

Effect of yoga on cardiac autonomic dysfunction and insulin resistance in non-diabetic offspring of type-2-diabetes parents: A randomized controlled study

Satish G. Patil^{a,*}, Manjunatha R. Aithala^a, Govindanagouda V. Naregal^b,
Amarnath G. Shanmukhe^c, Shalmon S. Chopade^c

^a Department of Physiology, Shri B.M.Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India

^b Department of Biochemistry, Shri B.M.Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India

^c Department of Medical Surgical Nursing, BLDEA's Shri B.M.Patil Institute of Nursing Sciences, Vijayapura, Karnataka, India

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ABSTRACT

Objective: The present study was aimed to determine the effect of yoga program on cardiac autonomic dysfunction and insulin resistance in non-diabetic offspring of diabetes parents.

Methods: A randomized passive-controlled study was conducted on 64 non-diabetic offspring of type-2-diabetes parents (mean-age:25.17years). Yoga group participants received yoga training for 8 weeks. Heart-rate variability (HRV) indices: low frequency (LF), high frequency (HF) and LF/HF ratio; fasting blood glucose (FBG), oral glucose tolerance test (OGTT) and insulin resistance (IR) were estimated at baseline and after 8-weeks of intervention.

Results: We found a significant decrease in LF ($p = 0.005$), LF/HF ratio ($p = 0.004$), IR ($p < 0.001$), OGTT ($p = 0.003$) and increase in HF ($p = 0.022$) in yoga group participants. Control group participants did not show any significant change in any variables.

Conclusions: Improvement in cardiac autonomic function and insulin resistance by yoga training implies that yoga can reduce the risk of development of diabetes in offspring of diabetes parents.

1. Introduction

Diabetes is a major health problem worldwide and the number of people with diabetes has substantially increased from 108 million (4.7%) in 1980 to 422 million (8.5%) in 2014 [1,2]. India has topped in the world with highest number of diabetic people (31.7 million) in 2000 followed by China (20.8 million) and USA (17.7 million) [3]. Diabetes population in India was increased to 68.2 million in 2015 [4] and a recent prevalence rate was 7.3% [5]. The rapid increase in prevalence of diabetes may be attributed to the decline in the mean age of onset of diabetes, affecting and involving the younger age group [6]. This increasing prevalence of diabetes in younger age group like children, teenagers and adolescents is a new and alarming facet of the epidemic of diabetes [6–8].

The risk of development of diabetes in children of single diabetes parent is 3.5 fold higher and in those with two diabetes parents is 6 fold

higher when compared with children without parental diabetes [9]. In a study on the prevalence of type 2 diabetes in the offspring of two diabetes parents, diabetes was observed in 50% of offspring, while 12% had impaired glucose tolerance [10]. The presence of pre-diabetes features such as hyperinsulinemia, insulin resistance (IR) or impaired glucose tolerance (IGT) [11–13] in non-diabetes offspring of parents with type 2 diabetes suggests a familial predisposition to diabetes. These pre-diabetes features were associated with cardiac autonomic dysfunction [14,15]. It has been shown that non-diabetes subjects with parental type-2 diabetes have increased sympathetic activation, decreased parasympathetic dominance and increased prevalence of cardiac autonomic dysfunction when compared with non-diabetes subjects without parental type-2 diabetes [14,15], suggesting a development of early autonomic dysfunction in the healthy offspring of parents with type 2 diabetes. Further, prospective longitudinal studies have implicated a causal role of autonomic dysfunction in the development of

* Corresponding author. Department of Physiology, Shri B.M.Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India.

E-mail addresses: sathupatil@yahoo.co.in (S.G. Patil), bharatimanju@ymail.com (M.R. Aithala), gvnaregal@gmail.com (G.V. Naregal), amargs31@gmail.com (A.G. Shanmukhe), shalmonchopade@gmail.com (S.S. Chopade).

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diabetes [16–22]. These findings suggest that autonomic dysfunction develops well-priorly and is involved in the pathophysiology of diabetes. So, we hypothesized that early detection and an early intervention to optimize the autonomic dysfunction may prevent reduce the risk of future development of diabetes in high risk individuals.

Yoga has a beneficial impact on glycemic control and insulin resistance in people with type 2 diabetes [23,24]. However, preventive effects of yoga on diabetes development are not clear and remain to be elucidated. As the strategy must be focused on primary prevention of diabetes in high risk individuals with cost-effective intervention [23,25], the present study was aimed to determine if yoga can improve the early cardiac autonomic dysfunction and insulin resistance, and reduce the risk of diabetes development in healthy offspring of diabetes parents.

2. Research design and methods

2.1. Ethics statement

Consent from the participants was obtained prior to randomization and recruitment to the study. The study was approved by the Institutional Ethical Committee of Shri B. M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University) India, as per the guidelines (2017) of Indian Council of Medical Research [26]. The study was registered in the Clinical Trial Registry-India (CTRI/2016/04/006877).

2.2. Study design and protocol

An open label, randomized controlled study was conducted on 64 non-diabetes and normotensive offspring of type-II diabetic parents with LF/HF ratio [a ratio of low frequency (LF) and high frequency (HF) component of heart rate variability: an index of autonomic balance] more than 2.5 [27], aged between 18 and 40 years. Subjects on any regular medical treatment, or taking vitamins/any herbal drugs; subjects with history of smoking, chewing tobacco and alcoholism were excluded from the study.

Volunteers for participation in the project were invited through advertisement. They were screened for eligibility and selected volunteers were allocated to either Yoga group (n = 32) or control group (n = 32) using randomization method. Random number table was used for randomization. The allocated randomization numbers were used to identify the volunteer during the entire study.

Yoga intervention was given to the participants of Yoga group for 1 h in the morning for five days in a week for 8 weeks under the supervision of the trained yoga instructor. Yoga protocol has been given in table-1. As no active intervention was scheduled for control group participants, they did their usual activities.

2.3. Data collection

Data was collected at baseline and after 8 weeks of intervention. Data was collected in the morning between 9.00 a.m. and 12.00 noon after a supine rest of 10 min. No yoga intervention was given on the day of data collection. All the participants were also instructed to avoid physical activity on the day of pre- & post-investigation. Blood samples were collected in the morning after overnight fasting. Total cholesterol (CHOD-PAP: cholesterol oxidase-peroxidase enzymatic method), triglyceride (GPO-PAP: glycerol phosphatase-oxidase method) and HDL cholesterol (PTA: Phosphotungstic acid method) was determined using commercial diagnostic kits (ERBA-MANNHEIM). Blood pressure (BP) was measured using digital BP monitoring system (OMRON HEM-7111).

2.3.1. Heart-rate variability

Cardiac autonomic function was assessed using short-term heart-

Table 1
Integrated yoga program.

Yoga Practices	Duration (60 min)
1. Starting prayer	1 min
2. Sukshama vyama (Loosening exercises)	10 min
3. Relaxation	2 min
4. Surya Namaskara (Sun salutation)	10 min
5. Relaxation technique	4 min
6. Yogasana: (stretching and maintaining posture with controlled breathing) Ardhakati Cakrasana, Padhastasana, Parivrtta Trikonasana, Ardha Matsyendrasana Bhujangasana, Dhanurasana, Sarvangasana, Matsyasana	10 min
7. Relaxation technique	3 min
8. Pranayama Kapalbhati (forced exhalation) Nadi suddhi pranayama (Alternate nostril breathing) Sitkari Bhramari	9 min
9. Meditation (om meditation)	10 min
10. Closing prayer	1 min

rate variability (HRV) analysis. A 5 min ECG in standard limb lead II configuration was obtained using a digital polygraph (Medicaid systems Pvt Ltd, India). ECG was inspected offline and data free from ectopic beats and noise was exported as R-R interval for further HRV analysis. Analysis of HRV was done by frequency domain method, as per the guidelines of a Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [27], using a HRV analysis software version-2.1 (Biomedical Signal Analysis Group, University of Kuopio, Finland) [28]. Power spectral density of the R-R interval was obtained by using a non-parametric Fast Fourier Transform (FFT) technique. The frequency range (0–0.40 Hz) in normalized units (nu) was divided into very low frequency (0–0.04), low frequency (0.04–0.15 Hz) and high frequency (0.15–0.40 Hz). Low-frequency (LF) reflects sympathetic tone (usually) while high frequency (HF) reflects parasympathetic tone. A ratio of LF and HF (LF/HF) indicates sympathovagal balance (overall balance between the sympathetic and the parasympathetic systems).

2.3.2. Glucose tolerance test

Oral glucose tolerance test (OGTT) was performed after an overnight fast. 75 gm of glucose in 300 ml of water was given to drink. Blood samples were collected at 0-h and 2-h for plasma glucose estimation.

2.3.3. Serum insulin

Fasting serum insulin concentration was measured using monoclonal antibody coated immunoassay (DIA source INS-EASIA Kit, DIASource ImmunoAssays, Belgium).

2.3.4. Insulin resistance

Insulin resistance (IR) was assessed using the Homoeostasis model of assessment-IR (HOMA-IR) index, which is defined as fasting insulin ($\mu\text{U/ml}$) times fasting glucose (mmol/l) divided by 22.5 and value above 1.64 were considered as abnormal [29].

2.4. Statistical analysis

Data was presented as mean \pm SD. Statistical significance was established at $p < 0.05$. An unpaired 't' test was used to find the difference between pre-intervention or baseline values of yoga and control groups. A paired t-test (parametric test for normal distribution data)

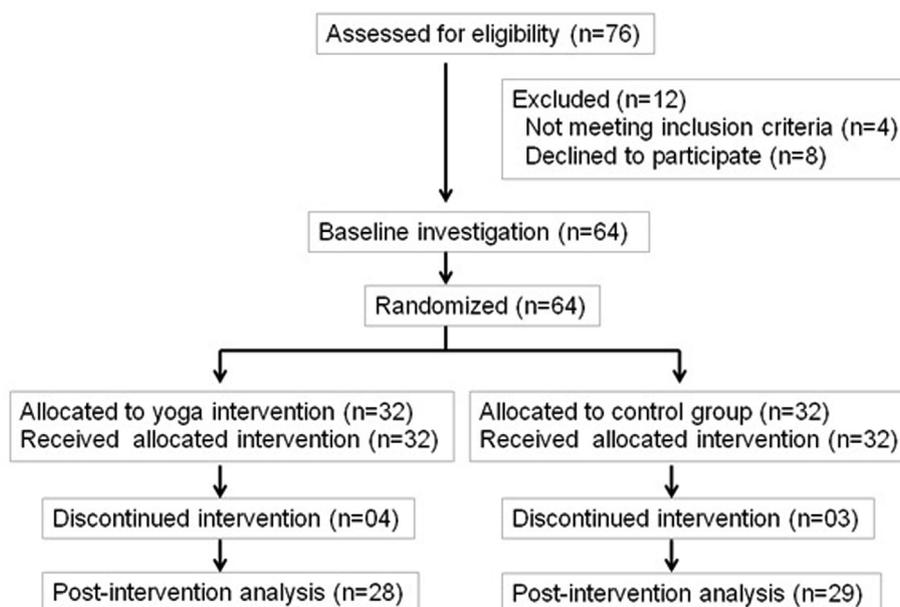


Fig. 1. CONSORT flow diagram.

and Wilcoxon signed rank test (non-parametric test for non-normal distribution data) was applied to determine the significant difference between pre-intervention and post-intervention values within the group. Analysis of Covariance (ANCOVA) was applied to find the differences in the post-intervention values between study and control groups. It determines the difference between the effects of intervention by controlling the pre-test values of both groups. Statistical analysis was done by using SPSS software.

3. RESULTS

3.1. Consolidated statement of randomized trial (CONSORT)

The flow of participants through the study has been depicted in the CONSORT flow diagram (Fig. 1). The subjects were screened ($n = 76$) for eligibility to the study. Among 76 subjects: 12 were excluded, 4 subjects were not meeting inclusion criteria and 8 subjects declined to participate in the study. A total of 64 subjects (normoglycemic and normotensive offspring of type 2 diabetes parents) were randomized and recruited to yoga ($n = 32$) and control group ($n = 32$) respectively. Seven subjects were lost to follow-up (4 participants from yoga group and 3 participants from control group). Post-intervention investigation of 28 participants from the yoga group and 29 participants from the control group was done. Finally, data of 57 participants was analyzed. Participant adherence to yoga training was 84%.

3.2. Baseline characteristics of participants

The baseline characteristics of the participants were shown in Table 2. The mean age of participants was 25.17 ± 7.36 and 25.55 ± 7.78 in yoga and control group respectively. Participants with parental history of single or both diabetic parents were included. However, most of the participants were having the history of single diabetic parent. As there was no significant difference in age, BMI, blood pressure and LF/HF ratio between the two groups, it implies an equal distribution of samples. The mean LF/HF ratio was 3.17 and 3.05 in yoga and control group participants respectively. The mean HOMA-IR was 3.34 ± 1.49 in yoga group and 2.74 ± 1.06 in control group, indicating that all the participants were insulin resistant [29]. Fasting blood glucose, serum triglyceride, total cholesterol and HDL cholesterol levels were within the normal range in the participants of yoga and

Table 2

Baseline characteristics of participants.

Variable	Yoga group (n = 28)	Control group (n = 29)	p-Value
	Mean \pm SD	Mean \pm SD	
Age (Years)	25.57 \pm 7.36	25.55 \pm 7.78	0.855
BMI (kg/m ²)	23.19 \pm 2.52	23.56 \pm 3.36	0.303
Systolic BP (mmHg)	122.21 \pm 9.17	119.6 \pm 9.03	0.907
Diastolic BP (mmHg)	77.57 \pm 6.21	76.72 \pm 6.64	0.567
Pulse Pressure (mmHg)	44.64 \pm 6.15	42.89 \pm 6.47	0.650
MAP (mmHg)	92.39 \pm 6.67	90.93 \pm 6.82	0.768
LF/HF ratio	3.18 \pm 0.53	3.05 \pm 0.58	0.430
HOMA-IR index	3.34 \pm 1.49	2.74 \pm 1.06	0.087
Fasting Blood Glucose (mg/dl)	88.86 \pm 13.98	83.79 \pm 11.64	0.250
Serum Triglyceride (mg/ dl)	100.6 \pm 37.03	100.35 \pm 22.73	0.095
Total Cholesterol (mg/ dl)	152.5 \pm 24.32	154.23 \pm 19.79	0.763
HDL Cholesterol (mg/dl)	52.46 \pm 15.89	51.07 \pm 11.82	0.062

Unpaired T test was applied to determine the difference between the baseline values of yoga and control group; BMI- Body mass index; MAP – Mean arterial pressure; LF/HF ratio is the index of the autonomic balance; HOMA-IR- Homoeostasis model of assessment-IR; Values are expressed in Mean \pm SD.

control group as well.

3.3. Heart-rate variability

Table 3 shows within-yoga and between-groups change in HRV (as an index of cardiac autonomic nervous system function). In a frequency domain analysis of HRV, we found a significant decrease in mean LF component from 59.63nu to 58.22 nu ($p = 0.005$) and LF/HF ratio from 3.178 to 2.771 ($p = 0.004$) and significant increase in HF component from 19.22 nu to 21.81 nu ($p = 0.022$) in yoga practitioners. While within the control group, there was no significant difference in HRV of the participants between baseline and post-two months. Between-group analysis shows a significant difference in LF, HF and LF/HF ratio between yoga and control groups. These findings indicate that yoga has significant beneficial effect on cardiac autonomic nervous system.

Table 3
Heart rate variability: changes within-group and between-groups.

Parameters	Yoga group			Control group			Between group	
	Pre-test	Post-test	Mean change (95% CI)	Pre-test	Post-test	Mean change (95% CI)	ANCOVA	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean changes	p value
LF (nu)	59.63 ± 1.59	58.22 ± 2.59	1.41 (0.23, 2.59) ^{b*}	59.23 ± 2.07	59.47 ± 1.64	-0.23 (-0.92, 0.44) ^b	1.64	0.020 [*]
HF (nu)	19.23 ± 2.89	21.81 ± 4.83	-2.58 (-4.77, -0.39) ^{a*}	20.07 ± 3.84	19.61 ± 3.08	0.47 (-0.79, 1.73) ^b	-3.05	0.024 [*]
LF/HF ratio	3.18 ± 0.53	2.77 ± 0.50	0.41 (0.13, 0.68) ^{b***}	3.05 ± 0.58	3.11 ± 0.54	-0.057 (-0.25, 0.13) ^a	0.47	0.005 ^{**}

*p < 0.05, **p < 0.01, ***p < 0.001; a: paired-t test; b: Wilcoxon Signed rank test.

Table 4
Glycaemic status, oral glucose tolerance test and insulin resistance: changes within-group and between-groups.

Parameters	Yoga group			Control group			Between group	
	Pre-test	Post-test	Mean change (95% CI)	Pre-test	Post-test	Mean Change (95% CI)	ANCOVA	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean change	p value
Fasting Glucose level (mg/dl)	88.86 ± 13.98	82.96 ± 10.68	5.89 (2.96, 8.83) ^{***}	83.79 ± 11.64	83.61 ± 8.59	0.18 (-2.44, 2.8) ^b	5.71	0.023 [*]
OGTT Post-2 hour glucose (mg/dl)	119.64 ± 19.12	112.18 ± 11.64	7.46 (3.21, 11.71) ^{b**}	120.45 ± 16.54	121.17 ± 16.77	-0.72 (-3.68, 2.24) ^a	8.18	< 0.001 ^{***}
Fasting insulin	14.98 ± 5.4	13.26 ± 4.51	1.63 (0.98, 2.28) ^{****}	13.19 ± 4.21	12.82 ± 3.21	0.37 (-0.26, 0.99) ^a	1.26	0.012 ^{**}
HOMA-IR	3.34 ± 1.49	2.74 ± 1.06	0.6 (0.37, 0.84) ^{****}	2.74 ± 1.06	2.65 ± 0.74	0.096 (-0.06, 0.25) ^a	0.504	< 0.001 ^{***}

*p < 0.05, **p < 0.01, ***p < 0.001; a: paired-t test; b: Wilcoxon Signed rank test.

3.4. Glycemic status, oral glucose tolerance test and insulin resistance

Table 4 shows within-yoga group changes in the glycaemic status and insulin resistance. Fasting blood glucose level was significantly decreased from 88.74 mg/dl to 83.07 mg/dl (p = 0.01) following yoga intervention for two months. Oral glucose tolerance test has shown a significant decrease in post-two hour glucose level from 119.77 mg/dl to 112.4 mg/dl (p = 0.003) in the participants of yoga group. HOMA-IR values more than 1.64 is considered as insulin resistance [29]. Higher HOMA-IR values of all the participants indicate that they were all insulin resistant. There was also a highly significant reduction in fasting insulin levels and insulin resistance. Fasting insulin level and HOMA-IR was reduced from 15.13 to 13.45 (p < 0.001) and 3.39 to 2.78 (p < 0.001) respectively. While in the participants of control group, there was no significant difference in blood glucose, OGTT and insulin resistance. There was a significant between-group difference in fasting blood glucose, OGTT, fasting insulin level and HOMA-IR. These findings suggest that yoga had high significant beneficial effect on glucose metabolism and insulin resistance.

4. Discussion

The present study investigated the effect of yoga program on cardiac ANS function, insulin resistance and glucose profile in non-diabetes but insulin resistant offspring of parents with type 2 diabetes. Significant beneficial modulations in cardiac autonomic function, insulin resistance and glucose tolerance by yoga training for 8 weeks in non-diabetes and normotensive offspring of type 2 diabetes parents were the major outcomes of the study. As per our knowledge, we are the first to report the preventive effects of yoga on type 2 diabetes in high risk individuals.

Early cardiac autonomic dysfunction has been shown in the healthy offspring of parents with type 2 diabetes [14,15]. An increased LF/HF ratio (index of sympathovagal balance) indicating a shift in the autonomic balance towards sympathetic dominance, was identified in insulin resistant offspring of type 2 diabetes parents [14]. Foss CH et al.,

have shown that non-diabetes subjects with parental type-2 diabetes have increased prevalence of cardiac autonomic neuropathy compared with non-diabetes subjects without parental type 2 diabetes [15]. Further, autonomic neuropathy was associated with increased fasting insulin level [15]. Prospective longitudinal follow-up (for 11–15 years) have found that diabetes was developed in those subjects who had autonomic dysfunction or impaired autonomic function at baseline [16–22], implicating a causal role of autonomic dysfunction in the development of diabetes. In the present study, we have observed a significant beneficial modulation in the cardiac ANS activity by yoga training for 8 weeks. Yoga practice has significantly decreased LF (nu) component of HRV by 2.4% and LF/HF ratio by 12.9%; and increased HF (nu) component of HRV by 11.8% suggesting a reduction in sympathetic tone and increase in parasympathetic tone respectively (wide table-2). This restoring of sympathovagal balance towards its normal parasympathetic dominance implies that yoga can stabilize the autonomic function in the offspring of parents with type 2 diabetes. There was no significant variation in the ANS function in participants of control group. We found three studies that investigated effect of yoga on ANS function in type 2 diabetes patients with contradictory outcomes [30–32]. One study has reported an improvement in parasympathetic activity with an intervention of integrated yoga therapy for one week [30], while Jyotsana P et al. have shown an improvement in sympathetic functions with no change in the parasympathetic function after a practice of Sudarshan Kriya Yoga (a form of yoga that involves rhythmic cyclical controlled breathing practices) for 6 months [31]. Singh et al. also showed a reduction in sympathetic activation after an intervention of selective yogasanas (stretching and maintenance of postures with controlled breathing) for 40 days in patients with type 2 diabetes [32].

In the present study, yoga practice had reduced the mean fasting insulin by 11.5% and mean insulin resistance by 18%. Though the fasting glucose was within normal range, there was a significant decrease in mean fasting blood glucose by 5.89 mg/dl and improvement in the glucose tolerance by 6.2% in yoga group participants. While control group participants did not show any significant difference in

their insulin, insulin resistance and glucose profile. A complex relationship exists between autonomic dysfunction, insulin and glucose metabolism. Autonomic nervous system has a bidirectional relationship with insulin and glucose [15–22,33,34]. Probable mechanism by which autonomic dysfunction leads to development of diabetes is that increased sympathetic activity leads to enhanced release of catecholamines resulting in hyperglycemia (through gluconeogenesis and glycogenolysis), decreased glucose tolerance, lipolysis (increased free fatty acids) and reduced insulin response to glucose leading to insulin resistance [35,36].

An intervention of integrated yoga training to the yoga group participants of present study included loosening practices, suryanamaskara (sun salutation), yogasanas (stretching and maintaining postures with controlled breathing), Kapalabhati (forced exhalation), pranayama (slow paced controlled breathing practices) and meditation. Each round of Suryanamaskar is associated with oxygen consumption of about 26 ml/kg/min and energy expenditure of 57.5 Kcal [37]. Yoga group participants practiced Suryanamaskar for 10 min (4 rounds) during each session, spending energy about 230 Kcal which is equivalent to energy spent during moderate aerobic exercise. Yogasanas (postures) are shown to be beneficial for glucose metabolism and insulin function [32]. Relaxation techniques, pranayama and meditation can improve breathing, relax mind-body and optimize autonomic functions [23,38–40]. These several techniques of yoga may induce favorable modulation in psycho-neuro-endocrine axis/mechanism of diabetes and may reduce the risk of its development in offspring of type 2 diabetes parents.

Yoga induced improvement in insulin resistance and glucose tolerance in offspring of parents with type 2 diabetes might be due to increased physical activity and beneficial modulation in autonomic function by reducing sympathetic overactivity and enhancing parasympathetic tone. However, it remains to be determined whether yoga had any favorable impact on the genetic factors and susceptibility, which is the limitation of the study. Control of diet is a primary concern in yogic management which was not recommended and also dietary habits of the participants were not collected that forms the second limitation of the study. Third limitation of the study is that follow-up of yoga group participants was not done after 8-weeks of intervention to confirm the duration of influence of yoga on them.

5. Conclusion

Beneficial modulations in cardiac autonomic function and reduction in insulin resistance by yoga training for 8 weeks implies that yoga can reduce the risk of development of type 2 diabetes in offspring of type 2 diabetes parents. Yoga can be used as an effective lifestyle modality for diabetes prevention. However, further long-term, prospective studies are required to confirm the preventive effects of yoga on diabetes development in high risk individuals.

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Conflicts of interest

No competing interest for any authors.

Author contributions

S.G.P designed and developed the protocol of this study. M.R.A and G.V.N recruited participants. A.G.S and S.S.C collected study data. S.G.P

and M.R.A proposed the analysis, interpreted data and wrote the manuscript. G.V.N, A.G.S and S.S.C reviewed and edited the manuscript. All the authors approved the submission of manuscript to Diabetes Care. S.G.P is the corresponding author and guarantor of this work and takes the responsibility for the integrity of the data.

Prior presentation

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