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C-Reactive Protein (CRP) Levels in a Young Adult Population with Major Depressive Disorder (MDD)

Jack Sawyer – Allied Health Sciences

Abstract

Objective: To investigate the relationship between Major Depressive Disorder (MDD) and inflammation assessed using serum C-reactive protein (CRP) in young adults. CRP has been associated with MDD in middle-aged and older adults, but the relationship has yet to be established in college-aged adults with MDD.

Methods: This ongoing cross-sectional study included 56 patients with MDD and 106 healthy age-matched controls. Depressed patients were recruited from mental health institutions across Connecticut, and were being treated for depression with a Second Generation Antipsychotic (SGA). Questionnaire data, anthropometric measurements and fasting blood draws were recorded for all participants.

Results: Young adults with MDD had significantly higher CRP levels than healthy controls ($p < 0.05$). Body Mass Index (BMI) and leptin were positively correlated with CRP ($p < 0.001$) in the MDD group, but not in the controls. Use of Oral Contraception (OC) was positively associated with CRP concentrations in both depressed and non-depressed subjects ($p < 0.010$). Using multivariate regression analysis, we were able to account for approximately 42% of the variability in CRP in the depressed population.

Conclusions: Our findings indicate that the relationship between CRP and MDD that has been established in older adults exists in young adults treated with SGA medication as well. The depressed population had significantly higher CRP and leptin levels, and BMI than controls, pointing to a possible role that adiposity and inflammation play in depression.

C-Reactive Protein (CRP) Levels in a Young Adult Population with Major Depressive Disorder (MDD)

Introduction

Major Depressive Disorder (MDD) is a debilitating mental health condition that impacts one's quality of life with a force equal to or greater than any other chronic illness (Dowlati et al., 2010). The Centers for Disease Control reports that 8% of the total U.S. population over age 12 currently suffers from MDD, with rates rising higher in specific populations, including young adults, and middle aged women (Centers for Disease Control, 2015). As with many other mental health disorders, depression is one of a complex etiology, making treatment a unique challenge for each individual.

Over the past decade, increasing evidence has indicated immune system dysregulation in the pathogenesis of MDD. Specifically, an inflammatory component has been highlighted (Raison & Miller, 2011). Several serum proteins, including C-reactive protein (CRP), have been implicated in this relationship between inflammation and depression. CRP, an acute phase reactant protein, is of particular importance in the inflammatory response system (IRS). CRP levels above 1 mg/dL can indicate a plethora of deleterious conditions including, cardiovascular disease (CVD), metabolic syndrome (MetS), and obesity, and levels above 0.3 mg/dL is characterized as low-grade inflammation (LGI) (Sørensen et al. 2014).

Although the association has been made between CRP and increased CVD risk, the link between CRP and MDD has remained unclear (Ma et al., 2011). Nonetheless, both Ma et al. (2013) and Cizza et al. (2009) reported elevated CRP in depressed middle-aged women using postmenopausal and premenopausal cohorts respectively. This association has been reported in middle-aged men as well (Vetter et al., 2013 & Vogelzangs et al., 2012). Additionally, Vogelzangs et al. (2012) described an association between elevated CRP levels with depressive symptoms in a relatively young population (mean age = 41.8), while Song et al. (2015) confirmed this in an elderly cohort (mean age = 72.1).

The startling fact that more than one-third of college students found it difficult to function due to depression during the past year make them an obvious population for depression research (Novotney, 2014). However, surprisingly few studies have examined the inflammatory link in college aged participants with depression, although these CRP studies have been repeated numerous times using middle-aged populations. The negative side effects of depression, while serious in all age groups, can manifest themselves in particularly detrimental ways in young adults. This study aimed to investigate whether CRP levels differ between a depressed 18-25 year old population when compared with a healthy aged match control group, and attempted to explain these possible differences.

Methodology

Participants & Design

A total of 56 depressed 18-25 year olds and 106 healthy age-matched controls were recruited. This depressed cohort was recruited from several mental health institutions in Connecticut. Patients were only included in the study if they were being treated with Second Generation Antipsychotics (SGAs) for their MDD. Exclusion criteria were defined as persons who were prescribed more than one Second Generation Antipsychotic (SGA) simultaneously, were prescribed a dose of SGA below expected doses for patients with MDD, or were prescribed medications that would interfere with laboratory tests or physical examination parameters. A control population of 106 healthy 18-25 year old college students was recruited from the University of Connecticut – Storrs Campus (UCONN). Subjects were only enrolled in the control group if they had no history of mental illness or treatment for any mental illness. This was ensured by screening each of the 106 control subjects over the phone before offering them participation in the study. In total, all 162 of these young adults underwent the same surveys, non-invasive physical examination, and blood work. The study was conducted jointly between the Institute of Living (IOL) in Hartford CT, and at UCONN. Written informed consent was obtained from all subjects prior to beginning the study. IRB approval was obtained separately from the IOL and from UCONN prior to beginning the study.

Measurement of Variables

Sociodemographic questionnaire. All study participants were administered a questionnaire conducted by trained personnel. The questionnaire relied on self-report data from the participants and was designed to account for possible covariates that were adjusted for after data collection. Questions contained content about alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT]), sleep quality (Pittsburgh Sleep Quality Index [PSQI]), and physical activity. All subjects were asked to report both their prescription and non-prescription medication use over the past three months. Depression scores were determined using the Hamilton Rating Scale for Depression (HAM-D), a validated questionnaire administered by trained staff used to diagnose depression (Hamilton, 1960).

Physical parameters. Immediately after the survey was completed, a non-invasive physical examination was performed on all subjects by trained personnel. Height (cm) and weight (lbs.) were measured using the same calibrated stadiometer and digital scale, and were measured to the nearest 0.1 cm and 0.1 lb. These measurements were used to calculate body mass index (BMI) for all participants. Blood pressure was measured using a Omron™ digital blood pressure monitor, HEM-712C. Bioelectrical Impedance Analysis (BIA) was measured using Tanita™ Body Composition Analyzer, TBF-300a. Waist and hip circumferences (cm) were measured using a tape measure and were measured to the nearest 0.1cm. All measurements were done in triplicate and averaged.

Fasting blood measures. Blood samples were collected in the fasting state (≥ 8 hours) in the morning by a laboratory professional certified in phlebotomy. Laboratory tests for CRP and

leptin were analyzed at clinical laboratories. CRP levels were measured in a clinical laboratory via a particle enhanced immunoturbidimetric assay on the Cobas 6000 /c501 (Roche Diagnostics, Indianapolis, IN). Leptin levels were measured using electrochemiluminescence in a commercial laboratory (Quest Diagnostics Nichols Institute, San Juan Capistrano, CA).

Statistical Analyses

Results are reported as means \pm standard deviation (SD). Descriptive statistics were used to characterize continuous and categorical variables collected from interviews, physical exams, and fasting blood draws, along with assessing normality of data. CRP levels were transformed to normalize the distribution. Independent T-tests and ANOVAs were used to compare mean CRP levels with other continuous, biological and behavioral variables. Correlations were run between CRP and various biomarkers and anthropometric measurements. P values <0.05 were considered to be significant. A series of multivariable linear models were run to analyze association of CRP with several independent variables. Included in these models were variables that were found to have significant correlations with CRP in simple linear regression models. All analyses were conducted using SPSS version 23.0.

Results

Demographic and descriptive characteristics are presented for all participants (N = 162) in the study (**Table 1**). This study consisted of 63 men with a mean age of 21.1 ± 1.99 and 99 women with a mean age of 20.6 ± 1.80 . Participants were stratified into two groups: patient (those with MDD and treated with a SGA) and control (healthy aged matched college students). Mean CRP and leptin levels were significantly higher in the depressed population than in the healthy control group ($0.44 \text{ mg/dl} \pm .84$ vs. $0.16 \text{ mg/dl} \pm .20$, $p=0.019$; $9.41 \text{ ng/mL} \pm 12.05$ vs. $5.22 \text{ ng/mL} \pm 4.91$, $p=0.015$). Overall, the MDD group were older, had higher serum triglyceride, insulin and glucose levels but lower cortisol and HDL levels than the control group. The MDD group also had significantly higher BMIs, waist and hip measurements than the control group (Table 1).

Table 2 and **Table 3** stratify CRP data based on gender and oral contraception (OC) use. There was no significant difference in CRP levels between depressed and healthy males (**Table 2**). Significant differences were seen however, when comparing depressed females, and healthy females from the control group ($.69 \text{ mg/dL} \pm 1.06$ vs. $.18 \text{ mg/dL} \pm .19$, $p=0.012$). Only females diagnosed with MDD (N=31) had abnormal CRP levels ($>0.50 \text{ mg/dL}$). Female participants were further stratified based on oral contraception (OC) use (**Table 3**). No significant differences in CRP levels were seen between depressed females who were taking OC and depressed females not taking OC, despite higher average CRP levels in the depressed cohort ($.98 \text{ mg/dL} \pm 1.56$ vs. $.55 \text{ mg/dL} \pm .73$, $p=0.306$). However, in the control group, females taking OC had significantly higher CRP levels than females not taking OC ($.25 \text{ mg/dL} \pm .18$ vs. $.11 \text{ mg/dL} \pm .17$, $p=0.002$).

We have found several correlations between different independent variables and CRP. In the MDD group, CRP was positively correlated with leptin ($r=0.585$, $p=0.000$) and BMI ($r=0.478$, $p=0.000$). When stratifying by gender in the MDD group, leptin was only significantly associated with CRP in females ($r=.503$, $p=0.004$), however BMI remained significantly correlated for males ($r=0.412$, $p<0.05$) and females (**Figure 1**). No relationship between BMI and CRP was seen in healthy males or females (**Figure 2**). We also found correlations between OC use and CRP. Leptin ($r=0.709$, $p=0.000$) and BMI ($r=0.670$, $p=0.001$) were positively correlated with CRP in depressed females not using OC. This relationship was not seen in depressed females ($r=.309$, $p=.386$; $r=.547$, $p=.102$) using OC or in healthy females (NO OC: $r=-.015$, $p=.930$; $r=.015$, $p=.930$; YES OC: $r=.049$, $p=.789$; $r=-.298$, $p=.098$), regardless of OC use.

Multivariate regression analysis determined the variability seen in CRP in the depressed population and control group by using significant correlates in the simple linear regression models. Our first model included just OC and Leptin and accounted for 38% of the variability in CRP values in the depressed population. This model only accounted for 15% of CRP levels in the control group. Our best predictive model consisted of OC, leptin, and number of days treated with a SGA, and was able to account for 42% of the CRP levels in depressed patients.

Discussion

CRP has been directly associated with MDD, a relationship that has been shown to be bidirectional (Matthews et al., 2010). To our knowledge, this is the first study to use an established MDD population with a healthy age-matched control group to examine the relationship between CRP and depression in young adults. Our findings indicate significantly higher CRP levels in a depressed college aged population compared to a healthy control group (Table 1). This confirms the findings of Topić et al. (2013) who reported that elevated serum CRP levels were significantly more common in middle aged MDD patients, than in healthy controls

Our results suggest that gender plays a role in CRP differences that we observed between depressed and healthy populations. In males, no significant differences in CRP were noted between the experimental and control groups (Table 2). However, females with MDD had significantly higher CRP levels when compared with the controls (Table 2). These results confirm the findings of Cizza et al. (2009) who observed a significant association between elevated CRP and MDD in premenopausal women (mean age = 35.5 years). Identical to our results, they also found BMI to be directly correlated with CRP in depressed women, but not in controls. These findings were also reported by Murabito et al. (2013), who observed that visceral adipose tissue (VAT) was associated with depressive symptoms in both pre- and post-menopausal women (mean age = 52.2 years). No relation between VAT and depression was seen in men. It is well established that VAT is associated with increased serum CRP levels in

both depressed and non-depressed populations (Murabito et al., 2013; Matthews et al., 2010; Sørensen et al. 2014), hinting at the unique synergy between adiposity and inflammation.

Due to its relationship to obesity, numerous studies have implicated leptin in the pathogenesis of depression. Leptin is a hormone synthesized by adipocytes that regulates satiety and energy expenditure. Both increased and decreased levels of the hormone have been linked to obesity (Considine et al., 1996). In addition to associations with BMI, serum leptin concentrations have been found to be elevated in both depressed patients and non-depressed patients with metabolic syndrome (Jiménez et al., 2009; Chirinos et al., 2013). Increased adiposity may lead to increased inflammation and leptin levels, while it has also been suggested that increased leptin levels can cause up-regulation of certain inflammatory cytokines, which may contribute to obesity and MDD (Sárvári et al., 2014). Our results showed that depressed females had significantly higher circulating leptin levels than depressed males. Consistent with previous studies (Morris et al., 2012), the depressed females in our cohort with high leptin levels also had significantly higher BMIs than the healthy controls, hinting at the well-established relationship between the two. Conversely, depressed males had similar leptin levels and BMI's to the healthy male controls. In our multivariate analyses, we found that leptin alone accounted for 31% of the variability in CRP levels in depressed patients, adding to the growing body of evidence that leptin may cause increased levels of inflammation. Based on our data, there appears to be gender differences that help to explain this relationship.

Second Generation Antipsychotics (SGAs) have been approved by the FDA as appropriate adjunct therapy for MDD and have been proven to be effective antidepressants in clinical trials (Roberts et al., 2015; Weisler et al., 2012). However, numerous studies have reported antipsychotic induced weight gain (AIWG) and increased levels of inflammation in patients treated with SGAs (Dieset et al., 2012; Zhang et al., 2004). Although AWIG has been well documented, the mechanisms involved are not fully understood. Elevated levels of inflammatory cytokines (e.g. CRP) and hormones (e.g. leptin) due to SGAs may be partially responsible, however studies are conflicting (Fonseka et al., 2016). While Dieset et al. (2012) found significant inflammatory activation by SGAs in adult psychiatric patients, Kim et al. (2011) found no difference in CRP levels among three different SGA treatment groups. The direction of causation between SGAs, inflammation, and hormonal factors is not yet clear, however numerous studies have described an association or relationship (Foneska et al., 2016; Sárvári et al., 2014; Victoriano et al., 2010). Although SGAs have been reported to cause increased inflammation, these effects were not seen in our study when stratifying for gender. When comparing the CRP levels of healthy males vs. depressed males treated with SGA, no significant differences were seen between the groups (.14 mg/dl \pm .22 vs .13 mg/dl \pm .17 p=0.849). However depressed females had significantly higher mean CRP levels when compared with the healthy female controls (.69 mg/dl \pm 1.06 vs. .18 mg/dl \pm .19, p=0.012). These findings highlight the complexity of the relationship between SGAs and inflammation. If SGAs were the

dominating factor in causing increased CRP in depressed patients, depressed males should have also had significantly higher CRP levels than their healthy counterparts. Instead, we found elevated CRP levels only in depressed females vs. healthy females. This could be because the depressed female cohort had significantly higher BMIs than healthy females, which has been strongly correlated with increased CRP (Shelton et al., 2015). It is also well established that SGAs alter fat and glucose metabolism due to increased leptin expression (Sárvári et al., 2014). No studies however, have examined whether these effects differ based on gender. Our findings indicate that a multifactorial relationship must be considered when attempting to explain CRP differences in a depressed vs. healthy population.

Another potential predictor of increased CRP in depressed college-aged adults is the use of OC. It is well established that OC use contributes to increased bodily inflammation in both adolescents and young adults (Pirkola et al., 2010; Raitakari et al., 2005). Sørensen et al. (2014), found OC use in healthy women (mean age = 38.6) to be a significant predictor of LGI and Raitakari et al. (2005) reported OC use to be the single most important determinant of elevated CRP levels in healthy women (mean age = 31.7). The mechanisms by which OC, in particular the hormone estrogen, interact with CRP remain unclear, however both biomarkers have been linked to increased CVD risk (Van Rooijen et al., 2006). We found no significant CRP differences between females taking OC vs. not taking OC in the depressed group (Table 3). However, significant differences in CRP levels were seen in the control group when stratifying for OC use, making OC a better predictor of CRP levels in the healthy young females, than in depressed young females. In addition, we found OC alone to account for 28% of the differences in CRP in control females. It is interesting to note that there were no differences in BMI, hip or waist circumferences in the female controls when stratifying for OC use, however CRP differences were still seen. According to our results, OC is associated with increased inflammation in healthy females, without contributing to any weight gain. This is not to say that OC has no bearing on CRP levels in depressed patients. We found that OC alone accounted for 20% of CRP differences in the depressed population. It is possible however, that the effects of OC are somewhat masked in the depressed group due to increased adiposity, diagnosis of MDD, and other medication use.

This study has several limitations. First, since this was a cross-sectional study, all data was collected at one time point. This gave us no access to baseline data on the depressed patients before they began treatment with an SGA. As a result, we were unable to see physical and biomarker changes that occurred in patients with MDD treated with SGA. Second, while most patients (77.8%) were taking Abilify and Seroquel, others (22.2%) were taking a different SGA type. In addition, the dosing and duration of SGA treatment varied from patient to patient, which possibly could have led to variability among biomarkers and anthropometric measurements. Third, our current MDD sample size, especially when stratifying by OC, was relatively small limiting our generalizability in this group.

College students are an important demographic in depression studies for numerous reasons including suicide, which is the second leading cause of death among college students (CDC, 2015). The negative side effects of depression, while serious in all age groups, can manifest themselves in particularly detrimental ways in young adults. Increased incidence of smoking, alcohol consumption, and lack of exercise are all common coping mechanisms, making treating and understanding depression in college-aged adults all the more crucial (Beiter et al., 2015). While the link between CRP and depression has been well established, we believe our study to be the first to examine the relationship between depressive symptoms and inflammation in a cohort of young adults (ages 18-25). To the best of our knowledge, no previous study has used a population with a mean age under 30, and most have only shown a relationship between CRP and MDD in middle-aged populations. By using a healthy-aged match control group, we were able to observe differences in mean CRP levels between the two groups, and by examining other independent variables collected, we have explained some of these differences.

Our findings indicate that the relationship between CRP and MDD that has been established in older adults exists in young adults treated with SGA medication as well. Significant differences in CRP, leptin, and BMI were seen when comparing a depressed, 18-25 year old population to a healthy age-matched control group, highlighting the important role inflammation plays in both adiposity and depression, and how it may connect the two conditions. In addition, we found that OC use and number of days taking a SGA contribute to CRP variability in a depressed population. Future studies are needed to confirm these findings and further understand the relationship of elevated CRP in patients with MDD in a larger, more diverse group of college-aged students.

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Table 1: Characteristics of Study Participants

	Total Sample (N=162)	Patient Population with MDD (N=56)	Healthy Controls (N=106)	p-value
<i>Sociodemographics</i>				
Age (years)	20.78	21.77	20.25	0.000
Gender				
Men, N (%)	63 (38.9)	25 (44.6)	38 (35.8)	
Women, N (%)	99 (61.1)	31 (55.4)	68 (64.2)	
<i>Physical parameters & Biomarkers</i>				
C-reactive protein (mg/dL), mean (SD)	.26 (.53)	.44 (.84)	.16 (.20)	0.019
Body mass index (BMI), mean (SD)	24.82 (5.91)	27.92 (8.23)	23.18 (3.21)	0.000
Insulin (uIU/mL), mean (SD)	11.62 (8.90)	15.37 (13.07)	9.64 (4.78)	0.002
Leptin (ng/mL), mean (SD)	6.67 (8.33)	9.41 (12.05)	5.22 (4.91)	0.015
Iliac Crest Average (cm), mean (SD)	82.31 (14.50)	90.80 (18.32)	77.82 (9.37)	0.000
Mid-iliac Waist (cm), mean (SD)	78.44 (14.17)	87.61 (16.98)	73.59 (9.38)	0.000
Hip (cm), mean (SD)	96.19 (12.52)	101.26 (17.41)	93.51 (7.77)	0.002
Triglycerides, mean (SD)	90.17 (45.21)	105.66 (59.05)	81.99 (33.34)	0.007
Cortisol (ug/dL), mean (SD)	22.96 (10.75)	18.54 (9.34)	25.29 (10.75)	0.000
High Density Lipoprotein (HDL), mean (SD)	58.69 (14.96)	53.95 (14.30)	61.20 (14.75)	0.003
Glucose	88.36 (8.43)	90.64 (9.03)	87.15 (7.87)	0.012

Table 2: CRP levels By Gender

	MDD (N=56)		Controls (N=106)	
	Males (N=25)	Females (N=31)	Males (N=38)	Females (N=68)
CRP (mg/dL), mean (SD)	.13 (.17)	.69 (1.06)*#	.14 (.22)	.18 (.19)

* p = 0.007 (MDD males vs. MDD females)

p = 0.012 (MDD female vs. control females)

Table 3: CRP levels by OC use

	MDD (N=31)		Controls (N=68)	
	YES female (N=10)	NO female (N=21)	YES female (N=32)	NO female (N=36)
CRP (mg/dL), mean (SD)	.98 (1.56)	.55 (.73)	.25 (.18)*	.11 (.17)

* p = 0.002 (Control YES females vs. Control NO females)

Figure 1: Body Mass Index (BMI) and C-Reactive Protein (CRP) in Females with Major Depressive Disorder (MDD)

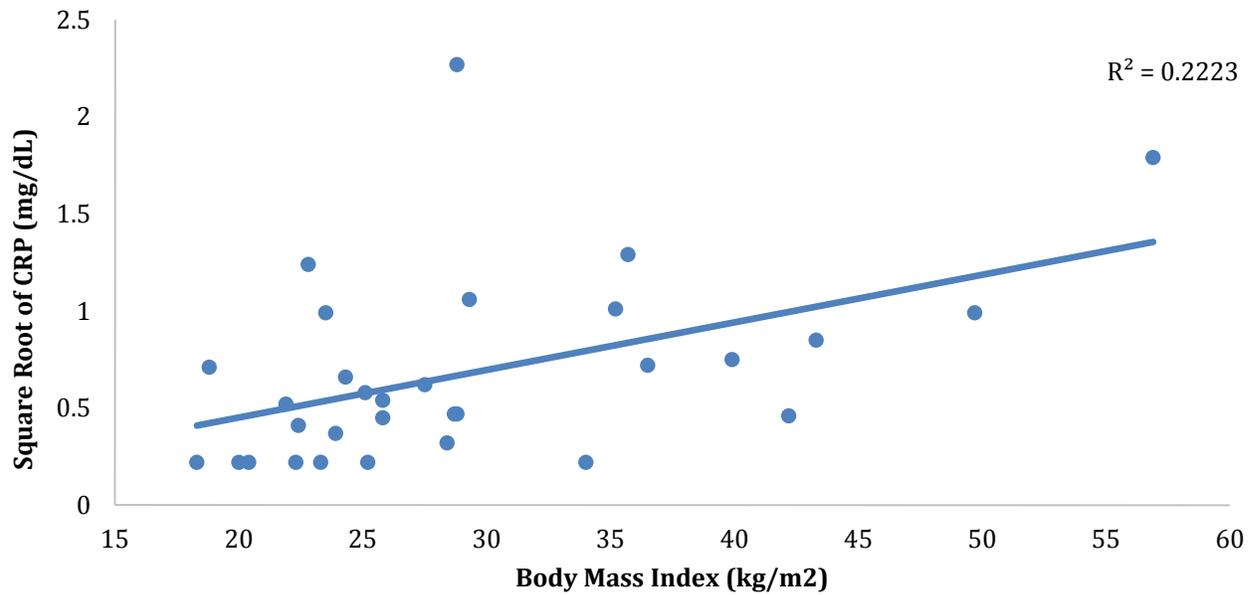


Figure 2: Body Mass Index (BMI) and C-Reactive Protein (CRP) in Females without Major Depressive Disorder (MDD)

