Discussion

Predicting and preventing diabetes: Translational potential of Ayurveda information on pre-diabetes

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ABSTRACT

Continued rise in incidence and prevalence of diabetes globally warrants an effective strategy for its prevention and control. Prevention of diabetes seems more logical to attempt seeing its health care burden, long dormancy, systemic affliction and poor general awareness.

Pre-diabetes is the intermediate state of erratic glucose metabolism without overt features of diabetes. This state seems to be a crossroad having a possibility to either convert into clinical diabetes, remain dormant or return to normal glucose control depending upon the efforts made. Unfortunately, due to the paucity of apparent clinical symptoms, this state embedded with reversal possibility, remains unexplored. Ayurveda account of *prameha purvarupa* (subclinical features of diabetes) may be proposed as the foundation upon which clinic-based pre-diabetes identification and subsequent prevention may be explored. Knowing the symptoms for their reliable proximity with upcoming diabetes may turn to be sensible sensitizers prompting the people to abort the disease process in an effective and timely manner. Considering diabetes from its *purvarupa* to complications as disease continuum and exploring the opportunities to intervene in order to prevent, or manage the disease on the basis of *shada kriyaa kaala* therefore, has a huge translational potential warrants an urgent exploration.

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1. Introduction

Diabetes has a historical precedence [1]. Its earliest written account is traceable back to 200 BC through ancient scriptures from Egypt, Greece, China, and India [2]. Diabetes draws its name from the analogy of its urine to a honey-sweet solution capable of attracting hexapods. Ancient Ayurvedic scripts related to medicine and surgery namely Charaka Samhita (400 BC), Sushruta Samhita (600 BC) and Vagabhatta provide an elaborate account of diabetes and its management under a syndromic condition diagnosable as *Prameha* (a Sanskrit term used to define increased frequency of urine) and *Madhumeha* (a Sanskrit term used to define a condition where urine becomes sweet and viscid as honey).

Though the knowledge about the occurrence of diabetes in the human population is millennium old, its real cure is still illusive and its net burden is continuously rising. International Diabetes Federation (IDF) predicts that from 451 million (18–99 year) people in 2017, global diabetic population is expected to reach 693 million by 2045. This is more worrying to know that about half of the people living with diabetes are living undiagnosed. An annual addition to the large pool of diabetes comes from an estimated population of 374 million people having impaired glucose tolerance turning at a rate of 5–10% annually into overt diabetes. Five million deaths are accounted annually to diabetes and the global annual expenditure on diabetes is exceeding to USD 850 billion [3], an amount 6 time greater than the net expenditure India spends upon its yearly total health care [4]. The diabetes prevalence, deaths and health care expenditure related estimates present a worrying view of burden over the health system the world is expecting in coming years.

Seeing the rapid annual increase in the prevalence of diabetics and a rapid conversion of pre-diabetics into clinical diabetics, predicting and preventing diabetes through clinical, biological, genetic and machine learning approaches seem highly reasonable [5]. The best clinical predictor so far studied for diabetes is

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adiposity, and baseline glucose is found to be the best biological predictor. Diabetes risk predictors have also been formulated for the purpose of population screening and segregating the people at risk. Indian Diabetes Risk Score (IDRS) was developed using four simple parameters namely age, abdominal obesity, family history of diabetes, and physical activity. It has shown to be a highly cost-effective way of testing for diabetes in a resource poor setting like India [6]. For diseases like diabetes, having a prolong turnaround period from pre-diabetes to clinical diabetes, absence of obvious warning symptoms, and immediate measurable impacts related to the slow progress of the disease added with poor awareness about the real cause of the disease leaves much to be explored related to its early clinical predictors and biomarkers to make its prevention an achievable goal. Currently, the impaired glucose tolerance test (IGTT) is the only gold standard to diagnose pre-diabetes. Employability of IGTT as a generic method to screen pre-diabetes however, remains questionable on the behest of the fact that about half of the clinical diabetic population in the world is still living undiagnosed.

2. Preventing diabetes through its early prediction: A lucrative proposition

Diabesity (obesity along with type 2 diabetes) has emerged as one of the biggest epidemic in human history. This was however seriously underrated as a global public health issue so far. Epidemiological propositions of diabetes in future are clear indicators that it can no longer be ignored [7].

To prevent type 2 diabetes mellitus (T2DM), a better understanding of the drivers of the epidemic is urgently needed. For the prevention of diabetes, the attention conventionally focused upon traditional risk factors including genes, lifestyle and behaviour in addition to the impact of intra-uterine events and epigenetic factors on future risk of diabetes in adult life. Diabetes risk through epigenetic changes can be transmitted inter-generationally creating a feeder to add to the epidemic. There is therefore, a never before urgency of preventing diabetes by working collectively on the drivers of the epidemic including genes and environment in an epigenetic context. Obviously the biological events as the intimate reflections of genetic and epigenetic consequences of various factors can come as the easiest catch of the pre-disease in a practical community-based health care setting.

To address this epidemic, a multi-level and multi-stake comprehensive approach is needed involving favourable policies and their practices inclusive of community partnership. This is highly important to screen the high risk individuals and to promote them to join tested intervention programs to abort the pathogenesis and minimization of the risk.

The biggest challenge however, is to screen and identify the people at high risk and convincing them to join accredited intervention programs. A high credibility and easy comprehensibility are two essential components required for the success of any diabetes prevention program based upon a screening tool. Any success of intervention will eventually depend upon how trusted and acceptable the screening methods are among the community [8].

3. Challenges in predicting and preventing diabetes

In the past two decades, prevention of diabetes has been brought down to the translational reality from initial efficacy based clinical researches [9]. In the randomized controlled setting, efficacy has been shown for lifestyle interventions, with progression to T2DM reduced by up to 58%, and with beneficial effects evident at 13 years follow-up [10]. Systematic reviews of such RCTs have identified 22 real-world diabetes prevention programmes [11].

Systematic reviews of the clinical studies focusing upon the success of diabetes prevention programs on the basis of outcome however, focused largely upon weight-loss as a major parameter of risk reduction. This eventually ignored many other important diabetes related risk components not being adequately represented by obesity alone [12].

Preventing diabetes has not been an easy to achieve target. There are many challenges in making of predicting and preventing diabetes, an achievable reality. Almost every suggestion related to prevention of diabetes relies upon identification of risk factors and their presumptive relation with diabetes followed by their subsequent reduction. Nevertheless, the people who do not have any clear warning feature related to diabetes find it hard to get convinced about any need for risk reduction in the absence of any visible risk and its foreseeable consequences. Pre-diabetes has not yet been realised for its clear clinical features which may be considered as the predictors of upcoming diabetes and hence, the diagnosis of pre-diabetes largely relies upon biological markers like IGTT and glycated hemoglobin (HbA1c) [13]. There had been clear voltage drops when efficacy trials related to diabetes prevention have been translated into real life practice [14]. Extending the benefits of a real-world diabetes prevention programs over extended period of time is also a major concern. Absence of demonstrable benefits in short time leads to programme drift denoting a deviation from protocol resulting in attenuated effects of the whole efforts. Lack of individualisation is also one important limitation of such public health intervention programs aiming at diabetes prevention. Looking at heterogeneous aetiologies and clinical spectrum of pre-diabetes including the variability of time lag between pre-diabetes and diabetes in individual cases also comes as a major limitation in the success of any diabetes prevention program.

4. Predicting and preventing diabetes: Taking cues from Ayurveda

This is quite evident now that the whole spectrum of pre-diabetes to diabetes actually represents a continuum of pathogenesis with a high variability in its progression from one end to another. To become more honest we can add diabetic complications also in the same continuum as these also represent the extension of the same continuum (Fig. 1). Seeing this, we find at least 3 points of interface in this cloud of diabetes pathogenesis continuum on the basis of clinical or biological markers. There can be an opportunity to prevent diabetes if biological and clinical markers of pre-diabetes are clearly known. Similar are the needs for the management of diabetes and prevention of its complications as 2nd and 3rd opportunities to act. In the diseases which take long sub-clinical course to become clinically visible, usually much of the damage may already have taken place before these become truly apparent. This very fact has a high relevance in degenerative, neoplastic, autoimmune, psychiatric and lifestyle diseases since here a disease is often discovered at a point already far from the scope of recovery [15].
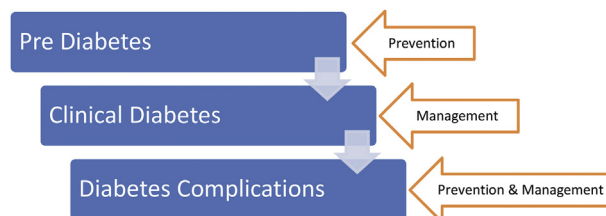

Fig. 1. Level of opportunities to act at various stages of diabetes.

There is a growing consensus that in many of these conditions, few sensitive biomarkers may help predicting the disease well before they are clinically visible. This is obvious that any such help may be of immense value in timely prevention of the disease and avoiding much of the health care burden required to manage the disease and its complications.

Recent advances in genetic testing, neuroimaging, nuclear magnetic resonance imaging and other health care technologies have allowed researchers to discover biological markers in various disease conditions. Some of these biomarkers can be detected years before the diseases actually present with symptoms allowing their clinical diagnosis. An early detection of a disease naturally has multi-level and impressive impacts on whole health care delivery system.

The postulate of continuum of a disease is explicitly depicted for Alzheimer's disease through "Jack" curve—proposing that different biomarkers emerge at different stages of disease hence providing the opportunity to act at multiple levels distinguishable as primary, secondary or tertiary prevention points [16].

It is in this purview, this may be highly pertinent to look at Ayurvedic biology and its proposition of pathogenesis continuum as multiple opportunities to act on the basis of precise knowledge of the pathogenesis even when the disease is not clinically visible.

5. *Shadakriyakaal*: The opportune time to intervene on the basis of precise knowledge of pathogenesis

Ayurvedic pathogenesis postulates 6 stages in a disease from its initiation to complications. These are also proposed to be six opportunities to intervene (called *shadakriyakaal*) during the course of a disease throughout its continuum (Fig. 2). Among these 6 stages, *vyakti* (manifestation) represents the disease through its clear clinical features. Stages prior to this, represent the preclinical to prodromal phases of the disease continuum. The stage of *sthana sanshraya* (settling of the disease causing material at a particular site) actually sets the stage for clinical manifestation of the disease and in this process itself starts reflecting through prodromal features. Depending upon the specificity of the disease causing material, such prodromal features may either be pathognomonic of a particular disease or generic, reflective of a wider category of diseases based upon the disease causing *dosha*. From *sanchaya* till the stage of *sthana sanshraya*, Ayurveda finds these as the stages where disease prevention is realistically possible since disease as an entity has not shaped yet. Looking at this proposition of Ayurveda, we see that we may actually have four levels of disease prevention from *sanchaya* to *shtana sanshraya* if these preclinical stages can be read

precisely. The biomarker proposition of identifying the disease stages in a continuum of pathogenesis seems to be a highly precise and technologically advanced version of clinical staging of a disease through reflections of stages of pathogenesis observable through subtle signs often hard to perceive. Ayurveda however proposes that each of 6 stages in *shadakriyakaal* may have their hallmark features which can be identified by creating awareness about them. This is also noteworthy that in association with the disease stage identification, Ayurveda further proposes their differential management plan suiting to avert the actual pathogenesis. Pre-clinical features in relation to few diseases are vividly described in Ayurveda although have rarely been utilised as a means to promote disease prevention planning in national health care delivery system. Seeing the difficulties associated with biological marking of pre-diabetes and near absence of its identifiable clinical features in contemporary medical literature, preclinical features of diabetes as described in Ayurveda may therefore have a special significance in diabetes prevention.

6. Pre-diabetes features detailed in Ayurveda texts

Diabetes is vividly described in Ayurveda in its full spectrum from aetiology to pre-clinical and clinical features and complications along with its stage-wise management. The pre-clinical description of *prameha* or *madhumeha* (as diabetes is known in Ayurveda) is so elaborate and vivid and is hard to be missed by anyone focusing upon diabetes prevention. While looking at various features claimed to be the pre-diabetic clinical features spread across various Ayurveda classics, we find that many features described as pre-diabetic features are actually extended proximally and continue to show up even when the diabetes is fully present clinically. On the contrary, there are many other features which are indicative of early stages of the disease only and vanish when the disease is further progressed. Any focus towards prevention of diabetes will eventually focus upon the features which are stage-bound and are sensitive to the particular stage of the disease. A comprehensive list of features categorised as *prameha purva-rupa* (pre-diabetic features) shows these features to be distinguishable into anatomical, physiological and neuro-cognitive categories (Table 1).

Looking carefully at the pre-diabetic features described in Ayurvedic literature, this can clearly be noted that all of these features are pathological consequences of an increase in sugar level in the body and its inadequate reach to the cells in order to produce adequate energy [17]. For example, in anatomical category the features like excessive growth of nails and hair clearly defines an affinity of glucose to nail and hair leading to their excessive growth. Glycation of nail proteins is one fine example of diabetic glycation related target organ damage [18]. Glycation of hair proteins and consequent changes in hair quality have long been the subject of diabetes research [19–21]. Glycation index of hair is also proposed as a non-invasive method to monitor glucose control in diabetics. The features like *ghanangata* (over nourished body parts) and *chikkanata dehe* (shiny body parts) are the cutaneous manifestations of diabetes which may often be reported as the first sign of diabetes or may develop at any time in the course of the disease. Skin thickening is frequently observed in patients with diabetes. Affected areas of skin can appear thickened, waxy, or edematous. These patients are often asymptomatic but can have a reduction in sensation and pain. Although different parts of the body can be involved, the hands and feet are most frequently involved [22]. There had been attempts to see if skin changes can be considered as clinical markers of pre-diabetes but these studies largely focused upon well-defined clinical entities like acanthosis nigricans (AN), skin tags (ST), diabetic dermopathy (DD), rubeosis faciei (RF),
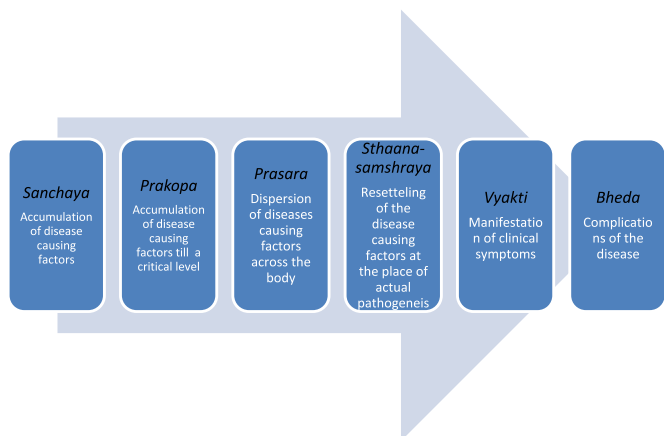

Sanchaya
Accumulation of disease causing factors

Prakopa
Accumulation of disease causing factors till a critical level

Prasara
Dispersion of diseases causing factors across the body

Sthaana-samshraya
Resetteling of the disease causing factors at the place of actual pathogenis

Vyakti
Manifestation of clinical symptoms

Bheda
Complications of the disease

Fig. 2. *Shadakriyakaal* as opportune time to intervene during the disease continuum.

Table 1
Pre-diabetes features described in Ayurvedic classics.

	Category	Classical description	Conventional meaning
1	Anatomical features	*Jatilibhuteshu kesheshu*	Thickening, coarsening and greasy hair making them difficult to be combed
		Ghanangata	Over nourished body parts
		Kesh −nakhati vriddhi	Excessive growth of nails and hair
		Chikkanata dehe	Shiny and smooth skin and body parts
2	Physiological features	*Maadhuryam aasyam*	Sweetness in mouth
		Mukh-taalu-kanth shosham	Dryness in mouth, palate and throat
		Pipaasa	Thirst
		Mutre ca mutradoshanam; madhur shukla mutrata	Turbid urine; Sweet and whitish urine
		Visra sharira gandha; swedo ca anga gandha	Pungent smelling body; excessive sweating and smelling
		Durgandham ca bhavaasya taalu gala jihva danteshu	Bad smell through mouth, palate, throat, tongue and teeth
		Hrinnetra jihva shravanopadeho	Smearing of chest, tongue, and ears with more dirt
		Malam kaye;	Excessive production of superficial body waste
3	Neuro-cognitive features	*Kara-paadayo suptata daho; Paridaaham suptata ca angeshu*	Burning and numbness in hands and feet; burning and numbness in various body parts
		Nidra-tandra ca sarvakaalam iti	Always feeling sleepy or drowsy
		Bhayyasan swapna sukhe rati ca	Increased liking for sitting or sleeping
		Sheet priyatvam	Increased likening for cold substances
		Shithilaangata	Dullness, lethargy

pruritus (PR), granuloma annulare (GA), necrobiosis lipoidica (NL), scleroedema diabeticorum (SD) and bullosis diabeticorum (BD) [23] rather than the early consequences of any diabetogenic mechanisms as is proposed in Ayurveda.

Physiological features of pre-diabetes are related to increased osmolality in body tissue due to increased body glucose levels. Increased thirst, dryness of mouth, throat, palate and tongue are reflective of on-going tissue dehydration [24] and these may become apparent well before the establishment of clinical diabetes. Sweet taste of mouth (*maadhuryam aasyam*) has also been proposed as a pre-diabetic feature in Ayurveda. Alterations in taste have previously been proposed as pre-diabetic features with reduction in sweet taste as precursor of increased liking of sweet. The studies however did not support this hypothesis of sweet taste reduction in pre-diabetics [25]. Salivary glucose levels are proven to be a reliable pre-diabetic marker [26] and this is proposed that salivary glucose estimation can serve as valid and non-invasive test for screening and diagnosis of diabetes and pre-diabetes. Excessive production of body-waste resulting in excessive smell from body and mouth are similar consequences of increased glucose levels in various body tissues and extracellular fluid compartments. Bad oral health has long been associated with diabetes; however, excessive body smell is yet to be proved for its connection with diabetes [27].

Numbness and paraesthesia of hands and feet is a highly recognised feature of pre-diabetes and diabetes. The commonest variant of neuropathy available in diabetes and pre-diabetes is distal symmetric sensorimotor polyneuropathy (DSPN). Studies suggest that between 25−62% of patients with idiopathic peripheral neuropathy have pre-diabetes [28]. Population-based studies indicates that there is a gradient in the prevalence of neuropathy with the highest frequency in diabetes mellitus, followed by people with impaired glucose tolerance, impaired fasting glucose, and normoglycemia.

Cognitive and sleep impairments are common to diabetes. Sleep disturbances are shown to be related to cognitive dysfunction [29]. Day-time somnolence is a frequent symptom found associated with diabetes hence, warranting a thorough enquiry [30]. Although in some studies day-time sleepiness is also found linked with hypoglycaemia [31,32], its cause is mainly attributed to poor glycemic control. Fatigue and laziness have been found associated with diabetes attributable to poor glucose entry into the muscle cells. Obviously, such symptoms may become apparent in pre-diabetes well before the diabetes is actually recognised through conventional biological markers. Studies are suggestive of psychological distress, including symptoms of anxiety, apathy, depression, fatigue and insomnia associated with increased risk of pre-diabetes and T2DM [33].

7. Exploring the possibility of developing a population-based screening tool for early detection of pre-diabetes by taking a lead from Ayurvedic literature

Although various studies are affirmative about many clinical features suggested in Ayurveda for their pre-diabetes linkage, confirmatory prospective population-based studies are required for converting them into any population-based screening tool. Many of the suggested features have yet been less understood and explored in the context of pre-diabetes and hence, have the possibility of opening a completely new horizon of diagnosing pre-diabetes on clinical basis. What essentially would involve in this process of making of a practically useable screening tool for pre-diabetes based upon the pre-diabetes features recommended in Ayurveda is identification of all such features scattered in various texts of Ayurveda, their translation from Sanskrit into a more comprehensible, contemporary and uniform meaning, defining the methods to explore the classical signs and symptoms in a population-based setting and finally designing a validated screening tool to screen the population for having any association with pre-diabetes. During this process, once the classical signs and symptoms are deciphered for their contemporary meaning and methods of screening in the general population, an affirmative association of these with IGT would be required through a prospective cohort study. Further to this associational establishment, these features may be explored for their differential association in diabetic, pre-diabetic, non-diabetic (people suffering with diseases other than diabetes) and healthy control through prospective and retrospective cohort studies. This exercise seems important from the perspective that the features enlisted as diabetes *purva rupa* are not limited to diabetic population alone and hence, these are essential to be identified for their prevalence in diabetic, non-diabetic (suffering with diseases other than diabetes) and healthy population to screen any obvious difference. This will help identifying the proportion of the people in pre-diabetic and diabetic population having a positive association of the aforesaid symptoms. Looking further, such studies may also help in establishing a temporal pattern of occurrence of pre-diabetic features which may eventually help in understanding the underlying pathogenesis and subsequently designing a tailor-made and precise prevention program suiting to individual needs. There

can be numerous applications of Ayurvedic knowledge of pre-diabetes in real world diabetes prevention programs. The most immediate is the development of a screening tool indicative of proportionate risk of developing diabetes in an individual based upon real sub-clinical findings. Keeping the chronology of the symptom arrival and mixing and matching it with Ayurveda concept of *shadakriyakaal* or stages of pathogenesis in the backdrop of individual susceptibility to develop diabetes, a prediction of the time lag between pre-diabetes and diabetes can also be proposed. Another interesting proposition is to explore the heterogeneity of diabetes on the basis of diverse etiological factors found associated with diabetes [34]. This may be presumed that a particular pre-diabetic feature may be indicative of a special set of etiological factors involved in the initial pathogenesis. Although still a hypothesis, we see that an exploration of ancient Ayurveda concepts of diabetes may help much towards its better understanding and subsequent effective prediction, prevention, and management. The proposition may have a strategic meaning for global health care system which is already overburdened with diabetes and its complications. This may have a particular meaning to India for it being the diabetes capital on one hand and owning the treasure of ancient knowledge of Ayurveda on the other.

Some momentum in this regard has started in the recent past. In 2016, the Ministry of AYUSH, Govt of India, decided to dedicate its National Ayurveda Day on the theme of "Prevention and Control of Diabetes through Ayurveda" under its flagship project of "Mission *Madhumeha*". A comprehensive document on 'National Protocol for Prevention and Control of Diabetes through Ayurveda (NPPCDA)' was launched on the occasion with objectives of promoting use of Ayurveda for prevention of diabetes; generating awareness about strengths of Ayurveda in diabetes; educating people for self-help; improving the surveillance; and effective management of diabetes and its complications. This was envisioned that this ambitious protocol will be implemented through the Public Health Infrastructure available under State Governments and Ayurveda colleges spread across the country as well as through practitioner's associations. As one significant improvement upon any previous attempt of preventing diabetes through Ayurveda, this protocol proposed a '*Madhumeha* Assessment Tool' (MAT) based on Ayurvedic concepts of diabetes in order to sensitise the people about diabetes, its common symptoms and Ayurvedic approach towards diabetes. The percept was to encourage the people for an early visit to Ayurveda hospitals if they fall under the risk category [35]. Such attempts are needed to be encouraged and promoted at every level but at the same time also demand a high precision and sincerity in application. When the program is promoted as a protocol, there are obvious questions about the process of its synthesis and reliability in what it is envisioned to achieve. Moreover, there shall also be a visible seriousness about plan of its implementation and analysis of the data obtained in order to improve it further on the basis of observations. Protocol in scientific literature per se is 'a detailed plan of a scientific or medical experiments, treatments, or procedures. In clinical trials, it states what the study will do, how it will be done, and why it is being done. It explains how many people will be in the study, who is eligible to take part in it, what study drugs or other interventions will be given, what tests will be done and how often, and what information will be collected [36]. Unfortunately, the much hyped document leaves much to be done before it may have any translational value.

8. Conclusion

This is beyond any doubt that preventing a disease has many fold advantages. Preventing a disease before it actually appears makes a serious sense from economical and resource-related issues which are needed to be employed in the disease management. Prevention has multitudes of secondary benefits in terms of prevention of loss of employability and productivity in affected population. These propositions are highly important in the context of diabetes although the attempts to prevent diabetes have not met with adequate success. Complexities associated with adherence of any long term protocol and poor appraisal of tangible benefits associated with such adherence are possible reasons of suboptimal benefits from diabetes prevention programs. Identifying the vulnerable people on the basis of sub-clinical features having a remote relation with upcoming diabetes may be a good strategy to ensure compliance with any such preventive program. Ayurvedic description of *prameha purva rupa* prompts about the clinical features which may have a future relation with diabetes. Screening the people on the basis of availability of such *purva-rupa*, assessing the risk on the basis of intensity and spectrum of such features, and making the people with high risk, aware about the possibility of reverting the diabetes from their doorstep seems to be a realistic plan for optimising any diabetes prevention and reversal program.

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