



EFFECT OF LEMON JUICE IN REDUCING BLOOD SUGAR OF PRE-DIABETES AND DIABETES PATIENTS: A COMMUNITY BASED PRAGMATIC RANDOMIZED TRIAL

Community Medicine

Gouri Kumari Padhy

Additional Professor, Department of Community and Family Medicine, AIIMS, Raipur.

Rashmi Yadav*

Assistant Professor, Department of Community Medicine, Government Medical College, Khandwa. *Corresponding Author

ABSTRACT

Patients with pre-diabetes and diabetes have significantly increased risk of macro and micro vascular complications. Food supplements have increasingly become attractive alternatives to prevent or treat hyperglycemia, especially for subjects with mild hyperglycemia. Objective of the project is to find effectiveness of lemon juice intake in reduction of blood glucose level among prediabetics, newly diagnosed diabetics and known diabetics with inadequate glycemic control. It is a pragmatic randomized controlled trial (community based study in ward no 18 of Raipur) of 20 wks duration. Independent t test, paired t test and Wilcoxon test will be used for statistical analysis. Positive results from this study may encourage researchers to conduct large scale multi centric studies. Food supplementation by lemon juice can be a feasible and cost effective intervention for treatment of mild hyperglycemia cases.

KEYWORDS

INTRODUCTION:

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world", with more than 62 million diabetic individuals currently diagnosed with the disease(1)(2). In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, (2). Current prevalence of prediabetes and diabetes among adult population in India is about 8-14% and 11-12% respectively (1)(2)(3). The number of diabetics in the country has doubled in last 25 years. About 90-98% of diabetics are of type 2 variety(1).

Patients with prediabetes and diabetes have significantly increased risk of macro and micro vascular complications. Early detection and correction of abnormal blood sugar level during early phase of life helps in reduction of morbidity resulting from the disease and its consequences. Currently, management of hyperglycemia includes pharmacological interventions, physical exercise, and change of life style and diet. Food supplements like bitterguard, amla, ginger, citrus fruits etc have increasingly become attractive alternatives to prevent or treat hyperglycemia, especially for subjects with mild hyperglycemia(5). Observing the potential of natural products, studies are being conducted to assess their effect in reduction of high blood

sugar. Several ethno pharmacological studies have shown beneficial effects of medicinal plants, complementary and alternative medicine therapies in diabetes patients (6)(7)(8)(9)(10)(11)(12)(13)(14).

Food supplements like lemon juice have been used for human consumption for centuries and their safety in human has been well established. Citrus fruit and juices have long been considered a valuable part of a healthy and nutritious diet and it is well established that some of the nutrients in citrus promote health and provide protection against chronic disease. Citrus fruits like lemon contain a range of key nutrients such as vitamin C, vitamin A, carotenes of various kinds, folate and fiber as well as very many non-nutrient phytochemicals (polyphenol etc.). Recently, the roles of bioactive non-nutrient components like phytochemicals, soluble fiber pectin in lemon have received increasing attention(15). Research has shown that lemon lowers the glycaemic index of other foods and decreases absorption of sugar we eat(16). Several studies report beneficial effect of consumption of lemon juice with lukewarm water in reduction of weight among obese. Some traditional literature mention about its blood sugar lowering action(17)(18),(19) (among persons with high blood sugar level), but scientific evidence showing effect of undiluted lemon juice in diabetes is sparse.

Review of literature:

Literature search was carried out to find out hypoglycaemic effect of various food supplementations. The summary of the search is mentioned in the table below.

S. N.	Type of food supplementation	No. of trials	Study population (Intervention Vs control)	Outcome (Effective In Reduction of blood sugar)	Study Duration- Population- Outcome	Source
1	Ginger	1	Diabetic	Y	12 wks—41-Y	6
2	Amla	4	Diabetic	3-Y 1-N	3m-120-Y 3m-43-Y 2m-49-N 3m-13-Y	5
3	Fenugreek	8	Diabetic	7-Y 1-N	1day--21--Y 10days--15--Y 15 days--10--Y 3m---40--Y 2m--25--Y 3m--60--Y 3m--69--Y 2m—11--Y 2m—7--N	5
4	Green tea	4	Diabetic	4-N	2m-66-N 3m-49-N 3m-43-N 4m-80-N	5

5	Bitter melon	8	Diabetic	7-Y	1day-14-y	5
				3-N	11wks-9-y	
					- -100-y	
					4wks-50-N	
					3m-40-N	
					7days-15-Y	
					4wks-143-y	
					3m-42—Y	
3m-40-N						
7days-15-Y						
6	Cinnamon	8	Diabetic-7	5-Y	40days—60-Y	5
			Pre diabetic	3-N	4m—79-Y	
					90days—109-Y	
					12wks—58-Y	
					6wks—25-N	
					90days—72-N	
					3m—58-N	
					4m-62-y	
7	Alovera	5	Diabetic	5-Y	6 wks—72—Y	11
			Pre diabetic		8 wks —45—Y	
			Pre diabetic		8 wks —136—Y	
			&		12 wks —90—Y	
			Diabetic		8 wks --72—Y	
			Diabetic			
Pre diabetic						
8	Wheat grass	1	Diabetic	Y	21 days-16-y	12
9	Red onion	1	Diabetic	Y	1day-42-y	13
10	Honey	1	Diabetic	N		14
	Lemon(diluted or undiluted)	No clinical trial to assess hypoglycemic effect				
	Lemon (rind)					
	Cucumber					

What new information this study is supposed to reveal?

- Whether consumption of undiluted lemon juice helps in reduction of blood glucose level among pre diabetics, newly diagnosed diabetics, and known diabetics with inadequate glycemic control?
- Whether consumption of cucumber helps in reduction of blood glucose level (among pre diabetics, newly diagnosed diabetics, and known diabetics with inadequate glycemic control)?
- Is consumption of undiluted lemon juice effective in reduction of blood pressure among hypertensive?
- Is consumption of undiluted lemon juice effective in reduction of central obesity among obese?
- What is the prevalence of subcategories of pre diabetes (IFG & IGT) among high risk population?

Research Question: Is consumption of lemon juice (for 12 wks time period) effective in reduction of blood glucose level among prediabetics, newly diagnosed diabetics and known diabetics with inadequate glycemic control, in comparison to cucumber?

Objectives:

- To find effectiveness of lemon juice intake in reduction of blood glucose level among prediabetics and newly diagnosed diabetics.
- To find effectiveness of lemon juice intake in reduction of blood glucose level among known diabetics with inadequate glycemic control

MATERIAL AND METHODS: It is a pragmatic randomized controlled trial (community based study in ward no 18 of Raipur) of 20 wks duration (2 wk baseline survey+12 wks intervention +6wks analysis & report writing).

Methodology for selection of study population for screening- A baseline survey of adult population >30 years will be carried out in study area to identify the high risk population (based on Indian Diabetes Risk Score) and previously diagnosed diabetes patient(self reported diabetes or available prescription/ medication/ blood test report indicating diabetes among >30 yrs adult population). The study area will be the field practice area of urban health training centre (UHTC), Department of Community Medicine (ward 18 having population of about 20,000). House to house visits will be carried out and all population of 30 years and above, present on the day of survey, willing to participate will be covered in the study.

The tool for data collection in baseline survey, will be a questionnaire for assessment of India diabetes Risk score (IDRS). The questionnaire has already been validated for Indian setting and has been used previously in studies done for diabetes risk screening. IDRS was developed by Mohan et al. and its parameters comprise of two modifiable (waist circumference, physical activity) and two non-modifiable risk factors (age, family history) for diabetes (20). Persons with risk score (IDRS) >60 will be included in screening for cost effectiveness purpose (high risk population). Data regarding previous history of diabetes will also be collected during baseline survey. Three house visits will be made in case the eligible participants are not available on the first visit. Participants who refuse to participate or those who cannot be contacted despite three house visits will be taken as non-responders.

Methodology for selection of study population for RCT- A screening test will be carried out among the high risk population and known diabetic patients to find out cases having high blood sugar level. In both the categories fasting and post glucose blood sugar will be measured for this purpose using glucometer. Persons having pre diabetes and diabetes will be identified among high risk population and patient with inadequate glycemic control (FBS>130 and 2 hr value >180 mg/dl) will be sorted from the previously diagnosed diabetes cases. All the participants identified in the screening test(provisionally eligible)will be subjected to venous blood test(FBS, 2 hr PGBS & HbA1C).Eligibility criteria will be reassessed after having the result of venous blood test(FBS, 2 hr PGBS) and application of inclusion exclusion criteria . The finally eligible participants giving consent for the study will be initially recruited to enter run in period of study. Those who show compliance in run in period will be finally recruited. The purpose of the study will be explained thoroughly to the participants and recruitment as study subjects will be done after a voluntary written informed consent was obtained from them.

Inclusion criteria-

- Identified eligible persons giving consent to participate in this study
- Pre-diabetics
- Newly diagnosed diabetics
- Previously diagnosed diabetics with inadequate glycemic control

Exclusion criteria- i) Presence of serious co morbidities, recent changes in the type or dose of medication, changes in diet or daily

physical activity, any acute illnesses or some chronic diseases including kidney, liver, cardiovascular, and gastrointestinal diseases, smoking, pregnancy and lactation

- ii) Any contraindication for intake of lemon juice (severe gastritis, allergy)
- iii) Compliance less than 70% during the run in period
- iv) Habit of consumption of lemon juice or cucumber in empty stomach on regular basis prior to the study
- v) Age > 90 yrs

Sample size required to find effect of lemon juice in reduction of blood sugar- Based on data from previous studies (6) (21)(22) by considering type I error level $\alpha=0.05$ with test power of 80%. , the sample size was computed to be 20 per group. As the study plans for cluster randomization, a design effect of 1.5 was considered, which gives 30 participants in each group. In order to compensate the possible loss to follow-up, a safety margin of 25% was determined, and therefore 38 patients were estimated in each group.

Study instrument-

- i) Questionnaire and measuring tape (for anthropometric measurement) for baseline survey
- ii) Measurement of blood glucose
 - a) FBS, 2 hr post glucose value using glucometer (to identify provisionally eligible study population)
 - b) FBS, 2 hr post glucose value using venous blood (confirmatory test to identify finally eligible study participants & to know effectiveness of intervention)
- iii) Measurement of HbA1c (to know effectiveness of intervention)
- iv) Weight machine, BP machine, Measuring tape, Questionnaire to assess compliance and measure other variable.

Consent and IEC- Permission from institutional ethical committee (IEC) has given for the study and registration with CTRI has also done.

Randomization and Intervention- For the purpose of intervention, the study participants will be divided into two groups using cluster randomization technique. The existing main road passing through ward 18 divides the study area into approximate two halves. Each half will be considered as one cluster. Area towards the right side of road will be named as A and towards left side as area B. Selection of area for intervention will be done by simple random technique (coin toss-head for intervention and tail for control). Study participants of intervention and control area will be asked to consume lemon juice and cucumber respectively. Consumption of lemon juice/extract from one lime) preferably in empty stomach during morning hour for 12wks will be advised for this purpose for intervention group (self administration by directly pouring the extracted juice in posterior part of tongue). The participants will also be advised not to consume any other food or fluid for at least 15 min after intake of lemon juice. Similarly consumption of one cucumber per day will be advised for the control group (cucumber in raw form as salad without addition of salt, preferably in morning hour). As placebo for lemon juice is not feasible; control group will be given another food supplementation i.e. cucumber. Cucumber will be selected for this purpose because of its high water content (95% water as content), easy availability, better acceptability, wide safety profile and relative inertness (as on date there is no scientific evidence reporting glucose lowering action of cucumber).

A run in period of 1 wk will be kept to assess acceptance of intervention before final recruitment (persons showing less than 70% compliance will be excluded from this study). Lemon juice and cucumber will be consumed under direct supervision during this run in period, (after initial demonstration by the instructors).

Follow up and outcome assessment- During the 12 week intervention period, the study participants will be contacted every week for supply of lemon and cucumber for next one week and to assess compliance related to intervention in previous week. About 10 lemons and 10 cucumbers of average size will be supplied each week for each participant in intervention and control group respectively (extra three to take care of pilferage, if any).Data regarding any problem related to intervention will also be collected during this period.

Follow up test for blood sugar level (fasting, 2 hrs post glucose, HbA1C) will be carried out after 12 wks of intervention. Blood samples will be collected in field and tests will be conducted in clinical

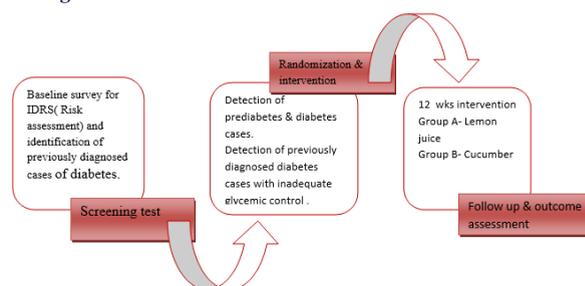
biochemistry lab of the institute. Proportionate reduction and absolute reduction will be measured(FBS for IFG group, PGBS for IGT group,HbA1C,FBS& PGBS for new diabetics and known diabetic with inadequate control group). Intention to treat analysis will be used to assess effectiveness of the intervention. Imputation technique for missing data will be done by substituting a fixed value, such as the group mean.

At the beginning of the study, information on socio-economic status of participants will be collected by means of a questionnaire completed through an interview. The report of daily dietary intake will be collected by a 24-hour diet recall questionnaire once at the beginning and at the end of the study. Similarly the reports of the level of physical activity, history of intake of other medications, at the beginning and the end of the study, will be obtained through interview.

Anthropometric parameters including height and weight will be measured at the beginning and the end of the intervention to calculate body mass index (BMI). Data regarding waist circumference and BP of enrolled study participants will be collected at the beginning and at the end of intervention. Standardization of instrument like weight machine, glucometer etc. will be carried out by measuring a known sample.

Statistical analysis- independent t test & Mann Whitney test using MS excel (data analysis software) will be used to compare quantitative variables between the two groups, for normal and non normal distribution variables, respectively. To compare data related to pre and post intervention period, paired t test and Wilcoxon test will be used. Differences with p-value <0.05 will be considered to be statistically significant. Effectiveness in different sub categories will be analyzed by applying ANOVA test.

Fig 1. Flow chart describing the progress of study participants through the trial



Implications: Positive results from this study may encourage researchers to conduct large scale multi centric studies. Food supplementation by lemon juice can be a feasible and cost effective intervention for treatment of mild hyperglycemia cases. Combination of lemon juice with oral anti-diabetic drugs or insulin may represent a better option to control hyperglycemia in diabetic patients, especially for those whose blood glucose levels are not well controlled by oral hypoglycemic drug/ insulin alone. The study may also reveal other beneficial effects of lemon juice like weight reduction, reduction of blood pressure etc. It will also give an additional benefit by providing Vit. C and antioxidants. These chemicals have major role in decreasing oxidative stress caused by hyperglycemia. It was reported that oxidative stress induces endothelial cell dysfunction and triggers the progression of atherosclerosis (6), thus increases the risk of cardiovascular disease in diabetes patients. Prospective follow up of enrolled participants who continue with consumption of lemon juice on their own, will throw some light regarding protective role of lemon juice in this context.

The study will reveal prevalence of IFG & IGT type of prediabetes and overall prevalence of prediabetes and diabetes among high risk population in a slum area. The study will also give idea about the reliability and correlation of various tests in assessment of glycemic control of diabetes persons (FBS Vs PGBS and HbA1C).

Early identification of at-risk individuals using simple screening tools like the Indian Diabetes Risk Score (IDRS) and early diagnosis of prediabetes and diabetes cases by screening test followed by appropriate lifestyle intervention at the end of the study, would greatly help in preventing or postponing the onset of diabetes or its complication, thus reducing the burden on the community and the nation as a whole.

REFERENCES:

1. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. *Indian J Med Res.* 2007 Mar;125(3):217–30.
2. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. *Australas Med J.* 2014 Jan 31;7(1):45–8.
3. Dasappa H, Fathima FN, Prabhakar R, Sarin S. Prevalence of diabetes and pre-diabetes and assessments of their risk factors in urban slums of Bangalore. *J Fam Med Prim Care.* 2015 Sep;4(3):399–404.
4. Association AD. 2. Classification and Diagnosis of Diabetes. *Diabetes Care.* 2015 Jan 1;38(Supplement 1):S8–S16.
5. Deng R. A Review of the Hypoglycemic Effects of Five Commonly Used Herbal Food Supplements. *Recent Pat Food Nutr Agric.* 2012 Apr 1;4(1):50–60.
6. Khandouzi N, Shidfar F, Rajab A, Rahideh T, Hosseini P, Mir Taheri M. The effects of ginger on fasting blood sugar, hemoglobin a1c, apolipoprotein B, apolipoprotein a-I and malondialdehyde in type 2 diabetic patients. *Iran J Pharm Res IJPR.* 2015;14(1):131–40.
7. Tsai C-H, Chen EC-F, Tsay H-S, Huang C. Wild bitter melon improves metabolic syndrome: A preliminary dietary supplementation trial. *Nutr J.* 2012;11:4.
8. Dans AML, Villarruz MVC, Jimeno CA, Javelosa MAU, Chua J, Bautista R, et al. The effect of *Momordica charantia* capsule preparation on glycemic control in type 2 diabetes mellitus needs further studies. *J Clin Epidemiol.* 2007 Jun;60(6):554–9.
9. Tongia A, Tongia SK, Dave M. Phytochemical determination and extraction of *Momordica charantia* fruit and its hypoglycemic potentiation of oral hypoglycemic drugs in diabetes mellitus (NIDDM). *Indian J Physiol Pharmacol.* 2004 Apr;48(2):241–4.
10. Liu Y, Cotillard A, Vatier C, Bastard J-P, Fellahi S, Stévant M, et al. A Dietary Supplement Containing Cinnamon, Chromium and Carnosine Decreases Fasting Plasma Glucose and Increases Lean Mass in Overweight or Obese Pre-Diabetic Subjects: A Randomized, Placebo-Controlled Trial. *PLOS ONE.* 2015 Sep 25;10(9):e0138646.
11. Zhang Y, Liu W, Liu D, Zhao T, Tian H. Efficacy of Aloe Vera Supplementation on Prediabetes and Early Non-Treated Diabetic Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients* [Internet]. 2016 Jul [cited 2017 Aug 4];8(7). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4963864/>
12. [cited 2017 Aug 4]. Available from: [http://www.rjpbcs.com/pdf/2017_8\(1\)\[274\].pdf](http://www.rjpbcs.com/pdf/2017_8(1)[274].pdf)
13. Eldin IMT, Ahmed EM, H.M AE. Preliminary Study of the Clinical Hypoglycemic Effects of *Allium cepa* (Red Onion) in Type 1 and Type 2 Diabetic Patients. *Environ Heal Insights.* 2010;4:71.
14. Bahrami M, Ataie-Jafari A, Hosseini S, Foruzanfar MH, Rahmani M, Pajouhi M. Effects of natural honey consumption in diabetic patients: an 8-week randomized clinical trial. *Int J Food Sci Nutr.* 2009 Nov;60(7):618–26.
15. Bahmani M, Eftekhari Z, Saki K, Fazeli-Moghadam E, Jelodari M, Rafieian-Kopaei M. Obesity Phytotherapy: Review of Native Herbs Used in Traditional Medicine for Obesity. *J Evid-Based Complement Altern Med.* 2016 Jul 1;21(3):228–34.
16. Diabetic Diet: How Lemon and Lemon Water Can Help Cure Diabetes - Health - Nigeria [Internet]. [cited 2017 Aug 9]. Available from: <http://www.nairaland.com/1572320/diabetic-diet-how-lemon-lemon>
17. Should You Eat More Lemons If You Have Diabetes? [Internet]. [cited 2017 Apr 21]. Available from: <https://www.verywell.com/benefits-of-lemon-and-diabetes-1087441>
18. Lemon and Diabetes | Healdove [Internet]. [cited 2017 Apr 21]. Available from: <https://healdove.com/disease-illness/Lemon-and-Diabetes>
19. Lemon Water Weight Loss Benefits [Internet]. [cited 2017 Aug 9]. Available from: <https://www.practo.com/healthfeed/lemon-water-weight-loss-benefits-3418/post>
20. Mohan V, Deepa R, Deepa M, Somannavar S, Datta M. A simplified Indian Diabetes Risk Score for screening for undiagnosed diabetic subjects. *J Assoc Physicians India.* 2005 Sep;53:759–63.
21. Kuzuya T, Iwamoto Y, Kosaka K, Takebe K, Yamanouchi T, Kasuga M, et al. A pilot clinical trial of a new oral hypoglycemic agent, CS-045, in patients with non-insulin dependent diabetes mellitus. *Diabetes Res Clin Pract.* 1991 Mar 1;11(3):147–53.
22. Joseph B, Jini D. Antidiabetic effects of *Momordica charantia* (bitter melon) and its medicinal potency. *Asian Pac J Trop Dis.* 2013 Apr;3(2):93–102.