SPECIAL PAPER

Exercise as a Non-Pharmaceutical Treatment Modality to Prevent Comorbidity of Type II Diabetes and Major Depression

Meredith J Barnes, BS
Department of Exercise Science Willamette University, Salem, OR

Junggi Hong, PhD, ATC
Assistant Professor, Department of Exercise Science Willamette University, Salem, OR

Corresponding Author: Junggi Hong, Ph.D, ATC, Assistant Professor Department of Exercise Science, Willamette University, Salem, OR

Abstract

Background: Type II diabetes and major depression are both considered epidemics in the United States, with a high rate of comorbidity. Although the diseases have a physiological connection, western medicine still treats them separately, with medications that often exacerbate the other condition and come with debilitating side effects. Exercise has been shown to be an effective treatment modality for both diseases separately, however, no research has been done on exercise as a treatment or preventative measure for the comorbidity of the two conditions.
Aim: The purpose of this study is to provide a comprehensive review of the literature regarding the efficacy of exercise for the treatment and prevention of comorbid type II diabetes and major depression.
Methodology: Academic Search Primere, Pubmed, Medline and Google Scholar were used to find sources. Search terms such as "type II diabetes, depression, exercise" were used. Sixty three studies were deemed appropriate for this literature review.
Results: Results indicate that exercise is effective at treating type II diabetes and major depression, and would also be effective at preventing the comorbidity of the two. Pharmaceuticals commonly used to treat the two diseases bring with them unwanted side effects which are often more debilitating than the original pathology, whereas side effects of exercise tend to be beneficial to one's health.
Conclusions: Exercise is an effective way to prevent comorbidity of major depression and type II diabetes without unwanted side effects. It should be implemented as the front line treatment for both type II diabetes and depression.

Key words: type II diabetes, depression, comorbidity, exercise

Introduction

Type II diabetes and major depression could be considered two of the most severe epidemics in the United States, considering that type II diabetes affects over eight percent of the U.S. population, and major depression affects around nine percent. Although both diseases are chronic and debilitating, current treatments for these conditions are limited, consisting predominantly of pharmaceutical medications which treat the symptoms as opposed to the etiology. This symptomatic treatment is more appropriate for short term, acute illness, not long-term diseases such as these; mainly due to the compounding effect of pharmaceuticals. This compounding effect is defined as the process by which chronic disease sufferers build tolerances to medications and have to take continually larger and larger doses to keep getting positive results. This leads to a concurrent compounding of side effects as well as increased risk of drug interactions (Boulton, 2005).

Lifetime prevalence of depression in type II diabetes has been found to be as high as 30 percent (Marcus et al., 1992). A meta-analysis preformed by Anderson, Clouse, Freedland and Lustman (2001), provided evidence that even when gender, geographic area, diagnostic criteria for depression, and type of diabetes were controlled for the prevalence of

depression was twice as high in those with diabetes compared to those without diabetes.

Although theoretical mechanisms connecting the occurrence of depression in type II diabetics have yet to be defined, one theory has proposed that the social stigmatisms and the burden of having a chronic disease contribute significantly to the risk of depression (Talbot & Nouwen, 2000). Not only this, but the complications that arise from type II diabetes are virtually unavoidable and tend to get worse with time.

Despite type II diabetes and depression having been shown to be linked both theoretically and physiologically (Lustman et al., 2000; Lustman et al., 1997; Lustman, Griffith, Freedland, Kissel & Clouse, 1988), common medicinal practices treat them as separate pathologies. Often, treatments for one condition not only disregard, but exacerbate the other or cause additional problems unrelated to the original pathology.

Most current pharmaceutical treatments provide only acute relief from symptoms and do nothing to ameliorate the chronic effects because they do not address the etiology of the condition. Although diabetics often take insulin, which treats the cause of the symptoms, taking prescription insulin does not address the problem that causes lack of insulin production in the body in the first place. This makes most pharmaceuticals unsuitable for chronic diseases such as type II diabetes and major depression, especially when the comorbidity of the two diseases is so common. Not only this, but the continuous use of pharmaceuticals creates a lifestyle that is increasingly reliant on medication.

With the prevalence of both diseases rising, there is clear need for new treatment approaches that decrease the risk for comorbid conditions. It has been suggested that one of the most effective ways to treat both these conditions simultaneously, without negative side effects, is lifestyle changes, such as increased exercise (Campbell & Campbell, 2004; Mezuk, Eaton, Albrecht & Golden, 2008). Though implementing lifestyle interventions is much more difficult than pharmaceuticals, they are the only way in which both type II diabetics and those suffering from major depression will be able to find effective, life long solutions for the condition, and prevent comorbidity. Exercise has been shown to be effective at treating type II diabetes and major depression separately (Roth & Holmes, 1987; Sigal et al., 2007; Steptoe, Edwards, Moses & Mathews, 1989), but there is limited research regarding the effects of exercise on the two diseases together. The purpose of this study is to provide a comprehensive review of the literature supporting and refuting the efficacy of exercise for the treatment and prevention of comorbid type II diabetes and major depression.

Methods

Academic Search Premiere, Pubmed, Medline and Google Scholar were used to find sources for this literature review. Search terms such as “type 2 diabetes, major depression, exercise” and combinations thereof were used in conjunction with such words as, “effects of, treatment of, and, cormorbid”. Centers for Disease Control and Prevention and National Health Institute websites were searched for relevant information regarding the respective diseases. Literature found to be irrelevant to the prevalence or treatment of either type II diabetes or major depression was excluded. Studies regarding the etiology, prevalence and treatment of type II diabetes were analyzed and reviewed, followed by studies regarding the etiology, prevalence and treatment of major depression. Finally, literature supporting and refuting the connection between the two conditions was reviewed and followed by a review of the literature supporting and refuting the use of exercise as a treatment modality for both conditions, separately and comorbidly. Only peer-reviewed literature was used in this review, unless opinions or consumer reports specifically relating to the topic were deemed necessary in order to understand the impact on a more personal level. A total of 63 studies were used in this literature review.

Comorbidity

When one examines the etiology and symptoms of type II diabetes and major depression, they do not appear to be connected. However, type II

diabetics have twice as high of a risk of developing depression as those without, with a lifetime prevalence of 30 percent (Anderson, Freedland, Clouse & Lustman, 2001; Marcus et al., 1992).

Persons with psychiatric disorders generally have more risk factors for developing type II diabetes when compared to those without, especially physical inactivity, sedentary lifestyle, unhealthy dietary choices, and obesity (Hayward, 1995). Even when no other diabetic risk factors are evident, those with depression appear to have higher concentrations of blood glucose (Winokur, Maislin, Phillips & Amsterdam, 1988). This could be attributed to the idea that poor glycemic control and increased depressive symptoms have a positively correlated relationship. Improvements in depression have been shown to result in improvements in glycemic control (Lustman et al., 1997; Lustman, Griffith, Freedland, Kissel& Clouse, 1988). This would imply that mood and behavior could have some effect over the severity of the diabetes and the rate at which the complications accelerate. Research also suggests that serotonin may be associated with physical health as well as mood. In a study with otherwise healthy subjects, low serotonin was associated with metabolic syndrome and heart disease (Muldoon et al., 2004), indicating that those with low serotonin may be at risk for poor physical as well as mental functioning (Young, 2007). Lower than normal serotonin levels have also been cited as a main cause of major depression. This indicates that low serotonin levels, which are also associated with poor glycemic control could be a physiological connection between type II diabetes and depression. Not only this, but some of the most common side effects of antidepressants are weight gain, hypertension, metabolism inhibition, changes in appetite and somnolence, all of which increase risks of adipose tissue build up and insulin resistance, leading to diabetes (Boulton, 2005; Sheehan, 2005; Consumer Reports Best Buy Drugs, 2011; Remick, Froese & Keller, 1989; Stahl, Grady, Moret & Briley, 2005; Wamboldt & Kapustin, 2006).

In a study by Golden et al. (2008), those being treated for type II diabetes showed up to an 86 percent higher chance of developing depression when compared to the control subjects, with normal glucose levels. However, those with untreated type II diabetes were actually at a decreased risk of depression when compared to controls. The same held true with pre-diabetics; the odds of those with impaired glucose levels developing depression were 20 percent lower than their control counterparts. This outcome could have many explanations, but the most potentially serious one would be that treatment for type II diabetes is possibly one of the main causes of the elevated risk of depression in type II diabetics. These results show that those diagnosed with type II diabetes who weren't being treated had a decreased chance of developing depressive symptoms, where as those who were being treated had as much as 86 percent higher odds of developing depression once lifestyle and socioeconomic variables had been accounted for. Depending on how advanced the diabetes is, there could be a dozen different complications accompanying the disease. Each complication carries with it added medication and treatments, and each medication also incurs its own complications and extra needed alleviations. Golden et al. (2008) suggest that the psychological stress of managing type II diabetes may induce depressive symptoms. It is also mentioned that treated type II diabetes may have a greater number of complications or comorbidities than those going untreated. This theory of complications causing depression is supported in previous literature; higher levels of depression have been associated with common complications such as neuropathy and retinopathy (Geringer, Perlmuter, Stern & Nathan, 1988; Miyaoka, Miyaoka, Motomiya, Kitamura & Asia, 1997).

A meta-analysis preformed by Anderson, Clouse, Freedland and Lustman (2001) provided evidence that, even when gender, geographic area, diagnostic criteria for depression, and type of diabetes were controlled for, the odds of depression were twice as high in those with diabetes compared to control subjects. However, they did not control for the type of treatment or number of complications. The authors suggest that depression has a

negative effect on ability to function and adherence to medical treatment, as well as glycemic control, increasing the risk of diabetes complications. DeGroot et al. (2001) make the argument that, if depression is correlated with hyperglycemia and hyperglycemia is correlated with the complications of diabetes, there may be a correlation between depression and complications of diabetes.

To further indicate this, a meta-analysis by Mezuk, Eaton, Albrecth and Golden (2008) showed that those with depression have a 60 percent increased risk of type II diabetes, however, type II diabetes only led to a subtle increase in risk for major depression. As a meta-analysis, the authors could not control for duration of the disease, number of complications, or type or amount of treatment for either depression or type II diabetes, and were limited by the quality of the research conducted. It has been suggested that other risks for depression may mask the occurrence of depression in type II diabetics. It has also been suggested that it is difficult to screen for depression in older adults, especially when brain function may be decreasing due to age (Gallo, Anthony & Muthen, 1994). This meta analysis provides solid evidence that depression does increase risk type II diabetes, but is ambiguous as to the relationship from type II diabetes to major depression.

It would appear that major depression directly leads to type II diabetes due to physiological changes in serotonin as well as symptomatic lifestyle changes such as reduced exercise and reduced physical activity. The connection from type II diabetes to major depression, however, is less clear. Although higher rates of depression have been found among diabetics (Anderson, Clouse, Freedland & Lustman, 2001), it has also been shown that those considered pre-diabetic and diabetic who weren't undergoing any treatment had lower rates of depression than non diabetics, and the only population which exhibited increased rates of depression was diabetics undergoing treatment (Golden et al., 2008). Other research indicates that, although there may be a link from type II diabetes to depression, it is not significant and may be caused by extrinsic factors (Mezuk, Eaton, Albrecht & Golden, 2008). This raises the question as to whether the treatment of or duration of diabetes leads to depression.

The reported side effects of hyperglycemia medication include diarrhea, stomach pain, constipation and heartburn. Although none of these side effects can be directly associated with depression, they contribute to patient burden and could be an integral component in the connection between type II diabetes and depression.

The stigmatisms that western society places upon chronic illness can be stressors in and of themselves. If one develops type II diabetes, not only do they have to deal with treating and monitoring their symptoms, but must constantly think of the disease during every day activities. Diabetes also comes with the extra worry regarding what other people are thinking about their actions. Each dietary and physical activity choice will be analyzed to a greater extent due to the constant stigmatism that type II diabetes carries with it. The simple question 'how are you?' becomes a complicated question when a chronic disease is present. The answer 'fine' is no longer applicable, clearly one is not fine when they have developed a chronic lifestyle-based disease. So what is the answer to that question? "Fine, considering the circumstances"? or "More fine than yesterday"? Does one judge their level of 'fine' based on insulin levels? These questions and concerns make it difficult for diabetics to enjoy as enjoyable of a life.

This question becomes even more complicated when considering a person suffering from depression. Since the disease itself brings to question ones self-worth, it is entirely probable that a person with depression would suffer even more from social stigmatisms than a diabetic.

As is evident, both type II diabetes and major depression carry with them heavy stigmatisms in today's society. The comorbidity of the two only increases those stigmatisms, as well as results in decreased adherence to treatments, decrease functioning, increased costs and decreased quality of life (Ciechanowski, Katon & Russo, 2000).

While this connection has been recognized by professionals and in the literature, few treatment modalities has been devised to treat

both conditions simultaneously. While evidence suggests that treating depression in type II diabetics may improve diabetic symptoms and increase life span, this treatment modality is geared more toward depression, not both (Lustman, Freedland, Griffith & Clouse, 2000; Gallo, Bogner, Morales, Post, Have & Bruce, 2005). Furthermore, all pharmaceuticals developed specifically for comorbid depression and diabetes are accompanied by side effects which cause higher drop out rates and lower adherence to the medication, worsening the condition of both diseases.

Since type II diabetes and depression are inter-related, and represent a significant cost to both individuals and communities, the ideal financial and health-related option would be a treatment that could prevent the comorbidity of the two diseases while eliminating the need for pharmaceutical treatments. By applying a treatment to a diabetic before depression occurs, one could possibly stave off the development of the comorbid diseases, and vice versa with depressed patients.

One treatment that has shown to be effective for both depression and type II diabetes separately is exercise (Sigal et al., 2007; Roth & Holmes, 1987; Steptoe, Edwards, Moses & Mathews, 1989). Furthermore, exercise does not come with the negative side effects of medication. Exercise is also more cost effective than medication, potentially only costing as much as a gym membership or personal trainer. While pharmaceuticals result in side effects including constipation, weight gain, somnolence and sexual dysfunction (Consumer Reports Best Buy Drugs, 2011), exercise tends to result in side effects such as weight loss, improved mood, increased life span, improved immune function, strengthened cardiovascular system and improved self image (Blumenthal et al., 1999; Sigal et al., 2007; Sigal, Wasserman, Kenny & Casteneda-Sceppa, 2004). One of the only potentially negative things about exercise is the time requirement, where as medication can be taken in about a second.

Exercise

Exercise is a sub category of physical activity. While physical activity includes any movement produced by the contraction of skeletal muscle requiring energy expenditure, exercise is structured physical activity that one specifically sets time for and plans in advance, with the intention of maintaining or improving physical fitness (Sigal et al., 2004). Exercise can refer to either aerobic or resistance exercise. Aerobic consists of muscular endurance and cardiovascular fitness exercise whereas resistance training focuses on muscular strength and anaerobic fitness.

Exercise and Type II Diabetes

The goal when treating type II diabetes is to achieve and maintain the nearest to normal possible blood glucose level (Eastman et al., 1993). Exercise has been shown to increase insulin sensitivity (Duncan et al., 2003), making it a logical, yet frequently overlooked treatment for type II diabetes. Both resistance and aerobic exercise could theoretically be equally good at treating diabetes, as muscle contraction stimulates the glucose uptake into the cell. Since both types of exercise involve muscle contraction, it is logical that both would result in improved glycemic control. Muscle contraction causes glucose receptors on the cell membrane to be expressed without the presence of insulin. Research indicates that insulin mediated and contraction mediated glucose uptake function on at least partially separate pathways (Ploug, Galbo, Vinen, Jorgensen & Richter, 1987). This allows glucose to enter the cell without the presence of insulin if contraction is present, and vice versa. Thus, in a person that has developed a resistance to insulin, exercise can bypass that part of the process and provide cells with the glucose they need to function (McArdle, Katch & Katch, 2007).

Resistance training has been proposed as a treatment for type II diabetes because it tends to build larger, stronger muscles than aerobic training. Muscle is the primary utilization site for glucose, so the more muscle one has, the more glucose can be removed from the blood stream, and utilized in the cell (Braith & Stewart, 2006). While, theoretically, resistance training should improve glycemic control and glucose tolerance, some research has shown that it has limited to no effect on either (Poehlman, Dvorak, DeNiro, Brochu & Ades,

2000; Banz, Maher, Thompson, Basset, Moore, Ashraf, Keefer & Zemel, 2003). Other research provides evidence that it produces similar results to aerobic exercise, and effectively reduces insulin resistance (Sigal et al., 2007). Furthermore, there is research supporting the idea that improved blood glucose only occurs when one performs resistance training at 70 percent or higher of the individual's one repetition maximum strength (1RM) (Braith & Stewart, 2006). Other research suggests that obese type II diabetics should not perform short term high intensity exercises, such as 70 percent of 1RM, due to the idea that it may actually increase blood glucose (Kjaer, Hollenbeck, Frey-Hewitt, Galbo, Haskell & Reaven, 1990). This conflicting literature would indicate that, while resistance training has its place in treating type II diabetes, more research is necessary. Until consensus is reached, it would be inefficient to use it exclusively.

Aerobic exercise has been shown conclusively to enhance insulin sensitivity acutely after exercise, and chronically with continuous training (Rogers, 1989; Walker, Piers, Putt, Jones & O'Dea, 1999). It is suggested that this increased insulin sensitivity is a result of increased muscle metabolism as well as changes in body composition (Boule, Haddad, Kenny , Wells & Sigal, 2001; Tuomilehto et al., 2001).

Aerobic exercise has been shown to also decrease body weight, blood pressure and blood triglycerides, while increasing HDL cholesterol levels. Along with these, one of the effects of aerobic training is reduced insulin resistance; some studies show as much as 30 percent improvement in insulin action (Bogardus et al., 1984). While light, moderate and high intensity aerobic training have all been shown to decrease insulin resistance, sprint interval exercise has not been shown to produce a significant difference (Brestoff et. al, 2009). This may be due to the anaerobic qualities of sprinting, but may also be related to the short duration of sprinting.

A key study by Sigal et al. (2007) showed that both resistance training and aerobic training result in a significant decrease in blood glucose levels, and that a combination of the two result in an even larger decrease. It is mentioned by the authors that the greatest reductions were seen in those with higher baseline values, and that those with lower baseline glucose values only saw significant decreases in the combination group. During the course of the study, almost twice as many members of the control group needed to increase their oral hyperglycemia medication when compared to members of the resistance, aerobic and combination groups. In comparison, those in an exercise group were 1.3 to 2 times more likely than the control group to decrease or discontinue oral hyperglycemia medications. Although these authors concluded that the combination therapy was the most beneficial, they did not take in to account the amount of time committed to each respective exercise. The combination group committed twice as much time to exercise as the aerobic and resistance group, considering they had to perform a full regimen of both exercises. Having committed twice as much time, it is only logical that the members of this group would see greater improvements.

With this information, it can be concluded that both resistance and aerobic exercise are effective treatment modalities for type II diabetes.

It can also be concluded that, while both types of exercise are effective, a combination of the two is the most effective.

Exercise and Major Depression

Medication is the most common treatment for depression, however, exercise has been receiving more attention lately as a possible treatment modality. Most studies have shown that exercise is at least comparable to medication in reducing depression levels (Blumenthal et. al, 1999). The effects of exercise on depression are problematic to study, mainly due to difficulty associated with recruiting the population. One of the most common problems encountered with using exercise as a treatment modality for depression is that the subject population is inherently unmotivated to exercise, or do any physical activity. In depression patients, adherence to treatments such as antidepressants or psycho-therapy is low. When a researcher includes exercise, adherence drops even lower. Another

problem arises when one examines the social interactions that are bound to happen in a gym or fitness area setting. In the case of depression, a person is already suffering from a mental condition where over sensitivity is a symptom, often particularly to issues regarding body image. When others are brought into the equation, the situation becomes more stressful and more likely to cause the patient to withdraw further from society.

While a gym setting may induce a withdrawn reaction from some individuals suffering from depression, others may react in an opposite manner. One of the benefits of exercise is that it's positively viewed both by the rest of society, and by the individual (Salmon, 2000). Humans, as a species, are genetically wired to view exercise as a positive action. From an evolutionary perspective, it is not only positive, but necessary. Based on this theory, when one partakes in exercise, it will raise self-esteem and body image. Exercise may also elicit positive feedback from peers and therefore increases sense of worth (Lawlor & Hopker, 2001). Exercise could also potentially pose as a distraction from negative thoughts (Lepore, 1997). As important as these social constructs may be, it is the physiological effects of exercise that provide the greatest changes.

It is unknown exactly how exercise physiologically affects depression, however, many mechanisms have been proposed. Changes in brain chemistry associated with depression, for the most part, involve serotonin. It is well known that serotonin is linked with happiness and feelings of well-being (Young, 2007; Neumeister, Young & Stastny, 2004). Serotonin is generally released from cells three times a second if one is at rest. If one is in non-rapid eye movement (NREM) sleep then that frequency decreases, and if REM sleep is occurring, serotonin-releasing cells are inactive. However, if one is active the release rate increases to five or more per minute (Jacobs, 1994). Based on this increase, one may infer that exercise can be beneficial to those with depression. Even if the synapses aren't working properly and some serotonin is being re-uptaken into the original cell, when exercise occurs, almost twice as much serotonin is being released, making it easier for the receiving cell to get the necessary serotonin.

Unlike type II diabetes, resistance training and aerobic training have shown to affect depression in a similar manner when used for treatment. Resistance training has been shown to significantly reduce certain measures of depression, as well as improve quality of life and social functioning (Singh, Clements & Fiatrone, 1996). It is hypothesized that the increase in social functioning and quality of life may be in part responsible for the reduction in depression.

Aerobic exercise has shown similar results, providing significant reductions in depression in a short amount of time (Dimeo, Bauer, Varahram, Proest & Halter, 2000). It has been suggested that aerobic exercise may be more effective than pharmaceuticals as a treatment modality for a depressive patient beginning a new treatment, as antidepressants take from two to four weeks to see any therapeutic effect.

Based on these results, one can determine that both resistance and aerobic exercise are effective treatment modalities for both depression and type II diabetes. If exercise is effective at treating both conditions, it can be concluded that it may be an effective treatment in preventing the comorbidity of the two.

Discussion

The literature agrees on the concept of exercise being equally, if not more, effective then pharmaceuticals at treating type II diabetes and major depression; especially in the cases of type II diabetes, in which part of the etiology is a sedentary lifestyle. Even though virtually all research and clinical specialists agree that exercise is an effective treatment modality for both type II diabetes and major depression, there is still a disconnect between the evidence and the application. It's been established that providing treatment for symptoms as opposed to etiology is not effective for chronic diseases such as type II diabetes and depression, however, western medicine continues to produce and apply treatments and medications that only provide relief from various symptoms instead of providing treatments for the cause of the disease, and often cause more problems in addition to the original pathology.

It has been shown conclusively that exercise is

equally as good as, if not better than, pharmaceuticals at treating both type II diabetes and major depression. If the evidence is pointing to exercise as an effective, non-invasive treatment modality with no detrimental side effects, why is society still implementing pharmaceuticals as a first line treatment? Type II diabetes and major depression have a high rate of comorbidity that is only compounded by pharmaceutical treatments. Exercise has been shown to be effective at treating both diseases separately, and it is likely that it would be effective at treating the diseases together, potentially preventing comorbidity.

Future Research

There is a great body of research regarding type II diabetes, depression, and their resulting comorbidity. There have also been many studies performed on the effects of exercise on both depression and type II diabetes. Although the etiologies of each respective condition are not completely clear, the research in this field can provide the reader with a moderately clear understanding of how type II diabetes and major depression are connected and how they affect each other. Research indicates the medications for treating hyperglycemia may be a cause of depression in type II diabetics. A study should be conducted regarding the occurrence of depression in type II diabetics being treated with pharmaceuticals and type II diabetics being treated with exercise. A complete understanding of neurotransmitters and their effect on depression would also be beneficial to the scientific community, as well as a deeper examination of insulin resistance and the factors that play in to it.

Conclusion

It's been established that exercise is effective for both type II diabetes and depression (Sigal et al., 2007; Roth & Holmes, 1987; Steptoe, Edwards, Moses & Mathews, 1989). If it is at least as good or better than the majority of medications for each condition, and carries with it no detrimental side effects, it is sensible to use it as a first line treatment modality. It's also been established that type II diabetes can lead to depression, and that depression can lead to type II diabetes. Since the comorbidity of the diseases is so prevalent in today's society, one would think that treatment modalities would gear toward the prevention and treatment of both diseases simultaneously. However, western medicine insists on treating them as separate conditions. Evidence points to the idea that it may, in fact, be the respective medications that cause this link between the two diseases. Whether or not medication is solely responsible for the connection between type II diabetes and depression, it clearly plays a role in the comorbidity and results in unwanted side effects. Although it is sometimes difficult to motivate those with chronic illness to exercise, lifestyle change such as increased exercise is the only way in which effective long term changes will occur. Pharmaceuticals focus on symptomatic treatment and therefore are not appropriate for inducing long term changes. Exercise should be implemented as a first line treatment modality for those with type II diabetes and major depression in order to prevent the comorbidity of the two diseases and treat the etiology of the original pathology.

References

Anderson, R., Freedman, K., Clouse, R. &. Lustman, P. (2001). The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 24;6: 1069-1077.

Banz, W., Maher, M., Thompson, W., Bassett, D., Moore, W., Ashraf, M., Keefer, D. & Zemel, M. (2003). Effects of resistance versus aerobic training on coronary artery disease risk factors. *Experimental Biology and Medicine*, 228: 434-440.

Baxter, L., Schwartz, J., Phelps, M., Maxxiotta, J., Guze, B., Selin, C., Gerner, R. & Sumida, R. (1989). Reduction of prefontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry*, 46: 243-250.

Blumenthal, J., Babyak, M., Moore, K., Craighead, E., Herman, S., Khatri, P., Waug, R., Napolitano, M., Forman, L., Applebaum, M., Doraiswamy, M. & Krishnan, R. (1999). Effects of exercise training in older patients with depression. *Archives of International Medicine*, 159: 2349-2356.

Bogardus, C., Ravussin, E., Robbins, D., Wolfe, R., Horton, E. & Sims, E. (1984). Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. *Diabetes*, 33;4: 311-318.

Boule, N., Haddad, E., Kenny, G., Wells, G. & Sigal, R. (2001). Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *Journal of American*

Medical Association, 286:1218-1227.

Boulton, A. (2005). Management of diabetic peripheral neuropathy. Clinical Diabetes, 23;1: 9-15.

Braith, R. & Stewart, K. (2006). Resistance exercise training: its role in the prevention of cardiovascular disease. *Circulation*, 113: 2642-2650.

Campbell, T.C. & Campbell, T. (2004). The China Study. BenBella Books, Dallas, TX.Centers for Disease Control and Prevention. (2011). National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

Centers for Disease Control and Prevention. (2011). Workplace health promotions: Depression. Atlanta GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011. <http://www.cdc.gov/workplacehealthpromotion/implementation/topics/depression.html> Retrieved September 20, 2011.

Ciechanowski, P., Katon, W. & Russo, J. (2000). Depression and Diabetes: Impact of depression symptoms on adherence, function, and costs. *Archives of International Medicine*, 160: 3278-3285.

Consumer Reports Best Buy Drugs. (2008). Treating chronic pain: The opioids. Consumers Reports: 1-23.

Consumer Reports Best Buy Drugs. (2011). The anticonvulsants: Treating bipolar disorder, nerve pain and fibromyalgia. Consumer Reports: 1-27.

Dall, T., Zhang, Y., Chen, Y., Quick, Q., Yang, W. & Fogli, J. (2010). The economic burden of diabetes. *Health Affairs*, 29;2: 297-303.

Dailey, G., Kim, M. & Lian, J. (2001). Patient compliance and persistence with antihyperglycemic drug regimens: evaluation of a medicaid patient population with type 2 diabetes mellitus. *Clinical Therapy*, 23:52-57.

DeGroot, M., Anderson, R., Freedland, K., Clouse, R. & Lustman, P. (2001). Association of Depression and Diabetes complications: A Meta-analysis. *Psychomatic Medicine*, 63: 619-630.

Dimeo, F., Bauer, M., Varaham, I., Proest, G. & Halter, U. (2001). Benefits from aerobic exercise in patients with major depression: a pilot study. *British Journal of Sports Medicine*, 35: 114-117.

Duncan, G., Perri, M., Tehriaque, D., Hutson, A., Eckl, R. & Stacpoole, P. (2003). Exercise training without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care*, 26: 557-562.

Eastman, R., Silverman, R., Harris, M., Javitt, J., Chiang, Y., & Gorden, P. (1993). Lessening the burden of diabetes: intervention strategies. *Diabetes Care* 16:1095–1102.

Furukawa, T., McGuire, H., Barbui, C. (2002). Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. *British Medical Journal*, 325:991.

Gallo, J., Anthony, J. & Muthen, B. (1994). Age differences in the symptoms of depression, a latent trait analysis. *Journal of Gerontology*, 49: 251-264.

Golden, S., Lazo, M., Carnethon, M., Bertoni, A., Schreiner, P., Diez Roux, A., Lee, H. & Lyketsos, C. (2008). Examining a bidirectional association between depressive symptoms and diabetes. *Journal of American Medical Association*, 299;23: 2751-2759.

Gore, M., Brandenburg, N., Dukes, E., Hoffman, D., Tai, K. & Stacey, B. (2005). Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. *Journal of Pain and Symptom Management*, 30; 4: 374-385.

Greenberg, P., Kessler, R,, Birnbaum, H., Leong, S., Lowe, S., Berglund, P. & Corey-Lisle, P. (2003). The economic burden of depression in the United States: How did it change between 1990 and 2000? *Journal of Clinical Psychiatry*, 64;12:1465-1475.

Hayward, C. (1995). Psychiatric illness and cardiovascular disease risk. E*pidemiological Review*, 17; 129-138.

Janetta, P., & Houlihan, L. (2004). Type 2 diabetes mellitus, etiology and possible treatment: preliminary report. *Surgical Neurology*, 61;5: 422-426.

Jacobs, B. (1994). Serotonin, motor activity and depression-related disorders. *American Scientist*, 82; 456-463.

Brestoff, J., Clippinger, B., Spinella, T., vonDuvillard, S., Nindl, B. & Arcieroa, P. (2009). An acute bout of endurance exercise but not spring interval exercise increases insulin sensitivity. *Applied Physiology, Nutrition and Metabolism*, 3;1: 25-32.

Kjaer, M., Hollenbeck, B., Hewitt-Frey, B., Galbo, H., Haskell, W. & Reaven, G. (1990). Glucoregulation and hormonal responses to maximal exercise in non-insulin-dependent diabetes. *Journal of Applied Physiology*, 68: 2067-2074.

Knowler, W., Barrett-Conner, E., Fowler, S., Hamman, R., Lachin, J., Walker, E. & Nathan, D. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metiformin. *New England Journal of Medicine*, 326;6: 393-403.

Lawlor, D. & Hopker, S. (2001). The effectiveness of exercise as an intervention in the management of depression L systematic review and meta-regression analysis of randomized controlled trials. *British Medical Journal*, 322: 1-8.

Lepore, S. (1997). Expressive writing moderates the relation between intrusive thoughts and depressive symptoms. *Journal of Personal and Social Psychiatry*, 73: 1030-1037.

Lustman, P., Anderson, R., Freedland, K., deGroot, M., Carney, R. & Clouse, R. (2000). Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care*, 23:934-942.

Lustman, P., Griffith, L., Clouse, R., Freedland, K., Eisen, S., Rubin, E., Carney, R. & McGill, J. (1997). Effects of nortyiptyline on depression and glucose regulation in diabetes: results of a double-blinded, placebo-controlled trial. *Psychosomatic Medicine*, 59:241-250.

Lustman, P., Griffith, L., Freedland, K., Kissel, S. & Clouse, R. (1988). Cognitive behavior therapy for depression in type 2 diabetes: a randomized controlled trial. *Annals of Internal Medicine*, 129: 613-621.

Madden, M., Tomsik, P., Terchek, J., Navracruz, L., Reichsman, A., Clark, T., Cella, P., Weirich, S.,

Munson, M. & Werner, J. (20110). Keys to successful diabetes self management for uninsured patients: social support, observational learning, and turning points: a safety net providers' strategic alliance study. *Journal of National Medical Association*, 103;3: 257-264.

Marcus, M., Wing, R., Guare, J., Blair, E. & Jawad, A. (1992). Lifetime prevalence of major depression and its effect on treatment outcome in obese type II diabetic patients. *Diabetes Care* 15:253-255.

Marin, H. & Menza, M. (2005). The management of fatigue in depressed patients. *Essential Psychopharmacology*, 6: 185-192.

Mason, B., Matsuyama, J. & Jue, S. (1995). Assessment of sulfonylurea adherence and metabolic control. *Diabetes Educator*, 21: 52-57.

McArdle, W., Katch, F. & Katch, V. (2007). Exercise Physiology: Energy, Nutrition, & Human Performance, sixth edition. Lippincott Williams & Wilkins. Santa Barbara, CA.

Melikian, C., White, J., Vanderplas, A., Dezii, C. & Chang, E. (2002). Adherence to oral antidiabetic therapy in a managed care organization; a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. *Clinical Therapeutics*, 25;3: 460-467.

Mezuk, B., Eaton, W., Albrecht, S. & Golden, S. (2008). Depression and type 2 diabetes over the lifespan; a meta analysis. *Diabetes Care*, 31;12: 2383-2390.

Miyaoka, Y., Miyaoka, H., Motomiya, T., Kitamura, S. & Asai, M. (1997). Impact of sociodemographic and diabetes related characteristics on depressive state among non-insulin-dependent diabetic patients. *Psychiatry and Clinical Neurosciences*, 51;4: 203-206.

Moret, C. & Briely, M. (2011). The importance of norepinephrine in depression. *Neuropsychiatric Disease and Treatment*, 7:9-13.

Muldoon, M., Mackey, R., Williams, K., Korytkowski, M., Flory, J. & Manuck, S. (2004). Low central nervous system serotonergic responsivity is associated with the metabolic syndrome and physical inactivity. *The Journal of Clinical Endocrinology and Metabolism*, 89;1:266.

Nathan, D., Buse, J., Davidson, M., Heine, R., Holman, R., Sherwin, R. & Zinman, B. (2006). Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*, 29;8:1963-1972.

National Institute of Mental Health. (2011). Depression. Bethesda, MD: National Institute of Health. <http://www.nimh.nih.gov/health/publications/depression/complete-index.shtml> Retrieved September 20, 2011.

National Institute of Health. (2009). Senior Health, Diabetic Retinopathy. Bethesda MD: National Institute of Health. <http://nihseniorhealth.gov/diabeticretinopathy/toc.html> Retrieved November 21, 2011.

Neumeister, A., Young, T. & Stastny, J. (2004). Implications of genetic research on the role of serotonin in depression: emphasis on the serotonin type 1A receptor and the serotonin transporter. *Psychopharmacology*, 174: 512-524.

Odegard, P. & Capoccia, K. (2007). Medication taking and diabetes: A systematic review of the literature. *The Diabetes Educator*, 33;6: 1014-1029.

Ploug, T., Galbo, H., Vinten, J., Jorgensen, M. & Richter, E. (1987). Kinetics of glucose transport in rat muscle: effects of insulin and contractions. *American Journal of Physiology*, 253:12-20.

Poehlman, E., Dvorak, R., DeNiro, W., Bronchu, M. & Ades, P. (2000). Effects of resistance training and endurance training on insulin sensitivity in nonobese, young women: a controlled randomized trial. *Journal of Clinical Endocrinology and Metabolism*, 85:2463-2468.

Remick, R., Froese, C. & Keller, F. (1989). Common side effects associated with monoamine oxidase inhibitors. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 13; 3-4: 497-504.

Rogers, M. (1989). Acute effects of exercise on glucose tolerance in non-insulin-dependent diabetes. *Medical Science Sports Exercise*, 21:362-368.

Roth, D. & Holmes, D. (1987). Influence of aerobic exercise training and relaxation on physical and psychologic health following stressful life effects. *Psychosomatic Medicine*, 49: 355-365.

Salmon, P. (2001). Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. *Clinical Psychology Review*, 21;1: 33-61.

Sheehan, D., Eaddy, M., Shah, M. & Mauch, R. (2005). Differences in total medical costs across the SSRIs for the treatment of depression and anxiety. *American Journal of Managed Care*,11; 12:354-361.

Sherwood, L. (2010). Human Physiology: From Cells to Systems. Brooks/Cole, Belmont, CA.

Sigal, R., Wasserman, D., Kenny, G. & Casteneda-Sceppa, C. (2004). Physical activity/exercise and type 2 diabetes. *Diabetes Care*, 27; 10: 2518-2539.

Sigal, R., Kenny, G., Boule, N., Wells, G., Prud'homme, D., Fortier, M., Ried, R., Tulloch, H., Coyle, D., Phillips, P., Jenings, A. & Jaffey, J. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized control trial. *Annals of International Medicine*, 147;6: 357-369.

Singh, N., Clements, K. & Fiatarone, M. (1997). A randomized controlled trial of progressive resistance training in depressed elders. The Journals of Gerontology Series A: *Biological Sciences and Medical Sciences*, 52a;1:27-35.

Stahl, S., Grady, M., Moret, C. & Briley, M. (2005). SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. *Central Nervous System Spectrums*, 10;9: 732-747.

Steptoe, A., Edwards, S., Moses, J. & Mathews, A. (1989). The effects of exercise training on mood and perceived copying ability in anxious adults from the general population. *Journal of Psychosomatic Research*, 33: 537-547.

Thirlaway, K. & Benton, D. (1992). Participation in physical activity and cardiovascular fitness have different effects on mental health ad mood. *Journal of Psychosomatic Research*, 36: 657-665.

Talbot, F., & Nouwen, A. (2000). A review of the relationship between depression and diabetes in adults: is there a link? *Diabetes Care* 23: 1556–1562.

Tuomilehto, J., Lindstrom, J., Eriksson, J., Valle, T., Hamalaien, H., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., Salminen, V. & Uusitupa, M. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine*, 344;18: 1343-1350.

Walker, K., Piers, L., Putt, R., Jones, J. & O'Dea, K. (1999). Effects of regular walking on cardiovascular risk factors and body composition in normoglycaemic women and women with type 2 diabetes. *Diabetes Care*, 22: 555-561.

Wamboldt, C. & Kapustin, J. (2006). Evidence-based treatment of diabetic peripheral neuropathy. *The Journal for Nurse Practitioners*, 4;15:370-378.

Winokur, A., Maislin, G., Phillips, J. & Amsterdam, J. (1988). Insulin resistance after oral glucose tolerance testing in patients with major depression. *American Journal of Psychiatry*, 145: 325-330.

Wong, D., Bymaster, F., Engleman, E. (1995). Prozac, the first selective serotonin uptake inhibitor and an antidepressant drug: twenty years since its first publication. *Life Science*, 57: 411-441.

Young, S. (2007). How to increase serotonin in the human brain without drugs. *Journal of Psychiatry Neuroscience*, 32:6; 394-399.

Appendix

Table 1

Drug	Treats	Side effects	Cost
Tricyclic Antidepressant	Depression, pain, insomnia	Dry mouth, blurred vision, cardiac arrhythmias, sedation, urinary retention, constipation, postural hypertension, addiction, seizures, hypertension	Around $60 per month
Anticonvulsant	Depression, pain	Dizziness, headache, edema, weight gain, rash, coordination problems such as speech and concentration, nausea, dry mouth, blurry vision, nervousness, anorexia, liver failure, suicidal thoughts	Anywhere from $4 to $860 per month
Selective Serotonin Reuptake Inhibitor	Depression, pain	Sexual dysfunction, appetite change, dizziness, lethargy, headache, agitation, generalized pain, nausea, depression, metabolism inhibition, anxiety, sleep disturbance, insomnia, gastrointenstinal disturbances, weight gain, withdrawal after discontinuation	Around $150 per month, ranging from $20 to $500
Seretonin-Norepinephrine Reuptake Inhibitor	Depression, obesity	Nausea, dry mouth, dizziness, insomia, somnolence, constipation, increased blood pressure, excessive sweating, sexual dysfunction, erectile dysfunction, increased heart rate, heart palpitation, urinary retention, headache, anxiety, changes in appetite, blurred vision, withdrawal after discontinuation	Anywhere from $50 to $540 per month, usually slightly over $100
Monoaimine Oxidase Inhibitor	Depression	Insomnia, sedation, hypotension, sexual dysfunction, hypomania, weight gain, edema, hypertension, muscle spasm, withdrawal after discontinuation	n/a
Tetracyclic Antidepressant	Depression, pain, insomnia	Dry mouth, dizziness, reduced seizure threshold	Anywhere from $40 to $200 per month