followed by an inability of β-cells to fully compensate and decreased insulin

secretion. Then, there is a complete inability to compensate for the insulin resistance, with a rapid increase of blood glucose concentrations and finally progression to full-blown diabetes with a reduction of β-cell mass through apoptotic cell death (52). The early stages of development can be associated with pre-diabetes (7). Pre-diabetic individuals may have impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), which are defined by the ADA as FPG levels of 100-125 mg/dL and 2-hour OGTT levels of 140-199 mg/dL, respectively (2). IFG, characterized by elevated fasting glucose levels, is related to hepatic insulin resistance, where elevated levels of glucose production are maintained through glycogenolysis and gluconeogenesis (15). There is also an impaired early insulin response during a glucose challenge, but the late-phase insulin response is retained, associated with a return of plasma glucose levels to baseline by the 2-hour time point during the OGTT (7). IGT mainly reflects skeletal muscle insulin resistance with a completely impaired insulin response to the glucose stimulus, resulting in a steady rise in plasma glucose levels during the OGTT (7). Skeletal muscles are the major sites of action by insulin for stimulating glucose uptake from the bloodstream, and contribute more to whole body insulin sensitivity than the liver (15). Therefore, subjects with IGT generally have greater whole body insulin resistance than subjects with IFG pre-diabetes alone (44). The different pathogenesis of IFG and IGT pre-diabetes may dictate different therapeutic targets for treatment. Reversal of pre-diabetes is important for preventing diabetes because the yearly progression rate to diabetes from pre-diabetes is 3.5-7.0% (44).

Components of the metabolic syndrome including abdominal obesity, hyperglycemia, and dyslipidemia are important contributors to insulin resistance, and patients diagnosed with metabolic syndrome carry a 2- to 4- fold increased risk for developing T2DM (41). Excess visceral abdominal obesity seems especially crucial because 90% of diagnosed T2DM patients

are overweight or obese (41). Adipose tissue releases a variety of anti- and pro-inflammatory adipokines and cytokines. Anti-inflammatory adipokines include adiponectin, TGFβ, and interleukin (IL)-10, and pro-inflammatory cytokines include TNF-α, leptin, and resistin (30). Obesity is a chronic state of low-grade inflammation characterized by increased circulation of pro-inflammatory cytokines and decreased levels of anti-inflammatory adipokines (30). Adiponectin improves insulin sensitivity and glucose metabolism, and can prevent chronic inflammation through down-regulation of TNF-α (30). IL-10 is important in preventing the synthesis of pro-inflammatory cytokines by immune cells (30). TNF-α contributes to insulin resistance by facilitating phosphorylation of insulin receptor substrate-1 (IRS-1), causing disruption of insulin signaling pathways and promoting lipolysis, which increases hepatic glucose production (30). Free fatty acids (FFAs) from lipolysis also inhibit the expression and translocation of the glucose transporter isoform GLUT4 in skeletal muscle (7). Leptin regulates food intake and energy balance, but fails to maintain homeostasis in obese individuals despite high circulating plasma levels due to leptin resistance. It also up-regulates expression of pro-inflammatory cytokines by immune cells (30). Resistin induces insulin resistance by stimulating secretion of other pro-inflammatory factors as well (30).

Current theory suggests that obesity, through elevated inflammatory cytokines, causes accumulation of misfolded/unfolded proteins in the endoplasmic reticulum (ER), a condition referred to as ER stress (27). The ER uses the unfolded protein response (UPR) to remove defective proteins, but the branches of UPR action can trigger inflammatory signal activation of the c-Jun-N-terminal kinases (JNKs) and nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) pathways (33). These pathways increase expression of pro-inflammatory cytokines in β-cells, and along with the cytokines released by visceral abdominal adipocytes, can further

induce ER stress (33). Chronic hyperglycemia from insulin resistance also leads to ER stress due to high demand of pro-insulin synthesis to produce high circulating levels of insulin, and severe cellular stress in β-cells can result in apoptosis (11). Oxidative stress related to the JNK pathway has been associated with decreased binding of pancreatic transcription factor PDX-1 to promoters, thus reducing insulin gene expression (24). Long-term elevated demand for insulin increases mitochondrial metabolic activity, inducing oxidative stress in the mitochondria and producing reactive oxygen species (ROS) that are especially damaging to β-cells, which have low levels of antioxidant enzymes (33). When coupled with hyperglycemia, increased FFA levels can cause lipotoxicity in β-cells, because the FFAs are not completely oxidized in the mitochondria, and non-oxidative FFA metabolism end products can be toxic to β-cells (7). These mechanisms result in lower insulin production and β-cell apoptosis, and create major insulin secretory defects.

Another important molecular mechanism for insulin action involves two incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) (24). β-cells contain incretin receptors that bind these hormones, causing an increase in intracellular cyclic AMP (cAMP), stimulating enhancement of insulin secretion, which is important immediately after a meal (24) Incretins up-regulate insulin gene transcription by increasing expression of the PDX-1 transcription factor, and GLP-1 increases the expression of the glucose transporter isoform GLUT2 to maintain insulin production and secretion in β-cells (7). Furthermore, incretins promote proliferation and growth of β-cells while suppressing apoptosis (24). In a diabetic state, the circulating levels of GLP-1 and GIP remain normal, but hyperglycemia down-regulates expression of the incretin receptors, thus reducing their effects (24). The combination of inflammatory factors, cellular stress, and inhibition of pro-survival

signals primes the β-cell for dysfunction and death in the final stages of the development of T2DM.

T2DM Treatments and Interventions

The most common methods for controlling and preventing T2DM are lifestyle interventions and pharmacological drug treatments (5, 32, 46, 48). Lifestyle changes are highly recommended for diabetes prevention because they have been proven effective and are less invasive. The large scale Diabetes Prevention Program (DPP) studied the effects of lifestyle changes of exercise and a low calorie, low-fat diet, versus the use of metformin, an oral anti-diabetic drug that is widely recommended as a first-line intervention for individuals with high risk for diabetes (17). Every participant had IGT, and 33% also had IFG at the onset of the study (17). The study found that lifestyle changes significantly improved cardiovascular disease risk factors and reduced incidence of diabetes and metabolic syndrome while metformin treatment had less efficacy (17). Despite the effectiveness demonstrated in this study, long-term maintenance of lifestyle changes by individual subjects can be difficult, and many will regain weight in the long term (7). Also, the DPP only included patients with IGT or IGT and IFG, so these results cannot be generalized to the population of people with isolated IFG, which has a different pathogenesis mechanism than IGT.

Metformin acts mainly by decreasing hepatic glucose production through inhibiting gluconeogenesis and improving insulin sensitivity (5). It has no effect on β-cell proliferation and insulin secretion, and causes minor gastrointestinal side effects in some cases (7). Although it is widely recommended, metformin does not consistently produce targeted diabetes control, and the clinical effectiveness is not well-established (10).

Thiazolidinediones (TZDs) bind the peroxisome proliferator-activated receptor-γ (PPAR-γ), which is involved in lipid metabolism, improves insulin sensitivity by reducing circulating FFAs, and slows destruction of β-cells (7). Rosiglitazone had a 60% reduction in diabetes incidence, and pioglitazone had a 70% reduction in patients with IGT, but both drugs are associated with weight gain and greater chance of congestive heart failure (7). Prolonged pioglitazone use may even be associated with increased risk of bladder cancer (48). Rosiglitazone is banned in Europe and under restricted use in the US (5).

GLP-1 analogs reduce hepatic glucose production and improve the GLP-1 response to protect and restore β-cell function and induce weight loss, but can cause nausea and vomiting (7). There is also risk for developing pancreatic cancer, and the clinical effectiveness has not yet been proven (4). DPP-IV inhibitors aim to increase the effect of incretins by inhibiting their degradation by DPP-IV, but no long-term studies exist (10).

Insulin secretagogues, such as meglitinides and sulfonylureas, bind to β-cells to stimulate the release of insulin and counteract the insulin secretory defect component of T2DM (48). However, both drugs have an increased risk of hypoglycemia and weight gain (5). Also, glycemic control is lost after long-term therapy and β-cell function continues to decline (7). Sulfonylureas still have debatable clinical efficacy, and may even be associated with cardiovascular toxicity (10). Direct insulin therapy is the most effective in lowering blood glucose, but can have increased risk of hypoglycemic episodes and weight gain, and does not demonstrate β-cell protective functions (46).

Unfortunately, the efficacy of currently available treatments for T2DM is limited by patient compliance, sufficient clinical proof, and often dangerous side effects. There is a need for safer and effective T2DM treatments and measures to prevent its development.

Traditional Chinese Medicine Theory and Acupuncture Background

Acupuncture has an immensely long history that traces back ten thousand years to the Stone Age when the first acupuncture needles were sharp stones. These devices later advanced into animal bone needles and then finally metal needles (9). The original classical texts detailing the practice of Traditional Chinese Medicine (TCM) and acupuncture first appeared around 1500 years ago during the Warring States Period (22). Among these texts is the famous *Yellow Emperor's Classic of Internal Medicine* (Huang Di Neijing), which includes the earliest record of simple obesity in Chinese literature (9). In this early text, the authors already began to demonstrate an understanding of different forms of obesity. They described types of obesity as fat and strong, fat and greasy, or constitutionally fat, which can be understood in modern medicine as hereditary obesity (9). Although there are some similarities and connections between Western medicine and Chinese medicine, the basic theory, language, and approach to diagnosis in TCM is significantly different.

Western medicine is dependent on hard scientific proof, including detailed physiology and anatomy. Chinese medicine has origins in the religion and beliefs of ancient people, and is heavily influenced by the concept of balance and cycles that were observed in nature (22). TCM recognizes five internal organs: lungs, spleen, kidneys, heart, and liver. These organs are believed to be responsible for the production, transformation, and movement of Blood and Qi, a form of vital energy, rather than the standard physiological functions understood by Western medicine. The lungs govern “clean” Qi that is obtained from respiration and “dirty” Qi that is expired, and controls the descending of this Qi. The spleen transforms the nutrients from food into Qi and is a cornerstone in the process of digestion. Kidneys are responsible for storing prenatal Qi, making them essential to life and a foundation for congenital constitution, and

govern fluids in the body. The heart transforms Qi into Blood, governs circulation, and stores the Mind and Spirit. The liver stores Blood and is critical in the regulation of smooth Qi flow throughout the body (22).

Most diseases are attributed to dysfunction in one or more of the internal organs and their related systems, resulting in imbalance and interference in natural Qi flow, which produces the state of illness. During diagnosis, the imbalances of the disease will be characterized according to four pairs of related conditions: interior/exterior, cold/hot, deficiency/excess, Yin/Yang. Interior or exterior refers to the location of the problem, either within the internal organs and bones or on the surface in areas like muscle and skin. Conditions can be classified as cold, associated with symptoms such as shivering and feelings of coldness, or hot, associated with inflammation and fever. The illness can also either be a deficiency or excess of Qi, and the result of an imbalance between the Yin and Yang energies of the body (22). Proper syndrome diagnosis is crucial in acupuncture because the same illness may result from different imbalances, and therefore the effective acupuncture points (acupoints) for treatment will be different.

Obesity, according to TCM, is characterized by several different classifications. If the spleen Qi is deficient, the functions of transformation and transportation of Qi from ingested nutrients could be impaired, and instead of producing energy, excess phlegm is produced that accumulates in the body. Chinese medicine considers phlegm-dampness and impaired water metabolism as key factors in the pathology of obesity. Deficient kidney Qi results in the retention of bodily fluids such as urine and sweat, causing congestion and condensation into phlegm as well. Since the liver governs the flow of Qi, when it is suffering from a deficiency, Qi distribution is not properly regulated and spleen Qi is negatively affected, impeding digestion. There can also exist heat in the stomach and intestines, which accelerates digestion, leading to

rapid development of hunger and excessive food intake. TCM also recognizes that lack of exercise and prolonged periods of inactivity contribute to the accumulation of body fat due to physical impairment of Qi flow, leading to Qi deficiency of the internal organs (9, 28). Obesity may result from different combinations of such factors, and requires proper diagnosis by an acupuncture practitioner to determine the appropriate acupoints for maximum effectiveness. Thus, the traditional practice of acupuncture inherently creates difficulty for setting scientific standards, because practitioners can vary the diagnosis and treatment depending on personal experience and opinion (49).

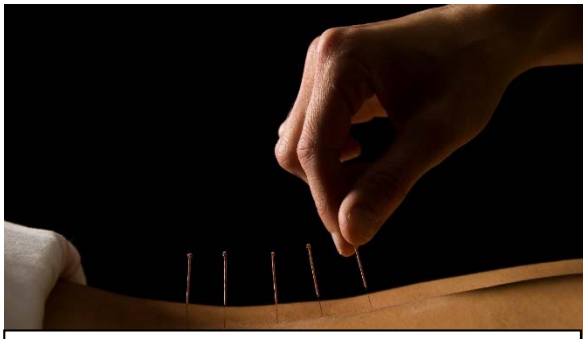
TCM is accepted as mainstream medical care among the Chinese population. A study in Taiwan examining the National Health Insurance Research Database found that 23% of valid beneficiaries of National Health Insurance used acupuncture during the 7-year period of 1996 to 2002, and among these people, 10.6% used it more than once a year (12). Western audiences, however, may find the abstract nature of TCM theory and lack of hard scientific proof challenging to accept. Even so, the significance of complementary and alternative medicine (CAM) use in the United States appears to be rising. A National Health Interview Survey in 2007 estimated that 3.1 million U.S. adults used acupuncture in the past year, and spent around $33.9 billion out-of-pocket on CAM treatments (40). A major barrier to the acceptance of alternative medicine is affording out-of-pocket payments when insurance companies deny coverage. However, a 2004 Kaiser Family Foundation and Health Research and Educational Trust survey found that acupuncture is one of the fastest growing CAM treatments covered by employers, and 50% of the large firms surveyed offered such coverage (40). As employer coverage increases, the improved accessibility of acupuncture may facilitate larger numbers of patients to seek treatment, highlighting the necessity of studies to confirm the efficacy of acupuncture.

On the international stage, the WHO has recognized acupuncture for the treatment of some diseases and symptoms that have been proven through controlled clinical trials. These include allergic rhinitis, essential hypertension, lower back pain, stroke, and rheumatoid arthritis (1). There are also diseases for which acupuncture has shown some therapeutic effects, but these conditions require more scientific studies and trials to prove its effectiveness. These conditions include Bells' palsy, alcohol dependence, osteoarthritis, type 2 diabetes, and obesity (1). In particular, we are interested in the effects that acupuncture may have on the condition of type 2 diabetes and obesity. Several studies have already been conducted on acupuncture and the dysfunctions associated with these two disease conditions, but results are still relatively inconclusive, and more detailed research is required.

Current Reviews on Acupuncture in Treatment of Obesity and Blood Glucose Control

While much of the mechanisms behind acupuncture remain unknown, it is currently believed that stimulation of acupoints activates peripheral afferent nerve fibers, which then interact with the central nervous system (CNS) to release a variety of neurotransmitters (28). Acupuncture can specifically increase neural activity in the satiety center of the hypothalamic ventromedial nucleus, responsible for regulating the sensation of satisfaction of hunger (6, 13). This appetite suppression may be a key contributing factor to the beneficial effects of acupuncture on reducing body weight. Studies also show that acupuncture can increase levels of β-endorphin in the plasma (13) and electroacupuncture (EA) can stimulate the release of β-endorphin from the adrenal gland to enhance insulin secretion (42) and activate an anti-inflammatory pathway (6). Increased activity of inflammatory factors in obesity can impair glucose tolerance and cause insulin resistance, eventually leading to full-blown type 2 diabetes (6), so the anti-inflammatory action of acupuncture may improve on these conditions.

Acupuncture to treat obesity and insulin resistance comes in many forms, including manual acupuncture, EA, auricular acupressure, and new laser needle technology. Manual acupuncture is performed with disposable, stainless needles that vary in length and diameter depending on the location of the acupoints. The location also determines the depth of insertion. Needles are adjusted until a sensation of Qi flow, described as numbness, swelling, or heaviness, is obtained. Then, needles are typically retained for 20 to 30 minutes (22).



[Photograph of manual acupuncture] Retrieved from http://acupunctureforhealthcare.com/wp content/uploads/2012/08/needling.jpg

[Photograph of EA] Retrieved from http://www.ebtherapy.com/services/electroacupuncture.html

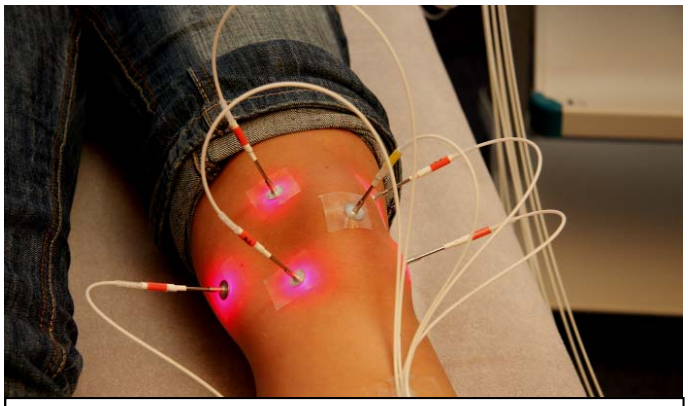
EA follows the same procedure for needle insertion, and once the sensation of Qi is present, an EA therapeutic apparatus is attached to individual needles that administers a certain frequency and intensity of current (51). Typically in clinical settings, the maximum setting that can be tolerated by the patient is used. However, in scientific investigations the frequency and intensity often differ among studies.

[Photograph of auricular acupressure]. Retrieved from http://www.yelp.com/biz_photos/manhattan-medical-manual-therapy-new-york?select=SNG8D7-I-

Auricular acupressure works within the micro-acupuncture system of the ear by stimulating ear acupoints either through needling or magnetic beads that can be stuck to the points (51).

Laser needling is a new technique that uses laser power to deliver stimulation to acupoints, and does not penetrate the

skin. The precise intensity can be adjusted, and patients do not directly feel the laser stimulation (28). Excluding laser needling, which is a relatively new procedure, many studies exist on the use of the different acupuncture treatments for obesity and other metabolic dysfunctions.



[Photograph of laser acupuncture] Retrieved from http://www.isla-laser.org/wp-content/uploads/Knieakupunktur.png

In a review of 44 randomized controlled trials (RCTs) on acupuncture and obesity, and 3 combined therapy studies, manual acupuncture showed greater reduction in measurements of obesity (body weight, BMI, waist circumference) and total blood cholesterol compared to no treatment, lifestyle modifications such as diet and exercise, and sham acupuncture controls (49). Manual acupuncture even showed greater efficacy than some Western weight loss drugs, like sibutramine, fenfluramine, and orlistat (49). Another review found some studies that determined manual acupuncture to be more effective than sham and lifestyle modifications, whereas other studies found no effect (6). A separate study showed that manual acupuncture decreased insulin levels in obese women, perhaps due to improving insulin sensitivity, which reduces the necessity of having excess levels of plasma insulin (18). However, overall the literature on the efficacy of manual acupuncture to reduce obesity and associated metabolic derangements is mixed.

The beneficial effects of EA in treating obesity and insulin resistance have been consistently demonstrated by the majority of available research (6). A study on the use of a single 15-Hz/10mA EA intervention in steroid-induced insulin-resistant rats found that the treatment improved insulin sensitivity by decreasing plasma free fatty acid (FFA) levels, and increasing the expression of insulin signaling proteins such as GLUT4 (29). In two studies on

fasted type 2 diabetic rats, treatment with 15-Hz/10mA EA decreased blood glucose and increased blood insulin (42). 2-Hz EA treatment at acupoint CV 12 (a popular point of acupuncture intervention) increased β-endorphin production from the adrenal glands, enhancing insulin secretion (28). The low frequencies of 15-Hz and 2-Hz EA appear to produce the most beneficial results, including anti-inflammatory effects, possibly due to stimulation of the vagus nerve and attenuation of sympathetic nerve activity, which can also improve hypertension by

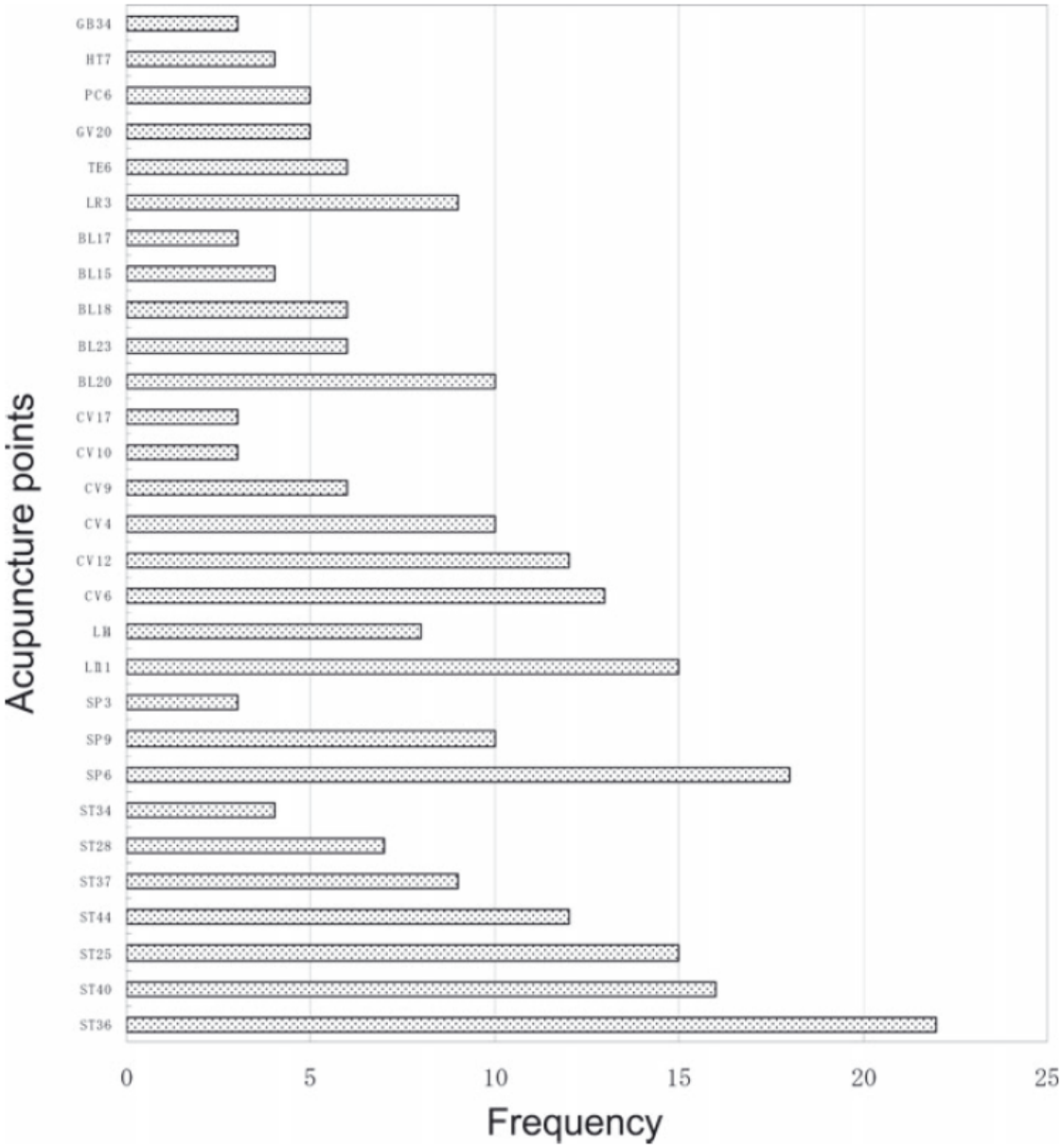


Figure 1 from "Acupuncture: is it effective for treatment of insulin resistance?"

reducing sympathetic activity regulated vasoconstriction (28). These effects have been mainly shown in rats and require confirmation in human diabetic subjects.

Auricular acupressure on certain acupoints is believed to block signals from the hypothalamus, suppressing hunger and appetite to assist in weight loss (35). However, the results are mixed and the precise effects of this treatment are difficult to quantify, because auricular acupressure is often used in conjunction with other types of acupuncture treatment. A non-randomized observational study on the weight reduction effects of combined EA and auricular acupressure treatment on women with simple obesity saw that the intervention decreased body weight, BMI, and waist/hip ratio compared to the baseline (51). A study on the effects of triple therapy using auricular acupuncture, diet, and exercise compared a control group with no intervention to an experimental group with just diet and exercise, and a second group with diet, exercise, and auricular acupressure on the ear hunger points (35). Although both experimental groups showed significant weight loss compared to the control group, there was no significant difference between them, demonstrating a lack of proof for additional advantages of this particular acupuncture treatment (35). Still, the fact that auricular acupressure is generally used with other acupuncture interventions could signify a complementary role instead of a stand-alone effect.

The Future of Acupuncture

Although significant progress has been made towards understanding and implementing acupuncture for the treatment of obesity and obesity-related diseases, there are still many questions that require further research. First, the overall quality of future studies must be assured to produce reliable and reproducible results. Obesity and related diseases are chronic conditions that necessitate long-term evaluation and follow-up. However, the longest acupuncture study

reviewed lasted for only 8-9 months, so the long-term efficacy of acupuncture remains to be determined (28). Two reviews on acupuncture and obesity used the Jadad scoring system for evaluating methodological quality based on randomization, blinding procedure (ideally double-blind), and subject withdrawal descriptions. Most of the studies scored low on the Jadad scale, especially ones originating in China, and these studies tended to show the most enthusiastic results in support of acupuncture effectiveness (28, 49). This apparent bias casts doubts on the reliability of the reported results. Future studies must clearly describe a randomization procedure and utilize an accepted standardized form of blinding. The practice of acupuncture is difficult to double-blind because the acupuncturist inserts the needles, and is aware of the acupoints being stimulated. The new technique of laser acupuncture is promising for double-blind studies as the acupuncturist can be unaware of whether the laser system is active (28). However, it is unknown how closely this can be compared to traditional acupuncture techniques. Some current methods for control and single-blinding include the use of non-penetrating sham needles at acupoints, needling in non-acupoints, and a non-penetrating, blunt "placebo" needle (28). A potentially enlightening study could examine the effects of the controls listed above, and determine the best procedure. Other controversies include the best type of acupuncture treatment, the most effective acupoints, and the combination of acupuncture with additional therapies such as lifestyle modifications and weight loss drugs. The results from many studies conflict, and although some acupoints are popular and commonly used, the complete set often differs between studies depending upon the acupuncturists involved (6, 13, 28, 49). A final additional point to consider is the efficacy of acupuncture in treating different levels of obesity, from overweight to severely obese, and in treating obese states with many microvascular and macrovascular complications.

Despite the volume of research that is still necessary, acupuncture has potential as a useful and safe alternative treatment for obesity and related diseases. Available drugs that impact insulin resistance directly have adverse side effects, including gastrointestinal problems and increased risk of heart failure and limb fractures (28). Conversely, acupuncture treatments rarely caused adverse outcomes and reported events such as minor bruising at the needle insertion site, nausea, and skin irritation, were not serious health risks (13, 49). Acupuncture may also prove more cost-effective than conventional treatments for obesity and related diseases, considering the cost of necessary supplies are less than costs of developing and distributing weight-loss drugs and performing surgeries. Further exploration into this field can contribute greatly to improving the health status of society.

Study Design

Specific Aims

Specific Aim 1: Confirm positive effect of manual acupuncture on reducing obesity

Previous studies on the effectiveness of manual acupuncture in reducing obesity have shown mixed results, and many of the studies are also affected by flawed study designs+ that cast doubt on the results obtained. In this study, we aim to improve upon the shortcomings of previous studies and implement a solid study design to test the effect of three months of biweekly acupuncture treatment on reducing obesity. Manual acupuncture is the most basic form of acupuncture and requires the least amount of technical equipment, making it easy and inexpensive to use. Therefore, it is important to accurately assess its potential.

Specific Aim 2: Confirm positive effect of manual acupuncture on improving insulin resistance

Insulin resistance is a metabolic dysfunction that often may develop with a state of obesity. It is also a precursor to type 2 diabetes and plays a key role in the progression of the disease. The effectiveness of acupuncture in treating insulin resistance also has mixed reports and requires further studies to confirm. In this specific aim, we will test the effect of three months of biweekly acupuncture treatment on reducing insulin resistance. If both insulin resistance and obesity can be treated with acupuncture, the rate of type 2 diabetes development may be decreased.

Specific Aim 3: Examine efficacy of chronic manual acupuncture in treating obesity and insulin resistance

Current studies of acupuncture in treating obesity and insulin resistance are all relatively short term, whereas these are chronic issues that require long term follow-up. It has been shown before that obese individuals may lose weight during a study but regain it afterwards. This

specific aim will attempt to fill the knowledge gap with a twelve month acupuncture intervention to reduce obesity and insulin resistance.

Study Design Overview

In this study, we use a 2 x 2 factorial design, comparing lean and obese groups that either receive acupuncture treatment or sham acupuncture for control. The groups will not receive any other interventions like exercise and diet changes.

Lean Acupuncture	Obese Acupuncture
Lean Control	Obese Control

Each group will have 100 participants. The subjects will first be sorted into lean or obese groups depending on BMI, and then randomly assigned to the treatment or control group using a random number generator. The study will be blinded to the researchers and the subjects. However, the acupuncture practitioners need to be aware of the groupings in order to give either the real acupuncture treatment or the control sham treatment.

The main outcome we are examining is a reduction in obesity among the participants. We will measure this using a DXA scan to assess the total fat content and body composition of each subject before and after the acupuncture treatment (25). A BMI score will also be recorded.

Our secondary outcome is examining the change in insulin sensitivity in participants as a result of the acupuncture treatment. This variable will be measured with a hyperinsulinemic-euglycemic clamp (31).

The participants receiving acupuncture treatment will be needled at acupoints CV12, CV6, ST25, ST36, ST40, SP6, SP9, and BL20. The participants receiving sham acupuncture will be needled

in the same manner at non-acupoints. Subjects in the acute study will be needled biweekly for three months and subjects in the chronic study will be needled biweekly for twelve months.

Subject Inclusion

Targeted Enrollment Table

White	58%
Hispanic/Latino	34%
Black	4%
Asian	2%
American Indian and Alaska Native	2%
Male	50%
Female	50%

Only adults aged 21 and older in Southern Arizona are considered for enrollment. This study will exclude diabetics.

The lean group will only contain individuals with BMI <25, and the obese group will contain individuals with BMI >25.

Timeline

1. Subject recruitment for acute and chronic study

2. Manual acupuncture biweekly course for three months (acute) and twelve months (chronic)

    - Body composition and insulin sensitivity will be assessed at the onset of the study and after every month.

3. Commence follow-up with subjects for six months after conclusion of treatment

Subject Protection

Since no children are included in the study, all adults are expected to provide consent for themselves by signing a waiver after being provided with information on all possible risks and benefits of the study.

Statistics

We will use an ANOVA test at the 5% significance level with a Bonferroni post-hoc analysis to examine the data.

Expected Outcomes

Specific Aim 1: We expect the BMI and adiposity levels of the individuals receiving acupuncture treatment to decrease significantly after three months, and the individuals receiving sham acupuncture to have no difference.

Specific Aim 2: We expect the insulin sensitivity of individuals receiving acupuncture treatment to improve significantly after three months, and the individuals receiving sham acupuncture to either have no change or further decreased insulin sensitivity.

Specific Aim 3: We expect the degree of obesity and insulin resistance to decrease significantly in individuals receiving acupuncture treatment as opposed to sham acupuncture. Additionally, we believe that individuals receiving chronic acupuncture treatment will maintain their metabolic improvements for a longer period during the follow-up compared to individuals who received acute acupuncture treatment.

Alternative Approaches

BMI category divisions: This study only uses a lean and obese comparison, but there are many different levels of obesity. The groups could be further divided up according to specific BMI ranges to pinpoint the level of obesity that can be effectively treated with acupuncture.

Insulin sensitivity level divisions: The subjects could also be separated into groups according to their insulin sensitivity level to examine the impact that acupuncture can have on improving minor versus extreme insulin resistance.

Ethnic differences: The prevalence of obesity and type 2 diabetes is different between various ethnic groups which suggests a genetic contribution to the development of these diseases. As such, the acupuncture treatment may also have a variable effect with different ethnic groups.

Different acupuncture therapies: Some other common acupuncture techniques include electroacupuncture, auricular acupressure, and laser acupuncture. In this study, we are only studying manual acupuncture, but the efficacy may be improved when used in conjunction with other complementary acupuncture methods.

Future Directions

If acupuncture is confirmed to have a positive effect on obesity and insulin resistance, the next step should be to identify the mechanisms by which acupuncture is treating these conditions. A possible option is taking muscle biopsies to measure the concentration of glucose transporters and other signaling molecules in skeletal muscle. Also, this study excluded diabetics, and it may be beneficial to research the possibility of acupuncture improving the state of type 2 diabetics, and perhaps even reversing the downward trend of pre-diabetics.

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