

Determination of Insulin Resistance and Dyslipidemia after treatment with selective Anti-Depressants in case of Major Depression

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How to cite this article: Somsubhra Chattopadhyay, Sharmistha Debnath, Sudeshna Ray et al. Determination of Insulin Resistance and Dyslipidemia after treatment with selective Anti-Depressants in case of Major Depression. Indian Journal of Public Health Research and Development 2023;14(3).

Abstract

Introduction: Depression can present a plethora of symptoms, such as loss of pleasure, feelings of guilt, low self esteem, and disturbed sleep or appetite. Selective Serotonin Re-uptake Inhibitors (SSRIs) are considered as the mainstay of treatment for depression. Several studies suggest that antidepressants increase the risk of developing metabolic complications including Insulin Resistance (IR) and dyslipidemia, thus leading to poor health outcomes. This study would provide a review of depression and IR and examine side effects of anti-depressants that are often used to treat depression.

Material & Methods: It was a cross-sectional analytical study conducted at the Department of Biochemistry, College of Medicine and Sagore Dutta Hospital, in collaboration with Department of Psychiatry. Patients attending the psychiatric OPD, who are newly diagnosed as Major Depressive Disorder (MDD) or recurrent depressive disorder were selected. Age and gender matched healthy family members of the patients were chosen as controls.

Results: Significant alteration of Body Mass Index (BMI), Hamilton Depression Scaling (HAM-D), High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL) with non-significant variation of HOMA-IR, Total Cholesterol and Triglyceride levels were found.

Keywords: Major Depressive disorder, glycemic index, HOMA-IR, Dyslipidemia, SSRI

Introduction

Depression is a very serious psychiatric disorder that can lead to profound emotional and physical ailments, including loss of interest or enthusiasm, lack of feelings of pleasure, feelings of guilt or low self-worth, and disturbed sleep or appetite¹. Recently it has

emerged as a major public health problem affecting large number to human populations worldwide irrespective of age. Women have been found to be more susceptible to develop depression than males and often have a more chronic course². Furthermore, the lifetime risk of developing depression increases

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to as high as 40% when co-morbid chronic medical illnesses such as diabetes and cardiovascular disease (CVD) are present³. CVD is the leading cause of morbidity and mortality worldwide, which is further influenced by the abundance of modifiable risk factors. The metabolic syndrome (MS), which is a cluster of cardiovascular risk factors like obesity, hypertension, hyperglycemia & dyslipidemia all of which further significantly increase the risk of CVD and type 2 Diabetes mellitus. These factors also appear to be involved in the pathophysiology of depression, and may account for the higher cardiovascular risk observed in this disorder⁴.

A combination of psychological and pharmacological therapies is the predominant treatment modalities for depression. Antidepressants are the mainstay of pharmacological intervention for moderate to severe depression which is used to alleviate mood and behavioral symptoms. Most of the widely prescribed classes of antidepressants are selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, escitalopram and sertraline. Other drugs like serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, desvenlafaxine, and duloxetine⁵⁻⁷, and tricyclic antidepressants (TCAs) such as imipramine, clomipramine, and desipramine⁸⁻¹¹ are also used.

SSRIs affect the lipid and carbohydrate metabolisms to a major extent. Symptoms including weight gain and dyslipidemia have been reported to be one of the most relevant reasons for the early discontinuation of anti depressant drugs¹².

Very little is known about the development of insulin resistance (IR) and dyslipidemia in major depression patients after treatment with antidepressant drugs. In some cases, depression is associated with physical inactivity and irregular dietary habits, which may further increase the risk of developing IR & diabetes. Studies suggest that many antidepressants increase the risk of developing metabolic complications including IR, thus leading to poor health outcomes. This study would provide a review of depression and IR and examine side effects of antidepressants that are often used to treat depression. Here we've tried to assess & compare the effect of several SSRI on the lipid and carbohydrate metabolism.

Aims & Objectives: To determine the occurrence of insulin resistance and dyslipidemia in patients with major depression treated with SSRIs.

Materials and Methods

Study type and design: A cross-sectional analytical study.

Study setting: It was conducted at College of Medicine and Sagore Dutta Hospital by Department of Biochemistry in collaboration with Department of Psychiatry.

Study population: Patients attending psychiatric OPD who are newly diagnosed as Major depressive disorder (MDD) or recurrent depressive disorder.

Inclusion criteria of cases: Patients 18-55 years newly diagnosed to have MDD (fulfilling DSM V criteria) or RDD (unipolar) at least three months of drug free period.

Inclusion criteria for controls: Age and sex matched healthy family members (brothers, sisters) of the patients.

Exclusion criteria:

Patients or controls with no other acute or chronic disorder e.g Diabetes mellitus, Hypertension, Hypothyroid or hyperthyroid, Seasonal Affective Disorder, other psychiatric disorder, dyslipidemia, malabsorption disorders, malignancy, liver cirrhosis or previous treatment with other anticonvulsants, patients having bipolar depression.

Sample size: 70 cases and 70 age and gender matched healthy controls.

Study duration with time scheduling: December 2021 to May 2022

Tools and techniques:

Every individual in both case & control group were asked to give written consent after explaining the whole process in language which is understandable to them. The confidentiality of the statement and reports were maintained with utmost priority.

5ml of blood sample after overnight fasting was collected along with the detailed history and

fulfilling the exclusion criteria. Serum was separated & collected after centrifugation.

Blood samples were analyzed for Fasting plasma glucose, Fasting Insulin level and lipid profile by following manufacturer's instructions with ERBA EM 360/640 Autoanalyzer.

HOMA IR was calculated by the formula - $[\text{Fasting insulin}(\mu\text{IU/ml}) \times \text{fasting blood sugar}(\text{mg/dl})] / 405$

Data was collected and analyzed by using statistical software.

Control and cases were grouped accordingly. Case group was using one of the SSRIs namely fluoxetine, escitalopram and sertraline. At the beginning of starting treatment the biochemical parameters were measured and clinically assessed for psychiatric function using Hamilton Depression Rating Scale (HAM-D) criteria. After 12 weeks the patients were reviewed again and assessed by the same criteria to know the effect. Exposure variable and descriptive analysis were done. Mean, median, standard deviation and distribution of data was assessed. Depending on the distribution of data statistical tools were used to find further significant analysis.

Results

Table 1: Demographic profile of cases & controls

| | Case (N=70) | Control (N=70) | P value |
|--------------------------------------|------------------------|------------------------|---------|
| Age(Years) Mean \pm SD | 35 \pm 4 | 39 \pm 5 | 0.35 |
| Gender | Male- 31 Female- 39 | Male- 35 Female- 35 | - |
| BMI Mean \pm SD | 27.93 \pm 0.66 | 28.11 \pm 0.11 | 0.43 |
| HAMD | 23.12 \pm 3.19 | — | |
| HOMA-IR Mean \pm SD | 1.21 \pm 0.21 | 1.23 \pm 0.24 | 0.78 |
| Cholesterol (mg/dl) Mean \pm SD | 203 \pm 21 | 210 \pm 21.38 | 0.58 |

Continue....

| | Case (N=70) | Control (N=70) | P value |
|----------------------|----------------|----------------|---------|
| TG Mean \pm SD | 180 \pm 21 | 185 \pm 32 | 0.45 |
| LDL Mean \pm SD | 97 \pm 5 | 98 \pm 9 | 0.78 |
| HDL Mean \pm SD | 57.2 \pm 3.1 | 52 \pm 5.1 | 0.56 |

Table 2: 12 weeks after treatment with SSRI case group

| | Before starting treatment | 12 weeks after treatment | P value |
|-------------|---------------------------|--------------------------|---------|
| BMI | 27.93 \pm 0.66 | 30.12 \pm 0.23 | <0.0001 |
| HAM D | 23.12 \pm 3.19 | 5.76 \pm 1.12 | <0.0001 |
| HOMA-IR | 1.21 \pm 0.21 | 1.13 \pm 0.33 | 0.893 |
| Cholesterol | 203 \pm 21 | 212 \pm 45 | 0.1317 |
| TG | 180 \pm 21 | 187 \pm 68 | 0.412 |
| LDL | 97 \pm 5 | 167 \pm 13.12 | <0.0001 |
| HDL | 57.2 \pm 3.1 | 45 \pm 3.12 | <0.0001 |

In our study, we saw that there was no significant statistical variation in TG, TC and HOMA- IR between the pretreatment and post treatment (after 12 weeks of SSRI treatment) findings.

However, there was significant alteration of BMI, HAM-D, LDL and HDL in the post treatment values. LDL was found to be significantly higher (167 \pm 13.12) after the 12 week treatment with SSRIs whereas HDL was significantly lower (45 \pm 3.12) after the treatment. The difference of BMI was also statistically significant. HAM-D scores after treatment was found to be lower (5.76 \pm 1.12) than the pre treatment values, which was statistically significant as well. It means that the patients responded well to the SSRIs.

This implies that the use of SSRIs in our study, attributed to the increase of LDL (bad cholesterol), decrease of HDL (good cholesterol), with decrease in depression symptoms, without affecting TG, TC and HOMA-IR significantly.

Discussion

In this study, we found that SSRIs have a negative impact on the lipid profile (LDL, HDL) and BMI with improvement of depression symptoms.

Depression induces certain pathophysiological pathways arising from the hypothalamic-pituitary-adrenal (HPA) axis. Inflammation can lead to lipid dysregulations like increased LDL, decreased HDL, hypertriglyceridemia, increased lipolysis and release of fatty acids. Deranged lipid profile pose as a risk factor for cardio vascular diseases. Disturbances in the HPA axis can lead to rise in cortisol and catecholamines which in turn increases heart rate and blood pressure.¹³

Pan SJ et al demonstrated the effects and mechanisms of the abnormalities in lipid metabolism caused by Fluoxetine (FLX) in patients and in a mouse model of depression. In the above mentioned study, they found that serum Triglyceride (TG), Total Cholesterol (TC) and Low Density Lipoprotein (LDL) levels were significantly increased in the depression patients after fluoxetine treatment. FLX treatment was found to significantly increase the hepatic TG levels in both control and depressive mice, compared to non-treatment, while the hepatic TC levels were not significantly altered by FLX treatment.¹⁴

Arain AA et al, in a 6 week study, observed that there was a significant reduction in total cholesterol and triglyceride levels following escitalopram treatment.¹⁵

In a partially randomized trial by Gasse C et al, conducted over a period of 3 years, an increase in total and free cholesterol and LDL correlated with improved antidepressant response, after treatment with escitalopram.¹⁶

Kesim M et al found an increase of insulin level but no change in blood glucose in patients treated with Sertraline for major depression. In their study, though insulin level increased but it was still in normal range (non-significant), so blood glucose level didn't change. Unlike our findings, they did not observe any significant changes in the HDL and LDL levels from pre-treatment but TG levels were significantly increased which can be due to increased insulin secretion and its anabolic effects. Sertraline, an SSRI, may increase insulin secretion as it increases insulin secretion in pancreas.¹⁷

Hepatic insulin sensitizing substance (HISS) is released from liver by the action of insulin. In the absence of HISS release, the response to insulin

is decreased and more insulin is secreted from the pancreas.¹⁸ Sertraline might prevent the release of HISS from the liver and may cause an increased insulin secretion to regulate glucose.¹⁷

Isaac R et al in their experimental study found that long term use of SSRIs inhibit insulin secretion and action inducing apoptosis of beta cells of pancreas. Insulin resistance finally leads to diabetes which is a menace of 21st century.¹⁹

Weight gain, one of the frequent side effects of SSRIs, finally leads to obesity which is associated with dyslipidemia, Coronary Artery disease (CAD), insulin resistance and overt diabetes.^{20,21}

Similar to our study, Olgunar Eker et al found that the baseline insulin values and HOMA index values were lower in the patient group than the control group although the difference was not statistically significant.²²

Conclusion

Depression is emerging as one of the leading mental health problems affecting all age groups and genders, worldwide. SSRI being the main stay of treatment but its having some negative effect on lipid profile. So before choosing the drug, need to be more cautious about the patients overall health profile for a better outcome overall

Limitations:

A larger study group and longer study period could have reassured more concrete results.

Conflict of interest: There was no conflict of interest in this study.

Source of funding: This study was self-funded.

Ethical Clearance: Approved by the institutional ethical committee of 'College Of Medicine & Sagore Dutta Hospital'.

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