Anti-diabetic effect of bitter gourd in pre-diabetics: blind randomized crossover trial in Moshi, Tanzania

Mark Swai & Christine Ludwig

Kilimanjaro Clinical Research Institute (KCRI)

at Kilimanjaro Christian Medical Center (KCMC)
Justification

- Diabetes rates are increasing, esp. developing countries
- 285 million people worldwide live with diabetes
- High rates of pre-diabetes of approx. 10% in Tanzania
- Prevalence of diabetes mellitus in urban areas approx. 4%
- Own study in Moshi area: 30% pre-diabetic, 8% diabetic
- Lack of access to adequate medical treatment (costs, distance)
  → reduced life expectancy and reduced quality of life
- Only a few randomized controlled trials with BG treatment available
- Need for studies with standardized and quality controlled bitter gourd material in order to provide evidence-based recommendations for the use of BG in glucose management
Study …

...Design: Cross-over single-blind randomized placebo-controlled intervention study

...Area: Moshi, Kilimanjaro Region, Tanzania

...Site: Kilimanjaro Clinical Research Institute

...Team: Medical doctors, nutritionists, nurses from KCMC (Tanzania) and Justus-Liebig University Giessen, Germany

...Objective:

To test whether a drink containing 2.5 g bitter gourd whole fruit powder is effective in lowering blood glucose levels in pre-diabetics
Recipes of Bitter Gourd & Placebo Sachets

Taste of bitter gourd masked with cucumber, cyclodextrins, and steviol glycoside
Placebo contained cucumber instead of bitter gourd
One sachet per day was diluted in 150 ml of water and drunk after the main meal

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Bitter gourd sachet</th>
<th>Placebo sachet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitter gourd powder (g)</td>
<td>2.5</td>
<td>---</td>
</tr>
<tr>
<td>Cucumber powder (g)</td>
<td>0.75</td>
<td>3.25</td>
</tr>
<tr>
<td>Alpha-cyclodextrin* (g)</td>
<td>0.75*</td>
<td>0.75#</td>
</tr>
<tr>
<td>Beta-cyclodextrin (mg)</td>
<td>75#</td>
<td>75#</td>
</tr>
<tr>
<td>Steviol glycoside (mg)</td>
<td>15#</td>
<td>15#</td>
</tr>
<tr>
<td><strong>Total (g)</strong></td>
<td><strong>4.090</strong></td>
<td><strong>4.090</strong></td>
</tr>
</tbody>
</table>

*containing 2% (v/w) of lemon peel oil
# within the range of the European and American allowances
Plant Materials

Treatment: Bitter gourd variety NS1020 from Namdhari Seeds Pvt. Ltd. (India):

• A dark green, high yielding, medium bitter variety
• High variety and quantity of compounds in the LC-MS fingerprint
• Grown and harvested at AVRDC – The World Vegetable Center (Taiwan) in 2012
• Harvested at marketable maturity stage 16 days after pollination
• Fruits were washed, cut and freeze dried. The dried pieces were ground to fine powder

Placebo: Cucumber variety MALINI™ from Seminis (India)

Grown and harvested at AVRDC – The World Vegetable Center (Taiwan) in 2012
Processing of Bitter Gourd & Placebo Sachets

Fruits were washed with clean water and afterwards dipped into a solution of 1-2% hydrogen peroxide.

Washed fruits including seeds and skin were chopped, freeze dried, and ground to fine powder (80 mesh).

Processing of the fruits was done by the food company Challenge Bioproducts Co., LTD, Taiwan® (ISO 22000 and HACCP).

 Powders of all ingredients were mixed and packed by TAI WON FOOD INDUSTRIAL CO., LTD, Taiwan (ISO 22000 and HACCP).

Sachets were labelled with a blinded code and shipped to Moshi, Tanzania in September 2013.
Study Flow & Outcome Measures

Run-in period (1 week)  Intervention (8 weeks)  Wash-out period (4 weeks)  Intervention (8 weeks)

A

Before treatment

N₁

After treatment

N₂

Before treatment

N₃

After treatment

N₄

B

Group 1 (AB-Sequence)  Group 2 (BA-Sequence)

Venous blood sample for fasting plasma glucose, glycated hemoglobin, insulin, high-density lipoprotein, total cholesterol, and triglycerides; measurement of blood pressure and anthropometrics

Capillary blood sample for fasting plasma glucose; measurement of blood pressure and anthropometrics
# Inclusion & Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>- BMI $\geq 27 - &lt; 35 \text{ kg/m}^2$</td>
<td>- Having diagnosed disease</td>
</tr>
<tr>
<td>- WC $\geq 80 \text{ cm}$ (women) $\geq 90 \text{ cm}$ (men) or a WHR $\geq 0.8$ (women) $\geq 0.95$ (men)</td>
<td>- Taking any kind of medication</td>
</tr>
<tr>
<td>Being pre-diabetic according to:</td>
<td>- High blood pressure ($&gt;160/&gt;100$)</td>
</tr>
<tr>
<td>- FPG $\geq 100 - 125 \text{ mg/dl}$ ($\geq 5.6 - 6.9 \text{ mmol/l}$) on two days</td>
<td>- Low blood pressure ($&lt;90/&lt;60$)</td>
</tr>
<tr>
<td>or FPG $\geq 100 - 125 \text{ mg/dl}$ and HbA1c $\geq 5.7% &lt; 7.5%$ on one day</td>
<td>- Being mentally ill</td>
</tr>
<tr>
<td></td>
<td>- Pregnancy or planned pregnancy</td>
</tr>
<tr>
<td></td>
<td>- Breast-feeding</td>
</tr>
<tr>
<td></td>
<td>- Having G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td>- Heavy alcohol consumption</td>
</tr>
</tbody>
</table>
Sample Size Calculation

• G*Power 3
• Alpha error: 0.05 and Power (1-beta error probability): 0.9
• Expected change in FPG: 10 mg/dl
• SD: 17 mg/dl
• Paired t-test
• Total sample size of 63
• Plus 30% drop out → 82 participants (41/41)

Ethical Clearances and Allowances were Obtained from:

- National Institute Medical Research (Tanzania)
- Tanzanian Food and Drug Authority (Tanzania)
- Kilimanjaro Christian Medical College (Tanzania)
- Justus-Liebig-University – Medical Department (Germany)
- Regional Medical Officer (Tanzania)
Pre-Screening & Screening

- July - October 2013
- Churches, mosuqe, banks, schools, KCMC, etc.
- Pre-screening: weight, height, age, blood pressure → 1,256 people
- Screening for pre-diabetes: → 382 people
  → **35% classified as pre-diabetic**, 14% as diabetic, and 51% as normo-glycemic
  → 19% eligible for the study: n = 74 (6% of all pre-screened volunteers)
  → 16% enrolled in the study: n = 62 (5% of all pre-screened volunteers)
Preliminary Results of Intervention Phase 1

- Weekly capillary fasting plasma glucose (FPG)
- HbA$_{1c}$ and FPG at N1 and N2
- Body weight
- Blood pressure
- Adverse events
Weekly Measurement of Capillary FPG

After the intervention, bitter gourd group showed lower average FPG levels than placebo group (ns)

There was a slight increase in average FPG levels during the intervention period in both groups

Possible explanation:

- Celebrations in Nov. and Dec.
**HbA$_{1C}$ & Lab FPG**

There were no significant differences between groups at baseline (n1).

No significant drop in FPG levels after bitter gourd treatment.

However, FPG levels of placebo group increased significantly ($p=0.018$) from n1 to n2.

After intervention bitter gourd group tended to have lower FPG levels compared to placebo group ($p=0.058$).

There were hardly any changes or differences in HbA$_{1C}$ levels.
Detailed Lab FPG Results

Under placebo more patients show increased lab FPG (A)

Under bitter gourd more patients show decreased lab FPG (A)

Overall, bitter gourd treatment decreased average lab FPG, while placebo group showed an increase (B)

Changes in lab FPG levels were significantly different between treatments (B)
Gender Differences

Analyzing data of females and males separately indicates a stronger and significant effect of bitter gourd on FPG levels in females compared to males.

No gender differences were found for bitter gourd’s effect on blood pressure. (not shown)

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Bitter gourd</td>
<td>p-value</td>
<td>Placebo</td>
</tr>
<tr>
<td>Lab FPG n1</td>
<td>5.32</td>
<td>5.32</td>
<td>ns</td>
<td>5.36</td>
</tr>
<tr>
<td>Lab FPG n2</td>
<td>5.56</td>
<td>5.10</td>
<td><strong>0.043</strong></td>
<td>5.21</td>
</tr>
<tr>
<td>Δ lab FPG</td>
<td>0.27</td>
<td><strong>-0.21</strong></td>
<td><strong>0.021</strong></td>
<td>-0.39</td>
</tr>
<tr>
<td>HbA1C n1</td>
<td>6.56</td>
<td>6.40</td>
<td>ns</td>
<td>6.71</td>
</tr>
<tr>
<td>HbA1C n2</td>
<td>6.68</td>
<td>6.51</td>
<td>ns</td>
<td>6.61</td>
</tr>
<tr>
<td>Δ HbA1C</td>
<td>0.13</td>
<td>0.11</td>
<td>ns</td>
<td>-0.10</td>
</tr>
</tbody>
</table>
Adverse events

• Flatulence, diarrhea, stomach pain, headache, dizziness, nausea, vomiting (esp. Bitter gourd sachets)
• No report of hypoglycemia
• Association of adverse events to sachet intake was not always clear
Additional observations

• Tight inclusion criteria helped to reduce the risk of adverse events, reduced standard deviation, but lowered the chance of finding sufficient number of participants within the given time frame (62 instead of 82)

• Drop out during the first intervention phase was lower than expected (12.5% drop out vs. 30% expected drop out)

• Overall drop out rate was 16%
Conclusions

- Bitter gourd treatment improved FPG levels compared to placebo
- This effect was more pronounced in women
- To our knowledge this is the first study testing a bitter gourd drink instead of pills or capsules
- Glucose tolerance test after glucose load (oGTT) may be more recommendable for future studies
- Data evaluation of blood lipids and second intervention phase will be important for further recommendations
- Further studies following this approach will help to define vegetable based dietary strategies to improve blood glucose control that are available for the poor
Acknowledgements

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• Funded by the German Federal Ministry of Economic Cooperation and Development
• Lab analyses are conducted at Kilimanjaro Christian Research Institute
• Data analysis was mainly conducted by Sandra D. Habicht, JLU Gießen