Effectiveness of Yoga as the Public Health Intervention Module in the Management of Diabetes and Diabetes Associated Dementia in South East Asia: A Narrative Review

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Keywords

Dementia · Diabetes · Public health · Yoga · Physical activity

Abstract

Background: Diabetes mellitus (DM) is widely spread in South Asian (ASEAN) and Indian sub-continent. The increasing healthcare costs of DM can be prevented in the developing world by improved public healthcare interventions. Modifiable risk factors of DM like sedentary lifestyle, obesity, and stressful conditions are associated with its progression; however, the epidemiological data collected by Public Institutions are limited. **Summary:** A review of published literature describing geographic distribution of DM and associated dementia in South Asian region, particularly India, was conducted with the purpose of assessing the feasibility and challenges associated with the Yoga-based risk reduction. PubMed and Google Scholar databases were searched for DM and dementia-related articles by using a combination of keywords: Diabetes, Diabetes related Dementia Southeast

Asia, Pre-diabetes, Yoga, lifestyle modification, Dementia and Exercise. The epidemiological data generated from these diseases have not prompted to any major public health policies. Yoga can be a cost-effective intervention for the prevention of Type 2 DM (T2DM) and its associated cognitive decline when detected early. If nationwide intervention of Yoga is brought about by the state, its integration in health care will become more meaningful and acceptable. **Key Message:** Studies suggest that Yoga and change in lifestyle can modify the health risks associated with T2DM and associated dementia if it is mainstreamed with the public health initiative of *Ayushman Bharat* scheme. © 2020 S. Karger AG, Basel

Introduction

Diabetes mellitus (DM) is a metabolic disorder spreading at an alarming rate in India, which is considered as the future “Diabetic capital”. An expected 66.8 million

population is faced with this condition [1]. Type 2 DM (T2DM) progression is characterized by insulin resistance resulting in increased level of blood glucose [2]. It may also develop due to genetic and non-genetic (age, obesity, sedentary lifestyle, and stress) risk factors [3] that are modifiable. The epidemic of diabetes is also related with various complications like dementia, Alzheimer's disease (AD), vascular dementia, heart attack, stroke, peripheral neuropathy, diabetic nephropathy, cerebrovascular diseases, diabetic retinopathy, diabetic foot, and so on. Hyperactivation of hypothalamic-pituitary-adrenal axis with increased cortisol production has also been noted in DM [4–6] but not studied adequately. Increased cortisol production is linked with stress, which is one of the main risk factors associated with dementia [4]. In this review, we have discussed how progression of T2DM increases the vulnerability toward dementia and whether intervention methods like Yoga practice can strengthen the existing public health policies for these twin diseases.

It is believed that through change in lifestyle and dietary habits, it is possible to control glucose levels (and dementia). Yoga with its eightfold path (*Yama, Niyama, Asana, Pranayama, Pratyahara, Dharana, Dhyana, and Samadhi*) helps in lifestyle paradigm shift and improves the overall well-being of an individual [3, 7], providing compelling evidence that high-risk individuals may be prevented from the development of T2DM and associated dementia by modification in the lifestyle. It has also been shown that the prevalence of DM decreases by 58% in such cases [3]. The literature review and policy framework that promote Yoga as a possible intervention for DM (and its related comorbidities) are discussed here in order to provide insights for future researchers and policy makers.

Methodology

This narrative review presents the current literature in the field of DM and diabetes-associated dementia along with the evidence of Yoga in the management of both in South East Asia (SEA). The following databases were included in the literature search: PubMed and Google Scholar. Literature search included the following keywords: Diabetes, Southeast Asia, Pre-diabetes, Yoga, lifestyle modification, Dementia and Exercise, Diabetes induced Dementia. We excluded the following study designs: case reports and case series papers. The systematic reviews, meta-analysis, randomized controlled trials (RCT), non-RCTs, and longitudinal and cross-sectional studies that assessed incidence and prevalence of DM and associated dementia in SEA and India were included. This also included the risk factors of DM and dementia besides the public health intervention programs like exercise and Yoga. These were presented as varying from the Western public health delivery model.

Prevalence of Diabetes

The World Health Organization (WHO) has estimated 422 million adults who are battling with DM, and this number is estimated to double by 2030. The T2DM constitutes almost 85% of the cases [8]. According to WHO “Global report on DM”, SEA has shown a rapid increase in both regions (i.e., rural and urban). The WHO estimated that 96 million people have DM in SEA, out of which 90% have T2DM. According to WHO, this has increased from 17 million (1980) to 96 million (2014).

India is ranked second behind China in the global incidence of DM. The maximum incidence of DM is seen in Mauritius (14.8%), where majority of Indians are settled. Currently, 73 million individuals are affected in India. This constitutes >8.8% of adult population [9] of which 49% are females and 51% are males. Sixty-three percent prevalence has been reported in rural population, whereas 37% in urban population [10]. The cities affected with DM show variable percentage of prevalence as shown in Table 1 [10]. According to World Diabetes Foundation report, people living with T2DM in India is expected to increase by 10% (123 million) in the year 2035. Many studies have also emphasized that Asian Indians have a greater risk of DM and have younger age of onset and lower body mass index (BMI) risk threshold in comparison to other Asian populations, whether they lived in India or in any other foreign country. This makes Indians the most vulnerable to DM and associated.

Prevalence of Dementia

According to a prediction by WHO, by 2050, approximately 2.1 billion of the world population individuals will soon attain an age above 60 years [11]. It is estimated that the total number of individuals living with dementia has witnessed more than twofold increase from 20.2 million (1990) to 43.8 million (2016). It is also estimated that the prevalence of dementia will approximate 100 million by the year 2050 [12]. The prevalence of dementia in SEA countries and rest of the world are mentioned in Table 2. However, none of these estimates have recorded the age of onset or association with dementia, thus neglecting an important comorbidity.

The prevalence rate of dementia (Table 2) in India differs widely according to the different regions. The cause behind this variation in prevalence rate is the variability in the selection of approaches and methodologies, screening equipments, inclusion criteria, influence of various ethnic, cultural and environmental factors besides its association with increase in diabetes [13]. However, in none of these studies, the relation of diabetes with dementia was comprehensively examined, leaving a void in our understanding of the threat diabetes will pose for the incidence of dementia.

Relationship between Diabetes and Dementia

Cognitive dysfunction manifests at a later period of life (>60 years). It is a complication of DM, predisposing diabetic patients to develop dementia making them susceptible to AD [14]. DM and dementia, the 2 prevailing diseases among the elderly, were studied by different investigators (Table 3). As mentioned, T2DM has a positive relationship with dementia, and hence, the declining cognitive function may render the elderly disabled [15–17]. Early-onset DM-related development of dementia remains unexplored in epidemiological studies, although some studies have reported that T2DM has an association with cognitive impairment (memory and executive both), vascular dementia, and AD along with other

Table 1. Prevalence of T1DM and T2DM in SEA countries and India [9, 10]

Prevalence of T1DM and T2DM in SEA countries			
DM	Diabetic status in SEA (WHO)		
	country	year 2000	year 2030
India (% DM in total population)	Thailand	1,536,000	2,739,000
8.8% (adult)	Sri Lanka	653,000	1,537,000
International Diabetes Federation [9], 2019	Nepal	436,000	1,328,000
Urban-rural wise distribution, %	Myanmar	543,000	1,330,000
Urban 63	Maldives	6,000	25,000
Rural 37	Indonesia	8,426,000	21,257,000
Akhtar and Dhillon [10], 2017	India	31,705,000	79,441,000
Gender-wise distribution, %	Democratic People Republic of Korea	367,000	635,000
Male 51	Bhutan	35,000	109,000
Female 49	Bangladesh	3,196,000	11,140,000
Akhtar and Dhillon [10], 2017	Total	46,903,000	119,541,000
Prevalence of DM in different regions of SEA-2013 (age: 20–79 years)		Prevalence of DM in different regions of India	
country	age-standardized prevalence, %	regions	percentage
Mauritius	14.8	Goa	17.7
India	9.1	Pondicherry	16.9
Sri Lanka	7.6	Tamil Nadu	16.1
Bangladesh	6.3	Kerala	13.6
Bhutan	5.8	Chandigarh	11.5
Nepal	4.9	Bihar	<3.5
Maldives	4.8	Madhya Pradesh	<3.5
Diabetes in SEA region: an update		Odisha	<3.5
		Himachal Pradesh	<3.5
		Akhtar and Dhillon [10], 2017	
DM, diabetes mellitus; T2DM, type 2 DM; WHO, World Health Organization; SEA, South East Asia.			

Table 2. Prevalence of dementia in India, SEA, and the world [12, 13]

Prevalence of dementia					
prevalence of dementia in India [13]		prevalence of dementia in SEA countries [12]		global prevalence of dementia [12]	
regions	percentage	countries	2016 (millions)	regions	2016 (millions)
South India	3.6	India	2.9	America	7.9
North India	0.84–3.39	Indonesia	1.1	Australia	0.2
Western India	2.44–4.1	Vietnam	0.6	Africa	4.1
East India	0.8–1.28	Thailand	0.5	Asia	19.2
		Bangladesh	0.4	Europe	9.0
		Philippines	0.3		
		Sri Lanka	0.1		
		Nepal	0.06		
SEA, South East Asia.					

Table 3. Longitudinal studies deciphering the association between DM and cognitive decline [15–17]

Study	Type of study	Sample size	Age, years	Aims of the study	Baseline	Follow-up (duration in years)	Outcome of the study
					cognitive decline	cognitive decline	
Zheng et al. [15], 2018	Longitudinal study (2005–2015)	5,189	65.6±94	Association between HbA1c, diabetes, and cognitive decline	9.4±3.3	4.9±1.5	Study shows increased rate of cognitive problems with diabetes
Hassing et al. [16], 2004	Longitudinal study (1991–1998)	274	83.52±33	To examine the cognitive ability affected by diabetes	27.7±2.3	16.9±2.3	This study suggests that T2D is associated with increased risk of cognitive impairment in older adults
Gregg et al. [17], 2000	Prospective cohort study (1986–1992)	682	71.8±5.0	Investigation the risk of dementia in patients with diabetes	1.10 (0.86–1.40)	1.04 (0.76–1.41)	Female diabetic patient has more risk (57–114%) for neurocognitive decline than non-diabetic patients

T2D, type 2 diabetes; DM, diabetes mellitus; HbA1c, glycated hemoglobin.

factors like hypertension, dyslipidemia, and apolipoprotein [18]. DM, as a risk factor for dementia, was postulated [19] when it was demonstrated that age increases the susceptibility of diabetes leading to dementia [20]. A study by Solanki et al. [21] reported that 48% of DM patients had characteristics similar to dementia. Positive correlation between DM and dementia was further reported in another study where association of apolipoprotein E (APOE) genotype was also indicated [22]. In another study, Khattar et al. [23] found cognitive decline in DM patients proving the link between DM and dementia. Imbalance of insulin and carbohydrate metabolism has been implicated in the progression of AD as the study showed neuroprotective role of glycemic control in T2DM [24]. In a large prospective study, Logroscino et al. [25] reported that women with T2DM showed very poor cognition compared to non-diabetic individuals. The study also reported that women on oral hypoglycemic medications for T2DM showed similar cognitive decline to non-diabetic individuals. Further studies have shown that among the oral pharmacological hypoglycemic treatments of DM, only long-term use of metformin therapy on DM patients has shown some protective effect on cognitive functions such as executive function, verbal learning and working memory [26, 27]. The long-term intake of metformin has various side effects on diabetes patients, such as gastrointestinal, weight loss, lactic acidosis, and decreased vitamin B12 levels. It is also contraindicated in kidney and hepatic insufficiency diseases [28]. These studies emphasize the need to diagnose or detect pre-diabetes or undiagnosed DM, and when diagnosed, appropriate non-pharmacological interventions can be advised, to prevent Dementia at the earlier stage. This calls for mass-level public health initiatives for general wellness of population.

Studies of Different Regions of India

Non-obese Asian Indian males suffering from T2DM, recruited from North India region, have shown high plasma glucagon

correlated with fatty liver disease. The glycemic index of patients with non-alcoholic fatty liver disease was found to be higher than T2DM patients without non-alcoholic fatty liver disease [29]. Recently, a survey conducted on North Indian population revealed that DM and pre-diabetes were extremely prevalent among adults [30]. A cross-sectional study was performed to estimate the DM occurrence in rural areas of Mandur and Goa. It was found to be 10.3%. The factors which were found to be associated significantly on bivariate analysis included triglyceride levels, high serum cholesterol, age, occupation, family history of disease, family income, smoking, obesity, and hypertension. These factors are independently associated variables for DM and dementia as suggested by multiple logistic regression analysis [31].

A study done in North East India industrial community showed that incidence of DM was associated with increasing age, family history, and lack of physical activity. Therefore, timely detection and treatment are key to its management [32].

Rural and Urban India Trends of DM

The views of urban Indians regarding management or treatment and self-care are essential in evolving healthcare structure where pluralistic approaches like allopathic and non-allopathic paradigms are acceptable. The researchers have proposed an Integrative Medicine model incorporating both traditional and modern medical approaches. The data analysis from a study showed that participants selectively involved in building healthcare plans and personalized sickness conditions facilitate physical, social, and psychological needs as these emphasize the socio-communal experience of DM. This prosocial development about DM in India is helpful for patients and for providing psychological relief [33].

The Phase 1 Indian Council of Medical Research-India Diabetes study was conducted with participants in 4 different states and union territories in India. This included Tamil Nadu, Maharashtra, Jharkhand, and Chandigarh. The physical activity index was

Fig. 1. Diabetes as a complex disorder associated with several factors leading to cognitive decline. The yellow lines represent the effect of exercise on obesity and inactivity, which in turn acts on impaired glucose secretion and insulin resistance to regulate DM. The red line represents the effect of Yoga on obesity, stress, impaired neurotransmission, and oxidative stress, thus further regu-

lating DM; it also prevents further deterioration of dementia. HPA, hypothalamic-pituitary-adrenalin; T2DM, type 2 diabetes mellitus; AGE, advanced glycation end product; N-methyl-d-aspartate; nNOS, neuronal nitric oxide synthases; IRS, insulin receptor substrate-1; TNF α , tumor necrosis factor- α .

analyzed by Global Physical Activity Questionnaire on 14,227 participants aged ≥ 20 years (urban – 4,173; rural – 10,054). The data showed very low percentage, that is, only 10% of individuals engage in physical activity and the remaining are inactive [34]. In another study of Indian Council of Medical Research-India Diabetes, the glycemic control, with self-reported DM among subjects, was analyzed by estimating glycated hemoglobin (HbA1c). Out of

14,277 individuals, there were 480 subjects with self-reported DM that included 254 urban and 226 rural localities [35].

Risk Factors Associated with Diabetes and Dementia

In the postmodern scenario, there is an increase in tendency for the development of T2DM and dementia in SEA population due to risk factors illustrated in Figure 1 [36]. The major risk

factors linked with T2DM are family history of DM and the candidate genes, besides growing age and obesity. Moreover, the environmental risk factors, lack of physical activity, excess alcohol intake, irregular sleeping patterns, and so on increase the chances for the development of T2DM [37, 38]. Likewise, in the case of dementia, the genetic factors play a major role in its development along with growing age and gender [39, 40], and so on. Some of the risk factors are common for both T2DM and dementia and represent an underlying link between these 2 diseases.

Age

It is widely believed that middle and older age group individuals are at greater risk of developing T2DM. The age group between 45 and 64 years has been found to be the most affected group; however, early onset of T2DM is now beginning to be seen during the first decade of life [41]. Among Asian Indians, the early onset of T2DM was found to correlate with adverse outcomes of poor glycemic control [42]. The comparative analysis of early and late onset of T2DM has shown worsening of glycemic index, lipid control, and risk of retinopathy in younger diabetics as compared to older diabetic individuals [43], but similar studies on its association and co-prevalence with dementia are lacking. Progressive age is known as one of the major risk factors for dementia as the number of cases of dementia is growing among elderly population [44]. In elderly, there are numerous cognitive factors that contribute toward various pathologies related with AD and dementia [45]. AD affects 1–3% of people from 60 to 64 years of age, 3–12% of people from age 70 to 80 years in western countries, and this proportion rises to 25–35% for people >85 years of age [46]. Furthermore, the parental history of dementia and APOE4 allele, along with growing age, further advances the risk of AD and dementia [47]. HbA1c, used as a diagnostic marker for T2DM, has also been found to be associated with cognitive impairment and dementia [48]. Studies have also suggested association of higher level of HbA1c with worse cognition among younger individuals while reversing the effect in very old ages [49].

Alcohol Consumption

A meta-analysis showed that there is 30% reduction of T2DM risk among individuals who have moderate alcohol (≤ 6 g/day alcohol) consumption as compared to high alcohol consuming individuals (i.e., ≥ 48 g/day) [50]. The specific types of alcoholic beverage can also be an important factor for understanding the risk of T2DM. A study showed that limited wine consumption could be related with decreased risk of T2DM as compared to beer or spirit, suggesting that moderate consumption of alcohol might be beneficial in preventing development of T2DM [51]; however, none of these studies are prospective in nature and thus cannot be extrapolated for public health policies. In contrast, the use of excess alcohol can lead to a permanent structural and functional brain damage and which can become more severe with additional vitamin deficiencies like vitamin B1 [29, 52]. Alcohol-related cognition impairment is of 2 types: alcohol-related dementia and Wernicke-Korsakoff syndrome. Visuospatial memory and executive functioning are affected in both the cases [29]. Contrary to this, an interesting 4-year follow-up study suggested that lower risk of AD was not associated with liquor, beer intake, but it was confined in individuals without

APOE epsilon-4 allele [31]. Furthermore, the different level of alcohol consumption manifests variability in cognitive outcomes [29].

Effects of Smoking

There are contradictory studies describing smoking as a risk factor for AD and dementia; some of these have reported smoking as a risk factor for dementia [53], while others found no correlation between the both [54, 55]. Smoking is also known to affect other risk factors associated with dementia-like cardiovascular diseases [56, 57]. In addition, the interaction of smoking with hereditary factors, viz. APOE, further enhances the chances for the development of dementia [58]. However, a report revealed that smokers with defective APOE e4 allele had negligible chances of dementia in comparison with the non-carrier smokers who are at a twofold risk of dementia and AD [59]. Smoking, when taken into account with age, enhances the risk for dementia in comparison with non-smokers. However, the relation of historical smoking with dementia remains unknown [60].

Body Mass Index

Obese people are at a higher risk for developing T2DM, dementia, and AD [61–63]. BMI and dementia exhibit a U-shaped relationship [61]. Contrasting relationship has been seen with BMI, dementia, and AD. Obese people (BMI >30) of 50 years of age are at higher risk of dementia than people with normal BMI, but a steady weight loss (annual 1 kg/m²) in older people was found to be associated with 35% increased risk of AD [61]. Furthermore, studies in relationship between DM, dementia, and BMI [62, 64] are tabulated in Table 4.

Gender

Biocultural models are widely used to understand how social pathways define biological consequences. In India, this is the first study of T2DM women that explored bicultural perspective. Using this model, authors analyzed, in a set of 280 females without diabetes and those with T2DM women for health, social roles, biological correlations, and their interrelationships that prevail between diabetes, social role attainment, psychological stress, and biochemical variables assessing blood sugar control, immune stress, and generalized inflammation. One of the unchangeable risk factors for dementia was gender and growing age, which further reflects that women are more prone for the development of AD in comparison with men. The levels of blood sugar and HbA1c have shown poor management in women. This is due to changing immune stress that often accompanies uncontrolled blood sugar [65]. Furthermore, studies with AD, vascular dementia, and gender are listed in Table 4 [66, 67].

Diet

In an Indian study that was designed as population-based cross-sectional survey (NFHS-3, 2005–2006), population of all states of India was surveyed to determine the rate of occurrence of DM associated with dietary factors listed in Table 4, which showed diet is another modifiable risk factor that is involved in risk for DM and can be exploited for prevention-related studies. However, the intake should be in an established relationship with clinical measures for outreaching the maximum benefits [68, 69]. Furthermore, the presence of aluminum in drinking water and deficiency of vitamins (Vitamin B6, B12, E, and C) in the food increases the risk related with dementia [70, 71].

Table 4. Risk factors for DM and dementia [62, 64, 66, 67, 70, 71]

Study	Type of study	Sample size	Aim of the study	Outcomes
<i>BMI</i>				
Anstey et al. [62], 2011	Meta-analysis	71,529	Aim to synthesize data between BMI and dementia in middle age and late life	U-shaped relationship between BMI and dementia. 35% increased risk for AD in middle age (40–59 years); 33% greater risk for vascular dementia in late-life (≥60 years), and 26% greater risk for developing any type of dementia
Bays et al. [64], 2007	Nation-wide US cross-sectional study	211,097	To find any association between BMI and prevalence of DM	Increased BMI showed a significant increase in association with DM
<i>Gender</i>				
Andersen et al. [67], 1999	Prospective cohort study	528 incident cases of dementia	Incidence of dementia among genders	With increase in age, women are at more risk compared to men but in vascular dementia there are no gender differences
Wang et al. [66], 2012	Population-based cohort study	615,529	Association between diabetes and risk of AD	Diabetic men showed that an incident density of AD was 0.82 per 1,000 and for diabetic women it was 1.15 per 1,000, a higher hazard ratio compared to men
<i>Diet</i>				
Agarwal et al. [68], 2012	National wide cross-sectional study	198,754	To examine the effect of diet on prevalence of diabetes	Fish consumption has been reported to be inversely proportional to the diabetes prevention, whereas intake of fruits, pulses, and beans could help in prevention. However, taking milk or curd, eggs, vegetables, other factors such as television watching, alcohol consumption, or smoking do not create significant effect
Agarwal and Ebrahim, 2013	National wide cross-sectional study	156,316	Assessment of legume intake associated with the lower risk of DM	Legumes intake was directly related to reduced risk of DM in women, but the opposite is found in men although in men the association is non-significant
DM, diabetes mellitus; AD, Alzheimer's disease; BMI, body mass index.				

Common Genes of Dementia, AD, and DM

Several studies have shown the link of DM and dementia (AD). These disorders are amyloidosis and are featured by fibrillary aggregation in pancreases (amylin aggregation) and brain (β -amyloid aggregation) [72]. Increased risk of dementia and AD in DM subjects suggests the interaction of some factors that play a role in both the disorders. APOE association has been found with dementia, metabolic disorders, and DM [72, 73]. Other genes like App, CEPBP, PARP1, PARK2, CXCR4, MT-CO2, CCR5, PIK3CD, and IGFIR have also been known to be involved in the cross-talk [73].

Lack of Longitudinal Studies in Southeast Asia and Indian Sub-Continent

Both dementia and DM are age-associated disorders with increased incidence in older age. In this context, longitudinal studies with long follow-up of populations are required in order to understand the progression and relationship between these 2 intertwined disorders. Most of the longitudinal studies have been undertaken

by China and USA with no matching studies from Indian population, making it difficult to allocate resources to predict comorbidities and manage rising health costs.

Current Therapies and Clinical Trials

There is a great need to develop preventive, curative, and cost-effective measures for DM and related dementia. Several drugs like memantine, donepezil, tacrine, rivastigmine, and galantamine have been approved and widely used for dementia and its associated disorders. Memantine inhibits glutamate activity and the other 4 are cholinesterase inhibitors. But these drugs only provide temporary relief by modifying the neuronal activities [74]. The improvements may not be significant and a number of side effects can be observed in the AD subjects [33, 74]. Similarly, the drugs for diabetes like metformin, sulfonylureas, and meglitinides, along with insulin, provide only symptomatic relief and glycemic control, but the permanent treatment is still to be discovered [34, 75].

Table 5. Failed clinical trials of anti-diabetic and anti-dementia drugs disease management by lifestyle modifications and integrative approaches [76–84]

Sr. No.	Drug, year	Termination phase	Reason	Country
1	Enhanced care transition, standard care transition (2016)	NA	Due to funding problems, slow recruitment and PI location change	Canada, Ontario
2	Insulin detemir, insulin NPH, diet/exercise (2017)	Phase 3	Very slow recruitment rate	India, Argentina, Brazil, Croatia, Egypt, Germany, Greece, Hungary, Israel, Italy, Republic of Korea, Lebanon, Malaysia, Mexico, Morocco, Poland, Portugal, Russian Federation, Serbia, South Africa, Spain, Taiwan, Turkey, United States
3	Bifeprunox, placebo (2008)	Phase 3	Slow enrollment	Czech Republic, Estonia, Israel, Poland, United States
4	Inhaled human insulin, insulin aspart (2008)	Phase 3	An analysis concluded that fast-acting inhaled insulin in the form it is known today, is unlikely to offer significant clinical or convenience benefits over injections of modern insulin with pen devices	India, Argentina, Romania, Slovakia, Taiwan, Thailand, Turkey
5	Rimonabant, glimepiride, etformin (2009)	Phase 3	Company decision taken considering demands by certain national health authorities	India, Chile, Denmark, Finland, Hungary, Italy, Republic of Korea,, Mexico, Puerto Rico, Romania, Russian Federation, Spain, Sweden, United States
6	Megestrol acetate, placebo (2007)	Phases 2, 3	2010 Due to difficulties in recruiting the patients following the inclusion criteria	Spain
7	Aliskiren, placebo (2014)	Phase 3	Lack of benefit and safety concern	India, Argentina, Austria, Belgium, Brazil, Canada, China, Colombia, Czech Republic, Denmark, Finland, France, Germany, Greece, Guatemala, Hungary, Italy, Japan, Republic of Korea, Lithuania, The Netherlands, Norway, Peru, Portugal, Puerto Rico, Singapore, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, United States, Venezuela
8	Pioglitazone, rosiglitazone, placebo, dietary supplement: vitamin D, placebo (2011)	Phase 4	FDA has placed the trial on full clinical hold	India, Argentina, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, Germany, Italy, Latvia, Mexico, The Netherlands, Norway, Pakistan, Peru, Philippines, Romania, Russian Federation, Slovakia, South Africa, Sweden, Thailand, United Kingdom, United States
9	Tesaglitazar, metformin (2006)	Phase 3	The development program has been terminated	India, Australia, Canada, Finland, Germany, Italy, Malaysia, Philippines, Singapore, Sweden, United Kingdom

There have been repeated efforts to discover anti-diabetic drugs, ranging from synthetic analogs, stem cells to herbal medicine, all of which have failed to rescue the disease despite huge investments (Table 5) [76–84]. Preventive medicine provides a health promotion pathway that is cost effective and accommodates wide range of evidence-based interventions ranging from Yoga, Tai chi, exercise, sports, and so on to meditation.

Prevention of Dementia

Livingston et al. [85] evaluated the population attributable fraction (PAF) of dementia. The PAF is defined as the reduction percentage of new cases over a period of given

time if a risk factor is eliminated. The following were the modifiable risk factors of dementia: education (either none or primary school only) for the age group <18 years; hypertension, obesity, hearing loss for the age group 45–65 years; smoking, depression, physical inactivity, social isolation, and diabetes in the age group of >65 years. The PAF estimates were calculated and reported as highest with hearing loss (23.0%) in 45–65 age group, followed by less education (19.1%) among <18 years age group and obesity (2.0%) in the age group 45–65 years [85]. A prospective population cohort study by Tari et al. [86] on cardiorespiratory fitness (CRF) and the associated risk of dementia mortality revealed that the population with highly fit CRF or improvement from unfit CRF to fit CRF showed a reduction of 30–40% in mortality and 40–50% reduction

in incidence related to dementia. In comparison to unfit, the fit CRF individuals showed a delay of 2 years in the dementia onset and increase of life span by 2–3 years [86].

Disease Management by Lifestyle Modifications and Integrative Approaches

External life events, for example, environmental factors, act as pivot in driving the disease pathogenesis. Chronic exposure to various environmental stressors adversely impacts human physiology by molecular alterations in the biological pathways, and this also influences the response to therapy. DM, being a major public health challenge and a heterogeneous disease, calls for better understanding of its pathogenesis, clinical manifestation, comorbidities, and future complications particularly dementia. Despite the heterogeneity of pathogenesis, DM is characterized by insulin resistance or relative insulin deficiency in the presence of hyperglycemia and represented with internal glycemic index parameters like HbA1c, fasting blood sugar, and so on [87]. Several observational studies from high-income countries have found environmental effects influencing T2DM. Cortisol and cytokines released in response to the environmental stressors accelerate the development and progression of chronic diseases like DM [88]. Meeting the patient requirements need consideration of both internal molecular alterations and the external factors that influence health and disease. Several controlled trials have reported that short-term Yoga training programs reduce stress, improve mood, and reduce catecholamine and cortisol levels and blood pressure in both healthy and adult diabetic populations (Fig. 1). Several genomic studies on dementia caregivers and healthy adults have found that Yoga induces beneficial epigenetic changes in regulatory pathways of inflammation, oxidative stress, and insulin secretion [89].

DM is a complex multifactorial metabolic disorder. The sedentary lifestyle conditions lead to an increase in obesity and visceral fat resulting in hyperleptinemia and impaired adiponectin assimilation. Stress causes hyperactivation of the hypothalamic-pituitary-adrenalin axis, triggering over-secretion of cortisol. The upregulated glucocorticoids and resulting insulin resistance cause the upregulation of interleukins, which may lead to cell death. This results in the impaired insulin secretion. A transient hypoglycemia-insulin resistance-hyperinsulinemia causes a trigger for advanced glycation end products that are responsible for the metabolic syndrome.

In the postmodern scenario, with increase in lifestyle disorders, the pharmacological efforts have not yielded much promising results and lead to the re-emergence of

alternative therapies [90]. Although physical exercise has been documented for weight management and lifestyle modification, Yoga scores high based on an overall well-being and whole-body treatment. It has been shown to act on mind-body level and successful in combating the metabolic disorder (Fig. 2).

The study carried out by Klarod et al. [91] was undertaken to understand the effects of exercise on prediabetic men. They reported that 3-week exercise training, when practised at moderate altitude, causes increased biological antioxidant activity of plasma without altering the fasting plasma glucose. Another study analyzed the effect of 3-week uphill and downhill walking on glucose metabolism and level of lipids among prediabetics. It was reported that after uphill walking, the level of glucose tolerance, triglycerides, and total cholesterol improved significantly. They also emphasized that, depending on individual preferences, both types of exercises were useful for the prevention of T2DM. Moreover, Baker et al. [92] also revealed that 6 months of aerobic exercise improved executive function, CRF, and insulin sensitivity in adults with impaired glucose tolerance. They also suggested that in glucose-intolerant adults, the aerobic exercises showed enhanced effects on cognition. A significant relationship between physical activity as well as aerobic exercise and the levels of brain-derived neurotrophic factor has also been reported in patients with AD.

Three months of Yoga intervention on 123 T2DM patients has shown reduced BMI, level of malondialdehyde, and glycemic control. Oxidative stress was also found to be regulated through Yoga intervention, which was ascribed to the elevated level of glutathione and vitamin C (Fig. 1).

The intervention of Yoga in Parkinson's disease patients has also shown positive results and improved quality of life. The depression scores were also found to have improved in those patients [93]. In addition, Yoga also has been shown to have positive effect on memory [94], attention, and verbal fluency of aged population [95]. Moreover, the impact of silver Yoga on aged population with dementia has shown promising results on mental health, which includes decrease in behavioral and depressive behaviors [96]. Thus, these studies, which report positive results, suggest that it could be used as a promising tool for various cognition-related disorders [97].

While obesity, hyperlipidemia, and stress are the risk factors for the development of diabetes and dementia, none of the drugs directly modify these risk factors as effectively as Yoga and exercise in a cost-effective manner. Several studies have even compared the role of endurance exercise and Yoga in managing T2DM, suggesting it to be more effective over exercise [98]. Yoga has been shown to

Fig. 2. Risk factors and genetic loci associated with diabetes and dementia.

not only alleviate anxiety and stress [99] but also obesity [100] and associated oxidative stress [101–103], thereby regulating diabetes-induced cognitive decline [104]. Similarly, exercise also controls obesity and alters the associated insulin signaling pathway that modulates insulin resistance responsible for the progression of T2DM. The effect of exercise on stress and the associated neurotransmission may be optimal, but the intermittent hypoxia caused due to various Yogic techniques and its possible effect on mitochondrial function are emerging as the predominant pathway for rescue of impaired insulin secretion and function [98]. The meta-analysis has shown better glycemic control in T2DM patients with Yoga as an intervention when compared to physical exercise [98]. In the Yoga-based lifestyle change program, significant reduction of glycemic index (fasting blood sugar, HbA1c), insulin resistance, BMI, and lipid profile has been reported. The significant reduction was also found in psychological parameters such as anxiety and depression leading to improvement in quality of life [105]. Yoga as intervention in case-control studies and RCTs has showed statistically significant results in the reduction of blood glucose levels, as shown in Table 6. This significant decrease in blood glucose levels helps to control T2DM effectively along with the medication treatment [106–110].

A study carried out on rural population of Gujarat showed mixed response of subjects about traditional healing. While some found it beneficial, others reported that healers are not effective. In this study, authors suggested that association between faith healers and medical practitioners may perhaps reduce the burden of mental illness. The study was undertaken to understand the efficiency of faith-based adaptations on psychological parameters like depression and anxiety [111]. Likewise, an exploratory study carried out on terminal cancer subjects analyzed the impact of storytelling approach to increase a sense of connectedness and intimacy. The study showed a small and significant enhancement on spiritual well-being after intercessory prayers [112].

Global Preventive Initiatives

The burden of DM and related dementia on global public health needs to be resolved. National and international initiatives taken up by the government, community organizations, and health systems through different schemes, programs, efficacy research trials, media, schools, workshops, and policies can implement some preventive and cost-effective measures to reduce the burgeoning cases of DM and dementia as well as the awareness among people. Several RCTs have shown efficacy in

Table 6. Yoga for the treatment of T2DM [106–110]

Study and year	Type of the study	Sample size	Controls	Intervention	Weeks	Primary outcomes
Mondal et al. [106], 2018	Prospective case-control study	20 T2DM (10 yogic intervention and +10 controls)	TAU	Yogic intervention: <i>suryanamaskara</i> ; 8 <i>asanas</i> ; two <i>kriyas</i> and <i>pranayama</i>	12	Statistically significant decrease in FBG, PPBG, and cholesterol levels
Sreedevi et al. [107], 2017	RCT	124 T2DM (41 yogic intervention+ 42 peer intervention + 41 control)	TAU	Yogic intervention: <i>suryanamaskara</i> ; deep relaxation muscle technique; <i>sanas</i> ; <i>pranayama</i>	12	Trend of improving blood glucose levels (FBG, PPBG, HbA1C); statistically significant diastolic blood pressure
McDermott et al. [108], 2014	RCT	41 T2DM (21 yogic intervention and 20 walking control)	Walking	Yogic intervention: <i>pranayama</i> ; loosening exercise; <i>standing asana</i> ; <i>supine asana</i> ; <i>prone asana</i> , <i>sitting asana</i> , relaxation	8	Significant decrease in weight, BMI, and waist circumference that are risk factors of diabetes
Singh et al. [109], 2019	RCT	37 T2DM (22 yogic intervention and 15 were on waitlist)	TAU	Yogic intervention: loosening exercises; <i>suryanamaskara</i> ; <i>asanas</i> ; relaxation	12	Statistically significant decrease in HbA1c, mean plasma glucose, and cholesterol levels in intervention group
Nagarathna et al. [110], 2012	RCT	277 T2DM (141 were on yogic intervention and 136 were on exercise)	Exercises on standing position; supine position; rest and lectures	Yogic intervention: breathing exercise; <i>shiithlikarana vyayama</i> ; <i>asanas</i> ; <i>bandhas</i> and <i>kriyas</i> ; <i>pranayama</i> ; meditation and lectures	36	Statistically significant reduction in FBG, LDL and medication requirement in statistical significant increase in HDL in yogic intervention group; also HbA1C, PPBG, total cholesterol, triglycerides, and VLDL decrease in both groups but better effect in yogic group

T2DM, type II diabetes mellitus; RCT, randomized controlled trial; TAU, treatment as usual; FBG, fasting blood glucose; PPBG, postprandial blood glucose; HbA1c, glycated hemoglobin; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein.

reduction of diabetic incidence by structured modification in lifestyle leading to weight loss. Diabetes Prevention Program (DPP) is one such research trial of United States (US) – National Institute of Health for US population. The emphasis on caloric reduction and increase in physical activity in one group of DPP has remarkably shown 58% reduction in diabetic incidence over 4 years across male and females, races and ethnicities, and proved metformin (second group) as safe and effective for diabetes, as also briefly discussed earlier. In 2010, a panel of Centers for Disease Control and Prevention and an international group took action toward weight management and primary prevention of T2DM, through various “immediate” and “strategic” actions, together with research in different populations across certain countries [113]. Immediate and strategic actions proposed by health care includes primary measures, evaluation of a uniform diagnostic criterion, screening, diagnosis, risk status, financial support for prevention programs, and promotion of research. Public health system involved in supporting intervention delivery, implementing National DPP and delivering it to convenient sites, identifying policies, insurances, and incentives for sustainability of prevention pro-

grams, and improving school, workplaces, or community sites to support a healthy lifestyle along with promoting research. More information about Centers for Disease Control and Prevention can be obtained from the site <https://www.cdc.gov>. Furthermore, financial incentives are provided to healthcare providers and organizations to provide high-quality care to healthcare purchasers. The US Centers for Medicare and Medicaid Services in USA is involved in such activities. US National Committee on Quality Assurance’s Healthcare Effectiveness Data and Information Set is involved in the assessment of risk factors and diabetes development. Likewise, National Institutes of Health-funded Studies to Treat or Prevent Pediatric Type 2 Diabetes study showed decreased prevalence of overweight and obesity in a school-based intervention.

China is one among the Asian countries that is at greater risk for developing DM. It bears a huge burden of DM; hence, several researchers in China have developed an intervention program that is useful for high-risk individuals. A major intervention study (diet and Exercise) was conducted in China on individuals with impaired glucose tolerance and followed up for 6 years. It was found that by using lifestyle intervention tools, that is,

diet and exercise, the incidence of conversion from pre-diabetes to diabetes was significantly reduced [114]. In a follow-up study of the same group after 20 years, it showed fewer occurrences (43%) of diabetes in comparison with control group [3, 115]. Moreover, this group was again followed after 23 years and showed decreased prevalence of cardiovascular diseases [116].

As obesity is a potent risk factor of DM and dementia, Brazil government has implemented various health policies time to time. In 1999, they took initiative by preventive and management programs for obesity for all the social groups and also developed the nationwide and inter-departmental programs [117]. The public policy structures focused on dietary and nutritional education (2012). In addition, the aim of Ministry of Health was the development of various academies for physical and health-promoting activities for the encouragement of physical activity. Brazil also promotes social participation and has developed variety of councils in multiple regions of the government, for example, The National Health Council (CNS) and the National Food and Nutritional Security Council [117].

Sri Lanka is also one of the main nations in SEA which is combating DM aggressively. There are various programs in Sri Lanka to manage, control, and create awareness about DM. They have launched various programs funded by different organizations and charitable trusts with the aim of spreading awareness about DM and the comorbidities associated with it among the community. Moreover, media has also played imperative role along with healthcare professionals for success of these national programs [118].

Indian Preventive Initiatives

India is home to huge number of diabetic patients in the world and will soon become the nation having maximum number of diabetic patients in the world. Therefore, to eradicate the problem of diabetes, Government of India has taken up various steps. The PMO has initiated the “fit India” program. Ministry of Health and Family Welfare started a National Programme for Prevention and Control of Diabetes, Cardiovascular Disease and Stroke in 10 districts of 10 states of India in 2008. The main logo in this scheme was “fitness is essential for survival”. National Programme for Prevention and Control of Diabetes, Cardiovascular Disease and Stroke through this program made provision of supplying free diagnostics and free drugs for NCD patients visiting 388 district NCD clinics and 2,115 community health centers NCD clinics across India (till March 2017) [119]. Under the same scheme, Odisha state

government supplied free anti-diabetic drugs and insulin to patients at government health centers. The state government subsequently increased annual drug budget of Rs 200 million for purchasing the medicines. The core objective for this programme was promotion of health among the community to understand the occurrence of high-risk individuals and prevention of disease. Hence, for the achievement of this objective, various methods were used like activities in school, workplace, and general population. Further, for risk analysis, screening, monitoring, and research programs were encouraged. Moreover, health workers were also motivated to perform their duty in the welfare of society and provide necessary information in the community to help them develop healthy habits and managing their health. By using simple community health methods, the risk for diseases like diabetes, cardiovascular diseases, and stroke was significantly decreased.

Ayushman Bharat

This is world's largest government-funded health insurance scheme that has been implemented to provide free essential diagnostics and treatment for non-communicable disorders with possible involvement of corporate social responsibility. This will have 2 components, namely, Health wellness and the National Health Protection to be provisioned through 150,000 wellness centers.

Initiatives for Ayushman Bharat

Yoga as an Alternative Intervention

According to world morbidity statistics, NCDs prevention and control are the major targets of universal health coverage. Cognitive dysfunction and dementia have been neglected as a complication of DM [120]. DM and dementia, being age-related disorders, are a major public health concern with its cost implication, thus indicating preventive, curative, and cost-effective measures should be required. There are several drugs to either provide temporary relief or control for the chronic diseases like DM and dementia, AD, cancers and stroke, and age-related macular degeneration (AMD). However, most of them have no permanent remedy. A wealth of resources have been invested in developing new drugs, but a good number of them have no clinical benefits and some even have adverse effects with overburdening cost implications.

Therefore, with burgeoning population and escalating health costs for the management of diabetes and associated dementia, a pragmatic cost-effective integrated approach of wellness and Yogic intervention is necessary.

Need for the Electronic Health Records

From ancient times, Yoga has been incorporated into cultural and physical activity and used for balancing emotional, physical, and spiritual health. In the growing era of modern medicine, evidence from clinical research is required to integrate various approaches in health care. Studies have shown Yoga effectiveness in symptomatic relief and improving patient outcomes in chronic diseases. Despite increased number of Yoga studies and substantial benefits in many NCDs, it remains unclear if the existing studies depicting beneficial aspect of Yoga can be applicable to other population, cultures, and religions. The underlying mechanisms behind the observed benefits still need to be clearly understood. Furthermore, cost-effectiveness studies and long follow-up studies need to be conducted. Electronic Health Records (EHR) consist of computerized healthcare system to store electronic health information including life events, medications, vitals, past medical history, laboratory data, and radiographs. This transformation has not only improved clinical outcome of individual patients but also created a scope for improving population health by conducting research. When clinical data are stored electronically that can be pooled for its quantitative analysis and better understanding of disease prognosis, diagnosis, treatment, and costs can be drastically reduced [121]. Implementing EHRs into *Ayushman Bharat* can potentially grow pool of clinical and biochemical data of patients with NCDs and the effect of Yoga intervention that can be internally assessed to analyze its comparative effectiveness and cost-effectiveness [122]. Further efficacy studies for Yoga from the pooled data will increase body of evidence for Yoga effectiveness on NCDs. Thus, Yoga can be widely advocated as a cost-effective non-pharmacological intervention and can be institutionalized in synchronization, co-operation, and collaboration with modern medicine by using EHRs.

EHRs and Opportunity of Research Trials

Researchers from India have been importing kits for many NCDs, yet there is an increased inflow of this equipment from the foreign countries. Due to insufficient patient data and research, India is not sufficiently able to generate adequate evidence. After the introduction of EHRs as a part of *Ayushman Bharat*, many biochemical kits can be developed in India. These could come to existence with wealth of patient data retrievable

and accessible from EHRs. This may also reduce the dependence of India on importing kits of many NCDs from foreign countries.

Insurance Policies for Major NCDs and Alternative Medicine

In the context of ever-rising healthcare costs, the importance of health insurance is enormous. Very few insurance schemes cover preexisting diseases including DM, dementia, cancer, hypertension, and asthma, and people who suffer remain deprived of comprehensive health coverage. It would be helpful if the recently launched *Ayushman Bharat* Health Insurance scheme caters to preexisting conditions like diabetes and dementia through cost-effective alternative therapies like Yoga [123], thereby preventing conversion of pre-diabetes into diabetes, mild cognitive impairment to AD, TIA into stroke, dry AMD into wet AMD, and even precancers into full-blown cancer by mere Yoga-based lifestyle change. The integration of both traditional and modern approaches can be positioned at an insurance premium across all districts in India through *Ayushman Bharat*.

Conclusion

DM is a metabolic disorder that is not treatable and can only be managed using some drugs. However, such treatment is not without side-effects. The high-risk individual can be screened by utilizing an Indian Diabetic Risk Score [124] based questionnaire that can be administered in a population level. A preliminary intervention is possible at the community level. It will be useful to halt the onset of diabetes and associated dementia by Yoga intervention. The modification of lifestyle factors such as dietary changes as well as physical inactivity through Yoga intervention can be a cost-effective approach in managing diabetes and associated dementia. India can play a lead role in leveraging Yoga technology in SEA through its recently standardized Diabetic Yoga Protocols and Level 1 and Level II accreditation programs for Yoga professionals. With such centers, the long-term studies examining the longitudinal effects of Yoga interventions among diabetics and dementia can also be launched.

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