Relation between Bipolar Mood Disorder and Seasonality of Serum Lipids

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ÖZET

İki uçlu duygudurum bozukluğu ve lipit döngüselliği ilişkisi

Giriş: Serum lipidleri ve duygudurum bozuklukları ilişkisi uzun yıllardır araştırılmaktadır. Son yıllarda yapılan araştırmalarla serum lipidlerinin mevsimsel döngüselliği gösterilmiştir. Buradan hareketle, epizodik ve döngüsel seyirli bir duygudurum bozukluğu olan iki uçlu bozuklukta serum lipidlerinin mevsimsel değişimini araştırmayı amaçladık.

Yöntem: Bakırköy Mazhar Osman Ruh Sağlığı ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi, Raşit Tahsin Duygudurum Merkezi'nde (RTDDM) iki uçlu duygudurum bozukluğu tanısıyla takip ve tedavisi sürdürülmekte olan hastalardan çalışmaya alınma-dışlama ölçütlerini karşılayan 79 hasta ve 38 sağlıklı kişinin, kontrollerde, 1 yıl boyunca her mevsimde, toplam dört kez serum lipidleri ölçülmüştür. Hasta ve kontrol gruplarındaki ortalama serum lipidleri ve mevsimsel değişimleri karşılaştırılmıştır.

Bulgular: İki uçlu hastaların ortalama kolesterol ve TG düzeyleri tüm mevsimlerde kontrol grubununkiyle benzer bulundu. Öte yandan hastaların HDL düzeyleri ise, kış mevsimi dışında tüm mevsimlerde kontrol grubundan daha düşük bulundu. Serum lipidlerinin mevsimsel değişkenliği değerlendirildiğinde, yalnızca ilkbaharda HDL-kolesterol düzeylerindeki değişimin kontrol grubuna göre anlamlı farklılık gösterdiği saptanmıştır.

Sonuç: Araştırmamızın kısıtlılıkları olmakla birlikte, iki uçlu hastalarda lipid döngüselliğini değerlendiren ilk çalışmadır. Hastalığın etiyolojisi ve seyrine ilişkin daha güçlü kanıtlar elde edebilmek için, karıştırıcı faktörlerin dışlandığı geniş izlem çalışmalarına gereksinim vardır.

Anahtar kelimeler: İki uçlu duygudurum bozukluğu, lipitler, mevsimsellik

ABSTRACT

Relation between bipolar mood disorder and seasonality of serum lipids

Introduction: The association between mood disorders and serum lipid levels has been evaluated for many years. Recently, it has been showed that serum lipid levels may have seasonal changes. From here, we aimed to evaluate seasonality of serum lipids in bipolar disorder which may be related with episodic and seasonal features.

Method: Mean serum lipid levels and seasonal differences of serum lipid levels were compared between 79 patients with bipolar disorder type I, who were followed in Rasit Tahsin Mood Disorders Outpatient Unit of Bakırköy Prof. Dr. Mazhar Osman Research and Training Hospital for Psychiatry, Neurology & Neurosurgery and 38 healthy controls, for one year.

Results: Mean cholesterol and triglyceride levels were similar between patients and controls for all seasons. Mean serum HDL levels were lower for all seasons, except winter in patients with bipolar disorders. When seasonal changes in lipid levels were evaluated, the only significant difference among the two groups was changes in spring HDL levels.

Conclusions: This is the first study that evaluates seasonality of lipid levels in bipolar patients, although it has some limitations. Long term, big sample-sized follow-up studies are required to get strong evidence for understanding aetiology of illness related with lipid levels among bipolar patients.

Key words: Bipolar mood disorder, lipids, seasonality

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INTRODUCTION

The role of serum lipid levels in psychiatric diseases has been researched for many years. Serum lipid levels have been studied in many psychiatric disorders including anxiety disorder, depression and schizophrenia, and their relation to suicide attempts and aggression has been investigated (1,2). Cholesterol levels were found to be low in depressive and manic patients (3-5), but this relationship could not be verified in some studies (6,7). Moreover, some papers stated that treatment changes cholesterol levels in periods of disease and emphasized the powerful relationship between mood disorder and cholesterol (8). A study published by Beasley et al. (9) claimed there could be a relation between mood disorders and low cholesterol levels in the brain. Ghaemi et al. (10) stated that cholesterol levels may be state dependend entity

influenced by acute mood periods, rather than trait marker. A group of researches in Spain found that there is a relationship between the most recent mood episodee and cholesterol and lithium levels in patients with bipolar mood disorder (11).

In contrast, many small follow-up studies and large cross-sectional studies conducted in the second half of the last century indicate that the cholesterol level is higher in the autumn and winter months, and lower in the spring and summer months (12-14). As a matter of fact, Rastam et al. (15) discussed the cyclical nature of cholesterol levels in their research, while Gordon et al. (16) emphasized that this cycle may be responsible for diagnosing a group as hypercholesterolemic.

The relationship between blood lipids and many psychiatric diseases (mainly mood disorders) has long been investigated. But while many aspects of this relationship have been studied, as far as we know, no research has been made on the relationship between the seasonal, cyclical nature of bipolar mood disorder and blood lipids in patients with bipolar mood disorder. We believe that the cyclical course of blood lipids and episodic course of bipolar disorder are closely related.

METHOD

The target population consists of bipolar mood disorder patients and the control group. Of the patients monitored and treated for bipolar mood disorder at the Raşit Tahsin Mood Center (RTMC) of the Bakırköy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, the study included 79 people between the ages of 18 and 65, who were being followed for bipolar mood disorder according to DSM-IV-TR, who were clinically in remission, who had come to the RTMC clinic for interview between July 15 and August 31, 2008, and who had signed an informed consent agreeing to participate in the study. The control group consisted of 38 people, including the spouses of patients with no blood relation and hospital personnel who met the study inclusion and exclusion criteria. Patients in a manic/hypomanic/depressive/mixed episode at the interview, illiterate patients, those with dementia or cognitive disability that would make it difficult to understand the criteria applied, those having a psychiatric disorder and those suufering from a disease that may affect serum lipids, those with mental retardation, those using antihyperlipidemics, and those abusing alcohol or substances were excluded from the study. The control group consisted of literate persons between the ages of 18 and 65, who signed the informed consent form agreeing to participate in the study, who do not have or are not being treated for a psychiatric disease, who have no history of bipolar disorder in first-degree relatives, who have no cognitive disability to an extent that would make it difficult to understand the criteria applied, who do not have mental retardation, and who do not use antihyperlipidemics.

For both the patient and control groups, serum lipids, serum sodium and albumin levels, and height and weight were measured after 12-hour fast four times over the course of the year. To better reflect seasonal qualities, these measurements were taken in the second half of the season, i.e., visit 1: July 15-August 31, 2008; visit 2: October 15-November 30, 2008; visit 3: January 15-February 28, 2009; and visit 4: April 15-May 31, 2009.

Laboratory Method: With the enzymatic method, total cholesterol, HDL, triglyceride (TG) levels were detected using the colorimetric Kodak Ektachem Clinical Chemistry Slide kit; VLDL by dividing the triglyceride level by five, and LDL by subtracting HDL and VLDL from total cholesterol.

Socio-demographic Data Form: The form was developed by the researchers to evaluate socio-demographic and clinical features of the patients. The form consists of questions about the age, education level, marital status, history of illness in the family, number of hospitalizations and treatment history. The form also contained a section where the serum lipid values of the patient/control measured every season were recorded.

Statistical Method: During the research, data collected with the socio-demographic data form was

Table 1: Comparison of average serum lipid levels

	Summer			Autumn			Winter			Spring		
	Avg.	**p**	**F**	**Avg.**	**p**	**F**	**Avg.**	**p**	**F**	**Avg.**	**p**	**F**
Cholesterol		0,23	1,4		0,58	0,3		0,28	1,1		0,84	0,03
Patient	174,1			180,9			180,7			181,2		
Control	188,5			192,1			194,5			191,3		
Triglyceride		0,49	0,5		0,20	1,6		0,11	2,4		0,32	0,9
Patient	140,8			140,9			144,7			154,5		
Control	134,9			143,6			151,5			155,2		
HDL		0,04*	4,2		0,004*	8,6		0,051	3,9		0,001*	11,3
Patient	47,2			47,7			47,9			40,6		
Control	52,3			51,0			50,2			45,1		
LDL		0,33	0,9		0,56	0,3		0,04*	4,3		0,95	0,1
Patient	98,7			104,2			99,2			110,3		
Control	109,1			112,4			114,0			115,1		

*p<0.05 statistically significant, compared with ANCOVA test by taking BMI and age as co-variations.

entered into SPSS PC 16.0 Windows version. The Chi-square test was used to compare gender and educational levels in the two groups, while the age variable was compared with the Student's t-test, since it conformed to normal distribution in both groups. Descriptive statistics were applied to qualities such as the drugs used by the patient group during the first visit, duration of the disease, and age of onset. The average serum lipid values of the patient and control groups in the four seasons were compared using the ANCOVA test, taking into account the potential effect of Body Mass Index (BMI) and age variables. The changes in serum lipid levels of the patient and control groups across the seasons were measured at four different times and compared using repeated measures ANOVA.

RESULTS

Socio-demographic Features

79 patients evaluated during the first visit, five (6.4%) could not be evaluated for their serum lipid levels as they did not come to the second visit or experienced an episode. A total of 67 patients (84.8%) were able to be evaluated for their serum lipid levels in the third visit and 63 patients (79.7%) in the last visit. The proportion of patients who came to all visits, were not experiencing an episode, and had their serum lipid levels measured was 70.8 percent (n=56). In the control group, the proportion of those who came to all visits and had their serum lipid levels measured was 72.9 percent (n=27). The gender and education level in the patient and control groups did not differ (p=0.769, p=0.234). In our study, the average age of the patient group was 34.5 (SD=8.7), while the average age of the control group was 39.4 (SD=9.7). When the average ages of bipolar patients and the control group were compared, the difference was statistically significant (p=0.01).

Clinical Features of the Patient Group

All of the patients were being followed and treated for bipolar disorder type I at the time of the study, and the average duration of the disease was 13.4 (SD=7.9) years and average age of onset of disease was 21.2 (SD=5.8). Around one third of patients used only one or two mood stabilizers, while 43 percent of patients used antipsychotics in addition to at least one mood stabilizer.

Comparison of Serum Lipid Levels

There was no difference between the patient and control groups in terms of average height and weight (p=0.40). All comparisons were made taking into account the potential effect of age and BMI, which was measured in every season, on the lipids. The average cholesterol and TG levels of bipolar patients and the

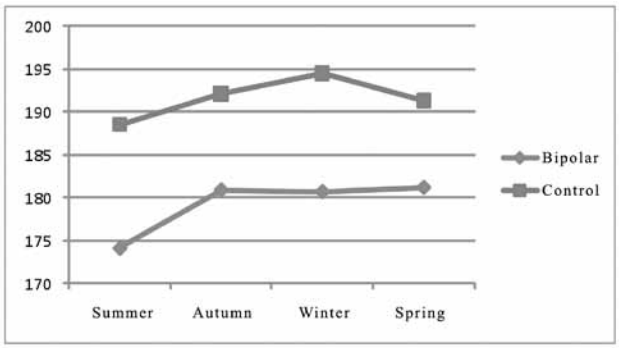

Figure 1: Seasonal change in average serum cholesterol levels

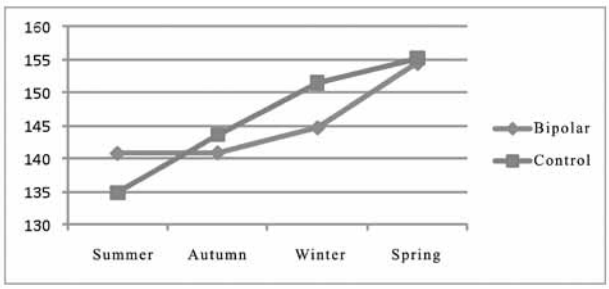

Figure 2: Seasonal change in average serum triglyceride levels

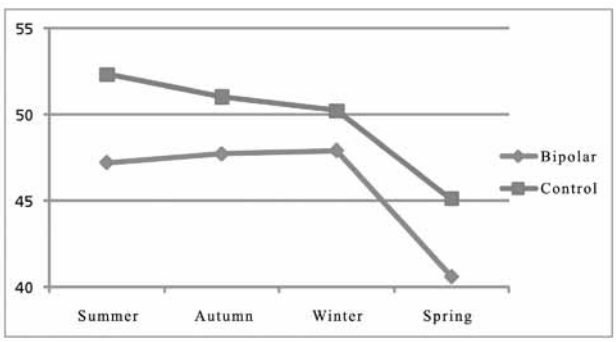

Figure 3: Seasonal change in average serum HDL levels

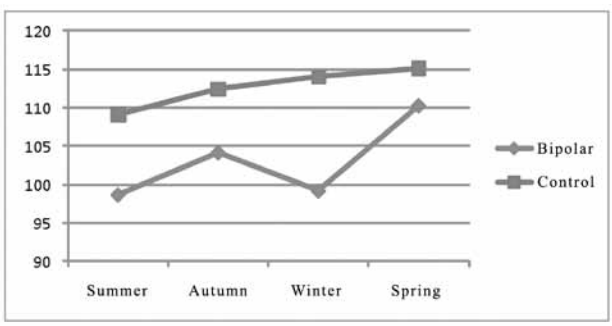

Figure 4: Seasonal change in average serum LDL levels

control group were found to be similar in all seasons (Table 1). In contrast, the HDL levels of patients were significantly lower in all seasons except winter (Table 1). When the average LDL levels of bipolar disorder patients and the control group were compared, the LDL levels of bipolar patients were found to be at a significantly low level only in winter (p=0.04, F=4.3).

Comparison of Seasonality of Serum Lipids

No statistically significant difference was detected for the seasonality of serum cholesterol, LDL and TG levels over the course of the seasons in the control and patient groups. However, for the patient group, HDL levels were significantly lower only in the spring (p=0.003). For the control group, the change in HDL levels was not statistically significant. Low HDL levels in bipolar patients was found to be independent of serum sodium and albumin levels (p=0.82 for sodium and p=0.34 for albumin).

DISCUSSION

When bipolar patients and the control group were compared with regard to their socio-demographic features, gender and education level were found to be similar, while the bipolar patient group was about five years younger than the control group. Although various studies in the literature stated that the risk of developing dyslipidemia increases at advanced ages (17,18), there is insufficient research examining the change in lipid levels with age. The low average serum lipid levels of the patient group in our study may be related to the low average age. However, the literature considers 60 years and above as the advanced age for dyslipidemia (17-19) and given that the average ages of the bipolar patient and control groups participating in our study were between 30 and 40, the difference in average age seems insufficient to explain the difference in lipid levels. Moreover, given that our research made comparisons by correcting for variables that may affect lipids, such as age and BMI, and that it evaluated the change in serum lipid levels over the course of the seasons, the effect of age on average serum lipid levels

loses its significance.

When we compared the average cholesterol levels of bipolar patients with those of the control group by making corrections for the potential effect of age and BMI, we did not find a difference in all seasons ($p>0.05$); this is in contrast to the literature where cholesterol levels were observed to be higher in winter and autumn (12-15,20). Since this research was conducted on samples with no psychiatric or other diseases, however, it may be expected to differ from our findings. In the literature, serum cholesterol levels in psychiatric diseases have been studied numerous times in the past and were stated to differ from general population (21-23). Different from the studies questioning the relationship between mood disorders and serum cholesterol levels (5, 24, 25), considering that all the patients in our study are euthymic, our results may reflect the nature of bipolar disorder. As a matter of fact, information obtained from both clinical research and animal studies supports the hypothesis that low cholesterol levels and low serotonin activity are related and this condition increases the risk of emergence of mania and depression (10).

Another opinion claims that the level of cholesterol is a state, rather than a trait specific to the illness. As a matter of fact, Ghaemi et al. (10) stated that cholesterol may be a state-dependent variable affected by acute mood periods, rather than a characteristic feature. Supporting the same opinion, a group of researchers in Spain found that cholesterol and lithium levels are related with the last episode in bipolar patients(11). Furthermore, serum cholesterol levels are considered to affect brain cholesterol levels, and brain cholesterol levels are considered to affect neurological functions. The cholesterol concentration in nerve cells may be affected substantially by the cholesterol content in the cell environment. The increases and decreases in nerve cell membrane cholesterol disrupt many functions of cell membranes, including connection of neurotransmitter receptors. In animals, the decrease in synaptosomal membrane cholesterol was found to be related to decline in serotonin receptors. And as it is well known, serotoninergic dysfunction is related to depression (26). On the other hand, decrease in serum cholesterol levels causes decrease in brain cell membrane cholesterol, which plays an important role in the fluidity and microviscosity of the cell membrane. As the lipid microviscosity of brain cell membranes is reduced, the reception of serotonin from membrane surfaces to brain cells with receptors decreases and causes the emergence of clinical disorders related to lack of serotonin (26). Although all of these hypotheses help us understand the relationship between mood disorder and lipid, they need to be investigated in greater depth.

Perhaps the most significant finding in our research is the detection of the change in mean HDL levels of bipolar disorder patients, which was significantly low ($p<0.05$) in all seasons except winter ($p=0.051$). In the literature, some research papers indicate that serum HDL cholesterol is lower in patients with major depression compared to the control group regardless of seasonal effects (27). The mechanism behind the fall in serum HDL levels is potentially related to hypercortisolemia, itself linked to dysfunction of the hypothalomo-hypophyseal axis (HPA). As it is known, HPA dysfunction intensifies the oscillation of glucocorticoids and therefore boosts insulin resistance, which brings about an increase in lipolysis through lipoprotein lipase inhibition. This increase in lipolysis in turn causes a rise in LDL, total cholesterol and TG levels, and decrease in HDL levels (28). Moreover, the variability in low circadian cortisol levels in healthy volunteers may result in higher TG and LDL levels and in lower HDL levels (29-31). Furthermore, given the relationship between HPA dysfunction and mood disorders (32), the low serum HDL we detected in bipolar patients may be related to the etiopathogenesis of the disease. As a matter of fact, Sagud et al. (33) observed in their study that HDL levels in bipolar patients not taking drugs during both manic and depressive periods were significantly lower than those of the control group, and inferred that this condition may be related to the bipolar disorder etiology. These results are limited, however, to explain the low HDL levels we detected in our research. Beside tihs, the fact that there is no research in the literature evaluating seasonal serum lipid variation in individuals with

psychiatric disorder makes it more difficult to interpret our results. However, the SEASON (Seasonal Variation of Blood Cholesterol Levels) study (20) evaluating seasonal cholesterol variation in general population found that serum cholesterol levels are distinctly high in winter months. According to this study, this variation may be related to the decline in blood lipid levels due to hemodilution associated with the effect of ambient temperature or the increase in physical activity, or possibly the joint effect of both. The rise in temperature causes depletion in the volume of intravascular fluid and the resulting passage of fluid from interstitial distance into intravascular area may cause hemodilution and decrease in serum lipid levels (34, 35). Additionally, the study reports that the increase in physical activity in summer and spring may be another factor. The expansion in plasma volume during physical activity causes hemodilution. The hypervolemia during physical activity may be related to two basic factors: the first is that the increase in renin activity and vasopressin levels associated with exercise boost the reuptake of sodium and water, and the second is that the increase in plasma albumin level causes hypervolemia and therefore hemodilution with the rising water bonding capacity of plasma (36, 37). In our study we also evaluated albumin and sodium levels, which may affect serum osmolality, but observed that they were not associated with a change in serum lipids. Since the diet and exercise habits of the patient and control groups were not evaluated, however, it is difficult to make any more deductions about intravascular volume and osmolality.

From the clinician's perspective, more important than the hypothesis that the hemodilution in summer months and hemoconcentration in winter months determines the difference in blood lipid levels is the relation of this difference with seasonal course of the bipolar disorder. The fact that some bipolar patients are distinctly affected by changes in season (38-41) suggests that the seasonal difference in serum lipids detected in our study may be related to the etiopathogenesis of the bipolar disorder in at least a group of patients. One of the limitations of our research, however, is that the patient group is being followed for a diagnosis of bipolar disorder type I and that the seasonal course of the disease cannot be evaluated. For this reason, the findings obtained do not reflect all of the bipolar patients. Another limitations of our research is that a rating scale is not used to determine that patients are in remission but rather only their being in good condition in clinical terms. That factors like diet and exercise, which may directly affect blood lipid levels, were not evaluated in either the patient or control groups, and that the control group was not evaluated in terms of psychiatric disorder in a structured interview even though they were chosen from among people with no history of psychiatric disease and who were not using any psychotropic drug at the time of the study enrollment are further limitations of the study. Since there is no research evaluating the seasonal variation of serum lipids in psychiatric patient group in the literature, this study is the first research to evaluate the effect of seasons on serum lipids in bipolar patients.

CONCLUSION

The relation between serum lipids and mood disorders has been researched for many years and attempts have been made to understand the emergence mechanism of the disease. However, there has not yet been sufficient, consistent, and clear proof of the relationship between mood disorders and serum lipids (7). Many research papers evaluated the serum lipids cross-sectionally and their relationship to the course of the disease was not questioned. The strongest evidences indicate that change in serum lipids can be a state-dependent factor affected by the course of the illness, rather than trait marker of the disease (10,11). We believe, however, that the significant decrease in HDL levels observed in the bipolar patient group in this study in all seasons except winter, as compared to the control group, may be related to nature of the disease. Despite the limitations in our study that factors that may affect serum lipids – other than such as weight, albumin and sodium (35) – were not evaluated in our research, and that all patients were being followed with the diagnosis of bipolar disorder type 1, we believe

that this study will contribute to the literature, since it is the first study in the literature, as far as we know, to question the relationship between the cyclical nature of serum lipids and bipolar disorder, and the findings provide hints as to the course and etiology of the disease.

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