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A CLINICAL EVALUATION OF DARVYADI GHANA VATI IN THE CASES OF PREDIABETES

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ABSTRACT

***P**rediabetes is the state in which some but not all of the diagnostic criteria for diabetes are met. It is often described as the "Gray area" between normal blood sugar and diabetic sugar levels. Prameha is a syndrome described in the ancient Ayurvedic texts that includes several variety of clinical conditions as described in modern medicine such as obesity, Prediabetes, Diabetes mellitus, and metabolic syndrome. Prameha has been described in detail in Ayurvedic lexicons. Charaka has given exhaustive description of the disease Prameha which ultimately progresses towards Madhumeha or the sweetness of urine in addition to Polyurea..In this emerging scenario the present clinical study was conducted in 60 patients to test the safety & efficacy of Ayurvedic formulation Darvyadi Ghana Vatiin cases of Prediabetes. In this series, a total 27 females and 33 male's cases were enrolled fulfilling the diagnostic criteria of Prediabetes as well as exclusion and inclusion criteria. The patients were randomly allocated into two groups, viz- Group A- on Metformin, Group B on Darvyadi Ghana Vati as per prescribed dosing schedule. The cases were assessed on subjective and objective parameters for three successive follow ups on every one month. At the end of clinical trial patients of Group A showed significant improvement on different parameters in comparison to Group B in case of FBS, PPBS, HbA1C%. There is no side effect found after trial treatment.*

Key words: Prediabetes, Diabetes mellitus, Darvyadi Ghana Vati

INTRODUCTION

Pre-diabetes is the precursor stage before diabetes mellitus in which not all of the symptoms required to diagnose diabetes are present, but blood sugar is abnormally high. This stage is often referred to as the "grey area." It should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease (CVD) and is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. Thus, it is a metabolic diathesis or syndrome, and it usually involves no symptoms and only high blood sugar as the sole sign. Worldwide more than 300 million people and 80 million Indian people are at risk of developing diabetes mellitus but they are unaware of it. Prediabetes is the state in which some but not all the diagnostic criteria for diabetes are present. Prediabetes is also known as borderline diabetes, chemical diabetes & touch of diabetes. The progression into Diabetes mellitus from Prediabetes is approximately 25% over 3 to 5 years. The overall prevalence of diabetes in India is to be 7·3% and the prevalence of pre-diabetes to be 10·3% as per WHO criteria or 24·7% as per ADA criteria.

Pre-diabetes is one of the clinical entity, which have been described in *Ayurveda* in the context of *Prameha.* The diathesis of Pre-diabetes can be correlated with centuries old diathesis of *Prameha/Madhumeha* as described in Ayurvedic lexicons. *Ayurveda* has emphasized that lifestyle errors are the major etiological factor for *Prameha.* The pathogenesis of *Prameha* seeks attention of physician because of involving the 3 *Doshas* with wide range of *Dushyas* i.e. 10 *Dushyas;* ranging from *Rasa* to *Ojas*. Itis a *Tridosajvyadhi* but *kapha Dosha* is predominant in the development of *Prameha*/Prediabetes. Involvement of 10 *duhsyas* indicates that it is a systemic *vyadhi* involving the whole body. When these condition remain in body for a long time then it may converted into *Madhumeha* vis a vis Diabetes mellitus. Due to wide spread pathogenesis this disease is difficult to be cured.

In *Ayurveda,* it can be categorized in two major categories: 1. *Sahaj Prameha*2. *Apathyanimittaj Prameha,* out of these *Apathyanimittaj Prameha* have close relation with the Prediabetes/Type-2 Diabetes mellitus. In *Ayurveda, SthulaPramehi* has also been described, which may be correlated with obesity and its role in the genesis of Prediabetes/Type-2 DM, which is managed by *Aptarpana* measures. The etiology, classification, pathogenesis, clinical features, prognosis, and management of *Apathyanimmitaj Prameha* are closely related to Prediabetes. So, ancient *Acharayas* told *Aptarpana* measures as guideline of management of *Apathyanimmitaj Prameha*. In *Ayurvedic* text clinical prodromal features of *Prameha* are described along with features of *Vataja, Pittaja* and *Kaphaj Prameha* are also mentioned, which indicates the preclinical stage/early stage/subclinical features of Diabetes mellitus. If in the early stage of *Prameha/*Pre-diabetes are not managed, it may lead to develop *Madhumeha*/Type-2DM. Besides, numbers of pharmacological and non- pharmacological measures are also described in *Ayurveda* for the treatment of *Prameha/*Prediabetes. Lifestyle modification, herbal, mineral and herbo-mineral formulation are an important therapeutic measures of *Ayurveda,* which are to be used for the management *Prameha* including *Madhumeha.*

The management of Prediabetes is still not satisfactory in conventional system of medicine. Therefore, the highly evolved description of *Ayurvedic* therapeutic in the line of prevention and management can be utilized for the management of *Prameha*/Pre-diabetes, which not only provides a new dimension for the management of Prediabetes but also emerged as important preventive tools for Type-2 Diabetes mellitus.

In recent years the incidence of Prediabetes is rising with an alarming rate globally along with its consequences in terms of type 2 DM, which is discussed in detail in this thesis. Many Diabetologist and clinical researchers believed that Prediabetes is a clinical disorder; it may lead to Type 2 Diabetes mellitus and its complications. Therefore, it is a preventable clinical entity through lifestyle modification & diet and by uses some herbal drugs. If in the initial stage of Prediabetes is not treated properly than it may progressed to Type-2 Diabetes mellitus, it becomes incurable and lead to several complications. It is estimated that 45-50% Pre-diabetic converted into Type-2DM within 3-5 years. Such types of consequences are well documented in *Ayurvedic* lexicons.

Researchers and scholars of biomedical sciences have recently conceived the idea of *Medas* as the principal *Dushya* of *Prameha,* opines that central obesity and deranged lipid metabolism are considered as the main pathogenic component, which is involves in the basic matrix of Prediabetes and Type-2 Diabetes mellitus. It is suggested that the major focus of research and development of

Diabetes mellitus should be move around Pre-diabetes and metabolic syndrome as a preventive measures.

Pre-diabetes can be managed with the help exercise, yoga, dietary control, and bio-purificatory measures of *Ayurveda*, which may not only control the lipid and sugar metabolism in the system but also control its progression into Type-2 Diabetes mellitus. Many *Ayurvedic* preparations are described in *Ayurvedic* text for the treatment of Pre-diabetes/*Prameha*, which break the process of disease at its initial level. It seems profitable to explore the possibilities of developing an *Ayurveda*- inspired line of management and medication for contemporary use today. Such an exercise of 'Reverse Innovation' in the management of Diabetes mellitus and its complications is considered because of the fact that modern management of Diabetes mellitus is really not satisfactory. In this regard, *Ayurvedic* formulation *Darvyadi Ghana Vati* is described in the context of *Pramhea* by *Charaka* is used to explore it possibility in cases of Pre-diabetes.

It is decided to assess the diathesis of disease in relation of *Ayurveda* and to clinically evaluate the safety and efficacy of *Darvyadi Ghana vati* in the cases of Prediabetes. Besides, attempts have been made to assess the impact of dominant sets *Deha Prakriti* on therapeutic response. The present study was conducted on 60 patients of Pre-diabetes divided randomly into two groups treated with *Darvyadi Ghana Vati* in one group and another one is control group treated with modern drug (Metformin). After parallel study of *Ayurvedic* therapeutics, the favorable or unfavorable observation will be made in terms of Demographic profile, clinical symptoms, fasting blood sugar, postprandial blood sugar, HbA1C%, BMI, serum cholesterol, serum triglyceride, *Deha Prakriti.*

Material & Methods: In the management of Prediabetes many drugs and drug formulations have been mentioned in modern medicine, which provide instant relief up to some extent, but there are tend to develop a number of adverse drug reactions and no permanent cure is visible. Metformin an antidiabitic drug has beneficial effects in the prevention or in the treatment of Prediabetes and Diabetes Mellitus. These are considered as safe and usually well tolerated by the patients.

Darvyadi Ghana Vati is an Ayurvedic formulation described in *Charak Samhita* in *Prameha chikitisa*for the management of *Prameha*.

"दार्वी सुराह्वं त्रिफलां समुस्तां कषायमुत्क्वाथ्य पिबेत् प्रमेही"

(ch.chi.6/26)

This formulation comprises of six herbal drugs as described below, which have pharmacological capacity to decrease blood sugar level and relieves the clinical symptoms without any unwanted and adverse effects. Therefore, this formulation will be tested in comparative manner with Metforminto search out its role in the management of Prediabetes.

METHODS OF CLINICAL STUDY

Selection of The Patients: Total 60 patients were selected irrespective of their sex, age, religion for the above study from the OPD/IPD of Department of Kayachikitsa, SSL Hospital, BHU. The patients were registered and details of interrogation, examinations and investigations were carefully

recorded in the proforma especially prepared for this purpose. Prior to enrolment, Institutional ethical approval and written inform consent were be undertaken.

AIMS AND OBJECTIVES

1. **AIMS AND OBJECTIVES :**

1. To put an over view on the concept of Prediabetes vis -a- vis *Prameha*.
2. To study the hypoglycemic effect of *Darvyadi Ghana Vati* on subjective and objectives parameters of Prediabetes.
3. To compare the safety & efficacy of trial drug with control group i.e. Metformine.
4. To evaluate the impact of *DehaPrakriti* on progression of Prediabetes to Type- 2 DM.

Ethical Approval: Ecr/526/Inst/Up/2014 Dt. 31.1.14

Nature of Study: Open randomized control clinical trial

Inclusion Criteria:

- Age 30-60 yrs.
- Family History of Diabetes, HTN, Dyslipidemia
- Plasma glucose level : Fasting : 100-125 mg/dl

  Postprandial : 140-199 mg/dl

•HbA1C%

Exclusion Criteria:

- Age <30yrs. and >60yrs.
- Type ll Diabetes Mellitus (NIDDM) with and without complications.
- Type l Diabetes Mellitus (IDDM) associated with and without complications.
- Diabetes due to endocrinopathies e.g. Phaeochromocytoma, Acromegaly, Cushing's syndrome, hyperthyroidism etc.
- Drug or chemical induced diabetes mellitus e.g. Glucocorticoids, Thyroid hormone, Thiazides, Phenytoin etc.

- Certain genetic syndromes sometimes associated with diabetes mellitus e.g. Down's syndrome, Klinefelter's syndrome, Turner's syndrome etc.
- Patients suffering from any severe systemic disease.

Grouping of Patients

The randomly selected patients were divided into two groups as given below:

Group A (30)	**Group B (30)**
Control Group	Ayurvedic drug
Trial drug- Tab Metformin 500mg	**Trial drug:** ***Darvyadi Ghana Vati*** **Anupana-** Lukewarm water
Dose – 500 mg OD before meal	**Dose-** 500 mg BD after meal

The selected patients were treated as above for full trial period and the findings were analyzed at the end of the trial.

Methods of Assessment Criteria To Assess The Trial Drug Response

The assessment of Prediabetes was done at the interval of 1 months on following basis.

i. Subjective Assessment This completely depends upon the symptomatology and its grades. Improvement in symptoms is directly proportional to the improvement in the patient's condition and his metabolic state.

***DehaPrakriti*:** In the present study the *Prakriti* of each patient was ascertained on the basis of individual structural and physiological variation. For this purpose a proforma was specially designed base on classical texts parameters with on an individual of a particular *Prakriti* (Dubey and Singh, 1970). Based on individual *Prakriti*, the Prediabetic patients were divided into three groups i.e. *Vatika, Paittika* and *Kaphaja.*

***ManasaPariksha*:** Assessment of *Manasa Prakriti* viz. *Sattvika Rajasika* and *Tamasika* was done based on parameters developed by Singh R.H., 1980.

Laboratory Profile:

1. Blood Examination :

- Routine blood was examined for total leucocyte count, differential leucocytes count and haemoglobin percentage to exclude any infection.
- Blood urea and serum creatinine were done to assess the renal status.
- Liver function test.
- Total serum cholesterol level.

2. Urine Examination :

Urine for each case was examined for specific gravity, reaction, sugar, albumin and acetone routinely and microscopic examination for crystals, casts and cells.

3. Blood Sugar Examination :

For the diagnosis of Prediabetes, blood sugar level was determined. The recommended values for diagnosis of Prediabetes are fasting blood sugar level 100-125 mg/dl, two hours after glucose load the blood sugar level 140-199 mg/dl.

4. Glycosylated Haemoglobin (HbA1C%)

ii. Objective Assessment

Objective assessment was done on the following basis

- BMI (body mass index)
- Fasting blood Glucose
- Postprandial blood Glucose
- Serum Cholesterol, Triglyceride
- HbA1C%

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Therapeutic Study

Selection of the Trial Drug

Selection of Trial drug:

In this present study, selected trial drug *Darvyadi Ghana Vati* has been taken from the "*Charaka Samhita*" of the *Prameha Chikitsa* context and the individual drugs are authenticated from Department of Dravyaguna, IMS, BHU.

Preparation of the Trial Drug

The useful part of Darvyadi Ghana Vati was taken from original sources and identified by the experts of the department of Dravyaguna and Rasa Shastra, Faculty of Ayurveda, IMS, BHU, Varanasi. The crude fine powder of six contents present in Darvyadi Ghana Vati was prepared by Ayurvedic Pharmacy, BHU, Varanasi. Out of six, each drug was present in equal quantity in churna.

Dosage & Duration: The prepared Darvyadi Ghana Vati was given 500 mg bid with luke warm water and Tab Metformin 500 mg- 1 OD, for 3 months.

STATISTICAL METHODS

All the data were collected in tabulated form and shown in graphic representation also. The intra-group comparison was done to see the effect of treatment using paired t test. For the inter-group comparison between the groups unpaired t test & one-way ANOVA (Analysis of Variance) was applied and value of t & f test was determined. Qualitative variables were assessed by Chi-square (χ^2) test for significant difference among the groups.

Observation & result:

Demographic Profile

I. Epidemiological

Age & sex

The study shows the incidence of Age and Sex of 60 patients of Pre-diabetes, it revealed thatthe registered patients were fall in the age range between 30 to 60 years. The sex incidence in 60 cases, the greater number of patients were male i.e. 33 (55%) followed by female 27 (45%) .

It is evident from the table that out of cases in the present series, maximum numbers of patients 50% were in age range i.e. 51-60 years. The next common age range was 41-50 years in which 31.6% were registered and rest are in 31-40 years i.e. 18.3%. This indicates that Pre-diabetes occurrence is common in middle age group.

Incidence of Sex in 60 cases of Pre-diabetes

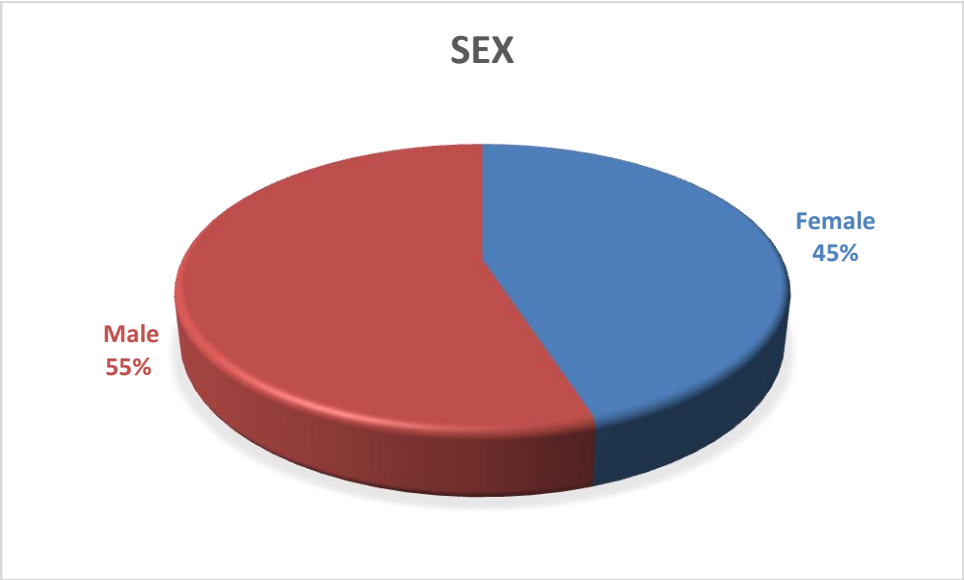
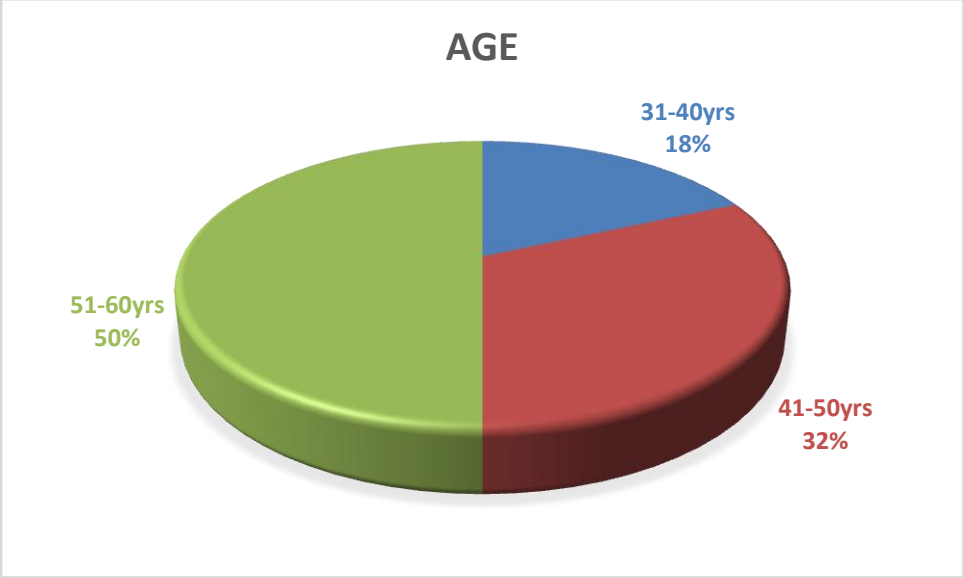


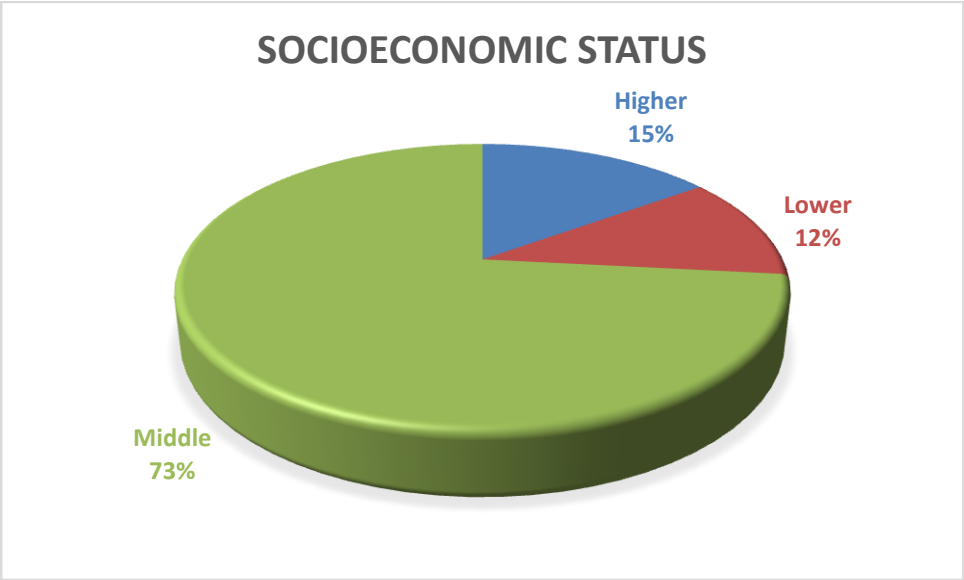
Fig-2: Incidence of Age in the 60 cases of Pre-diabetes



Socioeconomic status

The present study covered a cross section of the society. It was found that majority of them were from the middle Socioeconomic status i.e. 73.3% followed by 15% patients from higher and 11.7% from lower Socioeconomic status.

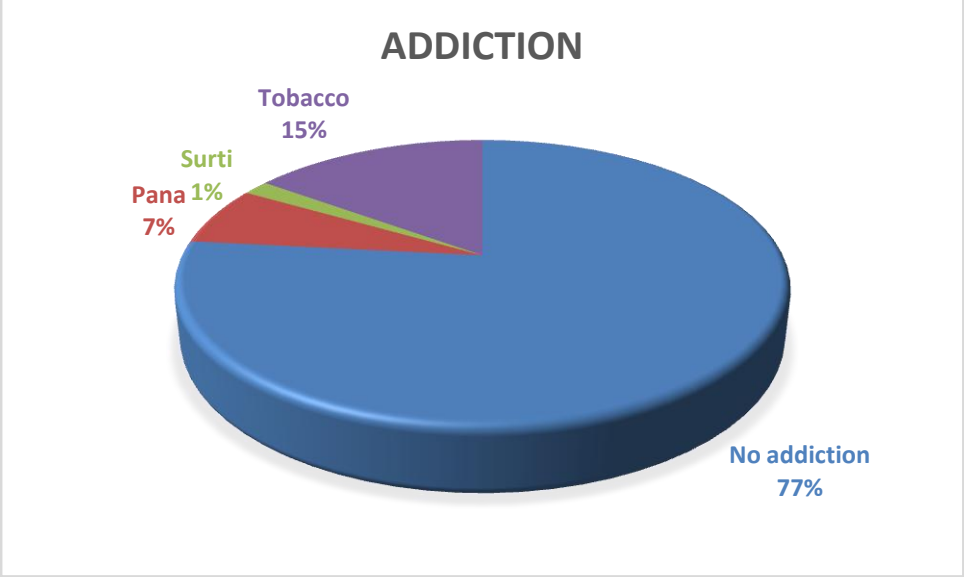
Incidence of Economic Status in 60 cases of Pre-diabetes



Addiction

The incidence of addiction in 60 cases of Pre-diabetes revealed that maximum numbers of the patients had no addiction i.e. (76.7%) followed by 23.3% of betel leaves (*Pana* + *Surti* + *Tobacco*).

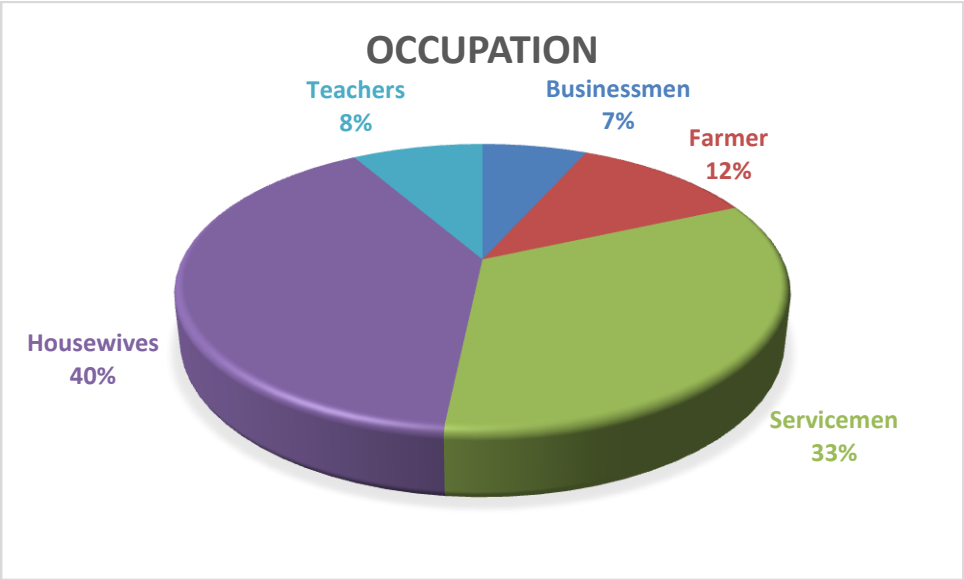
Incidence of Addiction in the cases of Pre-diabetes



Occupation

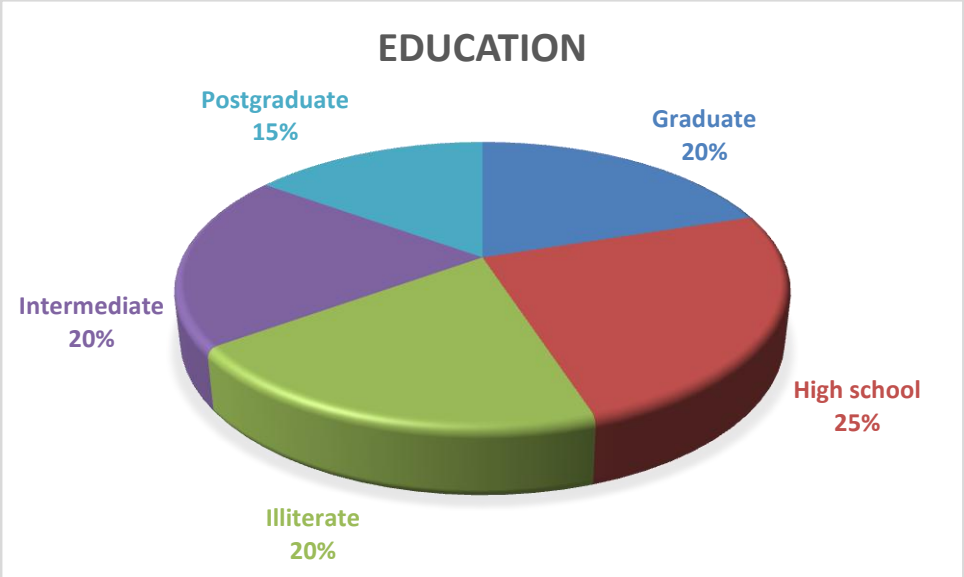
In occupational study the incidence of Pre-diabetes, was found to be higher (40%) in housewives followed by servicemen (33.4%), farmer (11.7%) teachers (8.3%) and businessmen (6.7%).

Incidence of Occupation in the 60 cases of Pre-diabetes



Education This study shows the educational status of 60 cases of pre-diabetes, it revealed that majority of the patients were high school 25% and 20% had completed their graduation, 20% intermediate education and 15% postgraduates education followed by 20% were illiterate (See table -6 & fig. - 6).

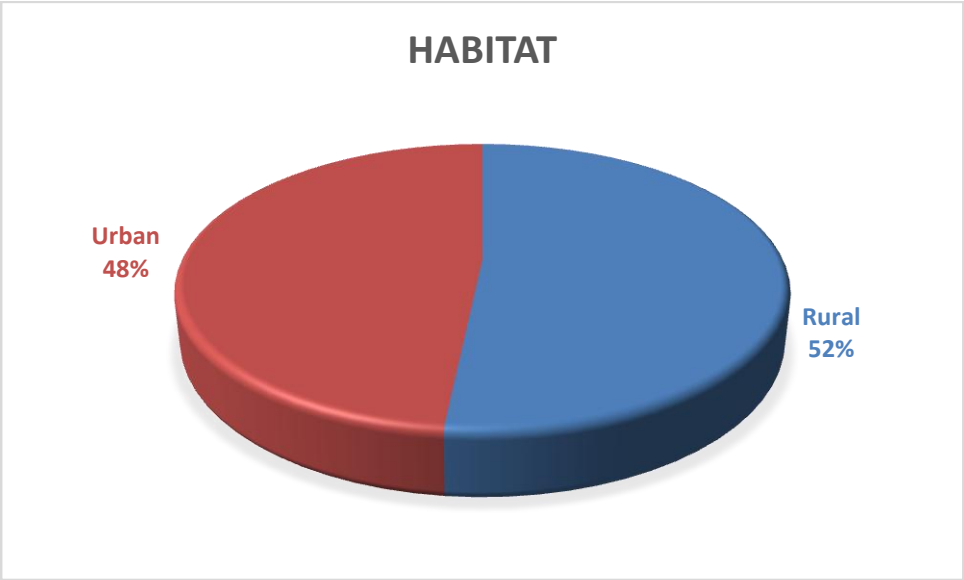
Incidence of Education in the 60 cases of Pre-diabetes



Habitat

The incidence of habitat in 60 cases of pre-diabetes shows that majority of the patients were residing in rural areas (51.7%) as compared to those residing in urban areas i.e. 48.3%.

Incidence of Habitat in the 60 cases of Pre-diabetes

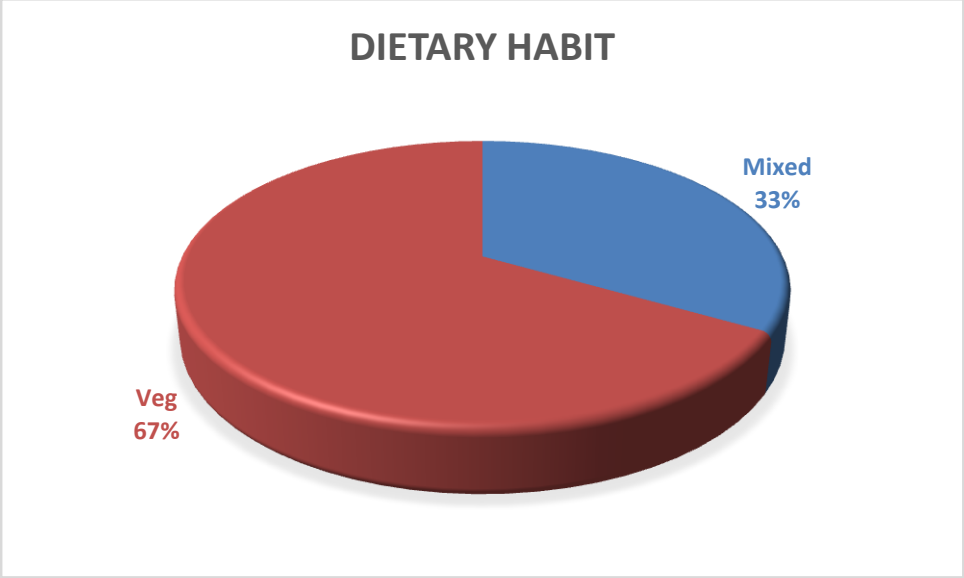


Dietary Habit

The present study reveals that 55% of the patients had mixed dietary habit, while 45% were purely vegetarians.

Thus, dietary pattern have a role with the incidence of Pre-diabetes.

Incidence of Dietary Habit in the 60 cases of Pre-diabetes

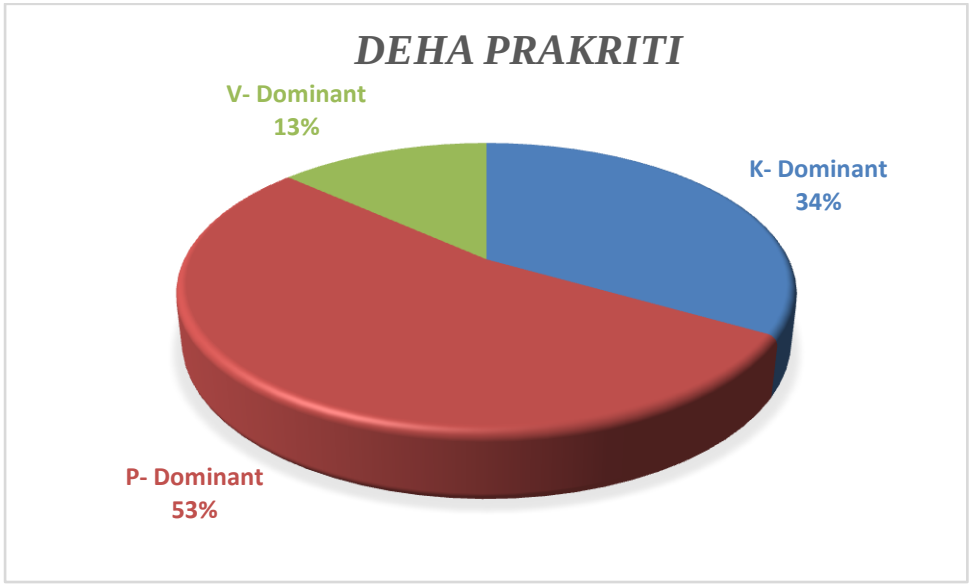


Constitutional Profile:

Deha Prakriti

The incidence of *Deha Prakriti* in 60 cases of Pre-diabetes shows that patients of *Pittaja* dominant *Prakriti*had greater risk (53.3%) for developing the disease than the *Kaphaja* (33.3%) and *Vataja* (13.3%) type of *Deha Prakriti*.

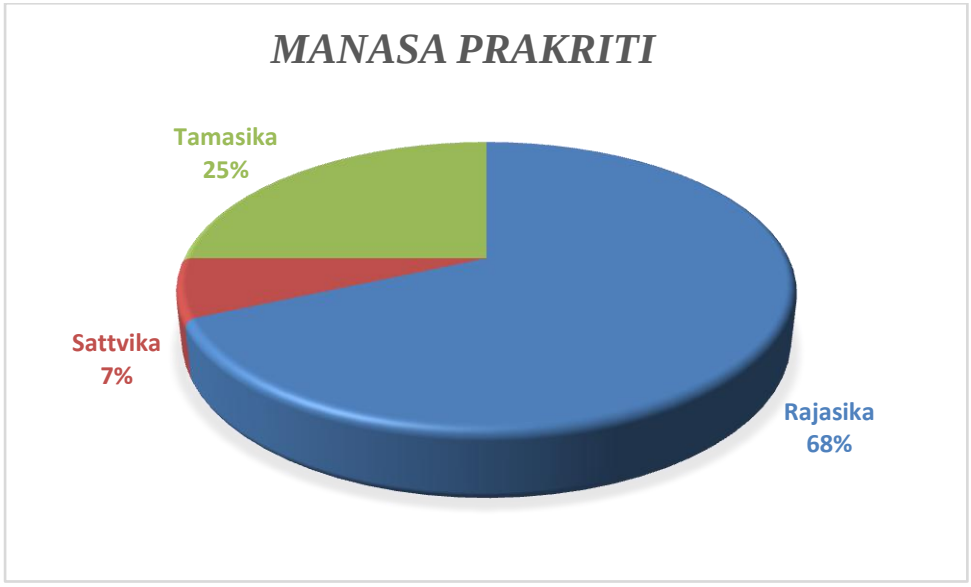
Incidence of *Deha Prakriti* in the 60 cases of Pre-diabetes



Manasa Prakriti

This epidemiological findings reveals that maximum (68.3%) patients belonged to *RajasikaManasa Prakriti* followed by 6.7% belonged to *Sattvika Manasa Prakriti*, rest 25% were fell in *Tamasika Manasa Prakriti* in this study.

Incidence of *Manasa Prakriti* in the cases of Pre-diabetes

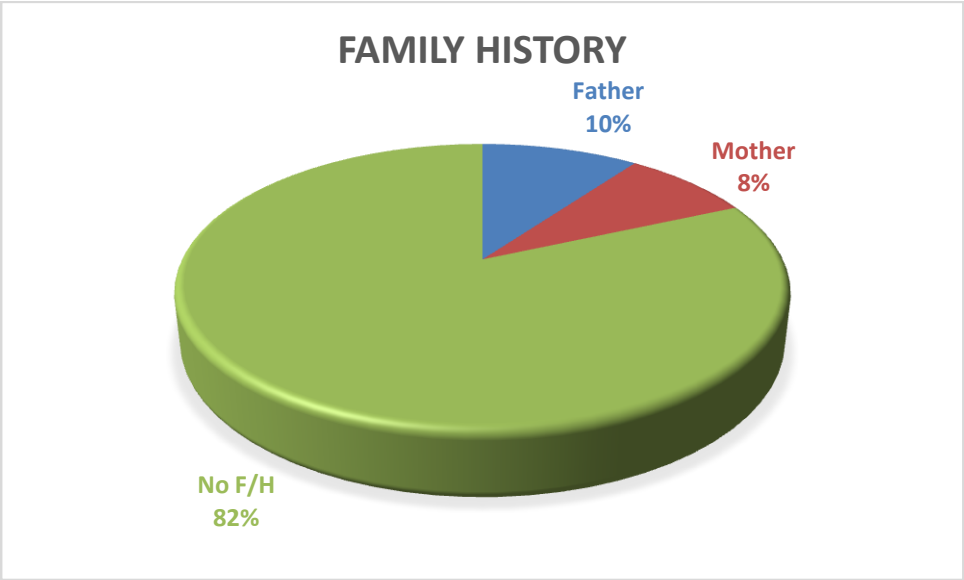


III. Clinical Profile:

Family history:

The present study of 60 cases of Pre-diabetes reveals that most of the patients have no family history i.e. 81.7% followed by 18.3% had positive family history of type-2 diabetes mellitus

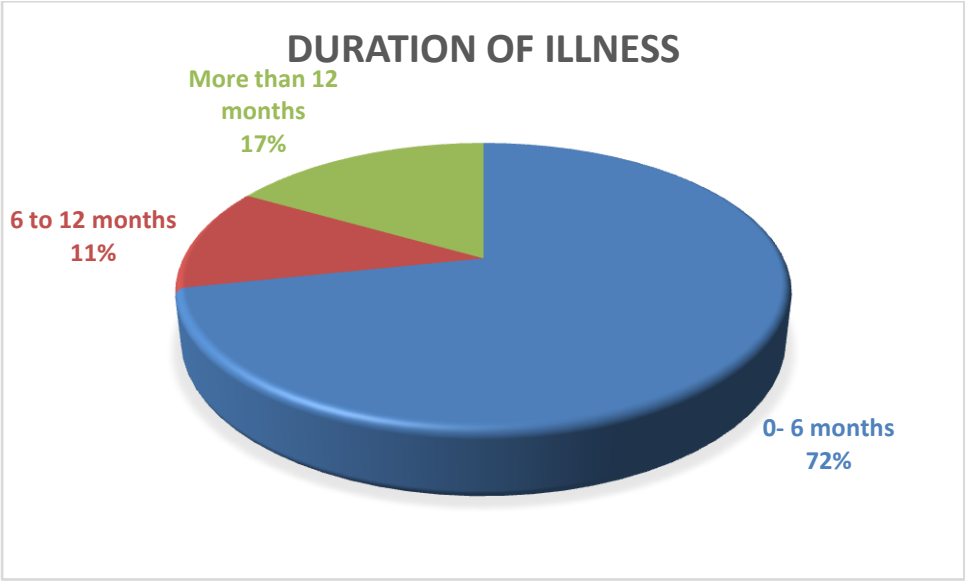
Incidence of Family history in the 60 cases of Pre-diabetes



Duration of Illness:

In this clinical study of 60 patients of pre-diabetes, most of the patients (71.7%) were in the duration of 0- 6 months followed by 11.6% between 6-12 months and rest were belongs to more than 12 months i.e. 16.7%.

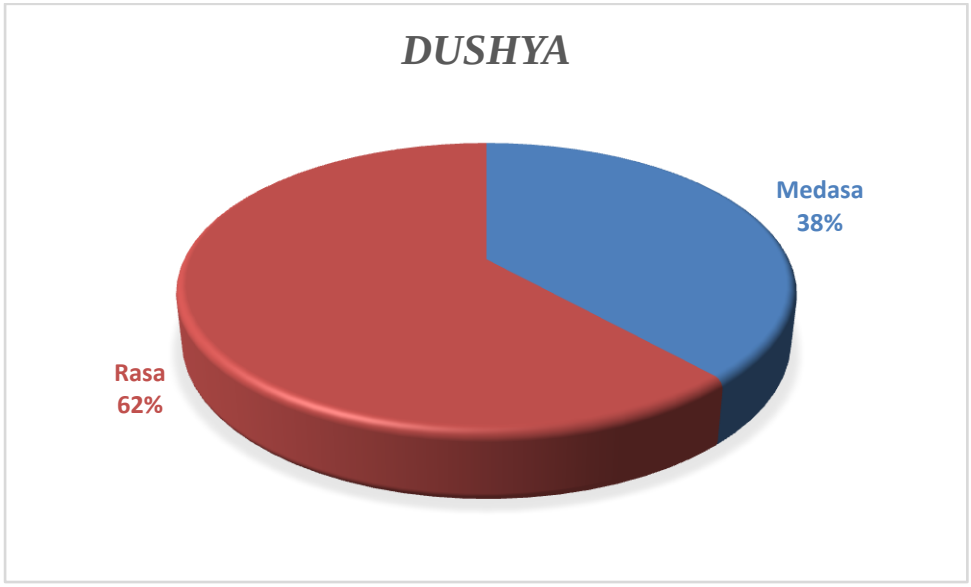
Incidence of Duration of illness in the 60 cases of Pre-diabetes



Dushya involvement

The present study shows that *Rasa* predominant *Dushya* has greater risk (58.33%) for developing the disease followed by the *Medasa* (41.67%) type of *Dushya*.

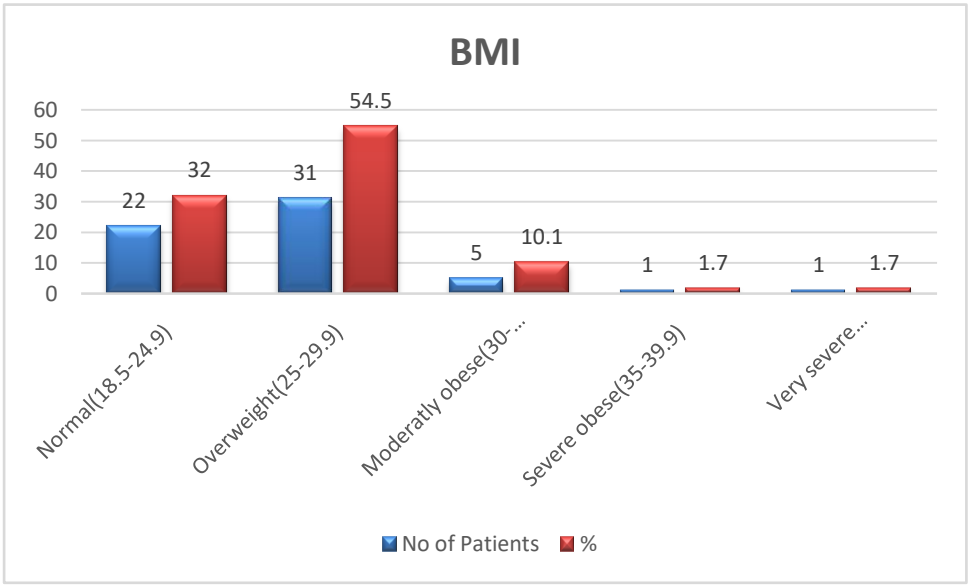
Incidence of *Dushya* in the 60 cases of Pre-diabetes



BMI Range:

In this clinical study most of the patients (54.5%) were in the BMI range (25-29.9) i.e. overweight followed by 32% were of normal BMI range group.

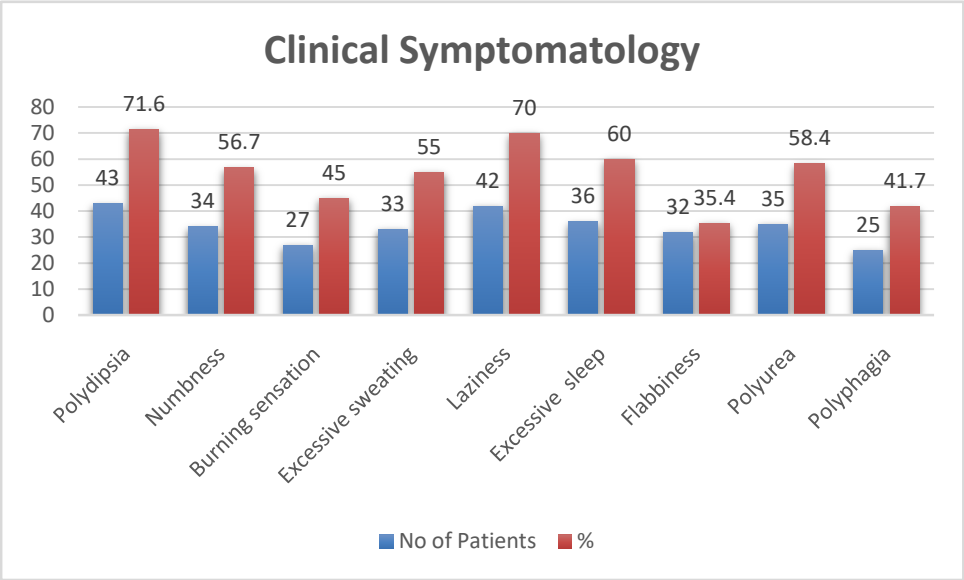
Incidence of BMI in the 60 cases of Pre-diabetic



Clinical Symptomatology in 60 cases of Pre-diabetes:

Incidence of clinical symptomatology in 60 patients of Pre-diabetes revealed that the maximum number of patients (71.6%) had Polydipsia followed by Laziness (70%), Excessive Sleep (60%), Polyurea (58.4%), Numbness (56.7%), Excessive Sweating (55%), Burning sensation (45%), Polyphagia (41.7%) and Flabbiness (35.4%**)**

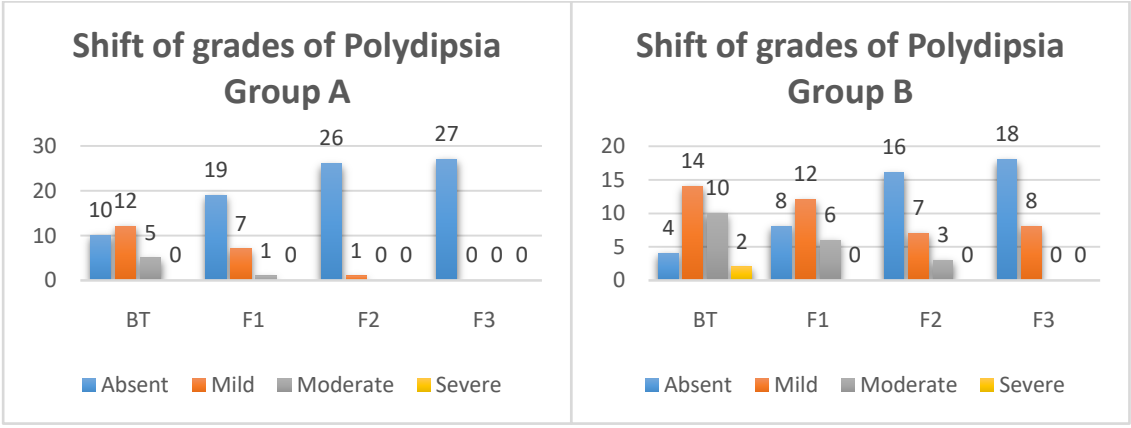
Incidence of symptoms in the 60 cases of Pre-diabetes



I. Therapeutic Studies and Clinical TrialClinical Symptoms Polydipsia

The study shows the significant shift of grades of Polydipsia in trial groups, it was statistically highly significant in both group, Group-A ($p<0.001$) and Group B ($p<0.001$). While comparing between the Group, the differences were significant in F1 & F2 ($p=0.009$) & ($p=0.036$) respectively but statistically not significant ($p>0.05$) in F3.

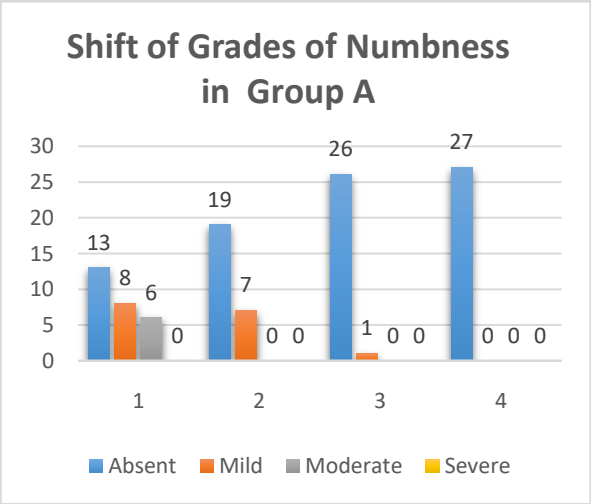
Showing significant favorable shift of grades of Polydipsia in 53 cases of Pre-diabetes.

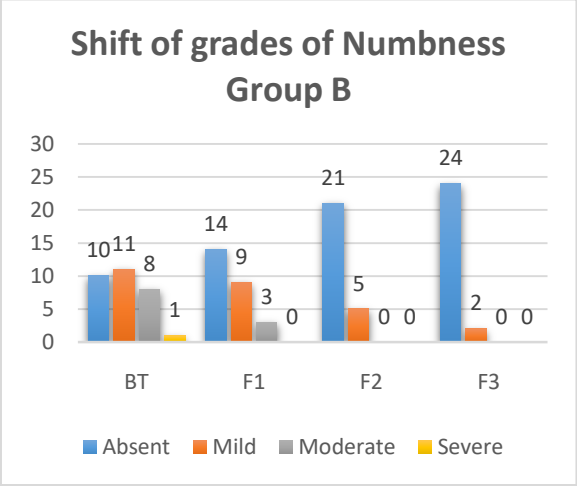


Numbness

The study shows the significant shift of grades of Numbness in different trial groups, it was statistically highly significant ($p<0.001$) in Group-A & Group-B, after 3 months of trial observation. Between the Groups comparison, it was statistically not significant.

Showing significant favorable shift of grades of Numbness in 53 cases of Pre-diabetes.





Burning sensation

The study shows the significant shift of grades of Burning sensation in different trial groups, it was statistically highly significant ($p<0.001$) in Group-A and Group-B, after 3 months of trial observation. While comparing between the Groups, it was statistically significant ($p=0.032$) in F2 and highly significant ($p=0.002$) F3, and not significant ($p<0.679$) in before treatment.

Showing significant favorable shift of grades of Burning sensation in 53 cases of Pre-diabetes

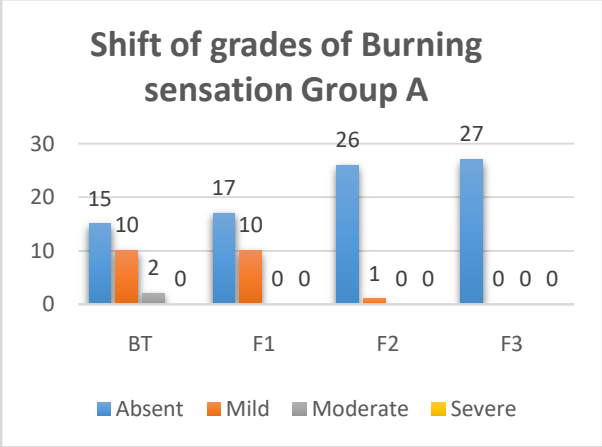


Fig-18.1

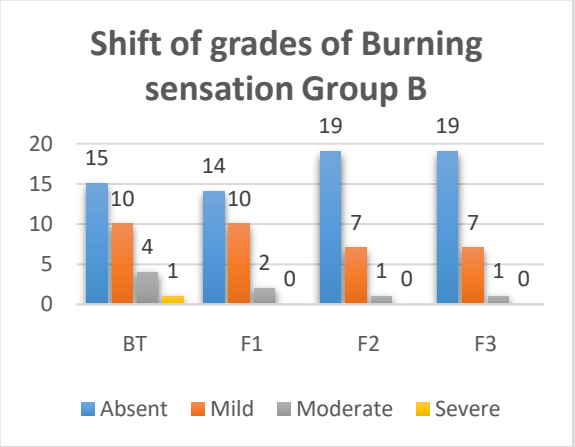
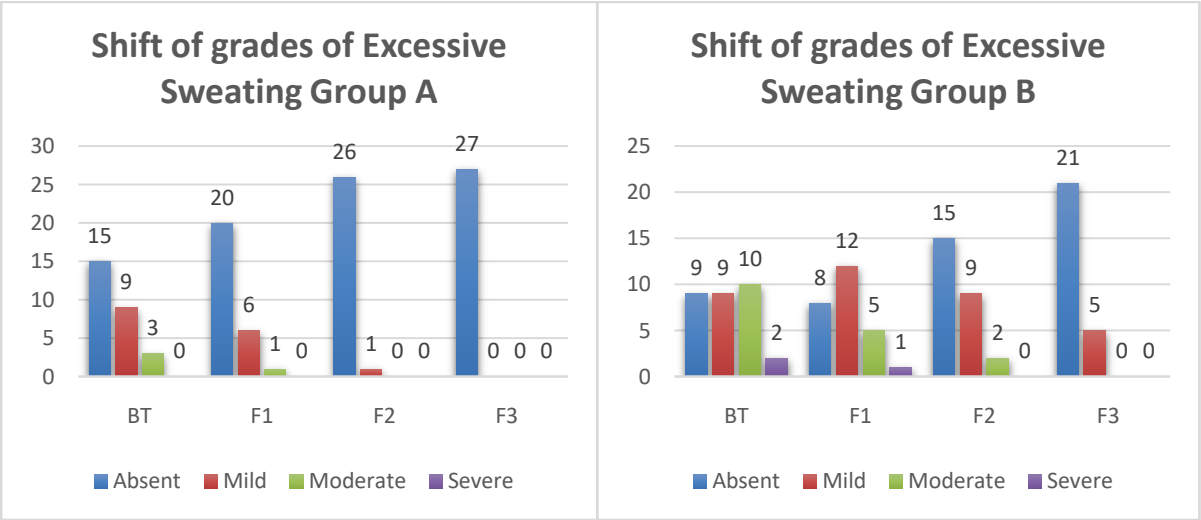


Fig-18.2

Excessive Sweating

The study shows the significant shift of grades of Excessive Sweating in different trial groups, shift of grade was statistically highly significant ($p<0.000$) in Group-A & Group- B, after 3 months of trial treatment. While comparing between the Groups, the difference were statistically significant ($p<0.05$) BT, F1, F2 & F3.

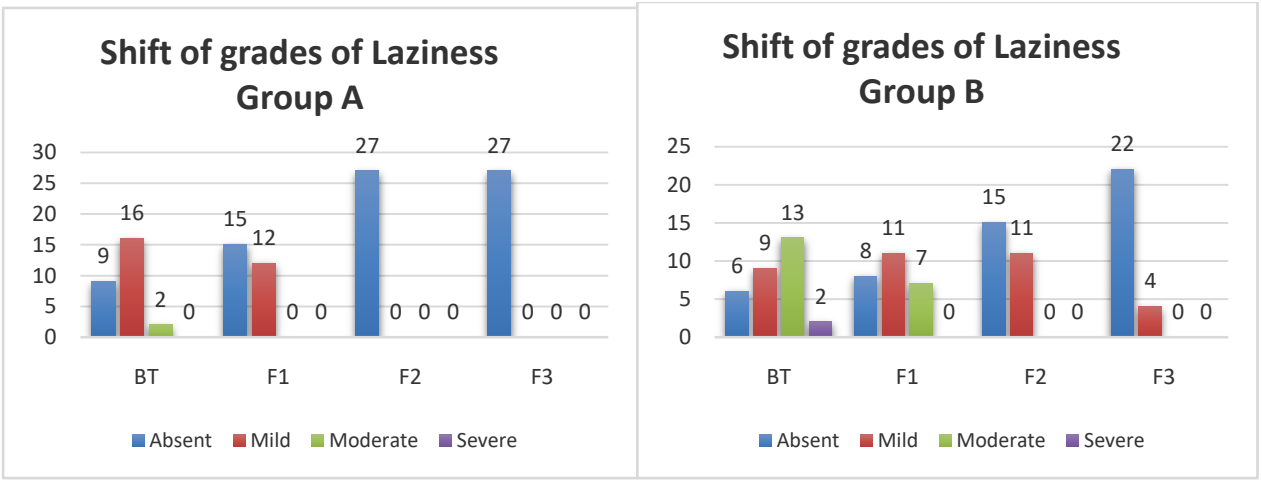
Showing significant favorable shift of grades of Excessive Sweating in 53 cases of Pre-diabetes.



Laziness

The study shows the significant shift of grades of Laziness in different trial groups, it was statistically highly significant ($p<0.001$) in Group-A & Group-B, after 3 months of trial observation. While comparing between the groups, it was statistically significant ($p<0.05$) in BT, F1 & F3 and highly significant ($p<0.01$) in F2.

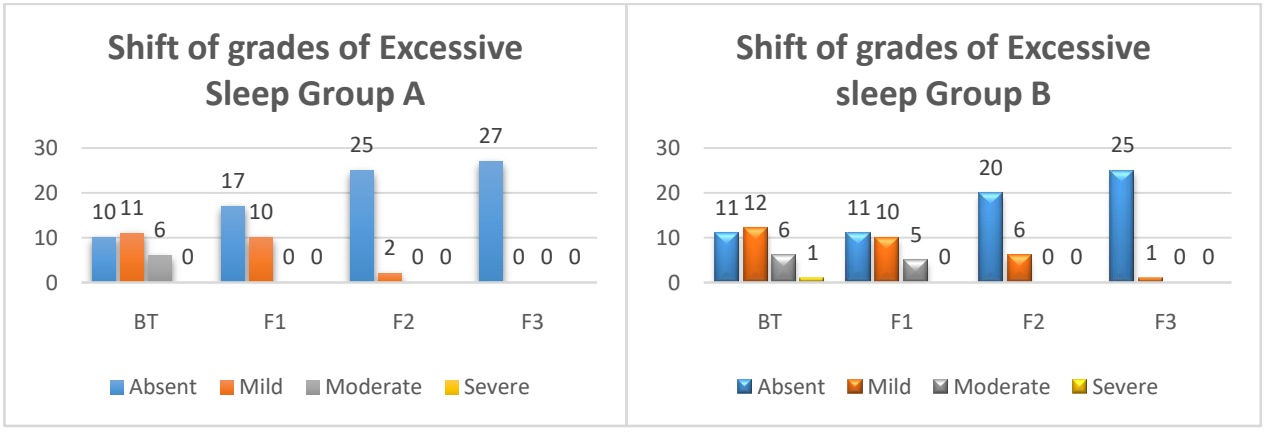
Showing significant favorable shift of grades of Laziness in 53 cases of Pre-diabetes.



Excessive Sleep

The study shows the significant shift of grades of Excessive Sleep in trial groups, it was statistically highly significant ($p<0.001$) in Group-A & Group-B after 3months of trial treatment. While comparing between the groups, it was statistically significant ($p<0.05$) in F1 and not significant ($p<0.817$) in BT, (0.111) in F2& ($p<0.304$) in F3.

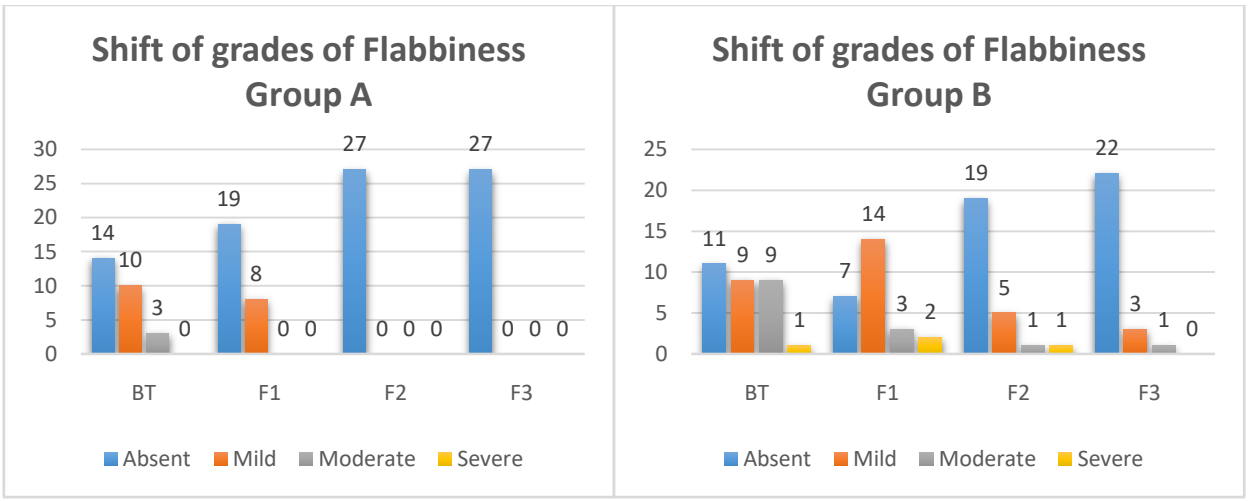
Showing significant favorable shift of grades of Excessive Sleep in 53 cases of Pre-diabetes



Flabbiness

The study shows the significant shift of grades of Flabbiness in different trial groups, it was statistically highly significant (p<0.000) in Group-A & after 3 months of trial observation. While comparing between the Groups, the differences were statistically not significant (p=0.133) in BT & (p=0.106) in F3 while significant in F2 (P=0.015) & highly significant in F1.

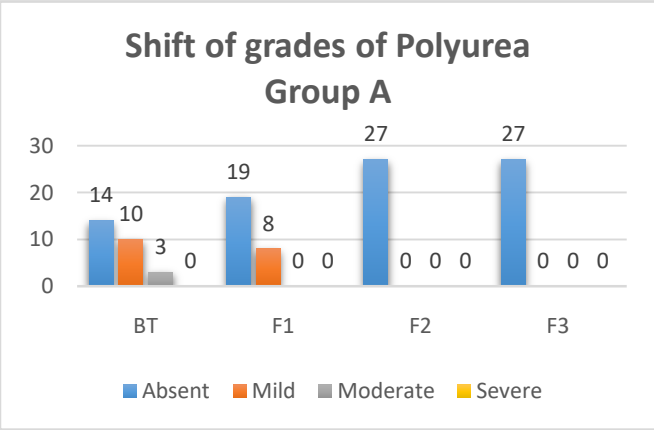
Showing significant favorable shift of grades of Flabbiness in 53 cases of Pre-diabetes.

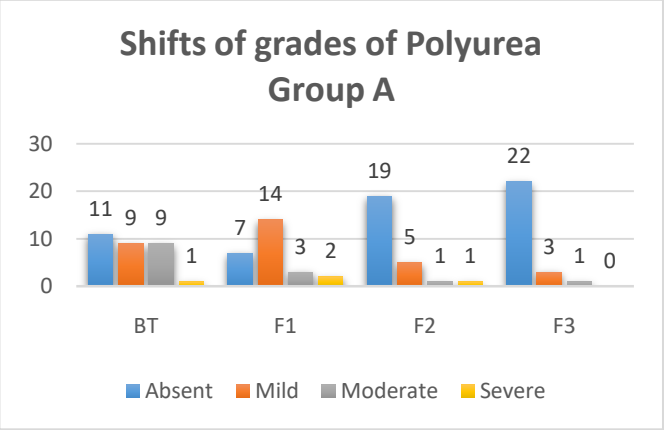


Polyurea

The study shows the significant shift of grades of Polyurea in different both the groups, it was statistically highly significant (p<0.000) in both the groups, after 3 months of trial treatment. While comparing between the Group, the differences were statistically highly significant (p=0.002) in F1, significant in F2 (P=0.015), while not significant in BT (p=0.133) & F3 (p=0.106).

Showing significant favorable shift of grades of Polyurea in 53 cases of Pre-diabetes.

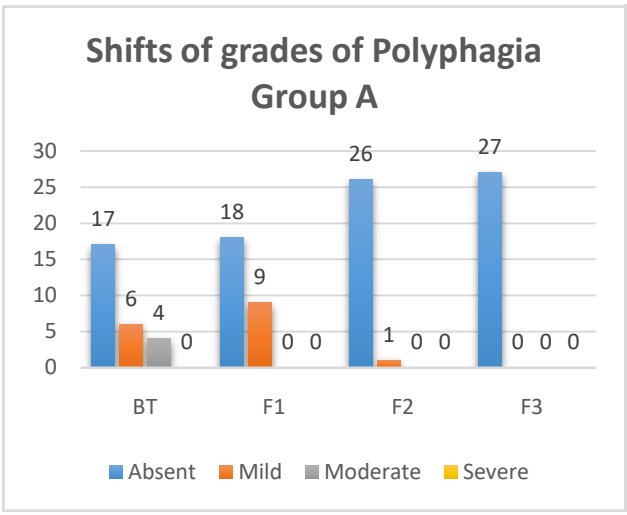


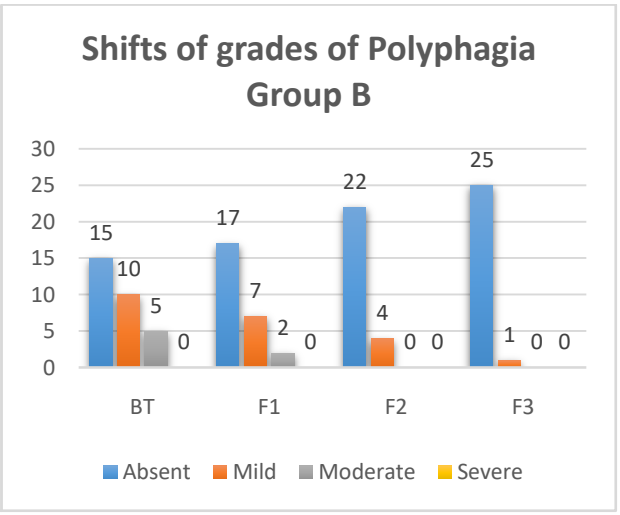


Polyphagia

The study shows the significant shift of grades of Polyphagia in both the groups but it was statistically highly significant ($p<0.001$) in Group-A & Group-B, after 3 months of trial treatment. While comparing between the Groups, the differences were statistically not significant in any group ($p>0.05$) at end of trial treatment.

Showing significant favorable shift of grades of Polyphagia in 53 cases of Pre-diabetes.





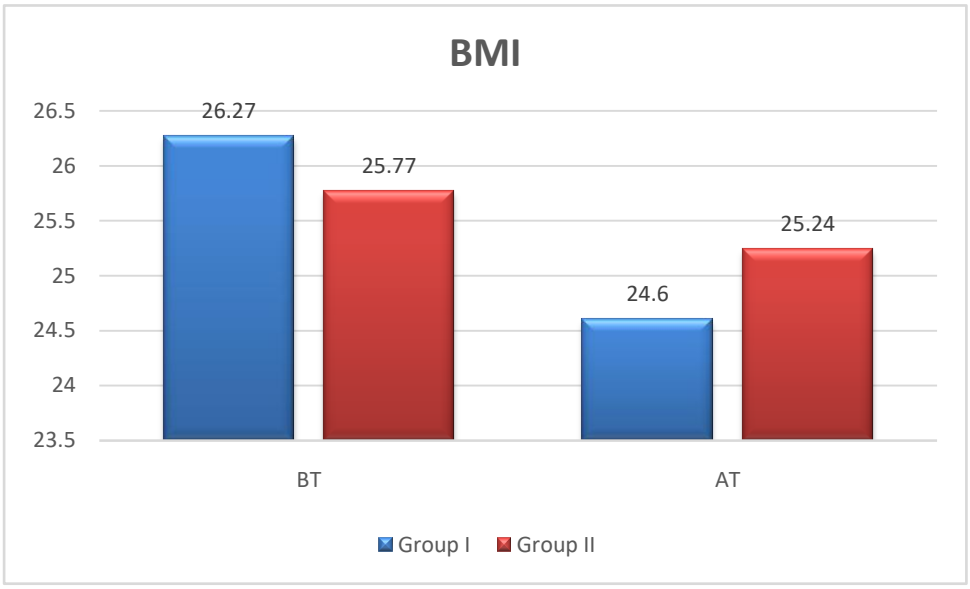
Changes in BMI

The BMI study shows that the initial mean and SD for Group-A was 26.27 ± 1.80, which decreased to 24.60 ± 1.46 after 3 months of trial treatment. The result was statistically highly significant ($p < 0.001$). In group B mean was decreased from 25.77 ± 5.08 to 25.24 ± 5.27, showing statistically highly significant result ($p < 0.001$) at the end of trial.

Intergroup comparisons (Unpaired t test) it can be concluded that results were statistically not significant ($p>0.05$).

The difference in means was highest in group A (1.67) followed by group A (0.535) respectively. Thus, the efficacy of given treatment was group A > group B.

Showing mild Changes in BMI in the 53 cases of Pre-diabetes



Fasting Blood Sugar

The blood sugar fasting in group A, the initial mean ± S.D. was 112.79± 10.70 which reduced to 95.60± 4.56 after complete follow-up, the improvement was statistically highly significant ($p<0.001$). In group B mean ± SD reduced from 117.13±11.74 to 100.81±12.83, showing statistically highly significant ($p< 0.001$) response in FBS.

On intergroup comparison (Unpaired t test), the result was statistically insignificant in BT, F1, F2 and F3 ($p>0.05$).

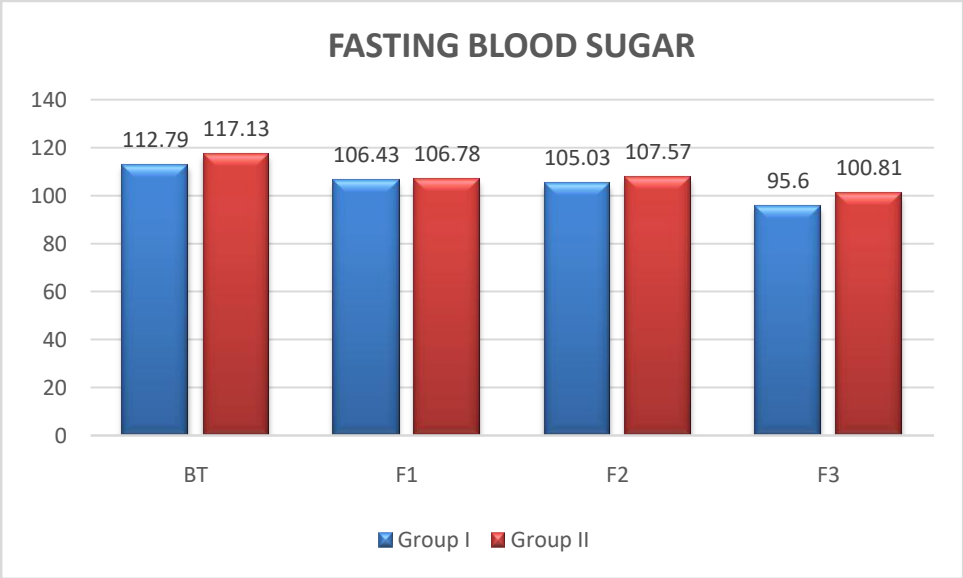
The reduction in means was highest in group A (17.19) followed by group B (16.32) respectively. Thus, the efficacy of treatment given to both the groups was in this order group A > group B. (See table -26 & fig. 26).

Table 26: Showing Changes in Fasting blood sugar in the 53 cases of Pre-diabetes

Group	FBS Mean ± SD				Within the group comparison Paired t Test (BT-F3)
	BT	F_1	F_2	F_3	
Group I (n=27)	112.79± 10.70	106.43± 20.45	105.03± 6.24	95.60± 4.56	17.18± 8.93 t= 9.998 p= 0.000
Group II (n=26)	117.13± 11.74	106.78± 14.52	107.57± 12.53	100.81± 12.83	15.11± 11.81 t= 6.524

					p= 0.000
Between the group **Unpaired t test**	t= 1.455 p= 0.151	t =0.073 p=0.942	t =0.940 p=0.352	t=1.983 p=0.053	

Fig-26: Showing Changes in Fasting blood sugar in the 53 cases of Pre-diabetes



Postprandial Blood Sugar

The postprandial blood sugar estimations in group A, the initial mean ± S.D. was 183.01±12.76, which decreased to 148.42±13.40 after 3rd follow-up, the reduction was statistically significant ($p<0.001$). In group B, the mean ± SD was decreased from 165.37±20.13 to 140.00±20.07 showing statistically highly significant ($p<0.001$) response.

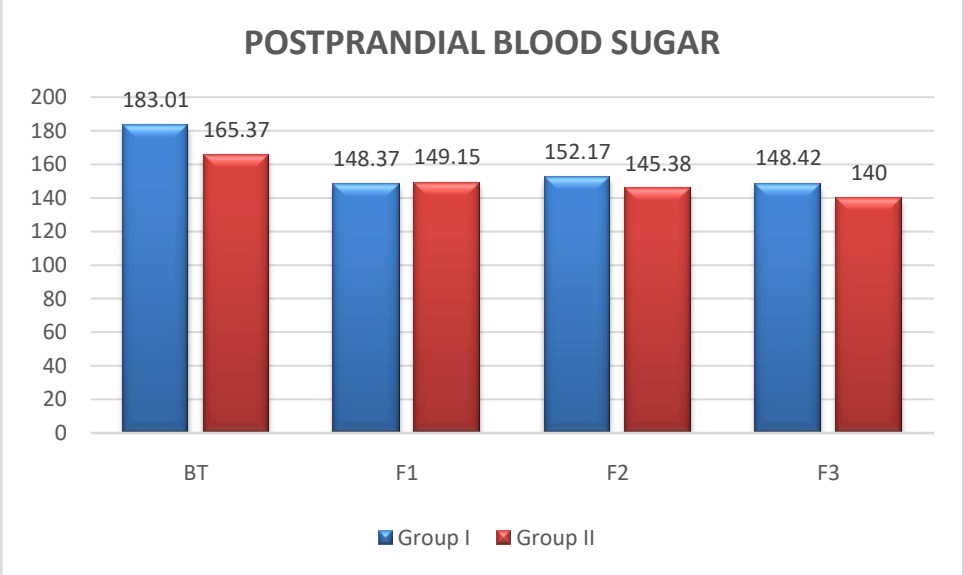
On intergroup comparison (Unpaired t test) the result was statistically significant in BT ($p<0.05$). In FU1, FU2 & FU3 there is no significant difference ($p>0.05$) between the net changes in PPBS between the Group A & B.

The difference in means was highest in group A (34.59) followed by group B (25.37) respectively. Thus, the efficacy of treatment given to both the groups was in order of group A > group B. (See table -27 & fig.27).

Table 27: Showing Changes in Post prandial blood sugar in the 53 cases of Pre-diabetes

Group	PPBS Mean ± SD				Within the group comparison Paired t Test 'p' and Mean difference ± SD
	BT	F_1	F_2	F_3	
Group I (n=27)	183.01± 12.76	148.37± 25.31	152.17± 15.83	148.42± 13.404	34.58±12.39 t=14.49 p=0.000
Group II (n-26)	165.37± 20.13	149.15± 28.64	145.38± 23.37	140.00± 20.07	27.38± 21.66 t= 6.444 p=0.000
Between the group Unpaired t test	t=3.900 p= 0.000	t =0.105 p=0.917	t =1.242 p=0.220	t=1.803 p=0.077	

Fig-27: Showing Changes in Post prandial blood sugar in the 53 cases of Pre-diabetes



Mean percentage fall in FBS & PPBS in different trial group

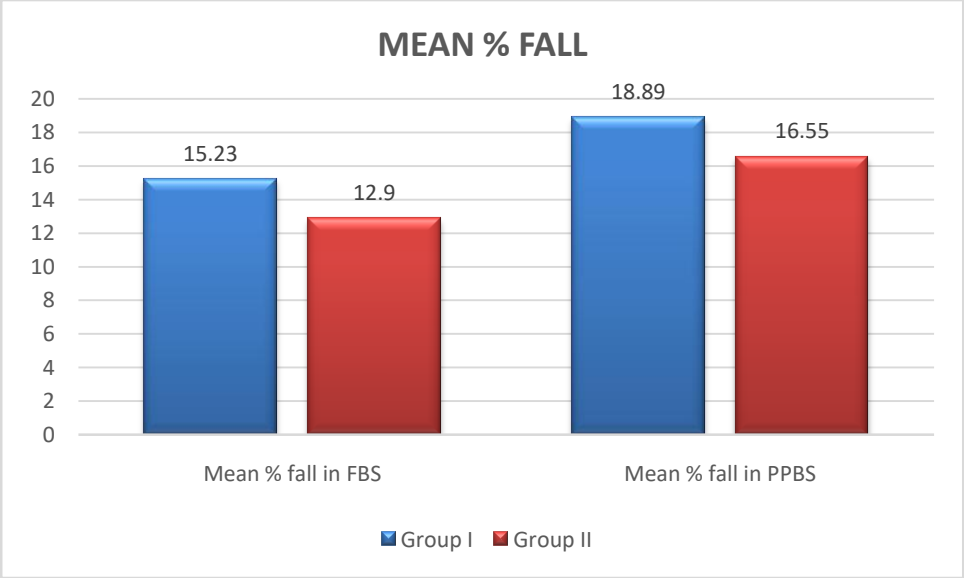
The control group shows maximum fall (15.23%) in fasting blood sugar level followed by Ayurvedic formulation group (12.90%). The rate of fall in postprandial blood sugar in Control group

was maximum (18.89%) followed by Ayurvedic formulation group (15.12%). (See table -13 & fig. 13).

Table 28: Mean percentage fall in FBS & PPBS in different trial group

Group	Mean % fall in FBS	Mean % fall in PPBS
I	15.23	18.89
II	12.90	16.55

Fig-28: Mean percentage fall in FBS & PPBS in different trial group



Serum Cholesterols

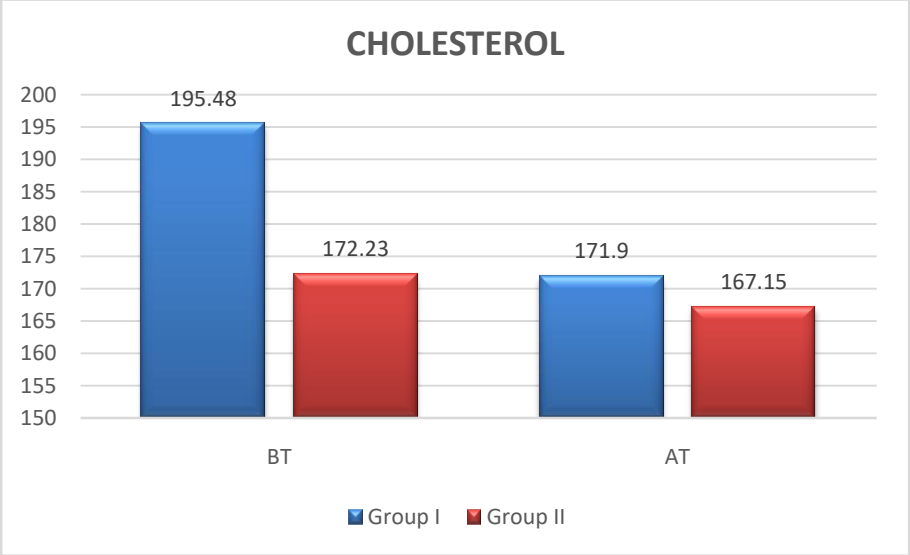
Serum Cholesterol value in group A, the initial mean ± S.D. was 195.48 ± 16.12, which decreased to 171.90 ± 14.55 after 3rd follow-up, the differences was statistically highly significant ($p<0.001$). In group B, the mean ± S.D was decreased from 172.23 ± 39.07 to 167.15 ± 26.81, showing statistically not significant ($p=0.228$) reduction in Sr. Cholesterol.

Intergroup comparison (Unpaired t test) show a statistically significant ($p>0.006$) changes in BT & not significant ($p=0.424$) changes in AT. But on the basis of mean reduction, maximum response goes in favour of Group A (23.58) followed by Group B (5.08). (See table -29 & fig. 29).

Table 29: Changes in Cholesterol Level in the cases of Pre-diabetic

Group	Cholesterol (Mean ± SD)		Within the group comparison Paired t test, 'p' and Mean difference ± SD
	BT	AT	
Group I (n=27)	195.48±16.12	171.90±14.55	23.57±7.55 t= 16.224 p= 0.000
Group II (n=	172.23±39.07	167.15±26.81	5.076±20.96 t= 1.235 p= 0.228
Between the group comparison Unpaired t Test	t= 2.851 p=0.006	t=0.806 p=0.424	

Fig-29: Changes in Cholesterol Level in the cases of Pre-diabetic



Serum Triglycerides

The Serum Triglycerides in group A, the initial mean ± S.D. was 156.94 ± 6.41 which was decreased to 137.87 ± 19.37 after 3rd follow-up, the changes being statistically highly significant ($p < 0.001$). In group B, the mean ± S.D was decreased from 154.96 ± 78.77 to 153.54 ± 67.51, showing statistically not significant ($p > 0.05$) reduction in Sr. TG.

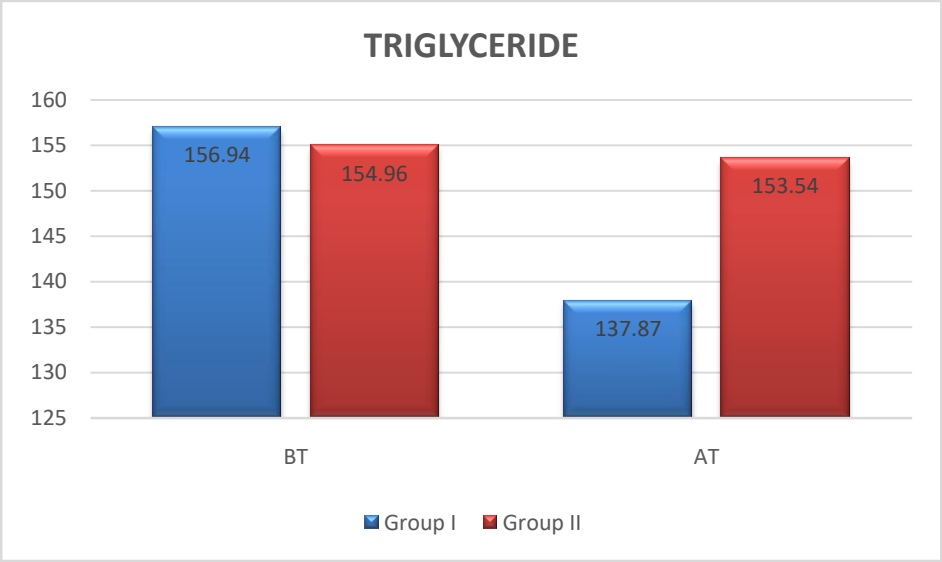
On intergroup comparison (Unpaired t test), the result was statistically not significant in both BT and AT ($p>0.05$).

The difference in means was highest in group A (19.07) followed by group B (1.42) respectively. Thus, the efficacy of treatment given in both the groups was in this order group A > group B. (See table -30 & fig. 30).

Table 30: Changes in Triglyceride Level in the cases of Pre-diabetic

Group	**Triglyceride (Mean ± SD)**		**Within the group comparison Paired t test (BT-AT)**
	BT	AT	
Group I (n=27)	156.94± 6.41	137.87± 19.37	19.08±3.66 t=5.209 p= 0.000
Group II (n =26)	154.96± 78.7783	153.54± 67.514	1.42±29.31 t= 0.248 p=0.807
Between the group comparison Unpaired t Test	t= 0.131 p=0.897	t=1.158 p=0.252	

Fig-30: Changes in Triglyceride Level in the cases of Pre-diabetic:



Serum Creatinine

The data of Sr. Creatinine shows that the initial mean and SD in Group-A was 1.03 ± 0.28 after 1½ years of treatment it reduced to 0.80 ± 0.18. The improvement was statistically highly

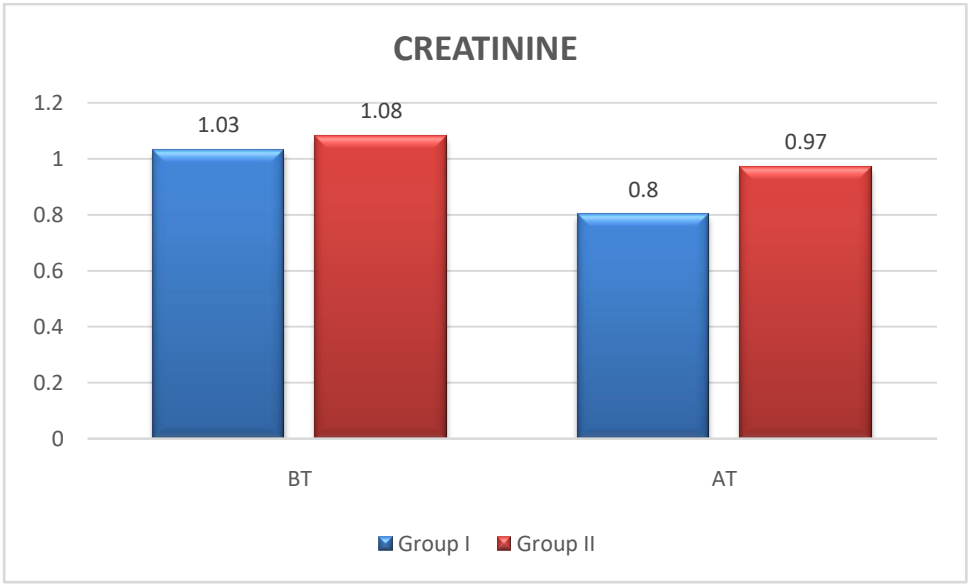
significant (p< 0.001). In Group-B the initial mean ± SD was 1.08 ± 0.35, after 3 months of treatment it reduced to 0.97 ± 0.16. The improvement in Sr. Creatinine was statistically not significant (p> 0.05).

While comparing in different groups there is statistically insignificant (p>0.05) change in Serum Creatinine in BT & highly significant (p=0.001) AT. (See table -31 & fig. 31)

Table 31: Showing Changes in Creatinine Level in the cases of Pre-diabetic

Group	**Creatinine (Mean ± SD)**		**Within the group comparison Paired t test (BT-AT)**
	BT	**AT**	
Group I (n=27)	1.03± 0.28	0.80± 0.18	0.22±0.16 t= 7.084 p= 0.000
Group II (n=26)	1.08± 0.35	0.97± 0.16	0.10±0.35 t= 1.506 p=0.145
Between the group comparison Unpaired t Test	t= 0.518 p=0.607	t=3.374 p=0.001	

Fig-31: Showing Changes in Creatinine Level in the cases of Pre-diabetic



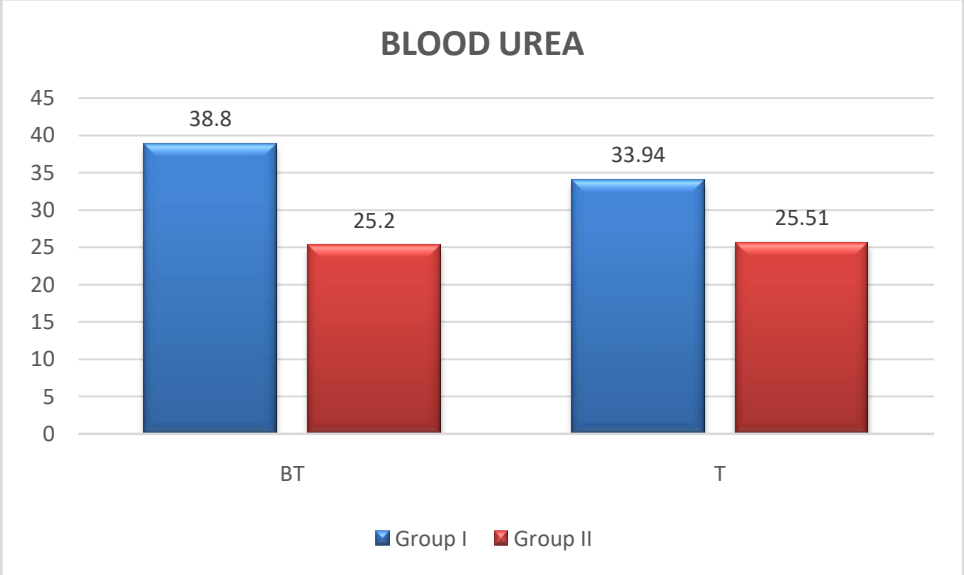
Blood Urea

The data of Blood Urea shows that the initial mean and SD in Group-A was 38.80± 7.40 after 1½ years of treatment it reduced to 33.94 ± 5.60. The improvement was statistically significant (p< 0.001). In Group-B the initial mean and SD was 25.20 ± 10.7, after 1½ years of treatment it reduced to 25.51 ±6.29, the improvement in Blood Urea was statistically not significant (p>0.87). While comparing in different groups the changes in Blood urea BT & AT were statistically highly significant (p<0.001) (See table -32 & fig. 32).

Table 32: Changes in Blood Urea Level in the cases of Pre-diabetes

Group	Urea (Mean ± SD)		Within the group comparison Paired t test (BT-AT)
	BT	AT	
Group I (n=27)	38.80± 7.40	33.94± 5.60	4.85±2.78 t= 9.081 p=0.000
Group II (n=26)	25.20± 10.74	25.51± 6.29	0.30±9.39 t= 0.163 p=0.872
Between the group comparison Unpaired t Test	t= 5.381 p=0.000	t=5.155 p=0.000	

Fig-32: Changes in Blood Urea Level in the cases of Pre-diabetes



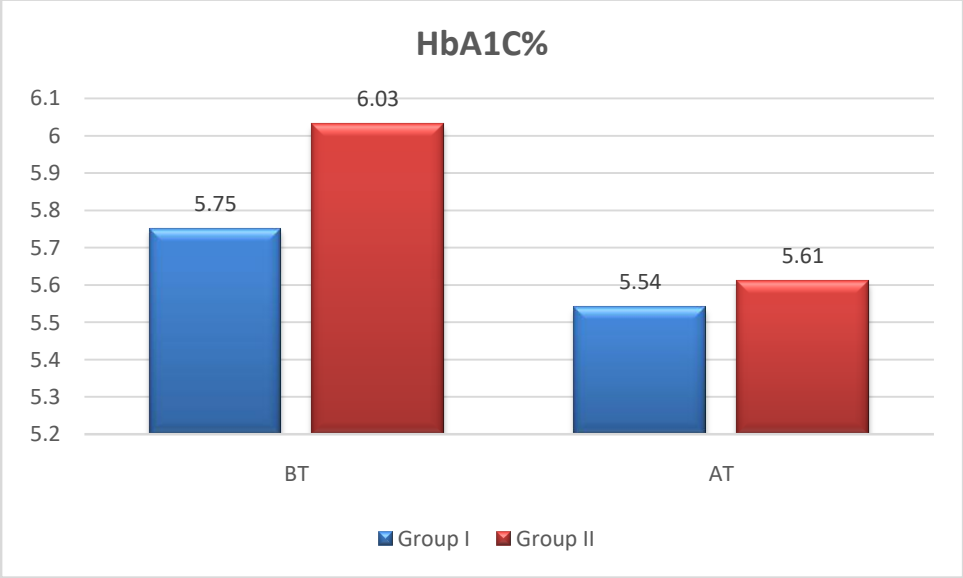
Glycosylated Hb%

The data of HbA1C% shows that the initial mean and SD in Group-A was 5.75± 0.22 after 3 months of trial treatment it reduced to 5.54 ± 0.26. The improvement was statistically highly significant (p< 0.001). In Group-B the initial mean and SD was 6.03 ± 0.46, after 3 months of trial treatment it reduced to 5.61 ±0.46, the improvement in HbA1C%s statistically highly significant (p<0.001). While comparing in different groups the changes in HbA1C BT is significant i.e. (p=0.005) but not significant (P>0.005) in AT. (See table -33 & fig. 33).

Table 33: Changes in HbA1C Level in the cases of Pre-diabetic

Group	HbA1C (Mean ± SD)		Within the group comparison Paired t test (BT-AT)
	BT	AT	
Group I (n=27)	5.75± 0.22	5.54± 0.26	0.20±0.17 t= 6.074 p=0.000
Group II (n=26)	6.03± 0.4608	5.61± 0.4636	0.43±0.30 t= 7.313 p=0.000
Between the group comparison Unpaired t Test	t= 2.945 p=0.005	t=0.649 p=0.519	

Fig-33:Changes in HbA1C Level in the cases of Pre-diabetic



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DISCUSSION

A retrospective analysis of resource material reveals that various references related to Prediabetes relevant are available under broad heading *Prameha* in the *Ayurvedic* classics. *Prameha* is a general term used in the classics for a variety of different metabolic disorders that hampers the ability of the body to process and utilize sugar properly. Medically, this is referred to as an inability of the body to metabolize glucose effectively due to diminished or exhausted Insulin secretion from pancreatic β-cells and Insulin resistance. This results in an abnormally high level of glucose in the blood, called hyperglycaemia.

It is a disorder, which is sparing neither the developing nor the developed nations. Recent prevalence data suggest that Diabetes mellitus is an increasing problem among rural population. (Hwang ck et.al, Diabetes Resl. Pract. 2012; 96(3): 271-85)

Prediabetes is the state in which some but not all of the diagnostic criteria for diabetes are met. It is often described as the "grey area" between normal blood sugar level and diabetic levels. While in this range, patients are at risk for not only developing type II diabetes, but also for cardiovascular complications. It is considered a pre-diabetic state, associated with Insulin resistance and increased risk of cardiovascular pathology, although of lesser risk than impaired glucose tolerance (IGT). IFG sometimes progresses to type II diabetes mellitus. There is a 50% risk over 10 years of progressing to overt diabetes.

The classical *Ayurvedic* literature is elaborately described the disease and discussion regarding aetiology, pathophysiology, symptomatology and the treatment modalities. While describing the pathophysiology of *Prameha*, the *Ayurvedic*texts include *Medas* (Adipose tissue), *Ojas* (Immune power), *Agni* (GI and cellular biofire) and *Ama* i.e. exogenous and endogenous reactive species, which play a major role in Prediabetes diathesis and its progression to Type-2 DM and its related complications. These observations of the ancient *Ayurvedicscholars* appear to be very outstanding regarding the nature of the disease, which strikingly compares with the conventional medical science of today. Because, it is now well known and gradually conceived that Diabetes mellitus results due to the metabolic derangement. Similarly, it is gradually conceived that there is a strong evidence of immune disorder and immunodeficiency in all diabetics and its related complications. *Medas* have strong association with Diabetes mellitus, Metabolic syndrome and obesity, which may lead to a variety of other disorders. *Medas* with or without *Ama* is predicted to play a major role in the Pathophysiology metabolomics of metabolic disorders. Now conventional medicine has yet found a way to bring the cases of Prediabetes & Diabetes mellitus under control upto reasonable extent but the effort is not finally conclusive. Because, conventional modern medicine have lot of hazardous effect on body and even some of them precipitate Diabetes mellitus. That is why search for better & effective medicine from other resources is going on.

The goals of prevention or to delay the onset of type II diabetes, preserving the function of the beta cells, and preventing or delaying the micro & macro vascular complications. Obesity is an extremely important environmental influence, therefore, exercise, weight loss, and drug therapies

have been studied. It has been found that lifestyle modification/ intervention provides the greatest benefit in Prediabetes for preventing the progression into Type - 2 Diabetes mellitus.

The American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) have developed lifestyle intervention guidelines for preventing the onset of type II diabetes:

- Healthy meals (low fat, low sugar, low salt diet)
- Physical exercise (45 minutes of exercise per day, five days a week)
- Reducing weight by as little as 5-10 percent can have a significant impact on overall health.

Persons with Prediabetes actually have the same complications as persons with diabetes. They run the risk of developing diabetic eye disease, nerve damage, and early diabetic kidney disease with excess protein in the urine. Patients with Prediabetes are also thought to already have an increased risk of heart and blood vessel disease.

Intensive weight loss and lifestyle intervention, if sustained, can substantially improve glucose tolerance and prevent progression from IGT to Type-2 diabetes. The Diabetes Prevention Program (DPP)study found a 16% reduction in diabetes risk for every kilogram of weight loss. Reducing weight by 7% through a low-fat diet and performing 150 minutes of exercise a week is the goal. The ADA guidelinesrecommend modest weight loss (5-10% body weight), moderate intensity exercise (30 minutes daily), and smoking cessation.

The progression to Type- 2 Diabetes Mellitus is not inevitable for those with Prediabetes. The progression into diabetes mellitus from Prediabetes is approximately 25% over three to five years.

The *Ayurvedic*texts have given great emphasis on diet and lifestyle modifications along with proper medications. Different management strategies have been outlined in the classics in the form of *Ahara, Vihara* and *Aushadha* according to constitutional profile of the patient and predominance of *Doshas*&*Dushyas.*

Thus, the present study entitled **"A Clinical Evaluation of *Darvyadi GhanaVati* in the cases of Prediabetes under the influence of *Deha Prakriti*"** has been focus on the curative aspect of Prediabetes and preventive aspect of Type-2 Diabetes mellitus.

The present work incorporates studies on *Prameha* vis-a-vis Prediabetes, which has been described under review of literature, apart from this, the present work also imposes on concepts of *Deha Prakriti,* Dietary measures & their relation with Prediabetes. Besides, modern literary review has been also described in detail by incorporating recent publications & reports.

The present work also aimed to evaluate the hypoglycaemic, hypocholesterolemic effect of selected *Ayurvedic*formulation.The special emphasis should be put on predominance of *Deha Prakriti* and its impact on therapeutic response.

The selected *Ayurvedic* formulation *Darvyadi Ghana Vati* it provides better nutrient at the level of *Dhatus*. Because it contains *Amalaki, Haritaki, Vibhitaki* which is mentioned as *Rasayana* drug &*Amalaki* is considered as best one for Prediabetic & Diabetics. Recent evidences also suggest that *Amalaki & Haridra* imports glucose lowering effects in Type-2 Diabetes (Pandey A.K. & Singh R.H.-2003). Besides, it was also considered relevant to evaluate the effect of above remedial measures in the treatment of Prediabetes and also include measurement of *Deha Prakriti* status of the Prediabetics and their influence on trial treatment.

In the present study, 60 Prediabetes patients of both sex and different age groups were selected from the OPD & IPD of *Kayachikitsa*, S.S. Hospital, IMS, BHU, Varanasi fulfilling the inclusion criteria set for this purpose. All the clinically and laboratory diagnosed patients were randomly divided into two groups and following trial therapy was given.

Group A: Control group (ongoing conventional treatment) i.e. Metformin 500 mg OD.

Group B: *Darvyadi Ghana Vati* 500mg BD after meal with lukewarm water.

After the initial registration all the patients were recruited in the respective trial groups and were given the treatment regularly as per schedule as mentioned in the chapter on material and methods. They were advised to come after one month interval for the assessment of therapeutic response in terms of subjective and objective parameters. The total duration of study was 3 months with monthly follow-ups. At each follow up the patient were assessed for blood sugar fasting and postprandial, BMI, lipid profile, blood urea and Sr. creatinine before and after trial treatment. Beside this, influence of *Deha Prakriti* status on therapeutic response was also assessed.

DEMOGRAPHIC PROFILE

The study consisted of 60 patients randomly allocated into two groups. The group A was treated with ongoing treatment (Metformin) and group B with *Darvyadi GhanaVati*. Out of 60 registered cases, 53 cases turned up for full follow-ups, 7 patients were dropped out from the study.

In this series of study, it was found that maximum patients belong to age group of 51-60 years (50%) and 41-50 years (31.6%) followed by age group of 31-40 years (18.3%). Majority of the patient (55%) were male. It does not directly indicate the predominance of disease in males but this may be due to limitation of time and study of a very short population group.In this study, middle age group people are highly affected. Hence, middle age groups people are more prone to Prediabetes because of socio-cultural impact for their survival. This also indicates that chances of Prediabetes gradually increasing with increase of age.

A study of religion reveals that the all patients belonged to Hindu Community (100%). This is again due to Hindu dominant society and study of very less or no population. The occupational study shows that most of the patients belong to House-wives (40%) followed by servicemen (33.4%), Farmer (11.7%), Teacher (8.3%) and Businessmen (6.7%). Housewives may be suffered by this disease due to their disturbed lifestyle, more stressful mental work, lack of exercise and familial conflicts in houses. Incidence of habitat shows that more patients were in rural group (51.7%) as

compare to urban (48.3%). It shows that this disease is not only limited to urban (48.3%), however increased incidence in rural (51.7%) may be due to lack of health awareness and impact of social & cultural changes in the era of globalization. Maximum patients of Prediabetes registered in present study were of middle class group (73.3%) followed by higher income group patients (15%) were almost equal to lower income groups (11.7%). Because middle class people suffer from variety of stressors in life for their survival. Further, this study resembles with the facts of *Sushruta* that this disease does not belongs to only rich persons only, that's why he has also described the management for poor and rich diabetics by adopting independent protocol..

Incidence of educational status fall maximum (25%) in High School followed by graduate, illiterate, intermediate (20%) and postgraduate (15%). It is showing that there is no relation of education with the disease incidence. A study of dietary habits reveals that 66.7% of patients were pure vegetarian while 33.3% were mixed dietary habit. In addiction history, 46 (76.7%) patients had no history of addiction. Some patients having more than one addiction, but the 15% of patients were found with Tobacco addiction, followed by *Pana* addiction (6.7%) and *Surti* (1.7%). The observations confirm that not only dietary habit but other factors such as stressors, life style errors, may also contribute a lot to this disease and other similar metabolic disorders. Tobacco addiction is common in present setting, recent evidences also goes in favour that tobacco & its product interfere in the metabolism of fat and further precipitate the coincident of Prediabetes & Diabetes mellitus.

CONSTITUTIONAL PROFILE

In this study, Seven *Deha Prakriti* (constitution) was analyzed and it was found that maximum number of patients were of *Pittaja* dominant*Prakriti* (53.3%) followed by *Kaphaja* (33.3%) and *Vataja* (13.3%). This shows the incidence of Prediabetes is more common in *Pittaja* followed by *Kaphaja*&*Vataja* type of *Deha Prakriti.* The incidence of *Manasika Prakriti,* in this study, no. of maximum patients was *Rajasika* 68.3%, *Tamasika* 25% and *Sattvik* 6.7%. This indicates that these groups of patients over react to stressful life conditions, which brings changes in the metabolism of carbohydrates, proteins & fats. Such types of persons are more prone to develop Prediabetes & other existing metabolic disorders. Their incidence needs to be confirmed by study on large sample of population.

CLINICAL PROFILE

The majority of the patients were registered with negative family history (81.7%). 18.3% of the total cases had the positive family history of diabetes in their first degree relatives (*BijaDoshaja*). Besides, it was also observed that maximum no. of Prediabetics fall in *Rasa* dominant *Dushya* (61.7%) followed by *Meda* (38.3%).

This indicates that not only familial impact but other factors also kept in mind at the time of describing etiopathogenesis of Prediabetes. This view is very relevant to concepts of *Prameha*/ *Madhumeha* of *Ayurveda* in which *Rasa & Medasa* are considered as an important factors involved in its diathesis.

While studying Body mass index of the patients it was found that most of them were having overweight (54.5%), normal (32%) & moderatly obese (10.1%). This is the strong evidence for the consideration that obesity as a factor for Prediabetes and it warrant us to consider the same at the time of management of Prediabetics.

The present study shows that the duration of illness in patients of Prediabetes, 71.7% had duration of illness 0-6 months, 16.7% were more than 12 months and 11.6% patients were 6-12 months, it indicates that majority of them were diagnosed accidently as Prediabetes. This warrant us to go for estimation of blood sugar level even though they were not complaining of Prediabetes related symptoms.

In this study, Incidence of clinical symptomatology in patients of Prediabetes revealed that the maximum number of patients (71.6%) had Polydipsia followed by, Laziness (70%), Excessive sleep(60%), Polyurea (58.4%), Numbness(56.7%), Excessive sweating(55%), Burning sensation (45%), Polyphagia(41.7%) and Flabbiness(35.4%). This reveal that the clinical features of Prediabetes described in *Ayurveda* are very scientific & comparable to the latest knowledge in this field that presentation of Prediabetes is atypical and required laboratorial estimation of blood sugar for its early detection.

In this way, we can early diagnose & prevent its progression to type-2 Diabetes mellitus & minimize their economic burden & incidence of other ailments.

THERAPEUTIC PROFILE

Besides this, 7 patients dropped out from the study due to some reason viz Family problem, lack of conviction to *Ayurvedic* treatment, transferable job and medical emergencies etc.

Within the group comparison (Friedman test) in Group-A (Metformin treated), initially Polydipsia was not observed in 10 patients rest 17 patients were in grade 1 & grade 2 finally all 17 patients were converted into grade 0 while in Group-B (*Ayurvedic formulation*) initially Polydipsia was in grade 0 in 8 patients rest 18 patients were in grade 1 & 2, after treatment 10 patients were converted into grade 0 & rest 8 patients were remain in grade 1.

In Group-A, initially Numbness was not present in 13 patients rest 14 patients were in grade 1 & 2 after treatment converted into grade 0 in all 14 patients while in Group-B Numbness was absent in 14 patients and in 12 patients in grade 1 & 2, after treatment which get converted into grade 0 in 10 patients rest 2 remained in grade 1.

In Group-A, initially Burning sensation was not present in 15 patients rest 12 patients were in grade 1 & 2 after treatment converted into grade 0 in all 12 patients while in Group-B Burning sensation was absent in 14 patients and in 12 patients in grade 1 & 2, after treatment which get converted into grade 0 in 6 patients rest 7 remained in grade 1 & 1 in grade 2.

In Group-A, initially Excessive sweating was not present in 15 patients rest 12 patients were in grade 1 & 2 after treatment converted into grade 0 in all 12 patients while in Group-B Excessive

sweating was absent in 8 patients and in 18 patients in grade 1, 2 & 3, after treatment which get converted into grade 0 in 13 patients rest 5 remained in grade 1.

In Group-A, initially laziness was not present in 9 patients rest 18 patients were in grade 1 & 2 after treatment converted into grade 0 in all 18 patients while in Group-B Laziness was absent in 8 patients and in 18 patients in grade 1 & 2, after treatment which get converted into grade 0 in 14 patients rest 4 remained in grade 1.

In Group-A, initially Excessive sleep was not present in 10 patients rest 17 patients were in grade 1 & 2 after treatment converted into grade 0 in all 17 patients while in Group-B Excessive sleep was absent in 11 patients and in 15 patients in grade 1 & 2, after treatment which get converted into grade 0 in 14 patients rest 1 remained in grade 1.

In Group-A, initially Flabbiness was not present in 10 patients rest 17 patients were in grade 1 & 2 after treatment converted into grade 0 in all 17 patients while in Group-B Flabbiness was absent in 7 patients and in 19 patients in grade 1, 2 & 3, after treatment which get converted into grade 0 in 15 patients rest 3 remained in grade 1 & 1 in grade 2.

In Group-A, initially Polyurea was not present in 14 patients rest 13 patients were in grade 1 & 2 after treatment converted into grade 0 in all 13 patients while in Group-B Polyurea was absent in 7 patients and in 19 patients in grade 1, 2 & 3, after treatment which get converted into grade 0 in 15 patients rest 3 remained in grade 1 & 1 in grade 2.

In Group-A, initially Polyphagia was not present in 17 patients rest 10 patients were in grade 1 & 2 after treatment converted into grade 0 in all 10 patients while in Group-B Polyphagia was absent in 17 patients and in 9 patients in grade 1 & 2, after treatment which get converted into grade 0 in 8 patients rest 1 remained in grade 1.

During the successive follow ups clinically it was observed that patients of Group-B (*Ayurveda* treated) showed improvements better in most of the symptoms except burning sensation, excessive sweating & Laziness, while modern treated (Group-A) patients responded better for these symptoms. This indicates that *Ayurvedic* drug has potency to convert the associated clinical symptoms of Prediabetes, which is comparable to the parallel control group.

Between the group comparisons (χ^2test), it was found that there was insignificant improvement in all the clinical symptoms in 3rd follow up except Burning sensation (p=0.002), Excessive sweating (p=0.017) and Laziness (p=0.034).

The BMI changes in all groups were statistically highly significant (P<0.001) while mean difference is more in Group-A.

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LABORATORY PROFILE

The drug treatment response was assessed in terms of blood sugar, fasting & Postprandial, HbA1C%, Sr. Cholesterol, Triglyceride, Urea and Sr. Creatinine were assessed to find out safety profile of trial drug.

Fasting Blood Sugar (FBS):

In this series the mean reduction in fasting bloodsugar was found to be statistically significant in both groups. The absolute mean changes in fasting blood sugar was 17.18 ± 8.93 ($P < 0.001$) in group-A & 15.11 ± 11.81 ($P < 0.001$) in group-B.

Between the group comparisons (Unpaired t test), before treatment and after treatment, It was observed that the changes in FBS were statistically not significant ($p>0.05$). This indicates that both the groups responded equally in terms of correction of FBS, but on the basis of mean changes, group A responded well up to the last follow ups.

Postprandial Blood Sugar (PPBS):

The mean reduction in PP blood sugar in both groups patients was found statistically highly significant. The absolute fall in PP blood sugar in terms of mean changes was 34.58 ± 12.39 ($P < 0.001$) in group-A and 27.38 ± 21.66 ($P < 0.001$) in group-B.

Between the group comparisons (Unpaired t test) after trial treatment the changes in PPBS were statistically not significant ($p>0.05$. This reflects that *Ayurveda* treated group & modern treated group equally responded well.

Mean Percentage Fall in FBS & PPBS:

The Control group A Prediabetic patients have showed slightly better percentage of fall in fasting blood sugar level (15.23%), in comparison to*Ayurvedic* formulation group B (12.90%) andthe percentage of fall in postprandial blood sugar level in Control group was (18.89%) followed by *Ayurvedic*formulation (18.59%). This is happened due to prompt action of modern hypoglycemic drug and show action of *Ayurvedic* formulation.

HbA1C%:

In the present study HbA1C% level of patients showed highly significant result ($p=0.000$) in both groups A& B. While in between the group comparison(Unpaired t test), the changes were not significant. Although the mean changes in HbA1C% is minimal in modern treated (Group A) and is slightly greater in *Ayurvedic* treated group (Group-B). It shows response of drug in terms of long term glycemic control. Hence, it can be used as an adjuvant with ongoing modern drug i.e. Metformin.

Serum Cholesterol:

In the present study the serum cholesterol level of patients in group A showed highly significant result (P < 0.000). While in group-B, the changes were statistically not significant (P >0.05). On intergroup comparison (Unpaired t test), it was observed that Sr. Cholesterol has significant change before trial treatment & insignificant changes after treatment. Probably this due to quicker action of Metformin, which is also correct & mobilize serum cholesterol from circulation.

Serum Triglyceride:

In the present study the serum triglyceride level of patients showed highly significant changes in group A (P =0.000). But the patients of Group B showed no statistically significant reduction in Sr. TG. On intergroup comparison, it was observed that Sr. TG has no significant changes before & after treatment.

Safety Profile :

Within the group and intergroup comparison, it was found that the changes in blood serum creatinine was highly significant (P = 0.000) in Group- A. While in group-B the changes were statistically not significant (P>0.05). On intergroup comparison, it was observed that serum creatinine showed significant reduction.

However, during the trial Blood Urea & Sr. Creatinine levels are within the normal range before treatment & after treatment. Sr. Bilirubin was also assessed and found that this was within normal range. Besides this, no significant changes were observed in case of ECG, CBC & Urine test before & after trail treatment. Suggesting that selected *Ayurvedic*drug& Metformin were safe as regards to renal function, liver function & cardiac function.

Factors influencing Therapeutic response :

The impact of *Deha Prakriti* were studied in both the groups of Prediabetics to assess the FBS, PPBS, HbA1C%, Sr. Cholesterol & Sr. Triglyceride before and after trial treatment. The results revealed significant decrease in fasting blood sugar all three sets of dominating *Prakritis* but the mean difference is more in *Vata Prakriti* patients after that *Kapha* dominant *Prakriti* in Group A. In Group B, the result is highly significant (0.000) only in *Pitta Prakriti*.

In Group A, postprandial blood sugar shows highly significant (0.000) changes in all three types of *Prakriti*, but on the basis of mean changes more response is observed in *Pitta Prakriti* (35.99) followed by *Kapha Prakriti* (34.86). In Group B, the effect is highly significant in *Pitta Prakriti*& significant in *KaphaPrakriti.* This observation suggest that *Pitta, Kapha Prakriti* patients have relatively greater degree of treatment response in blood sugar i.e. FBS & PPBS in relation to *Ayurveda* treated group. However modern drug treated patients shows significant FBS fall in *Vata*&*PittaPrakriti* patients & PPBS for *Pitta* dominant *Prakriti* patients followed by *Kapha* dominant *Prakriti*(0.000)patients.

The effort were made to evaluate the HbA1C% in both the trial groups on the basis of dominant sets of *Deha Prakriti.* It was observed that patients of *KaphaPrakriti* followed by *Pitta Prakriti* had shown significant reduction in HbA1C% ($p<0.05$) in group A, while patients in group B had shown highly significant reduction ($p=0.000$) in both *Kapha*&*Pitta* types of *Prakritis*.

In Group A, Sr. Cholesterol level had significant changes in all three sets of *Prakriti* but on the basis of mean changes (26.68) response goes in favour of *Kapha Prakriti*. In Group B, there is no significant changes in patients of all three *Prakriti*.

Triglyceride level had highly significant changes in patients of *Vata* & *Kapha Prakriti,* ($p<0.000$)Group A. In Group B, there was no significant changes in all three *Prakriti.*

The intergroup comparison (One way Anova) between these sets of *Prakritis* were found statistically insignificant for FBS, PPBS, Sr.Triglyceride, Sr. Cholesterol & HbA1C%.

This indicates that patients of *Vatika* type of personality are more prone to develop Type-2 DM & its related complication in near future and warrant to add some other drug for the management of *Vatika* type of Prediabetes.

Mode of action of Metformin:

Metformin has been the mainstay of therapy for diabetes mellitus for many years; however, the mechanistic aspects of metformin action remained ill-defined. Recent advances revealed that this drug, in addition to its glucose-lowering action, might be promising for specifically targeting metabolic differences between normal and abnormal metabolic signaling. The knowledge gained from dissecting the principal mechanisms by which metformin works can help us to develop novel treatments. The center of metformin's mechanism of action is the alteration of the energy metabolism of the cell. Metformin exerts its prevailing, glucose-lowering effect by inhibiting hepatic gluconeogenesis and opposing the action of glucagon.

The inhibition of mitochondrial complex I results in defective cAMP and protein kinase A signaling in response to glucagon. Stimulation of 5′-AMP-activated protein kinase, although dispensable for the glucose-lowering effect of metformin, confers insulin sensitivity, mainly by modulating lipid metabolism.

Recent observations suggest that metformin can impair oxidative phosphorylation by inhibiting mitochondrial phosphorylation complex 1. Although some have reported that very high metformin concentrations can suppress total cellular ATP levels, more subtle changes in the free ATP/ADP ratio might occur with concentrations of metformin that do not suppress total ATP, but do inhibit gluconeogenesis.

It is believed that metformin-mediated inhibition of hepatic glucose production (HGP) plays a major role in its glucose-lowering efficacy. Here, we determined that both metformin able to inhibit cumulative glucose production in primary cultured hepatocytes stimulated with glucagon.

AMPK activation is implicated as a mechanism for stimulation of glucose uptake in skeletal muscle, we assessed the effect of metformin on glucose uptake and AMPK activity in muscles. Incubation of isolated muscles with metformin resulted in an increase in the activity of both catalytic subunits of AMPK. This was coincident with a significant increase in glucose uptake that was also observed to be additive with the effect of insulin stimulation.[1]

Probable Mode of Action of *Darvyadi Ghana Vati* in Prediabetes

Darvyadi Ghana Vati is a promising herbal drug formulation, mentioned in *Charaka Samhita* for the management of *Prameha/ Madhumeha.* This formulation comprises of six herbal drugs as described below, which have pharmacological capacity to alter basic diathesis of *Prameha,* relieves the clinical symptoms and maintain the blood sugar level without any unwanted and adverse effects.

Based on the Pharmacological action

Properties of contents of *Darvyadi Ghana Vati*

S.No.	**Ingredients**	***Rasa***	***Guna***	***Virya***	***Vipaka***	***Doshakarma***
1.	*Amalaki*	*Pancharasa(except lavan),Amla pradhan*	*Guru, Ruksha, Shita*	*Shita*	*Madhur*	*TriDoshahar*
2.	*Haritaki*	*Pancharasa(except lavana), kashayapradhan*	*Laghu, Ruksha*	*Ushna*	*Madhura*	*VPK shamak*
3.	*Vibhitaki*	*kashaya*	*Laghu, Ruksha*	*Ushna*	*Madhura*	*TriDoshagna*
4.	*Devdaru*	*Tikta*	*Laghu, Snigdha*	*Ushna*	*Katu*	*KV shamaka*
5.	*Daruharidra*	*Kashaya,Tikta*	*Laghu, Ruksha*	*Ushna*	*Katu*	*KP shamak*
6.	*Nagarmotha*	*Tikta, Katu, Kashaya*	*Ruksha, Laghu*	*Shita*	*Katu*	*KP shamak*

1. Study of *Rasa* in combination

Rasa	**No. of Drugs**	**%**
Madhura	3/6	50.0
Amla	2/6	33.3
Lavana	0/6	0.0
Katu	3/6	50.0
Tikta	5/6	83.3
Kashaya	5/6	83.3

2. Study of *Guna* in combination

Guna	**No. of Drugs**	**%**
Laghu	5/6	83.3
Ruksha	5/6	83.3
Guru	1/6	16.7
Snigdha	1/6	16.7
Shita	1/6	16.7

3. Study of *Virya* in combination

Virya	**No. of drugs**	**%**
Ushna	4/6	66.7
Shita	2/6	33.3

4. Study of *Vipaka* in combination

Vipaka	**No. of Drugs**	**%**
Madhura	3/6	50.0
Katu	3/6	50.0

5. Study of *Karma* in combination

Karma	**No. of Drugs**	**%**
Pramehghna	3/6	50.0
Rasayana	2/6	33.3

Lekhan	1/6	16.7
Aampachak	1/6	16.7
Balya	4/6	66.7
Shothaghna	3/6	50.0

6. Study of *Doshaghnta* in combination

Dosha	**No. of drugs**	**%**
KV	1/6	16.7
KP	2/6	33.3
VPK	3/6	50.0

On the basis of *Ayurvedic* pharmacological properties of *Darvyadi Ghana Vati* probable *sampraptivighatana* can be understood as follows,

(1) PROBABLE ACTION ON *DOSHA*

*Prameha*is a *tridoshaj vyadhi* while *Kapha Dosha* is the main culprits. The combination shows main action against *Kapha Dosha*s by virtue of its *virya* (about 66.7% of total drugs have an *Ushna virya*. It also exhibits *tridosha shamaka prabhava*. After seeing *doshagnata* percentage, it is prove that the combination acts against *Tridoshas*.

(2) PROBABLE ACTION ON *DUSHYA*

From the *samprapti* of *Prameha*it is clear that the main *dushya* involved is *rasa, meda dhatu*. The combination shows, about 90% of total drugs have a *Katu & Kashaya rasa*. *Katu rasa* improves the jaliyansha and made first *dhatu* in proper form, so the combination will act on the *rasa dhatu*. After seeing karmas percentage, it is clear that the yoga has a *balya*(66.7%), *Pramehghna , Shothaghna*(50%),&*Rasayana(33.3).* It is prove that the *Vati* will act on the *Rasa dhatu*.

(3) PROBABLE ACTION ON *SROTAS*

The disease mainly exhibits *Atipravritti*&*Sanga* type of *Srotodushti.* The combination by the virtue of *Aampachak & Lekhan* property and also by the virtue of *Rukshaguna* (about 83.3% of total drugs) does *Srotomukh vishodhana* and relieves *Sanga*. By *Ushnavirya* (about 66.7% of total drugs) the yoga will act on *Atipravritti* and clean the *Srotasa.*

(4) PROBABLE ACTION ON *AMA*

An *Ama* means unripe and undigested *Annarasa*. It needs proper *Paka.* By the virtue of *Ushna virya* (66.7% of total drugs) and *Dipana-pachana* property, *Amapachana*will take place. This *Ampachana* causes *Strotomukh vishodhana. Devdaru* act as*Amapachaka*.

(5) PROBABLE ACTION ON *RUPA*

All the drugs used in *Darvyadi Ghana Vati* work on the disease *Prameha*collectively as well as separately. *Devdaru* is *Amapachaka,* so relieve *guruta, Haritaki, Amalaki &Devdaru is Pramehghan* so relieve I maximum symptoms like Polydipsia, Polyphagia, Polypepsia. *Haritaki*&*Amalaki* is *Rasayana*, so it controls the further damage of cells and also free radicals. So it seems that the formulation not only acts on symptoms of the disease, but also checks its progression by hitting the basic pathological process. *Haritaki, Amalaki*, *Vibhitaki & Nagarmotha* are *Balya* so help in *Daurbalya.*

The Present study reveals that Prediabetes was well conceived in *Ayurvedic* lexicons in the context of *Prameha*. In *Ayurveda, Vyadhi Kriyakala* described by *Sushruta* gives an idea about the consecutive stages of the disease and accordingly preventive measures can be contemplated to overcome complications. Early diagnosis of disease helps to cure the disease successfully without its progression. *Sthanasamshraya* stage of *Kriyakala* represents *Purvarupa,* which indicates the forthcoming disease. So, prescription of medications in the form of *Ahara, Vihara*&*Aushadh* in *Purvarupa* stage is more important for preventing the disease process to its successive stages. In this perspective patients having Prediabetic condition who are more prone to develop Diabetes in near future, were registered for the present clinical study.

In this study, the selected *Ayurvedic*formulation not only have encouraging results in terms of metabolic correction but also seems to be helpful to improve wellbeing in Prediabetic along with preventing long term complication by decreasing HbA1C%.. Besides, this studies also reveal that it not only normalize the blood sugar and also cut off its progression to DM. Thus, this approach of *Ayurvedic* classics have significant preventive & curative role in Prediabets and Type-2 DM respectively. The leads available from this work open new *Ayurveda*-inspired holistic approach to the management of Prediabetes & prevention of occurrence of Type-2 Diabetes Mellitus. Besides, it also has a potential to improve immune status & metabolic correction in Prediabetics. *Ayurveda* strongly believes that individuals *Prakriti* play a greater role in diathesis as well as management of disease. In this context we have tried lay down emphasis in relation to FBS, PPBS & HbA1C% and found that ancient age & idea is quite relevant, while planning the management of disease. Because response drug and measures are varied from person to person, either it is originated from green resource or red resource.Further studies on this line are suggested.

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