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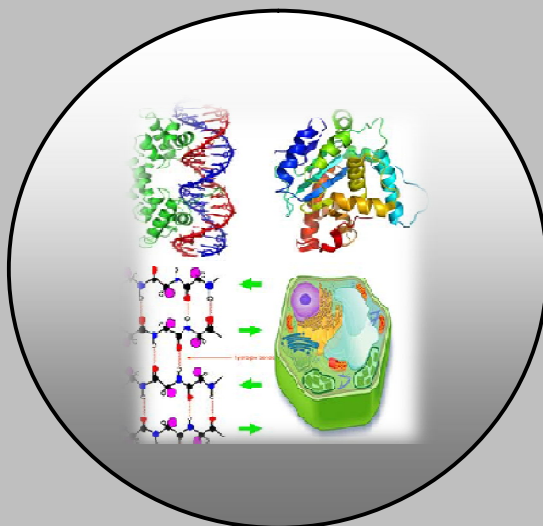
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A Study to Establish Co-Relation between Lithium Levels in Blood and Type 2 Diabetes Mellitus in Northern India

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ABSTRACT

To assess the correlation between serum lithium levels and Type 2 Diabetes Mellitus in Northern India, a case control study was undertaken among 50 patients with 25 having Type 2 Diabetes Mellitus and 25 age and sex matched controls at M.V. Hospital and Research Centre, Lucknow. Among 25 diabetic patients, 72% (n=18) had low serum lithium levels, whereas in control population 10% had low serum lithium levels ($p<0.01$). Mean waist circumference was higher in Diabetics compared to the controls. No statistical significant difference of body mass index between cases and controls found.

Keywords: Serum Lithium Levels, Type 2 Diabetes Mellitus and Body Mass Index.

INTRODUCTION

Lithium is found in variable amounts in foods. Primary food sources are grains and vegetables. In some areas, the drinking water also provides significant amounts of the element. Human dietary lithium intake depends on location and the type of foods consumed and varies over a wide range.

Traces of lithium were already detected in human organs and fetal tissues in the late 19th century, leading to early suggestions as to possible specific functions in the organism. However, it took another century until evidence for the essentiality of lithium became available. In studies conducted from the 1970s to the 1990s, rats and goats maintained on low-lithium ratios were shown to exhibit higher mortalities as well as reproductive and behavioral abnormalities. In human's defined lithium deficiency diseases have not been characterized, but low lithium intake from water supplies was associated with increased rates of suicides, homicides and the arrest rates for drug use and other crimes. Lithium appears to play an especially important role during the early fetal development as evidenced by the high lithium contents of the embryo during the early gestational period. The biochemical mechanisms of action of lithium appear to be multi factorial and are inter correlated with the functions of several enzymes, hormones and vitamins, as well as with growth and transforming factors. The available experimental evidence now appears to be sufficient to accept lithium as essential and a provisional RDA for a 70 kg adult of 1000 µg/day is suggested (Verlag Chemie, 1960, Scha"fer, 2000, Schulz, 1903 and Cade, 1949).

Lithium is normally present in all organs and tissues. Lithium is absorbed from the intestinal tract and is excreted primarily by the kidneys. Absorbed lithium is uniformly distributed in body water, with only a small difference between the extracellular and intracellular levels.

During embryonic development, organ lithium levels reach maximal values in the first trimester of gestation and subsequently decline. Animal studies have demonstrated that Lithium plays a role in the expansion of the pluri potential stem cell pool to more mature progenitor cells and blood elements. Primary dietary sources of lithium are grains and vegetables, which may contribute from 66% to more than 90% of the total lithium intake; the remainder is from animal derived foods. In general, diets rich in grains and vegetables may be expected to provide more lithium than diets rich in animal proteins (Kehrberg et al. 1991).

Diabetes Mellitus (DM) is a major global health problem that affects over 200 million individual's worldwide (Verlag Chemie, 1960 and Scha"fer, 2000). Type-2 diabetes is a chronic disease characterized by a disorder of the glucose metabolism associated with a reduced ability of tissues to respond to insulin. The main feature of type-2 diabetes is chronic hyperglycemia, which leads to the disturbance of carbohydrate, fat and protein metabolism. Diabetes arises through a combination of many factors—hereditary, inflammatory, dietetic and environmental. Although there are several hypotheses as aging, obesity and oxidative damage, the etiology of diabetes and its complications still is not clear (Schulz H 1903, Cade 1949, Kehrberg et al. 1991). In recent years, there has been increasing interest in exploring the exact role of trace metals in human health and various diseases (Hager et al.2000, Horrobin, 1991, Sapek, 1983, Bowen, 1996, Weiner, 1991, Zaldivar, 1989, Nevoral, 1988, Schweigart, 1962, Anke, et al.1983, Morris 1958, Lambert, 1983, Saunders, 1985 and Dawson, 1991). There is accumulating evidence that the metabolism of several trace elements is altered in diabetes mellitus and that these nutrients might have specific roles in the pathogenesis and progress of this disease (Schrauzer et al.1992).

On one hand, the homeostasis of trace elements can be disrupted by Diabetes Mellitus. Conversely, early imbalances of specific elements may play an important role in upsetting normal glucose and insulin metabolism.

The present study was designed to evaluate the levels of lithium in whole blood of Type-2 Diabetes Mellitus patients, to compare them with age matched healthy controls and to investigate the feasibility of combining them with an ensemble model for diagnosing purpose.

In a placebo-controlled study with former drug users (mostly heroin and methamphetamines) (De. Roos et al. 2001) 24 subjects (16 males and 8 females, average age 29.4 ± 6.5 years) were randomly divided into two groups, one receiving 400 μg of lithium per day in yeast, the other placebo, for four weeks. All subjects completed weekly self-administered mood test questionnaires.

In the Lithium group, the total (positive) mood test scores increased steadily during the four weeks of supplementation and specifically in the subcategories reflecting happiness, friendliness and energy. In the placebo group, the combined mood scores showed no consistent changes; the happiness scores actually declined.

The evaluation of trace element status in diabetic patients has been undertaken in several recent researches (Kronemann et al. 1983 and Creason, et al.1975). Some studies have focused on a single element in order to understand its specific biological role (Patt, et al. 1983). However, due to complex interactions among various elements, more researches have carried out multi elemental determinations (Pickett 1983). It is therefore necessary to use multivariate analysis to model the relationship between elements and a certain disease. In conventional practice, most of the modeling methods are based on building a single model with limited performance. Nowadays, the so-called 'ensemble' learning has gained increasing attention in various fields and has made a fundamental shift in the mindset of a predictive model designer, i.e., instead of trying to build a single model, one can instead resort to combine a set of simple models for a given task (Schrauzer et al. 1992 Anke et al. 1991, Baumann et al. 1983). Its main advantage is its ability to increase the sensitivity, specificity and accuracy of a classification/diagnosing model.

Aims and Objective

- To evaluate the levels of lithium in blood of Type 2 Diabetes Mellitus patients and to compare them with the age matched healthy control.
- To investigate the feasibility of using it for diagnosing purpose.
- To suggest measures for maintaining blood levels of lithium within normal range and to prevent Type 2 Diabetes Mellitus.

MATERIALS AND METHODS

It was a hospital based case control study in which 50 patients visiting the OPD of M.V. Hospital and Research Centre, Lucknow were randomly selected and divided in two groups:

25 were healthy adults with/without history of Diabetes Mellitus and the remaining 25 were patients with diagnosed Type 2 Diabetes Mellitus.

After taking a written consent, both these groups were subjected to estimation of blood levels of Lithium, Hba1c levels, Fasting Plasma Glucose (FPG), and anthropometric assessment.

Statistical analysis was done by SPSS software version 11.2. The values were expressed as Mean \pm SD. For related sample or independent sample analysis, paired and unpaired student's 't' test respectively was used for all parametric data. A p-value of <0.05 was considered significant.

Inclusion criteria

For cases:

- Patients with diagnosed Type 2 Diabetes Mellitus, irrespective of family history.
- Patients who were willing and cooperative to participate in the study.

For controls:

- Normal patients with or without family history of Diabetes Mellitus but not diagnosed as Type 2 Diabetes Mellitus.
- Controls those were willing and cooperative.

Exclusion criteria

- Patient with diagnosed Maniac Depressive Psychosis (MDP) / Bipolar disorder/ Huntington chorea.
- Patient with history of intake of lithium carbonate for the treatment of above mentioned disorders.
- Patients with any form of lithium supplementation in the diet.
- Patients with any kind of malignancy and are on any chelating agent.
- Patients with HbA1c levels ≤ 6.5 or ≥ 11.5 .
- Patients with evidence of any end target organ damage.
- Un co-operative and unwilling patients.

Investigations that were done

- Serum lithium levels
- HbA1c levels.
- Fasting plasma glucose (FPG) estimation.

RESULTS AND OBSERVATIONS

Twenty five patients with Type 2 Diabetes Mellitus fulfilling the inclusion and exclusion criteria were finally included as cases and 25 age and sex matched healthy persons without Diabetes were taken as control. Selection was done randomly.

The demographic data of cases and controls are represented in table 1 and shows that cases and controls have been matched for age, weight and height.

The serum lithium level in Diabetics was 0.3 ± 0.11 mmol/l and in control group was 0.5 ± 0.09 mmol/l. The difference was found to be statistically significant ($p < 0.01$)

Mean waist circumference in Diabetic patients was 94.08 ± 12.94 cm, same in control group was 88.53 ± 9.71 cm, and the difference was statistically significant ($p < 0.05$). Mean BMI among the cases was 24.41 ± 3.73 Kg/m² and among the control were 23.91 ± 3.01 Kg/m² which was not statistically significant ($p = 0.36$).

Table 2 shows the range of Hba1c levels and its corresponding serum Lithium levels amongst male and female patients.

Table 1.

Demographic , Anthropometric and Metabolic profile of cases and controls.		
Parameters	Diabetics(n=25)	Control(n=25)
Age (in years)	45 ± 10.45	46 ± 9.65
Weight (in Kg)	60.18 ± 8.54	62.84 ± 7.72
Height (in cms)	162 ± 0.53	164 ± 0.48
Waist (in cms)	94.08 ± 12.94	88.53 ± 9.71
BMI(Kg/m ²)	24.41 ± 3.73	23.91 ± 3.01
FBS (in mg/dl)	128.88 ± 13.72	110.87 ± 8.32
Hba1c	9.2 ± 2.01	6.2 ± 2.52
Serum lithium (mmol/l)	0.3 ± 0.11	0.5 ± 0.09

p-value (< 0.01)

Table 2.

SEX	Hba1c levels	Serum lithium(mmol/l)
Male	7.2-11.2	0.289-0.41
Female	7.0-11.0	0.31-0.40

DISCUSSION

Diabetes mellitus is a complex disorder affecting the metabolism of carbohydrate, fat and protein.

It is generally agreed that disturbed body distribution of trace elements and lithium are often found in human subjects with Diabetes Mellitus. In the present study diabetic subjects were found to have lower mean serum level of Lithium as compared with healthy controls which support the earlier reports (Anke M et al.1983, Morris 1958, Lambert J 1983, Saunders 1985). Lithium depletion has a negative impact on glucose homeostasis and insulin sensitivity in diabetic patients, presenting low Lithium status in Diabetics; therefore, Lithium supplementation may be beneficial in the management of the disease (Dawson EB 1991). **In present study among 25 diabetic patients, 72% (n=18) had low serum lithium levels, whereas in control population 10% had low serum lithium levels ($p < 0.01$).**

Type of therapy significantly affected the serum level of Magnesium, Vanadium, Lithium and Selenium, Their levels were significantly lower in patients using insulin as a treatment compared to those using oral hypoglycemic drugs. In an earlier study, type of therapy did not significantly affect plasma lithium level (Anke M. et. al.1983) which is against our finding. This decrease may be due to prolonged duration of the disease as those patients using insulin treatment in Type 2 Diabetes. They might have also received oral anti-diabetics for several years before starting the insulin, as the mean years of the duration of illness in the present study was higher in those on insulin therapy than those on oral anti-diabetics drugs, and in the present study it has been shown that the duration of the disease inversely affected serum levels of these elements.

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