SECTION XI

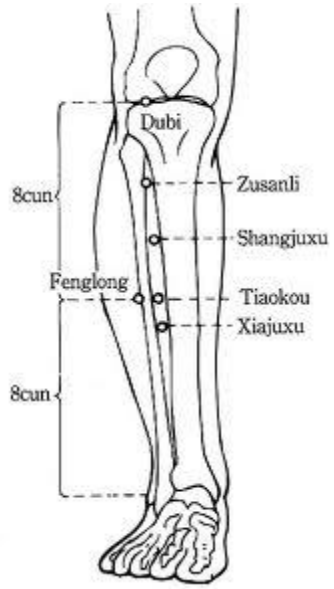
APPENDICES

Appendix 1

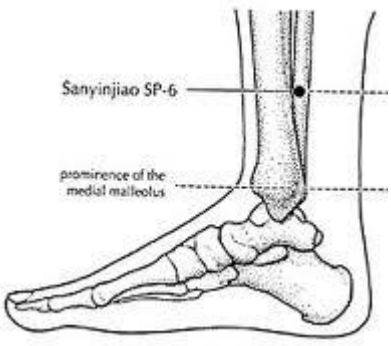
Acupuncture points for Diabetes

Appendix 1:

1. ***Zusanli*** **(St 36)** – the acupuncture point is located 3 inches below the lateral knee depression, one finger breadth from the lateral side of the anterior crest of tibia.

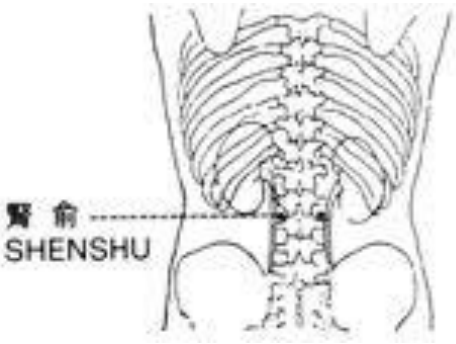


2. ***Sanyinjiao*** **(Sp 6)** – the acupuncture point is located 3 inches above the tip of inner ankle, on the posterior margin of the metatarsal bone.



3. ***Feishu*** **(UB 13)** – the acupuncture point located 1.5 inches lateral and inferior to the spinous process of the third thoracic vertebra in prone position.

4. ***Shenshu*** **(UB 23)** – the acupuncture point located 1.5 inches lateral and inferior to the spinous process of the second lumbar vertebra in prone position.



5. ***Zhongwan*** **(CV 12)** – the acupuncture point is located on the upper abdomen and on the anterior abdominal wall, 6 inches above umbilicus.

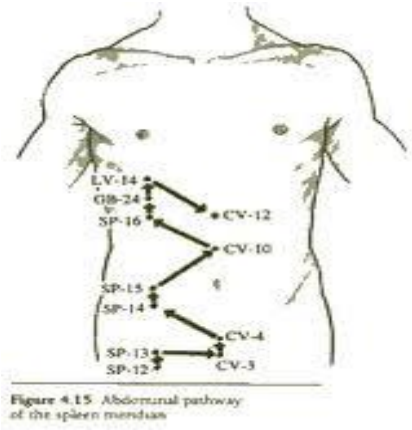


Figure 4.15 Abdominal pathway of the spleen meridian

Appendix 2

Yoga Module

Appendix – 2 Yoga module

Sl. No.	Practice	No. of rounds
1.	**Starting prayer**	
2.	**Breathing Practices**	
	-Hands stretch breathing	10
	-Hands in and out breathing	10
	-Ankle stretch breathing	10
	-Tiger breathing	5
3.	**Instant Relaxation Technique (IRT)**	
4.	**Loosening Exercises**	
	-Drill Walking	30
	-Twisting	10
5.	**Quick Relaxation Technique (QRT)**	
6.	**Asanas**	
	-Ardhakatichakrasana	3
	-Ardhachakrasana	3
	-Vrikshasana	3
	-Trikonasana	3
	-Vakrasana	2
	-Ardha Matsyendrasana	2
7.	**Deep Relaxation Technique (DRT)**	
8.	**Pranayama**	
	-Sectional Breathing	10
	-Nadishuddhi pranayama	12
	-Sitkari pranayama	9
	-Bhramari pranayama	9
9.	**Meditation**	
	-Breathe awareness	3 minutes
10.	**Closing Prayer**	

Appendix 3

Pilot Study Results

Appendix 3-

Pilot Study -Comparison of changes in ambulatory glucose profile before and after yoga

	Pre	Post	Difference	p value	Correlation co-efficient (pre & post) *r*
Mean daily glucose (mmol/L)	8.35±2.33	7.67±2.05	0.68±0.65	0.014*	0.96
S.D.	2.30±0.86	1.99±0.66	0.31±0.36	0.036*	0.92
MODD	1.97±0.71	1.67±0.56	0.3±0.38	0.048*	0.85
CONGA	7.38±2.29	6.74±1.99	0.64±0.73	0.031*	0.95
GRADE	6.21±5.85	4.79±4.92	1.42±1.74	0.04*	0.96
ADDR	19.73±12.25	15.33±9.25	4.4±4.67	0.022*	0.94
J INDEX	39.44±23.18	32.23±18.07	7.21±8.90	0.041*	0.94

*$p < 0.05$

Key:

S.D. – Standard deviation; **MODD** – Mean of daily differences; **CONGA** – Continuous overlapping of net glycaemic action; **GRADE** – Glycemic risk assessment in diabetes equation; **ADRR** – Average daily risk ratio

Appendix 4

Sample Size Calculation from the Pilot Study

Appendix 4 -

Sample size calculation

Variables	Correlation co-efficient (Pre-Post)	Effect size (d)	Required Sample size		
			Power **80**	Power **90**	Power **95**
MODD	0.85	0.797	15	**23**	31
Mean glucose	0.96	1.002	10	16	21
Glucose Dev	0.92	0.829	14	21	29
CONGA	0.95	0.866	13	20	27
GRADE	0.96	0.798	15	23	31
LI	0.86	0.829	14	21	29

Key:

S.D. – Standard deviation; **MODD** – Mean of daily differences; **CONGA** – Continuous overlapping of net glycaemic action; **GRADE** – Glycemic risk assessment in diabetes equation

Appendix 5

Main Study – Baseline Characteristics of both groups

Appendix 5

Main study- Baseline characteristics of both the groups

Baseline	Control	Intervention	p value
Age	55	56.7	0.48
Duration of Diabetes	16	14.83	0.53
HbA1C	7.747	7.607	0.16
Medication Score	1.9683	1.855	0.11
BMI	26.05	25.80	0.23

Appendix 6

Ethical Clearance Letters

स्वामी विवेकानन्द योग-अनुसन्धान-संस्थानम्
Swami Vivekananda Yoga Anusandhāna Samsthānam
(Declared as Deemed-to-be University under Section 3 of the UGC Act, 1956)
Eknath Bhavan, # 19, Gavipuram Circle, Kempegowda Nagar, Bangalore - 560 019
Ph: 080 - 2661 2669, Telefax: 080 - 2660 8645
E-mail: svyasa@svyasa.edu.in Website: www.svyasa.edu.in

RES/IEC-SVYASA/79/2015 March 21, 2016

To,
Dr. Ramesh M N
Associate Professor,
S-VYASA University,
Bangalore.

Reference:

"Efficacy of Yoga-based Lifestyle Intervention on Reversing β-Cell Dysfunction in Type 2 Diabetes". - Committee Approval of the above mentioned study.

Dear Dr. Ramesh M N,

We have received from you the following study related documents vide your letter dated September 20, 2015

1	Project Proposal
2	Informed consent form

Ethics committee meeting was held on October 17, 2015 at 2:00 PM to 5:00 PM at Eknath Bhavan, Bangalore. Above documents were examined and discussed in the meeting. After due consideration, the committee has decided to approve conducting the aforementioned study.

APPROVED
Subramanyal
INSTITUTIONAL ETHICS COMMITTEE
SVYASA, BANGALORE

स्वामी विवेकानन्द योग-अनुसन्धान-संस्थानम्
Swami Vivekananda Yoga Anusandhāna Samsthānam
(Declared as Deemed-to-be University under Section 3 of the UGC Act, 1956)
Eknath Bhavan, # 19, Gavipuram Circle, Kempegowda Nagar, Bangalore - 560 019
Ph: 080 - 2661 2669, Telefax: 080 - 2660 8645
E-mail: svyasa@svyasa.edu.in Website: www.svyasa.edu.in

This is to confirm that neither Dr. Ramesh M N nor any staff participating in this study were involved in the voting procedures and decision making.

The Institutional Review Board / Independent Ethics Committee (IEC) are expected to be informed about the progress of the study / any changes in the protocol and patient information / informed consent. The investigators are also expected to submit a copy of the final report to IEC for records.

This approval is valid up to the completion of the study at the site.

Please submit to the IEC, the status report of the study as per the SOPs.

The IEC is organized & operates according to the requirements of ICH-GCP, Indian Council of Medical Research Guidelines & Schedule Y.

Best Wishes,

Subramanya P.

Dr. Subramanya P,
Member Secretary,
Institutional Ethics Committee,
S-VYASA, Bangalore.

MADRAS DIABETES RESEARCH FOUNDATION

INSTITUTIONAL ETHICS COMMITTEE

Registered with Office for Human Research Protections (OHRP), US Dept. of Health & Human Service
IRB No. IRB00002640; IORG No. IORG0002118; Assurance No. FWA0002981
Registered with Drug Controller General of India. Registration No. ECR/194/Inst./TN/2013 Re-Registration No.: ECR/194/Inst./TN/2013/RR-16

Date: 08 Nov 2017

To
Dr.V.Venugopal
Principal Investigator
Madras Diabetes Research Foundation
Chennai-600 086

STUDY TITLE: Effect of Yoga on Ambulatory Glucose Profile in patients with Type 2 Diabetes

Subject Approval of the study documents by the Institutional Ethics Committee of Madras Diabetes Research Foundation for the above referenced protocol

Dear Dr.Venugopal,

This is with reference to your application letter dated 18 Aug 2017, the following documents were reviewed and approved in the convened Institutional Ethics Committee of Madras Diabetes Research Foundation meeting held on 24th Aug 2017 at 15.30 Hrs.

1. Study Protocol version 1.0 dated 31 Oct 2017
2. Participant Information Sheet and informed consent form English, version 1.0 dated 31 Oct 2017
3. Participant Information Sheet and informed consent form Tamil, version 1.0 dated 31 Oct 2017
4. Curriculum vitae of Principal Investigator

The convened meeting held on 24th Aug 2017 at 15.30 Hrs was attended by;

S.No	Name	Designations	Role in IEC	Gender	Affiliation
1	Dr.M S Jawahar	Former Deputy Director (SGR) Tuberculosis Research Centre, Chetpet, Chennai – 600031	Chairperson	Male	No
2	Dr.M.Balasubramanyam	Senior Scientist Madras Diabetes Research Foundation, Gopalapuram, Chennai – 86	Member Secretary	Male	Yes
3	Dr.Rema Mathew	1B Madaleine Court, 72 Spurtank Road, Chetpet, Chennai-600031	Expert Medicine	Female	No
4	Dr. CR. Anand Moses	Professor of Diabetology Govt. Kilpauk Medical College and Hospital, Chennai 600010	Expert Medicine	Male	No
5	Dr. K. Baraneedharan	Consultant - Internal Medicine & Diabetology Global Hospital #439, Cheran Nagar, Perumbakkam, Chennai, Tamil Nadu 600100	Expert Medicine	Male	No
6	Dr.Purna Shankar	Karna Prayag Trust Welfare Centre for Women and children, Teynampet, Chennai-18	Social Scientist	Female	No

7	Ms.K.Aparna Devi	Advocate, High Court, Chennai – 600001	Expert Legal	Female	No
8	Dr. C N. Ram Gopal	New no 31 A (old No 20) 1st Cross Street, Kasturiba Nagar, Adyar, Chennai - 600 020	Psychologist	Male	No
9	Mr.T.Shankar	Executive, Management Solutions, Gopalapuram, Chennai 600086	Lay Public	Male	No
10	Dr.Annabelle Rajaseharan	Dean Vinayaka Missions Medical College & Hospital, Keezhakasakudimedu,Kottucherry (P.O) Karaikal 609609,Pondicherry (U.T)	Expert Clinical Pharmacology	Female	No
11	Dr.R.Ramakrishnan	National Institute of Epidemiology, Chennai - 600077	Expert Epidemiology & Statistician	Male	No
12	Dr.Radha Venkatesan	Head of Molecular Genetics Madras Diabetes Research Foundation, Gopalapuram, Chennai-600086	Senior Scientist	Female	Yes

We approve the study to be conducted in its presented form. The approval is valid for a period of one year. Please be informed that the Ethics Committee is re-registered with the office of DCG(I) (Reg No.: ECR/194/Inst/TN/2013/RR-16).The Institutional Ethics Committee of Madras Diabetes Research Foundation expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to provide a copy of the final report.

We approve the assessments as specified in the clinical study protocol and the study can be conducted. We hereby confirm that neither Principal Investigator nor her/his team members participated in the voting procedures for the referenced study.

The Institutional Ethics Committee is constituted according to the Schedule Y of Indian & Drugs Cosmetic Act 1940 and Good Clinical Practice Guidelines issued by the Government of India Ministry of Health & Family Welfare (Department of Health), The Drugs & Cosmetic Act 1940 and The Drug and Cosmetic Rules 1945, Ethical Guidelines for Biomedical Research on Human Participants issued by the Indian Council of Medical Research New Delhi 2006 and ICH GCP guidelines & the Clinical Trials act 1987 (amended 1990). This Institutional Ethics Committee operates to the standards laid down in the ICH GCP guidelines published in 1997 and implemented in January 1998.

Yours Sincerely,

Dr.M.Balasubramanyam
Member Secretary
Institutional Ethics Committee of
Madras Diabetes Research Foundation
Chennai 600086

Appendix 7

Informed Consent & Patient Information Sheet

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

This informed consent is for men and women who are invited to participate in research on effect of Yoga on variations in blood glucose. The title of our research project is

"Effect of Yoga and Exercise on Ambulatory Glucose Profile in patients with Type 2 Diabetes"

Name of Principal Investigator : Dr. Venugopal V

Name of Organization : S-VYASA University

PART I: Information Sheet

Introduction

I am Dr.Venugopal V, a PhD student of S-VYASA University. We are doing a research on yoga and it's impact on variations in blood glucose levels. We will give you the necessary information regarding the research and invite you to be a part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with, about the research. There may be some words that you do not understand. Please ask me to stop when we go through the information and I will take time to explain.

Purpose of the research

Diabetes is a condition in which there is high blood glucose levels. Low glucose is also common in patients with diabetes who are on insulin or a few medication. Frequent and large fluctuations in blood glucose levels contributes to diabetes related complications. Correcting these fluctuations in blood glucose levels has been found to be very helpful in preventing complications related to heart, eyes and feet. This study aims at finding out the amount of variations in your blood glucose levels and if these variations are affected using yoga or exercise.

Voluntary Participation

Your participation in the research is entirely voluntary. It is your choice whether to participate or not. Whether you participate or not, the services you receive will remain the same and will have no influence. You may change your mind later and stop participating even if you agreed earlier.

Procedures and Protocol

We will explain the exact procedures that will be followed in this study on a step-by-step basis.

In the first visit, we will ask you a few questions about your health, stress level and your demographic details.

1. After your consultation with the doctor, you will be provided with a patch-like scanner on the back of your upper arm which will continuously record your glucose levels.

2. You might feel a gentle prick while applying the patch, but many say they don't even feel the pain of pricking.

3. At the end of the 14 day study period you will be returning back to the hospital to return the patch.

Duration

The research takes place over a period of 14 days. During the time, it will be necessary for you to stick to the yoga regime and also the lifestyle changes we administer you.

Side Effects

There are no side effects anticipated in this research study. However, you might experience hypoglycemic episodes- like feeling dizzy, fatigue or lack of consciousness due to variation in your blood glucose due to Yoga or Exercise.

Benefits

- Your 24 hour blood glucose levels would be continuously monitored for 14 days.
- Yoga class for diabetes will be taught free of cost.
- This study would help you learn the positive changes that had happened inside you in this period.

Reimbursements

No reimbursements or compensation are paid for participation in the research.

Confidentiality

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be coded and put away, and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock & key and the soft copies would be password protected. It will not be shared with or given to anyone except the research team.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect the way you are treated at your workplace. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.

Whom to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

Dr. R M Anjana
Endocrinologist
MDRF,
Chennai
Ph: 044-439688
dranjana@mdrf.in

Dr.V Venugopal
Yoga & Naturopathy Consultant
S-VYASA University
Bengaluru
Ph: +91 944922 3830
dr.venu@yahoo.com

This proposal has been reviewed and approved by Institutional Ethics Committee (IEC) of S-VYASA University and Institutional Review Board (IRB) of Narayana Health City, which are committees whose task is to make sure that research participants are protected from any harm.

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ & Thumb print of participant

Signature of witness _____

Date _____

Day/month/year

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Appendix 8

Raw Data

Raw data:

Sl_No.	Name	Age	Gender	Family History	Duration of DM	HbA1C	Medication score	BMI	Study_group
1	Int1	64	Male	No	25	8	1.6	28.4	Intervention
2	Int2	57	Female	No	8	7.9	1.6	33.6	Intervention
3	Int3	65	Female	Yes	33	7	1.9	23.1	Intervention
4	Int4	44	Female	No	18	7.5	1.5	32.2	Intervention
5	Int5	70	Female	No	18	8.1	2	21.2	Intervention
6	Int6	41	Male	Yes	10	7.7	2.1	23.9	Intervention
7	Int7	69	Female	No	9	7.6	1.6	22.6	Intervention
8	Int8	47	Male	No	12	7.6	1.6	22.9	Intervention
9	Int9	58	Male	No	15	7.5	2.25	29.9	Intervention
10	Int10	65	Male	Yes	20	8	2.3	20.7	Intervention
11	Int11	46	Female	Yes	10	7.8	2.15	23.9	Intervention
12	Int12	47	Female	No	10	7.8	2.4	24.9	Intervention
13	Int13	41	Male	Yes	10	7.7	2.1	24.1	Intervention
14	Int14	69	Female	No	9	7.6	1.6	25.4	Intervention

15	Int15	47	Male	No	12	7.6	1.6	25.3	Intervention
16	Int16	58	Male	No	15	7.5	2.25	35.5	Intervention
17	Int17	65	Male	Yes	20	8	2.3	25.8	Intervention
18	Int18	64	Male	No	25	8	1.6	23.7	Intervention
19	Int19	57	Female	No	8	6.9	1.6	23.2	Intervention
20	Int20	65	Female	Yes	33	7	1.9	33	Intervention
21	Int21	44	Female	No	18	7.5	1.5	23.1	Intervention
22	Int22	70	Female	No	18	7.6	2	29.4	Intervention
23	Int23	49	Male	Yes	14	8.1	1.6	25.8	Intervention
24	Int24	61	Male	No	7	7.3	1.8	22.4	Intervention
25	Int25	53	Female	Yes	8	7.7	1.7	21.9	Intervention
26	Int26	59	Female	Yes	11	7.3	2.1	24.7	Intervention
27	Int27	63	Female	No	9	7.2	1.7	25.2	Intervention
28	Int28	52	Male	No	12	7.9	1.9	22.6	Intervention
29	Int29	66	Female	No	22	8.2	1.9	29.2	Intervention
30	Int30	45	Male	No	6	6.6	1.5	23.4	Intervention

Sl_No.	Name	Mean_pre	Mean_post	SD_pre	SD_post	LI_pre	LI_post	MODD_pre	MODD_post	MAGE_pre	MAGE_post
1	Int1	163.73	141.94	32.03	20.19	572.39	225.63	26.95	14.27	70.87	39.04
2	Int2	136.81	116.57	26.05	22.02	434.46	267.37	25.04	20.71	63.21	46.01
3	Int3	130.62	129.13	23.8	21.22	411.17	333.71	17.34	15.03	60.98	60.63
4	Int4	118.7	112.01	20.73	16.24	220.86	182.17	18.18	11.86	59.29	40.41
5	Int5	98.05	77.92	21.76	12.57	297.09	103.87	17.54	8.77	51.55	24.77
6	Int6	155.83	125.17	37.51	24.98	883.44	389.99	34	20.69	79.48	56.06
7	Int7	166.45	139.23	43.08	24.91	989.26	362.2	39.98	22.48	105.25	55.32
8	Int8	154.87	125.88	27.44	20.6	727.13	359.57	23.01	19.35	70.3	45.9
9	Int9	149.12	89.46	40.13	26.62	1052.27	336.15	34.94	18.03	100.3	51.47
10	Int10	153.79	118.09	37.92	24.23	887.19	389.74	28.76	18.08	87.44	59.43
11	Int11	122.06	122.06	35.54	35.54	679.63	679.63	32.31	32.31	79.14	79.14
12	Int12	145.66	125.5	34.58	23.93	649.56	268.09	28.7	16.41	79.22	47.03
13	Int13	150.47	89.02	35.21	14.23	247.16	67.48	18.88	11.45	39.05	28.78
14	Int14	218.02	209.66	59.37	57.96	1286.99	1027.87	41.06	38.35	95.77	157.76

15	Int15	122.06	122.06	35.54	35.54	679.63	679.63	32.31	32.31	79.14	79.14
16	Int16	108.28	96.16	37.05	30.73	1224.04	895.93	33.31	24.93	104.06	80.72
17	Int17	147.86	145.4	45.35	38.72	1713.05	1132.21	31.9	34.26	113.63	91.9
18	Int18	119.84	112.54	28.71	28.44	826.7	920.49	23.76	22.28	77.37	62.77
19	Int19	116.11	105.53	22.02	21.24	762.59	803.89	21.89	20.58	55.29	63.44
20	Int20	139.45	122.28	48.66	43.02	901.62	646.28	45.21	26.78	117.82	101.69
21	Int21	150.23	137.73	54.76	43.76	1370.47	1193.91	48.36	45.87	122.9	104.59
22	Int22	221.87	182.18	58.3	39.02	1158.69	1105.55	55.28	41.18	100.68	99.15
23	Int23	130.99	131.85	18.98	20.83	399.58	365.69	18.32	16.82	43.95	51.88
24	Int24	136.86	90.11	41.17	22.81	592.26	152.19	27.54	15.25	68.63	35.73
25	Int25	128.91	87.82	24.8	9.98	454.97	52.92	14.66	4.75	57.64	17.53
26	Int26	139.45	122.28	48.66	43.02	901.62	646.28	45.21	26.78	117.82	101.69
27	Int27	135	88.58	28.47	18.06	238.58	53.42	24.43	15.7	56.03	26.18
28	Int28	148.65	85.85	34.4	15.65	260.42	71.15	19.43	11.65	38.8	29.52
29	Int29	137.4	103.85	40.99	17.02	590.19	136.27	27.79	12.82	68.63	35.51
30	Int30	140.17	111.85	40.84	17.02	580.99	136.27	27.84	12.82	68.47	35.51

Raw data (control):

Sl_No.	Name	Age	Gender	Family History	Duration of DM	HbA1C	Medication score	BMI	Study_group
1	Cont1	41	Male	Yes	11	8.1	2.2	22.5	Control
2	Cont2	65	Female	No	10	8	1.7	26.2	Control
3	Cont3	45	Male	No	13	6.9	1.7	27	Control
4	Cont4	56	Male	No	16	7.9	2.25	31	Control
5	Cont5	63	Male	Yes	21	8.3	2.5	27.2	Control
6	Cont6	62	Male	No	26	8.1	1.7	24.2	Control
7	Cont7	55	Female	No	9	7.3	1.7	24.1	Control
8	Cont8	63	Female	Yes	33	7.4	2	22.9	Control
9	Cont9	42	Female	No	18	7.9	1.75	29.9	Control
10	Cont10	47	Female	Yes	10	8.2	2	20.7	Control
11	Cont11	64	Female	Yes	17	8.4	2	25.6	Control
12	Cont12	51	Male	No	11	7.9	2.25	27.8	Control
13	Cont13	47	Female	No	8	7.3	2	30.6	Control
14	Cont14	51	Male	No	12	7.9	2	22.9	Control

15	Cont15	59	Female	No	17	7.7	2	29.9	Control
16	Cont16	61	Male	Yes	8	7.3	1.5	20.7	Control
17	Cont17	45	Female	No	11	7.8	2.25	30.4	Control
18	Cont18	46	Female	Yes	10	7.3	2.15	26.7	Control
19	Cont19	65	Male	Yes	20	8	2.3	24	Control
20	Cont20	58	Male	No	15	7.5	2.25	28.7	Control
21	Cont21	47	Male	No	12	7.6	1.6	25.8	Control
22	Cont22	65	Female	No	15	8	2	22.3	Control
23	Cont23	41	Male	Yes	10	7.7	2.1	21.9	Control
24	Cont24	68	Female	No	24	8	2.25	32.1	Control
25	Cont25	44	Female	No	15	7.9	1.5	22.1	Control
26	Cont26	65	Female	Yes	33	7.4	2	29.2	Control
27	Cont27	57	Female	No	10	7.3	1.75	27.7	Control
28	Cont28	62	Male	No	26	7.9	1.75	23.4	Control
29	Cont29	47	Male	Yes	15	7.4	1.9	24.2	Control
30	Cont30	68	Female	No	24	8	2	29.7	Control

Sl_No.	Name	Mean_pre	Mean_post	SD_pre	SD_post	LI_pre	LI_post	MODD_pre	MODD_post	MAGE_pre	MAGE_post
1	Cont1	105.54	93.41	23.85	20.68	412.73	220.55	17.32	18.72	60.98	57.01
2	Cont2	99.47	86.47	27.66	23.64	608.26	366.96	23.38	24.19	66.2	51.84
3	Cont3	204.64	127.25	42.11	30.66	687.5	467.89	39.28	25.63	89.08	75.7
4	Cont4	121.58	95.87	46.48	34.48	1169.11	856.49	32.13	28.14	107.91	80.51
5	Cont5	94.76	94.76	30.72	30.72	645.46	645.46	27.43	27.43	61.55	61.55
6	Cont6	139.88	140.05	46.12	38.93	757.3	569.95	36.71	31.28	106.66	83.41
7	Cont7	94.76	95.64	30.72	31.41	645.46	723.38	27.43	27.36	61.55	66.38
8	Cont8	122.09	109.63	31.39	29.13	620.9	584.41	24.89	24.98	77.14	71.25
9	Cont9	157.84	138.73	63.58	57.22	1252.56	1127.42	53.87	42.27	146.07	134.68
10	Cont10	195.23	211.65	56.5	44.41	1551.74	1108.51	56.79	56.87	120.54	111.03
11	Cont11	111.01	128.83	53.42	61.5	886.32	1115.9	42.35	56.81	141.13	155.25
12	Cont12	97.76	98.64	30.72	31.41	645.46	723.38	27.43	27.36	61.55	66.38
13	Cont13	139.1	132.96	67.06	67.2	1939.46	2642.05	60.55	63.38	146.14	164.81
14	Cont14	224.75	184.67	97.44	85.54	3270.43	2051.12	94.55	91.2	200.47	174.11
15	Cont15	177.41	133.71	63.03	46.01	1371.98	854.61	58.67	40.7	103.72	101.58

16	Cont16	179.28	189.82	96.94	97.26	3437.85	3773.8	68.41	75.1	245.63	243.65
17	Cont17	160.84	141.73	63.58	57.22	1252.56	1127.42	53.87	42.27	146.07	134.68
18	Cont18	125.09	112.63	31.39	29.13	620.9	584.41	24.89	24.98	77.14	71.25
19	Cont19	142.88	143.05	46.12	38.93	757.3	569.95	36.71	31.28	106.66	83.41
20	Cont20	97.76	90.12	30.72	24.3	645.46	412.1	27.43	24.93	61.55	54.21
21	Cont21	124.58	98.87	46.48	34.48	1169.11	856.49	32.13	28.14	107.91	80.51
22	Cont22	130.25	207.64	30.66	42.11	467.89	687.5	25.63	39.28	75.7	89.08
23	Cont23	102.47	89.47	27.66	23.64	608.26	366.96	23.38	24.19	66.2	51.84
24	Cont24	108.53	96.41	23.88	20.68	413.85	220.55	17.29	18.72	60.8	57.01
25	Cont25	192.23	208.65	56.5	44.41	1551.74	1108.51	56.79	56.87	120.54	111.03
26	Cont26	108.01	125.83	53.42	61.5	886.32	1115.9	42.35	56.81	141.13	155.25
27	Cont27	136.1	129.96	67.06	67.2	1939.46	2642.05	60.55	63.38	146.14	164.81
28	Cont28	221.79	181.67	97.51	85.54	3272.56	2051.12	94.61	91.2	200.47	174.11
29	Cont29	174.41	130.71	63.03	46.01	1371.98	854.61	58.67	40.7	103.72	101.58
30	Cont30	176.36	186.79	96.99	97.4	3438.3	3783.52	68.5	75.07	245.63	243.65

Appendix 9

List of Publications

REVIEW ARTICLE

Ethnic Disparity and Increased Prevalence of Type 2 Diabetes Among South Asians: Aetiology and Future Implications for Diabetes Prevention and Management

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Abstract: ***Background***: Type 2 diabetes mellitus (T2DM) is turning out to be a global health crisis. Currently available literature clearly indicates an increased risk of type 2 diabetes amongst South Asian population.

Objective: The objective of this narrative review is to explore the non-modifiable and modifiable risk factors of T2DM in South Asian population, including their beliefs, attitudes, socio economic and cultural barriers and also to explore the possible implications in designing culture specific diabetes prevention and management programs.

Method: This narrative review is based upon the data from individual studies and review article known to the authors. Additional relevant studies were identified through PubMed search on English-language papers published in 2000-2017 using the relevant keywords. Where appropriate, the reference lists of key papers were reviewed to identify additional studies of interest.

Results: Many genetic and environmental risk factors such as diet, physical inactivity, and sleep contribute to the increased prevalence of diabetes in the ethnic group. Providing more knowledge about diabetes and these risk factors might not be sufficient in this particular ethnic group. It is essential to address their beliefs, attitudes and the cultural barriers faced.

Conclusion: To overcome the health disparity in the South Asian ethnic group, various risk factors associated with diabetes, and the challenges faced are to be considered while designing future diabetes prevention and management strategies.

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1. INTRODUCTION

Ethnicity is a complex construct that comprises multiple genetic, psychosocial, socioeconomic, cultural and behavioural factors [1]. The prevalence and incidence of type 2 diabetes (T2DM) are higher in few ethnic populations than others. In the UK, the increased prevalence of T2DM is reported to be three times higher in Afro-Caribbean population and six times higher in South Asian (includes Indian, Pakistani, Bangladeshi and Srilankan) population, when compared to White Caucasian population [2]. For any given Body Mass Index (BMI) or waist circumference, South Asians have approximately 6% higher total body fat than Caucasians [3] and are more likely to develop T2DM at a younger age and associated co-morbidities such as worse glycaemic control, higher prevalence of hypertension, retinopathy and cardiovascular risk factors [4, 5]. A multi-ethnic study conducted in Singapore, found Indian immigrants to be at the highest risk of developing T2DM, and amongst individuals with diabetes, Indians are at the highest risk of developing cardiovascular complications [5, 6]. The increased relative risk of T2DM in the South Asian Population is observed not just in the native population, but also observed to remain higher even when they migrate to the developed countries as immigrants [2, 3, 6, 7].

The exact reason behind this ethnic and racial disparity is not clearly distinct. Though genetic risk factors are commonly attributed to the increased prevalence of T2DM in south Asians, the role of modifiable risk factors such as diet, physical activity and stress could not be ignored. This review initially explores the various modifiable and non-modifiable risk factors attributed to T2DM and the common barriers which contribute to the prevailing health disparity observed in south Asians, and later regarding the possible implications for the prevention and management of T2DM appropriate to this particular ethnic group.

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2. NON-MODIFIABLE RISK FACTORS

2.1. Genetic Predisposition

The pathogenesis of T2DM often involves two major components –Insulin resistance and β- cell dysfunction. T2DM is believed to develop due to the complex interplay of these components. However, there are ample evidences suggesting that there is a variation in the relative contribution of one of these 2 pathogenic factors across different ethnic groups. For instance, β cell dysfunction is more prominent than insulin resistance in Asian Indians with mild dysglycaemia [7].

Many theories have been put forth to explain this ethnic disparity and genetic susceptibility. One of the earliest theories, the 'Thrifty gene hypothesis' posits that millions of years ago, the genes of our ancestors underwent genetic modification (resulting in 'thrifty genes') to ensure efficient storage of fat [8]. This was necessitated as food availability was insecure and natural disasters such as fire, flood and famine were more rampant. Corroborating this, historical data on food reports that in the past 2,500 years, as many as 90 famines were recorded from the Indian sub-continent (which includes India, Pakistan, Bangladesh and Srilanka) [9]. Metabolic thriftiness ensured efficient storage of fat whenever food is available, resulting in transmission of metabolically efficient or 'thrifty' genes to the future generations. Evolutionary advantage endowed by thrifty gene turned into nemesis for human race as the future generations evolved out of hunter-gatherer mode to cultivators, where natural disasters like famine are not rampant anymore and the physical activity has been compensated by the invention of the modern equipment and sedentary lifestyle [10].

Another hypothesis, the 'Genetic trashcan hypothesis' postulates that multiple neutral gene mutations increase the risk of diabetes, when accumulated and concentrated in a population [11]. This hypothesis is equally intriguing, because 'diabetogenes', as the author suggests, are generally recessive [11]. The increased prevalence of T2DM in South Asian population could also be attributed to the fact that they are less exogamous [12], as exogamy and interbreeding exert a diluting effect on mutant genes, and many of the South Asian communities still have the custom of endogamous marriages than Caucasians, making them genetically more susceptible to diabetes [13]. A study conducted in Punjabi Sikhs from India showed an increased incidence in the autosomal recessive LGMD2C, which is attributed to the endogamy practised within the community [14] and is in line with the 'genetic trash can' hypothesis.

Recent advancements in genetics through Genome-wide Associated Studies (GWAS) and epigenetic studies facilitate in better understanding of intricate details regarding genes and genetic variations through various large scale genetic studies. The Text-minded Hypertension, Obesity and Diabetes candidate Gene (T-HOD) database report 563 identified genes to be associated with T2DM so far. The Genome-wide Associated Studies (GWAS) conducted on South Asian population found six novel signals by single nucleotide polymorphisms (SNPs) near GRB14, ST6GAL1, VPS26A, HMG20A, AP3S2 and HNF4A genes [15], apart from the commonly associated genes of T2DM such as PPARG, TCF7L2, FTO and CDKN2A [16]. In a multistage meta-analysis, a novel susceptibility locus at 13q12 in the SGCG gene which is associated with T2DM susceptibility was identified in the Punjabi Sikhs from India [14] and another study reported one more new susceptibility locus at 2q21 in the TMEM163 gene [17].

Epigenetics is an inheritable phenomenon affecting genetic expression without any changes at the gene sequence levels. The epigenetic changes observed in T2DM are often attributed to the *milieu interior* of the foetus before birth or due to nutritional stressors in early life [18, 19]. South Asian Women in general are at increased risk of gestational diabetes mellitus (GDM), which might be a possible contributor for the epigenetic modifications observed in South Asians [20]. Similarly, low birth weight and exposure to under nutrition inside the uterus are common in India, where 30% infants are born underweight [5, 19]. Foetal under nutrition (i.e. low birth weight infant) as well as over- nutrition (e.g. infant of a mother with diabetes) are known risk factors contributing to the risk of diabetes for the infant in future [18].

2.2. Age

Age is another non-modifiable risk factor of T2DM. A National Survey conducted in India reported the age of onset of diabetes in 54.1% cases to be 50 years [21]. The findings correlate well with the longitudinal study conducted in Canada on diabetes incidence, which reported that the median age of diagnosis of T2DM was lowest amongst South Asians (49 years) when compared to Afro-Caribbean (57 years) and Caucasian population (58 years) [22].

2.3. Modifiable Risk Factors

Environment plays a vital role in uncovering the latent genetic predisposition to diabetes. In the U.S, the prevalence of diabetes increased from 9.8% in 1988-1994 to 12.4% in 2011-12 [23]. This dramatic increase in diabetes prevalence in a span of around 30 years could not be attributed to sudden genetic mutations. Rapid increase in levels of urbanisation translating grossly to concurrent shifts in technology, infrastructure and increased use of automobiles leading to decreased physical activity, and unhealthy diet and affiliated factors such as increased psychological stress, depression and short sleeping hours are few of the other contributing factors associated with metabolic syndrome and T2DM in the Asian population.

2.4. Physical Inactivity

Physical exercise and leisure time physical activity help overcome insulin resistance and improve cardio metabolic profile, and are associated with 25-40% risk reduction in T2DM [24]. In spite of wide spread knowledge and awareness regarding the benefits of physical activity, many are still less active. One of the epidemiological studies from India reported that only 24.1% individuals are physically active and exercise 150 min/week [25]. South Asians have significantly lesser physical activity when compared to their Caucasian counterparts [24]. Data from health survey in the UK reported that, the levels of physical activity and fitness of South Asians were 50-75% lower than White Caucasians

[26]. Despite average carbohydrate intake remaining the same among Indian population in the last two decades, the prevalence of diabetes increased drastically from 8% (1980) to 16% (2006), which might possibly be due to the decrease in physical activity [27].

2.5. Diet

Diet plays a significant role in influencing insulin resistance and diabetes. Refined grains are directly associated with increased risk of diabetes (Odds ratio (OR) 5.3) while dietary fibre is inversely related (OR 0.31) [28]. When compared with unpolished brown rice, white polished rice contains lesser dietary fibre and fewer vitamins and minerals, which are potentially protective against T2DM. Moreover, the high glycaemic index of white rice is associated with increased insulin resistance [29]. An interesting observation was made in a study where the subjects with higher intake of rice had lower body mass index (BMI) than those with lesser intake of rice, however, the risk of diabetes was higher in the higher rice intake group. Deduction is that the high rice intake increases the risk of T2DM through a mechanism which is independent of weight gain [30]. This gains significance especially considering that cereals such as Rice and Wheat are the main staple food for the South Asian community, providing 60-70% of the total energy intake [27].

In addition to carbohydrates, dietary fats are also strongly implicated to insulin resistance. Habitual intake of dietary fats is directly proportional to increased insulin resistance, and studies show the adverse association of saturated fats with insulin sensitivity, independent of BMI [12]. Vegetable ghee, such as *Dalda* – a clarified butter which is being commonly used for cooking in India – contains a very high concentration of approximately 50% of *trans* fatty acids, which are associated with weight gain, increased cardio metabolic risk and insulin resistance [31].

2.6. Smoking

Approximately 50-60% of adult males in developing countries are regular smokers [32]. Smoking is associated with 44% increased risk of developing diabetes [33] and Indians are the second largest producers and consumers of Cigarettes in the World, next only to China [34]. Several biological mechanisms explain the association between smoking and T2DM. Among individuals with normal BMI, smokers are more likely to have abdominal obesity [35] and thus increased risk of insulin resistance and T2DM. Smoking decreases oestrogen in women and plasma testosterone in men, which further worsens insulin resistance, especially in men [36]. Animal models have shown that nicotine exposure, particularly in neonatal or prenatal stage, can lead to β-cell dysfunction and β-cell apoptosis [36, 37].

2.7. Socioeconomic Status, Social and Cultural Beliefs

Diabetes is not considered as a disease of the west or disease of the rich any more. Abundant literature is available explaining the contributions of socioeconomic status such as limitations in access to care, low or lack of insurance and other socioeconomic barriers increasing the burden of diabetes and its complications. Difference in socioeconomic status seems to influence diabetes differently in different countries. In developed countries, diabetes prevalence is significantly higher in the lowest socioeconomic groups, whereas in developing countries like India, situation is reverse with more diabetics in the higher socioeconomic strata. This could be because in developing countries, people in the lower socioeconomic sectors are believed to still continue with a more traditional lifestyle such as consumption of unrefined grains, walking as a primary mode of transport, physical labour, etc. protecting them from the risk factors associated with T2DM [38].

South Asian Women commonly expressed many cultural barriers towards regular physical activity. Few of the barriers worth mentioning are the modesty issues while doing exercise in a mixed-gender group, uncomfortable to wear traditional dresses while doing exercise, viewing exercise as culturally inappropriate and also religious beliefs. Men on the other hand, are influenced by the cultural belief that work should be given priority over spending time for exercise to maintain health [39, 40].

Beliefs and attitudes could be possible contributing factors. A study on the South Asian immigrants in US reported most of the immigrants to possess the knowledge that they are at an increased risk of developing T2DM. However, they attributed the increased risk to the external factors such as genetics, stress, fatalistic beliefs, citing destiny, '*karma*' or 'God's will' as more likely reasons for their increased risk. Resistance was observed with regard to cooking practices, as reducing the amount of ghee or oil was believed to leave the food tasteless and could even be shameful [41]. A qualitative study on Bangladeshi immigrants observed that, both men and women attributed larger body size as 'more healthy'. Refined sugar, beef, ghee, solid fat and spices were considered as 'strong' foods by the study participants, while raw foods were considered as 'indigestible'. Interestingly, physical exercise was believed to potentially exacerbate illness or physical weakness by participants of the study [42].

3. IMPLICATIONS FOR DIABETES PREVENTION AND MANAGEMENT

Health education is not merely a matter of determining 'deficiencies' in knowledge and meeting those deficiencies with educational materials such as leaflets, teaching seminars, or mass media programs [43]. Instead, educators should consider the differences in individuality and ethnicity, while trying to curb the rampant prevalence of T2DM among South Asians. Multiple risk factors are associated with T2DM in South Asian population and most of these risk factors are complicatedly interlinked. Although exercise is promoted in public health campaigns to increase overall physical activity levels, it is important to understand various socio-economic and cultural barriers associated with it in different populations, in order to deliver effective physical activity interventions [44]. Few of the socioeconomic barriers faced by South Asian women, as mentioned above, include wearing 'western' exercise clothing, expectation to remain in the home and lack of same gender venues to exercise. To overcome this disparity in health, a more culturally appropriate physical activity of the community, for instance Yoga,

which has shown a higher adherence rate than exercise [45], might be a more acceptable form of physical activity for the particular ethnic group. Further, the holistic effect of yoga on body and mind would help not only to de-stress, but also provide better glycaemic control [46, 47, 48], overcome insulin resistance, reduced inflammation and oxidative stress, improved lipid profile, cognition and Quality of Life [49, 50]. Similarly, diabetes awareness and incorporation of physical activity classes at the place of worship could also be a possible strategy to improve physical activity [51]. Diabetes education at the place of worship through a 'promoter' speaking the same language would be a culturally competent intervention to reduce the health disparity for ethnic minorities [52, 53, 54]. A study on Bangladeshi population also reported that they had higher regards for oral information from informal sources like friends, relatives and patients with diabetes [42], than formal lectures and leaflet information. The place of worship is reported to be the best place to change the attitudes and beliefs of the ethnic group towards diabetes, because religious leaders are generally seen as a trusted source of information and a study reported that the Bangladeshi religious leaders unanimously agreed that, to reject the importance of self-care and stating diabetes as 'God's will' is a complete misinterpretation of the religious teaching and must be addressed through religious education [55]. Diabetes prevention is as equally important as the diabetes management, as South Asians develop T2DM at a younger age when compared to their Caucasian counterparts. Inadequate physical activity observed in South Asians [26, 39, 44, 51] could be rectified by improving physical activity at schools, colleges and also workplace wellness [57]. Similarly, simple dietary modifications such as increasing regular fruits and vegetable consumption, which is generally observed to be lesser in South Asians [2, 22] which would also help prevent T2DM [57]. Early screening for T2DM or impaired glucose tolerance is of utmost importance. Rather than restricting the screening process to hospital settings, extending the services to residential locations, offices, educational institutions, places of worship, parks, community centers and street corners are found to be more effective ways of early screening in both immigrant and the native population [59, 60].

CONCLUSION

Diabetes prevention and management programs are to be tailor-made for the particular ethnic group rather than merely providing knowledge about T2DM and its risk factors. Evidences clearly suggest that they do possess knowledge about the condition; however, the observed ethnic disparities are more often due to their beliefs and attitude towards the condition than lack of knowledge. Interplay of genetic predisposition and environmental triggers is the possible contributors for the development of type 2 diabetes in South Asian Ethnic population, most of which are modifiable. Early identification of the risk factors and appropriate culture specific intervention would probably help reduce the health disparity in South Asians. A holistic and comprehensive lifestyle modification strategy, considering all the above mentioned facts would help not only in effective management, but also in prevention of T2DM.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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LETTER TO THE EDITOR

Moving beyond HbA1c and plasma glucose levels to understand glycemic status in type 2 diabetes mellitus

The glycemic status of patients with type 2 diabetes mellitus (T2DM) is widely assessed using HbA1c. The β-cell-centric model presupposes that all diabetes, including T2DM, originates from a common denominator, the abnormal pancreatic β-cell, and insulin resistance may not necessarily be the primary defect.[1]

A 60-year-old woman had been diagnosed with T2DM at 56 years of age and was on metformin 500 mg once daily for 4 years. The patient was interested in participating in an ongoing research project and provided informed consent prior to inclusion in the study. As part of the screening process, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), HbA1c, and fasting insulin (FINS) levels were measured in May 2017. Homeostasis model assessment of insulin resistance (HOMA-IR) and homeostatic model assessment of β-cell function (HOMA-β) were calculated from FPG (mg/dL) and fasting insulin (μIU/mL) as follows:

$$\text{HOMA}-\text{IR} = \text{FPG} \times \text{FINS}/405$$

$$\text{HOMA}-\beta\,(\%) = (360 \times \text{FINS}/\text{FPG} - 63) \times 100\,\%$$

A continuous glucose monitoring (CGM) sensor (Freestyle Libre Pro Flash Blood Glucose Monitoring SENSOR; Abbott, Oxon, UK) was also used to capture intraday variability in blood glucose levels.

Although FPG (86.2 mg/dL), PPG (136.6 mg/dL) and HbA1c (7.0%) levels were within the recommended target range,[2] three interesting observations were made: (i) CGM showed elevated glucose levels throughout the day (average 202 mg/dL), except around morning breakfast hours, when the patient's FPG and PPG readings were generally measured; (ii) HOMA-β showed 33.28% β-cell dysfunction with a normal HOMA-IR of 0.915; and (iii) the patient had low FINS levels (4.3 μIU/mL).

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It is quite interesting how the patient's elevated glucose levels were not reflected in the routine HbA1c screening. The application and efficiency of HbA1c as a solitary measure for the assessment of glycemic control is widely debated.[3] Variations in HbA1c among different ethnic groups have also been reported.[4] These reports suggest that measurement of baseline HbA1c levels alone may not always provide a clear picture of the glycemic status of an individual.[5] Although no glycemic variability was observed in the patient, β-cell dysfunction and low FINS levels were evident. The oral hypoglycemic agent (OHA) metformin could have reduced hepatic glucose production, resulting in reduced FPG and PPG levels. However, β-cell dysfunction and resulting low FINS levels in the patient were not effectively controlled with the current OHA, and this might necessitate the initiation of a second-line medication.

A β-cell-centric approach puts forth β-cell dysfunction as the primary defect in T2DM, which is not necessarily preceded by insulin resistance, because β-cell dysfunction occurs even before the diagnosis of overt diabetes or insulin resistance.[1] Therefore, the most favored initial therapy of metformin in T2DM may not be a suitable option for all patients, because β-cell dysfunction could also be a major player in the pathophysiology of T2DM, as in the present patient. Similarly, HbA1c or plasma glucose levels may simply reflect total glucose levels in the blood and may not necessarily accurately reflect the glycemic status of a patient.

Disclosure

None declared.

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Letter to the Editor

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Review Article

Potential Role of Yoga in Management of the Ominous Octet: Adding a New Facet to Type 2 Diabetes Management and Prevention

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Abstract

Global increase in the prevalence of diabetes places a huge economic burden upon health systems due to costs of management, especially in those with co-morbidities. Epidemiological studies show lifestyle interventions to be cost-effective in type 2 diabetes prevention and management. Exercise is a major component in these lifestyle interventions. However, exercise is contraindicated in advanced complications of diabetes such as proliferative retinopathy and also has increased risk of hypoglycaemia. Yoga is a form of low-to-moderate intensity physical activity, emerging as a widely practised form of complementary therapy in the management of various medical conditions. It is also believed to be a safe and cost-effective mode of physical activity in the primary and secondary prevention of type 2 diabetes. The 'ominous octet' model of DeFronzo puts forth the eight major pathophysiological abnormalities observed in type 2 diabetes. The current review explores the mechanism and 'potential' role of yoga in management of this ominous octet.

Keywords: Management, mechanism, ominous octet, type 2 diabetes mellitus, yoga

Introduction

The prevalence and incidence of diabetes mellitus is increasing worldwide at an alarming pace. The number of adults with diabetes was 194 million in 2006 and was predicted to reach 333 million by 2025.[1] But already, an estimated 425 million adults have diabetes and another 352.1 million adults have impaired glucose tolerance (IGT).[2]

Our knowledge and understanding of the pathophysiology of type 2 diabetes mellitus (T2DM) is ever expanding. The two common pathophysiological abnormalities observed in T2DM are insulin resistance and impaired β-cell function. The pathophysiology of T2DM is believed to commence with insulin resistance, which leads to glucotoxicity and decreased β-cell function.[3] However, according to the 'β-cell centric' approach,[4] β-cell dysfunction is the primary defect in T2DM which in turn leads to insulin resistance. Apart from insulin resistance (in muscles and liver) and β-cell dysfunction, the 'ominous octet' model of DeFronzo[5] refers to the involvement of brain, adipose tissue, gastrointestinal hormones, kidney and α-cells in the pathophysiology of T2DM and emphasises the need for a multiple drug combination to rectify the underlying pathophysiological defects and not simply aim at reducing the HbA1C levels.

A recent systematic review demonstrated that lifestyle interventions are better at reducing the incidence of T2DM than usual medical care in populations across different ethnicities and cultures.[6,7] Lifestyle interventions are also effective in secondary prevention of diabetes as shown in the Da Qing study, where participants in the lifestyle group had a 47% lower risk of diabetic retinopathy at 20-year follow-up.[8] Dietary modifications and exercise recommendations are the

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conventional lifestyle interventions recommended for the prevention and management of T2DM. Increase in moderate physical activity is associated with multiple benefits such as, improved insulin sensitivity, better glycemic control, reduced body mass index, improvement in lipid profile and other risk factors associated with diabetes such as obesity and hypertension.[9,10] However, physical exercise may need to be done with caution in patients with increased risk of cardiovascular events and comorbidities associated with microvascular and macrovascular complications such as diabetic neuropathy and proliferative retinopathy, which could worsen with intensive exercise programs.[11] Although the beneficial effects of physical activity are well established, adherence rate remains poor, as patients seem not to engage in regular physical activities for different reasons.[12-14] There is growing interest in alternative and holistic models to T2DM management which could possibly improve adherence.

Yoga is a mind/body practise based on traditional Indian philosophy, depicting the ideal way of life and is more than just a physical activity.[15] In terms of energy expenditure, it is similar to mild-to-moderate intensity exercise.[16] In addition to the physical movements *(asanas)*, yoga commonly involves multiple other components such as controlled respiration *(pranayama)*, relaxation and meditation *(dhyana)*. Many studies are emerging on the benefits of yoga in various diseases.[17] Findings from extensive studies suggest yoga to have multiple benefits in the etiopathogenesis of T2DM and associated complications such as improved glycemic control, lipid profile, improved cognition, nerve conduction velocity, weight loss, reduced inflammation,[18,19] oxidative stress,[20] and cardiovascular risk factors in T2DM patients.[21-23] Comparative studies on yoga versus exercise suggest that yoga is as effective if not superior to physical exercise in health-related outcome measures such as blood glucose, lipids, salivary cortisol and oxidative stress which are of greater significance in the primary and secondary prevention of T2DM, with additional benefits of improving subjective measures such as fatigue, sleep, pain and quality of life (QoL).[24,25]

The role of physical exercise as a part of the lifestyle intervention in the prevention and management of diabetes is well established.[26] The current narrative review aims at exploring the 'ominous octet' involved in the etiopathogenesis of T2DM and the potential role of yoga in correcting these pathological defects for an effective primary and secondary prevention of T2DM [Figure 1].

(HGP - Hepatic glucose production; AIR - Acute phase Insulin Release; GLP-1 - «Glucagon like peptide- 1; GABA - Gamma aminobutyric acid)

Figure 1: Pathways involved in the yogic management of type 2 diabetes mellitus

Yogic Management of the Ominous Octet

β-cell dysfunction

The defects in β-cell dysfunction primarily involve three components. First, the secretion timing disorder, where there is a reduction in the initial acute phase insulin release (AIR). Autonomic nervous system is attributed for >70% of the AIR.[27] AIR is generally abolished by vagotomy in rats[28] and by atropine in humans[29] which is suggestive of the pivotal role of vagal activity in AIR. Second is the quantitative disorder, in which there is an increase or decrease in the second phase insulin release. Third, the qualitative disorder, in which there is an increase in the proinsulin-to-insulin ratio.[30] An increase in the amount of proinsulin in circulation, which is attributed to the impaired cleavage capacity of the β-cells, is observed irrespective of the diabetes duration, suggesting that β-cell dysfunction need not necessarily occur after insulin resistance and might possibly precede the onset of clinically overt T2DM.[30]

Patients with T2DM have higher levels of oxidative stress. Subtle increases in the physiological concentration of the reactive oxygen species (ROS) might mimic a number of insulin-like effects, including increase in glucose transporters (GLUT) translocation, lipogenesis, decreased lipolysis,[31] and an increase in the glucose-stimulated insulin secretion.[32] However, chronic oxidative stress and free radical damage observed in T2DM plays an important role in inducing β-cell dysfunction, as β-cells possess limited defence against excess ROS production due to low levels of ROS-detoxifying enzymes.[33,34] Increase in oxidative stress leads to decreased transcription of the insulin gene by decreasing PDX1 and MafA binding.[35,36] Similarly, protein misfolding and resultant ER stress in the human β-cells is a major pathophysiological event in T2DM which is also associated with oxidative stress.[3]

Yoga studies showed a reduction in oxidative stress and increased anti-oxidant defence, by improving superoxide dismutase, glutathione, malondialdehyde, Vitamin C and Vitamin E profile.[37,38] γ-aminobutyric acid (GABA) induces membrane depolarisation and proliferation in β-cells, and thus increases insulin secretion.[39] A study comparing the effects of yoga with walking, found yoga to improve GABA levels better than walking.[40] Yoga reduces sympathetic activation and enhances parasympathetic activity through direct stimulation of the vagus nerve.[41,42] The positive impact of yoga on the autonomic

nervous system would possibly help overcome insulin secretion timing disorder as well. With improved antioxidant defence, GABA secretion and autonomic balance, yoga appears to have the potential to play multiple roles in preserving β-cell function associated with T2DM and metabolic syndrome.

Insulin resistance

Skeletal muscle is one of the major sites for disposal of ingested glucose in healthy individuals with normal glucose tolerance. Postprandial hyperglycaemia induces insulin secretion and the resultant increase in plasma insulin concentration stimulates glucose uptake in skeletal muscles.[40] Meanwhile, glucose uptake into skeletal muscles is stimulated through insulin-independent mechanisms as well, that are activated by muscle contractions, hypoxia and nitric oxide, all of which are shown to increase membrane translocation of glucose transporter 4 (GLUT 4).[44,45] In the insulin-resistant state (e.g., in T2DM and metabolic syndrome), the insulin-dependent glucose disposal in skeletal muscle is markedly impaired;[46] however, the capacity for the insulin-independent Adenosine 5'-monophosphate-activated protein kinase (AMPK)-mediated glucose uptake is still intact in the muscle cells of patients with T2DM.[47]

Yoga – *asanas* and *pranayama* have shown to improve insulin sensitivity in T2DM.[48] Insulin sensitivity is found to be significantly higher in regular practitioners of yoga.[49] The observed increase in glucose sensitivity could be attributed to the possible activation of AMPK through muscle contractions involved during yoga postures.[50]

Adipose tissue and inflammation

Increase in the pro-inflammatory markers and decrease in the anti-inflammatory markers are often observed in T2DM and prediabetes.[51] Adipocytes are now known to be the key regulators of glucose homeostasis. Adipokines play an integral role in the etiopathogenesis of T2DM and modulation of adipocytes could therefore be a useful therapeutic strategy in T2DM.[52]

Reduction in the pro-inflammatory markers such as tumor necrosis factor α, interleukin-6, C-reactive protein (CRP) and high-sensitivity CRP, and increase in the anti-inflammatory markers such as adiponectin are consistently reported through various studies on yoga.[53-55] Adiponectin activates AMP kinase of liver and thereby help reduce hepatic glucose production (HGP).[56] Role of adiponectin on improving endothelial nitric oxide synthetase (eNOS) and resultant increase in endothelial nitric oxide production is well established,[57,58] which is beneficial in the prevention of neuropathy, cardiovascular complications and improve delayed wound healing in diabetes. A systematic review on the effect of exercise on adiponectin states that moderate-intensity exercise programs have significant impact on the adiponectin levels.[59] This was ably supported by a study which found regular yoga practise to increase adiponectin levels.[53]

Brain

In 1854, the renowned physiologist Claude Bernard observed that a lesion in the floor of fourth-cerebral ventricle could induce diabetes and postulated that brain plays a central role in glucose homeostasis and diabetes pathogenesis. The notion remained popular up until the discovery of insulin by Banting and Best in 1921, and the identification of liver, muscle and adipose tissue as the principal target organs of insulin on glucose metabolism.[60] Furthermore, a strong evolutionary link is observed between neurons and the insulin-producing β-cells in various animals.[61,62] Even in higher animals, the hypothalamus senses blood glucose levels, in a similar way as the β-cells.[63]

The available literature clearly suggests a high degree of association between brain and glucose metabolism. There are many glucose-sensing neurons in the brain, particularly in hypothalamus (arcuate, ventromedial and paraventricular nuclei) which helps in systemic glucose homeostasis.[60,64] Injecting smaller doses of glucose or insulin into these discrete areas of the brain can lower blood glucose levels and increase liver insulin sensitivity, independent of the amount of insulin in circulation.[65] Administration of leptin into the third ventricle reverses insulin resistance and diabetes phenotypes in lipodystrophic mouse at doses too low to have any effect outside the brain and is ineffective otherwise when administered peripherally.[66] Conversely, deletion of receptors for either insulin or leptin from certain specific hypothalamic neurons causes systemic insulin resistance and glucose intolerance, indicating the physiological role of these neurons on systemic glucose metabolism.[67,68] brain-derived neurotrophic factor (BDNF) prevents apoptosis and preserves insulin-secreting capacity of β-cells.[69] Similarly, serotonin is also reported to increase β-cell proliferation.[70] Some yoga studies have reported improvement in the BDNF and serotonin levels following practise of yoga.[71,72] Conversely, disturbances in the glucose metabolism also affect the brain. HbA1C of more than 7% increases the risk of developing mild cognitive impairment by 4-fold.[73] T2DM is associated with a 1.5–2.5-fold increased risk of cognitive dysfunction.[74,75] A cognitive decline is observed very early, during IGT and metabolic syndrome.[76-78]

Bromocriptine is a sympatholytic D2-dopamine agonist approved for use as antihyperglycemic medication.[79] The mechanism of action of which is attributed to its dopaminergic activity in the brain and subsequent inhibition of sympathetic tone, thereby improving both insulin release and insulin sensitivity.[80] Yoga, in addition to reduction in the sympathetic tone and increase in parasympathetic tone, has also shown to increase dopamine levels.[81] A landmark study in yoga demonstrated that meditation facilitates cortical plasticity, and regular practitioners of meditation are observed to have increased cortical thickness, especially in areas associated with somatosensory, cognitive and emotional processing.[82] An improvement in cognitive brain functions of T2DM patients is also observed with regular yoga practise.[83] Further studies on yoga had shown increased gray matter in the limbic system, cerebral lobes and cerebellum, improved cerebral blood flow and activation of midbrain close to the hypothalamus.[84] Yoga, thus might play an important role in enhancing the brain

regulated glucose homeostasis mechanism, possibly through hypothalamic–pituitary–adrenal axis and potentially improve cognitive dysfunction associated with T2DM, albeit, more studies are required.

Glucagon

Elevated glucagon levels and hyperfunction of α-cells were demonstrated in individuals with T2DM in 1970. Indeed, the importance of α-cells in diabetes was observed way back in 1947, when Rodriquez-Candela reported that alloxan-induced diabetes of dogs could be ameliorated by removal of pancreatic α-cell remnants.[85] A more recent study with an animal model demonstrated that, even in complete insulin deficiency, blocking of glucagon action could possibly prevent the metabolic and clinical derangements seen in type 1 diabetic mice,[86] highlighting the importance of glucagon suppression in the pathogenesis of diabetes. Elevated fasting plasma glucagon levels lead to increase in the HGP[87] and decreased insulin sensitivity in animal models.[88] Similarly, the capacity of the liver to synthesise triglycerides (which independently causes insulin resistance) is enhanced during stress which is partly due to the action of glucagon through the cyclic adenosine monophosphate pathway.[89] GABA induces membrane hyperpolarisation in α-cells, resulting in suppression of glucagon secretion,[89] and as mentioned earlier, yoga improves GABA levels.[90,91]

Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is a potent incretin hormone, acting more like a 'master switch' in glucose metabolism by operating through multiple pathways such as increased glucose uptake of muscle and liver, inhibiting glucagon secretion, while promoting insulin and somatostatin secretion and delayed gastric emptying.[92] The gene encoding the GLP-1, the proglucagon gene has three known sites of expression, namely, α-cells, L cells of the large intestine and the nucleus tractus solitarius in the hindbrain, which is the nucleus of vagus nerve as well.[93] The role of vagus in the regulation of GLP-1 secretion has been clearly demonstrated in animal model. Bilateral subdiaphragmatic vagotomy in conjunction with gut transection and selective hepatic branch vagotomy completely abolishes the fat-induced and exogenous GIP-induced GLP-1 release, respectively, while stimulation of the distal end of the celiac branch of the subdiaphragmatic vagus nerve significantly increases the release of GLP-1.[94] GLP-1 inhibits gastric emptying and acts through the vagal afferent-mediated central mechanism,[95] which could positively be influenced by yoga due to its known property of vagal activation. However, this is purely speculative based on the known effects of yoga on the autonomic nervous system and robust studies are needed to establish the impact of yoga specifically on GLP-1 secretion.

Liver

The liver is the major organ of glucose metabolism and HGP and the main source of fasting hyperglycaemia, contributing to approximately 80% of diurnal hyperglycemia in T2DM.[96] An increase in the circulating blood glucose levels releases insulin and inhibit HGP, but this negative feedback is dysfunctional in T2DM. Increased flux of free fatty acids to liver and accumulation of liver fat are the major determinants of the decreased sensitivity of endogenous HGP to insulin.[97] Glucagon,[98] central nutrient and hormone-sensing in the hypothalamus, together plays a central role in regulating peripheral glucose homeostasis and mediate in the reduction of HGP through vagal nerve efferent signaling to the liver.[99]

Various meta-analysis and systematic reviews on the effect of yoga on T2DM consistently report a higher reduction in the FPG (fasting plasma glucose) levels, than PPG (post-prandial plasma glucose) levels, which suggests a reduction in the HGP.[11,99] Although the effect of yoga on HGP has not been measured directly so far, one could speculate that the aforementioned positive impact of yoga on glucagon and adiponectin would have an influence in reducing the HGP. An improvement in the lipid profile through yoga is attributed to the increased hepatic lipase activity, which affects the lipoprotein metabolism and increases uptake of triglycerides by adipose tissue.[91]

Glucose reabsorption

The kidney plays an important role in regulating glucose homeostasis. The inhibition of renal glucose reabsorption is one of the novel and effective strategies in the management of T2DM.[100] β-cell dysfunction could upregulate sodium-glucose cotransporter 2 (SGLT2) protein in the kidney of patients with T2DM. Both SGLT2 and glucose transporter 2 (GLUT2) are expressed more in the proximal convoluted tubules cells of T2DM patients than in healthy individuals, resulting in elevated renal glucose uptake and further worsening of hyperglycaemia.[101] Hypothalamic pro-opiomelanocortin deficiency improves glucose tolerance in mouse models, by increasing glycosuria and reduced sympathetic nervous system (SNS) activity which is attributed to observed glycosuria and improved glucose tolerance.[102] Likewise, the SNS activity reducing property of yoga might also help reduce renal glucose reabsorption, facilitating improved glucose tolerance and better glycemic control [Figure 2]. This is obviously an area for future yoga research.

Other Physiological and Metabolic Effects of Yoga

The blood glucose lowering effect of yoga could be attributed to the stretching and contraction movements often performed during physical asana postures in yoga, as muscle contraction improves glucose sensitivity and reduce blood glucose.[68,69] However, randomised controlled trials (RCTs) done in the past have found yoga to be as effective if not superior to physical exercises[20,21,103] and the benefits are not just restricted to the physical movements involved in yoga. For instance, *yoga nidra* ('yogic sleep') is a yogic technique which involves complete body relaxation without any physical movements. A 3-month study exploring the efficacy of *yoga nidra* in patients with T2DM found a significant reduction in the blood glucose levels when compared to the control group.[104] The

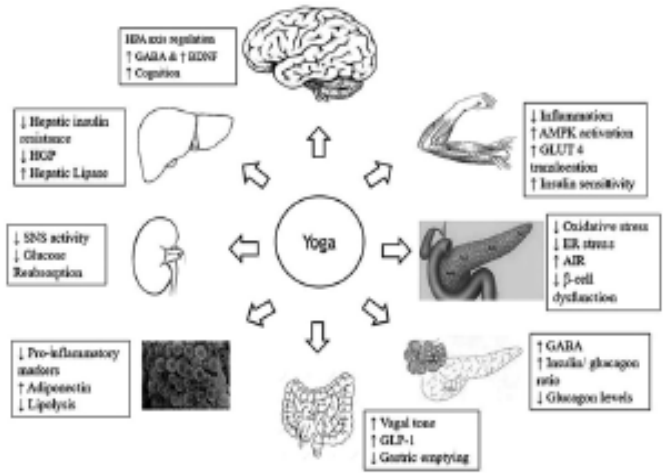

Figure 2: Summary of the hypothesized role of yoga in management of the 'Ominous octet' defects of diabetes (Adapted from Defronzo 2009)

study indicated that the reduction in blood glucose might not only be due to the physical movements involved but also through a possible reduction in the stress hormones or due to increased vagal activity.[105] Decreased vagal tone contributes to the etiopathogenesis of T2DM in multiple ways.[36,106] Reduced breathing rate increases vagal activation and decreases the influence of sympathetic branch of the autonomic nervous system, measured by an increase in heart rate variability and baroreceptor sensitivity.[107] Some studies report betterment of the complications associated with diabetes, like improved nerve conduction velocity,[108] cognition,[82] and QoL.[109] Autonomic dysfunction associated with T2DM is reported to be stabilised following yoga.[105,110] It is of interest that a couple of studies have reported a reduction in the medication score and insulin intake of T2DM patients,[111,112] suggesting a possible improvement in β-cell dysfunction, insulin resistance or any of the pathological abnormalities in the above-mentioned ominous octet, which was not observed with the control group on exercise-based lifestyle intervention.[113] Thus, yoga shows promising insights of becoming an effective complementary therapy in the prevention and management of T2DM.

Quality of Studies

Methodological flaws and bias are being reported in the systematic reviews of the past, on yoga studies in patients with diabetes.[18,19] Unlike drug trials, blinding might not be possible in yoga studies, providing a very low score while assessing the available RCT for bias. But still, high-quality RCTs, taking into account of the bias in study design, selection bias and publication bias are lacking and are very much essential to concretise the evidence available on the beneficial effects of yoga in diabetes. Meanwhile, the available evidence from RCTs and comparative studies are in line with the findings of nonrandomised and uncontrolled studies, thus indicative that the positive findings observed with yoga are not simply due to poor study design alone.

Admittedly, there are a few studies reporting yoga not to be beneficial as popularly 'claimed', on various dimensions of diabetes such as glycemic control,[9] inflammation,[22] and blood pressure.[113] Looking into the methodologies of these studies, it was observed that the duration of yoga intervention given was either once or twice a week, in comparison with the other yoga trials where the participants generally practise yoga three to five times a week. Yoga is more a way of life, to be practised ideally every day for health and well-being. Even if considered as just a form of physical activity, it should be practised 5 days a week to get the desired benefits.[16] Therefore, yoga might have a dose-dependent effect on glycemic control in T2DM. Future studies on yoga should be designed so as to remove the bias in methodology and reporting, with the recommended duration or 'dosage' of three to five times a week.

Cost-effectiveness of yoga interventions

A cost-effective and sustainable intervention for the primary and secondary prevention of diabetes would help increase the QoL, diabetes-free years of life, improved life expectancy, and on top, cost savings, reducing the economic burden in growing economy of many developing countries where the prevalence of T2DM is on the rise. Yoga would be one such cost-effective intervention where the cost involved is a onetime investment, where the patients learn yoga once under the direct supervision of a suitably qualified and experienced yoga professional and can practise on their own after getting sufficient training. Moreover, the adherence rate of yoga is found to be higher than other forms of physical activity, making it a more acceptable and simpler form of physical activity for T2DM.[114]

Future Directions

Few advantages of using yoga as a form of physical activity in T2DM are the relatively low cardiovascular demands when compared to other forms of exercises. Low impact makes it an easier and more simpler physical activity to practicse for people who are contraindicative for exercise. Unlike many 'traditional' therapies, yoga may be applicable to a larger population of T2DM patients as it appears to be safe and inexpensive.[115,116] The strength of most available research evidence on yoga is modest and necessitates more robust research design and unbiased reporting in the future. Nevertheless, the potential role of yoga in the primary and secondary prevention of T2DM is worth considering. Yoga could be a safe and cost-effective modality to prevent and manage T2DM.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Reviewer 1 comments:

1. Small typographical corrections required, like, in pg-10 instead of fig.2 it is mentioned as fig.1. There are few more on pg.37, pg.50 etc.

Reply: Apologies. Following changes are made as pointed out.

"**Pg. 10**: (Fig 2) changed to (Fig 1).

Pg. 37: 'compared the diabetic...' changed to 'compared to patients having diabetes..' and (Salas-Salvado et al., 2011) – bracket removed.

Pg. 50: '…culminate in disease..' changed to '…culminate as disease..' "

The whole document is again re-read for further typographical errors.

Thank you

2. Section 1.8 is too elaborate. It would have been fine if Yoga part was also described in detail. Herbal medicine part is dealt in great detail but a very short note on Yoga, this is also the same in literature review section.

Reply: Being a Yoga and Naturopathy consultant, I actually wanted my thesis to contain possible yoga and natural plant-based treatment for the management of type 2 diabetes (T2DM). Apologies. I shall remove the 'botanical medicine' section if it is too elaborate.

Further, Yoga part has been kept to the minimum in section 1.8 as I felt that it shall be discussed in detail in the chapter 2- 'Review of ancient literature' section and sections that follows.

However, I agree that literature review section has minimum notes on 'yoga for T2DM management' as well. Therefore, I would like to add the following to the 'Literature review' section.

"Patients with T2DM have higher levels of oxidative stress and studies on yoga have showed a reduction in oxidative stress and increased anti-oxidant defence, by

improving superoxide dismutase, glutathione, malondialdehyde, vitamin C and vitamin E profile (Hegde et al., 2011; Mahapure, Shete & Bera, 2008).

Glucose uptake into skeletal muscles could be stimulated via insulin independent mechanisms, that are activated by muscle contractions, hypoxia and nitric oxide, all of which are shown to increase membrane translocation of Glucose Transporter 4 (GLUT 4) (Henriksen, 2002; Zierath, Krook & Wallberg-Henriksson, 2000). In the insulin resistant state, as in metabolic syndrome and T2DM, the insulin-dependent glucose disposal in skeletal muscle is markedly impaired (Kahn, Hull & Utzschneider, 2006); however, the capacity for the insulin-independent Adenosine 5'-monophosphate activated protein kinase (AMPK) -mediated glucose uptake is still intact in the muscle cells of patients with T2DM (Koistinen et al., 2003). Yoga-*asanas* and *pranayama* has shown to improve insulin sensitivity in T2DM (Singh et al., 2008). Insulin sensitivity is found to be significantly higher in regular practitioners of yoga (Chaya et al., 2008). The observed increase in glucose sensitivity could be attributed to the possible activation of AMPK through muscle contractions involved during yoga postures (Zhang, Zhou & Li, 2009). Increase in moderate physical activity is associated with multiple benefits like, improved insulin sensitivity, better glycaemic control, reduced BMI, improvement in lipid profile and other risk factors associated with diabetes such as obesity and hypertension (Pischke et al., 2006; Aune et al., 2015). However, physical exercise may need to be done with caution in patients with increased risk of cardiovascular events and co-morbidities associated with microvascular and macrovascular complications like diabetic neuropathy and proliferative retinopathy, which could worsen with intensive exercise programs (Zinman et al., 2004).

Reduction in the pro-inflammatory markers like TNF α, IL-6, CRP and hsCRP and increase in the anti-inflammatory markers like adiponectin are consistently reported through various studies on yoga (Kiecolt-Glaser et al., 2012; Sarvottam & Yadav, 2014; Vijayaraghava et al., 2015). Adiponectin activates AMP kinase of liver and thereby help reduce hepatic glucose production (HGP) (Combs et al., 2001). Role of adiponectin on improving endothelial Nitric Oxide synthatase (eNOS) and resultant increase in endothelial nitric oxide production is well established (Hattori et al., 2003; Chen et al., 2003), which is beneficial in the prevention of neuropathy, cardiovascular complications and delayed wound healing in diabetes. A systematic review on the effect of exercise on adiponectin states that moderate intensity exercise programs have significant impact on the adiponectin levels (Simpson & Singh, 2008). This was ably supported by a study which found regular yoga practice to increase adiponectin levels (Kiecolt-Glaser et al., 2012).

Brain-Derived Neurotropic Factor (BDNF) prevents apoptosis and preserves insulin secreting capacity of β- cells (Bathina, Srinivas & Das, 2016). Similarly, serotonin is also reported to increase β-cell proliferation (Kim et al., 2010). Some yoga studies have reported improvement in the BDNF and serotonin levels following practise of yoga (Lee et al., 2014; Naveen et al., 2016). An improvement in cognitive brain functions of T2DM patients is also observed with regular yoga practise (Kyizom et al., 2010). **"**

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3. I feel that introduction could have had more information on micro & macrovascular complications, specially some mechanistic insight on why variation in glucose is more damaging than increased glucose itself.

Reply: Being an emerging concept in the T2DM, it was difficult to gather much

literature on the mechanism behind glycemic variability leading to micro & macrovascular complications, except '***increase in oxidative stress***' contributing to diabetes complications and increased protein glycation.

4. Continuing with the last comment, will be interesting if you can mention the reasons for GV.

Reply: The exact mechanism or reasons for GV is not clearly understood, but as for now it is being attributed to the medications, mainly insulin secretagogues and insulin. Inter- individual differences might also be a reason in a community based study, as no two individuals might have the same amount of beta cell dysfunction or glucose tolerance, even though the diagnosis reads the same as T2DM. Glycemic index of the food is also mentioned in the literature as one of the possible reasons for GV.

5. Though the work is focused and tries to describe a novel phenomenon in the form of yoga's effect on GV, feel that it is less to be considered a complete phd work. could have done a few additional experiments (see below).

Reply: We do agree that the results would have added more value if we could have measured ACh, GABA and a few oxidative stress markers as well. However, funding was a major issue, as we were able to obtain only around INR 2 Lakh from a CSR initiative for our pilot study and main study combined. As the idea of GV was a bit novel and first of its kind for a yoga study, we needed some data to write for funding to government agencies which we were not able to do then and are currently planning to apply for funding now. I would definitely like to work on the results further to understand the underlying mechanism of action in the future.

Further comments on results and discussion section:

6. What is the reason you would give for more normal distribution of data in the intervention group while not in the control group (table – 3, more parameters required to be tested with Wilcoxon test in the control group).

Reply: One possible reason might be that the intensity of walking in the control group might have differed from person to person (inspite of a general instruction of a moderate intensity walking which makes you 'slightly breathless'), when compared to

the same uniform yoga protocol delivered to the participants in the intervention group by the same yoga professional.

7. Is the values in table – 3 of 7 days or 14 days?

Reply: Pre values are calculated at the end
of 7 days

Post values are calculated between day 8 to 14.

As per the instructions from flash glucose monitoring manufacturers 'Abbott', five day blood glucose readings are required for the GV graph and for proper calculation of the inter-day and intraday variability, and to possibly minimize the confounding factors/deviations.

8. If the pre mean (in both groups) is of first 7 days then why big difference in control vs yoga group for MODD & MAGE? Was the control group walking from day 1?

Reply: Control group started walking only from day 8.

We were having the same doubts after looking at the data. Though MODD & MAGE are not directly proportional to the mean, as mentioned earlier, the big difference in GV measured using MAGE & MODD might be due to possible inter-individual differences.

9. Possible that I have not understood the design properly, is there any explanation for difference in pre mean for MODD and MAGE between control and yoga group?

Reply: Recruitment of the patients were primarily based on the HbA1C levels between 7% - 8.5%, medication score of > 1.5 with atleast one oral insulin secretagogue. Though the HbA1C criteria was broad, not many patients were having medication score of > 1.5 at the lower end of the HbA1C range and patients were on insulin when HbA1C was around 8.5% in the tertiary care hospital that we had recruited. Therefore, most of the patients who got recruited where within a tight range of 7.5% – 8%, giving us a somewhat similar mean glucose levels.

However, we could calculate the MODD & MAGE only at the mid-way of the study (i.e. after 7 days) and therefore we were not able to balance or control the wide difference between the two groups in MAGE or MODD during the initial recruitment

phase inspite of a somewhat a similar pre-mean.

10. In the discussion the 3 possible mechanisms all zero-in on autonomic nervous system modulation as the reason for difference between control and yoga groups. Then why was no effort put into measuring Ach, glp-1 or paracrine communication. You have mentioned previous studies with yoga showing impact on ach, gaba etc., but in a Ph.D. work this would have completed the story.

Reply: We definitely agree. As mentioned in comment 5, funding was a major issue for me as a full time PhD student and we are currently working on writing a proposal including the parameters that you had mentioned along with oxidative stress markers for further research on the topic.

Reviewer 2 comments:

Question 1.

It is a known fact that the effect of Yoga is long term. The time frame used for this study seems very short to have noticeable changes in the patients. That is also reflected in the data. There seems to be intra group variability also. Why such a short duration has been chosen and how these problems could be addressed in future needs to be clarified.

Answer:

The short duration of the intervention is one of the major strength as well weakness for our study. Research evidence does clearly show that yoga is effective while practising for long term of 3 months, 6 months & 12 month duration. However, the minimum duration and frequency of yoga required to bring about a significant change glucose levels in diabetes or in other words minimum 'dosage' of yoga required to bring about a noticeable change in the glucose levels and glucose homeostasis has not been studied so far and I personally wanted to explore this particular area through our study. Previous studies using a minimum duration of 3 months yoga for T2DM might have been carried out to measure HbA1C, as HbA1C was (/is) a robust prognostic marker for T2DM which could to be measured only after a 3 month period. As discussed in the thesis, HbA1C is not the only major marker to understand glycemic status anymore and

glycemic variability is gaining importance as a significant marker of glycemic status in the recent past. In our study, we noticed that yoga starts showing impact on the glycaemic variability as early as 7 days and we anticipate that with regular practise the effect would be sustained as far as they continue practising yoga. We definitely agree that we would have got a really valuable data if we could have followed them up with AGP data for a longer time at month 3, 6 &/ or month 12, but due to funding constraints we were not able to afford more than one AGP per patient. In the future, we would definitely overcome these issues for sure taking into account of your valuable suggestions.

2. This is a preliminary study according to the thesis. And hence the small no of Individuals studied. However, considering the intra group variability and the marginal changes in the various criteria studied, the significance of these changes cannot be concluded with confidence. How this can be addressed needs to be clarified.

Answer:

We were initially not sure about the sample size required for our study as this was first of its kind yoga study using continuous glucose monitoring as the primary variable. Henceforth, we conducted a pilot study and sample size was calculated based on the results of our pilot study (Appendix 4) with the guidance of a statistician. Power was actually set at 0.90 to get a sample size of 23, as we got a even lesser sample size of 15 or lesser for various parameters of power was set at 0.80. Accounting for the dropouts, we had set a sample size of 30 in each group. In the main RCT study, though there is statistically significant reduction within intervention group, between group differences are only marginal in few of the parameters. In this context, we agree that larger sample size might be required in the future studies to further validate and substantiate our findings. Effect size and Cohen's d has been calculated for the various parameters in Table 3.