Association of Predisposing Factors of Diabetes with six Stages of Disease Progression in Ayurveda (*Shatkriyakala*): A Cross-Sectional Pilot Study

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Abstract: Introduction: Diabetes has emerged as a global health crisis. It not only causes morbidity and mortality figures but deteriorates quality of life, national productivity and economic burden too. Besides this, no major advancement has been made for early diagnosis and prevention of diabetes. Clinical Staging of morbidity has been depicted in classical texts of Ayurveda modelled on pathogenesis.) This type of classification can serve as the basis of levelled and precise preventive interventions. Thus, identification of cases pertaining to each stage of pathogenesis based on validated parameters is a prerequisite. This research is a preliminary work on validation of clinical staging. This Ayurveda system of staging method can serve as a holistic model of prevention as it includes variable responsible host factors, etiology, risk factor stratification and grading of pathological state.

Aim: The present study aimed to explore the six stage pathogonomic model SKK (*Shat kriyakala* and its relevance in tracking pathogenesis at preclinical stages.

Materials and methods: A cross-sectional trial was conducted in forty- two subjects. Study participants were subjected to a questionnaire (Q2) to assess clinical features in latent and clinical stages of *Prameha* (~ Diabetes Mellitus) and biomarkers (CRP and Serum cortisol).Result: The mean score of SKK questionnaire was found maximum with the corresponding stages designed on the basis of predisposing factors and laboratory parameters.Conclusion: It can be inferred from the study that SKK may act as a tool to check pathogenesis at an early stage. The model may act as a potential paradigm for preventing diabetes risk as well as preventive care from a public health perspective.

Keywords: *Prameha*, *Shatkriyakala*, Pathogenomic, preventive strategy, biomarker, diabetes, risk

1. INTRODUCTION

Type 2 Diabetes mellitus is a metabolic disorder withincreasing global prevalence in the coming decades due to rising incidence of overweight and obesity.[1] Its global prevalence rate in 2019 is estimated to be 9.3%.[2]As per International Diabetes Federation (IDF) India has 77 million people living with diabetes (2nd most affected country)and estimated to be at top position by 2045.[3]In addition to overt diabetes, 352 million adults with impaired glucose tolerance are also at high risk of developing Diabetes worldwide.[4]In the earlier years this morbidity was considered to be affectingprimarily the middle aged and elderly. Recently, its increasing incidence is also observed in young adults.Shifting of the disease to young age group has raised the concern regarding earlier development of complicationas they are more exposed.[5]Despite the current existing burdens worldwide,very little advancements have been made in the matter of prevention and management.Delay in diagnosis of DM increases the cost of

management and worsens the prognosis.Classical texts in Ayurveda explain*Prameha*as a syndrome including clinical conditions associated with obesity, prediabetes, diabetes mellitus and metabolic syndrome. Ayurveda recognizes six stage models for progression of disease as*Shatkriyakala* (SKK).[6]*Kriya kala* (KK) is a temporal expression of events, where *Kriya*refers to the treatment plan with the objective of rectifying the disturbance in *Doshas*. *Kala* refers to the stages of progression of a disease.KKdenotes the detection of stage of disease, its progression. From the point of initiation of disease toits manifestation and even considering the stage of complication, each can be recognized by the care-givers. Its utility lies in adoption of measure according to each stage , thus the disparity in *Doshas* (bodily humors) and *Dushyas* (body tissues) can be dealt. [7]SKK provides the minute pathological changes manifested as a result of amalgamation of Doha and dushyas .Thisunique interpretation of the pathogenesis of a disease based on six stages including *Sanchaya*(accumulation), *Prakopa*(aggravation), *Prasara* (of spreading), *Sthanasamshraya* (localizationof*dosha* and interaction with body tissues), *Vyakti* (manifestation of disease) and *Bheda* (complication) which is comparable to natural history of disease in modern science including pre-pathogenesis and pathogenesis stages.

The pathological model of SKK can be utilized in four types of preventive strategies thus improving health status and lessening the burden due to NCDs. Various studies reported the role of lifestyle interventions in prevention of diabetes and reduction of relative risk to 40%-70% in pre-diabetics also.[8-12]Da Qing Diabetes Prevention Study (CDQDPS) documented that there is a 90% higher cumulative incidence of diabetes among subjects with Impaired glucose toleranceas compared to the control group.[9]Another similar study, Diabetes Prevention Program (DPP) Outcome Study has reported11% occurrence of diabetes in control group.[13]Overweight and obesity are reported with increased the risk of T2DM. [14-16]Dyslipidemia is identified as a major risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease. [17]The prevalence of dyslipidemia has been reported as 39.9%, 46.8%, and 59.3% in normal, prediabetes, and T2DM subjects respectively.[17-18]In above background the present study was planned to investigate for an instrument to check early pathogenesis in diabetes.The risk factors and the susceptible groups targeted were: the susceptible prediabetic, overweight, dyslipidemic and population having positive family history consuming etiological factors (diet and lifestyle). As the predisposing factors are modifiable by lifestyle changes and intervention, hence timely observations & effective change in life style and dietary habits or early intervention may help to arrest pathogenesis at early stage. The translation of the principles of Ayurveda can play a key role in formulating the public health stratagem.

2. MATERIAL AND METHODS

2.1. Study centre and population

The study was performed at Government Ayurvedic medical college,Delhi ,after ethical clearance(IEC No-IEC-AIIA/2019-PG-134) and clinical trial registry (CTRI NO- CTRI/2020/03/023795).The subjects visiting OPD and IPD of Government Ayurvedic Medical College,Delhi fulfilling the inclusion criteria of six stages of disease progression (SKK) were included in the study. The study was conducted from 15, October 2020 to 15 february,2021.

2.2 Study design

It was a cross-sectional pilot trial.The initial screening was done by Questionnaire 1 which was a validated proforma of CCRAS(Central council for research in Ayurvedic medicine)based on *santarpanajanya nidanas* (etiological factors) of diabetes.[19] An informed consent was taken from the Participantsscoring more than 10. They were further assessed on the basis of objective criteria (anthropometric measurements of weight, height, basal metabolic index (bmi) and laboratory parameters) based on risk factors associated with diabetesandgrouped in 6 stages as per inclusive criteria of each stage (Table 1).Those met inclusion criteriawere then assessed for clinical features (Questionnaire 2)and biomarkers (CRP and S. cortisol) to track the pathogenesis in break up model of Diabetes.42 subjects were enrolled in 6 groups (7 in each group) in the study.

2.3. Criteria for staging based on risk factors

Diabetes risk score based on variable like age, ethnicity, fasting glucose, cholesterol, BMI (body mass index), screening history, dietary and lifestyle factors,is shown to have better predictive value than either

IGTor IFG.[20-21]Hence these variable were chosen for designing the staging in consonance to the principle of SKK model relevant to *Prameha*, with increasing disposition at each further stage towards diabetes.

Stage 1, [*Sanchaya* - corresponding to the first stage of disease progressionwith initiation of exposure to risk factors] included healthy subjects without diabetes family history having normal BMI and laboratory parameters but indulging in consumption of*nidana*(etiological factors) of *prameha*(Nidana score ≥10). Stage 2, [*Prakopa* - characterized by continued indulgence in risk factors with features of *Kaphaprakopa*(obesity)], included overweight (BMI 25-29) subjects with positive family history havingnormal laboratory parameters andconsuming etiological factors of *Prameha*.Stage 3,[*Prasara* - corresponding to the movement of *kapha* and *abaddhameda*(fat metabolites) in *rakta*(blood circulation) in addition to stage 2 features], included obese subjects (BMI≥30) with positive family history,consuming etiological factors of *prameha* (Nidana score>10) and having lipid derangements. Stage 4[*Stanasamshraya* - manifesting with the prodromal symptoms of the disease *prameha*in addition to stage 3 features],includedobese subjects consuming *nidana* of *prameha*with positive family history,dyslipidemia categorized as prediabetics.Stage 5 [*Vyakti* – the stage of disease manifestation with clinical features] included patients (BMI>25) having diabetes from 1-5 years and FBS,PPBSandHbA1c level as given in table1.Stage 6 [*Bheda* – the stage of chronicity of disease or complications]included patients (BMI ≥25) having diabetes from more than 10 years and other parameters as in table 1.

Table 1: Criteria designed for staging based on laboratory and anthropometric parameters

Stage	BMI (Kg/m^2)	FBS (mg/dl)	PPBS (mg/dl)	HbA1c	Serum Cholesterol	Serum Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
1	<25	<100	<140	4-5.6%	<200	<150	≥60	<100
2	25-29.9	<100	<140	4-5.6%	<200	<150	≥60	<100
3	≥30	<100	<140	4-5.6%	≥200	≥150	<60	≥100
4	>25	100 -125	140-199	5.7%-6.4%	≥200	≥150	<60	≥100
5	>25	≥126	≥200	≥6.5 %	≥200	≥150	<60	≥100
6	>25	≥300	≥400	> 9%	≥200	≥150	<60	≥100

2.4. Sample size calculation:

Since no such study was done in past, therefore this was attempted as pilot and no sample size calculation could be done.

2.5. Sampling Method and Group Allocation:

Convenience Sampling was adopted to screen the subjects and those fulfilling the staging criteria as per the design were allocated to the respective groups till the desired number was attained in each group.

2.6. Data collection

2.6.1. Tool for data collection

A developed, validated and pretested interview schedule Questionnaire having open and close ended questions (Questionnaire 1) was used for screening on the basis of etiological factor consumption. Questionnaire 2 meants for the assessment of stages of shatkriyakala was developed and validated. The concept of *Shatkriyakala*, Nidana of Prameha, Poorvarupa, Rupa and *Upadrava* (and knowledge of contemporary medical science were used to develop the break up model of shatkriyakala of *Prameha* along with the inputs of experts. The developed questionnaire was then send to clinical experts for validation. Their inputs were recorded and incorporated. The statistical analysis for validation was done with the application of Cronbach's Alpha (CA) and ICVI (Item Content Validity Index) test.

2.6.2 Data collection procedure

To reduce bias, all interviews were conducted by a single investigator. Questionnaires 1 and 2 were administered by face to face interviews adopting WHO'Sstepwise approach for non-communicable disease surveillance.[22-23]

Step 1 : Demographic and behavioral data

In this step, risk factors were collected through face to face interview through Questionnaire 1.Each of them were inquired for age, sex, marital status, educational status, occupation type, dietary habits, physical activity, family history for diabetes, digestive power and addictions.

Step 2 : Physical measurements

Variables like weight, height,waist circumference and body mass index (BMI) were measured. A portable weight and height scale was used to measure weight and height of participants in standing position on flat surface.BMI 18.5-24.9 Kg/m^2 was considered as normal and 25 -29.9 Kg/m^2 as overweight and $\geq$30 Kg/m^2asobese.

Step 3: Biochemical measurements

Investigations of patients were done for screening purpose for which fasting blood sample was collected as per good clinical laboratory practices. Investigations FBS (fasting blood sugar),PPBS (Post prandial blood sugar),HbA1c (Glycated hemoglobin), LFT (Liver functional test), KFT (kidney function test), TSH (Thyroid stimulating hormone) were done for screening and those fulfilling the screening criteria were further tested for biochemical markers of serum cortisol and CRP (C-reactive protein). Dyslipidemiaand diabetes were diagnosed on the basis of American Diabetes Association and American Heart Asssociation criteria classification.[24-25]

Collected information covered socio-demographic information, dietary habits, anthropometric parameters, *agni* assessment, *prakriti* assessment and clinical features of the participants. The data thus captured was then entered in excel spreadsheet for statistical analysis.

2.7.Data analysis

The data entry spreadsheet was identified with unique UHID number to identify the participant.

SPSS version 26 was used for data analysis. Every analysis was performed on observed data The means of variables presented were compared using ANOVA (analysis of variance) test to show variability between groups. Correlation was calculated using disease progression stages from *sanchyavastha* to *Bhedavastha*as 1-6.

3. RESULTS

3.1 Socioanthropological variables

The mean age of participants was 36.7(S.D =10.4).Among them64% were males and 36% were females.56% were having education level above graduation. No participant was with missing data.Their socio- demographic variables are described in Table 2.

Table 3: Socio-demographic characteristics of participants

Variables	Frequency	Percentage
Sex		
Male	27	64.3
Female	15	35.7
Age group(years)		
20-30	12	28.6
31-40	9	21.4
>40	21	50
Level of Education		
Illiterate	5	11.9
High school	6	14.2
Intermediate	8	19
Graduate and above	23	54.7
Occupation		
Unemployed	2	4.7
Laborer	5	11.9
Government Job	8	19

Private Job	27	64.2
Socio-economic status		
Poor	15	35.7
Middle	15	35.7
Rich	12	28.6
Family history		
Positive	35	83.3
Negative	7	16.7

3.2 Behavioral characteristics

About 23.8% of the total participants were found consuming frequent alcohol. 69% of them were having sedentary life style and 80.9% were having disturbed sleep. Other behavioral characteristics of study participants are presented in Table 3.

Variables	Frequency	Percentage
Addiction		
Alcohol consumption	9	23.8
Tobacco chewing/smoking	6	14.3
Coffee	17	40.5
Prakriti		
Kapha-pitta	19	45.3
Kapha-vata	7	16.7
Pitta-kapha	7	16.7
Vata-kapha	9	21.4
Physical activity		
Sedentary	29	69
Moderate	8	19
Vigorous	5	11.9
Sleep		
Normal	8	19
Abnormal	34	80.9
<6 hrs	10	23.8
>8 hrs	24	57.1
Dietary habits		
Vegetarian	22	52.4
Mixed	20	46.7
Urination		
Normal (800-2000 ml/24 hours)	30	71.4
Abnormal(> 2000 ml. or less than 800ml/24 hours)	12	28.6
Digestive power		
Sama (normal)	12	28.6
Visama (irregular)	10	23.8
Manda (slow)	18	42.9
Tikshna (increase)	2	4.8

3.3. Outcome data (Assessment of clinical features and biomarkers)

3.3.1.Mean score of SKK in six designed stages

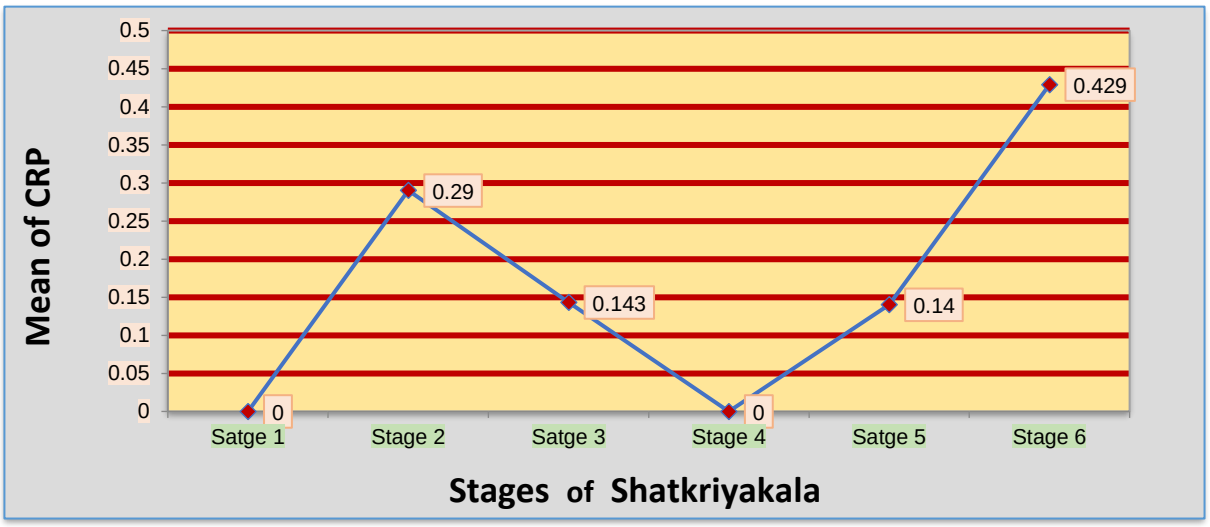
It was observed that the mean score for S1 was found highest in stage1, S2 showed maximum value in stage 2.The mean score of S3 was maximum in stage 3 and that of S4 was found to be highest among 1-4 stages in

stage 4 that was *Sthanasamshrayavastha*. Stage 5 and 6 were showing the highest value in S4respectively,as 73 and 81. (Table 4)

Stages of Kriayakala	Mean score of stages designated as per hypothesized criteria					
SKK-Q2	Stage1	Stage2	Stage 3	Stage 4	Stage 5	Stage 6
S1 (A1-A8)	50	22	18	35	28	31
S2 (A9-A19)	16	36	27	17	9	12
S3 (A20-A29)	12	13	43	10	15	17
S4(A30-A49)	20	29	30	61	73	81

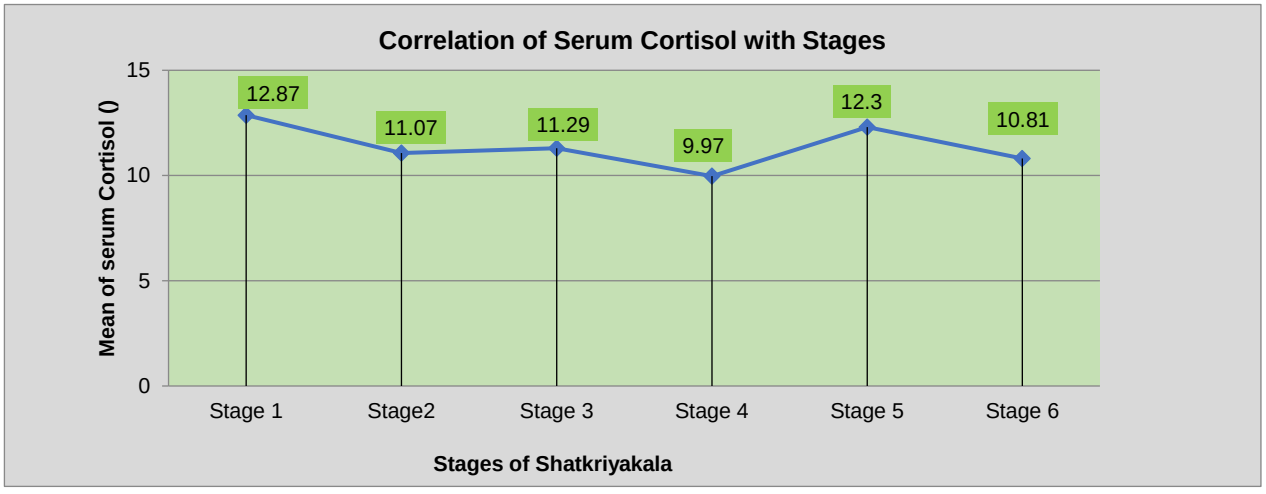
3.3.2. The correlation of CRP with stages (Graph 1)

A continuous increase in CRP (qualitative- slide/tube agglutination method) was observed from stage 4-6. However, no such trend was seen in initial 3 stages.



3.3.3.Correlation of S.Cortisol with stages (Graph 2)

No significant correlation of S. cortisol with stages was observed. The investigation revealed normal ranges of S.cortisol in each stage. However, some variation within the normal range was observed, it was maximum in *Sanchyavastha* followed by *Vyaktavastha* and least in *Sthanasamshryavastha*.



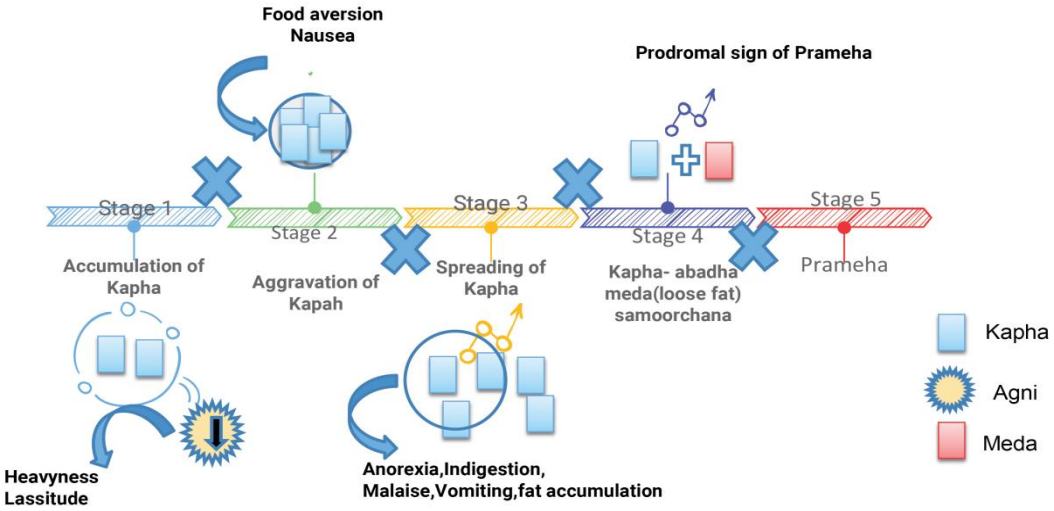
4. DISCUSSION

4.1.Significance of clinical features and biomarkers : Validating SKK pathological model

The clinical features of first four stages of SKK showed significant correlation with the disease progression staging as per staging criteria. Previous studies suggested that C-Reactive Protein is associated with the pathogenesis of diabetes.[26-27]Also in present study, continuous rise in CRP level was observed from Stage 4-6 which are disease progression stages (from pre-diabetics to complication), hence, may act as biomarker. Although trend noticed in first 3 stages was not clear. Moreover, more confirmatory results could have been achieved if same individuals would have been followed for inferential observations. On the basis of some previous studies, it was expected that S.cortisol level would show a continuous increasing trend.[28-29]But, the investigation revealed normal range for the same. However, some variation within the normal range was observed, which was statistically not significant. Though certain studies also revealed contrary finding consistent to the present observations.[30-31]Above observations are supported by classical description also where stress is not considered as the etiological factor of *prameha*.[32]An interesting trend noticed in the study was the dip of biomarkers level in *Sthanasamshryavastha* (Graph 1&2).As per Ayurveda, in *Sthanasamshrya* stage the *doshas* in circulation settle at some specific sites in the body tissueswhere they find congenial atmosphere for them to produce the disease through the process of *dosha-dushya*interaction. The observation of diminution in values of biomarkers in this stage associated with increased values in the previous and consequent stages, is a novel finding, which could be because of the lodging of the doshas in the body tissues, which would decrease their values in circulating body fluid i.e*Rakta* (blood) would diminish. However, to establish the clinical significance of this aspect with more conformity, the finding needs to be explored through continuous model on a large population along with consideration of confounders.

4.2 Clinical staging of disease : Signatures of *hetu-dosha*and*dushya* interaction

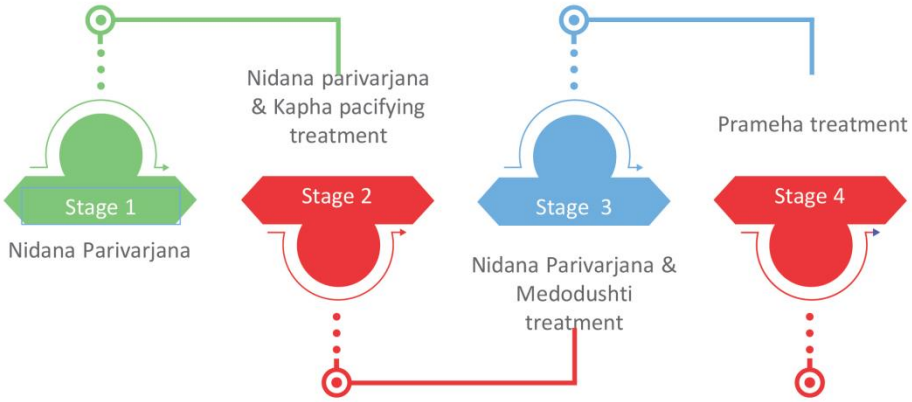
In contemporary science disease can be identified in two stages : Stage of suspection /manifestation and stage of complication while Ayurveda recognizes six pathogonomic stages of disease where first four (up to *sthanasamshryavastha*) are preclinical stages and on the basis of these stages effective strategies for the public health can be planned. For an instance, various molecular biomarkers (as per Ayurveda) can be detected at the time of spreading stage (i.e. *Prasara*) through the blood and body fluid.[33]This type of Clinical staging based on pathological pathways and mapping of disease may serve as an important pre diagnostic tool. Permutation & combination of *Hetu- Dosha-Dushya* can give direction of manifestation and progression of disease. (Figure 1)



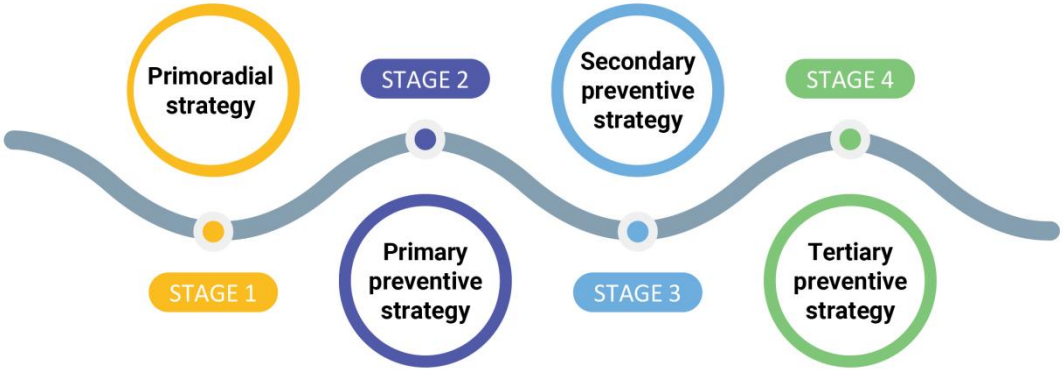
4.3 Risk stratification and early intervention strategy : An evidence based approach

By earlyscreening and stratifyingrisk factors a strategy to prevent further progression can be developed. As there are evidences supporting the role of early screening in better outcomes and prognosis of the disease. The risk

factors for diabetes i.e. overweight, obesity, faulty lifestyle, dietary pattern, dyslipidemia all are modifiable. Many longitudinal and cohort diabetes prevention studies has evidenced role of lifestyle interventions in prevention of diabetes.[34-35]This lifestyle modification programs deal with change in the modifiable risk factors of prediabetes and diabetes. Concept of SKK not only deals with prediabetic stage but also to previous latent pathognomic stages. The clinical application of SKK concept is that if accumulated *doshas* are expelled in initial stages they don't proceed further. On the basis of symptomatology the imbalance in doshas can be detected in initial three stages and corrected at that stage and thus the pathogenesis of disease can be arrested at earlier stage. In *Sthanasamshryavastha* (Stage 4) the primordial symptoms of disease are noticed. Early screening and breaking pathogenesis in stage 4 can even prevent the disease.This traditional knowledge can be strategized with modern tools of technology to detect predisposition and early diagnosis of disease. On the basis of symptomatology, at each stages therapeutic interventions can be employed at each stage to spread the pathogenesis further.(Figure 2)



Intervention in earlier stages prevents disease pathogenesis development and is easier, cost effective and with better longevity and quality of life. Delay in management leads to increased morbidity with complications and mortality, more economical burden, disability adjusted life years (DALY) and hence leading to gross productivity loss to the society. India, being a country with the highest demography in the productive age group on one hand, and increasing burden of diabetes parallel, on the basis of which predictions for being the diabetes capital of the world by 2045 are being made, it is very imperative for the Indian economy to focus on the implementation of preventive strategies at all levels. Several research studies have shown success of preventive interventions with sustained reduction in incidence of diabetes,[9],[34-35]diabetic complications[36-37] and mortality as well [38-39].The clinical implementation of SKK model is the basis of preventive strategies. (Figure3)



Limitation sand future direction

This pilot study was an attempt to assess the relevance of six stage model of SKK in pathogenesis of *Prameha*. More sensitive serum biomarkers including combination of c-peptide, micro RNA, oxidative stress markers and metaboglites like mannose can be used to trace the pathogenesis. Randomized control trial (RCT's) design can be implemented at each stage to restrict the progression.Measurements of variables is the fundamental concept of research methodology. Objective parameters to measure the variables can be done in future work.

5. CONCLUSION

Present study describes the relevance of pathological model of SKK in*prameha*with an emphasis on research areas to validate the concept of such models and implementation to improve health conditions and decrease burdens in NCD's. Ayurveda gives insights on the behavior of *doshas*at each stage, they can be further used to mark the progression of disease. Clinical staging is based on pathological pathways and mapping of disease progression may serve as an important diagnostic tool. The traditional knowledge integrated with modern technologies can serve as solution to detect predisposition factors for diabetes in its early stages and prevention strategies may be applied at each stage. Moreover, the criteria used to define the stages needs to be refined in accordance to the long term medical outcomes.

Conflict of interest

The authors declared no conflict of interest.

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