IMMUNOMODULATING EFFECTS OF RASAYANA DRUGS IN DIABETICS – A CLINICAL STUDY
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SUMMARY: Immune system plays an important role in pathogenesis of diabetes (DM). Besides hypoglycaemics, rasayanas are indicated in the management of DM. In several studies the immunomodulatory potentials of rasayanas have been proved. A clinical trial of three rasayana drugs, Asparagus recemosus (AR), Bacopa monnieri (BM) and Centella asiatica (CA) was carried out in diabetics. In this study, diabetics were found to have significantly lower levels of serum IgG, increased serum IgA and comparable levels of IgM. All drugs reverted levels of serum IgG levels in diabetics, however, statistical significance was attained only with AR. Further the increased IgA levels were brought back towards normal. These drugs also increased serum protein levels.

Key words: Diabetes, immunomodulation, rasayana, Asparagus recemosus, Bacopa monnieri, Centella asiatica, immunoglobulins

INTRODUCTION:

The incidence of Diabetes mellitus (DM) is rapidly increasing in urban population because of increased environmental risk factors like low physical activity, high calorie-intake, obesity and stress. At the same time, the rural and slum population continues to be affected with malnutrition related diabetes mellitus (MRDM). Immune system plays central role in the pathogenesis of DM and its complications. Patients of diabetes have a high incidence of organ specific auto antibodies and DM is associated clinically with several other autoimmune disorders. There is an increased incidence of infections which are more severe and more protracted in diabetics. Alterations in humoral l- and cell-mediated immunity and granulocyte functions leading to compromised host defence against a variety of infectious agents have been described in patients and experimental models of diabetes. Triola et al reported lower levels of IgG, higher levels of IgA and similar levels of IgM in diabetics compared to healthy controls.

The Ayurvedic concept of madhumeha is similar to D.M. The Understanding of madhumeha in Ayurveda dates back to 1000 B.C wherein, the role of diet, physical activity, obesity and genetics in the aetiopathogenesis and management of DM has been described. Along with hypoglycaemics diabetics were also prescribed rasayana herbs to prevent the complications. Rasayana therapy is used for promotion of health and to improve longevity along with physical and mental
strength (4,5) All these benefits are probably obtained by the promotion of ojas, a concept similar to the modern concept of immunity (6). Madhumeha is characterized by loss of ojas, thus, along with hypoglycaemics, rasayanas are prescribed in madhumeha to improve the ojas and prevent the complication, Satavari and brahmi are two very important rasayanas mentioned in Ayurveda. These drugs have been put to extensive experimental and clinical trials on modern parameters to prove their immunotherapeutic potentials, satavari is Asparagus racemosus (AR) of Liliaceae family, experimentally it has been found to protect animals against infections in normal and immunosuppressed status induced by hemisplenectomy or surgery (7) AR has been proved to be safe in both acute and subacute toxicity studies (8). There are two drugs known as Brahmi, one is Bacopa monnieri (Fam. Scrophulariacease, BM) and the other is Centella asiatica (Fam. Umbellifereae, CA). In an experimental study, the aqueous suspension of CA was found to possess immunostimulant activity 60% of that of recombinant α – 2b interferon, (9) Extensive experimental studies have been conducted to evaluate the psychopharmacological effect of BM. (10) Considering the role played by immune system in pathophysiology of Ayurvedic rasayanas, this collaborative clinical study was conducted at Institute of Medical Sciences, Banaras Hindu University, Varanasi by the departments of Dravyaguna (Faculty of Ayurveda), Pharmacology and Immunopathology, to evaluate the immunomodulatory effects of rasayana drugs in diabetics.

SUBJECTS

Subjects of the study were chosen form Diabetes- clinic of Department of Dravyaguna, Institute of Medical Sciences, Banaras Hindu University, Varanasi. The diabetics with more than thirty years of age, of either sex with diagnosed NIDDM on more then 3 years duration and not having any complications of diabetes were eligible to enter the study, Exclusion criteria are listed in the box. Patients developing complications of diabetes or infections during the study period were not included in final analysis. Inpatients with uncontrolled blood sugar, the level of blood sugar was controlled and the doses

| Exclusion criteria |
|--------------------|
| 1. Pregnancy        |
| 2. Patients with immune disorders |
| 3. Other chronic diseases |
| 4. Major surgery during last 6 months |
| 5. Patients on drugs affecting immune system |
| 6. Malnourished patients (BMI less than normal) |

do not include AR or BM or CA or simply placebo.

DRUGS

On the basis of Ayurvedic literature and experimental and clinical studies on modern scientific parameters, we chose shatavari (Asparagus racemosus, fam. Liliaceae) and two brahmis, viz. Bacopa monnieri, of scrophulariaceae family and centella asiatica of Umbellifereae. The plants were collected from the Ayurvedic garden of the Institute keeping in mind season soil and dried in shade as prescribed in Ayurveda. The ghanasattva (solid water extract) was
prepared from the whole plant. The extract was encapsulated to ensure blinding, uniformity of administration and for convenience of patients. One capsule contained 500 mg of the extract. Each drug was administered in the dose of 500 mg orally once a day (fixed dose) for a period of about a weeks, 2 hours after food or 1 hour before food to prevent any interference with its absorption.

RESULTS

The distribution of the patients in the study with respect to their age and duration of diabetes is shown in table 1. All the four groups were comparable with respect to the age and duration of diabetes.

This study shows what NIDDM Patients have statistically significant decreased serum IgG and increased serum IgA levels when compared to health controls. However, no significant difference was found in serum IgM levels (Table 2) After 4 weeks of treatment with the rasayana drugs, the IgG levels increased in all the treatment groups. However, this rise was significant only in patients treated with AR. In the placebo group, there was a non-significant decrease in serum IgG levels. Serum IgA levels were significantly decreases in AR treated group. In BM and CA groups. There was a decrease in IGA levels. Which was statically non-significant. On the other had. IgA levels were found to be slightly raised in placebo group after 4 weeks.

No appreciable change was seen in serum IgM levels in either group. S.protein as raised in all the 4 groups. Maximal rise was seen in AR treated group. But in none of the groups. It reached the significance leavel (Table3).

DISCUSSION

Diabetes mellitus is also associated with disturbances in the immune system as levels of immunoglobulins are reported to be altered. This shows that even patients with noncomplicated diabetes have raided levels of IgA. deceased levels of IgG and normal IgM in serum. This is inconformity with earlier studies and these play an important role in the progression of disease and development of complications. (3&12)

Immune mediated beta cell destruction is one of the important factors in the development of DM. The usefulness of immunomodulators in the treatment of initial phases of DM has been well established. (13) Stress precipitates DM and has a significant role in the progression. Infection prone diabetic patient is caught in the vicious cycle.

The role of immune system in the pathogenesis of madhumeha is also well appreciated in Ayurveda and the disease is known as ojomeha i.e the one characterized b deranged immune system. Rasayanas are particularly important in the ayurvedic management of DM. Rasayanas either directly act on immune system or can act on psycho-neuro –immune (PNI) axis to regulate immnue functions. (14) Experiments have reliably documented the effect of stress on immune function and existence of unsuspected connections between the nervous and immune system. (15) Several rasayana drugs including AR have shown antistress activities in experimental studies. (16) There man subtypes of Rasayanas and therapy can be individualised according to personality traits and requirement, e.g., ojovardhaka (immunomodulators Ramayana will be particularly useful in diseases involving of immune system like diabetes and medhya rasayana can be useful in mitigating the stress associated effects.
This study on rasayanas shows that AR, as mentioned predominantly balya drugs, is more effective in immune regulation. These effects may partly be due to modulation of the PNI axis as a result of antistress activity. Other drugs used, BM and CA, belonging to medhya to medhya rayasana group acting mainly on CNS did produce effect on immune system, however, significance level could not be achieved. Thus, balya rasayana drug, AR, acts mainly on the immune system and this is conformity with the ayurvedic concept of balya drugs.

This study clearly shows of AR on immune system, however, to assess the long term significance of the same and the mechanisms involved therein, further largescale studies of prolonged duration including more parameters are required. Advantages of safety, easy availability and low cost of herbs will always be there.

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Table -1
Distribution of patients in the study with respect to their age and duration of diabetes

| Age (year) | TOTAL No of Patients (N=40) | Placebo (n=12) | AR (n=11) | BM (n=9) | CA (n=8) |
|------------|-----------------------------|----------------|-----------|---------|---------|
| 34-40      | 6(15%)                      | 2(17%)         | 2(18%)    | 2(22%)  | 2(25%)  |
| 41-50      | 24(60%)                     | 7(58%)         | 7(55%)    | 5(56%)  | 5(62%)  |
| 51-60      | 9(23%)                      | 2(17%)         | 3(27%)    | 2(22%)  | 1(13%)  |
| >60        | 1(2%)                       | 1(8%)          |           |         |         |

Duration of Diabetes

| Duration of Diabetes | Placebo (n=12) | AR (n=11) | BM (n=9) | CA (n=8) |
|----------------------|---------------|-----------|---------|---------|
| 3-6 years            | 4(33%)        | 4(36%)    | 3(33%)  | 3(37.5%)|
| 7-10 years           | 5(42%)        | 4(36%)    | 3(33%)  | 3(37.5%)|
| 11-14 years          | 2(17%)        | 2(18%)    | 2(22%)  | 2(25%)  |
| >14 years            | 1(8%)         | 1(9%)     | 1(9%)   |         |
Table -2
Basal levels of Immunoglobulins in Diabetics and Health Adults

|                  | IgG                  | IgA                  | IgM                  |
|------------------|----------------------|----------------------|----------------------|
| Diabetics (n=40) | 993.75* ± 150.29     | 345** ± 34.42        | 143.50 ± 41.23       |
| Health volunteers (n=10) | 1145.50 ± 168.20 | 95.50 ± 40.90        | 148.70 ± 40.90       |

Values are expressed as Mean ± S.D.
*P<0.05
**P<0.01

Table -3
Effects of Rasayana Drugs on Serum Protein (g/dl) and Immunoglobulin (mg/dl) levels in diabetes

|                        | Serum IgG levels | Serum IgA levels | Serum IgM levels | Serum Protein levels |
|------------------------|------------------|------------------|------------------|----------------------|
|                        | Placebo (n=12)   | AR (n=11)        | BM (n=9)         | CA (n=8)             |
| Pretreatment           | 979.17 ± 137.28  | 963.64 ± 132.46  | 1027.8 ± 167.9   | 1018.75 ± 186.9      |
| Post treatment         | 975 ± 140.6      | 1104.5 ± 129.33* | 1061.1 ± 140.93  | 1050 ± 110.19        |
|                        | 345.8 ± 35.8     | 345.45 ± 37.5    | 344.4 ± 33.58    | 343.75 ± 35.8        |
|                        | 345.17 ± 41.67   | 281.8 ± 60.14*   | 328.89 ± 40.76   | 322.5 ± 30.12        |
|                        | 146.67 ± 32.0    | 148.18 ± 48.54   | 138.89 ± 40.76   | 137.5 ± 49.79        |
|                        | 144.17 ± 37.28   | 146.36 ± 39.06   | 142.22 ± 30.73   | 146.25 ± 46.58       |
|                        | 6.25 ± 1.1       | 6.175 ± 0.98     | 6.28 ± 0.96      | 6.21 ± 1.03          |
|                        | 6.34 ± 0.98      | 6.65 ± 0.7       | 6.36 ± 0.86      | 6.38 ± 0.96          |

Values are expressed as Mean ± S.D.
*P<0.05