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CO- RELATION BETWEEN DIABETES AND DEPRESSION: A NEED FOR FURTHER GENETIC ANALYSIS

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ABSTRACT

Out of all the major disease burdens diabetes and depression are the most common amongst metabolic disease and mental disorders, respectively. Both the diseases have more mortality rate than any other metabolic or mental disorders. Even though both do not share any common symptoms at first depression and diabetes share a common link as observed by many literature reviews. Patients with any of the two diseases are at more risk to develop the other disease than normal people. The literature review based study provides the base for finding whether or not in depressed patients, the genes associated with diabetes are getting differentially expressed or not. This can be easily done by sequencing for diabetes specific genes in clinically depressed patients. Which can provide more insights into the control of gene expression, and whether or not can it be reversed by treating either of the condition.

KEYWORDS: Depression, Diabetes, Co-morbidity, DNA Sequencing

In low and middle income countries, depression is a major disease burden which can be characterized by loss of interest in daily activity, sadness, anxiety, feeling of guilt, even, suicide attempts and self harm is often seen. Episodic depression can be put in mild, moderate and severe categories. According to WHO, a survey conducted in 2015 estimates the number of people suffering from depression is more than 300 million. Around every 1 person out of 4 people suffers from mental disorder at some time in their lives. Around 7.5% of world population contributed to global disability in 2015, because of depression. And behind more than 8, 00,000 suicide cases, depression was the sole reason. Not only physiological factors but cultural, social, economic and even biological factors contribute to the development of depression. (Chien *et al.*, 2013) (Shadrina *et al.*, 2018)

According to IDF.org prevalence of diabetes in India is around 8.8%, there was estimated 72, 946, 400 cases in year 2017, which includes both type 1 diabetes and type 2 diabetes, previously denoted as insulin dependent diabetes and insulin independent diabetes, respectively. Even though both types decreases glucose uptake and induces hyperglycemia in patients, they share different mechanism of pathogenesis. In type 1 diabetes there is selective destruction of beta islet of liver cells which produces the insulin and in type 2 there is development of insulin resistance which prevents insulin uptake and eventual glucose uptake from the blood. Genetics have a lot to contribute in the development of both types of diabetes. According to Dorman and Bunker, 2000 first degree relatives have around 6% increased chance of developing type 1 diabetes with compared to normal population and the first degree relatives are at 3 times more risk at developing type 2 diabetes (Florez *et al.*, 2003) (Gloyn, 2003) (Hansen, 2003).

There is high co-morbidity of metabolic disease and mental disorders. For example, a meta analysis of literature review study conducted by Liao *et al,* 2011, showed patients with schizophrenia on second generation antipsychotics had more chances of developing metabolic disorders like diabetes, hypertension and hyperlipidemia. Chien *et al,* 2013 conducted a population based study to examine the prevalence and incidence of hyperlipidemia with major depressive disorder. They found that patients with major depressive disorder had 14.4% increased chance of developing hyperlipidemia. Dortland *et al,* 2013 also found out that C reactive protein amount was higher in dyslipedemia and obesity.

There are many articles available showing the relation between depression and increased chance of developing diabetes and vice versa. Thomas Willis in the 17th century recognized the relation between depression and diabetes. Prevalence of type 1 and type 2 diabetes is as much as twice in patients with depression. As reviewed by Moulton *et al,* 2015 people with type 2 diabetes have 20% increased chance of developing depression while depression is linked with 60% increased chance of developing type 2 diabetes. Both type of diabetes show different association with diabetes. Min Yu *et al,* 2015 showed through a meta-analysis of numbers of articles showed there is 41% increased chance to develop type 1 diabetes and 32% increased chance of developing type 2 diabetes in depressed people. Hasan *et al,* 2014 observed incidence of diabetes in depressed groups was higher than non depressed groups and also suggested to include depression as regular screening regime for diabetes. A metanalysis conducted from 39 studies having 20, 218 subjects by Anderson *et al,* 2001 suggests the presence of diabetes doubles the chances of developing depression. A baseline assessment of 627 patients done by Bastelaar

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et al, 2010 showed that depressed patients have decreased glycaemic control than compared with patients with no depressed patients. A study conducted on 703 people Hein *et al,* 2017, showed the prevalence of type 2 diabetes with major depression was 21.19%. The demonstrated that the prevalence was higher than the study the study conducted by Vancampfort *et al*, the reason given by the author was the type 2 diabetes assessment was not made according to the criteria of the American Diabetes Association. A study conducted to find the relation between C-reactive protein and depressive symptoms with incidence of diabetes was done by Au *et al,* 2014, they showed after 63.2 months of follow up they observed the high CRP levels and depressive symptoms increased the chance of diabetes development. Bai *et al,* 2013 found that patients with bipolar disorder and patients with schizophrenia had increased chance of initiation of anti diabetic medication; however they did not find any risk in patients with major depressive disorder.

As reviewed by Moulton *et al,* 2015 different factors are involved in co morbidity of depression and diabetes. For example increased pro inflammatory cytokine destroys beta cells by apoptosis and causes insulin resistance (Pickup and Crook, 1998). And cytokine mediated inflammation reaction activates Hypothalamus-Pituitary Axis, increase in oxidative stress and can cause reduction in serotonin production.

A study done by Kemp *et al,* 2014 showed treating depressive symptoms in diabetic patients by giving them Pioglitazone which stimulates PPARɤ, a gene involved in development of diabetes.

Genome Wide Association Study which aims to identify disease associated single nucleotide polymorphisms has found the following candidates involved in prevalence of diabetes. (Table 1).

Table 1: Genes associated with diabetes

GENE	LOCUS
TCF7L2	10q25.2-q25.3
Adiponectin	3q27.3
FTO	16q12.2
PC 1	5q15
CDKAL1	6p22.3
CDKN2A/B	9p21.3
HHEX	10q2.33
BAZ1B	7q11.23
CRP	1q23.2
CAPN10	2q37.3
HLA-DQB1	6p21.3
INS	11p15.5
CTLA4	2q31-35
PPARɤ	3p25
ABCC8	11p15.1
KCNJ11	11p15.1
GLUT 2	3q26.2
GLUT 4	17p13.1
CRP	1q23.2
PCG-1α	4p15.2

IMPLICATION FOR FUTURE RESEARCH

Based on the literature review, the gene sequence variation related to diabetes from depressed patients should show more and frequent variations when compared to normal, healthy individuals. If the results obtained will be same as the hypothesis, the diagnosis of depression and diabetes may have a new lead. Depressed patients can be easily assessed to find at what extent their off-spring will have risk of developing the diabetes and if the depressive symptoms are controlled earlier it may have a positive effect on the patient and on their next generation too. And the finding may also give new insights into how lack of neurotransmitter can affect the gene expression.

All the studies conducted to show the relation between depression and diabetes was dependent upon literature reviews. Our study can be the first of its kind to go into genetic variations in depressed patients. Second thing is all the reviews are mostly from foreign countries. This initiative might be the first sequencing study in depressed patients in India which could give more promising and specific outcomes. As mentioned by Moulton *et al,* 2015 inflammation may act a factor for co -morbidity of depression and diabetes and no studies have been done to modify inflammatory treatment of depression in people with diabetes, our study can be moved forward based on this. Further , Circadian rhythms is also a factor in co-morbidity of depression and diabetes and increased sleep duration is observed in patients with depression (Prather *et al.*, 2015) and metabolic disease (Hall *et al.*, 2008), it can also be found that whether or not controlling sleep pattern have effect on the probable depression and diabetes related genes. Animal studies can clearly show the effects of biological process.

CONCLUSION

People with depression or diabetes are at greater risk of developing of the disease in coming time. As different factors are related with both of the disease progression, this unique co relational study would help to understand both the diseases more elaborately. The disease progression of diabetes could be halted if the diagnosis criteria can include depression as a symptom, which can be proven with the help of this study.

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