MECHANISMS OF WEIGHT GAIN IN PATIENTS WITH DEPRESSION

MECHANISMS OF WEIGHT GAIN IN MAJOR DEPRESSIVE DISORDER PATIENTS TAKING SEROTONIN REUPTAKE INHIBITORS

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Abstract

Individuals with mood disorders are particularly vulnerable to weight gain, due in part to an illness symptom profile that impacts appetite and energy and the iatrogenic weight-gain effects associated with psychotropic medications. The exact physiological mechanisms through which medication causes weight gain have yet to be clearly elucidated. The studies comprising this thesis examine changes in caloric consumption, physical activity and basal metabolic rate (BMR) in depressive disorder (MDD) patients starting on selective serotonin reuptake inhibitors (SSRIs). Since both depression and obesity have been linked to inflammation, we also monitored changes in cytokines and adipokines throughout treatment. In our sample, we observed a mean weight gain from baseline, prior to medication, to 6 months after the initiation of pharmacotherapy. We note that this weight gain is not likely due to increased caloric consumption, but could be related to the proportions of macronutrients being consumed and expended, as well as physical activity level. We also observed changes in adipokines and cytokines that are reflective of pharmacotherapy and not weight gain, even in the absence of clinical improvement. Collectively these studies have begun to shed light on the mechanisms involved in the weight gain experienced by MDD patients being treated with SSRI antidepressants. A better understanding of these mechanisms will lead to better management of the adverse metabolic side effects associated with psychotropic medication, and will improve patient compliance.

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CHAPTER 1: A review of the association between depression and weight change

Introduction

Major Depressive Disorder (MDD) is one of the most commonly diagnosed mental disorders in primary care settings, with a lifetime risk estimated to be 10% to 25% for women and 5% to 9% for men (American Psychiatric Association, 2000).

Depression is often accompanied by a clinical presentation that impacts the balance between energy intake and energy expenditure. In MDD, these symptoms include changes in appetite and/or weight, low energy or fatigue, restlessness, and insomnia or hypersomnia (DSM-IV-TR, 2000). Early reports on depressed patients have focused primarily on weight loss, noting a particular association between weight loss and severity of vegetative symptoms such as sleep and libido (Robinson et al., 1975; Paykel, 1977). More recently, however, weight gain began to be recognized in patients with depression and we now know that MDD is often associated with an increased prevalence of obesity. A study by Hasler and colleagues demonstrated an increased prevalence of weight gain in both adult men and women who had experienced depressive symptoms before the age of 17 (Hasler et al., 2005) and recent work from our group has shown a significant increase in weight in drug naive patients that start antidepressant therapy (Taylor et al., 2008). In a study by Weissenburger and colleagues 40% of depressed outpatients also experienced weight gain (Weissenburger et al., 1986) and there appears to be a high concordance between weight patterns and episodes of depression, wherein most patients who gained weight in one episode also gained weight in another (Stunkard et al., 1990).

Understanding the timing of both depression and obesity is complicated, however, and the direction of causality between obesity and MDD has been disputed in the literature. A recent study has reported a significant increase in visceral fat (independent of overall obesity) secondary to the onset of depressive symptoms (Vogelzangs et al., 2008), while another large cohort study concluded that common mental disorders increase future risk of obesity in a cumulative manner, such that chronic or repeated episodes put patients at a higher risk of obesity (Kivimaki, 2009). Other studies, however, have focused on the reciprocal relationship, noting there is an increased risk of developing a mental health illness in individuals that first develop weight problems (Atlantis & Baker, 2008; Bjerkeset, 2008; Luppino et al., 2010). This debate is still ongoing and it seems that for now, despite significant overlap between obesity and MDD, the directionality and relation between the two remains poorly understood and warrants further investigation.

Purported links between MDD and Obesity

Early reports linked weight gain in depressed patients with an illness that was milder in severity and used classification terms such as neurotic depression or depression with atypical features (Paykel, 1977; Davidson, 1982) to describe this phenotype. The clusters of symptoms associated with these classifications, however, have been shown to be weakly associated with the direction of weight change. The move away from trying to link a particular symptom cluster or clinical presentation

with weight change has shifted focus instead on particular behavioral patterns that may serve as predictors of weight.

One such behavior to be studied is disinhibition of dietary restraint. Herman & Polivy (1975) were first to investigate restraint and hypothesized that strong emotions such as anxiety or agitation, which are commonly experienced by depressed patients, interfere with self-control and, therefore, the strong emotions experienced during depressive episodes result in weight gain. This hypothesis was initially supported by findings that weight-conscious (restrained) patients almost invariably reported weight gain, whereas unrestrained patients reported weight loss. In a larger study, Weissenburger et al. (1986) expanded on these findings, pinpointing *disinhibition* of dietary restraint, as opposed to restraint *per se*, as the distinguishing feature between weight gainers and losers. A later study, however, reported that the association between disinhibition of dietary restraint and weight change becomes non-significant when controlling for BMI, age, and gender (Stunkard et al., 1991). This study also noted that BMI significantly correlated with weight change, suggesting that patients with relatively higher BMI are more likely to gain weight during depression but other specific predictors of the direction of weight change during depression remain unclear.

The association between diet and weight change in patients with MDD did not end with work on dietary restraint and more recent work has looked at food preference as being a possible mediating factor. Early studies reported an increased preference for carbohydrate- and fat-rich foods during depressive episodes in some

patients (Lieberman et al., 1986; Fernstrom, 1989), and while this preference was not found in everyone, Lieberman et al. (1986) suggested that when carbohydrate-rich food was administered to carbohydrate "cravers", they experienced relief from their depressed mood. This is thought to be related to the fact that ingesting carbohydrates releases insulin into the body, which stimulates the uptake of branched-chained amino acids (BCAA) into muscle. Since tryptophan is an aromatic amino acid, it is not affected by the insulin-mediated amino acid uptake into the muscle, causing an increase in the ratio of tryptophan to BCAA in the plasma (Wurtman & Wurtman, 1998). This increased ratio results in reduced competition at the large neutral amino acid transporter, causing an increased transport of tryptophan across the blood-brain barrier. The parallel rise in brain tryptophan leads to increased serotonin production through enhanced saturation of tryptophan hydroxylase, which converts tryptophan to serotonin (Fernstrom & Wurtman, 1971; Wurtman & Wurtman, 1998). Therefore, carbohydrate foods essentially mimic the effects of antidepressants by increasing the concentration of serotonin in the brain, though they confer a much more transient and less potent effect.

Other mechanistic explanations for the link between depression and obesity have focused on the hypothalamic-pituitary-adrenal axis (HPA), which is central to stress response. Hyperactivity of the HPA axis, leading to elevated levels of cortisol, has been identified as the most prominent neuroendocrine abnormality in MDD (Rubin, 1989; Chrousos & Gold, 1992; Deuschle et al., 1998; Burke et al., 2005). HPA activation can also occur as a result of high levels of inflammatory markers, which

have been linked to depression (Kyrou et al., 2006). The proinflammatory cytokines TNF-α, IL-1 and IL-6 are able to directly and indirectly stimulate synthesis and secretion of corticotropin-releasing hormone (CRH) and vasopressin from the hypothalamus. The cytokines can also directly induce secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland and glucocorticoids by the adrenal glands (Kyrou et al., 2006). The increased level of cortisol counters the activity of insulin and results in an inhibition of the peripheral uptake and utilization of glucose (Piroli et al., 2007), which in turn promotes the accumulation of visceral fat (Bjorntorp, 2001).

Weight Gain with Antidepressant Treatment

Psychotropic medications are often accompanied by a side effect profile that impacts energy balance and body weight. It has been well established that certain classes of medications such as atypical antipsychotics and mood stabilizers are often associated with significant increases in weight gain (Zimmermann et al., 2003) but perhaps because weight changes are often more subtle or gradual, the contribution of antidepressants to weight change has, until recently, received less attention (Benazzi, 1998; Fava, 2000).

The safety of antidepressants and their tolerability in terms of side effect profile has improved since the discovery of monoamine oxidize inhibitors (MAOI's) in the 1950's, and there are now a myriad of different antidepressants to available. The MAOI's, which required significant dietary restrictions were followed initially by

a class of antidepressants known as tricyclic antidepressants (TCA's), a group of drugs that did not require adherence to specific food choices in order to avoid potential life threatening interactions, but that were instead associated with potentially fatal cardiac arrhythmias and were associated with sedation, weight gain, and lethality in over dose. The push to improve upon antidepressant design lead to the development of selective serotonin reuptake inhibitors (SSRIs), a class that lacks cardiac effects, is safe in overdose, and generally has a better side effect profile than older antidepressants (Beaumont, 1989; de Jonghe, F. & Swinkles, 1992; Hale, 1993), making them the most widely prescribed class of antidepressants.

The initial evidence related to SSRI use and weight gain was quite positive, and in fact the SSRI fluoxetine (Prozac), had been linked to weight loss (Goldstein et al., 1997, Brambilla et al., 2005) and was recommended as a treatment for obesity. The anorectic effect of initial therapy with fluoxetine was later found to be transient in most people and weight was usually regained after 6 months of therapy, often continuing to rise with long-term use (Michelson et al., 1999; Ferguson, 2001; Hirschfeld, 2003; Aronne & Segal, 2003; Demyttenaere, 2008). Recent evidence in fact suggests that some SSRIs may confer weight gain that is comparable in magnitude to tricyclic antidepressants with long-term use (Kivimaki et al., 2010). In addition to weight gain, SSRIs have been associated with other metabolically adverse effects such as diabetes, hypercholesterolemia, and abdominal obesity (Raeder et al., 2006, Andersohn et al., 2009).

As a consequence of expanding knowledge regarding the association between SSRI's and weight change, the amount of literature examining this effect has increased and was comprehensively synthesized in a recent meta-analysis by Serretti and Mandelli that examined the effects of all currently available antidepressants on weight gain in both acute (4-12 weeks) and maintenance (> 4 months) treatment (Serretti & Mandelli, 2010). Results from this study confirmed the heterogeneity in the weight-inducing capacity of antidepressants, both between and within classes, and confirmed a linked between weight change and medication use.

Mechanisms of Antidepressant-Induced Weight Gain

The weight gain effect of SSRIs appears at first to be paradoxical since serotonin is known to reduce carbohydrate cravings and appetite (Bouwer & Harvey, 1996, Harvey & Bouwer, 2000). It has been suggested, however, that the long-term weight gain can in fact be explained by the imperfect selectivity of SSRIs, suggesting that with prolonged use, SSRIs may begin to have unwanted interactions with receptors other than their target 5HT-receptors. For instance, of the six currently available SSRIs, citalopram has the highest affinity for the H_1 histamine receptor, acting as an antagonist and increasing carbohydrate cravings with prolonged use (Harvey & Bouwer, 2000). In addition, paroxetine has been shown to have the highest affinity to muscarinic cholinergic receptors among SSRIs (Thomas et al., 1987; Hyttel, 1994). The antimuscarinic action of paroxetine would thus lead to the

anticholinergic side effect of dry mouth, which in turn may lead to increased ingestion of high-caloric liquids (Lindenmayer et al., 2001). The weight gain experienced with the TCA amitriptyline has also been linked to this antidepressant's high affinity for α-adrenergic, histaminergic, and cholinergic receptors (Schatzberg et al., 2007). It is also possible that weight gain is occurring as a result of decreased energy expenditure, as opposed to increased energy intake. Studies on TCA's have shown this class of antidepressants to be associated with a decrease in the basal metabolic rate (BMR) (Fernstrom et al., 1985) but to date no work in this area on SSRIs has occurred.

Conclusion

While it is clear that there is a strong association between MDD and obesity, the specific mechanisms mediating this association are poorly understood. The complex relationship is made more so by the use of antidepressants known to induce weight change. The issues related to MDD and weight change have become a significant health concern and, as a consequence, a number of prevention programs have been initiated by hospitals and governments to try to minimize the physical health problems that exist in these patients. While these programs are good in theory, they are problematic in that they are aimed at changing behavior but we do not yet know which types of behavior should be targeted in this population. Work needs to be done to address this gap in knowledge to help direct care and enable appropriate primary and secondary prevention.

CHAPTER 2: An overview of physiological markers of depression and obesity

Inflammatory Cytokines and Adipokines

Obesity predisposes individuals to an increased risk of developing many diseases, including atherosclerosis, diabetes, non-alcoholic fatty liver disease, certain cancers and immune-mediated disorders such as asthma (Calle et al., 2004; Wellen et al., 2005; Mannino et al., 2006). Part of this increased vulnerability is related to the ability of adipose tissue to function as an endocrine organ and secrete a wide range of hormones. Among the soluble mediators derived from adipocytes (fat cells) are the adipokines leptin, adiponectin and resistin, all of which are considered to play a role in the regulation of energy metabolism (Calle et al., 2004; Wellen et al., 2005; Mannino et al., 2006). Other products of adipose tissue that have been characterized include pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), and interleukin-6 (IL-6).

Obesity is associated with a chronic inflammatory response characterized by abnormal cytokine and adipokine production, increased synthesis of acute-phase reactants and the activation of pro-inflammatory signaling pathways (Wellen et al., 2005).

Leptin

Leptin is produced primarily by differentiated adipocytes and exerts influence on the central nervous system (CNS) by suppressing food intake and stimulating energy expenditure (Munzberg, 2010). It was initially identified as an anti-obesity hormone, acting as a negative feedback adiposity signal to control

energy homeostasis by interacting with its receptors in the hypothalamus (Elmquist et al., 1998). Under conditions of regular eating cycles leptin levels exponentially reflect the proportion of adipose tissue (Frayn et al., 2003) and the most important variable that determines leptin concentration is body fat mass (Speakman et al., 2002). As a consequence of its role in satiety, leptin was initially thought to have an application in obesity treatment but conversely, obese individuals often have increased leptin concentrations (Rosicka et al., 2003). The high leptin levels associated with obesity are thought to be caused by leptin resistance, much as high insulin levels in type 2 diabetic patients are a consequence of resistance to insulin. Leptin resistance may occur on several levels, including impaired transport of leptin across the blood brain barrier, reduced function of the leptin receptor, and defects in leptin signal transduction (El-Haschimi et al., 2000; Munzberg et al., 2005).

Leptin in Depression

Leptin plays a role in the bidirectional communication between the hypothalamic pituitary adrenal (HPA) axis and the adipose system; however, the relationship between these systems has not been clearly defined and most likely involves other as of yet unidentified factors. Leptin expression is ultimately stimulated by glucocorticoids (Dagogo-Jack et al., 1996) but chronic or high intensity stress offsets this stimulatory effect and causes a reduction in leptin levels (Sandoval et al., 2003). Studies have identified low leptin levels and depressive-like behaviours in rodents exposed to chronic stress, an effect that was reversed with

systemic and intrahippocampal infusion of leptin (Kim et al., 2006; Lu et al., 2006). In human subjects, there is no consensus on leptin levels in depressed patients, with some studies reporting elevated leptin levels (Antonijevic et al., 1998; Rubin et al., 2002; Esel et al., 2005), some reporting reduced leptin levels (Kraus et al., 2001; Jow et al., 2006), and some reporting no change (Deuschle et al., 1996, Kauffman et al., 2005). Possible explanations for these discrepancies may be related to the different clinical features of the groups, the number of subjects being investigated, and study design. For example, the study by Antonijevic and colleagues (1998) studied only 15 patients with depression, all of whom were normal weight, with leptin concentrations being evaluated nocturnally. In contrast, Kraus and colleagues (2001) studied 62 patients with depression with variable BMI's, and Deuschle and colleagues (1996) investigated 24 patients with depression, all of whom were suffering from loss of appetite. In addition, there may be a sexual diergism in leptin levels. The study by Esel and colleagues (2005) investigated leptin levels only in female patients with depression, noting an increase in leptin levels. This finding was consistent with the study by Rubin and colleagues (2002), who found increased leptin levels in women with depression but not in men with depression. Notably, this study also had low numbers, with only 12 women and 8 men in the depressed group.

Leptin is involved in modulating the immune response and increases the production of pro-inflammatory cytokines such as TNFa, IL-6 and CRP (Gainsford et al., 1996). Given that depression is considered to be a pro-inflammatory state (Goldstein et al., 2009), and that dysregulation of the HPA axis is at the center of the

shared biology between depression and obesity (Bornstein et al., 2006), it is of interest to study leptin levels in depressed patients while weight change is monitored.

Much like the role of leptin in depression, the effect of antidepressants on leptin levels remains controversial. One rodent study showed decreased leptin production in a group of stressed rats administered fluoxetine when compared to healthy control rats (Gamaro et al., 2008). However, the treated rats also decreased their consumption of sweet food, so it is possible that the low leptin could be in response to reduced food intake rather than a direct anorectic mechanism. In human studies, there has been some evidence to suggest that antidepressant treatment may lead to an increase in leptin concentration (Moosa et al., 2003; Esel et al., 2005; Himmerich et al., 2007). In one case, this effect was observed even with weight loss during fluoxetine treatment, although with no statistical significance due to a small number of subjects (Moosa et al., 2003). Since leptin production is stimulated by glucocorticoids, it is possible that these observed increases in leptin are a result of antidepressant-mediated HPA axis normalization and improvement in glucocorticoid receptor sensitivity (Himmerich et al., 2007). This is further supported by a study in which, despite improvement in depression scores, both high cortisol levels and leptin levels remained unchanged in depressed patients receiving treatment with the SSRI citalopram (Kauffman et al., 2005). Another study with the tricyclic antidepressant (TCA) amitriptyline and the SSRI paroxetine revealed no changes in leptin levels before and after treatment (Hinze-Selch et al., 2000), while

yet another study found variably increased leptin levels with the tetracyclic antidepressant (TeCA) mirtazapine, and no changes in leptin levels with Venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI) (Kraus et al., 2002).

Adiponectin

Adiponectin is primarily an adipocyte secretory protein involved in glucose and lipid homeostasis (Berg et al., 2002) but it is also expressed by skeletal muscle cells, cardiac myocytes and endothelial cells (Delaigle et al., 2004; Pineiro et al., 2005; Wolf et al., 2006). A negative correlation between obesity and circulating adiponectin has been well established, and serum levels of adiponectin are markedly decreased in individuals with visceral obesity and states of insulin resistance, such as non-alcoholic fatty liver disease, atherosclerosis and type 2 diabetes mellitus (Arita et al., 1999). Adiponectin regulates the expression of several pro- and anti-inflammatory cytokines and has been shown to both reduce secretion of and attenuate the biological effects of TNF-α (Aldhahi et al., 2003; Fernandez-Real et al., 2003; Ouchi et al., 2003) and to induce the production of anti-inflammatory cytokines such as interleukin-10 (IL-10) and IL-1 receptor antagonist (IL-1RA) (Maeda et al., 2002). Expression of adiponectin is also regulated by pro-inflammatory mediators such as IL-6, which have been shown to suppress adiponectin transcription and translation (Fasshauer et al., 2003a). Weight loss is a potent inducer of adiponectin synthesis (Bruun et al., 2003) and the decreased synthesis of adiponectin, as is observed in individuals who are obese, might lead to

dysregulation of the controls that inhibit the production of pro-inflammatory cytokines, thereby leading to the production of increased amounts of pro-inflammatory mediators. The HPA axis also plays a role in adiponectin regulation; adiponectin gene expression is reversibly down regulated by dexamethasone (Fasshauer et al., 2002) and glucocorticoids have been shown to inhibit adiponectin function (Fallo et al., 2004).

Adiponectin in Depression

Recently, low levels of adiponectin, the most abundant adipocyte-secreted plasma protein, have been observed in patients with depression and anxiety (Leo et al., 2006; Nagata & Yamada, 2006). The low levels of adiponectin observed in both obese individuals and lean depressed patients has led to the adiponectin hypothesis, which stipulates that low adiponectin and a depressed mood state in obese individuals may be interdependent on each other (Yilmaz, 2008). It has also been suggested that the resultant hypoadiponectinemia of obesity and depression is additive, with both conditions having a greater effect on adiponectin than either does alone (Zeugmann et al., 2010). Clinical studies examining adiponectin in depressed patients, however, have not been conclusive, with some studies unable to find the aforementioned decrease in adiponectin (Mamalakis et al., 2006; Weber-Hamann et al., 2007; Pan et al., 2008). Maintenance treatment with antidepressants might also affect adiponectin levels in depressed patients since compared to healthy

controls, higher levels of adiponectin have been observed in MDD patients in remission receiving either SSRIs or SNRIs (Leo et al., 2006). This suggests a possible anti-inflammatory role of antidepressants.

Resistin

The adipokine resistin is produced by adipocytes, macrophages, muscle and pancreatic cells (Holcomb et al., 2000) and its physiologic role in humans is still unclear (Flier, 2001). Initial studies demonstrated that obesity induced by a high-fat diet or mutation of the leptin gene or receptor is associated with increased circulating resistin concentrations (Shuldiner et al., 2001; Steppan et al., 2001; Ukkola, 2002) but other groups have observed opposite results, showing that resistin expression was down-regulated in genetically and diet-induced rodent models (Way et al., 2001; Milan et al., 2002; Rajala et al., 2003) and suppressed by free fatty acids (Juan et al., 2001). Some of this inconsistency may be explained by the resistin measures between studies. For example, the study by Steppan and colleagues (2001) showed higher serum levels of resistin in obese mice, whereas Milan and colleagues (2002) observed decreased resistin mRNA expression in the visceral adipose tissue (VAT) of obese mice. This could possibly be explained by post-translational regulation of resistin. In humans, adipose tissue from lean subjects has shown only weak expression of resistin (McTernan et al., 2002), whereas consistent expression of resistin has been found in morbidly obese

individuals (Savage et al., 2001). Overall, evidence that supports resistin as a mediator of obesity remains controversial.

While the primary function of resistin in humans has not yet been elucidated, its pro-inflammatory properties indicate it has a role in inflammatory processes (Kusminski et al., 2005) and is likely involved in the chronic inflammatory reactions associated with obesity (Gomez-Ambrosi et al., 2001; Rajala et al., 2003; Rea et al., 2004). Human resistin also stimulates synthesis of the pro-inflammatory cytokines TNF-α, IL-1, IL-6 and IL-12 (Kaser et al., 2003; Silswal et al., 2005) and in turn, resistin mRNA is markedly increased by the pro-inflammatory cytokines IL-1, IL-6 and TNF- α. In addition, factors such as pituitary, steroid and thyroid hormones and insulin modulate resistin expression. The interaction between leptin and resistin is also not yet fully understood, with a correlation between the two molecules being observed in healthy controls but not in patients with severe inflammatory disease (Kaser et al., 2003; Gomez-Ambrosi et al., 2001).

Resistin in Depression

To date, there have been 4 studies that examine the relationship between resistin and depression. One study on Chinese patients found no link between typical depression and resistin levels (Pan et al., 2008) while two more recent studies found a positive correlation between resistin levels and atypical depression, but no correlation in patients with typical depression (Pan et al., 2008; Lehto et al., 2010; Zeugmann et al., 2010). These results seem to support previous biological

data on differences between typical and atypical subtypes of MDD (Stewart et al., 2007). Another study found that patients with depression remitting under amitriptyline and paroxetine showed a decrease in resistin, while non-remitters showed no change (Weber-Hamann et al., 2007). This study does not state whether patients presented with typical or atypical MDD, but seems to support antidepressants' anti-inflammatory effect and the role of resistin in inflammatory response. While much remains to be discovered about the role of resistin, its links to inflammatory processes and an as of yet controversial role in depression makes it an interesting biomarker to continue investigating in depressed patients.

Tumor Necrosis Factor Alpha

TNF-α is a pro-inflammatory cytokine involved in systemic inflammation. It is primarily produced by macrophages, but a broad variety of other cell types including lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts, and neuronal tissue also contribute to TNF-α production. The first link between obesity and an increase in TNF-α expression was reported by Hotamisligil and colleagues (Hotamisligil et al., 1993) and their findings in rodents that adipocytes directly express TNF-α helped originate the concept of inflammation playing a role in obesity. These observations were paralleled by human studies that have shown increased TNF-α expression in the adipose tissue of individuals who were obese and decreased TNF-α expression after weight loss (Kern et al., 1995; Uysal et al., 1997; Fantuzzi, 2005). TNF-α is also regulated by other mediators linked

to adiposity, and its levels are increased by resistin, leptin, and IL-6 and decreased by adiponectin (Kaser et al., 2003; Silswal et al., 2005). TNF-α in turn plays a role in CRP production (Marino et al., 1997).

Interleukin-6

IL-6 is a circulating cytokine secreted by a number of different cell types including activated macrophages and lymphocytes. Adipocytes themselves can also produce and secrete IL-6 (Bastard et al., 2000; Sopasakis et al., 2004) and adipose tissue has been shown to contribute to 10–35% of circulating IL-6 plasma levels in resting, healthy humans (Mohamed-Ali et al., 1997). A number of factors influence IL-6 levels as it is inhibited by glucocorticoids and induced by insulin and catecholamines (Vicennati et al., 2002). IL-6 expression and secretion is also induced by TNF-α (Pang et al., 1994) and there is evidence that IL-6, in turn, regulates the release of TNF-α directly (Fasshauer et al., 2003b). IL-6 is also the primary mediator of hepatic CRP secretion (Marino et al., 1997).

C-Reactive Protein

CRP is an acute-phase inflammatory marker produced mainly in the liver (Blake et al., 2002) primarily as a result of stimulation by IL-6, (Pearson et al., 2003) although other inflammatory markers such as TNF-a may also play a role (Marino et al., 1997). This coupling of CRP levels to those of other inflammatory markers therefore results in an increase in CRP levels as a consequence of adiposity. This

ultimately leads to an increase in the levels of other pro-inflammatory cytokines, given that CRP can facilitate the release of IL-6 and TNF-α as well as increase the release of the soluble IL-6 receptor from macrophages and foam cells in the neointima (Pasceri et al., 2001; Verma et al., 2002).

Inflammatory Markers in Depression

Over the past decade, a strong research interest has developed regarding the connection between inflammatory response and depression. To date, numerous studies have explored pro-inflammatory cytokines in depressed patients. Most frequently, these studies have identified a marked increase in plasma levels of CRP and IL-6 in patients suffering from depression compared to healthy controls (Lanquillon et al., 2000; Ford et al., 2004; Alesci et al., 2005; Carvalho et al., 2008; Howren et al., 2009; Miller et al., 2009). TNF-α has also been widely studied and found to be elevated in depressed patients (Mikova et al., 2001; Hestad et al., 2003; Tuglu et al., 2003; Miller et al., 2009), however, studies exploring all 3 inflammatory markers have not been conclusive. A recent twin study evaluated levels of CRP, IL-6 and TNF-α in both monozygotic and dizygotic twins and found that twins with MDD had elevated levels of CRP and IL-6 compared to their co-twins, but with no significant difference in TNF-α levels (Vaccarino et al., 2008). The same study also found a larger association between MDD and inflammatory markers among dizygotic twins compared to monozygotic twins, supporting the idea that genes

promoting inflammation are involved in the pathogenesis of MDD (Vaccarino et al., 2008).

The causal relationship between inflammation and depression remains undefined. A recent longitudinal study suggests that depressive symptoms may precede a rise in mediators associated with increased inflammatory response (Stewart et al., 2009) and studies on rodents have demonstrated that administration of pro-inflammatory agents can cause sickness behaviours resembling depression (Yirmiya, 1996; Dantzer, 2001; Dantzer et al., 2008). It is therefore possible that the association between inflammation and depression involves complex bidirectionality through correlates of depression in the CNS (Howren et al., 2009). A depression-induced decrease of parasympathetic activity, for example, may lead to inflammation, which in turn would cause a cytokine-induced increase in HPA activity leading to higher cortisol levels and worsening depressive symptoms (Howren et al., 2009).

The effect of antidepressant treatment on inflammatory response has also been examined recently, under the assumption that since depression is associated with inflammation, a decrease in inflammatory markers would be reasonably expected with antidepressant treatment. Antidepressant treatment studies examining CRP levels, however, have not been conclusive, with some studies reporting a decrease in CRP post-treatment (Lanquillon et al., 2000; Tuglu et al., 2003; Tousoulis et al., 2009), while others have shown no change. (Corcoran et al., 2005; Piletz et al., 2009; Chen et al., 2010). Studies examining IL-6 have also been

variable, with some results suggesting a decrease in IL-6 post-treatment (Lanquillon et al., 2000) and others suggesting an increase in IL-6 (Chen et al., 2010). Similarly, treatment studies examining TNF-α have reported no change post-treatment in some cases (Chen et al., 2010; Kraus et al., 2002), and a decrease of TNF-α in others (Lanquillon et al., 2000). Notably, one study showed an increase in TNF-α levels with mirtazapine treatment, but this was likely due to substantial weight gain (Kraus et al., 2002). It is also interesting to note that antidepressant medication and response to antidepressant medication may differentially affect levels of CRP, IL-6 and TNF-α. In one study, CRP and TNF-α were elevated in depressed patients prior to any treatment (Lanquillon et al., 2000). However, while CRP decreased in all patients post-treatment, TNF-α only decreased in the patient subgroup that responded to medication. In the same study, pre-treatment IL-6 was found to only be elevated in the patient subgroup that did not respond to medication, suggesting that IL-6 can be used to dichotomize patients into responders and non-responders upon admission, and that TNF-α in particular is related to psychopathological improvement (Lanquillon et al., 2000).

Conclusion

The association between the physiological correlates of both depression and obesity is complex and we do not yet have a clear understanding of how these illnesses are linked. There does seem to be plausible evidence linking the conditions, however, and further exploration of this overlap may help us understand and treat both conditions.

CHAPTER 3: Changes in food consumption, physical activity, and basal metabolic rate in depressed patients treated with serotonin reuptake inhibitors

Abstract

Background: Patients with major depressive disorder (MDD) often experience weight gain, a problem that is complicated by the iatrogenic influence of antidepressants such as serotonin reuptake inhibitors (SSRIs). To date, little has been done to delineate the mechanisms that result in this weight gain. *Objectives:* To determine if there is a change in food consumption, activity level and/or BMR 3 and 6 months from baseline after the initiation of pharmacotherapy. We will determine if change in any of these predictor variables is associated with a change in BMI. *Methods:* Seven patients were evaluated via clinical interview to confirm a diagnosis of MDD. Patients were evaluated for anthropomorphic measures, physical activity, dietary intake, and basal metabolic rate (BMR) at baseline (prior to medication), 3 months, and 6 months. *Results:* Although not quite statistically significant ($p = 0.068$), patients consistently gained weight over the 6 months of treatment (baseline BMI: 31.2±4.0 kg/m^2, 6 months BMI: 32.2±4.8 kg/m^2). There was a significant decrease in caloric consumption over the 6 months of treatment ($p = 0.017$). There was a trend towards increased physical activity that was not statistically significant ($p = 0.91$). There was no observable trend in changes in BMR ($p = 0.78$). *Limitations:* The small sample size of this exploratory study was the most significant limitation. The validity of metabolic testing is also questionable in light of low respiratory exchange ratio (RER) values. *Conclusions:* It is unlikely that increased caloric consumption can account for the observed weight gain in our sample. Instead, further investigation on the consumption and expenditure of macronutrients, as well as physical activity, can

shed light on observed increase in weight. Even moderate weight gain can often result in noncompliance and premature discontinuation of treatment. Therefore, proper intervention for this common iatrogenic response necessitates a better understanding of the underlying mechanisms.

Keywords: Weight Gain, Major Depressive Disorder, Dietary Intake, Physical Activity, Basal Metabolic Rate

1. Introduction

The World Health Organization (WHO) estimates that there are more than 1 billion overweight adults globally, of whom at least 300 million are obese (Bifulco & Caruso, 2007). At the most fundamental level, overweight and obesity result from an imbalance between caloric intake and usage; however, there is no consensus as to whether the current obesity epidemic in North America is primarily the result of high levels of physical inactivity or high dietary intake of energy-dense foods. This issue becomes more complex in patients with mental illness due to the iatrogenic influence of psychiatric medication on metabolism.

Individuals with a mood disorder appear at particular risk for obesity (Fagiolini et al., 2002; Fagiolini et al., 2003; Hasler et al., 2004). The mechanisms leading to weight gain in individuals with mood disorders add another later of complexity to an already complex etiology. This is highlighted by the recent results of a large study which confirmed that overweight, obesity and extreme obesity were common in patients with mood disorders but was associated with patient and treatment variables in a complex manner (McElroy et al., 2004). Mood disorders are accompanied by a symptom profile that impacts appetite and energy, two key variables in weight regulation. Hypotheses speculating on the link between obesity and mood disorders also need to consider the contribution of pharmacotherapy; however, the mechanisms by which psychotropic medications induce weight gain are poorly understood. Possible mechanisms for SSRI-induced weight gain include an increase in appetite associated with clinical improvement (Benazzi, 1998),

carbohydrate craving (Bouwer & Harvey, 1996) and changes in serotonin 5-HT2c receptor activity (Sussman et al., 2001). It is also possible that SSRIs may influence energy balance by decreasing basal metabolic rate (BMR) in a similar way to some tricyclic antidepressants (Fernstrom et al., 1985). This study was therefore designed to examine the three main factors known to cause weight gain: food consumption, physical activity level, and BMR.

2. Objectives

The primary objective of this exploratory study is to determine if there is a change in food consumption, activity level and/or BMR 3 and 6 months from baseline after the initiation of pharmacotherapy. As a secondary objective, we will determine if change in any of our predictor variables; food consumption, activity level and BMR are associated with a change in BMI. We hypothesize that identifiable change in at least one of the 3 areas known to contribute to weight gain will become apparent in patients over 6 months, as previous work has demonstrated that, unlike in the general population, weight alteration occurs quickly in this population (Taylor et al., 2008).

3. Methods

3.1 Subjects

Seven patients who met the DSM-IV criteria for major depressive disorder (MDD) participated in this study. The patient population was limited to men and

women ages 18 to 60 (mean age = 46.4, SD = 11.3; 3 females) with single or recurrent episodes, non-psychotic, unipolar major depression (**Table 1**). Patients were recruited through the Mood Disorder's Clinic at St. Joseph's Healthcare (Hamilton, Canada), where they were diagnosed via the administration of the Structured Clinical Interview for DSM-IV (SCID). Participants were identified through review of patients having previously given consent to be approached for research studies. In addition, clinic healthcare providers, having obtained the patient's permission, identified to research staff potential participants. Research staff subsequently approached potential participants to explain the study, and obtain informed consent. Participants were assured that refusal to consent to contact or consent for participation in the study will in no way affect the care provided to the participant at St. Joseph's Healthcare. The study was also advertised at all Hamilton Hospitals through flyers provided to Hamilton Health Sciences. In addition, Campus Health physicians at McMaster University were approached regarding the study. In total, approximately 50 patients were approached about possible participation. Patients who were not interested in participating commonly cited lack of interest and distance as reasons for not participating.

Prior to the initiation of new pharmacotherapy, baseline measures were obtained. Patients were assessed via tools designed to record changes in three parameters known to impact weight: caloric consumption, physical activity and intrinsic BMR. Anthropomorphic measurements including weight, height and waist circumference were also obtained while mood symptoms were monitored at each

time interval using the 17-item Hamilton Depression Rating Scale (Ham-D; M. Hamilton, 1960), the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978), the Clinical Global Impression Scale (CGI; Guy, 1976), and the Global Assessment of Functioning Scale (GAF; American Psychiatric Association 1994).

Exclusion criteria for participants in this study included i) a lifetime history of alcohol or substance dependence, ii) current treatment with medications known to impact weight, other than those prescribed for the treatment of MDD (e.g. steroids, stimulants), iii) medical conditions known to impact weight (e.g. thyroid illness), iv) current involvement in an active weight loss program, and v) weight fluctuations of greater than 10 lbs. in the 6 months prior to study onset.

3.2 Data Collection

All measurements were obtained at baseline (prior to medication initiation), and then after 3 months and 6 months of pharmacotherapy. At each time interval, patients came in for two clinical visits. On the first visit, mood was assessed using the HAM-D, YMRS, CGI and GAF. Physical measures including weight, height, waist and hip circumference were obtained and a food diary and ActiTrainer monitor were given to patients with instructions (refer to section 3.6 below). Three to seven days later, patients came back for their second visit to return the completed food diary and ActiTrainer monitor. Patients were required to fast for 12 hours prior to this visit, and in this fasting state a BMR recording was obtained. For more detail on patient evaluation, see the case report form (CRF) in **Appendix 1** (page 84).

3.3 Anthropomorphic Measures

During the first clinical visit of each assessment interval, body weight was measured in pounds (later converted to kg) using a standard balance beam scale after patients were instructed to remove their shoes, jackets, and all objects from their pockets. Height was then measured barefoot using a standard stadiometer, with the back of the heels and back flat against the beam and these measurements were used to calculate body mass index (BMI), which has been shown to be a reliable correlate of fat mass in middle-aged men and women (Hasler et al., 2004). Waist circumference was measured twice using a plastic tape measure at the largest abdominal circumference to the nearest millimeter, and the average of the two measurements was used (Nicklas et al., 2004; Vogelzangs et al., 2008).

3.4 Dietary Assessment

A prospective method of a non-consecutive 3-day dietary record, with one day being a weekend day, was used for food intake data collection (Willett & Leibel, 2002), as it has been demonstrated that 3-day records are sufficient to estimate habitual energy intake to within 10% of the actual values in groups as small as 13 individuals (Basiotis et al., 1987). Food diaries were provided to all study participants and they were instructed both verbally and in writing to record all dietary information in as much detail as possible, including brand names. The Nutritionist Pro software, which has been validated and standardized, was then used

to calculate and assess the mean daily caloric intake (Kcal/day), percent dietary fat, and percent dietary carbohydrate intake.

3.5 Dietary Data Input

Studies comparing dietary assessment methods have shown that, when compared to food frequency questionnaires, 3-day dietary records correlated better with actual measured dietary components (Schaefer et al., 2000). In addition, 3-day dietary records have been found to correlate strongly with 7-day dietary records for caloric consumption (r = 0.79), fat intake (r = 0.74), and carbohydrate intake (r = 0.90) (Stuff et al., 1983). Despite this, limitations on dietary data collection have been a longstanding problem in nutritional epidemiology. The most notable limitation of dietary data collection is reporting error by the subjects (Michaliszyn et al., 2009; Scagliusi et al., 2009) and while eliminating reporting error is not feasible, measures were taken to decrease the potential of such errors. Upon each visit, patients were reinstructed on proper dietary recording, emphasizing details such as cooking methods and ingredients. Patients were also reassured that they should not feel embarrassed about any food, and that this study is non-interventional so we are not trying to change their diets.

When importing the data into the Nutritionist Pro software, some details were inferred on the basis of the most common variations of items. For instance, if an entry listed "slice of pizza" it was inferred that the slice was "pepperoni and cheese". In some cases, entries recorded by the patients were not found in the

Nutritionist Pro databases. For these entries, the most important nutritional components (i.e. number of calories, percent fat, carbohydrate, and protein) were searched online, and the closest match from the Nutritionist Pro databases were used. In addition, two investigators independently imported all dietary records into Nutritionist Pro and the resulting values were averaged. Subjectively, no major discrepancies were found between the two sets of entered data. To objectively test the inter-rater reliability, SPSS was used to determine intra-class correlations for caloric expenditure, percent fat intake, and percent carbohydrate intake. The two-way mixed model was utilized to test the absolute agreement between data sets. This model is appropriate when the same raters rate each subject and the raters are not drawn randomly from a population of raters (Shrout & Fleiss, 1979).

3.6 Physical Activity

Physical activity was monitored using the ActiTrainer personal activity monitor by ActiGraph. The ActiTrainer was designed to monitor human activity and record energy expenditure (calories spent during normal, everyday activity). This device is a small monitor (8.6cm x. 3.3cm x 1.5cm) that patients were instructed to wear at the hip and only remove when bathing. The ActiTrainer measures acceleration in the vertical plane using a uniaxial piezoelectric accelerometer. Data output is reported as activity counts using the manufacturer's software (ActiGraph, 2005). Since 80% reliability in the variance of activity is achieved with 3-4 days of monitoring (Trost et al., 2005), patients wore the ActiTrainer continuously for three

days (72 hours) at each time point. To account for different patterns of activity on weekends compared to weekdays (Metzger et al., 2008), patients wore the monitor for two weekdays and one weekend day. The ActiTrainer was set to record at 60-second epochs, compatible with caloric output algorithm.

3.7 Physical Activity Data Input

Data from the ActiTrainer monitors were downloaded to a computer through the ActiLife Software and imported into Microsoft Excel for analysis. It was also manually screened for periods in the data file that indicated that the patients were either not wearing the monitors or sleeping with no appreciable activity and these discrepancies were accounted for. To date, there has not been an established standard for eliminating such data and while some studies use periods in the data of zero accelerometer counts for ≥20 continuous minutes as indicative of the monitor not being worn (Stevens et al., 2007) other studies have set the criteria at ≥30 minutes of zero counts for eliminating data (Patnode et al., 2010). Since our population of MDD patients are expected to be generally less active than healthy individuals, we used the less conservative threshold of ≥30 minutes of zero counts as indicative of the monitor not being worn. After these periods were identified in the data, the remaining usable time was used to calculate mean activity counts/minute and mean steps/hour for each patient at each time point. Once the usable time for each accelerometer record was determined, the records were assessed for validity. While again there is no established minimum wear-time for an

accelerometer record to be considered valid, some recent criteria have ranged from ≥6h/day with a minimum of 4 days of recording (Jerome et al., 2009) to 10h/day of recorded data (Colley et al., 2010). For this study, we adopted the ≥6 h/day criterion and applied it to our 3 day recordings, though most of the recordings also met the 10h/day criterion.

The ActiLife Software also enabled the estimation of caloric expenditure. The software used patients' weight in kilograms in conjunction with both the Freedson and Work Energy equations to produce an estimation of caloric expenditure. The work-energy theorem uses the gravitational force on a person and the distance traveled (based on counts/minute) to calculate work, which is equivalent to change in energy (ActiGraph, 2005). The Freedson equation was derived from analyzing VO2 consumption in subjects walking and running on a treadmill (ActiGraph, 2005). This method is more accurate but requires activity counts of more than 1952. Therefore, the most accurate results can be obtained by selecting both equations; the work-energy theorem is used for counts equal to or less than 1952, and the Freedson equation is used for counts greater than 1952. After obtaining the total Kcal expenditure over 3 days, it was then divided by the total usable hours of data to produce a mean Kcal/hour data point.)

3.8 Metabolic Assessment

Metabolic assessment was performed at a resting state using the Moxus metabolic cart canopy system. Patients were required to show for testing in the

morning after a 12-hour fast after which time they would be required to lay flat for 20 minutes to achieve a resting state. Following the 20-minute resting period, the Moxus canopy hood was then placed over their head and a plastic seal was draped over their body. Patients were instructed to relax and simply breathe into the hood for 22 minutes while data was collected, with the Moxus was set to produce data at intervals of 10 seconds. The first 2 minutes of data from each recording was discarded to allow for stabilization of recordings and the remaining 20 minutes of data was used to obtain the required measures.

3.9 Metabolic Data Input

Several outcomes were of interest when examining the excel output files produced by the Moxus testing sessions. First, the resting energy expenditure (REE), which is reported in Kcal/min, was averaged over the 20-minute recording period to produce a single mean REE value. A simple calculation converted this value into a Kcal/day BMR value, which is an estimate of the total daily caloric expenditure at rest. The BMR value correlates strongly with body weight, so that individuals with a higher body mass are expected to have greater BMR values (Lazzer et al., 2009). In addition, relatively low BMRs have been found to be a predictor of weight gain in multiple studies (Buscemi et al., 2005; Griffiths et al., 1990; Ravussin et al., 1988).

Secondly, to better gauge the energy consumption of our patients relative to their weight, their resting oxygen consumption ($VO2_{rest}$) per kg of body weight were calculated. To do this, the $VO2_{rest}$ data was averaged over the 20-minute recording

period, and the mean was then divided by patients' weight. This produced a $VO2_{rest}$ value in ml O_2/min/kg of body weight. The accepted average of $VO2_{rest}$ is 3.5 ml O_2/min/kg, which is referred to as a metabolic equivalent (i.e. 1 MET = 3.5 ml O_2/min/kg) (Jette et al., 1990). The MET is a widely used physiological concept but it is worth noting that the adequacy of this convention has recently been investigated and found to overestimate actual VO2 by 35% in a large heterogeneous cohort of overweight individuals (average BMI = 30 kg/m^2) (Byrne et al., 2005). This overestimation was less extreme at 14% in individuals with normal weight (average BMI = 20 kg/m^2). Regardless of the accepted average for $VO2_{rest}$, it appears clear that higher body mass is correlated with lower $VO2_{rest}$ (Byrne et al., 2005). Therefore, it is of interest to monitor changes in oxygen consumption per kg of body weight in conjunction with any changes occurring in body weight.

The third measure of interest extracted from the Moxus files was the respiratory exchange ratio (RER), which is the amount of CO_2 eliminated divided by the amount of O_2 consumed. This value was calculated by the Moxus for each 10-second interval and was simply averaged over the 20-minute recording period to produce single mean RER data points. Under resting conditions, RER can be used as an estimate of the respiratory quotient (RQ), which is the ratio of CO_2 production to O_2 utilization. RQ is of interest in examining weight change since this ratio reflects macronutrient oxidation, with high values indicating relatively low fat oxidation and therefore increased fat accumulation (Marra et al., 2004). In fact, epidemiological studies have shown that high RQ values are predictive of body weight gain (Seidell

et al., 1992; Zurlo et al., 1990; Marra et al., 2004). It is well established that fat metabolism corresponds with an RQ value of 0.70, whereas carbohydrate metabolism corresponds with an RQ value of 1.0 (Sharpe et al., 2009). A balance between the utilization of both macronutrients corresponds with RQ values ranging from 0.8 to 0.9. Therefore, high fasting RQ values reflecting fat accumulation would be considered those near or above 1.0.

3.10 Statistical Analysis

To achieve our primary objective, we examined changes in nutritional intake, activity level and BMR from baseline presentation over a 6-month follow-up interval using a repeated measures ANOVA separately for each outcome treating interval (baseline, 3 month, 6 month) as within-subject factors and gender (male vs. female) as between-subject variable. In cases of unbalanced data where the data was missing completely at random (MCAR), a linear mixed-effects model (LMM) was used instead of repeated measures ANOVA.

To test our secondary objective we examined changes in BMI from baseline presentation over a 6-month follow-up interval using a mixed design ANOVA. We first assessed whether BMI did in fact change over time, using a repeated measures ANOVA with BMI as the outcome, treating interval (baseline, 3 month, 6 month) as within-subject factors and gender (male vs. female) as between-subject variable. We then used correlational analyses (Spearman's rank; two-tailed) to assess the relation

between BMI and 2 of our predictor variables: physical activity and food consumption. Correlation with BMR at this point would not yield meaningful results since baseline and 6 month values are available for only 3 patients. We also assessed the relationship between BMI and age, medication dose (equivalent mg paroxetine) and HAM-D score. All numeric variables, with the exception of age, which is fixed, and BMI, which is already standardized, were measured as percent changes in scores from baseline to 6 months.

4. Results

4.1 Primary Objective

Statistical analyses were done with SPSS version 17.0. Since repeated measures ANOVA assumes sphericity (equal variance for each set of difference scores), when sphericity could not be assumed the Greenhouse-Geisser estimate of sphericity (Ê) was used to adjust *p* values of *F* tests conducted on within-subject variables (Maxwell & Delaney, 2004). The individual values for all measures obtained at baseline, 3 months, and 6 months for the 7 subjects are presented together in one large table in **Appendix 2** (page 93).

Physical activity was assessed across 3 outcomes: activity counts (counts/minute), step counts (steps/hour), and caloric expenditure (Kcal/hour). There was no statistically significant changes for all 3 outcomes: activity counts ($F(2,10) = 0.37$, $p = 0.70$), step counts ($F(2,10) = 0.12$, $p = 0.89$), and caloric expenditure ($F(2,10) = 0.10$, $p = 0.91$). There were no significant interactions

between any of the physical activity measures and gender. Although none of the tests reached statistical significance, it is worth noting that all measures showed a mean increase from baseline to 6 months, with the mean Kcal expenditure increasing from 29.2±15.5 Kcal/hour at baseline to 34.6±18.0 Kcal/hour at 6 months (**Figure 1**). Activity counts and step counts paralleled the increase in caloric output; mean activity counts increased from a baseline value of 224.5±66.5 counts/minute to 244.3±84.3 counts/minute at 6 months, and mean step counts increasing from a baseline value of 370.8±116.2 steps/hour to 421.7±143.6 steps/hour at 6 months (see Appendix 2 on page 93 for details).

These results should be interpreted with caution, as they were not consistent, with 4 subjects showing an increase in activity and 2 subjects showing a decrease in activity. The calculated mean also excludes one subject, whose dramatic decline in activity from baseline to 6 months was determined to be an outlier using box plot analysis. The means including the outlier results for baseline and 6 months are 37.3±25.6 Kcal/hour and 34.9±16.5 Kcal/hour, respectively. This subject was contacted regarding these results and confirmed that physical activity was unusually elevated for 2 of the 3 days of data recording at baseline due to special circumstances. Figure 1 highlights the individual patterns of change in caloric output as well as the mean changes.

In assessing the compliance with the activity monitors, all 21 records for the 7 subjects met the ≥ 6 h/day cut-off of usable data (Jerome et al., 2009), although 3 days of recording were used in this study as apposed to the required 4 days set by

this criterion. In addition, 19 of the 21 records met the ≥ 10 h/day cut off of usable data (Colley et al., 2010). The mean wear-time for all 21 accelerometer records was 13.7±3.1 h/day. Considering the low number of subjects in this study, no accelerometer records were excluded from the analysis.

Diet records were imported into the Nutritionist Pro software separately by two investigators. Two-way mixed model intra-class correlations were used to determine the inter-rater reliability between the imported dietary data. The single measures intra-class correlation for the total caloric intake data entry was 0.976 (95% CI: 0.938 – 0.991, $p < 0.001$). The single measures intra-class correlation for the percent fat intake data entry was 0.887 (95% CI: 0.733 – 0.955, $p < 0.001$). Finally, the single measures intra-class correlation for the percent carbohydrate intake data entry was 0.919 (95% CI: 0.803 – 0.968, $p < 0.001$). Taken together, the intra-class correlations suggest very high concordance between the two investigators involved in dietary data entry.

Diet was assessed across 3 outcomes: caloric intake (Kcal/day), percent fat intake (%/day), and percent carbohydrate intake (%/day). Due to missing data, a repeated measures ANOVA analysis was not possible. Instead, LMM was used to assess the 3 metabolic outcomes. There was a significant decrease in overall caloric intake ($F(2, 9.99) = 6.33$, $p = 0.017$). However, there were no statistically significant changes in percent fat ($F(2, 10.96) = 1.30$, $p = 0.31$), and percent carbohydrate intake ($F(2, 10.46) = 1.07$, $p = 0.38$). Despite lack of significance, the 5 patients with a complete data at the 3 time intervals showed a mean decrease in percent fat intake

from baseline (31.8±12.7%) to 3 months (29.7±14.7%). This pattern was consistent with only 1 subject showing an increase in fat consumption from baseline to 3 months. The initial decline in fat consumption was followed by an increase in percent fat intake that exceeded the baseline mean at 6 months (37.6±9.3%), with 2 out of the 5 subject showing decreased fat intake from 3 months to 6 months. The 2 subjects with incomplete data showed a decline in fat intake. **Figure 2B** highlights the individual patterns and mean percent fat consumption over the study period.

Percent carbohydrate intake showed an opposing pattern with a consistent initial increase from baseline (46.6±14.6%) to 3 months (52.0±19.9%), with 1 patient showing a decrease. This increase was followed by a decrease at 6 months to a level comparable to the baseline mean (44.8±13.1%), with 1 out of the 5 patients showing an increase from 3 months to 6 months. **Figure 2C** highlights the individual patterns and mean percent carbohydrate consumption over the study period.

As previously mentioned, the effect of food consumption for the caloric intake outcome was significant ($F(2, 9.99) = 6.33$, $p = 0.017$). This is reflected in a dramatic decrease of mean daily caloric consumption from baseline (2,104±773 Kcal/day) to 6 months (1,574±807 Kcal/day), with 5 out of the 6 applicable patients showing a decrease in consumption. **Figure 2A** highlights the individual patterns and mean percent carbohydrate consumption over the study period.

Metabolism was assessed across 3 outcomes: BMR (Kcal/day), VO2 (ml/min/kg), and RER. Due to missing data, a repeated measures ANOVA analysis was not possible. Instead, LMM was used to assess the 3 metabolic outcomes. Using

this method, the effect of metabolism for all 3 outcomes was not significant: BMR ($F(2, 8.31) = 0.25$, $p = 0.78$), VO2 ($F(2, 8.19) = 0.18$, $p = 0.84$), RER ($F(2, 8.29) = 1.79$, $p = 0.23$). Examining individual subject values, no clear pattern for BMR emerges (**Figure 3A**). The 3 subjects with complete data at the three time intervals showed mixed results, which is reflected in the little mean changes for these subjects (2,606±545Kcal/day at baseline, 2,582±543Kcal/day at 3 months, and 2,603±384Kcal/day at 6 months). Three other subjects were missing baseline measures but had 3 and 6 months values. These subjects also showed mixed results over the 3 months period.

VO2 values exhibited a more notable pattern, with most subjects exhibiting an increased VO2 across time intervals.

As the LMM analyses suggests, the strongest pattern that emerged was in the RER outcome. RER values increased across time intervals for 5 of the 7 subjects. **Figure 3B** highlights the individual patterns and mean RER changes over the study period.

Ten of the 17 observed RER values were below 0.70. Since such values are rarely reported and may be indicative of ketogenesis (Schutz and Ravussin, 1980), a ketone analysis was conducted for 3 subjects to test for levels of β-hydroxybutyrate (BHB) at baseline and 6 months. The results from this assessment were plotted in conjunction with changes in RER values for the 3 patients (**Figure 4**). Examining Figure 4, it is clear that lower RER values were associated with higher BHB levels. In addition, RER and BHB levels were inversely related as two subjects showed a

decrease in RER with a corresponding increase in BHB levels, while the third subject showed an increase in RER with a corresponding decrease in BHB level. Despite this, none of the patients reached BHB concentrations that would be indicative of ketogenesis. Taken together, this suggests that RER values, and therefore BMR values, are inaccurate but may have a consistent error such that trends in RER and BMR could still be valuable to assess.

4.2 Secondary Objective

Anthropomorphic measures were assessed across three outcomes: BMI (kg/m^2), weight (kg), and waist circumference (cm). There was no significant change in any of the 3 anthropomorphic measurements obtained: BMI ($F(2, 10) = 3.56$, $p = 0.068$), weight ($F(2, 10) = 3.41$, $p = 0.074$), waist circumference ($F(2, 10) = 1.28$, $p = 0.32$). However, a trend toward an increase in BMI, waist circumference, and weight was observed.

Examining individual changes in waist circumference from baseline to 6 months reveals that 2 subjects had a notable increase for this outcome, while the remaining 5 subjects exhibited little change in either direction. This is reflected in the modest 2.0% difference between the mean waist circumference at baseline (107.7±9.4 cm) and 6 months (109.9±11.2 cm).

Despite little change in waist circumference, subjects consistently gained weight from baseline to 6 months, with the exception of 1 subject. The BMI mean increased from a baseline value of 31.2±4.0 kg/m^2 to a 6 months value of 32.2±4.8

kg/m^2 (**Figure 5**). Statistical analysis revealed no significant interaction between any of the anthropomorphic measures and gender. Figure 4 highlights the individual patterns and mean BMI changes over the study period.

Correlational analyses (Spearman's rank; two-tailed) were used to assess the association between BMI and 2 of our predictor variables: physical activity (represented by the caloric expenditure outcome) and food consumption (represented by the caloric expenditure outcome). We also assessed the relationship between BMI and age, medication dose (equivalent mg paroxetine) and HAM-D score. None of the correlations reached statistical significance. The strongest correlate with BMI was Ham-D score (ρ = -0.50, p = 0.59), with increased BMI being associated with decreased Ham-D scores. There was a moderate correlation between BMI and caloric intake (ρ = -0.36, p = 0.43), such that an increase in BMI was associated with a decrease in caloric intake. There was a weak correlation between BMI and caloric expenditure (ρ = 0.18, p = 0.70), such that an increase in BMI was associated with an increase in caloric expenditure. Medication dose and age were also weakly associated with BMI (dose: ρ = 0.25, p = 0.59; age: ρ = -0.18, p = 0.70), with larger increases in BMI weakly associated with larger dose increases and younger patients.

Power Analysis: Results from pilot data demonstrate a moderate-large effect size (Cohen's d = 0.51) for weight change over a six-month interval for a medication naive population treated primarily with citalopram, the SSRI with the best

documented weight profile (Taylor et al., 2008). Statistical power corresponding to this effect size, with the proposed sample size (n=34) and alpha set at 0.05 (two-tailed), will be greater than 0.80 (critical t-value = 2.03).

5. Discussion

5.1 Significance

This is an exploratory study designed to detect trends that will help focus further, larger studies designed to accurately delineate mechanisms of weight gain and direct appropriate interventions.

Little work has been done to establish the variables that contribute to weight gain in patients with mental illness receiving pharmacotherapy. This study represents the first time the 3 main mechanisms known to cause weight gain have been examined in this population. In terms of physical health outcomes, mental health patients are often viewed as representing a small subset of individuals upon whom the experiences of the non-mentally ill population can be generalized. This is misleading and this study represents the first time technology used to examine weight gain in the general population has been utilized to elucidate mechanisms of weight gain in this population.

In this study, we have observed a general trend towards weight gain in patients with MDD undergoing SSRI treatment. However, only 1 patient from our sample reached clinically significant weight gain after 6 months of SSRI treatment, with clinically significant weight gain defined as 7% or more of initial weight (Sachs

& Guille, 1999). It is possible that following this sample longer than 6 months after SSRI initiation would yield greater increases in weight. In the meta-analysis by Serretti and colleagues (2010), patients taking paroxetine (the SSRI administered to 6 of the 7 patients in the present study) gained less than 1 kg from initiation to maintenance phases between 4 and 7 months. However, following patients taking paroxetine for more than 8 months revealed a weight increase of just below 4 kg, suggesting that most of the weight gain occurring with paroxetine happens after 8 months of treatment. In comparison, we observed a mean weight gain of 3 kg in our sample over 6 months (from 96.1±16.8 kg to 99.1±17.6kg). One patient showed a particularly marked weight increase of 10.8 kg. Removing this patient from the mean calculation reveals a mean increase of 1.6 kg, which is comparable to the findings by Serretti and colleagues. It is, therefore, possible that more weight gain would be observed in our sample with more than 8 months follow-up.

Among the 3 predictor variables explored in this study, food consumption in terms of mean daily caloric intake has yielded the only statistically significant results. Results from the linear mixed-effects model analysis suggest that there is a decrease in caloric intake over 6 months of treatment with SSRIs ($F(2, 9.99) = 6.33$, $p = 0.017$). These results were unexpected, especially considering the moderate correlation found between increased BMI and decreased caloric intake ($\rho = -0.36$, $p = 0.43$). Furthermore, despite a general pattern towards increased BMI (from 31.2±4.0 kg/m^2 at baseline to 32.2±4.8 kg/m^2 at 6 months), 4 of the 7 subjects experienced an increase physical activity.

A possible explanation for this could be related to the proportions of macronutrients being consumed and expended. Under normal conditions, the body is able to switch completely between fat and carbohydrate oxidation, depending on environmental cues and energy demands. It has been suggested that this ability to switch between metabolic fuels is blunted in obese individuals, leading to metabolic inflexibility (Astrup, 2011). In the analysis of dietary intake, this study has demonstrated that the proportion of dietary fat generally increased in our patient population over the 6 months of treatment (from 31.8±12.7% at baseline to 37.6±9.3% at 6 months). In addition, our metabolic analysis has revealed a trend towards increases RER ($F(2, 8.25) = 3.26$, $p = 0.091$), which is normally indicative of decreased fat oxidation. It is, therefore possible that increased fat intake coupled with reduced fat oxidation could help explain the persistent weight gain with decreased caloric intake and increased caloric output. It is worth noting, however, that several RER values were below 0.70. Such values are rarely reported, and could possibly be explained by ketone production. Since hepatic production of ketones occurs at an RER value of zero, a net retention of ketones would result in reduced RER values (Phinney et al., 1980). Insulin resistance in type 2 diabetes can lead to the production of ketone bodies through the release of fatty acids from adipose tissue. It is well established that obesity is strongly associated with increased risk of metabolic and cardiovascular disorders including type 2 diabetes (Grundy, 2004). In addition, studies have linked depression and its associated symptoms with increased risk in the development of type 2 diabetes (Brown et al., 2005). It is

plausible that our population of overweight, depressed patients was experiencing some ketogenesis through a similar mechanism as that described in diabetic insulin resistance. However, although we did observe the expected inverse relationship between RER and BHB levels, studies reporting similar RER values have cited much higher BHB levels. Whereas in our study the highest observed BHB value was 0.41 mmol/L (corresponding to an RER of 0.626), studies have cited values greater than 2 mmol/L corresponding to similar RER values (Owen et al., 1967; Phinney et al., 1980). Additionally, we did not observe any BHB levels that would be indicative of insulin deficiency since all BHB results were below 0.5 mmol/L (Umpierrez et al., 1995).

Alternatively, the low values of RER may be due to methodological error, possibly an error in calibration that underestimates VCO2 or overestimates VO2 (Schutz and Ravussin, 1980). Our data shows a consistent pattern of increase in RER and plausible changes in BMR values. It is, therefore, possible that if there was calibration error occurring that it was consistent. In this case, RER values should not be used to make conclusions, but the pattern of increased RER taken with the increase in the proportion of fat consumption could still help explain the increase in body weight experienced by most patients. It is also possible that total caloric intake was underestimated in this study due to under-reporting of food consumption by subjects, as can often occur with self-reported food diaries (Scagliusi et al., 2009). However, this type of error should also be consistent since subjects who under-report would be expected to do so consistently for the 3 time intervals.

Due to the low power of this study (n = 7), non-significant results should be interpreted with caution. Additionally, it may be useful to examine trends in each of the outcome measures that did not yield significant results in statistical tests due to the low power of the study. In doing so, we note that weight gain seems to be consistent, as 6 patients increased in weight from baseline to 6 months (average = 3.7 kg), with 1 patient losing 0.9 kg.

Examining trends in physical activity changes we note that 4 of the 7 subjects increased their activity level and caloric expenditure, while 3 subjects decreased their activity. One subject who showed a decrease in activity was determined to be an outlier based on the extent of reduction from baseline to 6 months. This subject was contacted and confirmed that he had higher than normal activity during the baseline data collection due to special circumstances. The increase in physical activity experienced by some patients may be due to wellness. Though statistically non-significant, a quick correlational analysis reveals that there is a moderate to strong association between caloric output and Ham-D score (ρ = -0.50, p = 0.25), such that decreased Ham-D scores (indicative of clinical improvement) were associated with increased physical activity.

BMR data, as well as being incomplete, appears to offer no clear trend. The BMR of two patients increased considerably (one from baseline to 6 months, and the other from 3 months to 6 months). One patient showed a considerable decrease in BMR form 3 months to 6 months. Among the remaining three patients, two showed a minor decrease and one showed a minor increase in BMR. As mentioned earlier, RER

data, which is useful in evaluating the metabolic fuels being oxidized, did show a consistent increase, which is normally indicative of reduced fat oxidation. Due to possible methodological errors in metabolic testing, these results should be interpreted with caution.

In addition to examining trends in each of the outcome measures, a case-by-case analysis of each subject's outcomes was conducted and the results are presented in **Appendix 3** (page 95). From these results, physical activity seems to best explained weight fluctuations in many cases. This relationship may have been overlooked in the correlation analysis since the correlation only takes into account the baseline and 6 months values. Examining all intervals, we see that physical activity could help explain 5 instances of weight gain and 2 instances of weight loss. By contrast, caloric intake could only help explain 1 instance of weight gain and 2 instances of weight loss. BMR was useful in explaining 2 instances of weight gain, though based on corresponding RER values the BMR values may be inaccurate. Overall, at least one outcome measure could account for weight fluctuations for all but 2 subjects.

It is worth noting that only 1 of the subject remitted (Ham-D score ≤7) with treatment and 1 patient was classified as partial responder (≥50% reduction in HAM-D-17 score but still higher than 7) (Montes et al., 2004). Interestingly, the subject who responded the most to treatment also experienced the most dramatic weight gain, gaining 8.6 kg at 3 months and an additional 2.2kg at 6 months.

5.2 Limitations

The most significant limitation in this study was the low power due to a low number of participants. This is likely due to the inclusion criteria of the study. Because this study requires participants to be off antidepressant medication upon study initiation, recruitment was difficult at St. Joseph's Healthcare where the majority of patients are chronically ill and continuously on medication. Power analysis based on pilot data suggested that 34 subjects would be sufficient to achieve a power greater than 0.80 for this study. This was based on an observed effect size of $d = 0.51$, which corresponds to effect sizes reported in the literature ranging from moderate-large to large (Ferguson, 2001; Hulley, 2001; Maina et al., 2004; Dannon et al., 2007).

Another setback in this study was the BMR data collection. During active patient recruitment, a change in equipment location accompanied by some technical setbacks resulted in three patients having no baseline BMR measurements and one patient having no 3 months BMR measurement. In the statistical analysis, this missing data was regarded as missing completely at random (MCAR). The main consequence of this limitation was reduced power and inability to deduce patterns for this small sample.

Other limitations of this study lie in the nature of the measures being explored. For food consumption, the researchers had no control over the accuracy of the information being recorded through the dietary record. To minimize this, patients were given detailed instructions prior to initiation of every dietary record.

Similarly, the researchers could not ensure that activity monitors were being used as instructed by the patients. Since the monitors are not likely to be worn at all times as instructed, future studies should use data collection periods longer than 3 days (5 to 7 days is recommended) to ensure that there is enough usable data after filtering out intervals when the monitor seemed to be unworn.

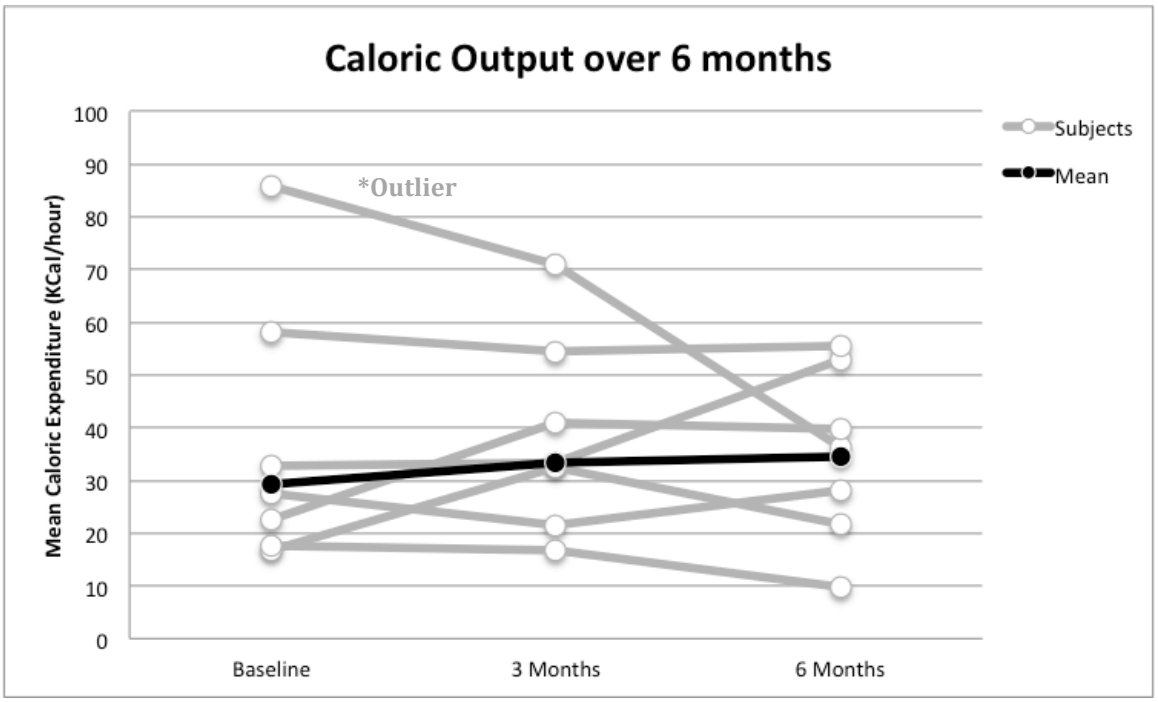
6. Conclusion

This exploratory study has begun to shed light into the mechanisms of weight gain experienced by MDD patients being treated with SSRIs. With a statistically significant decrease in caloric consumption, despite apparent weight gain, continued exploration will hopefully elaborate on metabolic changes. Physical activity also does not seem to be a major contributing factor in weight gain, though results were heterogeneous and warrant further investigation on larger samples. Clinically, it is of great importance to better understand the contributors and mechanisms of weight gain with psychotropic medication. Even moderate weight gain can often result in noncompliance and premature discontinuation of treatment. Proper intervention for this common iatrogenic response necessitates a better understanding of the underlying mechanisms.

Table 1 Clinical and demographic characteristics of study subjects.

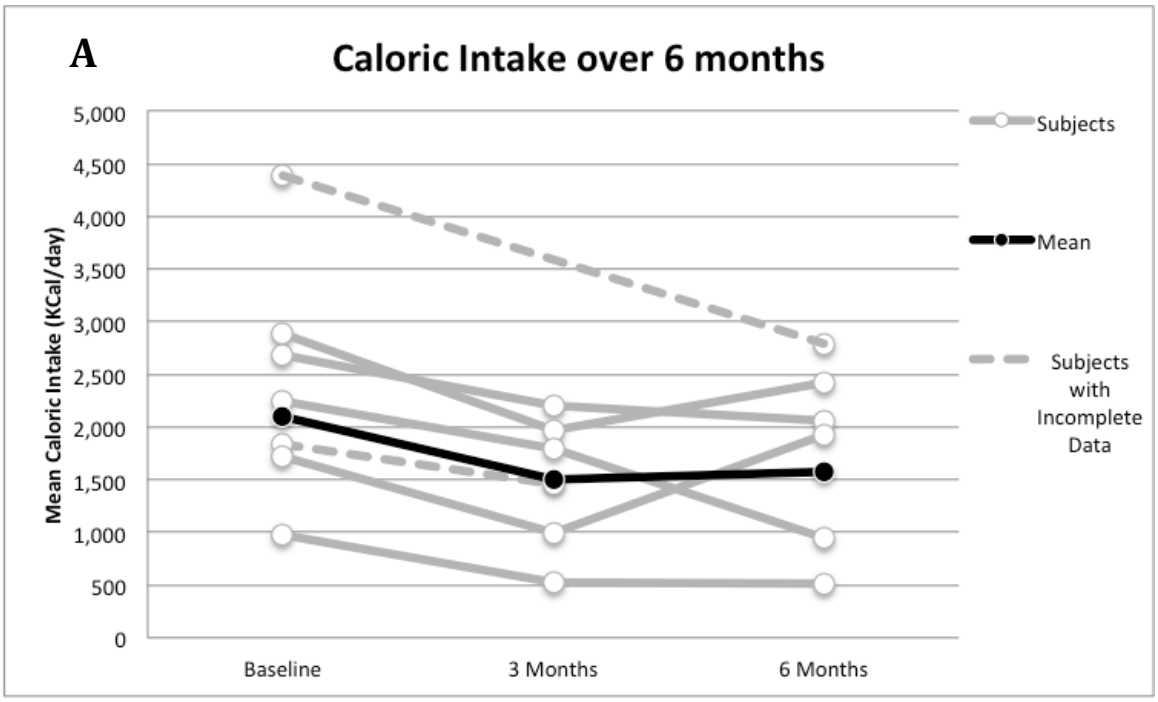
	DSM-IV Diagnosed MDD Patients (n=7)		
Age (at start)	46.4 ± 11.3		
Gender (female)	42.9%		
	Baseline	**3 Months**	**6 Months**
SSRI Dose (equivalent mg paroxetine)	23.1 ± 4.1	27.1 ± 7.6	31.1 ± 8.6
HAM-D17	18.7 ± 6.3	16.6 ± 6.8	16.6 ± 7.8
YMRS	0.7 ± 1.3	0.1 ± 0.4	0.1 ± 0.4
GAF	54.4 ± 7.3	57.3 ± 7.0	57.1 ± 9.0
CGI	4.0 ± 0.6	3.7 ± 0.8	3.9 ± 0.9

Figure 1 Caloric output over 6 months of treatment: individual values and mean

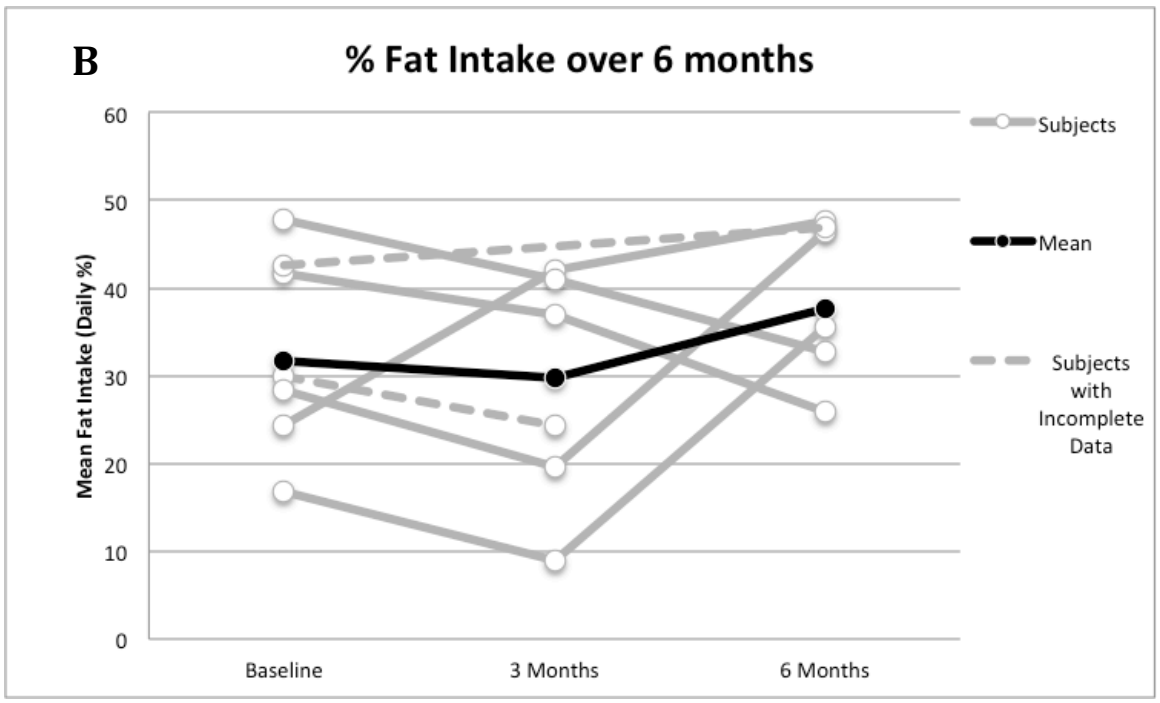


* Outlier subject values were not included in the mean.

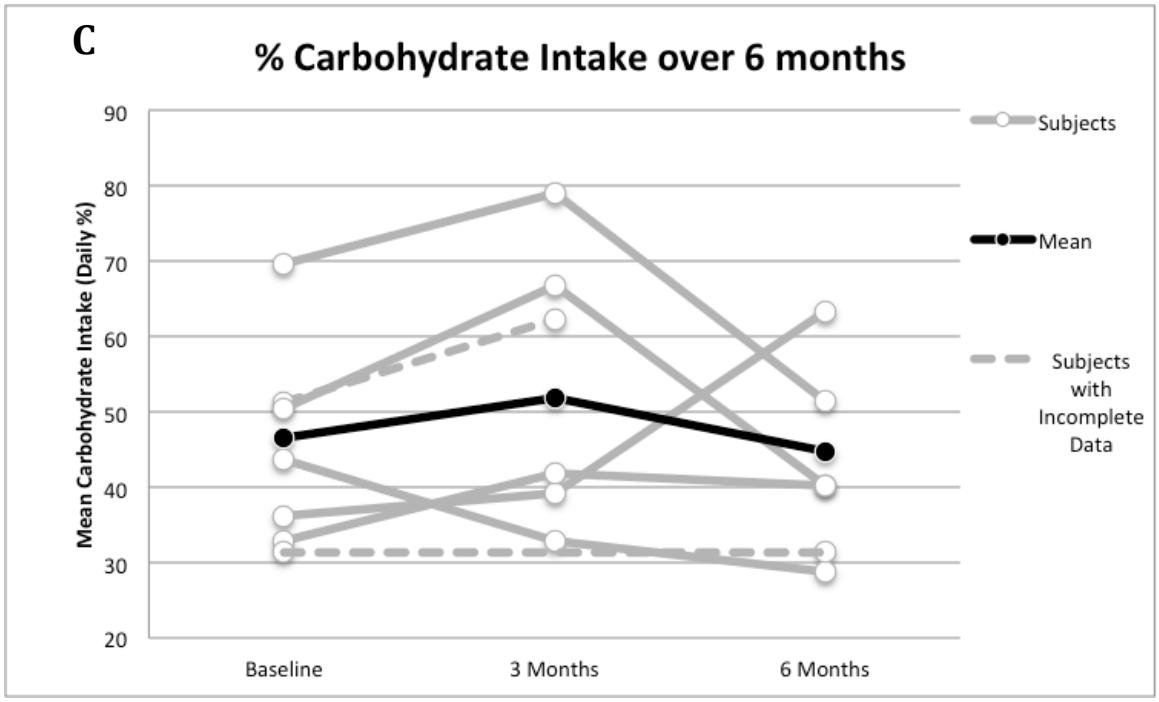
Figure 2 Dietary intake over 6 months of treatment: individual values and mean



* Subjects with incomplete data were not included in the mean.

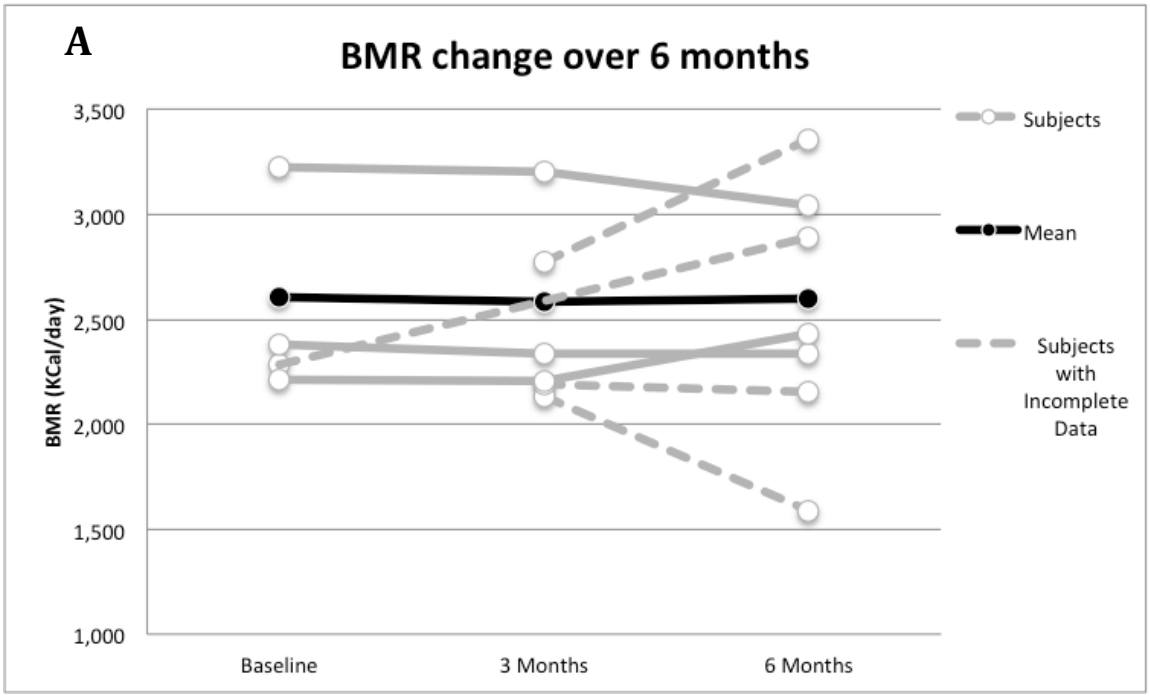


* Subjects with incomplete data were not included in the mean.

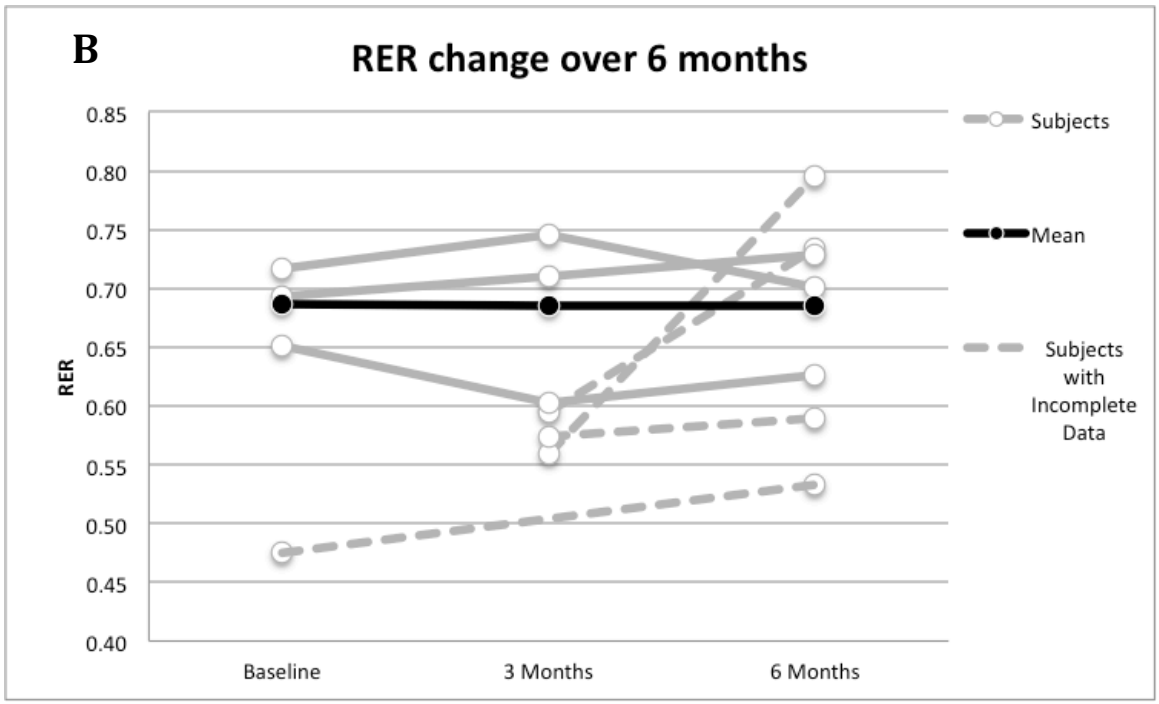


* Subjects with incomplete data were not included in the mean.

Figure 3 Metabolism over 6 months of treatment: individual values and mean



* Subjects with incomplete data were not included in the mean.



* Subjects with incomplete data were not included in the mean.

Figure 4 Respiratory Exchange Ratio compared with β-Hydroxybutyrate levels in 3 subjects over study period

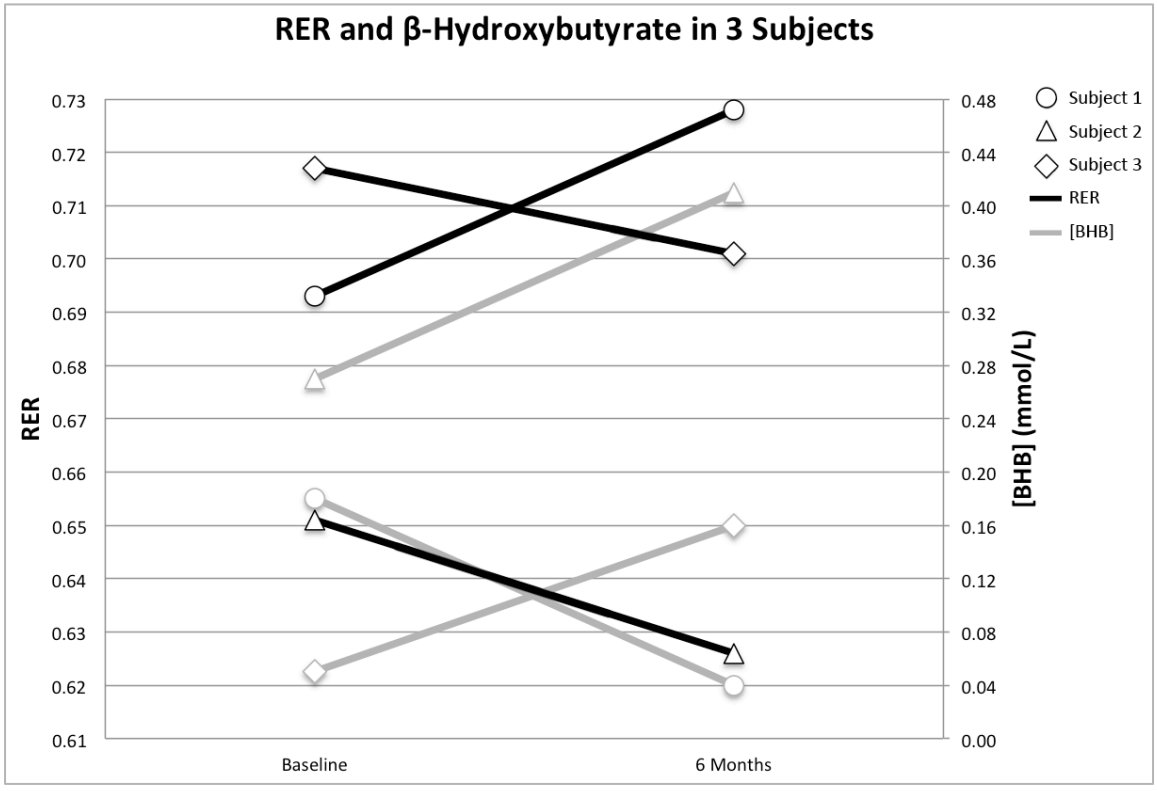
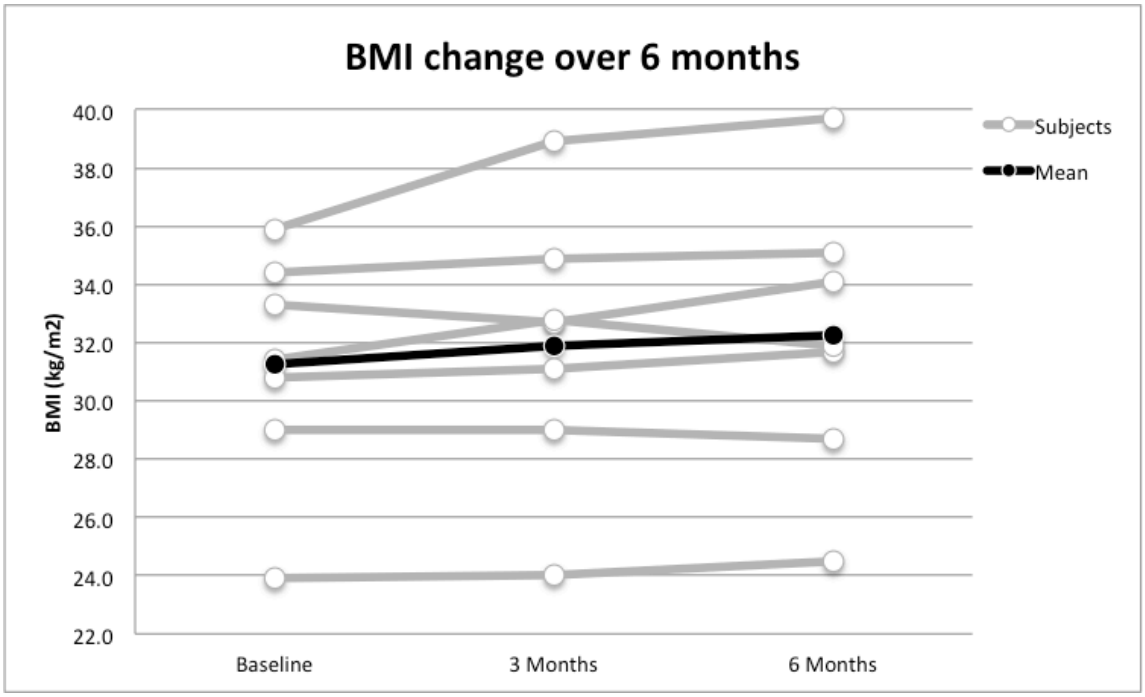


Figure 5 Body Mass Index over 6 months of treatment: individual values and mean



CHAPTER 4: Changes in inflammatory cytokines and adipokines in depressed patients treated with serotonin reuptake inhibitors

Abstract

Background: The adipokines leptin, resistin, and adiponectin; as well as the pro-inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) have been shown to play a role in both depression and obesity. Studies on these biomarkers have often reported conflicting results, and the directionality between these biomarkers and illness remains controversial. *Objectives:* To examine levels of the adipokines leptin, resistin, and adiponectin and the inflammatory markers IL-6, TNF-α, and CRP at baseline, prior to medication use, and 6 months after therapy. *Methods:* Seven patients were evaluated via clinical interview to confirm a diagnosis of MDD. Patients provided blood samples at their baseline and 6 months visits, which were used to determine levels of the 6 biomarkers. *Results:* There was a significant decrease in the concentration of resistin observed in our sample (24.54±4.55 ng/mL to 22.45±4.66 ng/mL; $p = 0.047$). There was also a nearly significant increase in adiponectin concentration over the 6 months (18.40±1.22 μg/mL to 18.80±1.31; $p = 0.061$). The remaining 4 biomarkers did not show statistically significant changes; leptin concentration increased slightly, IL-6 decreased slightly, TNF-α decreased slightly, and CRP showed no overall change (though most patients showed a decrease in CRP). *Limitations:* The small sample size of this exploratory study was the most significant limitation. *Conclusions:* The physiological changes represented by the 6 biomarkers are reflective of wellness as opposed to weight gain. This suggests that antidepressants may confer overall physiological changes in the direction of wellness, even when weight gain is

observed in the absence of clinical improvement. Continued investigation of adipokines and pro-inflammatory cytokines will provide a better understanding of the physiological mechanisms behind the metabolic side effects of antidepressants.

Keywords: Weight Gain, Major Depressive Disorder, Adipokines, Cytokines, Leptin, Resistin, Adiponectin, Interleukin-6, Tumor Necrosis Factor Alpha, C-Reactive Potein

1. Introduction

The adipokines leptin, resistin, and adiponectin have all been shown to play a role in the regulation of energy metabolism (Calle et al., 2004; Wellen et al., 2005; Mannino et al., 2006) although to date, the physiological mechanisms constituting this regulation are not completely understood. Leptin, initially identified as an anti-obesity hormone, has since been found to be increased in obese individuals, possibly owing to leptin resistance (Rosicka et al., 2003). Similarly, high concentrations of resistin have been linked to obesity induced by a high-fat diet (Shuldiner et al., 2001; Ukkola, 2002). In contrast, a negative correlation between obesity and circulating adiponectin has been established, and serum levels of adiponectin are markedly decreased in individuals with visceral obesity (Arita et al., 1999). In addition to their role in the regulation of energy metabolism, adipokines are now thought to play a role in depression. Although no consensus on the role of leptin in depressed patients has been reached, evidence from human studies (Kraus et al., 2001; Jow et al., 2006) as well as rodent studies (Kim et al., 2006; Lu et al., 2006) have reported a reduction in leptin levels associated with depression. Similarly, low levels of adiponectin have been observed in patients with depression and anxiety (Leo et al., 2006; Nagata & Yamada, 2006) and while very little is known about the role of resistin in depression, resistin appears to be elevated in patients with both atypical (Pan et al., 2008; Lehto et al., 2010; Zeugmann et al., 2010), and typical depression (Weber-Hamann et al., 2007).

Depression and obesity are both considered to be pro-inflammatory states (Wellen et al., 2005; Goldstein et al., 2009). It is, therefore, not surprising that levels of the pro-inflammatory cytokines interlukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) have all been found to be elevated in obese as well as depressed patients. However, depression studies evaluating all 3 cytokines have not been conclusive (Vaccarino et al., 2008).

2. Objectives

To examine levels of the adipokines leptin, resistin, and adiponectin and the inflammatory markers IL-6, TNF-α, and CRP at baseline, prior to medication use, and 6 months after therapy. We are interested in assessing if changes in any of these biomarkers are associated with weight change and/or selective serotonin reuptake inhibitor (SSRI) therapy over the study period of 6 months.

3. Methods

3.1 Subjects

The same 7 subjects from the prior analysis were used for this portion of the study with all 7 subjects participating in the adipokines and inflammatory makers portion of the experiment. For more information on recruitment, inclusion and exclusion criteria, and patients' demographic and clinical characteristics, refer to Table 1 at the end of Chapter 3.

3.2 Data Collection

Fasting morning blood samples were obtained at baseline (prior to treatment initiation) and after 6 months of SSRI treatment for each patient. Two red-top vacutainers were used to collect blood. The samples were allowed to clot for 30 minutes and were then centrifuged for 15 minutes before the serum was separated. Serum was frozen to -80 degrees Celsius. Adipokine and cytokine levels were measured with a commercial multiplex immunoassay kit [Human serum adipokine KIT (Millipore, Massachusetts, USA)]. Detection limits were 145.4 pg/ml for adiponectin, 6.7pg/ml for resistin, 1.6pg/ml for Il-6, 85.4pg/ml for leptin and 0.14pg/ml for TNF-alpha. For all assays the intra- and inter-assay coefficients were below 8 and 21%, respectively. For both measures, preparations of samples and reagents, assay procedures, calculation of results and assay parameters followed guidelines provided by the manufacturer.

3.3 Statistical Analysis

To assess changes in the levels of inflammatory markers and adipokines over 6 months of SSRI treatment, we used a repeated measures ANOVA separately for each biomarker, treating interval (baseline and 6 month) as within-subject factors.

We then assessed how changes in BMI and Ham-D score related to changes in the levels inflammatory markers and adipokines using correlational analyses (Spearman's rank; two-tailed). We assessed the correlation between the change in

BMI and Ham-D score from baseline to 6 months and the percent change in each biomarker from baseline to 6 months.

4. Results

4.1 Effect of Biomarkers Over Time

Statistical analyses were done with SPSS version 17.0. The individual values for all measures obtained at baseline, 3 months, and 6 months for the 7 subjects are presented together in one large table in **Appendix 2** (page 93).

Repeated measures ANOVA revealed a statistically significant change in resistin ($F(1, 5) = 6.83$, $p = 0.047$). Additionally, the change in adiponectin approached statistical significance ($F(1, 5) = 5.77$, $p = 0.061$). For the remaining 4 biomarkers, no statistically significant changes were observed: leptin ($F(1, 5) = 0.57$, $p = 0.48$), IL-6 ($F(1, 5) = 0.95$, $p = 0.38$), TNF-α ($F(1, 5) = 0.13$, $p = 0.74$), and CRP ($F(1, 5) = 0.01$, $p = 0.94$). There was no significant interaction between any of the biomarkers and gender.

As indicated by the ANOVA test, the largest and most significant effect was observed with resistin. The mean level of resistin decreased from a baseline value of 24.54±4.55 ng/mL to 22.45±4.66 ng/mL at 6 months, with all but one subject showing a decrease in resistin (**Figure 7**). The effect of adiponectin was nearly significant, with an increase in mean adiponectin from a baseline value of 18.40±1.22 μg/mL to 18.80±1.31 μg/mL at 6 months, with all but one subject showing an increase in adiponectin (**Figure 8**).

Although effects in the remaining 4 biomarkers did not reach statistical significance, it is worth noting the direction and magnitude of the changes that occurred over 6 months. The change in leptin was an overall increase from 7.47±0.55 ng/mL to 7.53±0.64 ng/mL, though results were variable with 4 subjects showing an increase and 3 subjects showing a decrease in leptin level (**Figure 6**). All but two subjects showed a decrease in the level of IL-6, but the changes were modest with a mean change from 11.07±2.00 pg/mL at baseline to 10.91±1.73 pg/mL at 6 months (**Figure 9**). Similarly, TNF-α levels decreased for all but 2 subjects, however the changes were very minute as reflected in the mean change from baseline to 6 months (4.75±1.54 pg/mL to 4.74±1.41 pg/mL; **Figure 10**). Levels of CRP decreased in 4 subjects, remained unchanged in 2, and increased in 1 subject. Overall, there was no mean change for CRP from baseline to 6 months (2.03±0.54 mg/L to 2.03±0.61 mg/L; **Figure 11**).

4.2 Biomarker Correlations

Correlational analyses (Spearman's rank; two-tailed) were used assess how changes in BMI and Ham-D score related to changes in the 6 biomarkers.

Change in BMI showed no correlation with change in leptin level ($\rho = 0.07$, $p = 0.88$), and only a weak correlation with change in resistin level ($\rho = 0.25$, $p = 0.59$) suggesting an increase in resistin as BMI increase. Neither of these associations, however, was statistically significant. Change in BMI correlated strongly with

adiponectin (ρ = 0.68, p = 0.094), despite lack of statistical significance. This suggests an association between increased BMI and increased levels of adiponectin. Change in BMI did not correlate with change in CRP level (ρ = -0.05, p = 0.91), but did correlate weakly with TNF-α (ρ = -0.11, p = 0.82) and strongly with IL-6 (ρ = -0.75, p = 0.052). This suggests that an increase in BMI is associated with a decrease in both TNF-α and IL-6. While the correlation with TNF-α did not reach statistical significance, the correction with IL-6 approached statistical significance.

Change in Ham-D score reflecting clinical response correlated only weakly with resistin (ρ = 0.29, p = 0.54), suggesting an association between lower Ham-D score (clinical improvement) and decreased levels of resistin. Changes in Ham-D score correlated moderately with levels of adiponectin (ρ = -0.38, p = 0.43), suggesting an association between clinical improvement and increased levels adiponectin. These correlations did not reach statistical significance. Changes in Ham-D score correlated strongly with levels of leptin (ρ = -0.86, p = 0.014), suggesting an association between clinical improvement and increased leptin levels. This association reached statistical significance. There was a weak correlation observed between changes in Ham-D score and IL-6 (ρ = 0.11, p = 0.82), as well as moderate to strong correlations with TNF-α (ρ = 0.50, p = 0.25) and CRP (ρ = 0.51, p = 0.25). Although these correlations did not reach significance, they suggest an association between clinical improvement and lower levels of inflammatory markers.

5. Discussion

This study examined the baseline concentrations and change over time in the adipokines leptin, resistin, and adiponectin and the pro-inflammatory cytokines IL-6, TNF-α, and CRP. Statistical analysis revealed a significant decline in the concentration of resisting ($p = 0.047$) from baseline to 6 months of SSRI therapy. In addition, an increase in adiponectin approached significance ($p = 0.061$). Changes in leptin concentration were the most variable with 4 subjects showing an increase and 3 subjects showing a decrease in leptin concentration at 6 months. Statistical analyses did not reveal any significant changes in the levels of the 3 pro-inflammatory cytokines. This is likely a reflection of the small magnitudes in change for these biomarkers as well as the low number of participants. However, it is notable that concentrations of IL-6, TNF-α, and CRP either decreased or remained unchanged for the majority of subjects.

With the exception of leptin, the remaining five biomarkers should exhibit opposing patterns of changes with weight gain and therapy-induced reduction of symptom severity. High leptin concentration is associated with obesity (Rosicka et al., 2003), whereas low leptin concentration may be associated with depression (Kraus et al., 2001; Jow et al., 2006). Therefore, increased weight and reduced symptom severity would both confer a rise in leptin levels. In contrast, resistin level is positively correlated with both obesity (Savage et al., 2001; Shuldiner et al., 2001; Ukkola, 2002) and depression (Weber-Hamann et al., 2007). Weight gain should therefore confer an increase in resistin, while reduced symptom severity should

confer a decrease in resistin. Low adiponectin has been linked to both obesity (Arita et al., 1999) and depression (Leo et al., 2006; Nagata & Yamada, 2006). In this case, weight gain should be associated with a decrease in adiponectin, whereas reduced symptom severity should be associated with an increase in adiponectin. Given the pro-inflammatory states of obesity and depression, weight gain should increase the three pro-inflammatory cytokines, while reduced symptom severity should decrease levels of the cytokines.

Our population of medicated MDD patients is expected to show a reduction in symptom severity as well as increase in weight. It is clear that in most cases the adipokines and cytokines cannot reflect both of these changes. With the exception of 1 subject, we observed weight gain in our population. Conversely, with the exception of a subject who remitted and a subject who partially responded to treatment, the majority of our subjects did not respond to medication. It would, therefore, be expected that changes in biomarkers would most likely reflect weight gain. Interestingly, however, changes in both adipokines and cytokines were largely reflective of reduced inflammatory response, as apposed to weight gain. Despite reduced inflammatory response, correlational analyses revealed only moderate associations between Ham-D score and adiponectin (ρ = -0.38), TNF-α (ρ = 0.50) and CRP (ρ = 0.51). Only weak associations were found between Ham-D score and both resistin and IL-6. This is likely due to the fact that most patients did not respond to treatment. Interesting, a strong negative correlation was found between Ham-D score and leptin (ρ = -0.86). Not surprisingly, the two subjects who responded to

treatment also showed the most significant changes in all six biomarkers (Appendix 3, page 95).

These results seem to suggest that therapy with SSRI antidepressants confer physiological changes that are reflective of reduced inflammatory response, even in the absence of reduced symptom severity. For leptin, these results may be in line with studies suggesting that increase in leptin may be a by-product of SSRI-mediated HPA axis normalization, irrespective of clinical improvement in depressive symptoms (Himmerich et al., 2007). Higher levels of adiponectin have been observed in MDD patients in remission receiving SRRIs and SNRIs (Leo et al., 2006). Results from the present study seem to suggest that this increase in adiponectin does not necessarily only occur with remitted patients, though strong conclusions cannot be made due to the low number of subjects in the present study. Similarly, our results were not in agreement with the study by Weber-Hamann et al (2007), in which remitted patients experienced a decrease in resistin levels while non-remitters showed no change. In our population, most non-remitters still experienced some degree of reduction in resistin concentration. While antidepressant studies examining changes in pro-inflammatory cytokines have reported variable results, the present study seems to support the anti-inflammatory role of antidepressants. This effect of reduced inflammation may, however be transient. Results from our lab have shown an initial decrease, followed by a significant increase in IL-6, TNF-α, CRP, and leptin in 42 patients with bipolar disorder medicated with various psychotropic medications (including antidepressants) and followed for 2 years (Taylor et al.,

submitted). It is also worthy to note that, in our current sample, patients may not yet have gained enough weight to offset the initial anti-inflammatory effects of the SSRIs; follow up over time would be needed to draw significant conclusions.

6. Conclusion

In order to better understand the physiological mechanisms behind the metabolic side effects of antidepressants, it is worthwhile to investigate the role of adipokines and pro-inflammatory cytokines. The present study suggests that antidepressants may in fact confer overall physiological changes in the direction of wellness, even when weight gain is observed in the absence of clinical improvement.

Figure 6 Leptin concentration over 6 months of treatment: individual values and mean

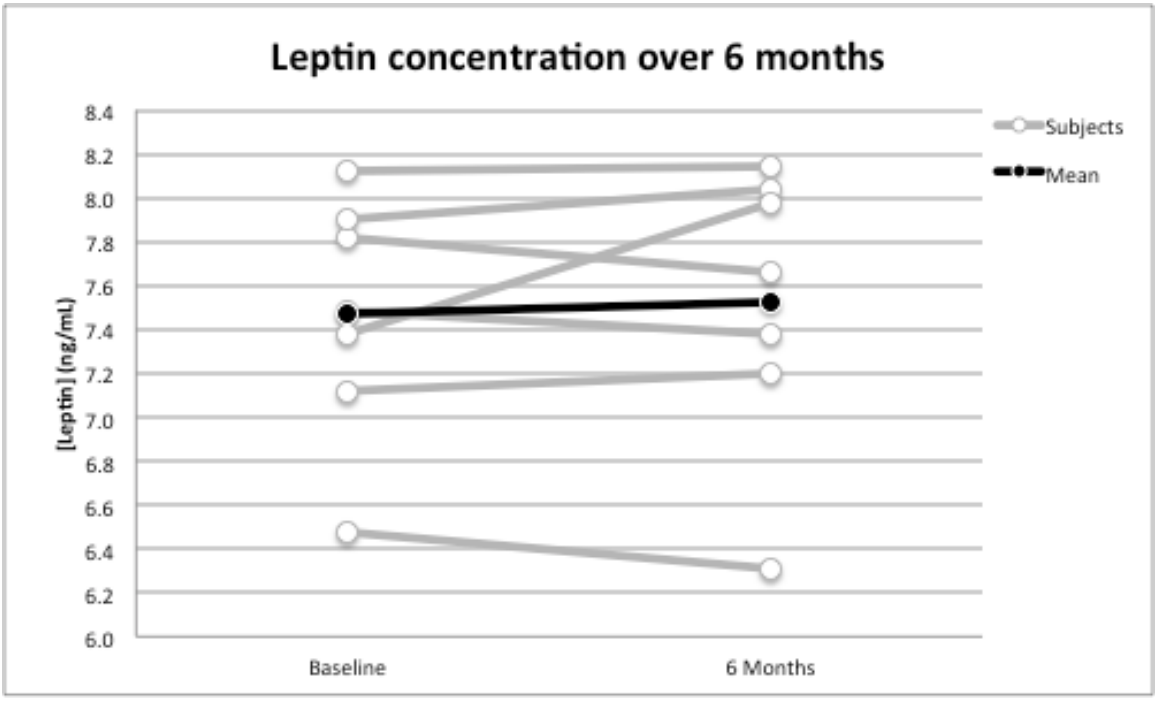


Figure 7 Resistin concentration over 6 months of treatment: individual values and mean

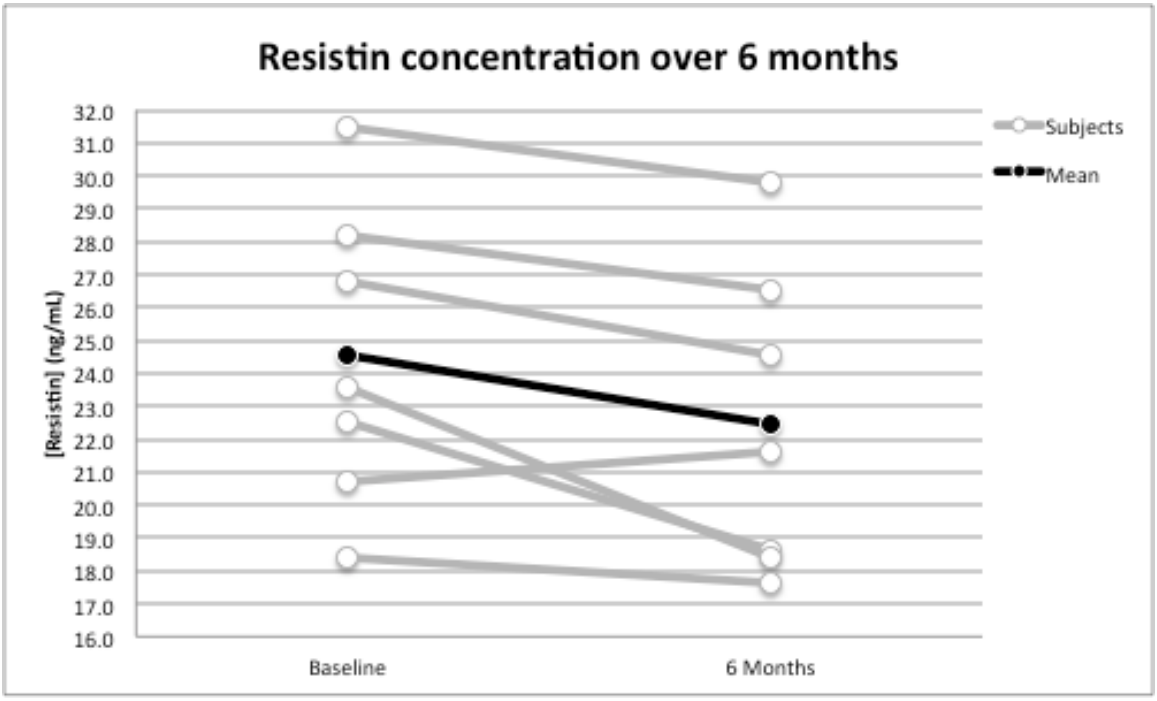


Figure 8 Adiponectin concentration over 6 months of treatment: individual values and mean

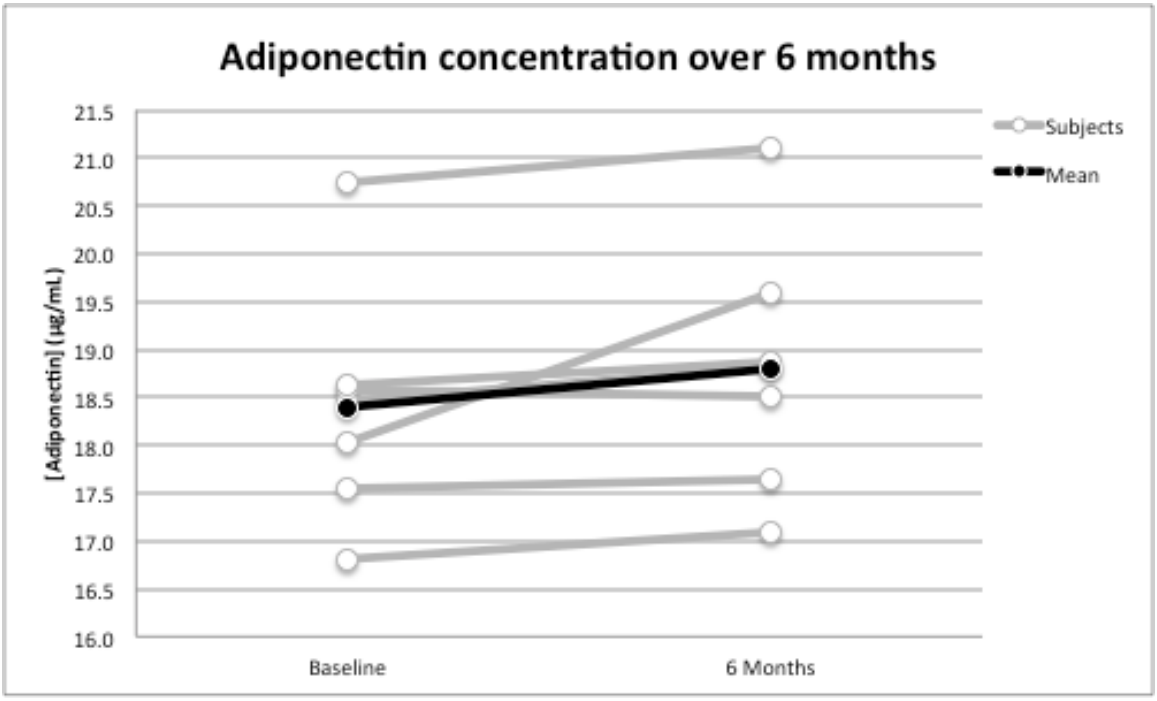


Figure 9 Interleukin-6 concentration over 6 months of treatment: individual values and mean

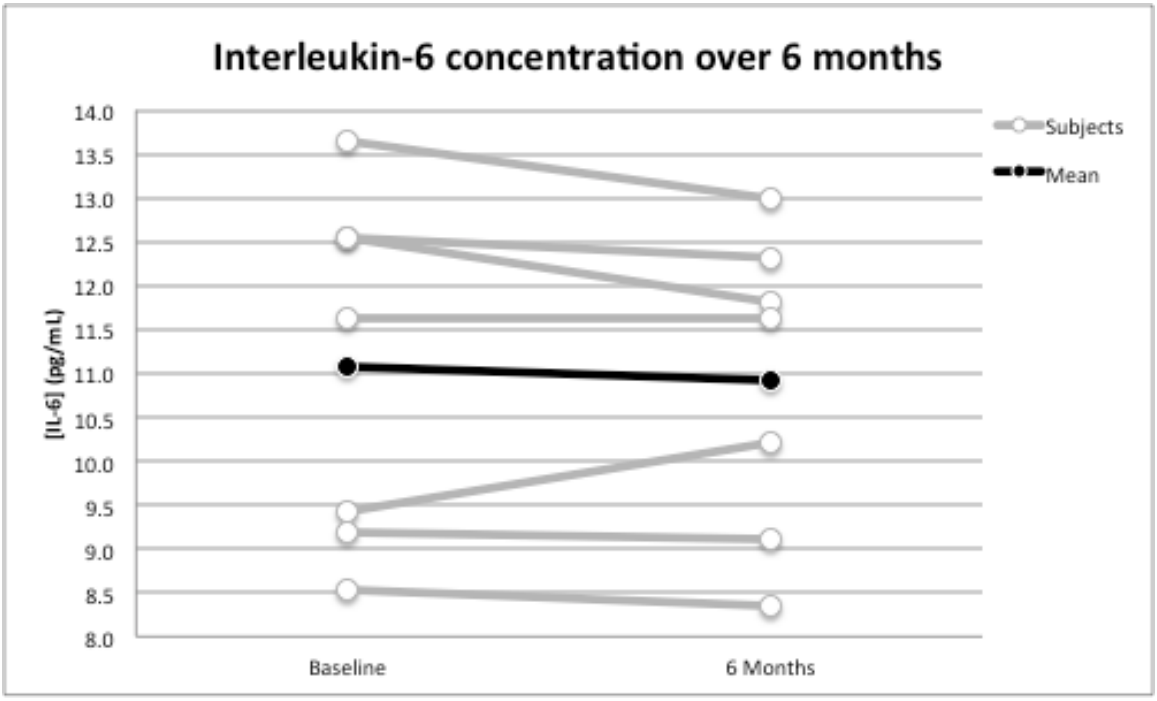


Figure 10 Tumor necrosis factor alpha concentration over 6 months of treatment: individual values and mean

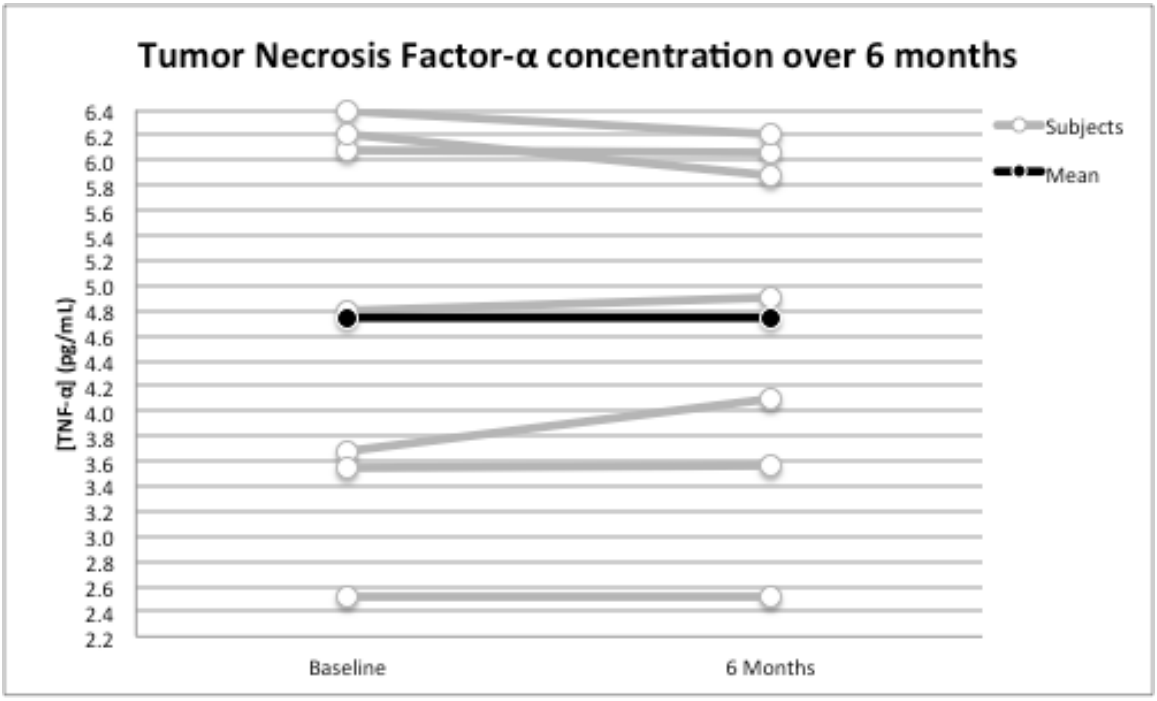
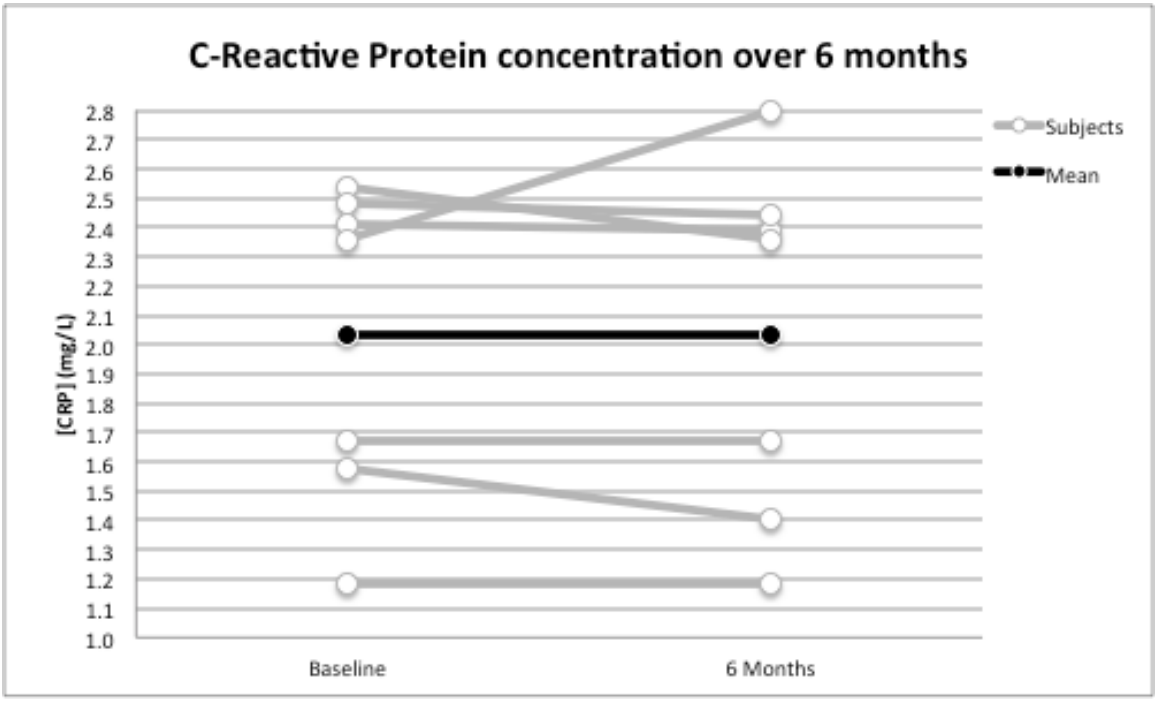


Figure 11 C-Reactive protein concentration over 6 months of treatment: individual values and mean



Afterword

The main purpose of this thesis was to comprehensively investigate weight gain in individuals undergoing pharmacotherapy. This study represents the first time the three main mechanisms know to cause weight gain have been examined in major depressive disorder (MDD) patients. More specifically, this exploratory study aimed to determine whether reduced physical activity, reduced basal metabolic rate, and/or increased caloric consumption could explain the weight gain often observed in this population. In our sample of 7 MDD patients, only 1 patient remitted with SSRI treatment, while another patient showed partial response. Despite this, all but 1 patient showed an increase in weight gain from baseline to 6 months of treatment, though weight gain was largely not clinically significant. Results from our dietary assessment revealed a significant and consistent reduction in caloric consumption over the 6 months of treatment, with a trend towards increased fat intake and no change in carbohydrate intake. In addition, while the validity of our metabolic testing is questionable in light of low RER values in the absence of ketosis, we did observed a trend towards increased RER, indicating a reduction in fat oxidation. Taken together, these results could, in part, help explain the weight gain we observed despite reduced caloric intake. It is possible that patients are consuming more fat in their diet, while at the same time oxidizing less fat. Over time, this would result in body fat accumulation. Initially, statistical analysis revealed no relationship between weight gain and reduced physical activity and in fact, it seemed as though most patients increased their physical activity at 6 months of treatment. A closer

inspection using case-by-case analysis for all 3 time intervals, however, revealed that in many cases, changes in physical activity could in fact help explain the corresponding change in weight.

The exact mechanisms of weight gain during SSRI treatment remain unclear but results from this thesis can help to direct future research in elucidating the mechanisms of weight gain. Notably, we have found no indication, both in pooled statistical analysis and in case-by-case analysis, that increased caloric consumption can account for the observed weight gain, instead noting the opposite trend. This would indicate that less focus on total caloric intake in weight loss programs for this group might be helpful. In addition, our results indicate that future research should continue to investigate the proportionality of consumed and expended macronutrients, as well as physical activity.

In addition to investigating the 3 main mechanisms know to cause weight gain, this thesis also explored changes in the adipokines leptin, resistin, and adiponectin; and the pro-inflammatory cytokines interleukin-6, tumor necrosis factor alpha, and C-reactive protein, all of which have been shown to play a role in both obesity and depression. Interestingly, we note that the overall changes in these biomarkers are in the direction associated with reduced inflammatory response, not weight gain, despite the fact that most of our subjects did not respond to treatment but did gain some weight. A possible explanation for this is that SSRI treatment initially causes a reduction in inflammation, which is consistent with a lot of current literature on the topic. Since these physiological changes are not predictive of

clinical improvement, this would then suggest that the changes in adipokines and pro-inflammatory cytokines initially observed in depressed individuals might be a consequence, rather than a cause of the mood disorder. Longer term follow up in a larger sample size would be necessary to see how significant weight gain and symptom change impact these biomarkers.

Future Direction

We have begun to explore the possible mechanisms involved in weight gain related to antidepressants. Results from this thesis suggest that future research should focus on metabolic processes that lead to inflexibility in switching between fat and carbohydrate oxidation. In addition, more detailed dietary assessment on a larger sample size would be useful in investigating particular food biases that may lead to weight gain in this population. While we have found an overall reduction in caloric consumption, it is still of interest to investigate closely the proportion of fats and carbohydrates that make up the diet of patients with depression being treated with SSRIs. Physical activity may also play a role in weight gain for this population. In addition to investigating overall physical activity as was done in this study, future research should aim to investigate patterns in activity through detailed activity logs in conjunction with monitoring activity with accelerometers. This would provide information about sleep habits and patterns of physical activity that may be relevant for this population.

To conclude, results from this thesis have begun to shed light on the mechanisms involved in antidepressant-mediated weight gain. Translation of such results into clinical practice is of great importance in being able to manage the adverse metabolic side effects associated with psychotropic medications. The ultimate goal would be to be able to reduce or eliminate these side effects in order to obtain better compliance with antidepressant medication.

APPENDIX 1: Example of case report form (CRF) used for patient evaluation

Mechanisms of weight gain in patients with major depressive disorder

Inclusion/Exclusion Criteria

Subject's ID Number: _____

Inclusion Criteria:

- In an age range of 20-60 years old **Yes** □ **No** □
- With single episode or recurrent major depressive disorder **Yes** □ **No** □
- Starting an antidepressant at completion of the baseline visit **Yes** □ **No** □

Exclusion for Participants and Healthy Controls

- Currently involved in an active weight loss program **Yes** □ **No** □
- Have had weight fluctuations more than 10 lbs in the last 6 months **Yes** □ **No** □
- Experiencing psychotic symptoms **Yes** □ **No** □
- Use of medications known to influence weight aside from those prescribed for the treatment of MDD (e.g. Stimulants, Steriods) **Yes** □ **No** □
- Having a medical condition that has been shown to impact weight (e.g. thyroid illness and/or PCOD) **Yes** □ **No** □
- History of substance or alcohol dependence **Yes** □ **No** □
- Current substance or alcohol abuse **Yes** □ **No** □

Signature of Principal Investigator _____

Date _____

Mechanisms of weight gain in patients with major depressive disorder
Screen Visit

Subject's ID Number: _____

Date Consented: _____ Date of Assessment: _____

1. <u>Diagnostic, Demographic and Assessments:</u>

DOB: _____ Gender: Male □ Female □

SCID = Dx. of _____ HamD □ YMRS □ CGI □ GAF □

Con. Med. Sheet □ Genetic specimen obtained: **Yes** □ **No** □

Indicate current alcohol use: _____

Indicate current drug use and type of use: _____

Current medical conditions: (√ all that apply or please list.)

high blood pressure □	high cholesterol □	thyroid disorder □	diabetes □	pcod □
chronic lung disease □	heart disease □	headaches □	arthritis □	gallbladder □
seizures/epilepsy □	asthma/allergies □	kidney disease □	liver disease □	ulcers □
clotting disorder □	anemia □	cancer □	chronic pain □	

2. <u>Psychical Measures</u>

Weight _____ cm Height _____ cm BMI _____

3. Daily food diary explained and given □

4. Activity monitor explained and given □

5. Remind subject that BMR requires they are fasting for 12 hours prior to testing □

Additional Comments:

_____

_____

Completed By _____

Mechanisms of weight gain in patients with major depressive disorder

Drug Name	Dose	Indication	Status/Changes

Subject's ID Number: _____ **Con. Med. Sheet**

Mechanisms of weight gain in patients with major depressive disorder
Baseline Visit- #2/D8

Subject's ID Number: _____

Date of Assessment: _____

1. Daily food diary returned □
2. Activity monitor returned □
3. Basel metabolic testing completed □

Name & dose of medication started: _____

Additional Comments:

_____
_____
_____
_____

Completed By _____

Mechanisms of weight gain in patients with major depressive disorder
3 Month Visit - #3/D90

Subject's ID Number: _____

Date of Assessment: _____

1. **Diagnostic, Demographic and Mood Assessments:**

- □ HamD
- □ YMRS
- □ CGI
- □ GAF
- □ Con. Med. Sheet

Completed By _____

2. **Psychical Measures**

Weight _____ cm Height _____ cm BMI _____

3. Daily food diary explained and given □
4. Activity monitor explained and given □
5. Remind subject that BMR requires they are fasting for 12 hours prior to testing □

Additional Comments:

_____
_____
_____
_____

Completed By _____

Mechanisms of weight gain in patients with major depressive disorder
3 Month Visit - #4/D93

Subject's ID Number: _____

Date of Assessment: _____

1. Daily food diary returned □
2. Activity monitor returned □
3. Basel metabolic testing completed □

Name & dose of medication started: _____

Additional Comments:

_____
_____
_____
_____

Completed By _____

Mechanisms of weight gain in patients with major depressive disorder

6 Month Visit - #5/D180

Subject's ID Number: _____

Date of Assessment: _____

1. **Diagnostic, Demographic and Mood Assessments:**

- □ HamD
- □ YMRS
- □ CGI
- □ GAF
- □ Con. Med. Sheet

Completed By _____

2. **Psychical Measures**

Weight _____ cm Height _____ cm BMI _____

3. Daily food diary explained and given □

4. Activity monitor explained and given □

5. Remind subject that BMR requires they are fasting for 12 hours prior to testing □

Additional Comments:

_____
_____
_____
_____

Completed By _____

Mechanisms of weight gain in patients with major depressive disorder
6 Month Visit - #6/D185

Subject's ID Number: _____

Date of Assessment: _____

1. Daily food diary returned □
2. Activity monitor returned □
3. Basel metabolic testing completed □

Name & dose of medication started: _____

Additional Comments:

_____
_____
_____
_____

Completed By _____

APPENDIX 2: Individual subject values for all measures at each time interval

Individual subject values for all measures at each time interval

Subject	BMI			Weight (kg)			Waist (cm)			Caloric Output (Kcal/hour)			Activity Counts (counts/min)			Step Count (steps/hour)			Caloric Input (Kcal/day)			Fat Intake (%/day)			Carb. Intake (%/day)		
Time Interval	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**3M**	**6M**
1	33.3	32.7	34.1	106.6	104.8	109.3	108.0	106.2	108.3	16.6	32.4	21.6	133.0	257.5	164.4	236.0	560.4	298.3	2,891	1,964	2,428	41.6	37.0	25.9	36.2	39.2	63.3
2	30.8	31.1	31.7	91.2	92.1	93.9	113.3	111.8	112.1	85.8	71.0	36.3	728.7	642.8	308.3	1059.5	806.3	455.1	982	523	514	24.3	42.1	47.6	43.8	32.9	28.7
3	23.9	24.0	24.5	63.0	63.5	64.9	90.9	90.3	91.9	17.5	16.9	9.8	236.2	228.8	131.4	457.5	332.9	241.1	1,840	1,452	---	29.9	24.4	---	51.3	62.3	---
4	35.9	38.9	39.7	101.2	109.8	112.0	107.3	118.4	118.8	32.8	33.3	52.8	244.6	237.4	341.4	343.2	440.1	594.2	2,684	2,199	2,062	47.8	41.1	32.7	32.8	41.9	40.3
5	29.0	29.0	28.7	97.1	97.1	96.2	100.8	105.6	98.2	27.5	21.5	28.1	210.4	180.6	225.5	355.4	223.9	355.0	1,715	996	1,922	28.4	19.6	46.45	50.5	66.8	40.3
6	34.4	34.9	35.1	96.6	98.0	98.4	118.8	118.7	118.9	22.5	41.1	39.8	189.7	313.4	298.5	281.0	477.0	494.1	2,249	1,799	947	16.8	9.0	35.5	69.7	79.1	51.5
7	31.4	32.8	31.9	117.0	122.2	118.8	114.6	120.0	121.1	58.3	54.5	55.6	333.2	278.8	304.8	551.7	523.9	547.4	4,390	---	2,794	42.6	---	46.9	31.4	---	31.4
Mean	**31.2**	**31.9**	**32.2**	**96.1**	**98.2**	**99.1**	**107.7**	**110.1**	**109.9**	***29.2**	***33.3**	***34.6**	***224.5**	***249.4**	***244.3**	***370.8**	***426.4**	***421.7**	***2,104**	***1,496**	***1,574**	**31.8**	**29.7**	**37.6**	**46.6**	**52.0**	**44.8**
SD	**4.0**	**4.7**	**4.8**	**16.8**	**18.2**	**17.6**	**9.4**	**10.6**	**11.2**	**15.5**	**13.6**	**18.0**	**66.5**	**45.4**	**84.3**	**116.2**	**126.5**	**143.6**	**773**	**707**	**807**	**12.7**	**14.7**	**9.3**	**14.6**	**19.9**	**13.1**

**Activity means exclude Subject 2 (outlier); Dietary means exclude Subjects 3 and 7 (missing data); Metabolic means excluded Subjects 1-4 (missing data)*

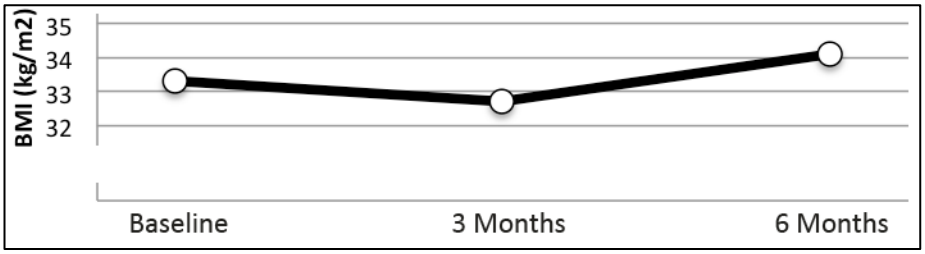
Subjects	BMR (Kcal/day)			RER			VO_2 (mL/min/kg)			Leptin (ng/mL)		Resistin (ng/mL)		Adiponectin (µg/mL)		TNF-α (pg/mL)		IL-6 (pg/mL)		CRP (mg/L)	
Time Interval	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**6M**	**B**	**6M**	**B**	**6M**	**B**	**6M**	**B**	**6M**	**B**	**6M**
1	2,258	---	2,892	0.475	---	0.533	3.29	---	4.05	7.82	7.66	26.80	24.54	17.54	17.64	6.08	6.06	13.65	12.98	2.41	2.39
2	---	2,771	3,355	---	0.595	0.734	---	4.55	5.23	7.48	7.38	20.70	21.64	18.46	18.81	3.68	4.10	9.18	9.11	1.67	1.67
3	---	2,135	1,590	---	0.559	0.796	---	5.13	3.53	6.48	6.31	18.40	17.60	20.74	21.10	2.52	2.51	8.54	8.34	1.18	1.18
4	---	2,189	2,153	---	0.574	0.590	---	3.02	2.91	7.90	8.04	28.20	26.54	18.02	19.59	6.21	5.88	12.54	11.80	2.54	2.36
5	2,381	2,334	2,335	0.693	0.710	0.728	3.62	3.53	3.55	7.12	7.20	22.56	18.64	18.59	18.50	3.54	3.56	9.42	10.20	1.58	1.40
6	2,210	2,207	2,430	0.651	0.602	0.626	3.41	3.39	3.70	7.38	7.98	23.60	18.40	18.62	18.88	6.40	6.20	12.54	12.32	2.48	2.44
7	3,227	3,205	3,043	0.717	0.745	0.701	4.05	3.82	3.77	8.12	8.14	31.50	29.8	16.81	17.10	4.80	4.90	11.62	11.64	2.36	2.80
Mean	***2,606**	***2,582**	***2,603**	***0.687**	***0.686**	***0.685**	***3.69**	***3.58**	***3.67**	**7.47**	**7.53**	**24.54**	**22.45**	**18.40**	**18.80**	**4.75**	**4.74**	**11.07**	**10.91**	**2.03**	**2.03**
SD	**545**	**543**	**384**	**0.033**	**0.075**	**0.053**	**0.33**	**0.22**	**0.11**	**0.55**	**0.64**	**4.55**	**4.66**	**1.22**	**1.31**	**1.54**	**1.41**	**2.00**	**1.31**	**0.54**	**0.61**

Subjects	Dose (mg paroxetine)			Ham-D 17 Score			GAF Score			CGI-S Score		
Time Interval	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**3M**	**6M**	**B**	**3M**	**6M**
1	26	40	40	21	20	26	55	57	50	4	4	5
2	20	20	40	27	23	25	49	50	48	5	4	5
3	30	30	37.5	7	10	9	69	64	65	3	3	3
4	26	30	30	20	11	7	49	64	68	4	3	3
5	20	30	30	23	25	22	51	50	51	4	5	4
6	20	20	20	17	8	11	58	65	67	4	3	3
7	20	20	20	16	19	16	50	51	51	4	4	4
Mean	**23.1**	**27.1**	**31.1**	**18.7**	**16.6**	**16.6**	**54.4**	**57.3**	**57.1**	**4.0**	**3.7**	**3.9**
SD	**4.1**	**7.6**	**8.6**	**6.3**	**6.8**	**7.8**	**7.3**	**7.0**	**9.0**	**0.6**	**0.8**	**0.9**

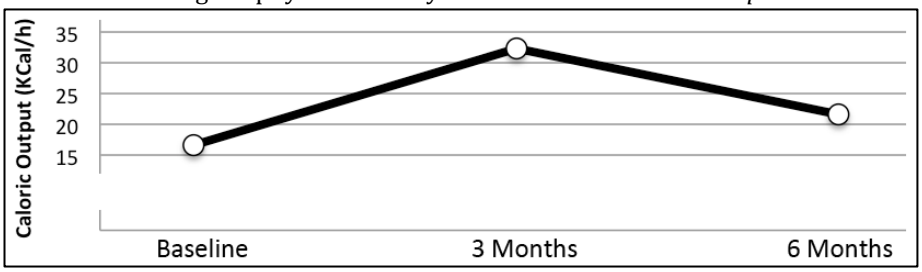
APPENDIX 3: Individual subject analyses

Subject 1

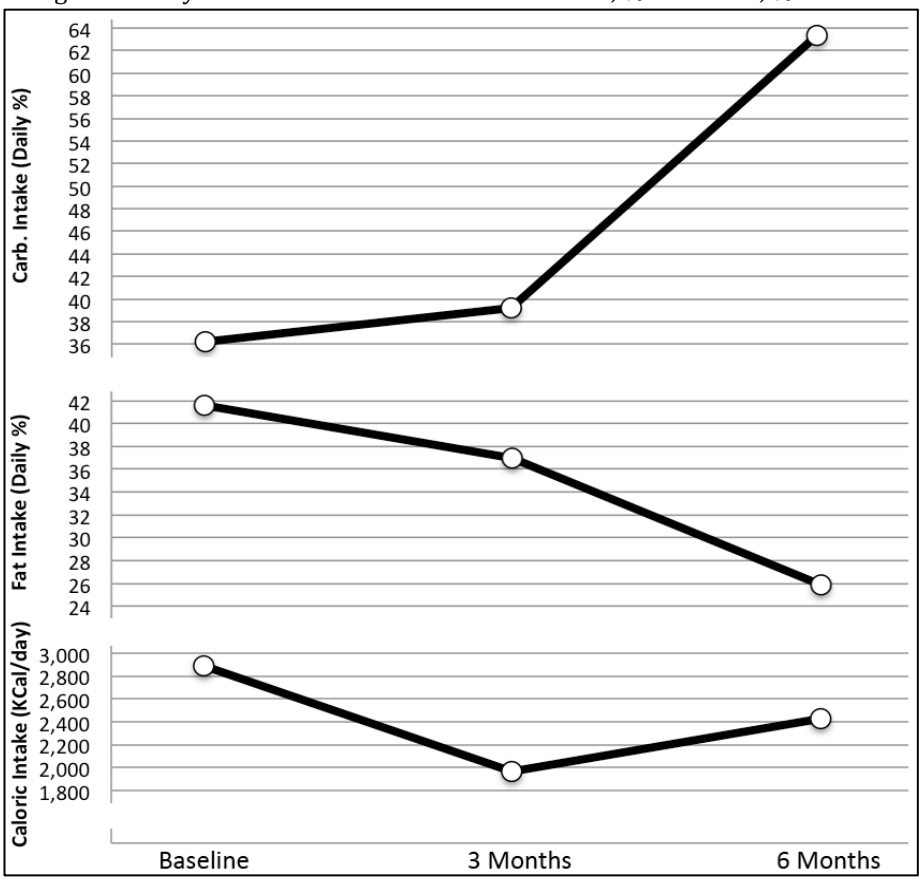
Change in BMI over 6 months



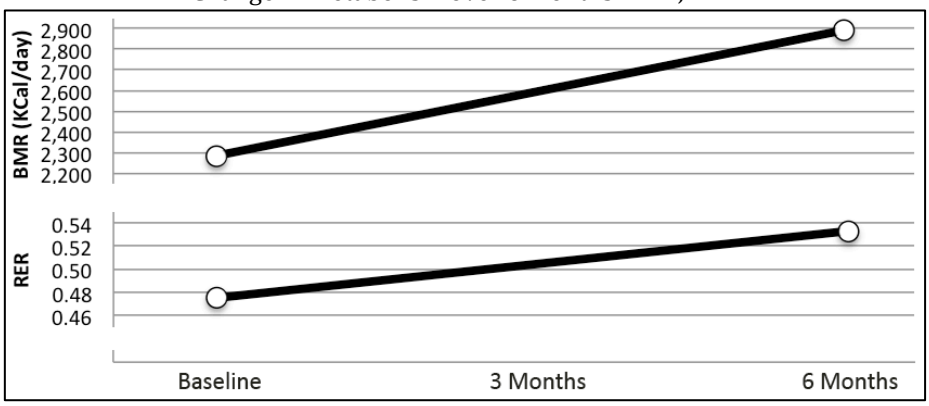
Change in physical activity over 6 months: *Caloric Output*



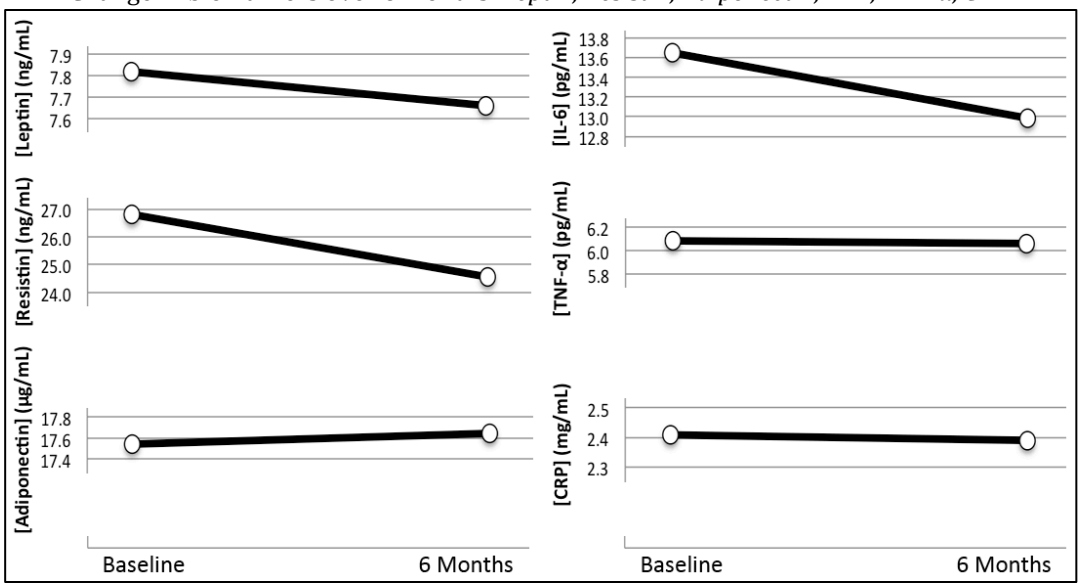
Change in dietary intake over 6 months: *Caloric Intake, %Fat Intake, %Carb Intake*



Change in metabolism over 6 months: *BMR, RER*



Change in biomarkers over 6 months: *Leptin, Resistin, Adiponectin, IL-6, TNF-α, CRP*



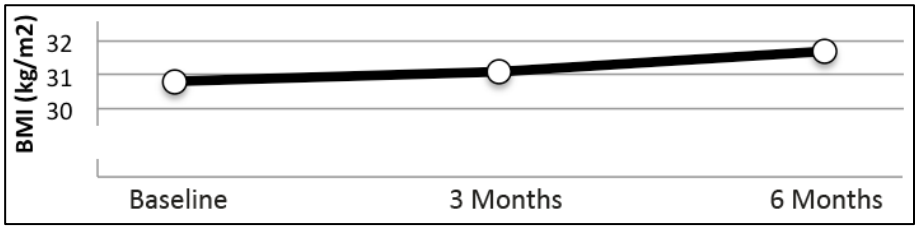
Analysis

This subject experienced weight loss at 3 months. The initial weight loss can be explained by increased caloric output through physical activity and decreased caloric intake. At 6 months, the patient gained weight, which may be attributable to decreased physical activity and increased caloric intake. This subject also seems to experience increased carbohydrate cravings throughout the study period. The increase in BMR at 6 months is puzzling, and may be due to calibration error in light of extremely low RER values both at baseline and 6 months. A ketone assessment to check for ketosis was not possible for this patient.

This subject did not respond to treatment, with a HAMD-17 score increase from 21 at baseline to 26 at 6 months. Interestingly, the subject experienced a decrease in resistin and an increase in leptin and adiponectin, which are consistent with reduced symptom severity. The subject also showed decreased in inflammation (lower IL-6), which is reflective of wellness. None of the biomarker changes were consistent with weight gain.

Subject 2

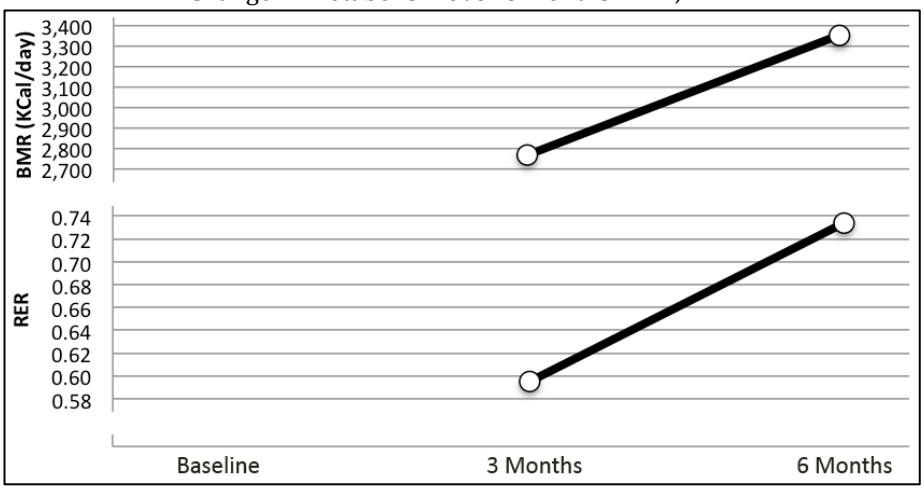
Change in BMI over 6 months



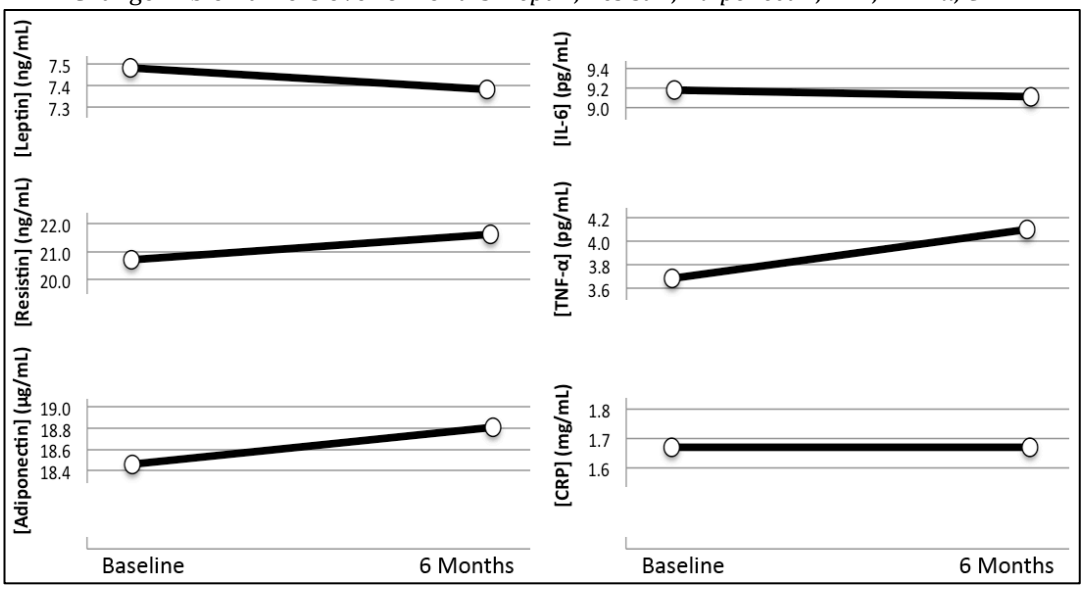
Change in physical activity over 6 months: *Caloric Output*

Change in dietary intake over 6 months: *Caloric Intake, %Fat Intake, %Carb Intake*

Change in metabolism over 6 months: *BMR, RER*



Change in biomarkers over 6 months: *Leptin, Resistin, Adiponectin, IL-6, TNF-α, CRP*



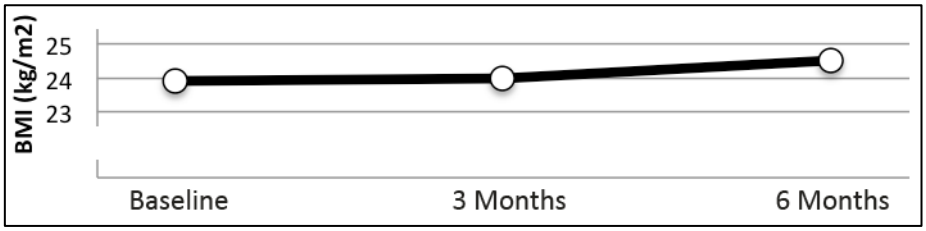
Analysis

This subject experienced weight gain at 3 months and 6 months. This continuous weight increase may be attributable to a dramatic decrease in physical activity that offsets the observed decreased caloric consumption. This subject's physical activity decreased was flagged as an outlier, with confirmation from the subject that his activity at baseline was unusually high. However, the persistent dramatic decline at 6 months could give validity to this pattern of decreased caloric expenditure. The increase in BMR from 3 months to 6 months is puzzling, and may be due to calibration error in light of low RER values. A ketone assessment to check for ketosis at 3 months was not possible for this patient.

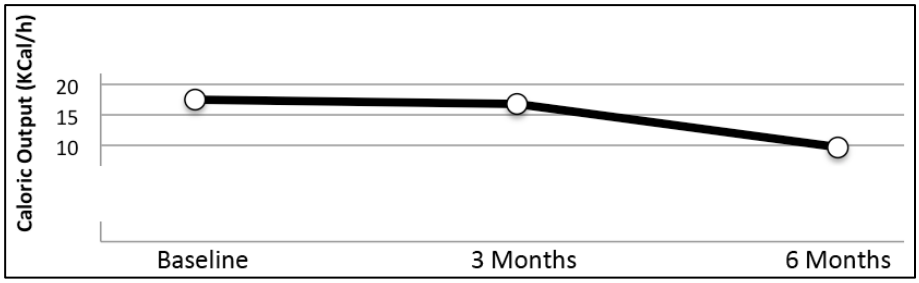
This subject did not respond to treatment, with a HAMD-17 score decrease from 27 at baseline to 25 at 6 months. The subject experienced increased resistin and inflammation (elevated TNF-α), which are consistent with weight gain. However, the subject also showed an increase in adiponectin, which is consistent with reduced symptom severity.

Subject 3

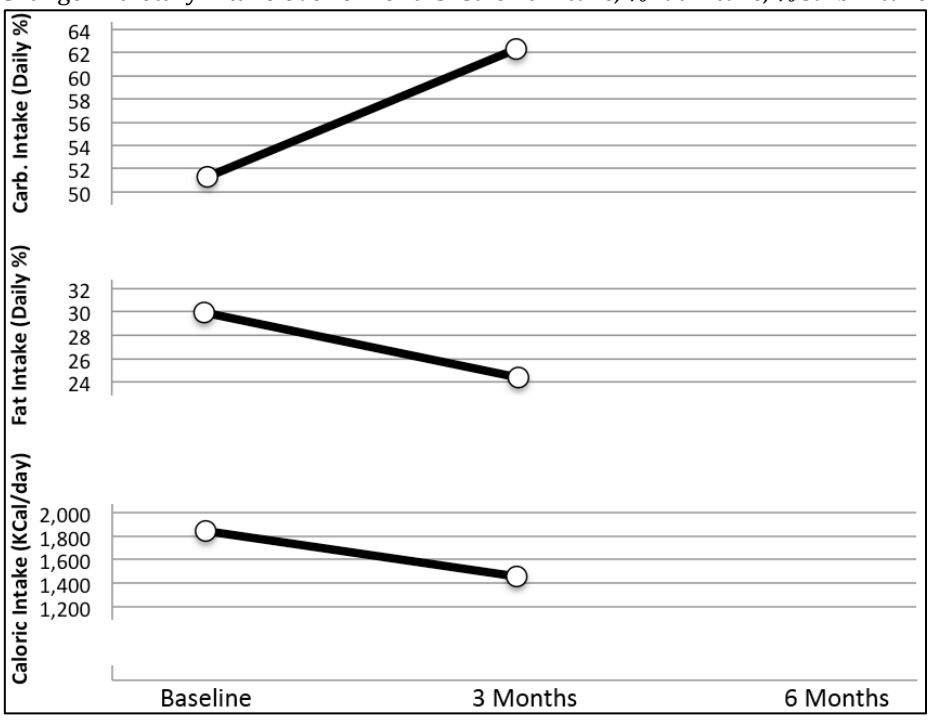
Change in BMI over 6 months



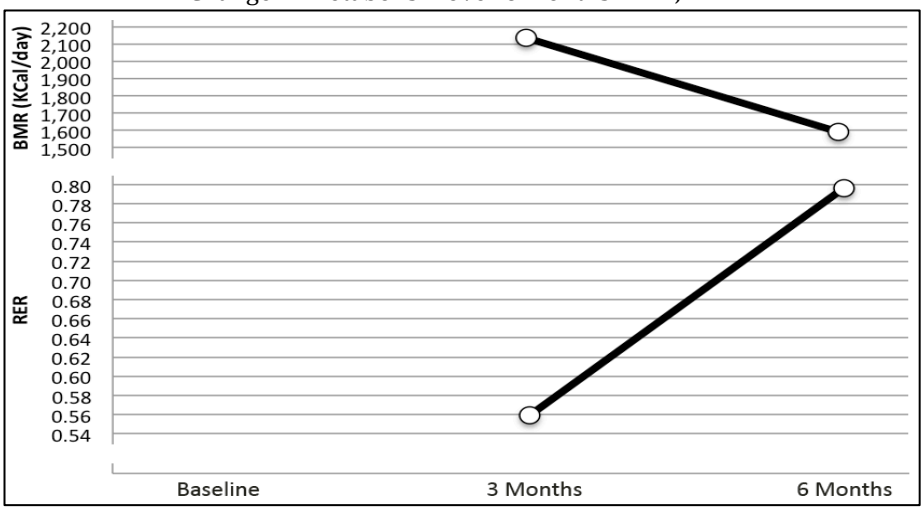
Change in physical activity over 6 months: *Caloric Output*



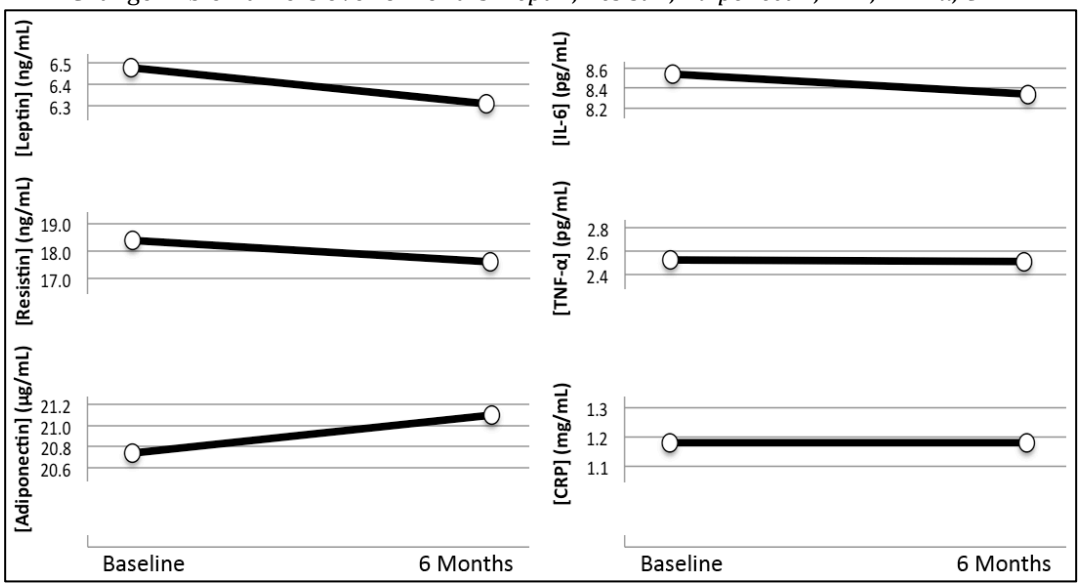
Change in dietary intake over 6 months: *Caloric Intake, %Fat Intake, %Carb Intake*



Change in metabolism over 6 months: *BMR, RER*



Change in biomarkers over 6 months: *Leptin, Resistin, Adiponectin, IL-6, TNF-α, CRP*



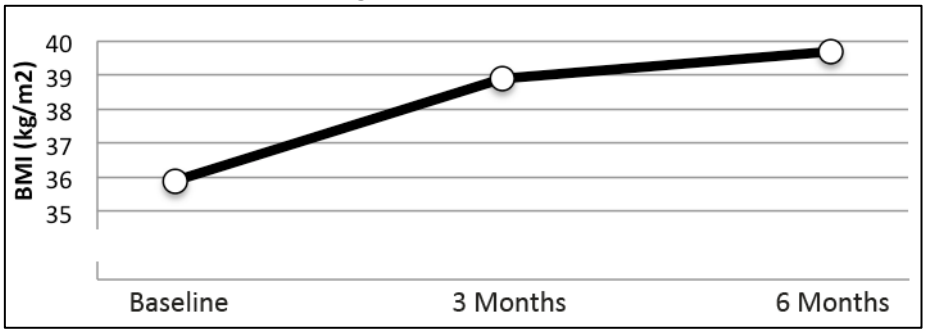
Analysis

This subject experienced weight gain, particularly between 3 months and 6 months. This weight increase may be attributable to the decrease in physical activity, which is also more pronounced between 3 months and 6 months, and decrease in BMR for the same interval. However, the decrease in BMR may be exaggerated by calibration error in light of low RER values at 3 months that cannot be assessed for possible ketosis. Dietary data is missing for the 6 months visit, although a decrease in caloric input was observed at the 3 months interval when little weight change occurred.

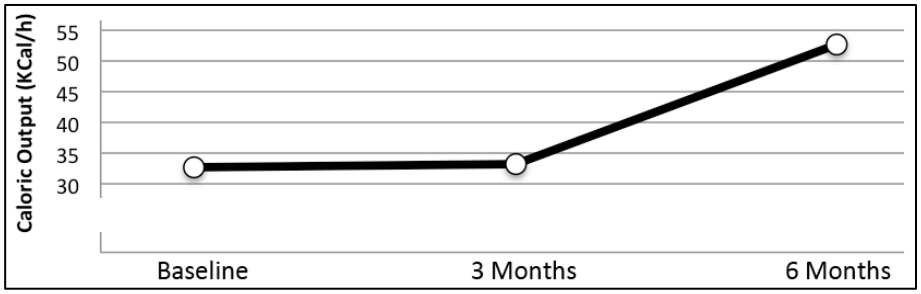
This subject did not respond to treatment, with a HAMD-17 score increase from 7 at baseline to 9 at 6 months. Interestingly, the subject experienced decreased resistin and increased adiponectin, which are consistent with reduced symptom severity. The subject also showed decreased inflammation (lower IL-6), which is reflective of wellness. None of the biomarker changes were consistent with weight gain.

Subject 4

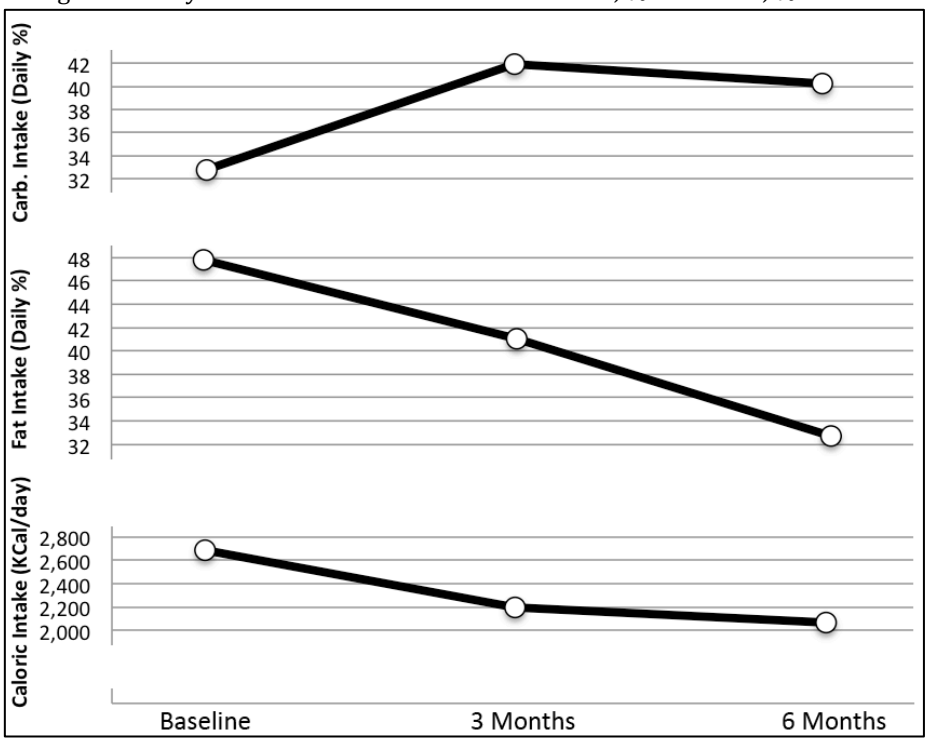
Change in BMI over 6 months



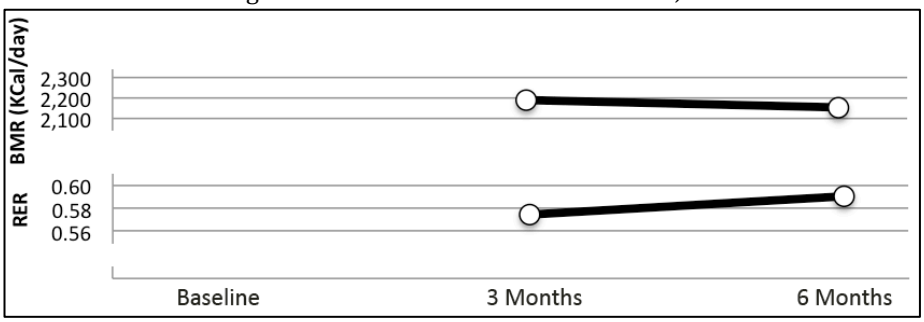
Change in physical activity over 6 months: *Caloric Output*



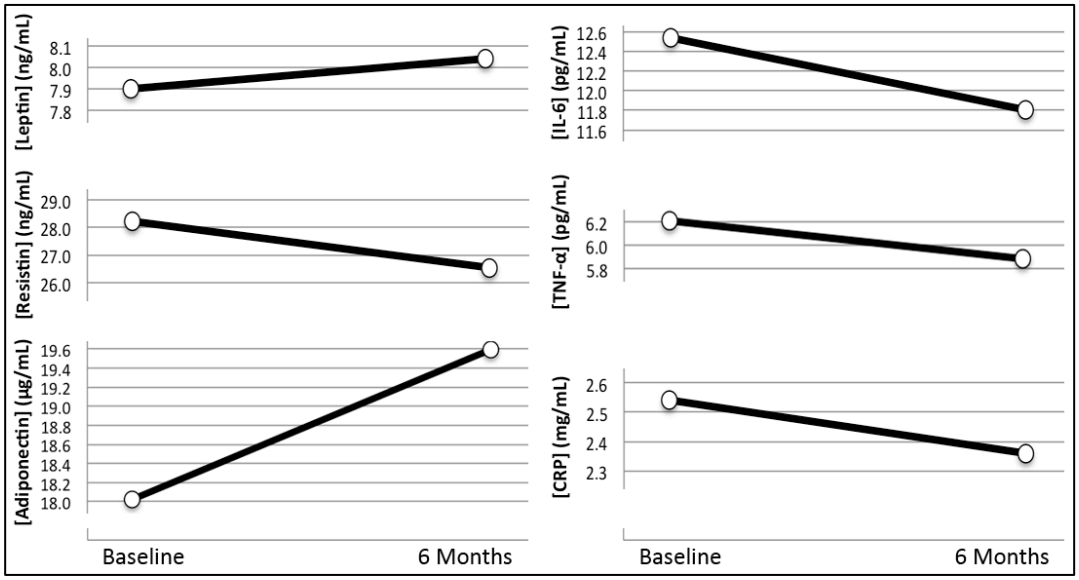
Change in dietary intake over 6 months: *Caloric Intake, %Fat Intake, %Carb Intake*



Change in metabolism over 6 months: *BMR, RER*



Change in biomarkers over 6 months: *Leptin, Resistin, Adiponectin, IL-6, TNF-α, CRP*



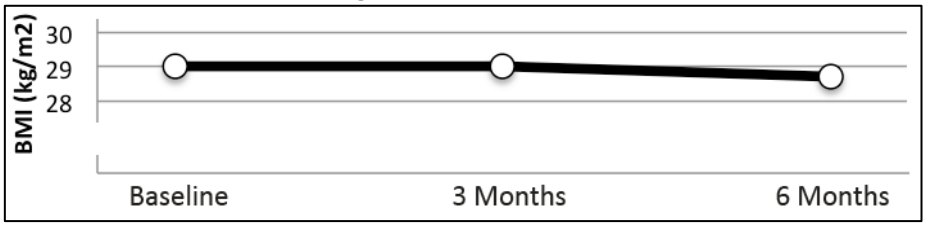
Analysis

This subject experienced weight gain at 3 months and 6 months. This weight increase was persistent despite increased caloric expenditure and decreased caloric consumption. BMR decreased slightly from 3 months to 6 months. However, RER values are too low to be considered accurate without a ketone assessment, which is not available for this subject.

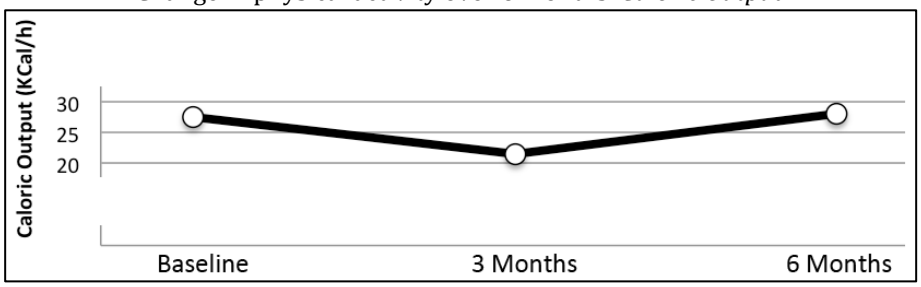
This was the only subject who responded fully to treatment, with a HAMD-17 score decrease from 20 at baseline to 7 at 6 months (remitted). This response to treatment is reflected in the biomarker analysis. The subject experienced increased leptin and adiponectin, as well as decreased resistin, all of which are consistent with reduced symptom severity. The subject also showed decreased inflammation (lower IL-6, TNF-α, and CRP), which is also reflective of wellness. Only the increased leptin was consistent with weight gain.

Subject 5

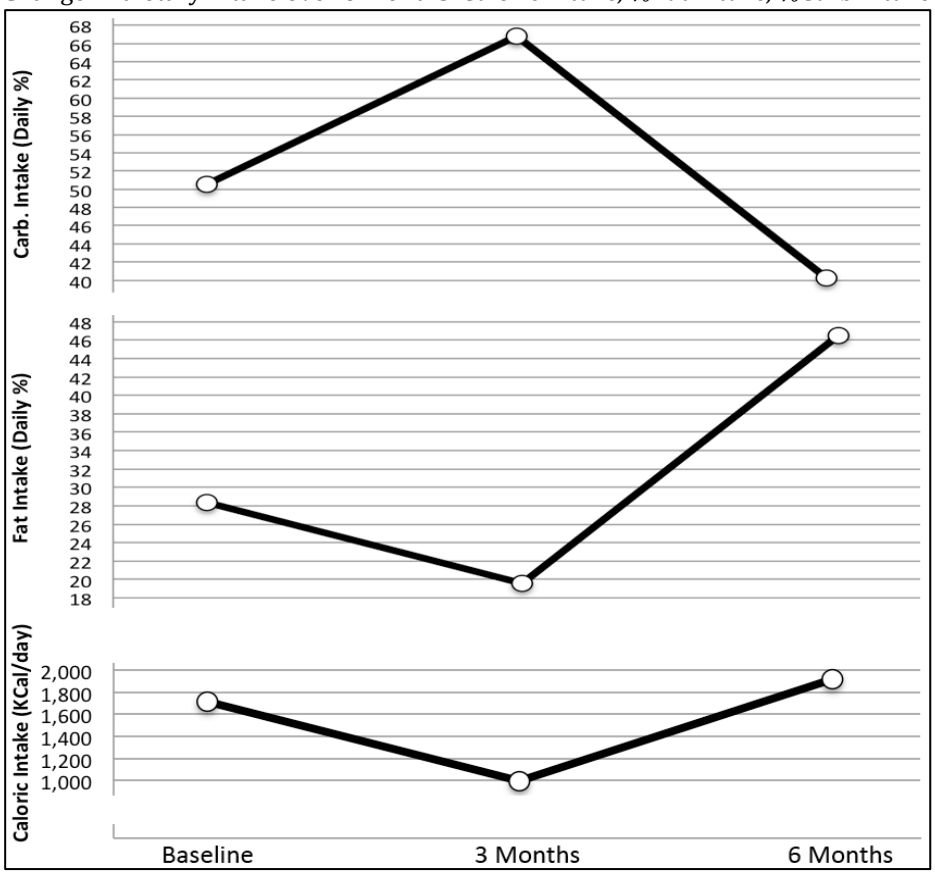
Change in BMI over 6 months



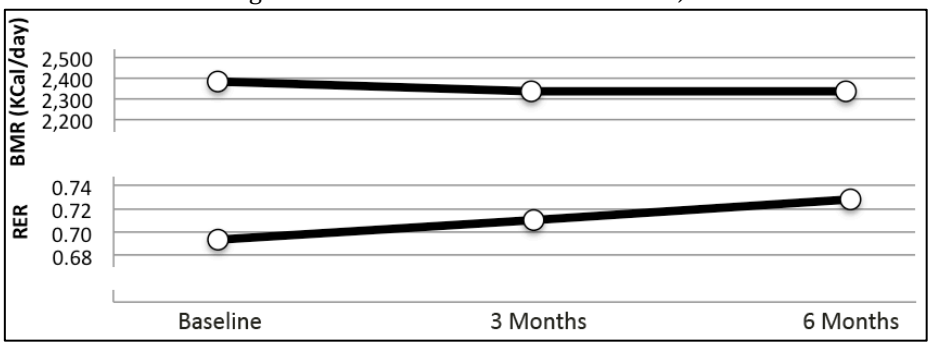
Change in physical activity over 6 months: *Caloric Output*



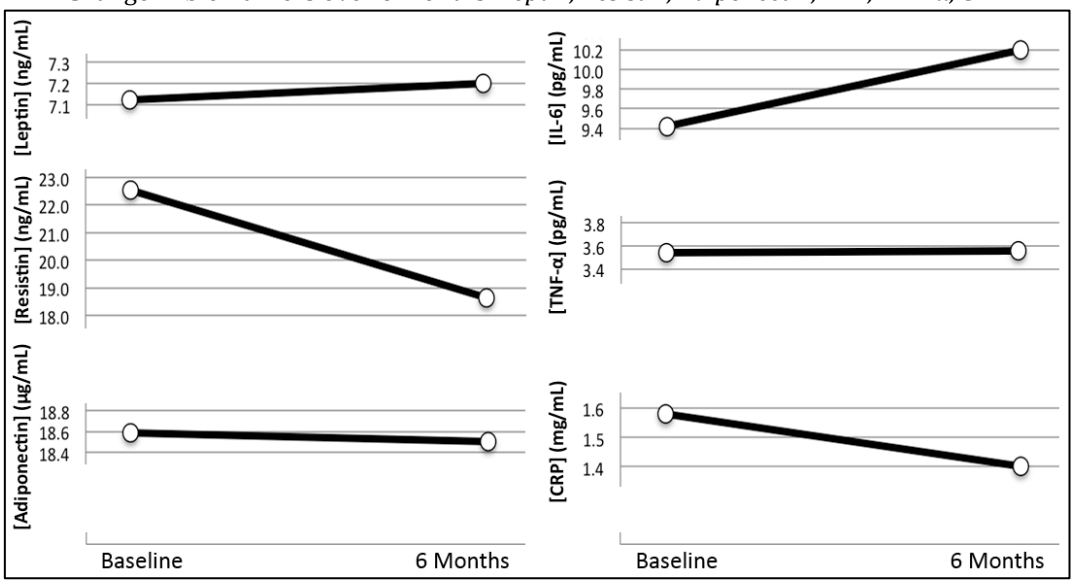
Change in dietary intake over 6 months: *Caloric Intake, %Fat Intake, %Carb Intake*



Change in metabolism over 6 months: *BMR, RER*



Change in biomarkers over 6 months: *Leptin, Resistin, Adiponectin, IL-6, TNF-α, CRP*



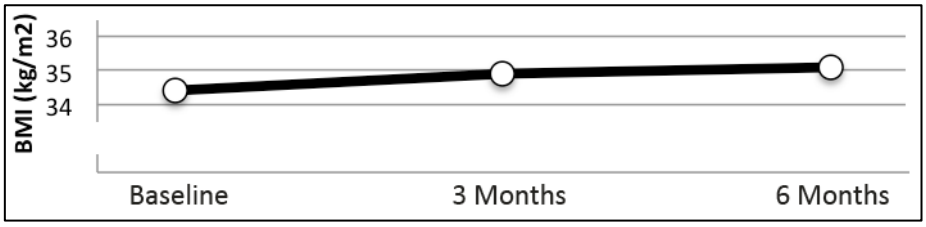
Analysis

This subject experienced relative stability in weight over the 6 months of treatment. This is reflected in little physical activity and BMR change over the study period. The subject showed an initial decrease in caloric intake. However, at 6 months the caloric intake returned to a level that is comparable to the baseline value. Overall, this subject did not seem to experience significant fluctuations in any of the 3 main outcomes, which is consistent with the subject's lack of significant weight fluctuation.

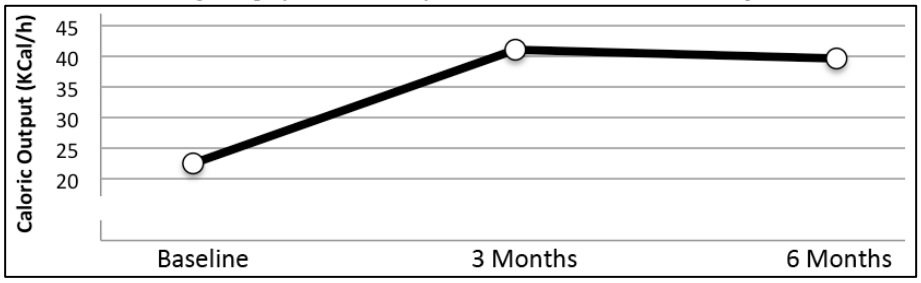
This subject did not respond to treatment, with a HAMD-17 score decrease from 23 at baseline to 22 at 6 months. The subject experienced increased leptin and decreased resistin, which are consistent with reduced symptom severity. The subject's inflammatory markers showed conflicting results, with an increase in IL-6 indicating increased inflammation and a decrease in CRP indicating reduced inflammation. Changes in leptin, resistin, and CRP are consistent with reduced symptom severity, whereas the change in IL-6 is consistent with weight gain.

Subject 6

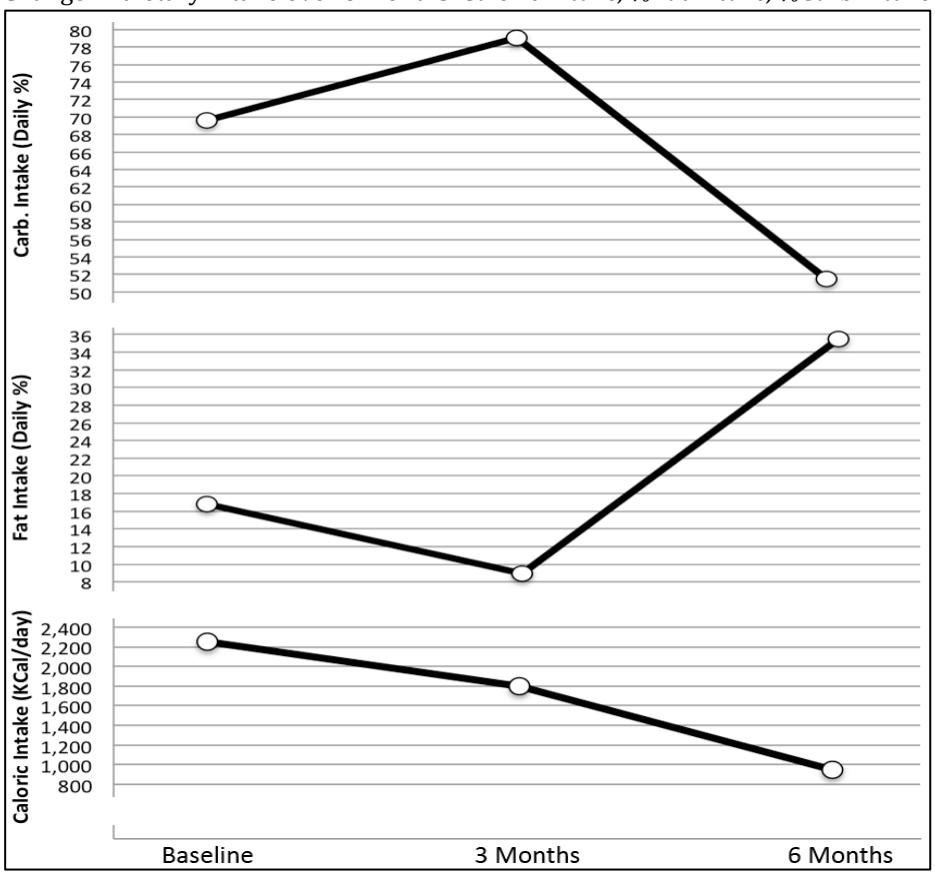
Change in BMI over 6 months



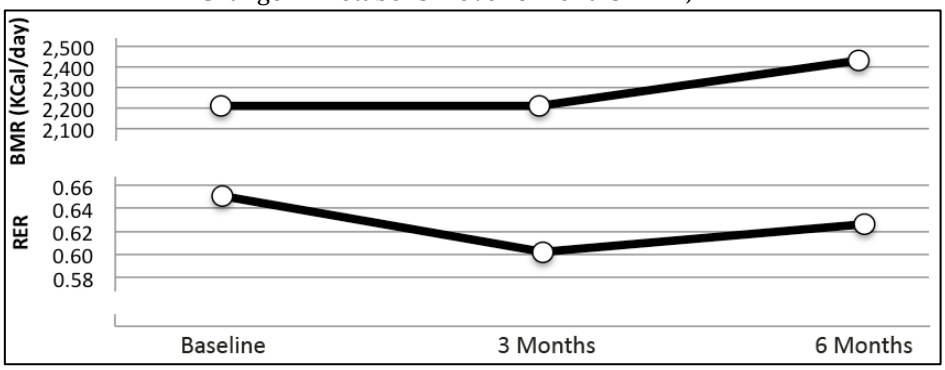
Change in physical activity over 6 months: *Caloric Output*



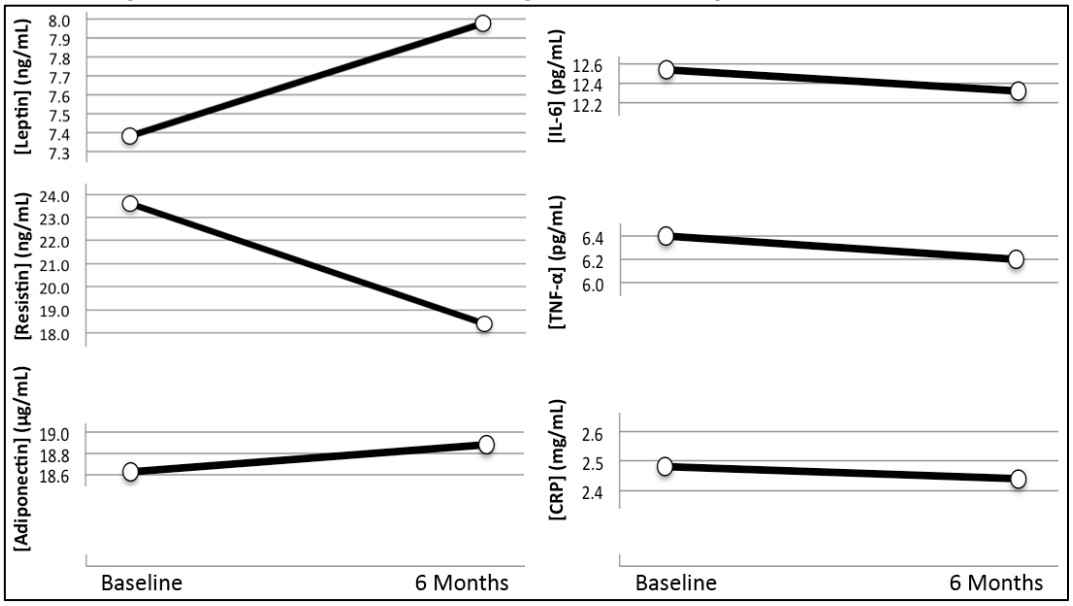
Change in dietary intake over 6 months: *Caloric Intake, %Fat Intake, %Carb Intake*



Change in metabolism over 6 months: *BMR, RER*



Change in biomarkers over 6 months: *Leptin, Resistin, Adiponectin, IL-6, TNF-α, CRP*



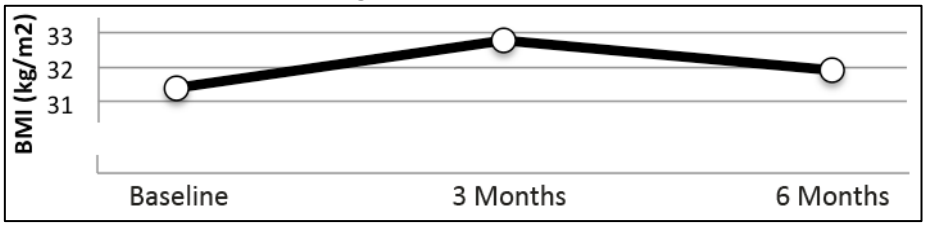
Analysis

This subject experienced weight gain, particularly at the 3 months interval, despite increased caloric expenditure, decreased caloric consumption, and increased BMR. However, BMR values were accompanied by very low RER values. A ketone test revealed that the subject's β-hydroxybutyrate (BHB) level was slightly elevated at baseline (0.27 mmol/L) and increased further at 6 months (0.41 mmol/L) as the RER value decreased. Although BHB levels were slightly elevated, the subject was not ketotic, and therefore the RER and BMR values may be inaccurate.

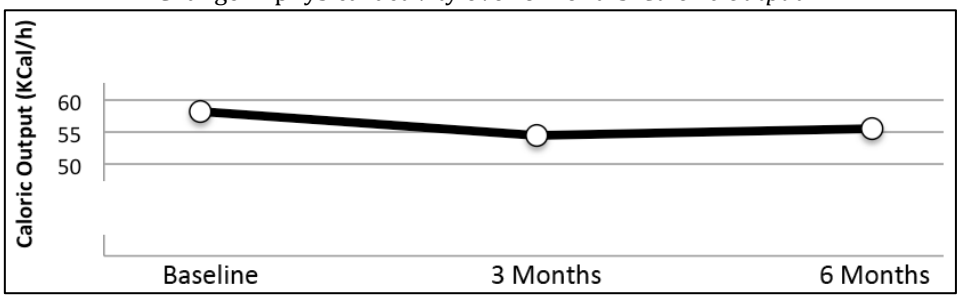
This subject was a partial responder, with a HAMD-17 score decrease from 17 at baseline to 8 at 3 months, although HAMD-17 score did increase to 11 at 6 months. This response to treatment is reflected in the biomarker analysis. The subject experienced increased leptin and adiponectin, as well as decreased resistin, all of which are consistent with reduced symptom severity. The subject also showed decreased inflammation (lower IL-6, TNF-α, and CRP), which is also reflective of wellness. Only the increased leptin was consistent with weight gain.

Subject 7

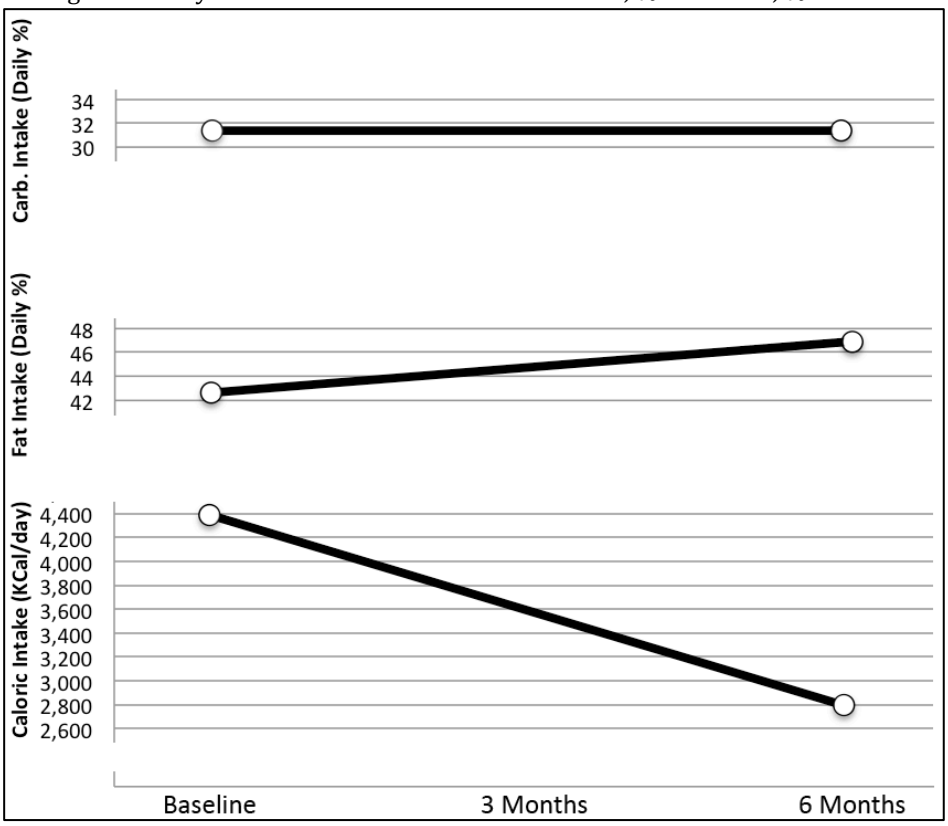
Change in BMI over 6 months



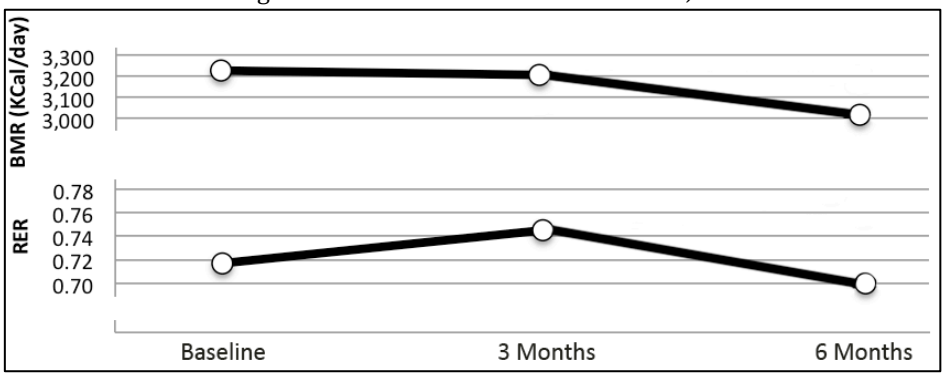
Change in physical activity over 6 months: *Caloric Output*



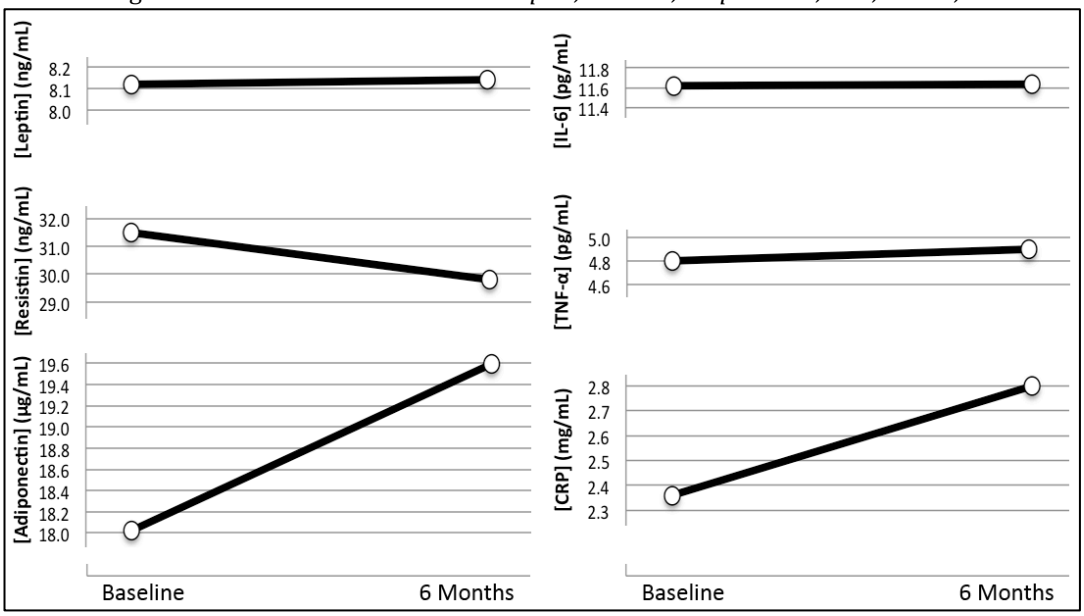
Change in dietary intake over 6 months: *Caloric Intake, %Fat Intake, %Carb Intake*



Change in metabolism over 6 months: *BMR, RER*



Change in biomarkers over 6 months: *Leptin, Resistin, Adiponectin, IL-6, TNF-α, CRP*



Analysis

This subject experienced weight gain at 3 months, which could be explained by a slight decrease in physical activity for this interval. BMR remained relatively the same and the dietary record was not returned for this interval. The subject lost weight by 6 months, but still weighed more than at baseline. This decline in weight could be explained by the dramatic decrease in caloric intake, which may have offset the slight decrease in BMR. At 6 months, physical activity remained stable.

This subject did not respond to treatment, with no change in HAMD-17 from baseline to 6 months, remaining at a score of 16. The subject experienced decreased resistin and increased adiponectin, which are consistent with reduced symptom severity. However, the subject experienced an increase in CRP, which is consistent with weight gain.

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